ISBN: 978-93-48620-46-0

ADVANCES IN PHARMA AND HEALTH SCIENCE RESEARCH VOLUME I

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Bhumi Publishing, India
First Edition: April 2025

Advances in Pharma and Health Science Research Volume I

(ISBN: 978-93-48620-46-0)

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Published by:

Bhumi Publishing

BHUMI PUBLISHING

Nigave Khalasa, Tal – Karveer, Dist – Kolhapur, Maharashtra, INDIA 416 207

E-mail: bhumipublishing@gmail.com

PREFACE

The field of pharmaceutical and health sciences has witnessed unprecedented advancements over the past few decades, driven by relentless research, technological innovation, and an ever-increasing demand for improved healthcare solutions. The book "Advances in Pharma and Health Science Research" aims to serve as a comprehensive platform to showcase the latest trends, developments, and breakthroughs in these dynamic disciplines.

This volume brings together original research articles, review papers, and case studies from academicians, researchers, healthcare professionals, and industry experts from across the globe. The topics covered span a wide array of subjects—including drug discovery and development, pharmacology, clinical research, biotechnology, health informatics, public health strategies, and emerging therapeutic techniques. Each chapter reflects the contributors' commitment to addressing contemporary challenges while paving the way for innovative solutions in patient care and treatment modalities.

The book is intended for scholars, students, professionals, and practitioners who are engaged in pharmaceutical and health science sectors. We believe that this compilation will not only enhance their knowledge but also inspire collaborative research and interdisciplinary discourse for future advancements.

We are deeply grateful to all the contributors for their scholarly inputs and to the editorial team for their meticulous efforts in bringing this work to fruition. We also extend our sincere thanks to the institutions and organizations that supported the contributors in their research endeavors.

As you delve into the chapters, we hope this book enlightens your understanding, encourages scientific curiosity, and contributes meaningfully to your academic and professional journey.

- Editors

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GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Muthukumar S*, Venkatesan N, Imran Fareeth A. M., Meeran Mydeen I,
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Abstract:
GRDDs are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important drugs. GRDFs greatly improves the pharmacotherapy of stomach by releasing the drug locally and thus results into high concentration of drug at the gastric mucosa which can be sustained over a longer duration of time. GRDFs enable prolonged and continuous release of the drug to the upper part of Gastro intestinal tract (GIT) and this significantly extend the duration of drug release and improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient. The purpose of this Book is to briefly describe the gastro retentive drug delivery (GRDD), factors related to GRDD, its advantages disadvantages, and emphasis is given over its significance over conventional form of drug deliveries.

Keywords: Gastroretention, Conventional Drug Delivery, Anatomy of GIT, GIT's Physiology Applications, Evaluation.

Introduction:
The most practical and favored method of distribution to the systemic circulation is oral administration. In the pharmaceutical industry, oral controlled release drug delivery has recently attracted more attention because to its potential to improve therapeutic benefits such patient compliance, formulation flexibility, and convenience of dose administration. Medications with a short half-life and easy absorption from the gastrointestinal tract (GIT) are rapidly removed from the bloodstream. For these medications to have therapeutic effect, frequent administration is necessary. The creation of oral sustained controlled release formulations aims to circumvent these restrictions by releasing the medication gradually into the gastrointestinal tract and sustaining a long-term, efficient drug concentration in the systemic circulation. Following oral administration, this type of drug delivery would remain in the stomach and release the medication in a regulated fashion, allowing the medicine to be constantly delivered to the gastro intestinal tract absorption location. By extending the gastric residence period, gastro retentive

drug delivery targets site-specific drug release in the upper gastrointestinal tract (GIT) for either local or systemic effects. The gastric retention time (GRT) of medications can be considerably extended by gastro retentive dose forms because they can stay in the stomach area for extended periods of time. GRDDS help these medications by [(5)]

- Increasing their Bioavailability
- Effectiveness of the treatment and potential dosage reduction.
- Reduction in therapeutic level fluctuation by the long-term maintenance of consistent therapeutic levels
- Cut down on drug waste
- Increases the solubility of medications that are less soluble in high pH environments, such as weakly basic medications like papaverine and domperidone. [(5)]

Anatomy of Gastrointestinal Tract

There are three primary areas that make up the gastrointestinal tract:

1. The stomach
2. The duodenum, jejunum, and ileum of the small intestine
3. The large intestine

The gastrointestinal tract (GIT) is a continuous muscular tube that runs from the mouth to the anus. Its physiological activities include secretion, motility, digestion, absorption, and excretion. The GIT's arrangement, from the stomach to the large intestine. Before its load (chyme) is released through the pyloric sphincter and into the small intestine at a regulated rate appropriate for digestion and absorption, the stomach's primary job is to store and combine food with gastric secretions. The stomach holds roughly 50 milliliters when it is empty, but when it is full, it can hold up to one liter

Mucus: Composition and Function

Specialized goblet cells produce the complicated viscous adherent secretion known as Mucus. These goblet cells, which are glandular columnar epithelial cells, surround every organ that comes into contact with the outside world. Mucus is known to perform a variety of tasks in these areas, including lubricating objects for passage, maintaining a hydrated epithelium layer, acting as a barrier against pathogens and harmful substances, and acting as a permeable gel layer that permits gas and nutrient exchange to and from the underlying epithelium Water (>95%) and mucin, which are glycoproteins with a remarkably high molecular weight (2–14 X106 g/mol), make up the majority of mucus. This "viscoelastic soup" also contains lipids, proteins, and mucopolysaccharides. The macromolecules that make up the densely entangled network of mucin glycoproteins attach to one another via non-covalent connections. Mucus's structure and rheological characteristics are largely determined by this molecular interaction.[(3)]

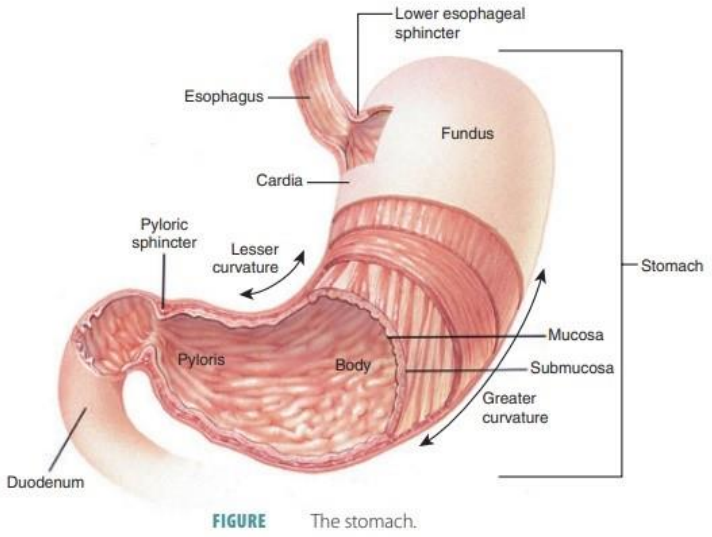

Fig. 1: Structure of stomach

Physiology of Gastrointestinal Tract

The stomach is separated anatomically into three parts: the fundus, body, and antrum pylorus. While the antrum is the primary location for mixing motions and serves as a pump for stomach emptying through pushing activities, the proximal portion, which is composed of fundus and body, serves as a reservoir for undigested material. Both fed and fasted phases involve gastric emptying. Nonetheless, the two states exhibit different motility patterns. An inter digestive sequence of electrical events occurs during the fasting state, alternating between the stomach and intestine every two to three hours. This is known as the migrating myoelectric cycle (MMC) or inters digestive myoelectric cycle, and it is further separated into the four phases listed below.

- Phase I (Basal phase)
- Phase II (Pre burst phase)
- Phase III (Burst phase)
- Phase IV

Table 1: Four phases in migrating myoelectric complex (MMC)

Phase	Statement	Time span (min)
Phase 1	Also called basal phase. This stage does not have any contractions	30–60
Phase 2	Also called pre burst phase. This stage has irregular contractions	20–40
Phase 3	The good food material migrates distally due to regular contraction at maximum frequency	10–20
Phase 4	Transition period between phases 3 and 1	0–5

1. Phase 1 (Basic phase) lasts 30 to 60 minutes and is characterized by sporadic contractions.

2. The pre burst phase, or phase 2, lasts 20–40 minutes and is characterized by contractions and sporadic action potentials.
3. Phase 3 (Burst phase) lasts 10–20 minutes and is characterized by brief, strong contractions.
4. Phase 4 takes place between phases 2 and 1 of two consecutive cycles and lasts for 0–5 minutes. The pattern of contractions shifts from the fasted to the fed condition following the consumption of a mixed meal. This pattern, which includes constant contractions similar to phase 2 of the fasted state, is sometimes referred to as the digestive motility pattern. Food particles are pushed towards the pylorus in a suspension when these contractions reduce their size to less than 1 mm. The delayed start of MMC during the fed state causes the stomach emptying rate to slow down.13 orally administered controlled released dosage forms are susceptible to problems such as short stomach residence time and unexpected gastric emptying rate, according to scintigraphy studies measuring gastric emptying rate. [(4)]

Advantages

Among the many benefits of gastro retentive drug delivery systems (GRDDS) are the following:

- **Increased patient compliance:** GRDDS can help patients take their medication more easily by lowering the frequency of dose.
- **Increased bioavailability:** GRDDS can improve the absorption of medications with limited windows for absorption.
- **Increased therapeutic efficacy:** GRDDS can keep drug plasma concentrations constant, which can increase a medication's therapeutic impact.
- **Targeted delivery:** GRDDS has the ability to administer medicine to a particular location, which may be helpful in the treatment of stomach disorders.
- **Decreased dose dumping:** GRDDS can assist in preventing drug waste.

Disadvantages

- Retention in stomach is not desirable for drugs that cause gastric irritations. **e.g. NSAID**
- Drugs are degraded in the acidic environment of stomach. **e.g. Insulin**
- Drugs are undergone significant first pass metabolism **e.g. Nifedipine**
- Drugs have limited acid solubility **e.g. Phenytoin**
- Floating drug delivery systems require high level of fluid in stomach to float and work effectively.[(1)]

Factors Affecting Gastro Retentive Drug Delivery System

When creating gastro retention dosage forms, a number of factors pertaining to the anatomy and physiology of the stomach must be taken into account.

1. **Size of particles:** For it to pass through the pyloric valves and enter the small intestine, it should be between **one and two millimeters.**
2. **Density:** The dosage form's density should fall between **1g and 2.5g/cm3.**

3. **Dimensions:** The dimensions must be larger than **7.5 mm.**
4. **Dosage form shape:** 90–100% gastric retention durations (GRT) are demonstrated by ring and tetrahedron devices with flexural moduli of **22.5–48 KSI (keto pound/inch2).**
5. **Individual or many units:** Larger safety margins, coadministration of various units, and a predictable release profile make many units desirable.
6. **In fed states:** Food intake GRT is longer.
7. **Nature and caloric content:** GRT is raised by indigestible polymers, fatty acid salts, increased calorie content, increased acidity, and meals high in fat and protein.
8. **The low frequency of MMC:** It causes the intake GRT frequency to increase 400 times.
9. **Posture:** It differs in upright ambulatory and spine-related situations.
10. **Gender GRT:** It is shorter in women than in men.[(2)]

Approaches of GRDDS

Fig. 2: Approaches of GRDDS

1. Floating Drug Delivery System

Because floating drug delivery systems (FDDS) have a **lower bulk density than gastric fluids,** they stay buoyant in the stomach for an extended amount of time without influencing the rate at which the stomach empties. The medication is gradually removed from the system at the appropriate pace while it is floating on the contents of the stomach. The residual system is drained from the stomach following medication release. As a result, the GRT rises and the variations in the plasma drug concentration are better managed.

Mechanism of Floating System

The medicine is gradually released from the system at the appropriate pace while it is floating on the stomach contents. Following drug release, the stomach's residual system is emptied. But in addition to a minimal amount of stomach content required to properly implement the buoyancy retention principle, a limited amount of floating force is also necessary to maintain the dosage form's dependability on the meal's surface. The device works by continually measuring the force equal to F as a function of the amount of time needed to keep the submerged objects in place. In

order to avoid the disadvantages of unpredictable intragastric buoyancy capability variations, the device aids in optimizing FDDS with regard to stability, stability, and endurance of floating forces generated. Where F is the total vertical force, Df is the fluid density, Ds is the object density, and v is the volume, F=F buoyancy-F gravity = (Df-Ds) gv

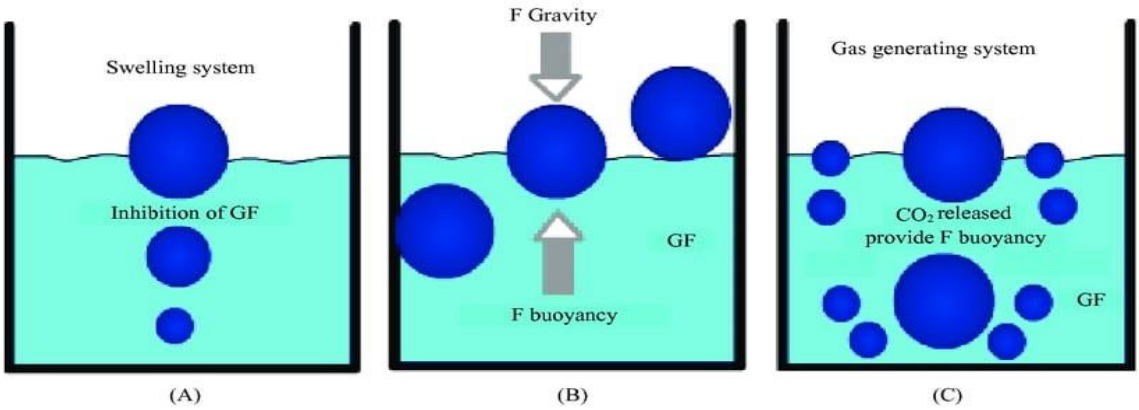

Fig. 3a: Mechanism of floating system

Classification of Floating System

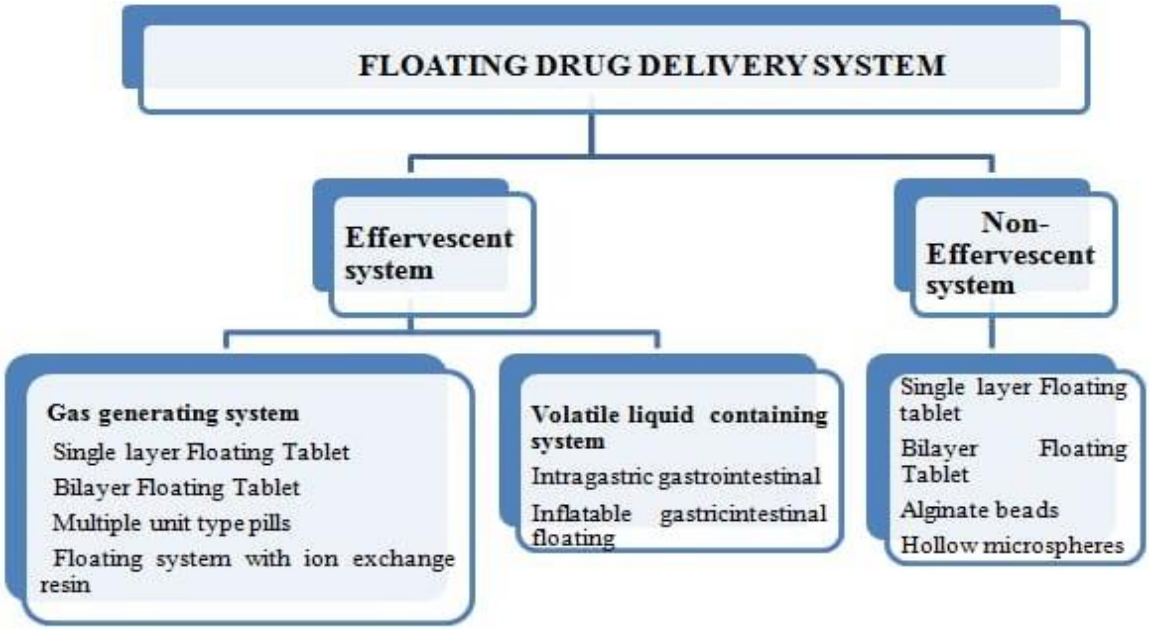

Fig. 3b: Classification of floating system

Effervescent System

In order to create carbon dioxide (CO_2) gas, effervescent systems use gas generating agents, carbonates (like sodium bicarbonate), and other organic acids (like citric and tartaric acid) in the formulation. This lowers the system's density and causes it to float on the gastric fluid. An approach is to add a matrix that contains a liquid section, which creates gas that evaporates at body temperature. Two types of these effervescent systems were further distinguished.

1) Gas generating system

2) Volatile liquid containing systems

1) Gas generating system

By using effervescent interactions between carbonate/bicarbonate salts and citric/tartaric acid, these buoyant delivery methods release CO2, which becomes trapped in the system's jellified hydrocolloid layer, lowering its specific gravity and causing it to float above stomach content.

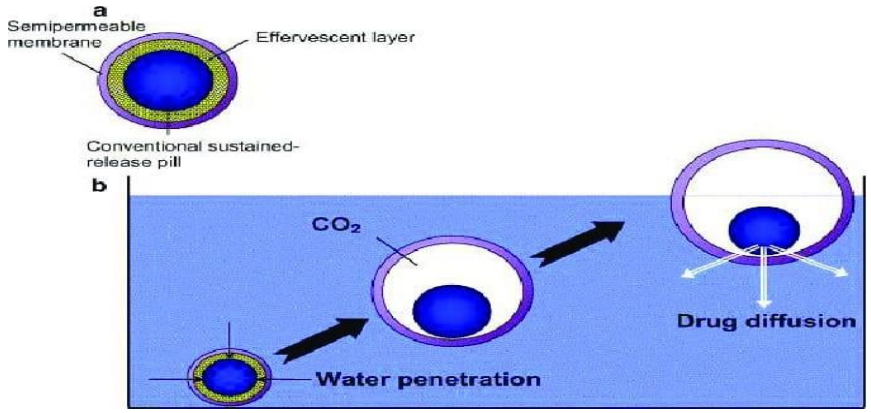

Fig. 4: Gas generating system

Single Layer Floating Tablets

These are created by carefully combining the medication inside the matrix tablet with the CO2 producing chemicals. These float in the stomach for a long time, slowing down the rate of gastric emptying since their bulk density is lower than that of gastric fluids. The floating system gradually releases the medication at the proper rate, and the leftover system is then removed from the stomach. As a result, the GRT rises and the variation in the plasma drug concentration is better controlled

Bilayer Floating Tablets

These are compressed tablets and also contain two layers i.e.

(1) Immediate release layer

(2) Sustained release layer.

Multiple Unit Tablets

These systems are made up of double-layered, sustained-release capsules that resemble "seeds." Effervescent agents make up the inner layer, and a swellable membrane layer makes up the outer layer. The system first sinks when submerged in body-temperature dissolving media, but it later forms enlarged pills that resemble balloons and float because of their decreased density. The production and entrapment of CO2 within the systems is the cause of this decreased density.

Ion Exchange Resin

To increase the dosage form's gastric emptying time, ion-exchange resins, a multiple-unit kind of oral floating dosing system, have been developed. The drug-resin complex beads that make up the system are laden with bicarbonate ions then covered with a polymer that is hydrophobic. The way the system is set up, bicarbonate and medication ions are swapped out for chloride ions once the beads go to the stomach. The polymeric-coated resins capture the produced CO2, which causes the beads to float. [8]

2) Volatile Liquid Containing System

Intra Gastric Floating System

The medication reservoir is enclosed within a micro porous compartment, and these devices can be made to float in the stomach thanks to a flotation chamber that can be vacuumed or filled with air or a harmless gas.

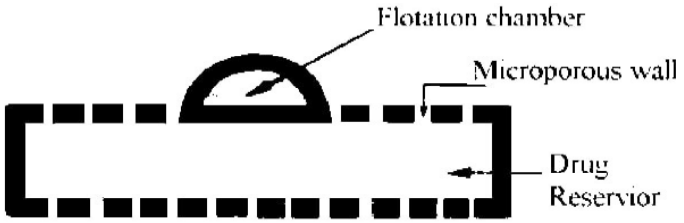

Fig. 5: Intra gastric floating system

b) Inflatable Gastrointestinal Drug Delivery System

In order to inflate the chamber in the stomach, these systems feature an inflatable chamber that holds liquid ether that gasifies at body temperature. In order to create these systems, a drug reservoir—which might be a drug or an impregnated polymeric matrix—is loaded into an inflated chamber and then sealed in a gelatin capsule. The medication reservoir and inflated chamber are released when the capsule dissolves after oral administration. The medication reservoir compartment in the stomach is automatically inflated and held in place by the inflatable chamber. The medication is continually pumped into the stomach fluid from the reservoir.[5]

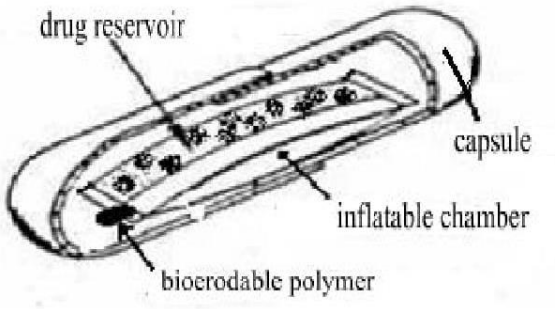

Fig. 6: Inflatable floating system

B) Non-Effervescent System

The mechanism of polymer swelling or bio adhesion to the mucosal layer in the GI tract is the foundation of non-effervescent FDDS. Gel-forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides, matrix-forming materials like polycarbonate, polyacrylate, polymethacrylate, and polystyrene, as well as bio adhesive polymers like chitosan, are the most often used excipients in non-effervescent FDDS. The following are the several types of these systems:

Single-Layer Floating Tablets

They are made by closely combining the medication with a gel-forming hydrocolloid, which maintains a bulk density of less than unity while swelling when it comes into contact with gastric fluid. These dose forms are buoyant due to the air retained by the inflated polymer.

Bilayer Floating Tablets

A bilayer tablet has two layers: an immediate release layer that releases the first dose from the system, and a sustained release layer that absorbs gastric fluid and forms an impermeable colloidal gel barrier on its surface. This layer keeps the tablet buoyant in the stomach by maintaining a bulk density of less than unity.

Alginate Beads

Calcium alginate that has been freeze-dried has been used to create multi-unit floating dosage forms. Calcium alginate can be precipitated by dropping sodium alginate solution into an aqueous solution of calcium chloride, resulting in spherical beads with a diameter of around 2.5 mm. A porous system that can sustain a floating force for more than 12 hours is created by separating the beads, snap-freezing them in liquid nitrogen, and then freeze-drying them for 24 hours at -40°C. Over 5.5 hours was the extended residence period provided by these floating beads.[16]

Hollow Micro spheres (micro balloons)

To extend the dosage form's gastric retention time (GRT), micro balloons or hollow microspheres filled with medications in their other polymer shelves were made using straightforward solvent evaporation or solvent diffusion evaporation techniques. Polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, and low methoxylated pectin are among the polymers frequently employed to create these systems. The number of polymers, the plasticizer-polymer ratio, and the formulation solvent all affect buoyancy and drug release from the dosage form. For more than 12 hours, the micro-balloons continuously floated on top of an acidic dissolving medium that contained surfactant. Since hollow microspheres combine the benefits of a multiple-unit system with good floating, they are currently regarded as one of the most promising buoyant systems.[9]

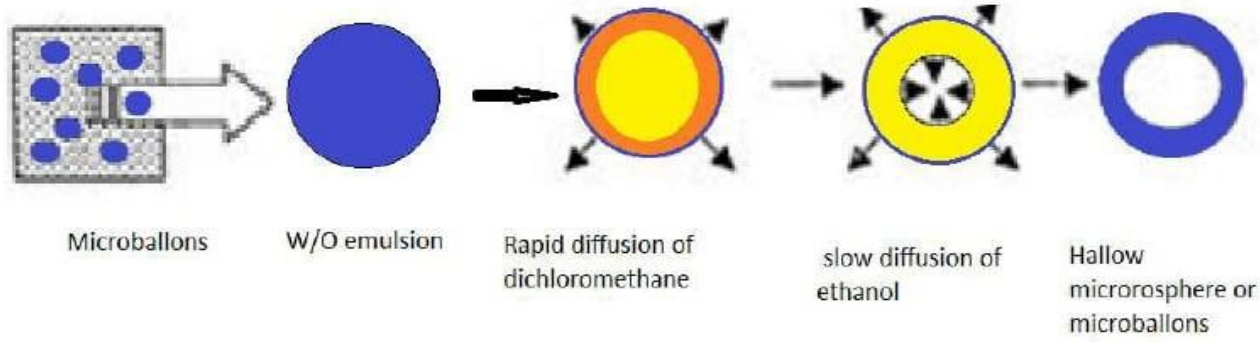

Fig. 7: Hollow microspheres or Micro balloons

2. Muco Adhesive System

A mucoadhesive polymer found in mucoadhesive medication administration systems sticks to the gastric mucosal surface and prolongs the drug's gastric retention in the stomach. Because mucoadhesive polymers can stick to the mucus gel layer, they are highly helpful excipients in the

GRRDS. These polymers can be semi-synthetic (like HPMC, Carbopol, and sodium carboxymethyl cellulose) or natural (like sodium alginate, gelatin, guar gum, etc.). Polymer adhesion to mucosal membranes might be receptor-mediated, bonding-mediated, or hydration-mediated. The hydrophilic polymer becomes sticky and mucoadhesive following hydration in hydration-mediated adhesion. Chemical or mechanical bonding is examples of bonding mediated. Van der Waal forces or ionic or covalent bonds between the polymer molecule and the mucosal membrane are examples of chemical bonding. Certain polymers and particular receptors exhibit receptor-mediated adhesion. The polymers can be cationic or anionic or neutral.(6)

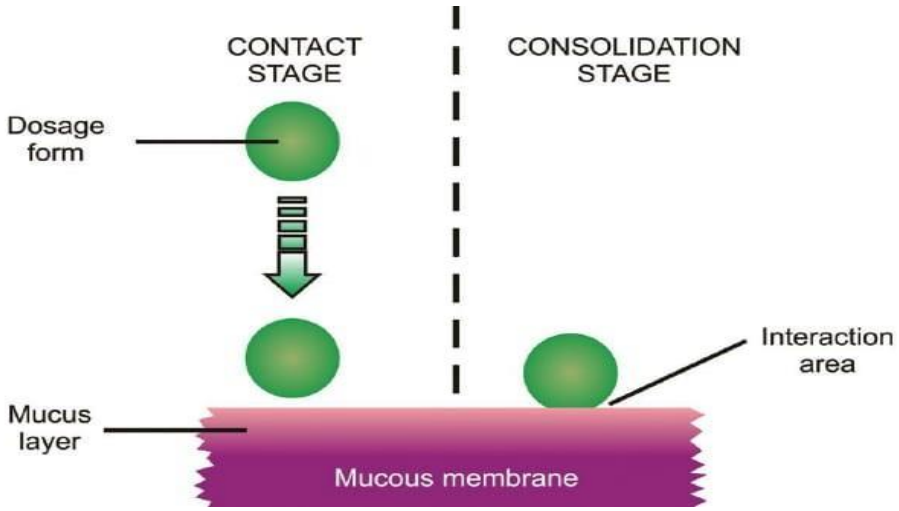

Fig. 8: Mucoadhesive system

3. High Density System

These systems, which have a density of roughly **3 g/cm3,** are kept in the stomach's antrum and can tolerate its peristalsis. The only significant disadvantage of such systems is that producing formulations with high drug concentrations (>50%) and achieving a density of roughly 2.5 g/cm3 is technically challenging. This method entails creating dosage forms with a density that must be higher than the density of typical stomach contents (~1.004gm/cm3). These formulations are made by either coating the medicine on a heavy core or combining it with inert substances including titanium oxide, zinc oxide, iron powder, and barium sulfate. Up to 1.5–2.4 gm/cm3 of density was added by the materials. It appears that a density of about 2.5 gm/cm3 is required for a notable extension of the stomach residence duration. However, there was no evidence of this system's efficacy in treating humans. And no system has been marketed. (10)

4. Raft Forming System

For the delivery of medications for gastrointestinal infections and illnesses, raft-forming systems have drawn a lot of interest. When stomach fluids come into touch with a viscous cohesive gel, each part of the liquid expands, creating a continuous layer known as a raft. This is one of the mechanisms underlying the development of rafts. Due to the low bulk density produced by CO_2 production, this raft floats on stomach contents. In order to make the system less dense and float on the stomach contents, the ingredients typically include a gel-forming agent and alkaline

bicarbonates or carbonate that cause CO_2 to form. The system consists of sodium bicarbonate, an acid neutralizer, and a gel forming agent (such as sodium alginate). When the raft comes into contact with gastric fluids, it floats on the fluids and acts as a barrier between the stomach and the esophagus, preventing reflux of the gastric contents (such as gastric acid) into the esophagus.[8]

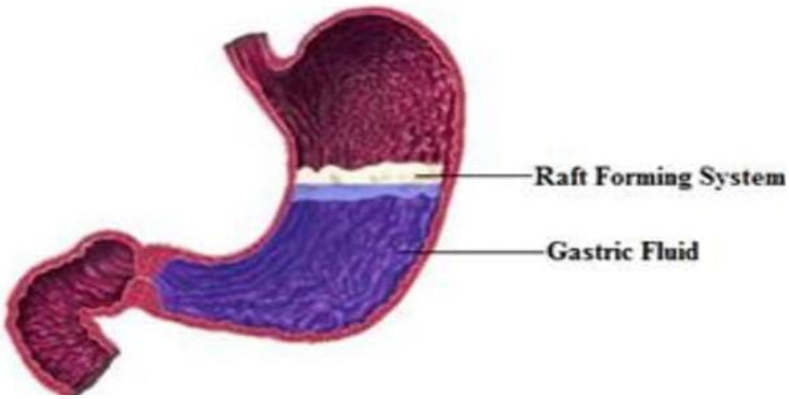

Fig. 9: Raft forming system

5. Swelling System

These are the dosage forms that swell so much after eating that they are unable to pass through the pylorus. Consequently, the dosage form remains in the stomach for an extended amount of time. Since these systems have a propensity to stay blocked at the pyloric sphincter if their expanded diameter exceeds 12–18 mm, they may be referred to as "plug type systems." The degree of cross-linking between the polymeric chains maintains the equilibrium between the magnitude and duration of swelling. A high degree of cross-linking slows down the system's capacity to inflate while preserving its structural integrity over time.[9]

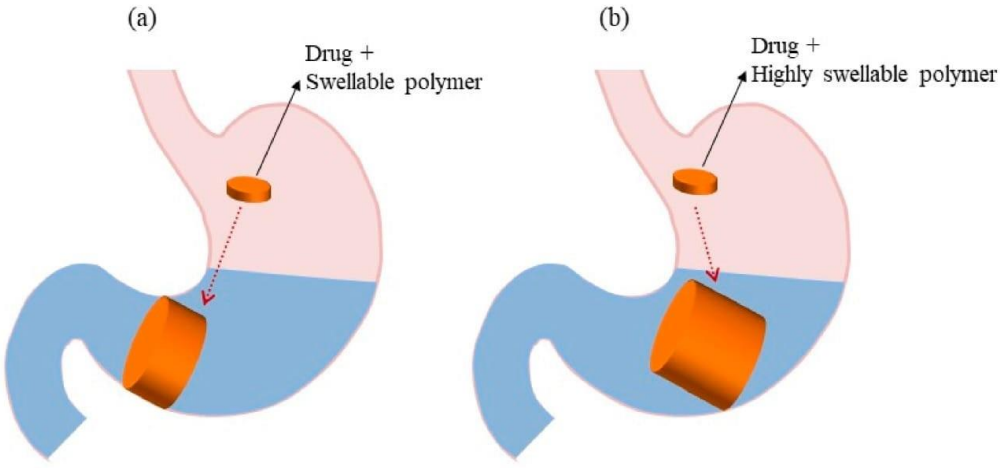

Fig. 10: swelling system

6. Magnetic System

The basic concept behind this technique is that the dose form has a tiny internal magnet, and a magnet is positioned on the abdomen above the stomach. The dosage form's stomach residence time can be extended for an extended amount of time by using an extracorporeal magnet. [6]

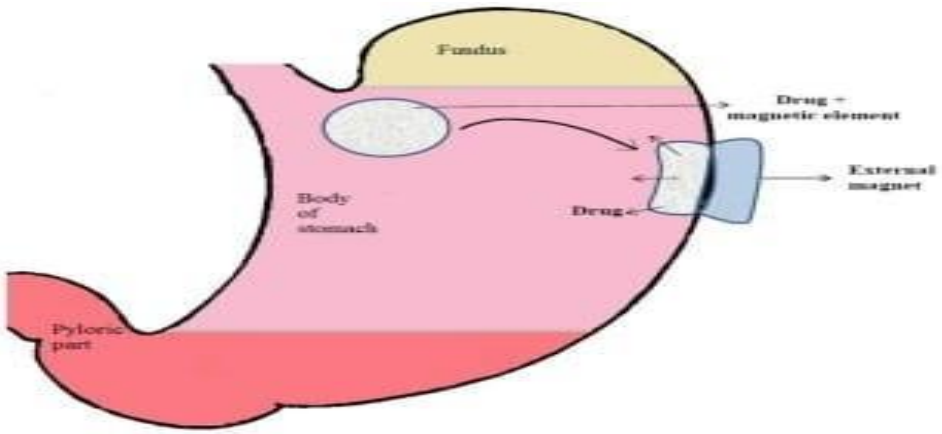

Fig. 11: Magnetic system

7. Superporous Hydrogels

Unlike traditional types, these are swellable systems. Conventional hydrogel absorbs water extremely slowly; it may take several hours to achieve equilibrium states, during which time the dosage form may evacuate too soon. Due to capillary wetting through interconnected open pores, super porous hydrogels with pores larger than 100 µm expand to equilibrium size in a matter of minutes. They have the mechanical strength to endure the strain from gastric contraction and grow to a bigger size. Coformulation of a hydrophilic particle matter Ac-Di-Sol accomplishes this. [3]

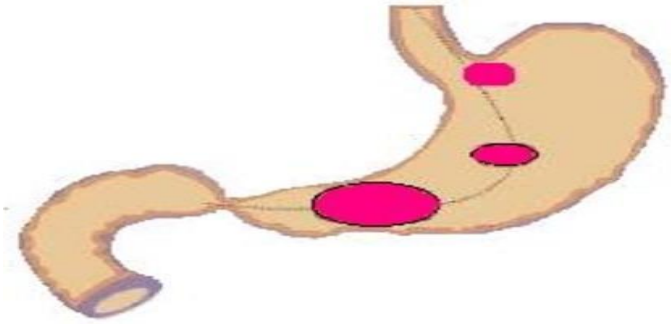

Fig. 12: Super porous hydrogels

List of Drugs Formulated in Multiple Unit Forms of Floating Drug Delivery Systems Drug Dosage form

1. Verapamil Hydrochloride Floating Microparticles
2. Ketoprofen Floating Microparticles
3. Ranitidine Hydrochloride Floating Granules
4. Metronidazole Floating Beads
5. Lansoprazole Floating Micro Pellets Meloxicam Low-density Multi particulate system
6. Diltiazem Hydrochloride, Theophylline and Verapamil Hydrochloride Foam Based Floating Microparticles
7. Nifedipine Hollow Microsphere Acetohydroxamic Acid Floating Microsphere

8. Piroxicam Floating Microsphere Risedronate Sodium Granules Diltiazem Hydrochloride Gran [11]

Evaluation Parameters of GRDDS

1. Shape of Tablets

Compressed tablets were examined for form under a magnifying glass. Using a graded vernier caliper, the breadth and dimensions were ascertained. Three tablets were randomly selected from each mixture, and the thickness of each tablet was measured.

2. Hardness

The ability of a tablet to withstand mechanical shocks depends on its hardness level. A Monsanto hardness tester was used to assess the tablets' hardness. It was said in kg/cm square. Three pills were selected at random, and their hardness was assessed.

3. Tablet Density

One important consideration for floating tablets was tablet density. The tablet only floated when its density was less than that of the gastrointestinal discharge (1.004). The algorithm that supplied the density was used to determine the simulations V = r2h d = m/v

4. Friability

A Roche Fabricator was used to assess the tablets' friability. Percentages were used to express it. First, ten capsules were put in a frit after being weighed (initial W). The friability test was modified to run up to 100 rpm or at 25 rpm for four minutes.

5. Weight Variance Test

Ten tablets were chosen at random from each group and estimated independently in order to confirm weight variance. A slight variance in pill weight was allowed by the US Pharmacopoeia.

6. Buoyancy or Floating Test

Before the dose form was put into the fake gastrointestinal fluid, chronograph devices were employed to measure how long it stayed buoyant. The total floating time (TFT) is the total amount of time that stays buoyant, whereas the floating lag time (FLT) or buoyancy lag time (BLT) is the amount of time needed for the dosage form to appear on the medium's surface.

7. Drug Content Analysis

The drug content % indicates the overall amount of the drug that was included in the mixture. It must adhere to the restrictions set forth by traditional monographs. The drug content was ascertained using spectroscopy techniques, titrimetric methods, near-infrared spectroscopy (NIRS), and a spectrometer for inductively coupled plasma atomic emission (ICPAES).

8. In – Vitro Drug Release

Tests for dissolution are carried out using a dissolving device. Samples are continuously removed from the dissolution media and replenished, and their drug content is assessed when the proper dilution is present. [12]

Applications

1. Bioavailability: Compared to the administration of non-GRDDS controlled release polymeric formulations, the bioavailability of controlled release GRDDS is noticeably improved. Numerous distinct processes pertaining to drug absorption and transit in the gastrointestinal tract work together to simultaneously affect the extent of drug absorption.

2. Site Specific Drug Delivery Systems: These systems are especially useful for medications that are absorbed from the intestines in a certain way, such as furosemide. Medications are delivered to the stomach slowly and under supervision, which reduces systemic exposure to the medications and produces adequate local therapeutic levels. It lessens the negative impact that medications have on the bloodstream. Furthermore, a site-directed administration system's extended stomach availability may help lower the frequency of dose.

3. Sustained Drug Delivery: This method forbids the passage of high doses from the pyloric aperture. Nicardipine hydrochloride sustained-release floating capsules were created and were evaluated in vivo Plasma concentration time curves shows a longer duration for administration (16 hours) Sustained release floating capsules as compared with conventional capsules (8 hours). Hydro dynamically balance system (HBS) can remain in stomach for prolong periods and hence the drug release in sustained manner for prolong period of time.

4. Enhancement of Absorption: Drugs with low bioavailability due to site-specific absorption from the upper portion of the GIT may be candidates for formulation as floating drug delivery devices, which would maximize absorption. These dosage forms can be kept in the stomach area for an extended amount of time because to their floating ability, allowing for maximal absorption rate.

5. Minimize Adverse Effect at the Colon: The quantity of medication that reaches the colon is reduced when it is retained in the stomach's HBS systems. Thus, the drug's undesirable effects in the colon might be avoided. The GRDF formulation for beta lactam antibiotics, which are only absorbed from the small intestine and whose presence in the colon causes the development of microorganism resistance, is justified by this pharmacodynamics aspect. [(11)]

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OSMOTIC DRUG DELIVERY SYSTEM

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Abstract:
Traditional oral medication delivery methods provide the drug with an immediate release and an efficient concentration at the intended location. Unpredictable, continuously fluctuating plasma concentrations could be the outcome of this dosage regimen. As a result, numerous regulated medication delivery systems are created. Among these, osmotic drug delivery systems (ODDS) and pulsatile drug delivery systems (PDDS) are becoming more and more significant because they improve patient treatment efficacy and compliance by delivering the medicine at precise times based on the course and physiological requirements of the disease. They regulate the drug's delivery by using the osmotic pressure theory. To a significant extent, the drug's release is unaffected by GIT physiological variables. Both targeted and systemic medication delivery are possible with these methods. The theoretical concept of drug delivery, types of oral osmotic drug delivery systems, factors influencing the drug delivery system, the benefits and drawbacks of these delivery systems, the fundamentals of the osmotic system, evaluation parameters, marketed status, and, last but not least, recent developments are all "highlighted" in this book.

Keywords: Osmotic Drug Delivery, Osmosis, Osmogen, Oral Drug Delivery

Introduction:

Oral drug delivery is the most effective and convenient option for administering various drugs due to its large active surface area compared to other methods. In conventional oral drug delivery systems, the drug is released instantly. Effective concentration at the target site can be achieved by irregular administration of excessive doses. This kind of dosing pattern outcome is volatility in therapeutic plasma concentrations, leading to noticeable adverse effects in some situations. Moreover, the rate and extent of absorption of drug from conventional dosage forms may vary greatly depending on factors such as presence of excipients, physicochemical properties of the drug, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Uncontrolled fast medication release may result in local gastrointestinal or systemic harm. To circumvent the drawbacks of traditional dosage forms, formulations are designed using various methodologies, such as sustained/controlled drug administration. There are three primary types of controlled-release medication delivery systems:

transdermal, There are two systems: **intravenous and oral**. Oral CR delivery systems use osmotic pressure to distribute active substances in a regulated manner. Drug release from these systems is largely independent of pH and other physiological conditions, and can be controlled by optimizing drug and system attributes. Alza Corporation R of USA was the first to develop an oral osmotic pump.[1]

Advantages:

1) Following an initial latency, they often provide a zero-order release profile.
2) The release mechanisms are independent of drug concentration.
3) Maintaining stable blood levels within the therapeutic range.
4) Fewer side effects.
5) Deliveries can be delayed or pulsed as needed. 6) Drug release is independent of stomach pH and hydrodynamic conditions.
7) They are well-defined and understood.
8) The delivery rate is independent of external disturbance, including GI motility.
9) Enhanced drug bioavailability.
10) Reduced inter patient variability.
11) Decrease the frequency of dose.
12) Improved patient compliance.
13) Increased safety margin for high-potency medicines
14) Drug release from OCODDSs has a significant in vitro-in vivo correlation within certain limits
15) Higher release rates than those achieved with traditional diffusion-based drug delivery methods are achievable.[2]

Disadvantages

1) Expensive.
2) If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
3) Hole Size is critical in case of Elementary osmotic System.
5) Drug release from the osmotic systems is affected to some extent by the presence of food.
6) Retrieval of therapy is not possible in the case of unexpected adverse event.
7) Rapid development of tolerance.[2]

Osmosis and its Principle:

Osmosis: The passage of solvent molecules over a semipermeable membrane from a lower concentration to a higher concentration is known as **osmosis.**

Osmotic Pressure: The force used to prevent solvent flow on the side with a higher concentration. Osmotic pressure is the term for it. The concentration of the solute that contributes to osmotic pressure determines this colligative feature.

Principle: An osmotic pressure proportional to concentrations is displayed by solutions with the same solvent and solute system but varying concentrations. An osmotic medication delivery system can thereby maintain a steady osmotic pressure and, consequently, a steady influx of water. This causes the drug's zero order release rate to remain constant. The core's osmotic pressure and the drug's solubility determine how quickly the osmotic pump releases the medicine. These methods are therefore appropriate for the delivery of medications that have a moderate solubility in water. The following equation describes the link between osmotic pressure and temperature and concentration:

π=n2RT

where,

n2 is the solute's molar concentration in the solution and

π is the osmotic coefficient.

R is the gas constant.

T stands for absolute temperature.[2,3]

Basic Components of OSDDS:

Drugs:

Osmotic systems work best with medications that are used for long-term treatment and have a short biological half-life (2–6 hours). Numerous medication options, including carbamazepine, metoprolol, oxyprenolol, nifedipine, glipizide, and diltiazemhydrochloride, are designed for osmotic distribution. [4-10]

Osmotic Agent:

A concentration gradient is maintained across the membrane by osmotic agents. They also help to maintain medication homogeneity in the hydrated formulation and produce a driving force for water absorption. Typically, osmotic components are ionic substances made up of hydrophilic polymers or inorganic salts.

Examples: **Salts of inorganic acids that dissolve in water**

Lithium, sodium, or potassium chloride; potassium or sodium hydrogen phosphate; magnesium chloride or sulfate .

Salts of organic acids that dissolve in water

Sodium ascorbate, magnesium succinate, sodium benzoate, sodium citrate, sodium and potassium acetate

carbohydrate

Lactose, maltose, sucrose, and mannose.

Organic polymeric osmogents and amino acids that dissolve in water

Polyethylene oxide, polyvinyl pyrollidone, sodium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxyethylmethylcellulose, methylcellulose, and others. [4-10]

Hydrophilic and Hydrophobic Polymers:

These polymers are employed in the creation of osmotic systems, which create drugs with matrix cores. The choice is determined by the drug's solubility as well as the quantity and rate at which the drug will be released from the pump.

There are two types of polymers: **swellable and non-swellable**. Swellable polymers are typically utilized in pumps that carry medications that are only slightly soluble in water because of their ability to swell, which raises the hydrostatic pressure inside the pump.

When it comes to extremely water-soluble medications, non-swellable polymers are employed. Because they are osmogenic, ionic hydrogels such sodium carboxymethyl cellulose are preferred.

Examples:

Hydrophilic polymers:

High molecular weight poly(vinyl pyrrolidone), hydroxyl ethylcellulose, carboxymethylcellulose, and hydroxyl propylmethylcellulose.

Hydrophobic polymers:

Materials such as wax and ethyl cellulose. [4-10]

Flux regulating agents:

By adding flux-regulating agents to the layer, delivery methods can be designed to control the fluid's permeability. While hydrophobic materials tend to reduce the flow, hydrophilic substances increase it. Materials that are significantly impermeable to water, such as insoluble salts or insoluble oxides, can also be employed for this purpose.

Examples:

Hydrophilic substances:

Polyhydric alcohols, polyalkylene glycols, and polyethethylene glycols (300–6000 Da)

Hydrophobic substances:

Alkyl or alkoxy-substituted phthalates (such as diethyl phthalate or diethoxyethylphthalate) [4-10]

Wicking Agents:

A substance that can attract water into a delivery device's porous network is known as a wicking agent. There are two types of wicking agents**: swellable and non-swellable**.

Wicking agents work to create channels or a network of enhanced surface area by transporting water to surfaces inside the tablet's core.

Examples:

Alumina, niacinamide, titanium dioxide, kaolin, and colloidal silicon dioxide. Polyester, polyethylene, magnesium aluminum silicate, bentonite, poly (vinyl pyrrolidone), sodium lauryl sulphate (SLS), and mpyrol[4-10]

Semipermeable membrane:

The semipermeable membrane housing is a crucial component of the osmotic drug delivery system. As a result, the formulation of osmotic administration depends on the choice of polymeric membrane. The membrane should be biocompatible, have adequate wet strength and water permeability, be rigid and non-swelling, and be thick enough to support the pressure inside the device, among other qualities. Osmotic devices can be coated with any polymer that is impermeable to solutes but permeable to water.

Examples:

Cellulose butyrate, ethyl cellulose, cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate, and eudragits[4-10]

Coating Solvents:

Inert inorganic and organic solvents that do not negatively affect the core, wall, or other materials are appropriate for creating the polymeric solution utilized to fabricate the osmotic device's wall.

The following solvent mixes can be used: methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3), acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), etc.

Examples:

Carbon tetrachloride, cyclohexane, methylene chloride, acetone, methanol, ethanol, butyl and isopropyl alcohols, ethyl acetate, and water[4-10]

Plasticizers:

Plasticizers improve the fluids' workability, flexibility, and permeability while lowering the temperature of the wall's second order phase transition or its elastic modules.

Typically, 100 parts of wall-forming materials contain between 0.001 and 50 parts of a plasticizer or a combination of plasticizers.

Appropriate polymers should be non-toxic, exhibit permanence—as evidenced by their strong propensity to stay in the plasticized wall—have a high degree of solvent power for the materials, and be compatible with the materials across the temperature and processing range.

Examples:

Alkyl adipates, triethyl citrate and other citrates, trioctyl phthalates and other phthalates, acetates, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides, halogenated phenyls, and dialkyl phthalates[4-10]

Pore Forming Agents:

These substances are especially utilized in the construction of controlled porosity or multiparticulate osmotic pumps, as well as pumps for drugs that are poorly soluble in water. A microporous membrane is created by these pore-forming chemicals.

A pore forming may create the microporous in situ by leaching it while the system is operating. The pore-formers might be either solid or liquid, organic or inorganic.

Components in a polymer solution may also volatilize to form pores in the wall, or chemical reactions within the polymer solution may evolve gases before or during application of the solution to the core mass, producing polymer foams that function as the porous wall.

Channels should form once the pore-formers are removed, and they should be non-toxic. The channels turn into a fluid transmission route.

Examples:

Alkaline metal salts including potassium chloride, potassium phosphate, sodium chloride, sodium bromide, and potassium sulfate, among others,

Alkaline earth metals including calcium nitrate and chloride,

Sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, and diols are examples of **carbohydrates.**

Polyols, including polyvinyl pyrrolidone and polyhydric alcohols[4-10]

Classification of Osmotic Drug Delivery System:

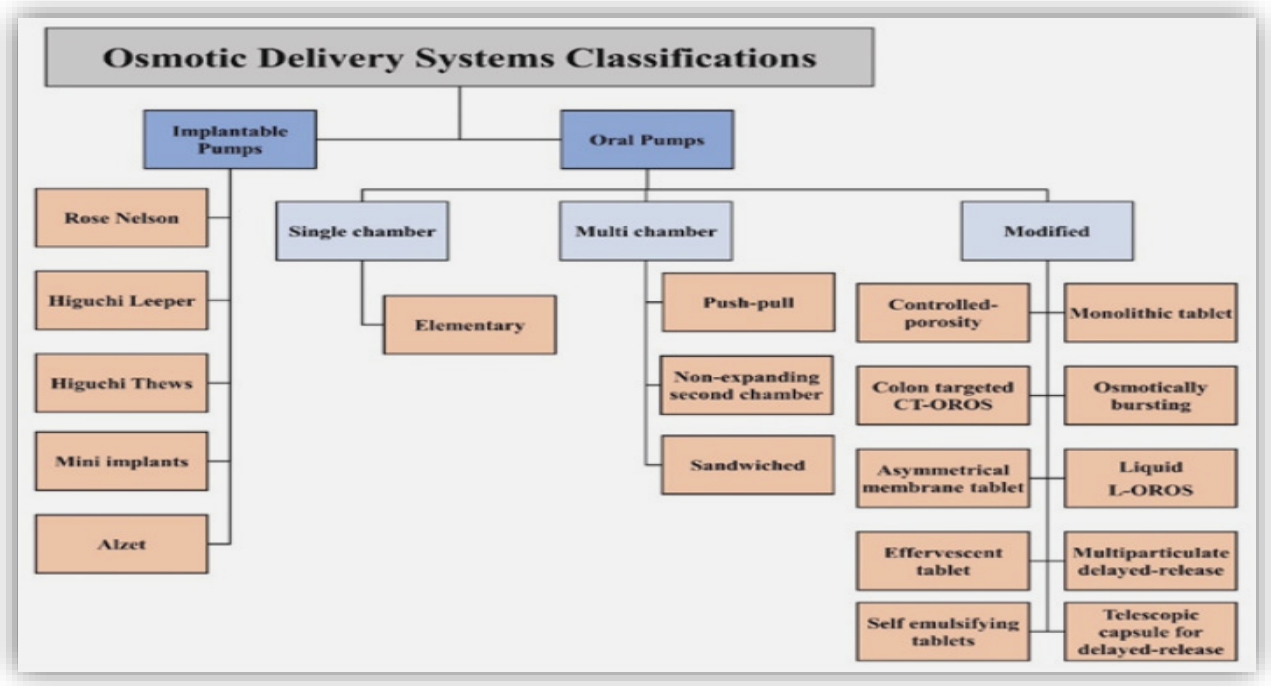

Fig. 1: Classification of osmotic delivery system

Implantable Pumps:

1) Rose Nelson Pump:

The first osmotic pump was described by two Australian physiologists, Rose and Nelson, in 1955. They were interested in getting medications into sheep's and cattle's stomachs.

- An orificed drug chamber.
- A salt chamber that holds extra solid salt and has an elastic diaphragm.
- A compartment with water.

A stiff semi-permeable membrane divides the medication and water chambers. Water is moved from the water chamber into the salt chamber by the difference in osmotic pressure across the membrane. This water flow causes the rubber diaphragm dividing the salt and drug chamber to dilate, increasing the capacity of the salt chamber and allowing the drug to be pumped out of the device.

The formula for the Rose-Nelson pump's pumping rate is

dm/dt=dv/dt*c.

where,

Drug release rate is equal to dm/dt. dv/dt is the water flow volume entering the salt chamber. c is the Drug concentration in the drug chamber.[4]

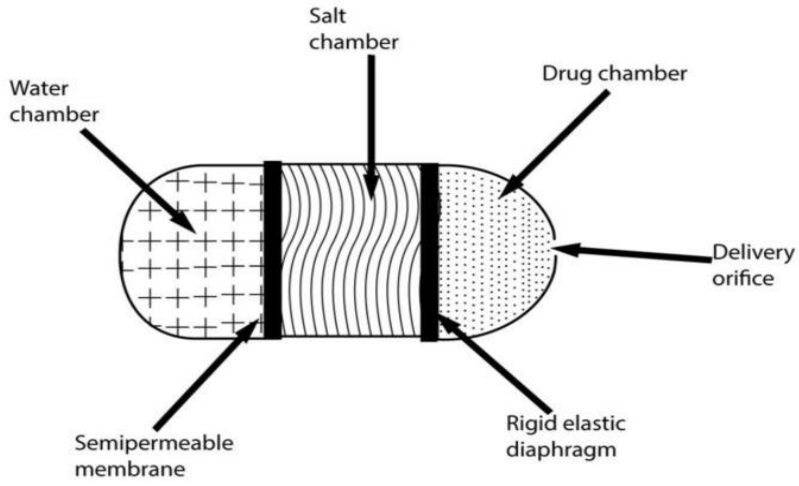

Fig. 2: Rose nelson pump

2) Higuchi Leeper Pump:

Early in the 1970s, the Alza Corporation created a simpler version of the Rose Nelson pump, which is represented by the Higuchi Leeper pump design shown below. The fact that this pump lacks a water chamber and is triggered by water absorbed from the surroundings gives it an advantage over the Rose Nelson pump. This indicates that the medicine is placed into the pump after it has been manufactured and stored for weeks or months before usage.[4]

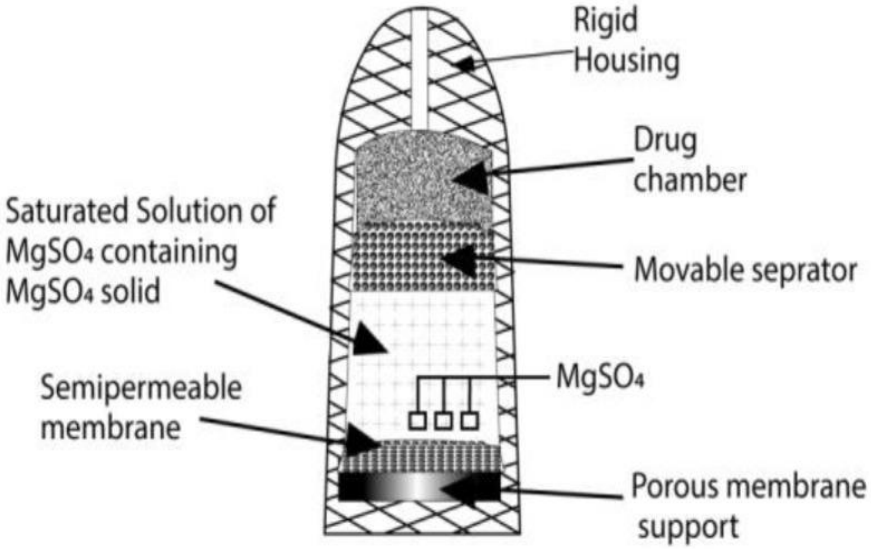

Fig. 3: Higuchi Leeper pump

3) Higuchi Theeuwes Pump:

Early in the 1970s, Higuchi and Theeuwes created a Rose Nelson pump that was comparable. The pump's solid exterior casing is the semipermeable wall itself. Before use, the device is loaded with medication. The salt utilized in the salt chamber and the permeability of the outer membrane casing determine the time course of the drug release when the device is placed in an aquatic environment.[4]

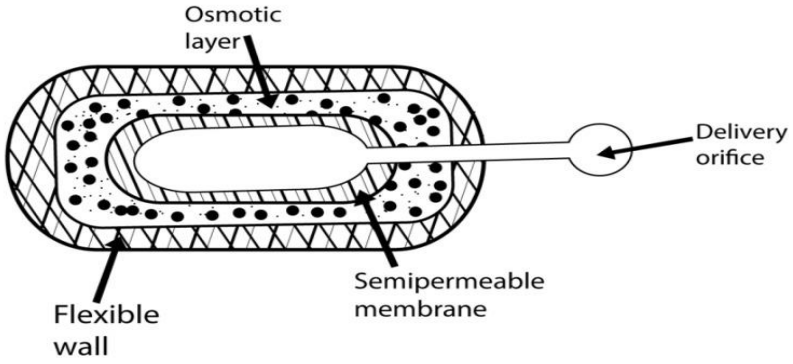

Fig. 4: Higuchi Theeuwes pump

4) Mini Osmotic Pump:

Mini osmotic implantable pumps were initially designed by Alza Corp. for experimental studies in animal models. These pumps operate on osmotic pressure difference between a compartment within the pump, called the salt sleeve and the tissue environment in which the pump is implanted. The high osmolality of the salt sleeve causes water to flux into the pump through a semipermeable membrane which forms the outer surface of the pump. As the water enters the salt sleeve, it compresses the flexible reservoir, displacing the test solution from the pump at controlled, predetermined rate. Because the compressed reservoir cannot be refilled, the pumps are designed for single use only.

5) Alzet Osmotic Pump:

Implantable Alzet micro pumps are used in lab animals for scientific objectives. A hydrocarbon-based thermoplastic elastomer creates a collapsible reservoir, and an osmotic agent coating surrounds it. There is another layer on top of this one: a semi-permeable membrane composed of a combination of cellulose and ester. The medication is put into the reservoir. The medicine is released from the device when water enters through a semi-permeable membrane and reaches the osmotic agent layer, which generates internal pressure.

The amount of water that passes through the selectively permeable wall and the drug concentration in the solution determine the drug release rate. The semi-permeable walls' permeability can be managed to regulate this rate.

The device comes in three different capacities: 100 µL, 200 µL, and 2 mL. Its medication delivery rates fall between 0.11 and 10 µL/h.[5]

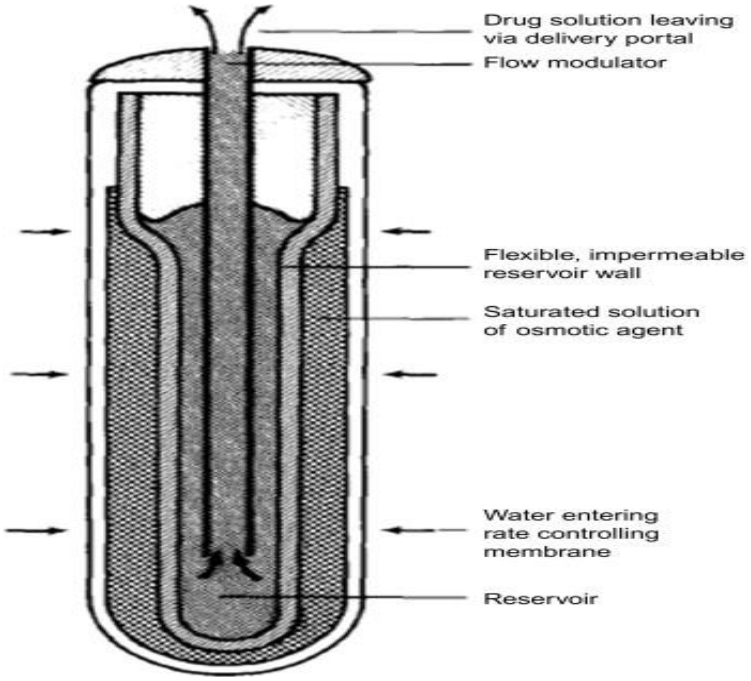

Fig. 5: Alzet Osmotic pump

Oral Osmotic Pump:

1) Single Chamber Osmotic Pump:

i) Elementary Osmotic Pump:

Theuwes created the basic osmotic pump in 1974. A novel medication delivery method that uses an osmotic mechanism to administer the medicine at a regulated rate is the elementary osmotic pump.

The following factors provide control: a) the water permeation capabilities of the semipermeable membrane enclosing the forming agent; and b)the formulation's osmotic qualities.

The rate-controlling semipermeable membrane encloses the osmotically active substance in this system. A tableting machine is used to compress a medication with an appropriate osmotic

pressure into a tablet, creating the device. Next, a semi-permeable membrane typically made of cellulose acetate is applied to the tablet, and a tiny hole which ranges in size from 0.5 to 1.5 mm is drilled through the membrane. This can be done with a mechanical drill or by laser drilling using a CO_2 laser beam that has a wavelength of 10.6 microns. Water enters through a semi-permeable opening when the gadget is in operation. Producing osmotic pressure by imbibition into the core. The volume of the solvent and the medication solution are proportionate. The drug release rate is zero-order, meaning it never changes. Before continuous delivery starts, there must be a half-hour to an hour lag period while the system develops zero-order rates. A steady drug release rate is present in roughly 60–80% of the medication. This technique is thought to work well with medications that have a moderate water solubility.[6]

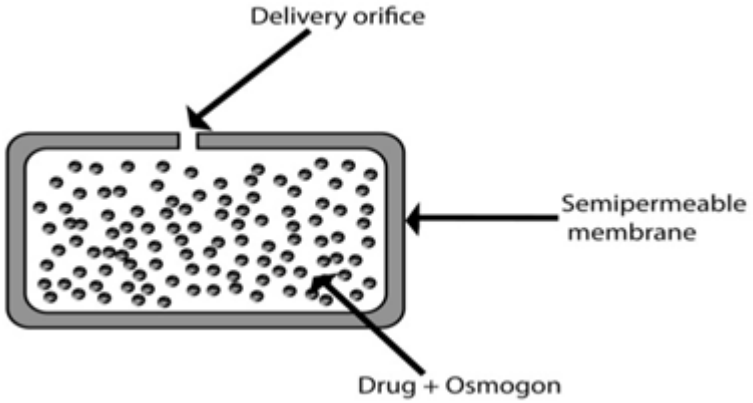

Fig. 6: Elementary Osmotic pump

Multi Chambered Osmotic Pump:

1) Push Pull Osmotic Pump:

There are two compartments in this arrangement, and an elastic diaphragm separates them. This system was introduced by Alza Corporation. The medication is kept in the upper compartment and is connected to the outside world via a drug delivery hole. There is an osmotic agent in the lower compartment, which lacks an opening.

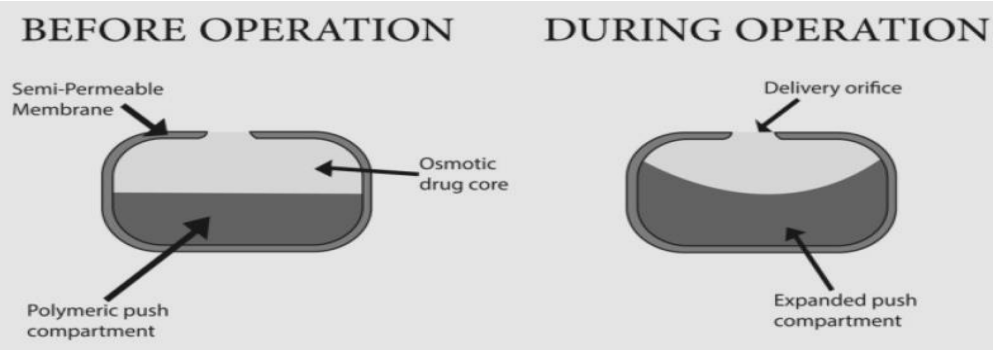

Fig. 7: Push Pull osmotic pump

This sort of pill contains 60–80% of its weight in the drug compartment and 20–40% in the osmotic compartment. Water imbibition takes place in both compartments upon contact with

watery surroundings, and the lower compartment without an opening begins to enlarge. when a result, the medication is released through the aperture when the diaphragm pushes toward the upper compartment. Water is drawn into the device from the lower compartment, which causes expansion and pushes medications through the opening. Carbopol may make up 20–40% of the push layer. The expense of this gadget is significant, and the local medication release is a drawback.[6]

2) Sandwiched Osmotic Pump:

This has two drug layers, two delivery orifices, and a sandwiched polymer push layer. SOTS may be the best option for medications that are likely to produce local inflammation of the stomach mucosa because the middle push layer, which contains the drug and the swelling agent, is released from the two orifices on opposite sides of the tablet when it is placed in an aqueous environment.[6]

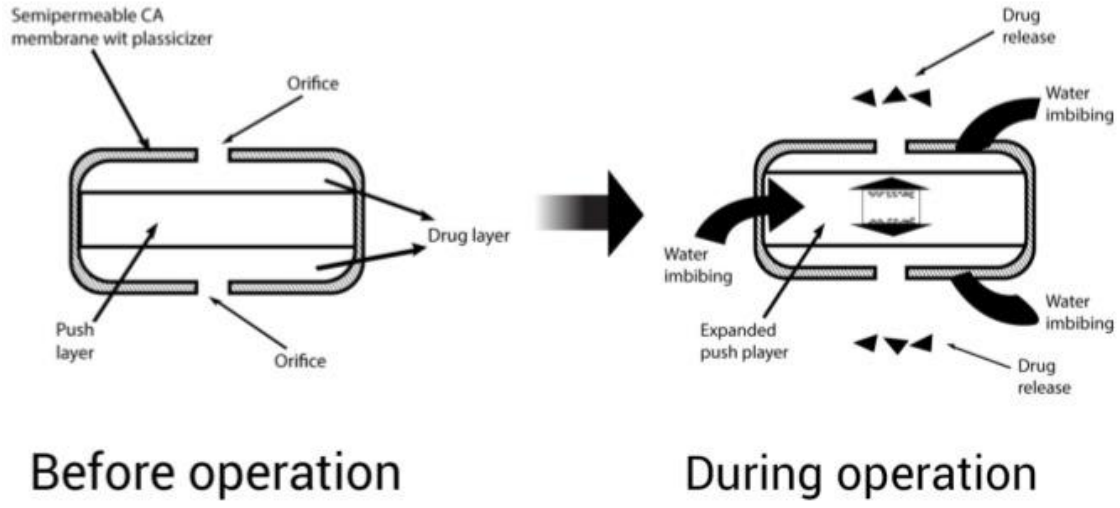

Fig. 8: Sandwiched osmotic pump

3) Osmotic pump with non expanding second chamber:

A device that has a second chamber that is not expanding falls under the second category of multi-chamber systems. This group can be further subdivided into two groups according on the function of the second chamber. One type of these devices uses the second chamber to dilute the medication solution that exits the device. This is helpful because in certain cases, GI tract inflammation may occur if the medication leaves a saturated solution of the oral osmotic systems. This kind of apparatus is made up of two stiff compartments. The medicine is placed in the second chamber, while the first chamber has an osmotic agent that is biologically inert, like sugar or a basic salt like sodium chloride. When both chambers are in use, water is pulled through the semi-permeable membrane.

After combining with the drug solution in the drug chamber through the connecting hole, the osmotic agent solution created in the first chamber exits through the microporous membrane that

makes up the chamber wall. Relatively insoluble medications could be administered using the apparatus.[6]

Specific Types:

1) Controlled Porosity Osmotic Pump:

The controlled porosity osmotic pump is available in single or multipurpose dose forms. In either case, the drug's core is encircled by an asymmetric membrane that serves as the delivery method. A mixed solvent system regulates the phase inversion process that makes up the membrane. The process of evaporation is Water can pass through the membrane, but solutions and insensitive pore-shaping agents that are applied to the surface cannot pass through it. Polymer compositions that were water-permeable but insoluble when exposed to water absorb small amounts of water-soluble additives. Subsequently, the controlled porosity walls developed an interesting sponge-like structure that was significantly permeable to dissolved pharmacological agents and water. The solubility of the drug in the tablet core, the thickness of the coating, the amount of soluble components in the coating, the water permeability of the semi-permeable membrane, and the variation in osmotic pressure across the surface all affect the release rate of these systems. However, the pH and agitation of the release medium, the rate of drug release, and the osmotic pressure are all unaffected. The aforementioned robust outcomes are the consequence of all these variables being under the designer's control and not changing under physiological conditions.

The formula for the water flow rate into the device is 39

$dv/dt = Ak / h (Dp-DR)$.

where, A is the membrane's area,

Dp is the osmotic pressure differential, and

k is the membrane's permeability.

DR is hydrostatic pressure differential.[11]

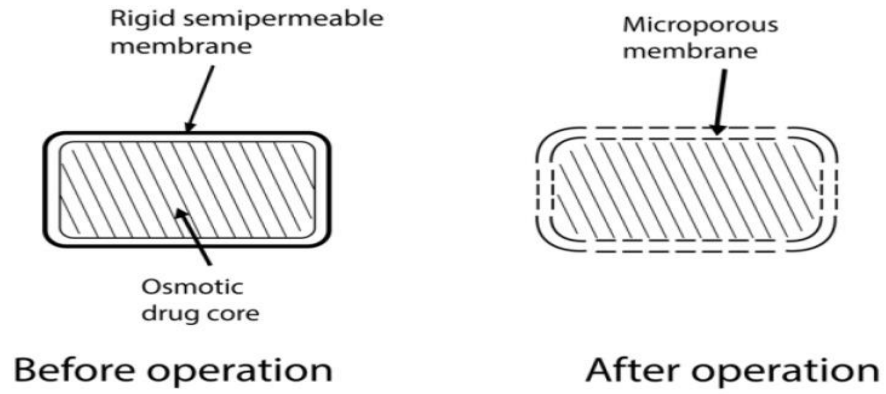

Fig. 9: Controlled porosity osmotic pump

2) Monolithic Osmotic System:

This technique uses a water-soluble substance dispersed in a polymer matrix. Drug particles are encapsulated in polymers. The medicine is released into the surrounding environment when the

system comes into contact with the aqueous environment because the water imbibitions of the active agents break the polymer matrix capsule. This process begins in the polymer matrix's external environment and then progressively moves into the matrix in a sequential manner. These structures have zero-order control over drug delivery kinetics. The primary principle is the osmotic pressure.[7]

3) Colon Targeted Oral Osmotic System (OROS-Ct):

The Colon Targeted Oral Osmotic System (OROS-Ct) is a controlled method of delivering drugs to the colon once or twice daily. For the regulated distribution of colonic medications, the device is equipped with five to six enteric coating and osmotic push-pull units loaded with hard gelatin capsules.The outer shell of the product stops fluid from entering the stomach when it comes into touch with GI fluids, and it dissolves once it gets to the intestine. Water seeps into the center, causing the push compartment to bulge. Concurrently, a flowable gel is created, which is pushed out through the delivery orifice at a set pace.[7]

4) Osmotically Bursting Osmotic Pump:

Baker used an osmotic bursting mechanism to create a controlled-release delivery device. This system lacks a delivery orifice, and its orifice scale is less than that of the conventional osmotic system (EOP). Water is absorbed and hydraulic pressure builds up within when it is placed in a wet environment. This process continues until the wall cracks and the contents are released into the surrounding environment. The semi-permeable membrane's area and thickness can both regulate the release of the medication. This technique works well for delivering pulsed release.[7]

5) Asymmetrical Membrane Osmotic Tablet:

Asymmetric membrane capsules are made up of a product with a center encircled by an asymmetric membrane, meaning that a thicker, porous section protects a relatively thin, dense zone. In contrast to a traditional gelatin capsule, the asymmetric membrane capsule releases the active substance over time rather than dissolving quickly since its wall is composed of a water-insoluble polymer like cellulose acetate.[8]

6) Liquid Oral Osmotic System:

Designed to deliver drugs in liquid form, the Liquid OROS combines the benefits of high bioavailability and prolonged release. These kinds of devices are perfect for the regulated administration of liquid medication formulations, such as lipophilic self-emulsifying formulations (SEF). These are of three types: -LOROS hard cap, LOROS soft cap, Delayed liquid bolus delivery system. A liquid drug layer, an osmotic engine or push layer and a semi-permeable membrane coating are included in each of these devices. When the system gets in contact with the aqueous environment, water gain access through the membrane and causes the stimulation of the osmotic layer. The liquid solution is forced to be delivered from the delivery orifice by the hydrostatic pressure created inside the device as a result of the osmotic layer

expanding. Alza has created osmotic systems for liquid distribution. Its technology is known to increase drug permeability and makes it possible to give insoluble medications in aqueous fluids.[12]

7) Osmotic Effervescent Tablet (EOT):

In this system, effervescent substances in a dosage form react with acid in the surrounding environment to produce carbon dioxide. The drug's precipitate is dispensed by this expanding gas avoids obstruction of the orifice. When a medication is poorly soluble at low pH, this mechanism can clog the delivery aperture and precipitate at the gastric Ph Sodium bicarbonate is typically utilized in this procedure.[8]

8) Multiparticulate Delayed-Release System:

In this system, a semi-permeable membrane, such as cellulose acetate, is applied to pellets that contain a pure medication, either with or without an osmotic agent. When this gadget comes into touch with the watery atmosphere, water enters the core and creates a saturated solution of soluble components. Rapid membrane expansion and hole development are caused by the water flow caused by the gradient of osmotic pressure. Zero-order kinetics typically govern the drug's and osmotic components' release through these pores.[8]

9) Self Emulsified Osmotic Tablet:

For medications that were practically insoluble or only marginally soluble, self-emulsifying agents were added to the tablet's fundamental composition. Roughly 40% of pharmaceuticals on the market have low water solubility. The self-emulsifying agent stabilizes plasma concentrations and enhances medication bioavailability and regulated release rate. This emulsifies hydrophobic medications. Polyoxyethylene castor oil with ethylene oxide, polyoxyethylene glyceryl recinoleate, glyceryl laureates, glycerol (sorbiton oleate, stearate, or laurate), and other common surfactants are used for this purpose.[6]

10) Telescopic Capsule for Delayed Release:

This apparatus is made up of two chambers: one holds the medication and an escape port, while the other has an osmotic engine and a layer that resembles wax between the two sections. The intended active agent is placed in one of the components of the delivery device during the human or automated filling process. The bilayer tablet containing the osmotic engine is positioned in the completed cap part of the capsule, with the barrier pointing to the closed end of the cap and the exposed barrier layer, and the convex osmotic layer pointing to the closed end of the cap. The open end of the filled vessel is inserted into the cap's open end, and the two components are compressed until the cap, osmotic bilayer tablet, and vessel fit together tightly. The osmotic engine expands and applies pressure to the first and second wall components attached to the slidable when fluid is submerged in the dispensing device's casing.

There is a slight pressure difference between the reservoir's interior and usage environment because the volume of the reservoir holding the active agent is maintained constant throughout the delay period. As a result, there is very little net flow of the pressure-driven ambient fluid into the reservoir.[8]

Evaluation of Osmotic Tablet:

Pre compression parameters of osmotic pump tablets

1) Angle of repose
2) Tapped density
3) Bulk density
4) Compressibility index (Carr's index)
5) Hausner's ratio.

Post compression parameters of osmotic pump tablets

1) Thickness
2) Hardness
3) Friability
4) Weight variation
5) Uniformity of drug content test
6) In vitro dissolution studies
7) Scanning electron microscopy (SEM).[10-13]

Marketed Products:

Trade Name	Active ingredient	Design system
Alpress LP	Prazosin	Push -Pull
Acutrim	Phenylpropanolamine	Elementary pump
Cardura XL	Doxazosin	Push –Pull with time delay
Covera HS	Verapamil	Push -Pull
Ditropan XL	Oxybutinin chloride	Push -Pull
Dynacirc CR	Isradipine	Push -Pull
Invega	Paliperidone	Push -Pull
Efidac 24	Chlorpheniramine maleate	Elementary Pump
Glucotrol XL	Glipizide	Push -Pull
Minipress XL	Prazocine	Elementary Pump
Procardia XL	Nifedipine	Push -Pull
Sudafed 24	Pseudoephedrine	Elementary Pump

Fig. 10: Marketed products

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TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract:
Transdermal drug delivery systems (TDDS) have emerged as a promising method for the administration of therapeutic agents, offering several advantages over conventional oral and injectable routes. TDDS utilizes the skin as a route of drug absorption, delivering drugs at a controlled and consistent rate over extended periods. The primary benefit of this system includes the avoidance of first-pass metabolism, which is a common limitation of oral drug administration, as well as improved patient compliance due to its non-invasive nature. This chapter focuses on the key components of TDDS, with a particular emphasis on the mechanisms of drug penetration through the skin, formulation preparation, the role of penetration enhancers, and evaluation methods. Various strategies, including chemical and physical penetration enhancers, are explored to improve drug absorption and overcome the skin's protective barrier. This chapter provides an in-depth review of the current progress in the design, development, evaluation and market trends of TDDS.

Keywords: Transdermal Drug Delivery System, Penetration Enhancers, Transdermal Permeability**,** Stratum Corneum**,** Physical Enhancers, Chemical Enhancer

Introduction:

Transdermal Drug Delivery Systems (TDDS) are non-invasive methods of administering medication through the skin into the bloodstream. These systems have evolved from traditional herbal remedies, ointments, creams, and gels to modern patch technology as shown in figure1.

The first transdermal patch, **Transderm Scop**, was introduced in **1979** for motion sickness treatment. The development of transdermal drugs progressed between **1950-1980**, alongside advancements in sustained-release drug formulations like **Spansule (1952)**.

A **transdermal therapeutic system** is a self-contained dosage form that ensures controlled drug delivery through the skin into the bloodstream. A **transdermal patch** is a medicated adhesive patch applied to the skin, designed to release a drug at a predetermined rate.

These systems provide benefits such as improved patient compliance, controlled drug release, and avoidance of the gastrointestinal tract, making them an essential advancement in modern drug delivery.[1]

Fig. 1: Transdermal patch

Advantages [2]

- Easy to use.
- Avoids First pass metabolism.
- Self medication is possible.
- Reduces frequency of dosing.
- Have fewer side effects than oral medications or supplements.
- Pain less, non-invasive way to deliver substances directly into the body.

Disadvantages [2]

- Limited skin permeability.
- Significant lag time.
- Skin irritation and allergic response.
- Usually reserved for drugs which are extremely potent.

Ideal properties of TDDS[3]

Transdermal Drug Delivery Systems (TDDS) require specific **drug-related, patch-related, and additional properties** for effective performance.

- **Drug-Related Properties:** The drug should have a low molecular weight (<500 Daltons), balanced lipophilicity and hydrophilicity, low melting point, and high potency. It must also be non-irritating and suitable for controlled release.
- **Patch-Related Properties:** The patch should have good adhesion, be comfortable and flexible, prevent moisture loss, and be easy to apply and remove. Cost-effectiveness is also important.[4]
- **Additional Considerations:** TDDS should avoid first-pass metabolism, provide controlled drug release, and enhance patient compliance.

These factors ensure the safe, efficient, and convenient delivery of drugs through the skin into systemic circulation.

Anatomy and physiology of skin

The **skin** is an essential part of the **integumentary system**, playing a vital role in temperature regulation and protection against the environment. It covers an area of about **2m²** and weighs **4.5-5 kg**, accounting for **16% of total body weight** in adults. The thickness varies from **0.5mm (eyelids) to 4.0mm (heels)** as shown in figure 2.[5]

Layers of Skin

1. **Epidermis** – The outermost layer, made of stratified squamous epithelial cells. It includes:
    - **Stratum Corneum**: Forms the main barrier with keratinized, dead cells.
    - **Stratum Lucidum**: A clear layer of flattened cells.
    - **Stratum Granulosum**: Contains keratohyalin granules.
    - **Stratum Spinosum**: Known for spine-like projections connecting cells.
    - **Stratum Basale (Germinativum)**: Produces new skin cells.
2. **Dermis** – The inner layer composed of collagen fibers, fibroblasts, and histiocytes. It has:
    - **Superficial Papillary Layer**: Contains blood vessels and nerve endings.
    - **Deeper Reticular Layer**: Surrounds hair bulbs and sweat glands.
3. **Subcutaneous Layer (Hypodermis)** – A fat-rich layer providing **insulation, cushioning, and energy storage**. It contains smooth muscles like **arrector pili**, responsible for **goosebumps**.

Skin Appendages

- **Sweat Glands**: Regulate body temperature and aid in drug absorption.
- **Hair Follicles & Sebaceous Glands**: Produce sebum, containing lipids for skin protection. The **skin acts as a primary barrier** for percutaneous absorption, making it crucial in drug delivery systems.

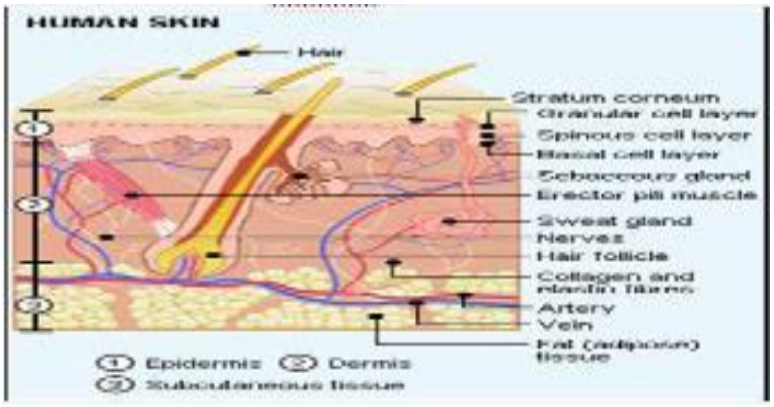
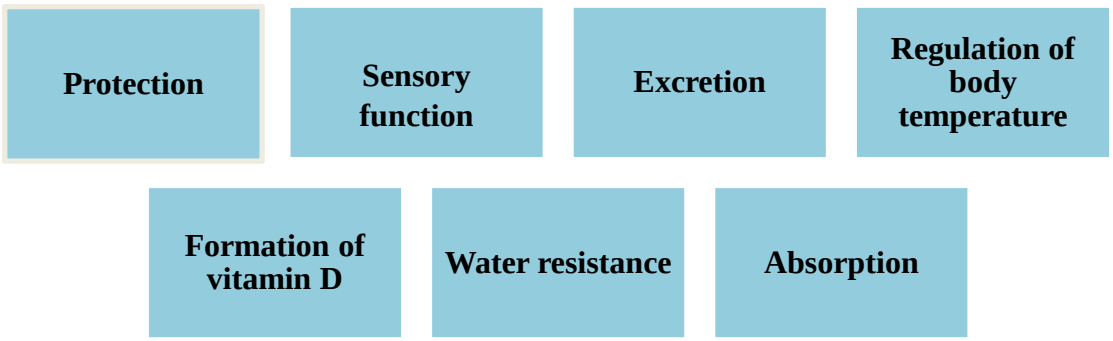


Fig. 2: Human skin

Function of skin



Fundamentals of skin permeation

The rate of permeation across the skin can be expressed accordingly Fick's First law,

$dQ/dt = P_s (C_d – C_r)$

Where dQ/dt - Rate of permission

P_s - Permeability coefficient

C_d - Concentration of skin penetrant in donor compartment (Stratum corneum)

C_r - Concentration of skin penetrant in receptor compartment (body)

Pathways of drug absorption through the skin

a) Transfollicular route (Shunt pathway)

Transfollicular route is the shortest pathway that drug has to follow to reach the systemic circulation that provides a large area for diffusion of drugs.

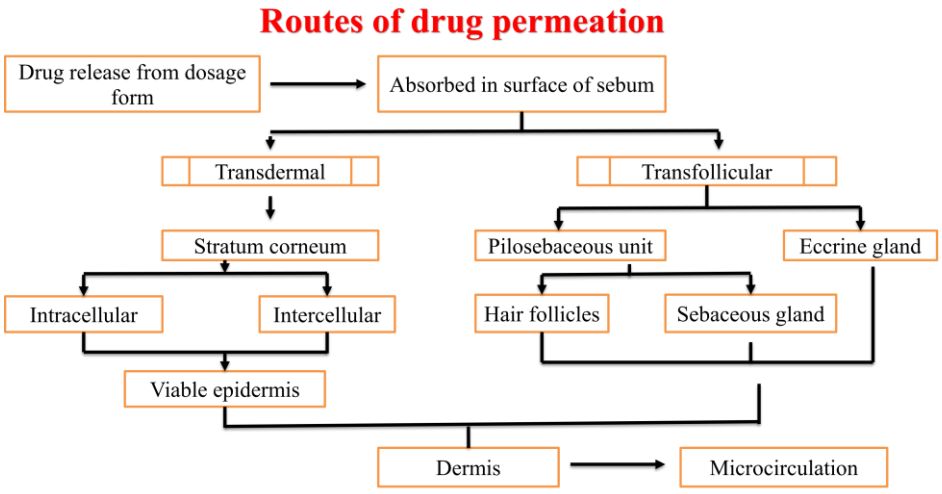
b) Transcellular route

Drug delivering through this route passes from corneocytes which has highly hydrated keratin creating hydrophilic pathway.

The drug passes through the corneocytes of stratum corneum.

c) Intercellular route

The drug diffuses through the continuous lipid matrix present between the cells. [6]



Factors affecting Transdermal permeability:

Transdermal drug transport occurs mainly by **passive diffusion** through the **stratum corneum**. Several factors influence permeability:

1) Physico-Chemical Properties of the Drug and Delivery System

- **Diffusion:** Smaller molecules (<500 Daltons) diffuse more easily.
- **Partition Coefficient:** A lipid/water partition coefficient ≥1 is ideal for better absorption.
- **pH Conditions:** Extreme pH can damage the skin, while moderate pH affects drug flux.
- **Concentration Gradient:** Higher drug concentration increases diffusion.
- **Vehicle:** Determines drug release but does not enhance penetration.

- **Composition of Drug Delivery System:** Affects drug release and permeability by altering skin hydration or lipid interaction.
- **Molecular Size & Shape:** Smaller molecules (≤400 Daltons) penetrate faster.[5]

2) Biological Conditions of the Skin

- **Lipid Film:** Acts as a protective layer; its removal decreases permeability.
- **Hydration:** Increases skin permeability.
- **Temperature & Humidity:** Higher temperature and humidity enhance drug absorption.
- **Race:** Variations in melanin content may affect permeability.
- **Age:** Young and adult skin is more permeable than older skin; children are more sensitive.
- **Anatomical Site:** Skin thickness varies across body areas, affecting permeability.

Basic components in TDDS

Transdermal Drug Delivery Systems (TDDS) consist of essential components that ensure effective drug release and skin absorption.

1. **Polymer Matrix / Drug Reservoir**
    - Controls drug release and must be **biocompatible, stable, and non-toxic**.
    - Should allow proper drug diffusion and be easily manufactured.
2. **Drug**
    - Should be **potent, non-irritating, and soluble in both oil and water**.[6]
    - **Ideal properties:**
        - Molecular weight **< 1000 Daltons**
        - Melting point **< 200°C**
        - Dose **< 20 mg/day**
3. **Permeation Enhancers**
    - Substances that **increase drug penetration** through the skin into the bloodstream.[18,19]

Mechanism of Permeation Enhancers:

1. **Disrupting the Stratum Corneum** – Enhancers disturb the lipid matrix, increasing fluidity and allowing drug diffusion.
2. **Changing Drug Partition Coefficient** – Enhancers improve drug solubility for better skin penetration.
3. **Modifying Protein Structure** – Interaction with skin proteins like keratin increases permeability.
4. **Opening Tight Junctions** – Some enhancers disrupt cell junctions, allowing easier drug passage.[9]

Types of Permeation Enhancers:

1. **Chemical Enhancers:**
    - **Water** – Hydrates skin and opens pores.
    - **Surfactants** – Reduce interfacial tension, aiding penetration.
    - **Hydrocarbons** – Disrupt lipid layers for better absorption.
    - **Azone & Pyrrolidones** – Increase lipid fluidity, creating drug reservoirs.
    - **Essential Oils & Fatty Acids** – Improve skin permeability (e.g., menthol, oleic acid).
    - **Alcohols & Sulphoxides** – Extract lipids and swell stratum corneum (e.g., DMSO).[10]

2. Physical enhancers

❖ An enhancer is a technique that modify the penetration facility of drug physically is called physical enhancer.

A. Sonophoresis (Phonophoresis)

- Uses ultrasound waves (20 kHz - 16 MHz) to enhance drug penetration as shows in figure 3.
- **Mechanism:**
    1. Increases lipid fluidity for easier transcellular drug diffusion.
    2. Forms microbubbles, creating pores for larger molecules like proteins and vaccines.
    3. Increases skin permeability due to localized heat absorption.
- **Examples:** Lidocaine, dexamethasone.

Fig. 3: Sonophoresis

B. Iontophoresis[13]

- Uses electrical impulses (0.5 mA/cm²) to deliver ionized drugs as shows in figure 4.
- **Mechanism:**
    - Two electrodes (Anode + and Cathode -) create an electrical potential, enhancing drug penetration.
    - Controls the drug delivery rate by modulating current intensity and duration.

- **Examples:** Fentanyl, lidocaine.

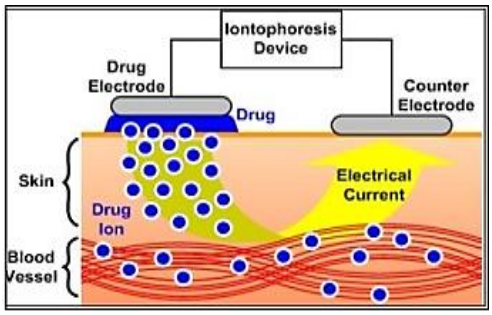


Fig. 4: Iontophoresis

C. Electroporation

- High-voltage electrical pulses create nano-sized pores (20-200 nm) in skin membranes.[14]
- **Types:**
    1. **Irreversible electroporation:** Used for tumor treatment.
    2. **Reversible electroporation:** Used in medicine and biotechnology.

D. Microneedles

- Tiny needles (100-500 µm) penetrate the stratum corneum and epidermis for drug delivery as shows in figure 5.[15]
- **Examples:** Hydrocortisone, lidocaine, salicylic acid.

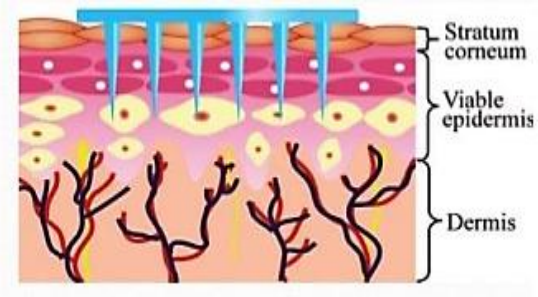


Fig. 5: Microneedles

E. Macroflux Technique

- Uses a titanium disk with 300+ microprojections (<200 µm) to create skin micro-channels.
- Delivers large molecules like insulin, hormones, and vaccines without nerve stimulation.

F. Metered-Dose Transdermal Delivery

- A drug solution with volatile/non-volatile solvents is applied to the skin.
- The solvent evaporates, leaving a drug film that forms a skin reservoir for sustained release.

G. Radiofrequency (RF) Ablation

- Uses RF waves (10 kHz – 900 MHz) for controlled tissue heating and cell ablation.
- Commonly used in electro-surgery and tumor ablation.[16]

H. Laser Ablation

- High-energy laser pulses create microchannels in the stratum corneum to improve drug permeation as shows in figure 6.
- **Example:** Insulin delivery.

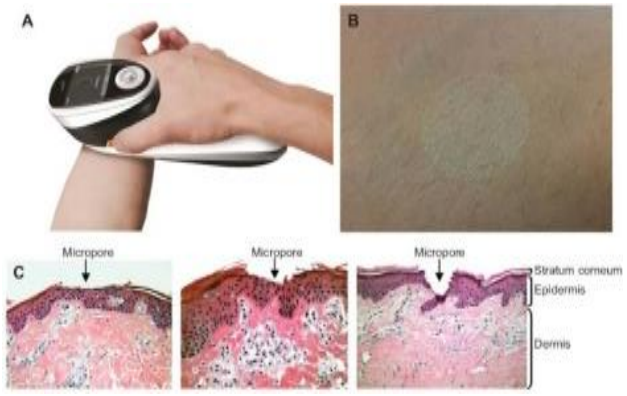


Fig. 6: Laser Ablation

3. Other Components

- **Backing Laminates:** Prevent drug loss and protect the patch.
- **Release Liner:** Covers the adhesive and is removed before application.
- **Excipients (Plasticizers, Solvents):** Improve patch flexibility and drug stability.

Preparation of Transdermal Drug Delivery Systems (TDDS)

Transdermal Drug Delivery Systems (TDDS) are classified into different types based on their design and drug release mechanisms.

A. Polymer Membrane Permeation-Controlled TDDS

- The drug reservoir is enclosed between a drug-impermeable backing layer and a **rate-controlling polymeric membrane**.
- Drug release occurs only through the membrane.

Components:

- **Drug Reservoir:** Dispersed in a polymer (e.g., polyisobutylene), suspended in a viscous liquid (e.g., silicone fluid), or dissolved in solvents (e.g., alcohols).
- **Rate-Controlling Membrane:** Can be microporous or nonporous (e.g., ethylene vinyl acetate copolymer).
- **Adhesive Layer:** Hypoallergenic and drug-compatible (e.g., silicone adhesive).

Examples:

- **Transderm-Nitro:** Used for once-a-day angina treatment.
- **Transderm-Scop:** Provides 3-day protection against motion sickness.

B. Adhesive Dispersion-Type TDDS

- Drug is homogeneously dispersed within a **hydrophilic or lipophilic polymer matrix** (e.g., silicone elastomers, polyurethanes, polyvinyl alcohol).

- The medicated polymer is molded into discs and attached to an occlusive baseplate.
- The adhesive polymer is applied as a **rim** around the medicated disc to hold the patch in place.

C. Polymer Matrix Drug Dispersion-Type TDDS

- Drug is dispersed in a **pressure-sensitive adhesive polymer** (e.g., polyacrylate).
- The adhesive polymer is coated onto a backing laminate using solvent casting or hot melt techniques.
- **Advantages:** Produces a **thinner and smaller patch** compared to reservoir-type systems.

D. Drug Reservoir Gradient-Controlled TDDS

- A modified version of the **polymer matrix drug dispersion-type** system.
- The **drug concentration is varied incrementally** along the diffusion pathway, forming a **gradient** in the multi-layered adhesive system.
- **Example:**
    - **Nitroglycerin-releasing TDDS (Deponit system)** for controlled vasodilation.

E. Microreservoir Dissolution-Controlled TDDS

- A **hybrid system** combining features of **reservoir** and **matrix dispersion-type** drug delivery systems.
- The drug is **suspended in micro-sized reservoirs** within a polymer matrix.
- Controlled release is achieved by **partitioning** the drug from the liquid compartment to the polymer coating membrane and then to the skin.

Key Parameters Affecting Drug Release:[7]

- **Partition coefficients (Kl, Km, Kp)** determine drug movement across different layers.
- **Diffusivities (Dl, Dp, Ds)** affect the rate of drug migration.
- **Solubilities (Sl, Sp)** influence how much drug can be dissolved in each phase.

Example:

- **Hormonal TDDS** combining progestins and estrogens for **weekly fertility regulation** in females.

Evaluation

These evaluation are predictive of transdermal dosage form and it classified into following[10,11]

I. Physicochemical evaluation

A. Thickness
B. Weight uniformity
C. Folding endurance
D. Percentage moisture content
E. Percentage moisture uptake

F. Drug content determination
G. Content uniformity test
H. Flatness
I. Tensile strength
J. Evaluation of adhesive

A. Thickness of the patch

- The thickness of the drug-loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

B. Weight uniformity

- The prepared patches are to be dried at 60°C for 4h before testing.
- A specified area of patch is to be cut in different parts of the patch and weighed in a digital balance.

The average weight and standard deviation values are to be calculated from the individual weights.

C. Folding endurance

- It determines the folding capacity of film.
- A strip of the specific area is to be cut evenly and repeatedly folded at the same place till it breaks.
- The number of times the film can be folded at the same place without breaking gives the value of the folding endurance.

D. Percentage moisture content

- The prepared films are to be weighed individually and are to be kept in a desiccator containing fused calcium chloride at room temperature for 24hr.
- After 24hr, the films are to be reweighed to determine the percentage moisture content.
  Formula
  Percentage moisture content = Initial weight - Final weight ×100 by Final weight

E. Percentage moisture uptake

- The weighed films are to be kept in a desiccator at room temperature for 24hr, which contains saturated solution of potassium chloride in order to maintain 84% RH.
- After 24hr, the films are to be reweighed to determine the percentage moisture uptake from the below mentioned formula:

Percentage moisture uptake = Final weight -Initial weight ×100 by Initial weight

F. Drug content determination

1) Accurately weighed portion of film (100mg) is dissolved in 100ml of suitable solvent & shaken continuously for 24 hr, then sonicated

2) After sonication and subsequent filtration, drug in solution is estimated spectrophotometrically by appropriate dilution.

G. Content uniformity test

1) 10 patches are selected and content is determined for individual patches. If 9 out of 10 patches have content between 85% to 115% of specified value, patches pass the test.

2) If 3 patches range 75% to 125%, then additional 20 patches are tested. If these 20 patches have range 85% - 115%, then patches pass the test.

H. Flatness

1. A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study.
2. For flatness determination, one strip is cut from the centre and two from each side of patches.
3. The length of each strip is measured and variation in length is measured by determining percent constriction.
4. Zero percent constriction is equivalent to 100 percent flatness.
5. % constriction = $\frac{L1 - L2 \times 100}{L1}$

   L2= Final length of each strip

   L1 = Initial length of each strip

I. Tensile strength

1. To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates.
2. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley.
3. The weights are added gradually to the pan attached with the hanging end of the thread.
4. A pointer on the thread is used to measure the elongation of the film.
5. The weight just sufficient to break the film is noted.

J. Evaluation of adhesive

A. Peel adhesion test

B. Tack properties

C. Thumb tack test

D. Probe tack test

E. Rolling ball test

F. Quick stick (Peel tack) test

A. Peel adhesion test

- In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion.[20]
- Molecular weight of the adhesive polymer, and amount of additives are the variables that determine the peel adhesion properties.
- A single tape is applied to a stainless steel plate or a backing membrane of choice and then the tape is pulled from the substrate at a 180º angle, and the force required for tape removal is measured.

B. Tack properties:

- It is the ability of the polymer to adhere to substrate with little contact pressure. Tack is dependent on molecular weight and composition of polymer.

C. Thumb tack test:

- It is a qualitative test.
- The force required to remove thumb from adhesive is a measure of tack.

D. Probe tack test

- Force required to pull a probe away from an adhesive at a fixed rate is recorded as tack as shows as fig20.

E. Rolling ball test

- This test involves measurement of the distance that stainless steel ball travels along an upward facing adhesive as shows as fig 21.
- The less tacky the adhesive, the further the ball will travel.

F. Quick stick (Peel tack) test

- The peel force required required the bond between an adhesive and substrate is measured by pulling the tape away from the substrate at 90 at the speed of 12 inch/min.

Example Products of TDDS

1. Nicotine

- **Indication**: Smoking cessation.
- **Brand Examples**: Nicoderm CQ, Nicotrol.
- **Description**: Nicotine patches are one of the most well-known and widely used TDDS products to help smokers quit by providing a steady, controlled dose of nicotine.

2. Hormones

- **Estrogen**
  - **Indication**: Hormone replacement therapy (HRT) for menopause.
  - **Brand Examples**: Estraderm, Vivelle-Dot.
- **Testosterone**
  - **Indication**: Hypogonadism.

- **Brand Examples**: Androderm, Testoderm.
- **Description**: Both estrogen and testosterone patches are used in hormone replacement therapies, particularly for treating hormonal deficiencies or imbalances.

3. Fentanyl

- **Indication**: Chronic pain management, particularly in cancer patients.
- **Brand Examples**: Duragesic.
- **Description**: Fentanyl is a potent opioid used in the management of chronic pain. The TDDS allows for a steady release of fentanyl over several days, improving patient comfort.

4. Clonidine

- **Indication**: Hypertension, opioid withdrawal.
- **Brand Examples**: Catapres-TTS.
- **Description**: Clonidine is used to treat high blood pressure and can also help with opioid withdrawal symptoms. The transdermal patch delivers the drug gradually, helping maintain stable blood pressure.

5. Scopolamine

- **Indication**: Motion sickness, nausea.
- **Brand Examples**: Transderm Scop.
- **Description**: Scopolamine patches are used to prevent nausea and vomiting, especially for patients undergoing surgery or those suffering from motion sickness.

6. Nitroglycerin

- **Indication**: Angina (chest pain).
- **Brand Examples**: Nitro-Dur, Minitran.
- **Description**: Nitroglycerin is used to prevent chest pain associated with angina. Transdermal patches allow for a continuous release of the drug, reducing the frequency and intensity of angina episodes.

7. Buprenorphine

- **Indication**: Opioid addiction treatment, pain management.
- **Brand Examples**: Butrans, Belbuca.
- **Description**: Buprenorphine is used to treat opioid addiction and manage moderate to severe pain. The TDDS provides a controlled release of the medication, reducing cravings and withdrawal symptoms.

8. Lidocaine

- **Indication**: Localized pain relief.
- **Brand Examples**: Lidoderm.

- **Description**: Lidocaine patches are used for localized pain, such as post-herpetic neuralgia or other nerve pain conditions.

9. Methylphenidate

- **Indication**: Attention Deficit Hyperactivity Disorder (ADHD).
- **Brand Examples**: Daytrana.
- **Description**: Methylphenidate patches are used in the treatment of ADHD, providing a controlled release of the stimulant over the course of the day.

10. Diclofenac

- **Indication**: Pain and inflammation relief.
- **Brand Examples**: Voltaren.
- **Description**: Diclofenac patches are used to treat joint pain and inflammation, such as in osteoarthritis, providing localized relief.

Market Trends and Outlook

- **Growth Factors**: The global **transdermal drug delivery systems market** is expanding due to factors like the rise in chronic diseases, an aging population, increased patient preference for non-invasive methods, and advancements in formulation technologies.
- **Challenges**: Some challenges in the market include skin irritation, drug delivery limitations for large or hydrophilic molecules, and the cost of developing new transdermal systems.

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PARENTERAL DRUG DELIVERY SYSTEM

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Abstract:
Injectable formulations have been developed to sustain the action of drugs in the body over desired periods of time. These delivery platforms have been utilized for both systemic and local drug delivery applications. The current study provides an overview of parenteral drug delivery systems, including administration routes, formulation of parenteral, container types, and evaluation tests. Parenteral preparations are pyrogen-free, sterile liquids that include one or more active substances in doses or multidose. They're given to you via injection, infusion, or implantation into your body. Parenteral injections provide the advantages of a quick onset of action and instant systemic absorption. The quality of raw materials, excipients, and equipment maintenance must all be such that the active substance and final formulation remain stable. Parenteral administration is the most popular and efficient way for delivering active pharmaceutical ingredients with low bioavailability and medications with a narrow therapeutic index. A number of technological breakthroughs in parenteral medication administration have resulted in the creation of sophisticated systems that allow drug targeting and the sustained or controlled release of parenteral medicines. This Chapter help for detail information regarding parenteral dosage form.

Keywords: Parenteral, Injectable, Stability, Excipients.

Introduction:

Drug delivery is defined as the means by which treatment is administered to the patient. Traditional routes for drug delivery includes parenteral, oral and topical. The preferred delivery route for patient is the oral route. However, the nature of the drug often makes it impossible so that a parenteral formulation has to be chosen. Parenteral delivery systems can be classified in different ways but are typically divided into 2 major categories-

Sterile products and non-sterile products (e.g. rectal and nasal formulations). The term parenteral is scientifically applied to preparations administered by injection through one or more layers of skin. Parenteral drug delivery system ensures that the drug reaches specific target areas of the body via blood and lymphatic systems. It allows the researcher to have control over pharmacological parameters, serum levels, tissue concentrations, elimination of the drug from the body and other factors. United States Pharmacopoeia defines a small volume injectables (SVI) as an injection that is packaged in containers labelled as containing 100 ml or less. Parenteral products are optimized during their development to provide the requisite solubility (per the required dose), stability and syringe ability. In addition, these products must meet the desired requirements for the rate of drug release based upon the dosage form and biopharmaceutical properties. Finally, its important that parenteral products be evaluated for their potential to cause tissue damage and or pain associated with the injection of the formulation.

Advantages of Parenteral Formulations

- Parenteral formulations offer several advantages over other pharmaceutical products and are suitable for-
- Patients who cannot take drugs orally in Emergency situations.
- Drugs those are inactivated in the gastrointestinal tract or susceptible to first-pass metabolism in the liver.
- Drugs that require a rapid onset of action (primarily intravenous administration).
- Providing sustained drug delivery (implants, intramuscular depot injections).
- Targeted drug delivery-injection at the site of action.
- Delivering fluids, electrolytes, or nutrients (total parenteral nutrition to comatose patients)
- Providing precise drug delivery by intravenous injection or infusion utilizing pharmacokinetic techniques that can be carried out in hospitals, ambulatory infusion centres and in home health care.

Disadvantages of parenteral preparations include;

- Potential for Sepsis, Thrombophlebitis, Fluid overload, Air embolism, or Extravasation.
- Psychological distress to the patient.
- Require specialized equipment, devices, and or techniques to prepare and administer drugs.
- Potential for pain upon injection.
- Potential for tissue damage upon injection.
- Risk of needle injuries and exposure to blood-borne pathogens by health-care worker.

- Increased morbidity associated with long -term vascular access devices.
- Disposal of needles, syringes, and other infusion devices requires special consideration.

Small volume parenteral (SVP) formulations are relatively simple. They comprise of active ingredient(s), a solvent system (preferably aqueous), minimal number of excipients. Injections are primarily solutions containing the active ingredient and other substances. Product solutions are available either as "ready-to-use" (e.g. amobarbital sodium for injection) or solutions after reconstituting lyophilized powder (e.g., Gemser) or crystalized dry powder products (including many injectable cephalosporins). Some solution may contain only the drug, e.g., vancomycin hydrochloride solution after reconstitution. Some products are suspensions in which the drug is suspended in a suitable medium, again either commercially available as a ready-to-use suspension (e.g., Humulin N) or reconstituted as a suspension rather than as a solution (e.g. Amoxicillin for injectable suspension). Injectable products are either single dose or multiple doses. Multiple-dose injections must contain an antimicrobial preservative agent(s), and the volume of injection should not exceed 30 ml.

Formulations

Small-volume injectables are usually considered small volume solutions in vials or ampoules but are available in a variety of dosage forms and packaging systems.

1.Liquids

Small-volume injectables liquids are primarily aqueous solutions. Although usually aqueous they may be mixtures of water with glycols, alcohol or other non-aqueous solvent. Many injectable formulations are manufactured by dissolving the drug and any excipients, adjusting the pH, sterile filtering the resultant solution through a 0.2nm membrane filter and, where possible, autoclaving the final product.

Aqueous solutions

Aqueous, ready-to-use SVIs contain active ingredient, additional substances, if necessary and water as the solvent. Water-for-injection (WFI) USP is the solvent of choice for aqueous SVIs. An essential requirement of WFI is its freedom from pyrogenic contamination.

Non- aqueous solutions

Several SVIs are marketed as oily solutions. The oil must be of vegetable origin because of safety, purity and biocompatibility considerations. Sesame, olive or cottonseed oil is most commonly used. Oils for injection must meet following USP requirements

Solid paraffin test (measurement of oil clarity);

Saponification value between 185 and 200;

Iodine value between 79 and 128; and

Test for unsaponifiable matter and free fatty acids.

2. Solids

SVIs are available as sterile dry solids that must be reconstituted with diluent, usually sterile WFI USP, before being administered as a solution or suspension. Sterile dry SVIs are prepared using two primary methods.

Freeze-drying

Most commercial sterile dry powders are manufactured by freeze-drying, also called as Lyophilization.

Powder-filled

Many SVI antibiotics, particularly the injectable Cephalosporins, as well as other molecules are manufactured by sterile crystallization of the active ingredient and aseptically filling the sterile powder into the final container.

3. Suspensions

With sterile suspensions, the active drug ingredient is suspended in a liquid carrier before administration. Commercial suspensions are either ready to use or dry powders reconstituted as suspensions. Major concerns with the suspension dosage forms are 1.Resuspendability of the drug in the vehicle to permit homogeneous filling of the product into the container and to provide homogeneous dosing when withdrawing from the container; 2. Caking or settling of the drug, resulting in a physically unstable product; and 3. Syringe ability (the ability to withdraw a homogeneous dose from the vial into a syringe) and injectability (the ability to eject the product through the needle into the patient).

4. Emulsion

Emulsions are mixtures of oil ad water-based vehicles with an appropriate surface -active agent to facilitate and maintain the miscibility of the oil-in-water phase.

Vehicles

1. Aqueous Vehicle

The vast majority of injectable products are administered as aqueous solution because of the physiological compatibility of water with body tissues. Additionally, the high dielectric constant of water makes it possible to dissolve ionisable electrolytes, and its hydrogen bonding potential

facilitates the solution of alcohol, aldehyde, ketone and amines. The water of suitable quality for compounding and rinsing product contact surface may be prepared either by distillation or reverse osmosis. Only by these two methods it is suitable to separate adequately various liquid, gas, and solid contaminating substances from water. Prior to distillation, water to be used as a source for WFI is usually subjected to Chlorination. Carbon treatment, deionization, and sometimes reverse osmosis.

Table 1: Various types of water described in United States Pharmacopoeia

Types	Preparation	Pyrogen	Comments
Purified water USP	Distillation or ion Exchange	No	Pharmaceutical solvent
Water for Injection USP	Distillation or reverse osmosis Not sterile.	Yes	Must be used with in 24 Hours stored below 5 degrees centigrade or 8 degrees centigrade; used for manufacture. Of parenteral products to be sterilized
Sterilewaterfor Injection USP	Distillation or reverse osmosis	Yes	Same as WFI; single-dose containers; also used to reconstitute sterile solids and dilute sterile solutions
Bacteriostatic water for Injection USP	Distillation or reverse osmosis	Yes	Multiple and single dose
Sterile water for Irrigation USP	Distillation or reverse osmosis	Yes	1 Litre or larger, wide mouth, does not meet particulate matter requirements for LVI; labelled "For Irrigation Only"

After distillation it is filtered and then stored in a chemical-resistant tank (stainless steel, glass, or blocked tin) at a cold temperature around 5 degrees centigrade or at an elevated temperature between 65 to 85 degrees centigrade to inhibit microbial growth and prevent pyrogens formation is used as excipients in the production of parenteral and other preparations where product endotoxin content must be controlled and in other pharmaceutical applications, such as cleaning certain equipment and parenteral product-contact components'WFI must be prepared fresh and pyrogen free. Other USP requirement includes not more than10 parts per millions(ppm). Of total solids, a pH of 5.0 to 7.0, absence of chloride, sulphate, calcium, ammonium ions and carbon dioxide, and limit for heavy metal and organic material.

2. Water – miscible Vehicles: Water miscible solvents are used in parenteral, principally to enhance drug solubility. They also serve as stabilizers for those drugs that degrade by hydrolysis. Mixed solvent systems may be irritating to increase toxicity, especially when present in large amount or higher concentration. Therefore, non-aqueous solvent system must be carefully screened and tested to ensure that they exhibit no pharmacological action, are non-toxic, non-]irritating and compatible and stable with all ingredients of the formulation.

3. Non aqueous Vehicles: Drugs that are insoluble in aqueous systems are often incorporated in metabolizable oils. The oil must be of vegetable origin (sesame, olive, or cottonseed oils are most commonly used) because of safety, purity, and biocompatibility considerations. Oils for injection must meet USP requirements;

Solid paraffin test (measurement of oil clarity);

Saponification value between 185 and 200;

Iodine value between 79 and 128; and

Test for unsaponifiable mater and free fatty acids. Oil injections are only administered intramuscularly. The storage of these preparations is important if stability is to be maintained. The oils most commonly used are corn oil, cottonseed oil, peanut oil and sesame oil.

Solutes

To provide efficacious and safe parenteral dosage forms, excipients are frequently incorporated in the formula to maintain stability, control product attributes, ensure sterility or aid parenteral administration. A low microbial level will enhance the effectiveness of either the aseptic or terminal sterilization process used for drug products. Likewise, non pyrogenic ingredients enhance the non-pyrogenicity of the finished injectable products. Chemical impurities should be virtually non-existent in active pharmaceutical ingredients for parenteral because impurities are not likely to be removed by the processing of products. The USP includes in this category, all the substances added into the preparations to improve or safeguard product quality. The added substance(s) may; Increase and maintain drug solubility.eg. complexing agent and surface-active agent. Provide patient comfort by reducing pain and tissue irritation as do substances added to make a solution isotonic or near physiological pH. Enhance chemical stability of the solution, as do antioxidants, inert gases, chelating agents and buffer. Enhance physical and chemical stability of freeze-dried products as do cryoprotectant and lyoprotectant. Protect the preparation against the growth of microorganism's as do preservatives. Sustain and or control drug release (polymer) by maintaining the drug in a suspension dosage forms (suspending agents usually polymer and surface-active agents), establishing emulsifying dosage forms (emulsifying agents usually amphiphilic polymer and surface-active polymer)

1. Solubilizers

Solubilizers are used to enhance and maintain the aqueous solubility of poorly water-soluble drugs. Liquid solubilizers act by reducing the dielectric constant properties of the solvent system, thereby reducing the electrical conductance capabilities of the solvent system, thereby reducing the electrical conductance capabilities of the solvent, and increasing the solubility of hydrophobic or non-polar drugs. Example of liquid cosolvents includes glycerine, polyethylene glycol (300,400, and 3350), propylene alcohol, and ethanol, Cremophor EL and sorbitol. Surface-active agents increase the dispersibility and water solubility of poorly soluble drugs owing to their unique chemical properties of possessing both hydrophilic and hydrophobic functional groups in the same molecule. Example of surface -active agents include polysorbate 80 (polyoxyethylene sorbitan mono-oleate), polysorbate 20, Pluronic F68, lecithin, etc. Solid solubilizers act by forming soluble inclusion complexes in aqueous solution. Complexing agents include Beta-cyclodextrins, capitols, polyvinylpyrrolidone, carboxymethylcellulose sodium.

2. Antimicrobial age

Antimicrobial preservatives serve to maintain the sterility of the product during its shelf-life and use. They are required in preparations intended for multiple dosing from the same container because of the probability of accidental contamination during repeated use. They are also included in some single-dose products that are aseptically manufactured to provide additional assurance of product sterility.

Table 2: Antimicrobials used in sterile products

Antimicrobial Agents	MIC Range	Amount Most Often Used
Benzalkonium chloride	0.005-0.03	0.01
Benza thorium chloride	0.005-0.03	0.01
Benzyl alcohol	1.0-10.00	1.0
Chlorobutol	0.2-0.8	0.5
Chlorocresol	0.1-0.3	0.1-0.25
Cresol	0.1-0.6	0.3
Parabens (methyl, ethyl, propyl, butyl esters)	0.05-0.25 methyl 0.005-0.03 other	0.18 0.02
Phenol	0.1-0.8	0.5
Phenylmercuricnitrate	0.001-0.05	0.002
Thiomersal	0.005-0.03	0.01

The level of efficacy obtained will vary according to the chemical structure of the preservative, its concentration, the physical and chemical characteristics of the medicinal product (especially pH) and the type and level of initial microbial contamination. Very few antimicrobial

preservatives are acceptable. Most substances with antimicrobial activity are irritating and toxic at relatively low concentrations and usually have stability limitations (hydrolytic or oxidative degradation). They can be incompatible with the drug and formulation ingredients and can interact adversely with packaging components. The USP provides a test for anti-microbial preservative effectiveness to determine that the antimicrobial substance or combination adequately inhibits the microbial growth in parenteral products. Sufficient activity is provided in the product when there is no significant increase in the number of Candida albicans or Aspergillus Niger, and the number of viable vegetative organisms (Escherichia coli, pseudomonas aeruginosa and Staphylococcus aureus) is reduced to not more than 0.1% (three log cycles) of the inoculum (10 to the power 5- ten to the power 6 viable cells/ml) and remains below that level within the 28-day (test) period Antimicrobial agents fall into five basic classes of chemicals; the quaternary ammonium compounds, alcohols, esters, mercurial and acids.

Buffers

Buffers are systems consisting of either a weak base and the salt of weak base or a weak acid and a salt of weak acid. These are used to maintain the pH level of a solution in the range that provides either maximum stability of the drug against hydrolytic degradation or maximum or optimal solubility of the drug in solution. Drug solubility may also be strongly dependant on the pH of the solution. Parenteral products should be formulated to possess sufficient buffer capacity to maintain proper product pH. The concentration of buffer depends on strength of buffer capacity required to maintain the PH level with in the desired range. Obviously, the higher the concentration, the greater the buffer capacity. Factors that influence pH include product degradation, container and stopper effect, and diffusion of gases through the closure and the effect of gases in the product and in the headspace. The ideal pH to select for parenteral would be 7.4, the pH of blood. Extreme deviation from this pH causes some complications. Above pH 9, tissue necrosis often occurs while below pH 3; extreme pain and phlebitis are experienced. The commonly buffer system used in small volume parenteral are given

Table 3: Buffers commonly used in Parenteral and Ophthalmic products

pH	Buffer System	Concentration (%)
3.5-5.7	Acetic acid- acetate	1-2
2.5-6.0	Citric acid – citrate	1-5
6.0-8.2	Phosphoric acid-phosphate	0.8-2
8.2-10.2	Glutamic acid -glutamate	1-2

Antioxidants

Antioxidants are used to reduce the oxidation of active substances and excipients in the finished product. Oxidative degradation can be accelerated by light and by the presence of mineral

impurities, due to the formation of free radicals. The antioxidant maintains the product stability over the shelf life of the product. There are three types of antioxidants as given in table

Table 4: Antioxidants used in sterile products

Type	Definition	Example
True antioxidant	These are thought to block chain reactions by reacting with free radicals.	Butylated hydroxyl toluene
Reducing antioxidant	These have a lower Redox potential than the drug or excipient they are protecting.	Ascorbic acid
Antioxidant synergists	These enhance the effects of antioxidants	Sodium edetate

Increasing oxidation potential of the drug minimizes the oxidation of the drug. Lowering the pH of the solution will increase the oxidational Displacing the air (oxygen) in and above the solution by purging with. inert gas, such as nitrogen can also be used as a mean to control oxidation of sensitive drugs. Antioxidants commonly used in SVP are given in table

Table 5: Antioxidants used in SVPs

Antioxidant	Concentration Range (%)	Antioxidant	Concentration Range (%)
Sodium bisulphate	0.05-1.0	Butylated hydroxyanisole	0.005-0.02
Sodium sulphite	0.01-0.2	Butylated hydroxytoluene	0.005-0.02
Sodium metabisulfite	0.025-0.1	L-and D-ascorbic acid	0.02-1.0

5. Chelating

Chelating agents are added to complex and inactivate metal ions such as copper, iron and zinc that generally catalyse oxidative degradation of some molecules. Sources of contamination include raw material impurities; solvents such as water, rubber stopper, and containers. Sodium salt of Ethylene diamine tetra acetic acid (disodium EDTA) has been found to enhance the activity of some antioxidants by chelating metallic ions that would otherwise catalyses the oxidative reactions. Citric and tartaric acid are also employed as chelating agents.

6. Tonicity Adjusters

It is important that injections administered intravenously should be isotonic or nearly so. Because of osmotic pressure changes and the resultant exchange of ionic species across red blood cell membranes, non -isotonic solutions, particularly if given in quantities larger than 100 ml, can cause haemolysis or crenulation of red blood cells (owing to hypotonic or hypertonic solutions, respectively). A variety of agents are used in sterile products to adjust tonicity. Most common

are simple electrolytes such as sodium chloride or other sodium salts and non- electrolytes such as glycerine and lactose. If the formulation is hypertonic, the degree of hypertonicity and the intended route of drug administration need to be considered. If the formulation is still hypotonic (i.e., <280mOsm/Kg as measured by a commonly used osmometer), tonicity adjusting agents are added until the formulation is isotonic. For intravenous administration, hypertonicity values up to approximately 360nmOsm/Kg are not considered harmful.

Sterilization of Parenterals

Sterility is defined academically as the total absence of viable life forms. Some parenteral dosage forms may be filled into their presentation forms or systems of containment under controlled but non-sterile conditions and then exposed to a sterilization process; these are referred to as terminally sterilized products. Terminal sterilization must be the method of first choice for all sterile pharmaceutical products. There is a variety of terminal sterilization processes; thermal, chemical, or by ionizing radiation. But quite frequently dosage forms cannot withstand any of these treatments without loss of efficacy. In these cases, recourse is made to aseptic manufacture.

Methods and conditions of sterilization

Sterilization may be carried out by one of the methods described below.

Terminal Sterilization Wherever possible, a process in which the product is sterilized in its final container (terminal sterilization) is chosen.

Steam sterilization (heating in an autoclave Sterilization)

By saturated steam under pressure is preferred, wherever applicable, especially for aqueous preparations. For this method of terminal sterilization, the reference conditions for aqueous preparations are heating at a minimum of 121 degrees centigrade for 15 minutes. The use of biological indicators intended for steam sterilization is Bacillus stearothermophilus (for example, ATCC 7953, NCTC10007, NCIMB 8157, OR CIP 52.81) is recommended

Dry heat sterilization

Dry heat sterilization is carried out in an oven equipped with forced air circulation or other equipment specially designed for the purpose. For this method of terminal sterilization, the

reference conditions are a minimum of 160 degrees centigrade for at least 2 hours. Spores of Bacillus subtilis (for example, var. Niger ATCC 9372, NCIMB 8058 or CIP 77.18) are recommended for the preparation of biological indicators.

Ionising radiation sterilization

Fumigation by this method is achieved by exposure of the product to ionising radiation in the form of gamma radiation from a suitable radio- isotopic source (such as cobalt 60) or of a beam of electrons energised by a suitable electron accelerator. For this method of terminal sterilization, the reference absorbed dose is 25 Ky. During the sterilization procedure the radiation procedure the radiation adsorbed by the product is monitored regularly by means the established dosimetry procedures that are independent of dose rate. Biological indicators may be used to monitor routine operations, e.g. spores of Bacillus pumilus (for example, ATCC 27.142, NCTC 10327, NCIMB 10692 or CIP 77.250).

Gaseous sterilization:

This method of sterilization is only to be used where there is no suitable alternative. It is essential that penetration by gas and moisture into the material to be sterilized is ensured and that it is followed by a process of elimination of the gas under conditions that have been previously established to ensure that any residue of gas or its transformation products in the sterilized product is below the concentration that could give rise to toxic effects during use of the product. The use of spores of Bacillus subtilis (for example, var. Niger ATCC9372, NCIMB 8058 or CIP 77.18) is recommended for ethylene oxide.

Filtration Sterilization

Certain active ingredients and products that cannot be terminally sterilized may be subjected to a filtration procedure using a filter of a type that has been demonstrated to be satisfactory by means of a microbial challenge test using a suitable test micro- organism. A suspension of Pseudomonas diminuta (ATCC 19146, NCIMB 11091, or CIP103020) may be suitable. Solutions are passed through a bacterium- retentive membrane with a nominal pore size of 0.22 nanometre or less or any other type of filter known to have equivalent properties of bacteria retention.

Factors that can affect filter performance generally include-

- Viscosity and surface tension of the material to be filtered,
- pH
- Compatibility of the material or formulation components with the filter itself,
- Pressures,
- Flow rates,
- Maximum use time,
- Temperature,

- Osmolality,
- And the effects of hydraulic shock

Filters are of two basic types, **depth filter** and **membrane filter**

Depth filter rely on combination of tortuous pathway and adsorption to retain particles or micro-organisms. They are made from material such as diatomaceous earth, inorganic fibres, natural fibres, and the major advantage of depth filters is their ability to retain large quantities of particles. Disadvantages of depth filter include grow-through and reproduction of micro-organism. Tendency of filter component to slough during line surges and retention of some liquid in the filter.

Membrane filter is made from cellulose ester derivatives.The advantages of membrane filter include no retention of product, no media migration, and efficiency independent flow-rate pressure differential. The major disadvantage of membrane filter is low capacity before clogging and need to prewash the filter to remove surfactant.

Filter Integrity Test Methods Integrity testing sterilizing filters is a fundamental requirement of critical process filtration applications. FDA Guidelines require integrity testing of filters used in the processing of sterile solutions such as (LVPs) and (SVPs).dependent on the diffusional flow and upstream volume.

G. Packaging of Parenterals

The packaging system is an integral part of the parenteral product, providing long-term protection and maintenance of physical and chemical stability of the product formulation. Packaging is a major source of particulate contamination and can contribute to physical and chemical degradation of the product. Extractables are the source of leachable contamination arising from a product formulation's contact with its package materials. Extractables are frequently generated by interaction between products and their packaging (e.g., glass vials and stoppers) over time, depending on solvent and temperature conditions. Extractables and leachable can have a significant impact on drug products, especially highly active biopharmaceutical drug formulations, which may contain just femtograms of their active ingredient.

Parenteral packaging must provide the maintenance of the microbiological integrity of sterile product until the time of use of its content. the establishment of sterile product integrity is necessary to ensure the maintenance of two extremely important product condition; total product attribute within label claim specification and product sterility prior to use. Parenteral packaging includes ampoules, rubber stoppered vials and bottles, plastic bags and bottles, glass and plastic syringes and syringe vial combinations. Glass containers have traditionally achieved widespread acceptability for parenteral products because of their relative inertness".

1. **Container Types.**
2. **Glass -** Glass is employed as the container material of choice for most SVI's .The three types of glass recognized by USP for parenteral use are (see table 1.8) Type I: Borosilicate glass (highly resistant) Type II: Treated soda lime glass Type III Soda lime glass

Table 8: Types of Glass used for Pharmaceuticals

Types of Glass	USP Test	Size (Ml)	Limit (Ml of 0.02n HCl)
Type I: Borosilicate glass (highly resistant)	Powdered glass	All	1.0
Type II: Treated soda lime glass	Water attack	100 or less over 100	0.07 0.2
Type III: Soda lime glass	Powdered glass	All	8.5
NP General purpose Soda lime glass	Powdered glass	All	15

Type 1 is borosilicate and is the least reactive as measured by a standardized alkalinity test run on powdered (ground) samples. Type II and III glass are soda lime, with type II being surface treated with sulfate, sulfite, or sulfide to make it less reactive. Type I glass is, theoretically, the best all purpose. glass for injectables and should be the only glass that is used with alkaline products. However, it is significantly more expensive than types II and III. Type II glass is often used for solutions that remain below pH 7.0 during their shelf life, while type III glass can be used for dry powders that are reconstituted. The particular glass container intended for use must be an integral part of product stability program. Amber glass containers are often used where the product is suspected of being a light sensitive. The amber color is imparted by addition of iron and manganese oxides, the cations of which are known to catalyze the oxidative reactions. Studies have shown that these ions are extracted from glass and that the decomposition rate of several drugs, thimerosal, amitriptyline and L-ascorbic acid is enhanced in amber glass containers 34.

Rubber- Rubber formulations are used as rubber closures, rubber plungers and other applications. The formulations can be very complex contain the basic rubber polymer, many additives such as plasticizers, fillers, vulcanizing agents, pigments, activators, accelerants, and antioxidants. Many of these additives are not fully characterized for content or purity and can be sources of physical and chemical degradation problems in parenteral products. The most common rubber polymers used in SVI closures are natural and butyl rubber. Silicone and neoprene also are used but less frequently in sterile products. Autoclavable rubber compounds used in small-volume parenteral are indicated in table 1.99

Table 9: Types of Rubber used for Parenteral Product Closures

Type	**Additives**	**Water-Vapor Permeation**	**Potential Reactivity with Product**
Butyl	Moderate	Low	Moderate
Natural	High	Moderate	High
Neoprene	High	Moderate	High
Polyisoprene	High	Moderate	Moderate
Silicone	Moderate	Very	Low

The physical properties considered in the selection of a particular formulation include elasticity, hardness and tendency to fragment and permeability to vapor transferred. It is recognized that physical and mechanical properties of a parenteral system affect seal integrity however physical and/ or microbiological testing approaches may be used to challenge seal integrity. Test procedure used for monitoring package integrity are dye immersion testing using either pressure or vacuum, seal force testing to monitor initial residual seal force of closure system as well as the value of the sealing force over time, and finally the monitoring of the performance of growth media-filled containers under different test condition The microbial challenge can consist of;

- Static aerosol challenge
- Static immersion challenge
- Static ambient challenge
- Dynamic immersion challenge

Plastic

Plastic packaging has always been important for ophthalmic drug dosage forms and is gaining in popularity for injectable dosage forms. Thermoplastic polymers have been established as packaging materials for sterile preparation. Such as large volume parenteral ophthalmic solution and small volume parenteral. Three principal problem areas exist in using these materials; Permeation of vapor and other molecule in either direction through the wall of the plastic container. Leaching of constituent from the plastic into the product. Sorption (absorption and/or adsorption) of drug molecule or ions on the plastic material. One of the major advantages of using plastic packaging material is that they are not breakable as in a glass also, there is substantial weight reduction. Most packaging material has the disadvantage that they are not as clear as glass and therefore inspection of the contents impeded.

Stability Aspects of Parenteral Products

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions The major ethos of stability testing

is to provide evidence that the quality of the product doesn't vary with time, under the influence of a range of different factors including temperature, humidity and light. Stability testing provides the scientific evaluation of finished product in determining the shelf-life consideration for the label and governs the suitability of any formulations to be active for the duration of any intended dosing regimen. It also plays a significant role in the development of a product down the drug development pipeline providing information which is useful in facilitating decisions and understanding the product/formulation in greater detail 38. In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use (see table 10).

Table 10: Stability Study Protocol for Pharmaceutical Products

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long Term	25 degrees centigrade RH -5 percentage	12 months
Intermediate	30 degrees centigrade RH-5 percentage	6 months
Accelerated	40 degrees centigrade RH – 5 percentage	6 months

It is up to the applicant to decide whether long term stability studies are performed at 25 ±2°C/40%RH± 5% RH or 30°C±2°C/35% RH ± 5) % RH. If 30°C±2′°C/35% RH ±5) % RH is the long-term condition, there is no intermediate condition. If long-term studies are conducted at (25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change. "Significant change" for a drug substance is defined as failure to meet its specification. Accelerated stability testing is also performed on drugs by exceeding the storage condition parameters. The accelerated stability testing differs from the forced degradation study by only exposing drugs to elevated changes in the intended storage conditions with the goal of determining how the drug will react to short-term conditions outside of the intended storage condition. Intermediate stability testing, running concurrently, involves exposing drugs to storage conditions between the intended conditions and accelerated conditions. The intermediate storage conditions might also cause significant changes in the drug. However, if the purity and physical appearance of the drug remain unaltered, then the specifications for storage could be increased and valuable knowledge on the shelf life of the drug will be determined. Therefore, stability testing should encompass several storage conditions, whenever possible, to ensure greatest understanding of the drug's shelf life 39.The ICH guidelines suggested the specifications for the new chemical drug substances and parenteral products. Accordingly, the following tests may be applicable to parenteral drug products. Uniformity of dosage, pH, Sterility, Endotoxins/pyrogens, Particulate matter, Water content,

antimicrobial preservative content, antioxidant preservative content, extractability functionality testing of delivery system, osmolarity, particle size distribution, Dispersibility, Reconstitution time

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GREEN SYNTHESIS OF SILVER NANOPARTICLES

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Abstract:
The green synthesis of silver nanoparticles (AgNPs) is a green nano technology development based on natural reducing agents from fungi, microbes, and plants for the replacement of toxic chemicals. It not only fits the agenda of environmental sustainability but also results in nanoparticles that exhibit wide-range antimicrobial activities and have promising applications in medicine, electronics, and catalysis. Important parameters like pH, temperature, and precursor concentration are tuned to manipulate particle size and shape. Advanced characterization techniques, like UV-Vis spectroscopy, TEM, SEM, and XRD, confirm the structure and properties of AgNPs. While some difficulties, for instance, invariability in the use of natural extracts, or scaling remain, green synthesis promises to become an emerging trend toward sustainable material science and technology development.

Keywords: Silver Nanoparticles, Green Synthesis

Introduction:

Nanotechnology holds immense potential to tackle significant technological and environmental challenges and the green synthesis of silver nanoparticles stands out as a remarkable example. This innovative approach represents a paradigm shift, moving away from traditional chemical synthesis toward environmentally friendly, biologically inspired methods. By minimizing the ecological footprint of nanoparticles production, green synthesis aligns perfectly with sustainability goals. The impact of this technology extends across diverse industries, including aerospace, food packaging, electronics, agriculture, medicine, and health care, where it continues to unlock new possibilities. The implications of some parameters on green synthesis are discussed in detail on AgNPs' characterization techniques.

Fundamentals of Nanoparticles

1. Conceptual Definition

The small structures known as nanoparticles are defined by: Fabrication, modification, and characterization of nano structures with diameters ranging from 1 to 100 nm are classified as nanotechnology. Quantum mechanical behavior has fascinating representations Quantum behavior that governs particles' properties in the lower range of this spectrum typically causes

them to have different properties than their macro scale counterparts. Their electrical conductance, chemical reactivity, and fluorescence, among other processes, are size-dependent. Higher surface area to volume ratio Nanoparticles' "higher surface area-to-volume ratio" compared to bulk materials means that because of their small size, they have much more surface area than the volume of a larger particle This resulting in higher reactivity and unique properties.[1]

2. Quantum Mechanical Properties

Size-dependent electronic structures

Size-dependent electronic structure of nanoparticles" means that the electronic character of a nanoparticles varies dramatically with its size. This is mainly because of the quantum confinement effect, which occurs when electrons are trapped in a very small space, resulting in discrete energy levels and different behaviors from bulk materials. The electronic structure of a nanoparticles becomes quantized as the particle size decreases which influences its optical, electrical and chemical properties.

Quantum confinement effects:

When a material is reduced to the nano scale, electrons are confined inside the particle size, forming discrete energy states and different optical and electric properties than the bulk material. This phenomenon is referred to as the "quantum confinement effect" of nanoparticles.

Altered optical and electronic properties:

The "quantum confinement effect," where electrons are trapped in an infinitely small volume and result in changes in their energy levels, is a major factor in the optical and electronic properties of nanoparticles compared to those of their bulk materials. It is size-, shape-, and surface chemistry-dependent.

Nanoscale quantum tunneling phenomena:

A means of describing quantum tunneling is as a nano scopic or quantum mechanical process by which a particle passes over a barrier which it cannot do according to classical accounts. This element of the particle is relevant in some physical phenomena, including the nuclear fusion that occurs in the Sun.[2][3]

Silver Nanoparticles:

Silver nanoparticles (AgNPs) typically have a size range of 1 to 100 nanometer. As a result of their long history of antibacterial and antiviral properties, silver nanoparticles find use in a wide range of applications including medicinal application, fashion, protective surface finishes, and healing of wounds. Like silver there are Gold, copper, magnetic cobalt, nickel and semiconductor materials form the majority of metallic nanoparticles and carbon-based materials form the majority of non-metallic nanoparticles are including medicine, electronics, and industry due to their unique properties which can be utilized in diagnostics, drug delivery

systems, cancer therapy (photo thermal therapy) and imaging (MRI) also used in wound dressings, medical implants, and drug delivery.

1. Molecular Structure

Crystalline lattice configurations

The crystalline structure of silver nanoparticles is face-centered cubic (FCC) can be determined by using X-ray diffraction (XRD) which generalize crystalline lattice structure.

Atomic arrangement principles

The silver nanoparticles can have different atomic structures like face-centered cubic (FCC), icosahedral, and decahedral. The structure is based on the nanoparticle size, and nanoparticles size and morphology are based on the synthesis route.

Face-centered cubic (FCC): Silver nano crystals with an edge for a unit cell equal to 4.086 Å can exist as FCC crystals.

Icosahedral: One of the possible icosahedral symmetries of silver molecular nanoparticles is an inner hollow interior shell covered with a dodecahedral outer shell.

Decahedral: Silver nanoparticles may possess decahedral faces.

Surface plasmon resonance characteristics

When silver nanoparticles are irradiated with light, an optical effect known as surface plasmon resonance (SPR) is observed. Absorption and scattering of light by specific wavelengths are the characteristics of SPR.

2. Characteristics

Silver nanoparticles are more efficient at light absorption and scattering compared to non-plasmonic nanoparticles of the same size. Wavelength of 400-420 nm is where the absorption spectra of the silver nanoparticles peaks. The size-dependent optical characteristics of silver nanoparticles make them either scatter or absorb, depending on the size of the nanoparticles. The optical response of silver nanoparticles is shape dependent. The refractive index at the local surface of a nanoparticle determines its optical properties. silver have used Exceptional electrical conductivity as metal material. Interconnected conduction channels in silver nanoparticles give them high conductivity. Silver nanoparticles are used in superconductors, circuit wires, and conductive inks. Scientists are very keen on silver nanowires because of their mechanical properties and high conductivity. Commercial indium tin oxide (ITO) can be replaced with silver nanowires in the future. Silver paste is a paste conductor. Silver is used as a sheath in superconductors and thermal management systems. Antimicrobial capabilities of AgNPs cause DNA damage, which results in cell death. AgNPs can rupture bacterial cell membranes thrrough Inhibit protein synthesis or suppress protein synthesis. AgNPs Generate reactive oxygen species which generate reactive oxygen species with the capability of interacting with cellular components such as lipids, DNA and proteins. Prevention of biofilm formation to prevent

microbes from binding to surfaces or eliminate intermolecular forces. As compared to bulk silver material, silver nanoparticles (AgNPs) are more or enhanced catalytic potential active because of their colossal surface area-to-volume ratio, through which more active sites are available to participate in chemical reactions. They are therefore effective catalysts for various applications like dye degradation, reduction of organic pollutants, and even enzyme-catalyzed reactions. The small size and special electronic properties are responsible for this characteristic.

3. Antimicrobial Capabilities

Broad-spectrum antibacterial action:

Silver nanoparticles have broad-spectrum antibacterial properties and hence they are excellent therapeutic drugs for the treatment of bacterial infectious diseases and drug-resistant bacteria control.

Mechanism of cellular membrane disruption:

The cytoplasmic membrane and cell wall are broken upon release of silver ions (Ag+) from silver nanoparticles attached to or traversing such membranes. Ribosomal denaturation occurs when protein synthesis is blocked by silver ions that denature the ribosomes then Release of silver ions (Ag+) by AgNPs could potentially cause destruction of proteins, DNA and cell membranes. AgNPs destroy cell membranes with their potential for the generation of reactive oxygen species, causing cell membrane destruction.

AgNP interaction with cell wall proteins AgNPs are able to disrupt and degrade the cell wall through reaction with proteins containing sulfur from the cell wall. AgNPs bind to phosphorus-rich material. for example, DNA to be toxic and prevent cell division. AgNP deposition within cell wall pits cause denaturation of the membrane through deposition within the cell wall pits. AgNPs can penetrate the cytoplasmic membrane directly in a bid to liberate the organelles from the cell. Inhibition of the production of proteins by microorganisms Through de-phosphorylation of bacterial peptide substrates' tyro-sine residues and ribosomes' denaturation in the cytoplasm of the cell, silver nanoparticles (AgNPs) suppress protein synthesis in microorganisms.

Denatured ribosome of Protein synthesis is inhibited by the production of silver ions by AgNPs that denature cytoplasmic ribosomes. Dephosphorylate tyro-sine residues AgNPs inhibit microorganism growth by the mechanism of dephosphorylation of tyro-sine residues at significant bacterial peptide substrates. Intercalation in DNA Helix AgNPs hinder the process of transcription in microorganisms by intercalation in the DNA Helix.[4][5]

Green Synthesis Methodology

Green synthesis is a technique of synthesizing nanoparticles with the help of plants, bacteria, or fungi in place of toxic chemicals. The aim is to produce bio compatible and eco-friendly products.

1. Biological Reduction Agents

A) Plant-Based Systems

Biological reducing agents to reduce metal ions to nanoparticles. Biological reducing agents are bacteria, fungi, yeast, viruses, algae and plants. Plant-Based Systems explores the various ways biological materials from plants can be utilized for practical applications:

Medicinal plant extracts

Plants have been a major source of medicinally active compounds throughout human history. This is a discipline of isolating and applying plant bio active chemicals to therapeutic uses. Alkaloids, flavonoids, terpenes and glycosides are a few of the natural compounds that possess medicinal activity. Taxol from Pacific yew is applied to cancer, while artemisinin from Artemisia annua is applied to malaria. The extraction methods employed for the isolation of these valuable constituents include processes such as solvent extraction, steam distillation and supercritical fluid extraction. To ensure consistent potency and purity of the extracts, quality control and standardization become unavoidable, employing techniques such as mass spectrometry and high-performance liquid chromatography (HPLC).

Photosynthetic organism utilization photosynthetic organisms:

Micro algae cultivation for the production of high-value compounds like pigments and omega-3 fatty acids, bio-fuels and nutritional supplements. They may be constructed as closed photo bioreactors or open ponds. Integration of photosynthesis in wastewater treatment allows algae to produce biomass and recycle nutrients. Both resource recovery and environmental clean-up are benefitted. Synthetic photosynthetic system development to replicate natural photosynthesis in an attempt to sequester carbon dioxide and produce energy in a sustainable way. This involves research into electron transport systems and light-harvesting materials.

B) Microbial Synthesis Approaches.

Bacterial Strain Selection:

Bacterial strain selection is a crucial first step in microbial synthesis that involves: the orderly segregation and discrimination of bacterial strains based on their metabolic capabilities, growth, and genetic stability. The strains must grow actively under routine fermentation conditions and possess moderate nutritional needs. For example, relative to stringent anaerobes, facultative anaerobes offer greater flexibility of process conditions. Metabolic efficiency of The strains chosen must convert substrates into the desired products effectively with minimal byproducts. This includes consideration of factors such as as metabolic flux distribution, product yield, and substrate specificity. They having Genetic stability Across several generations, strains must be capable of preserving their productive traits even when they are exposed to extreme amounts of genetic drift or loss of preferred phenotypes. This is especially critical in industrial

applications.also contain Stress tolerance in Stable production entails tolerance to various environmental stresses such as temperature variations, osmotic pressure, and pH variation.

i. Fungal Metabolic Pathways

The versatility of metabolic activities of fungal systems presents distinct strengths for biosynthesis. Primary metabolism which Fungi are excellent producers of organic acids, proteins, and lipids through established pathways. For example, the tricarboxylic acid cycle is widely utilized to produce citric acid by Aspergillus niger. Secondary metabolism which organisms produce useful compounds such as antibiotics, statins, and other bioactive compounds. The pathways tend to involve intricate regulatory mechanisms and intricate enzyme cascades. Post-translational modifications Because they can carry out complex protein modifications, fungi are useful in the manufacture of glycoproteins and other altered bio molecules. Utilisation of biomass on Farm waste can be utilized as useful products owing to the capacity of many fungi to degrade complex substrates such as lignocellulose.

ii. Actinomycetes-mediated Reduction

Actinomycetes have been celebrated for their versatile bio synthetic potential, especially in reduction reactions. These bacteria possess a range of oxide-reductases that are capable of selectively reducing the following through enzymatic reduction reactions like Alcohols' carbonyl groups, Double bonds in carbon atoms, Nitrogen atoms to amines, Scaffolds of complex molecules. Bio synthetic benefits on There are different benefits that actinomycetes offer for reduction reactions. High stereo selectivity in product formation moderate conditions of operation in Biologically friendly and renewable processes which Ease in handling complex substrates. Process optimization requires careful control of Oxygen levels, Redox cofactor availability, Substrate concentration, pH and temperature conditions.

iii. Enzymatic Reduction Systems

Oxido reductases enzymes facilitate vital biological redox reactions. They catalyze the passing on of electrons from a molecule (the reductant) to another (the oxidant). Their active sites have particular co-factors such as NAD+/NADH, FAD/FADH2, or metal ions that allow electron transfer. For instance, alcohol dehydrogenase employs NAD+ to oxidize alcohols to aldehydes reducing NAD+ to NADH. The enzymes have very high substrate specificity and their three-dimensional shape positions reactants in the most favorable way for electron transfer. Typical examples are dehydrogenase, oxidase, and reductase that are necessary for cellular metabolism. Protein-Mediated Reduction Mechanisms which complexes protein structures that allow for regulated electron transfer.

The proteins form specialized micro environments that modulate the reduction potentials of substrates and enable thermodynamically unfavorable reactions. They frequently utilize quantum tunneling effects to transfer electrons over large molecular distances with high efficiency. The

process usually involves several protein domains collaborating - one domain anchors the substrate and other houses the catalytic site with associated co-factors. Illustrations are the electron transport chain proteins in mitochondria and the photosynthetic reaction centers in chloroplasts. Cellular Enzyme Complexes are extensive, ordered complexes of several enzymes that perform coupled reduction reactions. They exhibit complex supra molecular organization wherein enzymes are arrayed in precise locations to allow substrate channeling and increased efficiency of the reactions.

The complexes usually have regulatory sub units whose activity can be adjusted according to the requirements of the cell. An excellent example is the pyruvate dehydrogenase complex with several copies of three distinct enzymes functioning together in the conversion of pyruvate to acetyl-CoA. These complexes are usually associated with membranes and are important for energy metabolism as well as for bio synthetic pathways.[4][5][6]

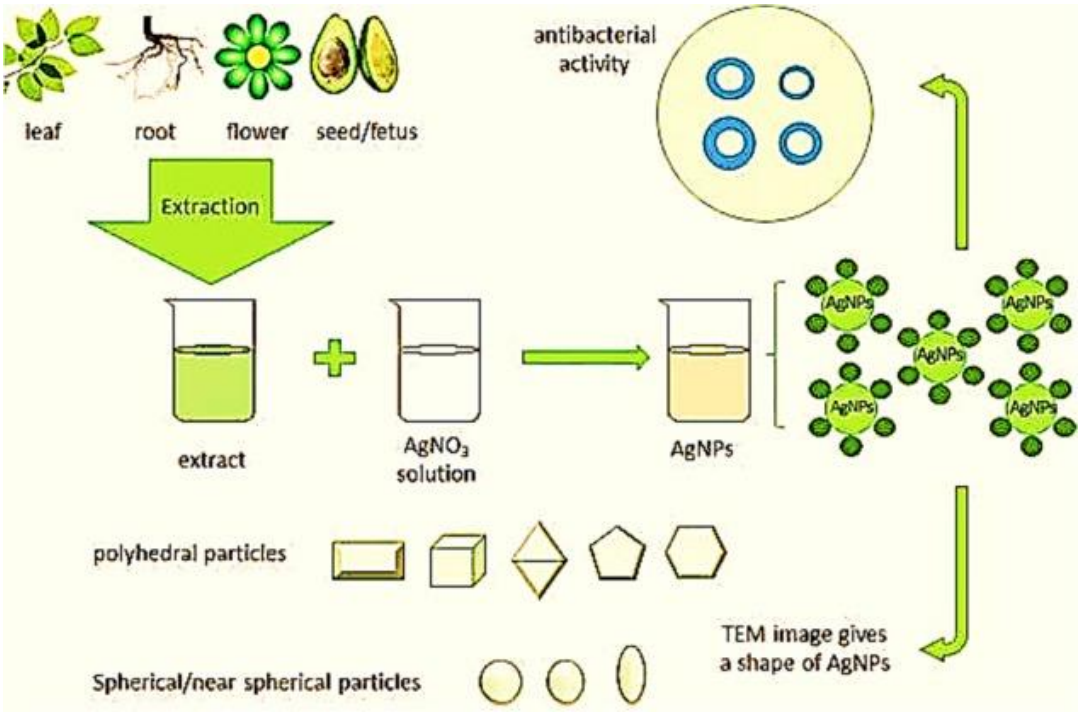
2. Fundamental Principles

Minimal Environmental Disruption This principle is aimed at creating processes that preserve ecosystem equilibrium. The main features are designing chemical reactions to run under mild conditions (moderate pressure and temperature) to minimize environmental effects. For instance, employing aqueous reaction media rather than organic solvents where possible, and using closed-loop systems that release minimal waste into the environment. The strategy also involves appropriate containment and handling practices to avoid unintentional releases into the environment. Lesser Chemical Toxicity This includes choosing and designing lower toxicity chemicals with similar functionality.

Non-toxic or less toxic substitutes to standard hazardous chemicals, practicing the principles of green chemistry like atom economy and performing comprehensive toxicological testing. Some examples include substituting toxic organic solvents with supercritical CO2 or ionic liquids for extraction and creating water-based substitutes for chemical treatments. This principle is designed to use sustainable raw material and feed stock. It involves substituting feed stock and materials that are biomass-based for petroleum based, using sun power and wind energy for chemicals processing and substituting existing chemical products through the development of alternatives based on biology. It encompasses making plastics out of biotic materials and agriculture waste and agricultural waste feed stocks for use in chemical production.

Energy-Efficient Processes This aims to maximize energy use in chemical processes. The major strategies are the design of reactions at lower temperatures and pressures, the use of catalysts to minimize activation energy demands, heat recovery systems, and process integration maximization. For instance, the application of enzymatic reactions at room temperature rather than high-temperature chemical processes and the use of micro reactor technology for enhanced heat and mass transfer efficiency. Biodegradability Considerations guarantees that products and

intermediate compounds are able to be degraded naturally without detrimental environmental impacts. The design of molecules with biodegradable linkages, prevention of persistent organic pollutants and evaluation of degradation pathways under different environmental conditions. Examples are the creation of biodegradable polymers with hydrolyzable bonds, and the assurance that degradation products are non-toxic and environmentally friendly[7].



Preparation Techniques

1. Phytochemical Reduction Method

Extract Preparation Protocols

Preparation of plant extracts is an important initial step in phytochemical reduction.

Fresh Plant Material Selection: Gentle washing and cleaning of plant materials to eliminate impurities. Controlled drying to preserve bio active compounds. Fine grinding to provide increased surface area for efficient extraction then consider Solvent Selection and Extraction. Selection of suitable solvents according to target compounds (ethanol, methanol, water, or mixed solvents). Sequential extraction with solvents of rising polarity. Standardized Soxhlet or maceration extraction method used for Preliminary concentration and filtration of crude extracts.

Quality Control Measures: Documentation of plant source, collection time, and storage conditions. Standardization of particle size and extraction duration. Implementation of sterile techniques to prevent contamination. Temperature-Controlled Reduction is critical to effective phytochemical reduction.

Thermal Optimization: Accurate temperature monitoring during the reduction process can Gradual heating trends to avoid breakdown of heat-sensitive compounds and Employment of

water baths or temperature-controlled reactors is Incorporation of cooling cycles based on needes.

Temperature Zones:

- Initial reduction stage: 25-40°C for gentle processing
- Active reduction stage: 40-60°C for best reaction kinetics
- Final stabilization stage: controlled cooling to room temperature

Equipment Requirements:

Digital temperature controllers with accurate readouts, Double-jacketed vessels for even heat distribution, Temperature logging systems, Insulation measures to prevent heat loss

Concentration Optimization Strategies:

Optimal concentration is achieved by precise control of several parameters: Process through Monitoring and adjustment of pH during the reduction process, Optimization of agitation speed for efficient mixing and Optimization reaction time according to reduction kinetics. Determination of solvent-to-extract ratio.

Concentration Control:

Monitoring of extract concentration regularly using proper analytical techniques Staged concentration processes to avoid over saturation Vacuum system implementation for gentle concentration. Application of rotary evaporators with pressure and temperature control

Quality Assessment:

Periodic sampling and analysis in concentration of extracts stability testing. Standardization of product specification of final stage Recording optimization parameters for reproducibility.

2. Microbial Bio-Reduction

Metabolic Pathway Manipulation:

Microbial bio-reduction entails manipulating metabolic pathways to maximize the reduction of target molecules. The process entails manipulating electron transport chains, increasing certain enzymes and diverting carbon flux. Critical elements involve up-regulating reductase gene products, adjusting co factor regeneration systems (such as NADH/NADPH) and metabolic bottleneck engineering to promote reduction reactions.

Controlled Growth Environment is the way for Bio-reduction success is largely a function of ensuring optimal conditions for microbial growth. This includes temperature control in strain-specific ranges (usually 25-37°C for mesophilic organisms). pH control to ensure enzyme activity and cell viability also Dissolved oxygen levels, usually requiring anaerobic or microaerobic conditions. Presence of Nutrient availability has carbon sources and trace elements. Substrate concentration control to avoid inhibition and Accurate mixing and mass transfer to provide uniform conditions.

Strain-Specific Reduction Mechanisms is Microorganisms utilize diverse bio-reduction mechanisms were Enzymatic systems Certainly strains apply individual reductases to reduce target compounds. Electron transport chains is Numerous organisms are capable of transferring electrons to substrates directly by utilizing specialized proteins. Co factor dependencies has Various strains exhibit specific co factor (FAD, NAD(P)H) requirements for reduction reactions. Metal-dependent mechanisms are Certain microbes utilize metal ions as electron intermediates. Membrane-bound vs. cytoplasmic reduction systems are Distribution of reduction machinery differs among strains.

3. Enzymatic Synthesis

Enzyme Immobilization Techniques is used for Enzyme immobilization is crucial for industrial applications of enzymatic synthesis, offering benefits like re-usability and enhanced stability. Physical Adsorption when the enzymes are held on to supporting materials by weak forces such as van der Waals interactions, hydrogen bonds, and hydrophobic interactions.

Activated carbon, silica gel and clay minerals are among the general supports. This procedure is straightforward but can be victimized by leaching of enzymes. Covalent Binding Explained Enzymes become chemically attached to support materials via functional groups such as amino, carboxyl or hydroxyl groups. This forms strong and stable bonds that disallow enzyme leaching. Some popular supports are agarose beads, cellulose, and man-made polymers. The problem is to keep the enzyme active during binding. Entrapment - Enzymes are physically trapped in semi-permeable polymer networks or sol-gel matrices. This is for protection of enzymes with free diffusion of substrates. Alginate, polyacrylamide and silica sol-gels are some of the materials used which mass transfer limitations may also cause disadvantages.

Cross-linking - Enzymes are cross-linked with one another by bi functional reagents such as glutaraldehyde to create enzyme aggregates. This results in carrier-free high activity retention immobilized enzymes. The process can be combined with crystallization (CLECs) or aggregation (CLEAs).

Reaction kinetics analysis enzyme kinetics understanding is crucial to optimize enzymatic synthesis:

Michaelis-Menten Kinetics - This basic model explains substrate concentration vs. reaction rate. The most important parameters are Km (substrate affinity) and V-max (maximum reaction rate). These parameters are used to optimize substrate concentrations and forecast reaction progress. Inhibition Effects - Product inhibition is common in enzymatic synthesis, influencing reaction rates and yields. Knowledge of inhibition mechanisms (competitive, uncompetitive, or mixed) facilitates the design of strategies such as in-situ product removal to overcome these constraints. Temperature and pH Effects the Enzyme activity generally exhibits bell-shaped curves with temperature and pH. Investigation of these relationships enables the determination of optimal

reaction conditions while taking into account enzyme stability. Temperature also influences substrate/product solubility and reaction equilibrium.

Mass Transfer Effects - External and internal diffusion may control reaction rates in immobilized enzyme systems. A study of these effects optimizes particle size, porosity, and mixing conditions.

Substrate specificity exploration enzyme specificity must be understood and utilized for selective synthesis:

Natural vs. Non-natural Substrates Although enzymes developed for particular natural substrates, several can accept analogous molecules. Systematic substrate analog screening identifies new synthetic opportunities.

Structure-Activity Relationships Examination of the influence of substrate structure on enzyme activity offers a basis for prediction of new substrates.

Protein Engineering

Enzyme natural substrate specificity is typically limited for biotechnological purposes, but engineering enzymes provides sound methodologies to widen substrate range using rational design based on structural knowledge, which relies on computational simulations and structural knowledge to identify good mutations. Directed evolution by random mutagenesis generates diverse populations of enzyme mutants that can be screened for higher or new activity, enabling researchers to apply the rules of evolution to create new enzymes with higher characteristics for use in biotechnology.

Multi-enzyme Systems

Multi enzyme association greatly enhances synthetic potential by providing for cascade reactions that can convert intricate substrates through successive catalytic steps without the need for intermediate purification. Co factor regeneration systems combined with silver nanotechnology can increase catalytic efficiency by providing constant supplies of vital co factors such as NAD(P)H or ATP and employing the silver nanoparticles as electron donors or redox mediators. Dynamic kinetic resolution processes that utilize silver nanomaterials provide potent methodologies for achieving pure compounds through the integration of enzymatic resolution with metal-catalyzed racemization in which silver nanoparticles have been used as both antimicrobial agents and as selective catalysts capable of accelerating reaction rates and product yields.[5][6][7][9]

Characterization Methods

1. Spectroscopic Techniques

UV-Visible Spectroscopy: Silver nanoparticles show a typical surface plasmon resonance (SPR) which occurs due to the collective motion of conduction electrons when exposed to electromagnetic radiation, and as such, UV-Visible spectroscopy is a crucial analytical method

for their identification. The nanoparticles normally show a sharp absorption peak between 380-450 nm, with the precise peak depending on particle size since larger particles induce a red-shift in the absorption maximum. The peak width of the absorption corresponds to the particle size distribution, with broader peaks representing a wider range of sizes of nanoparticles within the sample. UV-Visible spectroscopy is the method of first choice for confirming AgNP formation upon synthesis and enables real-time observation of reaction progress via monitoring of SPR band changes. This method allows for particle size and distribution estimation without involving more sophisticated equipment, in addition to offering a tool to evaluate nanoparticles stability over time through observation of peak shifts that may be suggestive of aggregation or surface alteration. UV-Visible spectroscopy is also an invaluable quality control instrument in batch silver nanoparticles production to ensure consistency and reproducibility among manufacturing methods.

Fourier-transform infrared spectroscopy: Fourier-transform infrared spectroscopy measures vibrational modes of molecules by analyzing infrared light absorption, proving particularly useful for studying surface chemistry and capping agents as it identifies functional groups present on nanoparticles surfaces, shows interactions between stabilizing agents and silver surfaces, reveals chemical modifications during synthesis, confirms the presence of capping/stabilizing agents, studies surface functionalization, investigates bio-conjugation, analyzes interaction mechanisms between AgNPs and ligands and verifies successful surface modification.

Raman Spectroscopic Analysis: Based on the inelastic photon scattering, is greatly improved using the surface plasmon resonance of silver nanoparticles (AgNPs) using Surface-Enhanced Raman Spectroscopy (SERS). The technique yields rich molecular fingerprint information and is highly sensitive owing to the SERS effect, allowing detection of trace quantities of surface-immobilized molecules. It shows typical phonon modes for silver-ligand interactions and enables the analysis of surface chemistry at the molecular level and research into particle-molecule interactions. It also allows monitoring of chemical reactions on the surface of a nanoparticle as well as detecting trace analytes by using AgNPs as SERS substrates. This method also assists in elucidating the binding modes between AgNPs and target molecules. 6.2 Microscopic Examination

Transmission Electron Microscopy: TEM gives high-resolution images of silver nanoparticles, depicting their size, shape, and internal structure. The procedure starts with sample preparation by depositing a drop of the suspension of silver nanoparticles onto a carbon-coated copper grid. After 10-15 minutes of air drying, any excess liquid is wiped off using filter paper. The grid is then loaded in the TEM sample holder and mounted in the microscope chamber. The microscope is to be used at an acceleration voltage of 80-200 kV, depending on the sample thickness and

resolution required. Images are normally taken at various magnifications between 20,000x and 300,000x to view individual particles as well as their distribution patterns. The images obtained can be analyzed with specialized software to ascertain particle size distribution and morphology.

Scanning Electron Microscopy: SEM analysis indicates the surface topology and morphology of silver nanoparticles. Preparation involves first coating the nanoparticle sample on a clean silicon wafer or metal stub with double-sided carbon tape. Sputter coating with a thin layer of gold or carbon (5-10 nm) is required for non-conductive samples to avoid charging effects. The sample is then installed in the SEM chamber and examined under high vacuum. Standard operating conditions are an acceleration voltage of 5-20 kV and a working distance of 8-15 mm. Secondary electron imaging mode is typically employed for topographical analysis, whereas back scattered electron mode can be used to generate compositional contrast. Several areas must be imaged at different magnifications (1,000x to 50,000x) to provide representative characterization of the sample.

Atomic force microscopy protocols:

AFM offers three-dimensional surface contours of silver nanoparticles with nanometer resolution. The sample preparation requires the deposition of a diluted nanoparticle suspension on a freshly cleaved mica substrate or highly flat silicon wafer. Allow the sample to dry thoroughly under dust-free conditions. To acquire the best possible images, AFM must operate in tapping mode (also known as intermittent contact mode) in order to limit sample damage. The cantilever spring constant must be 20-50 N/m and the resonant frequency 200-400 kHz. Scanning parameters are usually a scan rate of 0.5-1 Hz, scan size 500 nm to 10 μm, and 512 x 512-pixel resolution. More than one area must be scanned to sample representatively. Height, amplitude, and phase images must be taken in parallel to give complementary data on particle size, distribution, and surface characteristics. Particle heights, surface roughness, and 3D representations of the nanoparticle topography can be analyzed using post-processing software.

3. Structural Analysis

X**-Ray diffraction methods:**

Silver nanoparticle crystalline structure and phase.Measures lattice parameters, crystal orientation, and mean particle size by the Debye-Scherrer equation that Displays typical peaks for silver at certain 2θ angles (38.1°, 44.3°, 64.4°, and 77.4°) for (111), (200), (220), and (311) planes and Helps determine the face-centered cubic (FCC) structure characteristic of silver nanoparticles also Can indicate the presence of impurities or oxide formations.Facilitates crystallite size and strain measurement in the nanoparticles Selected area electron diffraction are Supplied with precise information regarding the crystallographic structure at the nanoscale which Produces diffraction patterns that validate the crystalline nature of silver nanoparticles. Displays concentric rings or spot patterns based on the crystallinity Facilitates identification of crystal

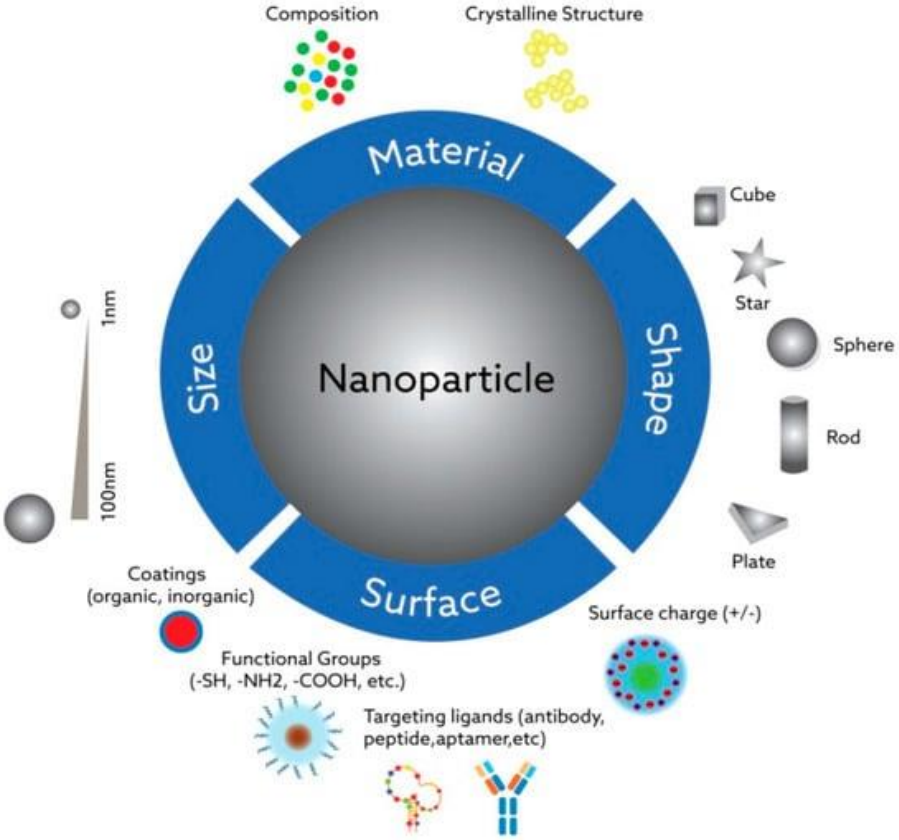
planes and calculation of d-spacing it assists in confirming the single-crystalline or polycrystalline character of the nanoparticles carried out in combination with TEM imaging for thorough analysis Enables real-time observation of structural changes under varied conditions.

Energy-dispersive X-ray spectroscopy:

Verifies the elemental purity and composition of silver nanoparticles Gives quantitative silver content and trace element analysis and displays characteristic silver X-ray peaks at certain energy levels Allows elemental mapping of distribution throughout the sample assists in the detection of surface modifications or coatings on the nanoparticles. detect the presence of stabilizing agents or capping materials which is useful for quality control and verification of synthesis procedures.[10]

Classification Systems

1. Morphological Categorization



Spherical Configurations

Spherical silver nanoparticles are the most widely synthesized and researched morphology. Homogeneous surface area-to-volume ratio that allows for uniform surface reactions. Typically 10-100 nm in diameter. Synthesis methods include mainly chemical reduction by citrate or borohydride. Improved plasmonic characteristics with typical absorption peak between 400-450 nm. Applicability to antimicrobial coatings, biosensing, and catalysis owing to high surface energy. Better colloidal stability than other morphologies

Triangular Nanostructures

Also referred to as triangular nanoplates or nanoprisms, these structures have:Three-sided geometry with sharp vertices and flat surfaces. Edge lengths usually between 40-100 nm with thickness of 5-15 nm. Distinctive optical properties with tunable surface plasmon resonance in the visible to near-IR range. High electromagnetic field enhancement at the vertices also Synthesis is usually by photochemical methods or seed-mediated growth are Very useful in photo dynamic therapy and surface-enhanced Raman spectroscopy (SERS)

Hexagonal Arrangements

Hexagonal silver nanoparticles have Six-sided symmetrical structure with distinct faces. Typically created through regulated crystal growth mechanisms having Typical size range of 30-150 nm. Improved stability as a result of their crystalline character such as High plasmonic coupling among neighboring faces with Optical sensing and electromagnetic field enhancement applications. Synthesis usually needs accurate control of reaction conditions

Rod-like Structures

Silver nano rods are distinguished by Long, cylindrical shape with aspect ratios of usually 2-10. Length is in the range 50-200 nm with diameters under control. Two separate surface plasmon resonance bands (transverse and longitudinal). Directional optical and electronic properties also Synthesis via seed-mediated growth or template-directed routes. Applications in optical wave guides and polarization-dependent devices and Improved photo thermal properties over spherical particles

Cubic Configurations

Silver nano cubes exhibit: Six equivalent square faces with sharp edges and corners Edge lengths commonly between 30-200 nm. Well-defined crystallographic facets (typically {100} faces). Strong localized surface plasmon resonance at edges and corners, also synthesis via polyol process with selective capping agents. Improved catalytic performance resulting from high surface energy at the edges higher SERS activity over spherical analogues.

2. Size-Based Segmentation

Nano-scale classification techniques:

Nano-scale classifying methods incorporate a range of methods for studying and classifying nanoparticles by particular features. Such methods involve initial particle size classifying between the 1-100 nm category, along with the measurement of aggregation states that can be classed as single, cluster-like, or networked aggregates. Morphological classification is also important, encompassing the detection of shapes in forms like spherical, rod-shaped, triangular, or cubic particles. Methods such as dynamic light scattering (DLS), transmission electron microscopy (TEM), and scanning electron microscopy (SEM) are widely used to analyze size distributions, giving quantitative information on the dimensions and particle distributions.

Besides, the estimation of the polydispersity index is fundamental in determining uniformity or deviation of particle size in a certain sample, signifying its use in nano-scale research.

Dimensional precision methods: Consist of high-resolution electron microscopy measurements, dynamic light scattering (DLS) methods, atomic force microscopy (AFM) analysis, zeta potential analysis for size stability, fractionation methods for size separation and online size monitoring systems.

Performance correlation analysis: Consists of research on size-related antimicrobial activity, studying the correlations between surface area and volume ratios, and studying the effects of particle size on optical properties. In addition, particle size is determined to quantify catalytic activity, establish size-based bio compatibility, answer size needs for diverse applications, and test stability and aging behavior by size.[7][9]

Discussion:

Evolution in synthesis technology that bridges natural resource utilization with high-performance materials science. the green method of silver nanoparticles as a revolutionizing technique which combines nanotechnology with eco-friendly practices.

Use of Natural Reducing Agents: Extracts from natural sources vegetation, microbes, or other bio-sourced materials—carry out the role of reducing metal ions to their metallic form, in this case, silver and stabilizing formed nanoparticles. These have their native bio-active entities (flavonoids, steroids, and phenolic acids, for example) that help effect controlled nucleation and growth while minimizing the need for toxic chemicals.

Optimization of Reaction Parameters: The process of synthesis is greatly affected by parameters like pH, temperature, and concentration of silver precursors and natural extracts. These parameters need to be optimized for fine-tuning to control particle size, shape, and dispersion. The chapter reiterates that slight variations in these parameters may result in extreme changes in the morphology and stability of the nanoparticles.

Strong Characterization Techniques: Various analytical methods confirm the synthesis and quality of the nanoparticles. UV-Vis spectroscopy verifies the formation of AgNPs through characteristic plasmon resonance peaks, while TEM and SEM offer information on morphology and size distribution. Furthermore, XRD highlights the crystalline nature (usually face-centered cubic) of the particles, and FTIR analysis provides proof of the organic capping layers from the natural extracts.

Comparison with Traditional Methods: The discussion places green synthesis side by side with traditional chemical processes that tend to use harmful reagents and high-energy conditions. Although the green process is economical and environmentally friendly by nature, it suffers when it comes to reproducibility because of unpredictability in nature-based raw materials. The chapter advocates for universal protocols and collaborative research to resolve these issues.

Multiple Applications and Future Perspectives: Green-made silver nanoparticles are promising in antimicrobial coatings, bio-sensing, and catalysis. The chapter emphasizes that the natural capping agents can possibly improve bio-compatibility, leading to wider biomedical applications. It also recommends future studies to prioritize hybrid synthesis routes, process optimization, and life-cycle assessments to maintain scalability and long-term environmental gains.

Conclusion:

The green synthesis of silver nanoparticles presents an interesting paradigm shift for the technology of nanomaterials by placing environmental sustainability at the forefront without sacrificing efficiency.

Eco-Friendly Breakthrough: Green synthesis utilizes the reducing potential of natural molecules to minimize the environmental impact of nanomaterial production. This process not only steers clear of toxic waste products, it also uses low-cost, renewable materials.

Challenges and Opportunities: While variability in the natural extract composition creates challenges to reproducibility of results, such complexity also provides scope for new research. Closing the gap between laboratory experiments and industrial production will involve very careful optimization as well as interdisciplinary collaboration.

A Green Future for Nanotechnology: The potential uses of AgNPs in many fields—ranging from medicine to environmental monitoring—highlight the importance of further investigation. The chapter invites ongoing innovation in optimizing reaction conditions and combining with traditional methods to overcome current challenges. In the end, the green synthesis approach is a major step toward balancing technological progress with environmental responsibility. This brief summary reiterates the vision of a future where sustainability is the force behind innovation in nanotechnology, offering not only better performance but also a cleaner, safer industrial future.

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PERSONALISED MEDICINE

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Abstract:
As a medicinal herb, Viola odorata is used to treat liver problems and ease the discomfort associated with cancer. The current work used a 4T1 breast cancer model to examine the cytotoxic, antioxidant, and anti-metastatic effects of Viola odorata hydro-alcoholic extract (VOE). Following VOE treatment of 4T1 breast cancer cells, the MTT test was used to assess cell viability. For 21 days, the implanted mice received treatment with varying concentrations of VOE (50, 150, and 250 mg/kg). Serum levels of carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA15-3), lactate dehydrogenase (LDH), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), and catalase (CAT) and superoxide dismutase (SOD) were assessed. The rate of metastasis in lung, spleen, and liver tissues was examined. The viability of 4T1 cells was considerably reduced by VOE. In tumours identified by immunohistochemical examination for Ki-67 and CD31 expression, respectively, VOE markedly reduced cell proliferation but not vasculature. In comparison to the control group, VOE raised the Bax/Bcl-2 ratio in the VOE250-treated group. When compared to controls, serum analysis revealed that treatment with 250 mg/kg of VOE significantly decreased LDH levels (but not ALP and GGT). There was no discernible linear relationship between tumour size and CEA and CA15-3 levels. Rats treated with VOE250 showed an increase in CAT activity, while the VOE50 group showed a decrease in CAT and SOD activities. Compared to the other VOE dosages, VOE250 dramatically reduced the rate of liver and lung metastases. Consequently, Viola odorata impacts antioxidant activity, metastasis, and 4T1 cell cytotoxicity for breast cancer.

Keywords: Breast Cancer, Personalized Medicine, Telepharmacy, 3D Bioprinting.

Introduction:

Medical care that is customised for each patient, including prevention and treatment plans, is known as personalised medicine (PM). The term "personalised medicine" has no agreed-upon definition. However, the Council Conclusions on Personalised Medicine for Patients, published in December 2015 by EU Health Ministers, defined PM as a medical model that uses phenotypic and genotypic characterisation of individuals (e.g., molecular profiling, medical imaging,

lifestyle data) to determine a person's propensity for a disease, enable timely and targeted prevention, or tailor the right therapeutic strategy for the right person at the right time[15]. A revolutionary change in healthcare, personalised medicine represents a move away from standardised procedures and towards customised care. It recognises the importance of lifestyle, environment, and genetic composition in determining health and response to therapy[1]. Fundamentally, personalised medicine is based on a comprehensive analysis of a person's genetic makeup using genomic sequencing. This enables medical practitioners to identify particular genetic variants and mutations influencing drug metabolism, treatment response, and disease susceptibility[2]. The availability of reliable diagnostic techniques that allow the selection of the best therapeutic solution to improve patient outcomes is crucial to the effective use of personalised medicine. The Food and Drug Administration and manufacturers both closely monitor these products[4]. In the twenty-first century, the goal of personalised medicine is to provide each patient with the right medication at the right dosage at the right time[3]. Additionally, by identifying genetic predispositions and risk factors, personalised medicine enables tailored prevention tactics, so empowering preventive treatment.

This customised approach has a lot of promise in several areas of healthcare:

Accurate Identification:

Personalised medicine enables earlier and more accurate diagnosis through the discovery of genetic markers and molecular patterns associated with certain diseases, leading to more targeted and effective therapies[5].

Tailored Care:

By lowering the possibility of negative side effects or treatment resistance, personalised medicine makes it possible to choose therapies based on each patient's unique likelihood of success. Patients may experience improved results and a higher standard of living as a result[6].

Care Prevention:

Personalised medicine makes it easier to create individualised prevention strategies by assessing a person's genetic predispositions and risk factors. In order to reduce the risk of disease and enhance wellbeing, this includes lifestyle modifications, screening techniques, and early interventions[7].

Medical Research:

Clinical research is becoming more innovative thanks to personalised medicine, which makes it easier to develop novel treatments and interventions that target certain genetic variants or biochemical pathways. This tactic may hasten the advancement of medical research and the release of innovative therapies onto the market[8].

What is Personalised Medicine and how its work?

Precision medicine, another name for personalised medicine, is a method of treating and preventing illnesses that considers each person's unique genetic, environmental, and lifestyle characteristics. Personalised medicine seeks to customise medical care and therapies to each patient's unique traits rather than using a one-size-fits-all strategy[9].

Genetic Data:

Analysing a person's genetic composition to determine how their genes affect their health, risk of disease, and reaction to therapies is a common practice in personalised medicine. To find DNA changes that could make a person more susceptible to certain diseases or alter how they react to drugs, this may entail genetic testing[10].

Customised Treatment Programs:

Healthcare professionals can create individualised treatment programs that are more efficient and possibly safer than generic treatments14 based on this genetic information as well as additional variables including lifestyle decisions and environmental exposures. For instance, some cancer treatments can target particular genetic alterations found in a patient's tumour, improving results and reducing adverse effects[11].

Strategies for Prevention:

Preventive measures based on each person's particular risk factors are another focus of personalised medicine. Healthcare professionals can suggest tailored therapies to lower the chance of getting specific diseases by identifying genetic predispositions to those ailments or lifestyle variables that may increase risk[12].

Observation and Modification:

A patient's health and response to therapy may be continuously monitored as part of personalised medicine in order to make necessary adjustments. To evaluate the effectiveness of a treatment and determine whether any changes are required, this may involve routine genetic testing, biomarker monitoring, or other diagnostic procedures[13].

Fig. 1: Benefits of personalized medicines

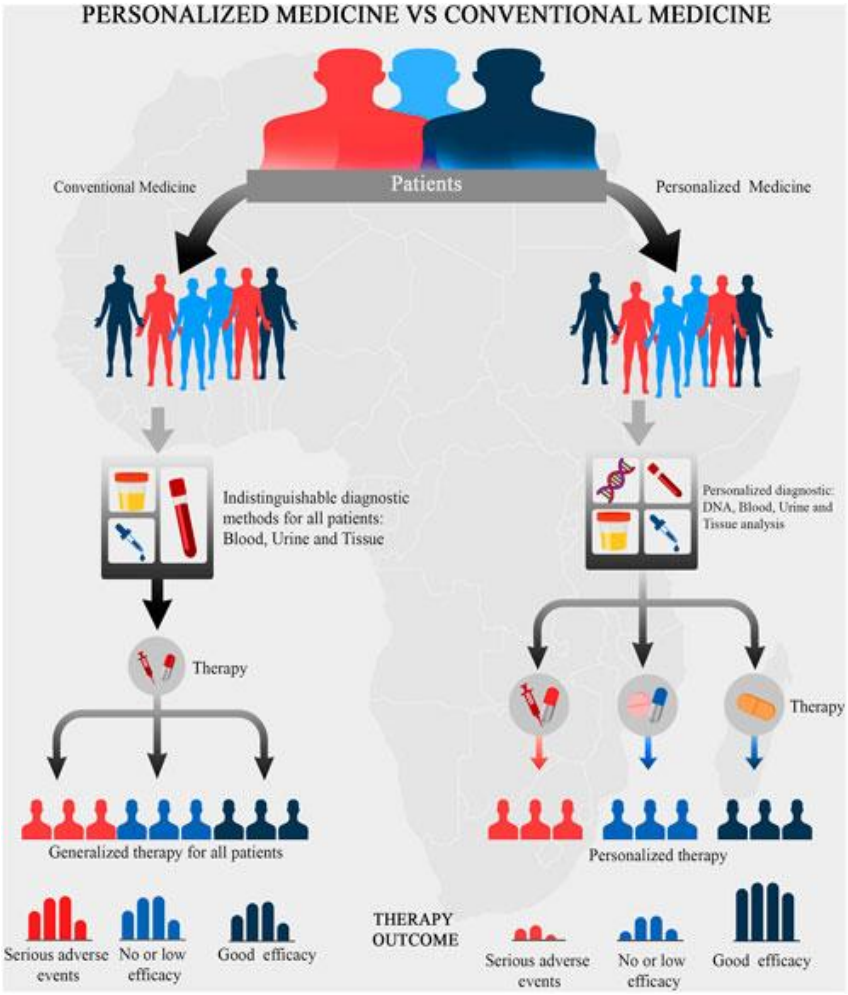

Fig. 2: Personalized medicines vs Conventional medicines

3D Bioprinting for Personalised Medicine

3D bio printing is a cutting-edge manufacturing technique that uses computer software to create three-dimensional items layer by layer. The pharmaceutical business may benefit greatly from this technology, especially when it comes to producing personalised dosage forms with different geometries, drug release patterns, and medication combinations[16]. By creating patient-specific implants and prostheses from medical imaging, 3D bio printing may more easily close the gap between diagnosis and therapy, which is one of its main benefits in personalised healthcare. Additionally, it is expected to progress regenerative medicine, gene therapy, and cell therapy. The development of 3D bio printing has increased the production of therapies and made personalised medications possible[17]. Showing early promise for developing customised drug formulations. Taking into account elements like pharmacogenomics polymorphism, which influences how various people react to pharmaceuticals depending on their genetic composition, this technology has developed to meet the demands of individual patients[18]. The 3D bio printing method is a useful tool for developing highly customised and efficient systems for biological applications, such drug screening, because it makes it possible to quickly produce materials

containing several cell kinds in a matter of hours. These constructions can be employed immediately for applications such as drug screening or in vitro culture followed by implantation for customised therapies after printing. Several methods for creating spheroids are demonstrated, including hanging drop, non-adherent surface use, micro patterning, and microfluidics in below Figure 3.

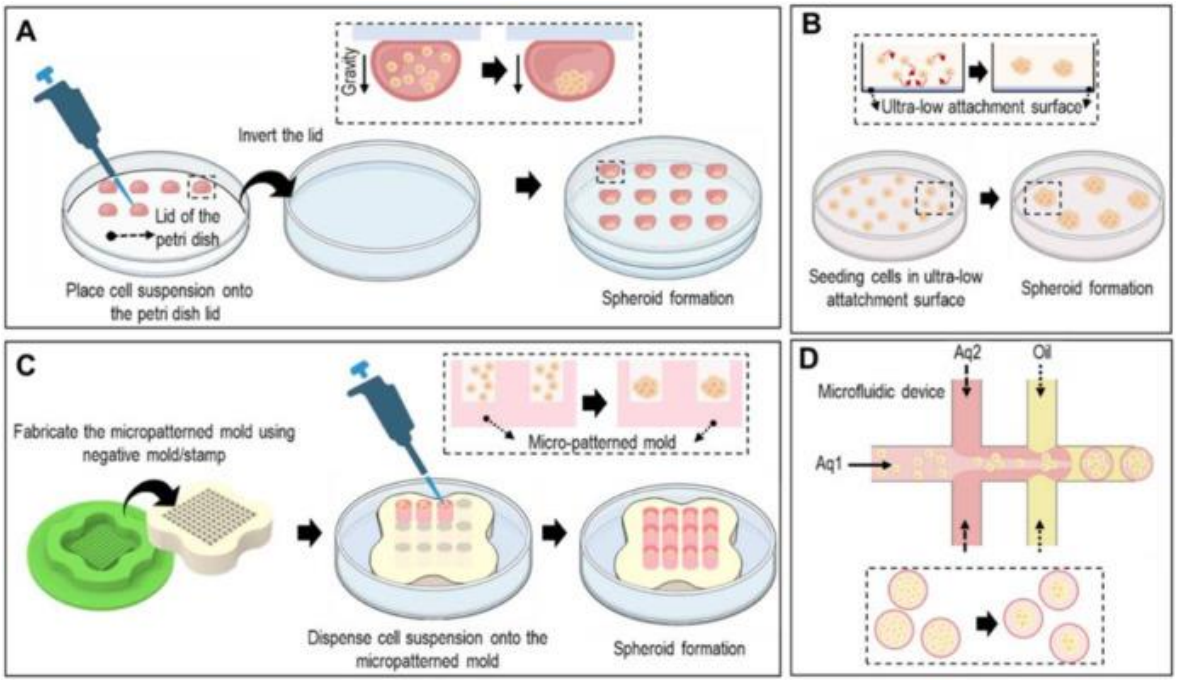

Fig. 3: Different methods for creating cell spheroids. A) A hanging drop that triggers cell aggregation through surface tension and gravity; B) a non-adherent surface that applies low attachment surfaces to trigger cell self-assembly into spheroids; C) a micro-patterned mould that uses cell seeding into the mould; and D) a microfluidic method that creates spheroids using immiscible fluids and precise flowrate control. Reprinted using the Creative Commons Attribution License 2024 from Ref. [19].

Boyer and colleagues have effectively utilized 3D bio printing technology to create spheroid isolates for cell culture applications, a testimony to how 3D bio printing can significantly aid research in the biological sciences. In order to house cell-laden droplets that promoted the creation of individual spheroids, they designed cell culture inserts with a unique feature—a negative or hemispherical gap at the bottom. After being seeded into these 3D-bioprinted structures for 72 hours, various cell types—such as human intestine smooth myocytes, human glioblastoma U87 MG cells, or mesenchymal stem cells from the human placenta—naturally gathered into clusters to produce spheroids. By modifying cell density, this technique made it possible to alter spheroid diameter, offering a great platform for screening bioactive substances[20]. To screen medications, TMZ, and IFO, Ma *et al.* created a two-chamber tissue model system

based on 3D micro-scale perfusion. The elements, configuration, and information on drug toxicity are displayed in Fig. 4.

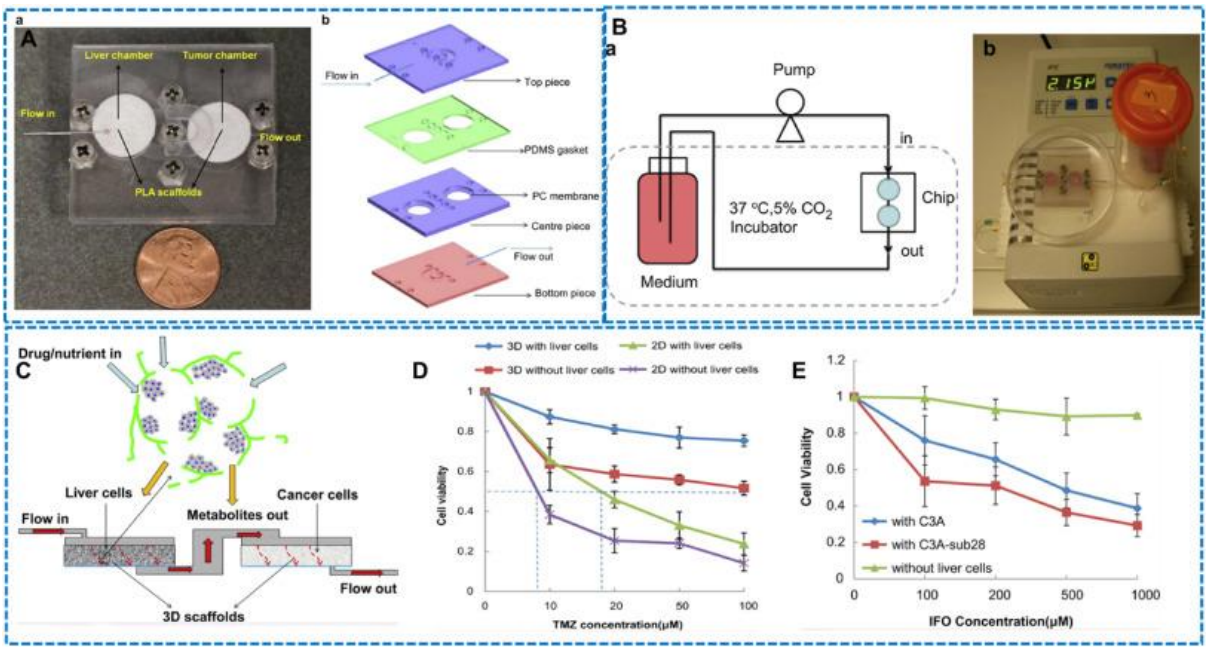

Fig. 4: A) 3D tissue device model (a) A 3D tissue model-assembling device. (b) The components of the device. B) The schematic (a) and setup of the 3D tissue model (b). C) Porous polymer scaffolds enable improved media exchange and flow with cellular aggregates. D) The dosage-dependent results of the experiments. Cells were exposed to 0, 10, 20, 50, and 100 µM TMZ following a 24-hour culture. E) The dose-dependent response to IFO toxicity. IFO metabolised by C3A-sub28 cells exhibited the most cytotoxicity (∗: $p < 0.05$). For GBM cells without metabolism, IFO was substantially less harmful ($p < 0.01$). Reprinted from Ref. [21] with Elsevier 2012 permission.

3D Bio Printing Technologies used in Pharmaceutical Development

Inkjet Printing Method

In general, inkjet printing describes systems which use pattern generating devices to digitally control and place small liquid drops on a substrate. In pharmaceuticals, appropriate mixtures of drug, along with suitable excipients (known as ink) are deposited as small drops in a layer wise fashion on a suitable substrate. Continuous inkjet printing (CIJ) and drop on demand (DoD) are the two main inkjet printing platforms.

Continuous Inkjet Printer:

As the name implies, continuous inkjet printers continuously eject a stream of liquid droplets on a substrate, even when the droplets are not needed. In this case, a pressure wave is created into the ink stream, which causes the nozzle to vibrate and break up the ink into uniformly sized droplets before ejecting the droplets out of the nozzle. Because this printing technology ejects droplets continuously, ink is wasted. The printing technology's benefits include high-speed

continuous droplet generation, which prevents clogging of the nozzle, but its drawbacks include low resolution and costly maintenance.

Drop-on-Demand Inkjet Printer:

Unlike continuous inkjet printers, which eject droplets due to external pressure, drop-on to each nozzle, and located within the printhead (19), these printers use a trigger signal to eject liquid drops from the printhead only when necessary, depositing the drops onto a substrate. They usually have a large number of nozzles (100–1000, but specialised printheads comprise of only one). This technology is relatively simple, offers high precision, and is inexpensive.

Thermal Inkjet Printer:

Here, droplets are released by a trigger mechanism that uses thermal energy, and they subsequently leave the nozzle. The printheads contain embedded resistors that are immediately exposed to the fluid (ink) and generate heat when an electric current is induced. A bubble forms inside the volatile fluid as a result of this heat, and as it expands, a tiny amount of fluid is ejected from the nozzle as a droplet (Fig. 1a). This technique's primary drawback is the use of high resistor temperatures (200–300°C), which may cause the thermolabile active substances to degrade.

Piezoelectric inkjet printer (PIJ):

The primary benefits of this technique include its ability to operate at room temperature using less volatile and more biocompatible fluids. It is made up of a piezoelectric element or actuator that changes its shape in response to an electric voltage, creating a pressure that causes the fluid (ink) to be ejected out of the nozzle. Once the element returns to its original shape, the nozzle is reloaded with the fluid and is ready to be activated again (21,24) (Fig. 1b).

Is Personalised Medicine Truly Personalized?

Just by using the word "personalised," many people would believe that personalised medicine is also personalised. Does this actually happen? The President's Council specifically refers to subpopulations rather than individual patients, but the Wikipedia definition concentrates on the individual patient. On the other hand, it is unclear from the National Cancer Institute description if personalised medicine is more focused on the individual or a subgroup. When we examine popular instances of personalised medicine, what conclusions can we make? A subset of women with early-stage breast cancer had a HER2-positive tumour, according to the HER2-trastuzumab application. Trastuzumab, which works well for HER2-positive tumours, is therefore available to this population. However, many see this as an example of stratified medicine or subgroup medicine because all of the women in this subgroup receive trastuzumab in the same manner (e.g., the same dosing schedule)[14]. In addition to acknowledging this, the President's Council goes one step further and declares unequivocally that this type of treatment is still considered personalised medicine. The purist can therefore draw the conclusion that the majority of

contemporary instances of personalised medicine are not indeed personalised. Depending on one's point of view, one can either argue that personalised medicine hasn't arrived yet or embrace a more expansive definition and assert that it has. Since there is no clear differentiation between personalised and stratified medicine, the definitions given above take into account both points of view.

Healthcare organisations, from hospitals to public pharmacies, are using 3D bio printing to increase medicine access and possibly lower total drug use. Emergency response teams, military activities, and disaster areas can all benefit from the quick drug production capabilities that 3D printers provide[22,23,24]. The procedures for creating the nanocomposite, a potential mode of action, and verifying its effectiveness in MCF-7 cell lines are displayed in Fig. 5.

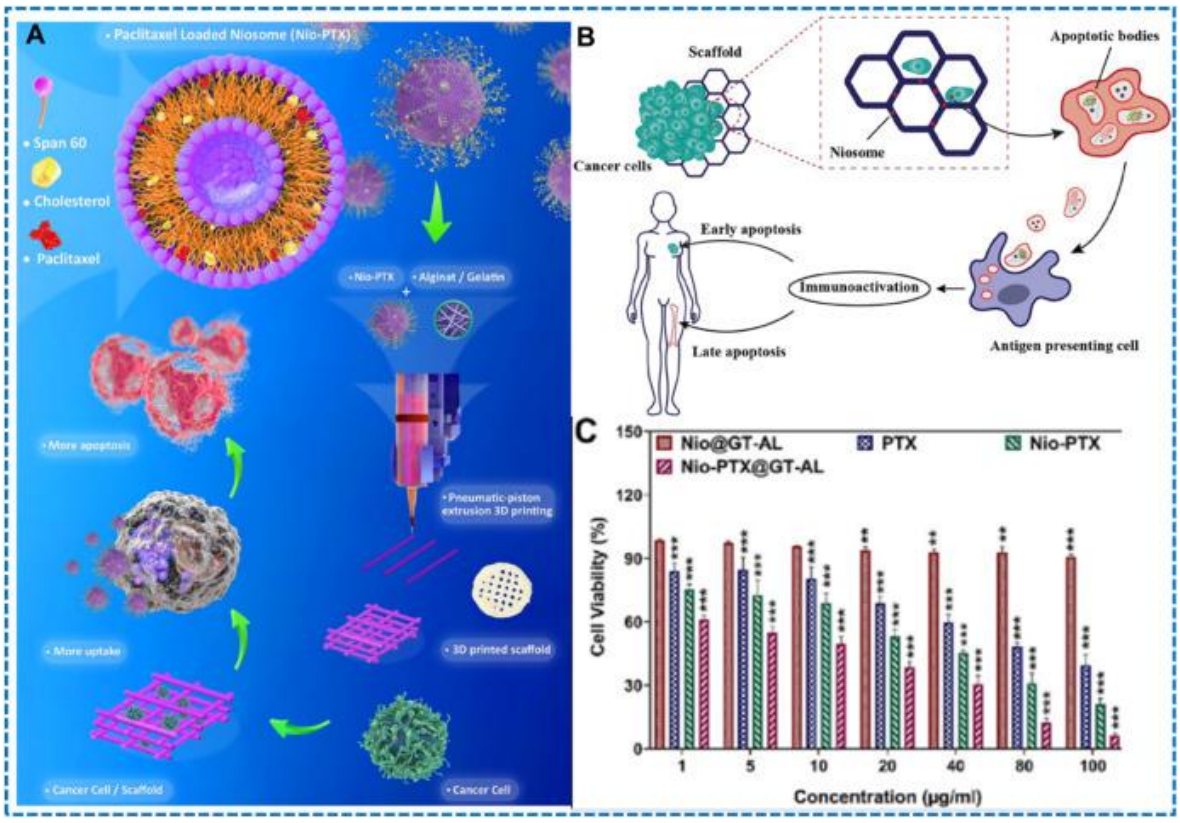

Fig. 5: A) Using 3D bio printing, paclitaxel-loaded niosomes functionalised by a cross-linked gelatine/alginate composite were synthesised on a large scale and evaluated for anti-cancer properties in vitro. B) The immune system may be activated at possible metastasis sites by late apoptosis, which could strengthen Nio-PTX@GT-AL's anti-metastatic action. C) MTT results on the MCF-7 cancer strain after 48 hours using free-PTX and noisome-based formulation. The formulation based on niosomes is more cytotoxic than Free-PTX on MCF-7. Reprinted from [25] with Elsevier 2023 permission.

Types of 3D Bioprinting

Clinical bio printing has demonstrated advantages over conventional methods. First, imaging techniques like MRI, CT, and ultrasound help create a computerised three-dimensional model of

the damaged tissue[26,27,28,29]. As a result, a wide range of materials, bioactive compounds, and cell types are used for the production of bio-inks, depending on the specific defect, location, and functional needs. By carefully layering bio-inks, 3D bio printing aims to mimic the innate cellular architecture and restore the natural structure and functionality of complex tissues[30]. In a therapeutic context, the bio-printing method has demonstrated advantages over conventional methods. First, imaging techniques like MRI, CT, and ultrasound help create a computerised three-dimensional model of the damaged tissue. Using computer-aided design, the scaffold's internal and external configuration—including its porosity and pore dimensions—is incorporated into the 3D reconstruction of the damaged tissue. As a result, a wide range of materials, bioactive compounds, and cell types are used for the production of bio-inks, depending on the specific defect, location, and functional needs. By carefully layering bio-inks, 3D bio printing aims to mimic the innate cellular architecture and restore the natural structure and functionality of complex tissues. In order to promote their connectivity and the creation of the desired three-dimensional structure, biomolecules or cells are carefully deposited onto a substrate in a pre-configured pattern. Because bio-printing uses live things like cells and tissues, it must adhere to stringent guidelines that are similar to those for real tissues. These guidelines cover things like vascularity, biocompatibility, and sensitivity to growth hormones, and printing techniques. The creation and selection of bio-inks is an essential step in the bio-printing process. Specialised materials known as "bio-inks" closely mimic the extracellular matrix seen in nature. They are composed of biomaterials, bioactive substances, and living cells. When selecting the best bio-inks, a variety of factors, such as cellular viability, biocompatibility, and rheological properties, must be carefully optimised to guarantee successful printing and post-printing behaviour. Additionally, factors like crosslinking techniques, mixing tactics, and storage conditions can significantly affect the final printed object's usefulness and structural integrity. These elements may also significantly affect how well bio inks work.

A comprehensive understanding of these selection criteria and fabrication processes is necessary to make bio-inks that efficiently enable tissue engineering and regenerative medicine applications to create bio printed tissues and organs. Printability and biocompatibility should be balanced in the bio ink. In order to expedite printing and enhance cell viability after printing, the most recent developments in bio inks have focused on optimising rheological properties. Among the most promising bio ink materials currently in use are alginate, gelatine, hyaluronic acid, and gelatine methacrylate (Gel MA). Gel MA is a commonly used material because of its easily cross-linked nature and mechanical qualities that may be adjusted to give more control over the printed structure. Its modification with methacrylate groups, which permits photo-crosslinking, makes it perfect for precise layer-by-layer printing. Furthermore, due to their improved printability and biocompatibility, bio inks based on alginate-gelatine composites have grown in

popularity. Alginate offers structural stability, whereas gelatine promotes cell attachment and offers flexibility. Better cell survival and more accurate tissue architectures are the results of the combined effect. Hyaluronic acid-based bio inks are used because of their improved water retention and biocompatibility.

Various 3D bio printing techniques and the detailed procedure have been demonstrated in Fig. 66.

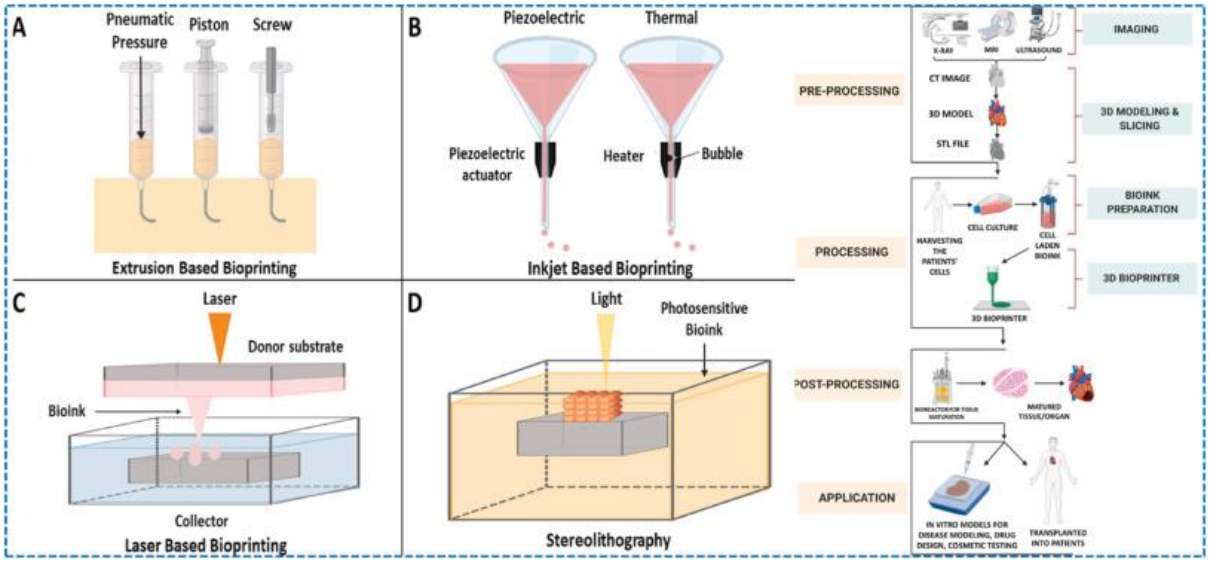

Fig.6: A variety of 3D bio printing techniques, including extrusion-based, inkjet-based, laser-based, and stereo lithography. It also includes a schematic that shows the pre-, processing-, and post-processing stages of the process. Reprinted with permission from Elsevier 2021 from Ref. [31].

Significance of Personalised Medicine

Precision medicine, sometimes referred to as personalised medicine, is a paradigm change in healthcare that uses a patient's genetic composition to enhance treatment results and provide therapies that are much more individualised than the conventional "one size fits all" strategy[32].

In addition to improving treatment efficacy and minimising negative effects, this also aims to increase patient adherence and possibly lower healthcare expenses. Innovations in technology, especially 3D bio printing, have made it possible to produce medications that are tailored to each patient's particular needs[33]. This includes the capacity to blend various drugs into a single dose form that suits the unique therapeutic requirements of a patient.

Patients' distinct traits, especially their genetic, physiological, or pathological profiles, are taken into consideration by personalised treatment. Individual variations in patients' genes and drug responses can have a substantial impact on the efficacy and safety of pharmaceuticals, according to the fundamental tenet of personalised medicine. As a result, treatment plans are being created to maximise results for patients who share a number of traits[34]. Patient care will be significantly

impacted by the advancement and use of personalised medicine, which will result in the creation of safe and effective drugs that are adapted to each patient's unique biology[35].

Telepharmacy

Similar to telemedicine, tele pharmacy is a relatively new term that describes the delivery of pharmacological services. Numerous tele pharmacy models have been developed as a result of strategies to remove obstacles to receiving pharmacy services. Tele pharmacy is defined by the National Association of Boards of Pharmacy as "the delivery of pharmaceutical care to patients at a distance via the use of telecommunications and information technologies[36]". Without a chemist physically present, tele pharmacy provides clinical pharmacy services including prescription dispensing at a distance. Services including pharmaceutical order evaluation, dispending and compounding, drug information services, patient counselling, and therapeutic drug monitoring are typical tele pharmacy offerings[37]. Therefore, tele pharmacy employs cutting-edge technology that enables a licensed pharmacist in one location to oversee a pharmacy assistant or technician in another location while they dispense medications via computer linkages that are connected by audio and video[38].

The rapid expansion of information and telecommunication technologies during the 20th century has had a significant impact on healthcare delivery in many countries. The Internet has made consumers more knowledgeable and has increased their expectations of healthcare professionals; however, a lack of healthcare services and qualified healthcare professionals, particularly in rural and regional areas, frequently prevents patients from receiving the proper treatment and care[51,52]. According to the National Association of Boards of Pharmacy, tele pharmacy is "the provision of pharmaceutical care through the use of telecommunications and information technologies to patients at a distance." It is a more recent concept that refers to the provision of pharmaceutical services, similar to telemedicine[53]. Various models of tele pharmacy have been developed as a result of strategies to address the obstacles to accessing pharmacy services. Without a chemist physically present, tele pharmacy provides clinical pharmacy services including prescription dispensing at a distance. Services including pharmaceutical order review, dispensing and compounding, drug information services, patient counselling, and therapeutic drug monitoring are typical tele pharmacy offerings[54]. Therefore, tele pharmacy employs cutting-edge technology that enables a licensed pharmacist in one location to oversee a pharmacy assistant or technician in another location while they dispense medications via computer linkages that are connected by audio and video[55].

Types of Telepharmacy Models

Types	Process
Traditional full-service pharmacy	Like traditional pharmacies, this tele pharmacy site encompasses services such as filling prescriptions, medication reviews, and patient counselling. These tele pharmacy sites have complete drug inventories that include prescription and over the counter medications along with other-health-and beauty aids and other general merchandise.
Hospital tele pharmacy	Prescriptions are prepared at the central pharmacy and are delivered to the rural sites. Audio and video computer links are used to deliver patient counselling and education.
ADM'S	Pharmacist at a central location upon receiving drug order (electronically or by fax) confirms the patient profile, conducts proper drug utilization review, and finally instructs the ADM to release the medication. With the help of audio and video computer links, patient counselling is then conducted.
Remote consultation sites	Hospital pharmacist in urban medical center reviews processes and verifies the prescriptions that are issued and electronically sent from rural hospitals. Automated dispensing machine (ADM) is used to electronically release the pre-packaged medication. A nurse or pharmacy assistant at rural end double- checks the label and medication prior dispensing them to patients. The pharmacist from central (urban) location monitors the verification process and involves in consultation between the patients, nurses, or physicians when required via videoconference link.

How Does Telepharmacy Work?

Generally speaking, a small rural hospital, pharmacy, or clinic in a remote location is linked to a widely used service model in a larger urban centre that has better access to pharmacist staff often around-the-clock. Videophone systems, innovative software, and automated dispensing machines enable this connection[39]. After verifying that the prescription matches its label by scanning the bar code, the pharmacy technician or nurse in the remote location applies the label and gives it to the patient. To make sure the correct prescriptions have been filled and dispensed, the pharmacist at the central end can visually watch the technician's or nurse's work. To make sure the patient understands the proper usage and administration of the medication, the central chemist offers a two-way video consultation at the conclusion of the procedure[40]. In another instance, a wireless mobile technology cart has been created for use in distant hospitals to enable doctors and nurses

in the patient care area to have round-the-clock access to the chemist for in-person consultation and conversation.

Clinical Benefits and Challenges of Telepharmacy

Access to Healthcare Services:

Easy access to healthcare services in rural and isolated areas is the main benefit of tele pharmacy. In isolated and rural areas, regular access to prescription drugs and chemists are acknowledged as essential components of providing patient-centered healthcare.2 In isolated places where access to healthcare services has been lost or is in danger of being lost, chemists can offer top-notch pharmaceutical care services.

This situation was resolved by the development of many tele pharmacy models, which allowed for full-service operations that included drug utilisation reviews, patient counselling, patient education, and the active engagement of central and remote chemists using a variety of technologies.

Economic Benefits:

Tele pharmacy offers a number of financial advantages. According to reports, opening a new pharmacy is far more costly than hiring a pharmacy technician for tele pharmacy and purchasing the necessary equipment. Multiple locations can be served by a single, qualified chemist. Costs are therefore kept to a minimum in light of the growing pharmacist pay scale and additional costs associated with recruiting more pharmacists for rural locations. According to a tele pharmacy model aimed at the low-income population, more than 60% of patients would have had trouble paying for their prescription drugs in the absence of the model. According to a study by Garrelts et al.23, tele pharmacy can save a multihospital health system an estimated $1,132,144 a year.

Patient Satisfaction:

Telehealth offers the benefit of patient satisfaction when it comes to medication access and information in rural locations. Older patients skipping visits because they didn't want to leave their homes used to be one of the main obstacles in the clinic. Pharmacists may now check patients' prescriptions without needing to travel thanks to remote technology. Patient satisfaction and trust in the service have grown as a result. Patients in rural communities prefer to receive pharmacy services locally through tele pharmacy services rather than having to travel outside of their community, according to a US study that aimed to determine the underlying factors determining patient satisfaction based on healthcare delivery mode or community-specific factors.

Effective Patient Counselling:

Patients are more satisfied with tele pharmacy in terms of the time needed to receive medication and the chemist's advice. Pharmacists advise adopting webcam-enabled tele pharmacy services because they offer greater privacy and longer counselling time, according to a study on tele

pharmacy-related services and outcomes conducted in the USA. Another study demonstrated the effectiveness of tele pharmacy counselling by demonstrating the metered-dose inhaler procedures utilising compressed video rather than the conventional package insert instructions.

Early Examples of Personaliased Medicine

It should be noted that personalised medicine can be used not only for the treatment of disease but also for the early detection and prevention of disease. We give some historical examples of personalised disease treatments here and discuss early detection and prevention in the next section, as advancements in personalised disease detection and prevention are much more recent. There have been many examples of interventions tailored to individual patient profiles, almost all of which are based on genetic profiles. There are two main ways that the human body uses conventional pharmacotherapies, or medications, to treat illness. A drug must first cause the body to react. The body absorbs the medication in the first stage of this reaction, which happens in phases. Before the drug may start to have an impact, it must first be transported throughout the body, where it may be "bio transformed" or metabolised into beneficial components. Lastly, any leftover medication or drug ingredients are eliminated. These procedures are sometimes grouped together under the general term "pharmacokinetics" and are generally known as a drug's "ADME" (Absorption, Distribution, Metabolism, and Excretion). Warfarin is a common blood thinner that can result in a potentially fatal adverse drug reaction if not used as prescribed. Warfarin is partially metabolised by the gene CYP2C9 and targets a specific gene, VKORC1. Individual differences in the pharmacologic and pharmacokinetic characteristics of Warfarin result from naturally occurring genetic diversity in both the VKORC1 and CYP2C9 genes, which in turn causes individual differences in how each person reacts to the medication. As a result, the US Food and Drug Administration has advised that when determining a person's warfarin dosage, the individual's genotype be taken into account. This means that the dose should be tailored to the person's unique genetic variations in the VKORC1 and CYP2C9 genes[41]. CML, or chronic myelogenous leukaemia, is treated with imatinib. Imatinib suppresses tyrosine kinase, an enzyme that is elevated when two genomic areas fuse together: the breakpoint cluster region (bcr) and the Abelson proto-oncogene (abl). This fusion event, also known as the "Philadelphia chromosome" or "bcr-abl fusion," occurs in numerous tumours that contribute to the development of CML. Nevertheless, the bcr-abl fusion mutation is not present in the tumours of every person with CML. Imatinib is therefore usually only administered to specific CML patients who have this fusion event.

Future Implications of Personalised Medicine

Healthcare: Transitioning from Reactive to Predictive Our current reactive healthcare model will give way to a fully predictive one, which is the biggest change that personalised medicine will bring about. Modern medicine mostly treats symptoms after they arise, whereas tomorrow's

medicine will foresee health issues before they arise. With the ability to detect predispositions to thousands of illnesses decades before symptoms manifest, genomic and multi-omics screening will soon become commonplace from birth or even during pregnancy. These forecasts will get more complex as computing power and AI algorithms increase. Extremely Customised Intervention Beyond forecasting, personalised medicine offers treatments that are matched to each person's unique biochemistry with never-before-seen accuracy.

AI in medicine can take many different forms, ranging from the purely virtual (such as deep learning-based health information management systems and active physician guidance in treatment decisions) to the cyber-physical (such as targeted Nano robots for drug delivery and robots that assist the attending surgeon)[42]. Many image-based detection and diagnosis systems in healthcare can now perform as well as or better than clinicians in some situations thanks to AI technology' ability to identify complex patterns and hidden structures[43]. AI-enabled clinical decision-support systems could help physicians with EHR data extraction and documentation procedures, improve intelligence to support decision making, and lower diagnostic errors[44]. AI will be able to solve issues that are currently unsolvable thanks to emerging computational advancements in natural language processing (NLP), pattern recognition, effective search, prediction, and bias-free reasoning[45,46]. The development of medications for the "average patient" using a crude pharmaceutical technique will eventually give way to modular treatment systems. This change will be fuelled by several new technologies: Pharmacogenomics 2.0: Based on a thorough metabolic profile, future systems will forecast the best medicine choice and exact dosage, going beyond the crude gene-drug interaction recommendations of today. Custom Biologics: To precisely address unique genetic variances, cutting-edge cell therapies, customised antibodies, and gene editing methods like CRISPR will develop.

Applications of Personalised Medicine

These are a few significant uses for personalised medicine. Detecting illnesses early on by improved surveillance, which enables more potent therapies or therapeutic choices. Avoiding generic "one size fits all" prescribing techniques in order to reduce avoidable drug-related problems and side effects. Maximising therapeutic efficacy by making sure the right medication is taken and taking into account any genetic variations that can affect how the medicine is metabolised when establishing dosage schedules Supporting those at elevated risk of developing diseases by encouraging and aiding with adherence to available preventative techniques. Detecting illnesses early on by improved surveillance, which enables more potent therapies or therapeutic choices. Avoiding generic "one size fits all" prescribing techniques in order to reduce avoidable drug-related problems and side effects. Maximising therapeutic efficacy by making sure the right medication is taken and taking into account any genetic variations that can affect how the medicine is metabolised when establishing dosage schedules. Encouraging and helping

people who are at a higher risk of contracting diseases to follow the available preventative measures.

Conclusion:

Given that clinically meaningful inter-individual variation has been and will continue to be identified, personalised medicine—the process of characterising a patient on multiple levels (e.g., genomic, biochemical, behavioural, etc.) that may provide insight into how they respond to an intervention—is essential. Modern biomedical technologies like DNA sequencing, proteomics, and wireless monitoring devices have made it possible to identify this diversity, hence highlighting the necessity of some degree of medical personalisation. In the near future, it might be challenging to resolve a few other personalised medicine-related problems. For instance, the requirement for extensive data gathering to pinpoint the variables that discriminate against groups of people who would gain more from a certain intervention may raise privacy concerns and raise the possibility that the information about those people may be misused[47,48]. A major change in healthcare is represented by personalised medicine, which provides individualised treatments based on a patient's genetic, lifestyle, and disease-related characteristics. This strategy has enormous potential to improve patient outcomes, reduce negative side effects, and transform healthcare. Personalised medicine enhances treatment efficacy and encourages a proactive and preventative approach to healthcare by customising medicines for certain patient groups and genetic markers[49]. Additionally, personalised medicine encourages innovation in diagnostics, medication development, and healthcare delivery, resulting in more effective and significant medical interventions. The long-term advantages of personalised medicine are significant, including increased patient satisfaction, lower healthcare costs, and advances in medical research, even though there may be initial implementation-related difficulties and costs[50].

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OCULAR DRUG DELIVERY SYSTEM

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Abstract:

Topical administration for ocular therapeutics is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity. Topically applied ocular drugs have to reach the inner parts of the eye and transcorneal penetration is believed to be the major route for drug absorption. Corneal absorption is much slower process than elimination. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ideal ophthalmic dru delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently, it is imperative to optimize ophthalmic drug delivery; one of the ways to do so is by addition of polymers of various grades, development of in situ gel or colloidal suspension or using erodible or non erodible insert to prolong the pre corneal drug retention.

Keywords: Ophthalmic Drug Delivery, Corneal Drug Delivery, Barriers of Opthalmic Drug Delivery System, Methods to Overcome Barriers.

Introduction:

The eye's drug disposition properties make it the most intriguing organ. Due to its ease and safety for ocular chemotherapy, topical medication delivery is typically the preferred approach in the majority of cases. The occular drug delivery system is a unique method of medication delivery that allows the drug to be injected into the eye's cull de sac chamber. The primary reason for ocular medication delivery is the requirement to treat ocular illnesses. Anatomical and physiological obstacles make it difficult, and they can influence how well drugs enter the eye after being administered through a variety of ways (such as topical, systemic, and injectable). Ocular drug delivery system is convenient and allows for local drug delivery, topical administration in the form of eye drops is recommended for the treatment of anterior segment illnesses.[1,2] Low bioavailability and inadequate medication absorption. Ocular drugs are usually delivered locally to the eye. Required drug loading, release rate, and ocular retention time of drug delivery systems depend on the potency, bioavailability, and clearance of the drug at the

target site. Drug-loading capacity of the formulation is limited by the material properties and size constraints of the eye. [1,2]

1. The blood-retinal barrier (BRB) restricts medication penetration into the retina.
2. To treat posterior segment illnesses, high vetreal medication concentrations are required (by intravitreal injection or implants).
3. Ophthalmic preparation is specialized sterile preparation of dosage form designed to be instilled onto the external surface of the eye (topical), administered inside (intraocular) or adjacent periocular to the eye or used in conjuction with an ophthalmic device.
4. Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time.

Ideal Requirements for Occular Drug Delivery:[3]

1. A no. of requirements must be considered in the preparation of ophthalmic solution, suspension or ointments.
2. These includes: sterility, clarity, buffer, buffer capacity and pH, tonicity, viscosity, stability, comfort, additives, particles size, packaging and preservatives.
3. The ophthalmic solutions are formulated should be sterile, isotonic, and buffered for stability and comfort.
4. Solution must be free from foreign particles.
5. Sterilization represents the major requirement of eye product.

Structure of the Eye:

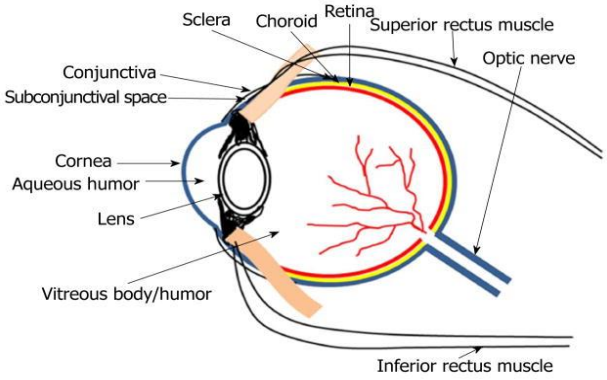

Fig. 1: Eye

Layers:

Sclera: The strong, white outer coating of the eye

Choroid: The layer of blood vessels lining the back of the eye

Retina: The light-sensitive nerve layer in the rear of the eye

Parts:

Cornea: The transparent, clean front window of the eye that concentrates light

Iris: The colorful portion of the eye that regulates how much light enters

Lens: The transparent portion of the eye that focuses light onto the retina.

Optic Nerve: The visual signals are transmitted from the retina to the brain via a bundle of nerve fibers.

Vitreous Humour: The transparent, gel-like substance

Macula: The central part of the retina that allows us to see fine details.

Anatomy of the Eye:

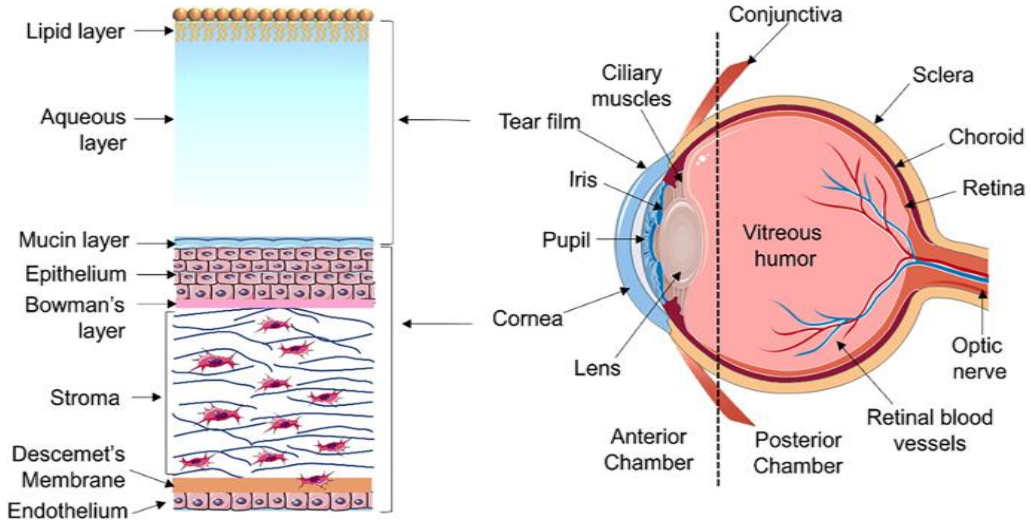

Fig. 2: Anatomy of the eye

Human eye is composed of

- Anterior chambers
- Posterior chambers.
- The anterior segment is composed of tear film, cornea, pupil, lens, and ciliary body.
- The posterior segment is composed of conjunctiva, sclera, choroid, retina, vitreous humor, and optic nerve.
- The structure and quantity of tears are controlled by orbital glands and epithelial secretions. Cornea is the front portion of the eye that conveys and focuses light into the eye. It is divided into epithelium, stroma, and endothelium. The epithelium is made of five to seven layers of firmly connected cells. Stroma is a water-based compact layer. ▪The endothelium preserves the transparency of the cornea.
- Iris is the colored portion of the eye which controls the quantity of light penetrating the eye.
- The dark center opening in the middle of the iris is called pupil.
- The pupil changes its size according to the available light.
- Lens is transparent portion that focuses the light into retina. The ciliary body is made of pigmented and non-pigmented ciliary epithelia, a stroma, and ciliary muscles. Capillaries of ciliary body allow communication between anterior and posterior segments.
- Vitreous humor is a gel-like, clear, avascular connective tissue that exists between the eye lens and the retina. It is made of 99.9% water, hyaluronic acid, ions, and collagen.

- The conjunctiva is a delicate transparent membrane lining inside the eyelids and shelter the frontal surface of the sclera.
- It is a mucous membrane that is composed of three layers, an outer epithelium, a substantia propria enclosing nerves, lymphatic and blood vessels, and a submucosa layer linked to the sclera.
- The sclera is a continuous of cornea. It is made of collagen and mucopolysaccharides. Choroid is vascular layer that is located between retina and sclera.
- The retina is thin film of tissue composed of neural and glial cells covering the back of the eye.
- It produces electrical impulses that are delivered through the optic nerve to the brain .[9,10]

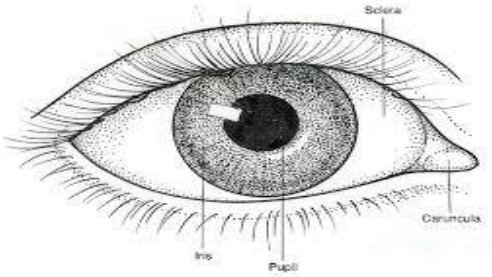

Fig. 3: Diagrammatic rerpresentation of eye

1. Routes of Ocular Drug Delivery:[3,6]

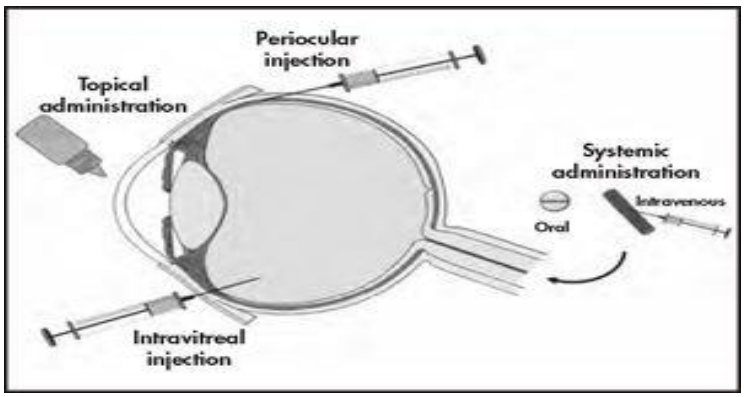

Fig. 4: Ocular routes for drug delivery system

1.1 Topical Administration:

- The drug product is applied to the eye surface to achieve topical drug administration.
- Because of its affordability, patient compliance, and ease of administration, topical treatment is still the most used method. Disorders of the anterior segment are typically treated with topical.
- Eye drops only briefly come into contact with the surface of the eye. Other preparations, such as ointments, gels, and ocular inserts, can enhance the topical administration.
- When applied topically, the corneal route (cornea-aqueous humor intra ocular tissue) and the non-corneal route (conjunctiva-sclera-choroid retinal pigment epithelium) are the two main absorption pathways.

- The short contact of drug on the corneal surface it partitions to the epithelium and in the case of lipophilic compounds it remains in the epithelium and is slowly released to the corneal stroma and further to the anterior chamber.
- After eye drop administration the peak concentration in the anterior chamber is reached after 20–30 min.

Fig. 5: Topical administration of eye

1.2 Subconjuctival Administration:

- Pharmaceutical formulations are utilized to create controlled release formulations that distribute medications to the posterior segment and direct the postoperative healing process.
- An active substance is injected beneath the conjunctiva during a subconjunctival injection.
- The conjunctival epithelium acts as a barrier that restricts the passage of substances that are soluble in water.
- In the case of injection, an initial accumulation of the drug is formed that acts as a depot that undergoes slow depletion.
- In this route, the drug avoids elimination by the conjunctival blood and lymphatic circulation and must cross the sclera and choroid to reach the retina. A small incision in the conjunctiva must be made in order to deliver subconjunctival/episcleral implants

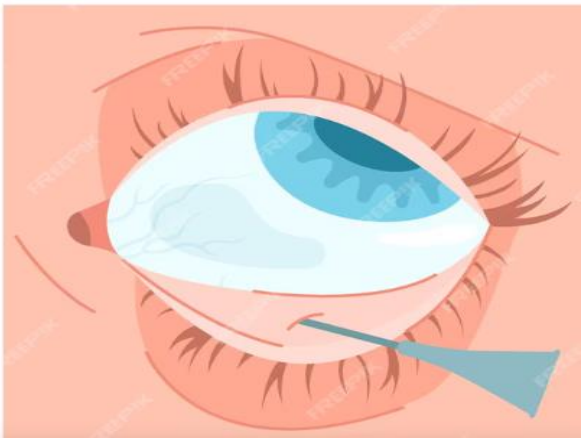

Fig. 6: Subconjuctival administration

1.3 Intraviteral Administration:

- In intravitreal administration, the needle is inserted perpendicular to the sclera, between the horizontal and vertical rectus muscles, in order to release the drug in the vitreous chamber where it is distributed and reaches different targets in the posterior eye segment.

- After intravitreal administration, drug concentrations at the blood-ocular barriers are clearly higher than those obtained after topical or systemic administration.
- At this level, drug clearance can occur through the anterior or posterior pathways. Any drug can pass through the anterior route by diffusion through the vitreous humor to the posterior chamber.

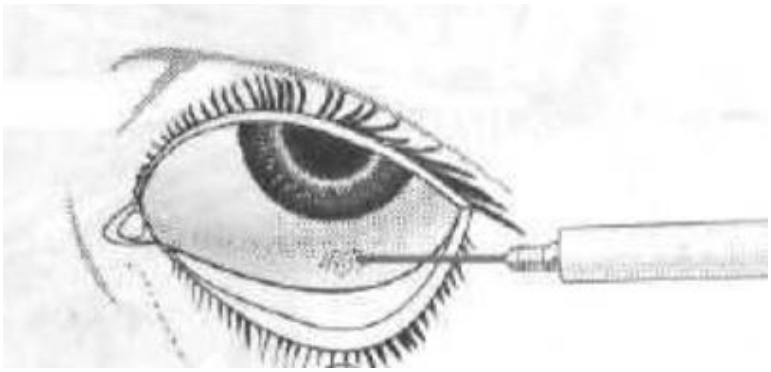

Fig. 7: Intravitreal administration

The following characteristics are required to optimize ocular drug delivery system.

- Good corneal penetration
- A Prolonged contact time of drug with corneal tissue.
- Simplicity of instillation and removal for the patient.
- A non-irritative and at ease form usually the viscous solution should not irritate lachrymation and reflex flashing
- Finally appropriate rheological properties.

Advantages of Occular Drug Delivery System:

1. A more precise dosage. To get beyond the adverse consequences of conventional systems' pulsed dosage.
2. To distribute drugs in a regulated and continuous manner.
3. To lengthen the corneal contact time in order to boost the drug's ocular bioavailability. Effective adhesion to the corneal surface can accomplish this.
4. To offer targeting inside the eye's globe in order to stop damage to adjacent eye tissues.
5. To get past defense mechanisms such conjunctival absorption, lacrimation, and drainage.
6. To make the patient more comfortable, increase their compliance, and enhance the medication's therapeutic effect.
7. To improve the delivery system's housing.

Limitation of Occular Drug Delivery System:

1. Termination of the dosageform is not possible during emergency
2. Interference with vision
3. Short contact time of drug solution on eye surface
4. Poor bioavailability, Instability for dissolved drug and use of preservatives.

2. Barriers to Occular Drug Delivery:[4]

2.1 Drug Loss from the Occular Surface:

- After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes.
- Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.
- Smallmolecular weight drug dose is absorbed into systemic circulation rapidly in few minutes. This contrasts the low ocular bioavailability of less than 5% . Drug absorption into the systemic circulation decreases the drug concentration in lacrimal fluid extensively. Therefore, constant drug release from solid delivery system to the tear fluid may lead only to ocular bioavailability of about 10%, since most of the drug is cleared by the local systemic absorption.

2.2 Lacrimal Fluid –Eye Barrier:

- Corneal epithelium limits drug absorption from the lacrimal fluid into the eye.
- The corneal epithelial cells form tight junctions that limit the paracellular drug permeation.
- Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs.
- In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

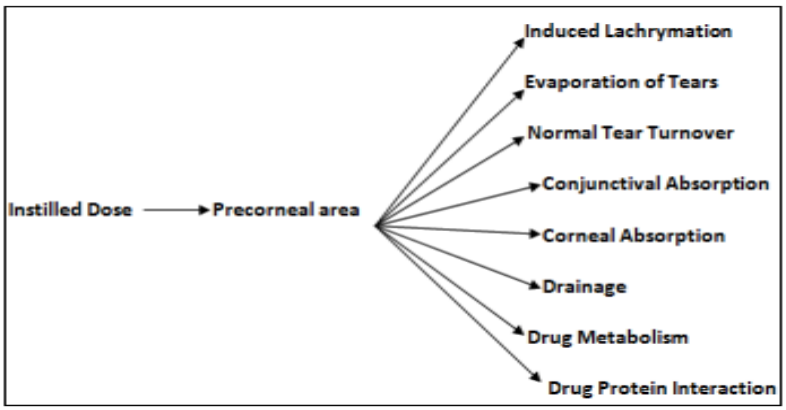

Fig. 8: Drug elimination pathway from precorneal area

2.3 Blood Occular Barrier:

- Blood – ocular barriers are present in the blood stream, which protect the eye from Xenobiotics
- It comprises of two parts namely blood – aqueous barrier and blood-retina barrier.

  a) The anterior blood-eye barrier works to prevent the entry of hydrophilic drugs present in plasma to the aqueous humor and also limits the entrance humor and also limits the entrance of plasma albumin in aqueous humor.

b) The posterior barrier which resides in between the eye and stream of plasma consists of retinal pigment epithelium (RPE) and retinal.

3. Method to Overcome Barrier:

3.1 Formulation Approach to Improve the Occular Bioavailability:

3.1.1 Viscosity Enhancer:

- Viscosity enhancers Viscosity-increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should correspond to a slower elimination from the preocular area, which lead to improved precorneal residence time and hence a greater transcorneal penetration of the drug into the anterior chamber. It has minimal effects in humans in terms of improvement Precorneal factors that influence bioavailability of topically applied ophthalmic drugs.
- Examples of polymers are polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxylethylcellulose, hydroxylpropyl methylcellulose (HPMC) and hydroxypropyl cellulose capillaries resulting in tight wall junction.

Gel Formulation (Sol to Gel System):

- Sol-solution-Remains as a solution in a eye drop bottle-free flow into eye.
- Gel –Remains gel on contact with eye-in presence of temperature pH ions.
- Gels are generally liquid, but behave like solids due to their three-dimensional cross-linked structure within the liquid. On the other side, if the gels have extremely high viscosity, they cannot improve bioavailability; instead, they will control the release, which leads to reduced frequency of dosing to once a day. The highly viscous solution even leads to blurred vision and matted eyelids, which substantially decrease patient's compliance.
- In aqueous gel, viscosity building agents, such as PVA, polyacrylamide, poloxamer, HPMC, Carbomer, polymethylvinylether, Maleic anhydride, and hydroxylpropylethylcellulose are incorporated, whereas hydrogel or swellable water-insoluble polymers give rise to controlled drug delivery systems.

Fig. 9: Liquigel

3.1.3 Penetration Enhancer:

Increasing the permeability of the corneal epithelium can increase the commercial autonomy of the entire cornea. The typical epithelial lining of the cornea is a strong molecule that moves tissue. One of the methods used to increase the bioavailability of ophthalmic drugs is to rapidly

increase the credit score of corneal permeability using appropriate substances known as invasive enhancers or admission enhancers. Transporting the drug from the cornea to the receptor site is the rate limiting step.

Permeation enhancer increases corneal uptake by modifying the integrity of the corneal epithelium.

3.1.4 Eye Ointments:

- Ointments are usually formulated using mixture of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to body temperature and are non irritating to the eye.
- Ointments may be simple base where the ointments form one continuous phase or compound bases where a 2 phased system (eg., an emulsion) is employed.
- As a solution or as a finely micronized powder the medicinal agent is added to the base either.
- Upon instillation in the eye, ointments break upinto small droplets and remain as a depot of drug in the cul-de-sac for extended periods.
- Therefore in improving the bioavailability and in sustaining drug release ointments are useful.
- Although safe and well tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation.
- Popular for pediatrics.

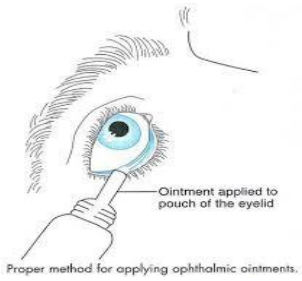

Fig. 10: Eye ointment

3.1.5 Gel Formulation:

- Gels are known to be significantly dilute cross-linked systems, which show rigidity in the steady-state. Gels are generally liquid, but behave like solids due to their three-dimensional cross-linked structure within the liquid. On the other side, if the gels have extremely high viscosity, they cannot improve bioavailability; instead, they will control the release, which leads to reduced frequency of dosing to once a day.
- The highly viscous solution even leads to blurred vision and matted eyelids, which substantially decrease patient's compliance. In aqueous gel, viscosity building agents, such as PVA, polyacrylamide, poloxamer, HPMC, Carbomer, polymethylvinylether, Maleic

anhydride, and hydroxylpropylethylcellulose are incorporated, whereas hydrogel or swellable water-insoluble polymers give rise to controlled drug delivery systems.

3.1.6 Eye Drop:

- Sterile, isotonic, liquid preparation meant to instill into the eye.
- Limited ocular absorption-only <5% of drug absorbed

Preparation:

- All ingredients are completely dispersed in solution.
- Sterilization is must.
- Isotonicity must be adjusted by class 1/class 2 methods (Physical pharmacy)

Fig. 11: Eyedrop

3.1.6 Prodrug:[5]

- The principle of prodrug is to enhance the corneal drug permeability through modification of the hydrophilicity of the drug.
- With in the cornea and after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound.
- Thus the ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it also has high enzyme susceptibility.
- Example: antiviral medication ganciclovir and acyclovir are the suitable prodrug.

4. Novel Ocular Drug Delivery System:[7,8]

4.1 Nanoparticles:

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres.

In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix.

Nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues.

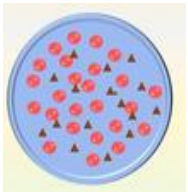

Fig. 12: Nanoparticles

Fig.13: Nanocapsule

Nanoparticles are small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from precorneal pocket. Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time. Polyethylene glycol (PEG), chitosan and hyaluronic acid are commonly employed to improve precorneal residence time of nanoparticles.

4.2 Niosomes:

- These are bilayer vesicles containing nonionic surfactants. Excellent personalization of lipophilic and hydrophilic materials. Niosomes decrease alkaline drainage, encourage more time at home, and alter visual bioavailability.
- It is inherently non-biodegradable and non-biodegradable. It was used to transport cyclopentrate and was given the definition of nios. Take medication regardless of pH. This represents a fundamental improvement in visual bioavailability. Niosome levels are coated with polymer Carbopol and chitosan.

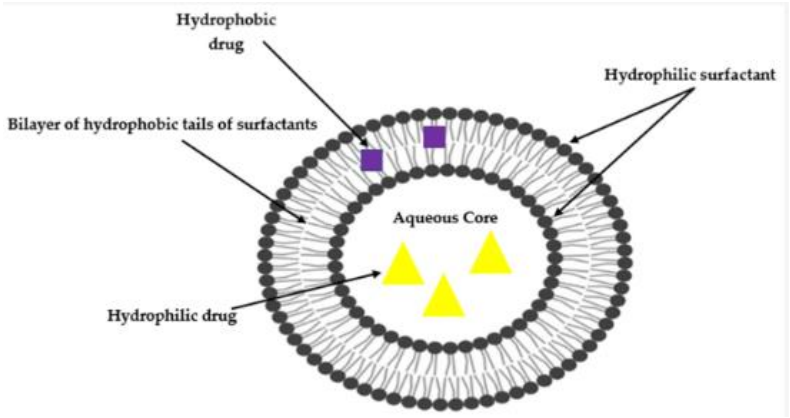

Fig. 14: Niosomes

4.3 Microneedles:

- Microneedles based techniques is an emerging technique for delivery posterior ocular tissues. This technique may provide efficient treatment strategy for vision threatening posterior ocular diseases such as age-related macular degeneration, diabetic retinopathy and posterior

uveitis, puncturing of sclera and depositing drug solution or supra chordal space facilitate diffusion of drug into deeper ocular tissues.

- Microneedles (MLs) are micrometer sized needles, or arrays of such fabricated by adapting microelectronics tools. Applying MLs to biological membranes can create tiny transport pathways, thereby allowing drugs to permeate across these barriers. To date, numerous MI. fabrication approaches have been utilized, resulting in a variety of shapes, sizes, materials and configurations. Enhanced drug delivery into the cornea and anterior segment of the eye can he achieved by insertion of MLs across the corneal epithelium. Various polymeric MLs have found great use in intrascleral drug delivery. According to their delivery mechanism.
- Ocular MLs can be categorized into four types such as
- solid microneedles
- drug-coated microneedles
- dissolving microneedles and
- hollow microneedies

4.4 Sonophoresis:

- It involves the application of a sound field at frequencies higher than 20KHz to improve drug transport across biological membranes including ocular barriers.
- The mechanism for ultrasound enhanced drug delivery takes into account non thermal and thermal effects with ultrasound parameters.
- Corneal permeability enhancement is generally a result of stable cavitation at low ultrasound intensities, whereas both stable and inertial cavitation play important role at higher ultrasound strengths.

4.5 Liposomes

- Liposomes are lipid vesicles with one or more phospholipid bilayers enclosing an aqueous core. The size of liposomes usually ranges from 0.08 to 10.00 μm and based on the size and phospholipid bilayers, liposomes can be classified as small unilamellar vesicles (10–100 nm), large unilamellar vesicles (100–300 nm) and multilamellar vesicles (contains more than one bilayer).
- Liposomes represent ideal delivery systems due to excellent biocompatibility, cell membrane like structure and ability to encapsulate both hydrophilic and hydrophobic drugs. Liposomes have demonstrated good effectiveness for both anterior and posterior segment ocular delivery.
- For drug delivery to anterior segment of the eye, efforts are mainly put toward improving precorneal residence time by incorporating positively charged lipids or mucoadhesive polymer in liposomes.

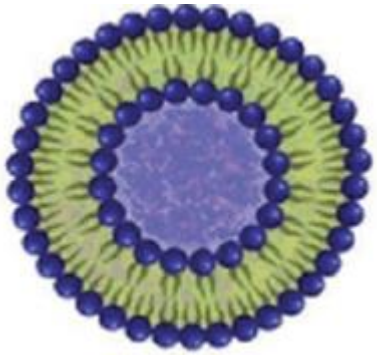

Fig. 15: Liposome

4.6 Intravitreal Injection:

Injection is directly given into the posterior segment via parts plana for delivering drugs overcome all barriers. Various studies on antiviral agents like ganciclovir, foscarnet and cidovir and antibiotics like cefazolin, amikacin, moxifloxacin, ceftizoxime, ceftazidine, and gentamicin steroids dexamethasone, triamcinolone acetone and monoclonal antibodies rituximab

4.7 Ocular Implants:

- Ocular implants are drug eluting devices specially designed for local sustained drug release over a long periods. Device are surgically implanted into the vitreous humor by incision at the pars pana and drug placement near the retina.
- There are two types of ocular implants,
- Biodegradable.
  Non-biodegradable implant
- They are prepared by using polymer like polyvinyl alcohol (PVA), ethylene vinyl acetate and polysulfone, capillary fibre. They offer prolonged controlled release with near zero order kinetics. Commercially available such preparation arevitrasery and Retisert. Biodegradable implants are prepared by PLA, PGA, PLGA and PCL. Examples include surodex, and ozurdex. These implants offer sustained dexamethasone release for the treatment of intraocular inflammation and macular edema.

4.8 Ophthalmic Inserts:

- Ocular insert(occusert) is sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal drainage.[11,12]
- It shows diffusion controlled release.
- It consists of a central reservoir of drug enclosed in specially designed microporous membrane allowing drug to diffuse from reservoir at precisely predetermined rate.
- Inserts are available in different varieties depending upon their composition and applications.

4.8. a) Classification:

1.Insoluble ocular inserts – Diffusional insert (ocusert)

a)Reservior system -Osmotic inserts

b)Matrix System- Contact lens

2. Soluble ocular inserts

a)Based on natural polymers – eg.,collagen

b)Based on synthetic polymers eg.,cellulose derivatives, HPMC,HPC etc.,

3. Bio – erodible ocular insert (SODI) **(**Soluble Opthalmic Drug Inserts)

4. Others Ocular therapeutic -Collagen shields, Ocufit, Minidisc.

Opthalmic Inserts:

- Opthalmic insert are solid patches, which when placed in the conjunctival sac of the eye, slow down the rate of drug release. Ocular inserts overcome the problem of frequent dosing by maintaining drug concentration in an effective manner and give rise to controlled, sustained and continuous drug delivery. Some examples of ocular inserts are pilocarpine nitrtate, dexamethasone, Tropicamide and Timolol maleate.
- The Ocusert release its medicament through diffusional release its medicament through diffusional release mechanism. The diffusional systems are composed of a central reseivor of drug enclosed in a specially designed semipermeable or microporous membranes which allow the drug to diffuse through the reservoir at a precisely determined rate. For example: (Pilocarpine ocusert).
- The typical pulse entry type drug release behaviour observed with eye drops, suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system.
- Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency.

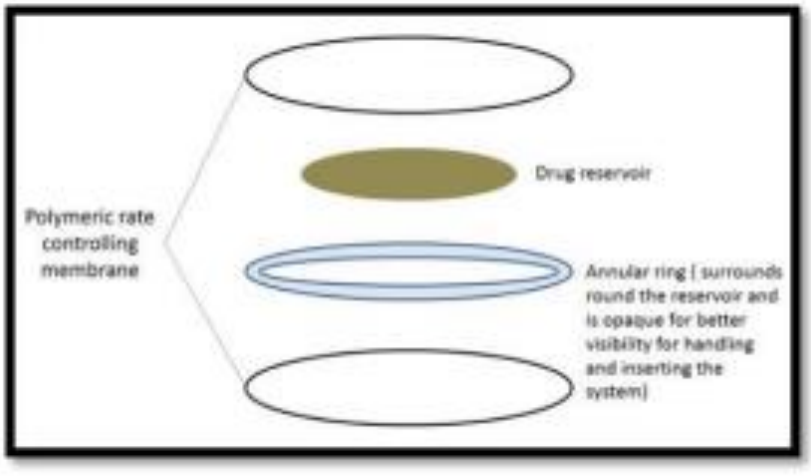

Fig. 16: Structural organization of occusert

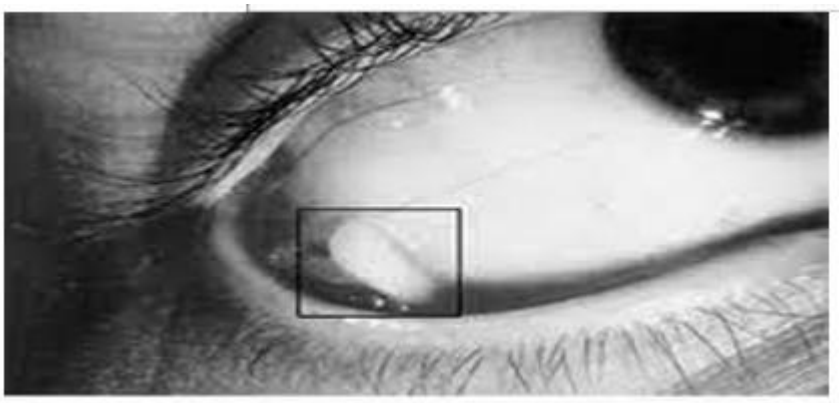

Fig. 17: Opthalmic inserts

- The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment. They are composed of polymeric support with or without drugs, the latter being incorporated as dispersion or a solution
  in the polymeric support.

4.8. b) Soluble Ophthalmic Insert:

Soluble Ocular Drug Insert (SODI) is a small oval wafer developed for space pilots who could not use eye drops in weightless conditions. It is sterile thin film of oval shape made from acryl amide, N-vinyl pyrrolidone and ethyl acrylate called as ABE. It weighs about 15-16 mg. It is used in treatment of glaucoma and trachoma. It is inserted into inferior culde-sac and gets wets and softens in 10-15 seconds. After 10-15 min film turns into a viscous polymer mass, after 30-60 minutes it turns into polymer solutions and delivers drug for about 24 hours.

4.8. c) Bioerodible Ocular Insert:

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants.

4.8.1advantages of Ocusert:

- Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles;
- Possibility of releasing drugs at a slow, constant rate;
- Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site);
- Reduction of systemic absorption (which occurs freely with eye drops via the nasolacrimal duct and nasal mucosa);

- Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;
- Increased shelf life with respect to aqueous solutions;
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions; Possibility of incorporating various novel chemical technological approaches**.**
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions;
- Possibility of incorporating various novel chemical technological approaches.

4.8.2 Disadvantage of Ocusert:

- A capital disadvantage of ocular inserts resides in their 'solidity', i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a formidable, physical and psychological barrier to user acceptance and compliance.
- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix.
- The occasional inadvertent loss during sleep or while

4.9 Contact Lens:

Contact lenses are thin curve shaped discs designed to be placed over the cornea. After playing over the cornea and contact lens adhere to the surface of the eye because of interfacial tension. Usually contact lenses are prepared with polymers such as siliconehydrogel and poly hydoxy ethyl methacrylate. Contact lenses loaded with drug and (or) drug loaded nanocarriers have been developed for ocular delivery the several active drug such Timolol, dexamethasone, beta blockers antihistamines and antimicrobials have been used for anterior delivery. They soaked in drug solvent and absorb water (water soluble drugs).

Fig. 18: Contact lens

4.9.a Lacriset/Ocufit:

The Ocufit is a sustained release, rod shaped device made of silicone elastomer, patented in 1992 and currently developed by Escalon Ophthalmics Inc. It was designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and new-born babies are planned. They lack preservative useful for dry eye syndrome. Lacrisert is useful in treatment of keratitis whose symptoms are difficult to treat with artificial tear alone. It is inserted into cul-de-sac cavity where it absorbs water from conjunctiva and cornea, forms a hydrophilic film which stabilizes tear film for hydration and lubrication of cornea. It dissolves in 24 hours.

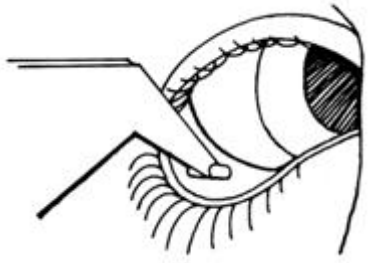

Fig. 19: Lacriset

5. Disorders of the Human Eye:

5.1 Cataract:

The term cataract refers to any cloudiness or opacity of the normally transparent crystalline lens of the eye. A cataract may or may not cause a loss of vision, depending on the size of the opacity, its density, and its location. Severe cataracts are a major cause of treatable blindness throughout the world.

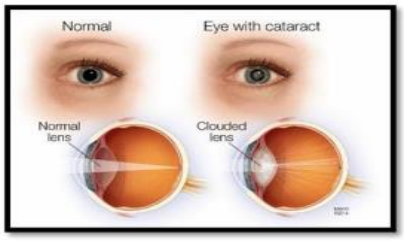

Fig. 20: Cataract

Oxidative damage caused by free radicals is considered to be an important factor in aging and the development of chronic diseases, including cataract formation. For this reason, many of the dietary supplement recommendations focus on antioxidants which can neutralize the oxidative damage caused by free radicals.

5.2 Conjuctivitis:

Conjunctivitis is an inflammation of the conjunctiva, the transparent mucous membrane lining the inside of the eyelids and the white of the eyeball. Normally the white, or sclera, is clearly visible through the conjunctiva, but when the conjunctiva is inflamed, its normally invisible

blood vessels become engorged, making the eye appear red. Conjunctivitis may be caused by many types of infectious agents, such as viruses or bacteria, as well as by toxic, chemical, and allergenic irritants.

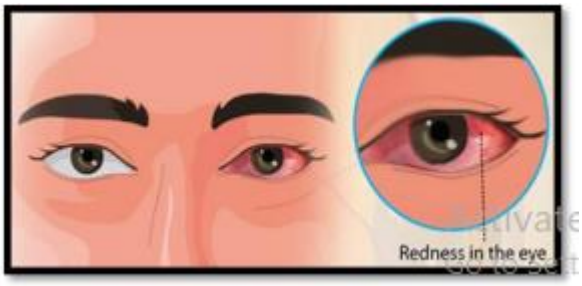

Figure 21: Conjuctivitis

5.3 Night Blindness:

Impairment of the vision normally possible in dim light is called night blindness, or nyctalopia. It may be an early sign of vitamin A deficiency because that vitamin plays a major role in the cells of the eye sensitive to dim light.

Figure 22: Night blindness

Night blindness is also a manifestation of various eye disorders such as glaucoma and optic nerve disease. It is often the earliest symptom of retinitis pigmentosa, a chronic and progressive inflammation of the retina. One form of the condition, called congenital stationary night blindness, is hereditary.

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BIOELECTRIC MEDICINE: AN EMERGING TREND IN PHARMA AND HEALTHCARE

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Abstract:
Bioelectric medicine, also known as electroceuticals or neuromodulation therapy, is reshaping the landscape of modern therapeutics by integrating advances in bioengineering, neurobiology, and digital health. Unlike traditional pharmacotherapy that often targets biochemical pathways systemically, bioelectric medicine operates by modulating electrical signals in specific neural circuits, offering precision, fewer side effects, and enhanced therapeutic outcomes. This manuscript explores the scientific basis, current developments, technological advancements, clinical applications, ethical considerations, and future prospects of bioelectric medicine in the context of the evolving pharmaceutical and healthcare industries.

Keywords: Bioelectric, Bioengineering, Digital Health, Pharmaceutical, Healthcare

Introduction:

The pharmaceutical industry is undergoing a paradigm shift. For decades, the dominant approach in healthcare has been the development and administration of pharmacological agents to alter biological pathways. However, many diseases—especially chronic, inflammatory, or neurological conditions—pose significant therapeutic challenges due to drug resistance, side effects, and the complexity of biological systems. As an alternative or complement to pharmaceuticals, bioelectric medicine emerges as a novel modality that employs targeted electrical impulses to modify disease-specific neural activity [1].

By intervening in the neural reflex arcs that regulate immune, endocrine, and metabolic responses, bioelectric medicine provides real-time, closed-loop, and minimally invasive solutions for chronic diseases. Its potential is underpinned by a deeper understanding of the human nervous system and its regulatory control over virtually every organ system [2].

Scientific Basis and Mechanisms

The foundational principle of bioelectric medicine is that electrical signals in the body—especially in the autonomic nervous system—can be harnessed therapeutically. Neural pathways not only relay sensory and motor functions but also regulate immune responses, inflammation, metabolism, and organ function. By targeting key nerves such as the vagus nerve, phrenic nerve, or sacral nerves, it is possible to modulate physiological processes and correct pathological states [3].

For example, stimulation of the vagus nerve can activate the cholinergic anti-inflammatory pathway (CAP), a neuroimmune reflex that suppresses pro-inflammatory cytokine production like TNF-α and IL-6 [4]. This mechanism has been demonstrated in both preclinical models and human trials, particularly in conditions like rheumatoid arthritis and Crohn's disease [5].

Technological Innovations

The feasibility of bioelectric therapy has greatly improved due to advances in several technological domains:

1. Miniaturization and Biocompatibility

The development of microelectronic devices that are biocompatible and minimally invasive has enabled chronic implantation with fewer complications. Devices such as microelectrode arrays, wireless neuromodulators, and flexible bioelectronics can be embedded in or around target nerves without disrupting surrounding tissue [6].

2. Closed-loop Systems

Unlike traditional stimulators that deliver fixed signals, closed-loop systems use real-time biofeedback (e.g., heart rate, glucose levels, cytokine concentrations) to tailor stimulation protocols. These systems enhance therapeutic precision and minimize adverse effects [7].

3. Wireless Power and Data Transmission

Recent innovations in wireless telemetry, power harvesting, and energy-efficient chips enable long-term, battery-free operations of bioelectronic devices. This is particularly useful in chronic disorders requiring lifelong treatment [8].

Clinical Applications

Bioelectric medicine is currently being investigated or applied in a range of disorders:

1. Autoimmune and Inflammatory Diseases

Stimulation of the vagus nerve has been shown to downregulate systemic inflammation in rheumatoid arthritis, with significant reductions in disease activity score (DAS28) and inflammatory markers [5].

2. Cardiovascular Disorders

Baroreflex activation therapy (BAT), targeting the carotid sinus, has shown promise in patients with drug-resistant hypertension by enhancing parasympathetic tone and lowering blood pressure [9].

3. Metabolic Disorders

Modulating hepatic or vagal afferents has been shown to influence insulin sensitivity and glucose homeostasis, offering new avenues for treating type 2 diabetes and obesity [10].

4. Neurological and Psychiatric Disorders

Bioelectric therapies have FDA-approved indications in drug-resistant epilepsy and major depressive disorder through vagus nerve and deep brain stimulation (DBS), respectively .

5. Gastrointestinal and Urological Disorders

Sacral nerve stimulation is used to treat urinary incontinence, fecal incontinence, and irritable bowel syndrome, by restoring autonomic balance in the pelvic region [10].

Regulatory, Ethical, and Implementation Challenges

While bioelectric medicine is advancing rapidly, its clinical translation requires addressing several challenges:

- Regulatory Approval: Bioelectronic devices are regulated differently from pharmaceuticals, necessitating new safety and efficacy evaluation frameworks. The FDA has published guidelines specific to neuromodulation devices, though more harmonization is needed globally [10].
- Ethical Concerns: As these devices can affect brain and autonomic function, issues of informed consent, data privacy, and psychological effects must be thoroughly considered, especially in vulnerable populations.
- Access and Cost: Implantable devices can be expensive and require surgical procedures, limiting access in low-resource settings. Development of non-invasive and low-cost devices remains a priority.

Future Perspectives

The field is moving toward bioelectronic precision medicine, integrating AI and machine learning to optimize neuromodulation strategies. Future devices may be capable of detecting biomarkers (e.g., cytokine levels) and adjusting stimulation parameters in real-time without physician intervention.

Synthetic biology and optogenetics may also play a role in next-generation electroceuticals by creating biohybrid systems that combine electronics with living tissue. The long-term vision is to create personalized, adaptive, and minimally invasive treatments that target the root cause of diseases—neural dysregulation [10]

Conclusion:

Bioelectric medicine represents a transformative advancement in modern healthcare, offering a novel therapeutic paradigm that modulates neural circuits through precise electrical stimulation rather than relying on traditional pharmaceuticals. This approach not only minimizes systemic side effects but also enables real-time, targeted interventions for complex chronic conditions such as epilepsy, rheumatoid arthritis, depression, and metabolic disorders. With rapid developments in neurotechnology, bioelectronics, and artificial intelligence, bioelectric medicine is evolving into a personalized, adaptive treatment modality capable of responding dynamically to physiological changes. Emerging applications extend beyond symptom management, showing potential for disease modification and long-term control. As the field progresses, integration with digital health platforms, wearable biosensors, and closed-loop systems promises to further

enhance its effectiveness and accessibility. However, challenges related to cost, ethical concerns, regulatory frameworks, and long-term safety must be addressed to ensure widespread adoption. Ultimately, bioelectric medicine is not just an emerging trend but a foundational pillar of the future of medicine, poised to redefine therapeutic strategies and improve outcomes across a broad spectrum of diseases

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INTRANASAL COVID VACCINE: A REVIEW

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Abstract:

The latest threat to global health is the ongoing outbreak of the respiratory disease that was recently given the name Coronavirus Disease 2019 (COVID- 19). It was rapidly shown to be caused by a novel coronavirus that is structurally related to the virus that causes severe acute respiratory syndrome (SARS). An intranasal vaccine stimulates a broad immune response – neutralizing IgG, mucosal IgA, and T cell responses. Immune responses at the site of infection (in the nasal mucosa) – essential for blocking both infection and transmission of COVID-19. Invading the mucosal surface by inducing local microbial-specific immune responses, nasal delivery of vaccines functions as a "first entry block," i.e., block the pathogen entry, increasing the overall efficacy of the vaccine. Intranasal administration is a non-invasive route for drug delivery, which is widely used for the local treatment. The development of additional vaccine administration methods, including intranasal, oral, topical, pulmonary, vaginal, and rectal, is currently gaining traction in the vaccine market. The nasal route presents the most promising opportunity for vaccine administration. Convenience and safety can be improved, and it can also trigger both local and systemic immune responses, which could possibly offer protection from pathogens at the point of entry. The development of nasal vaccines presents both possibilities and difficulties.

Keywords- Nasal Vaccines, Sars-CoV-2, iNCOVACC, Nasal Anatomy

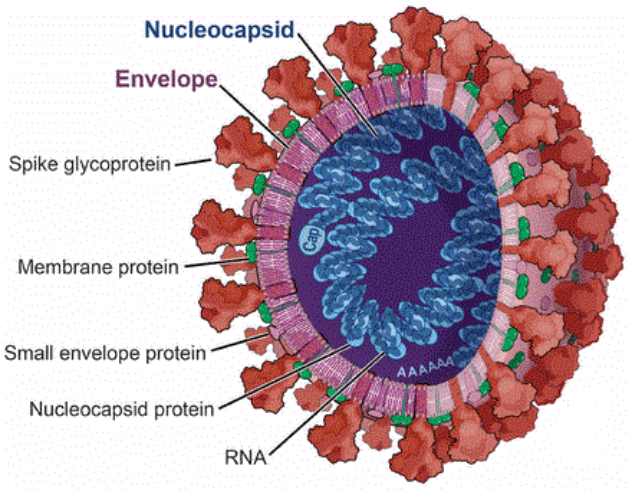
Introduction:

Vaccines make use of unique ability of the human immune system to react and remember harmful material it comes into contact with. An ideal vaccination should offer quick, long-lasting protection by preventing from serious illness, hospitalization, and death.[1] In Dec 2019, China became the first country to report the COVID-19. Then, it has spread at an unprecedented, terrifying rate over the entire planet.[2] COVID 19 caused by novel corona virus, which named as severe acute respiratory syndrome corona virus 2 (SARS – COV-2).[3] Corona viruses are a highly diverse family of enveloped positive-sense single-stranded RNA viruses.[4] A variety of COVID-19 vaccines, mRNA vaccines, DNA vaccines, viral vector vaccines and inactivated virus vaccines, have been developed after a great deal of research. These include recombinant

vaccines, plant-based vaccines, immune-informatics-based multi-epitope subunit vaccines, artificial intelligence, CRISPR/Cas technology-based vaccines, nano-vaccine, and others.[5,6]

SARS-CoV-2 Viral Particle and Genome Organization

A corona virus has a lipid bilayer wrapping with spike-like projections on a glycoprotein surface. Spike protein (S), Membrane protein (M), Envelope protein (E), Nucleocapsid (N), and RNA genome make up the majority of its structural components (R). In addition to the receptor-binding motif, the S-protein comprises two additional domains or subunits. These are the S1 subunit (bilobular receptor-binding domain) and the S2 subunit (stalk fusion domain).[1] A stacked collection of 3' coterminal subgenomic (sg) mRNAs that are produced through discontinuous transcription during subgenome-length minus-strand RNA synthesis is used to produce the structural and accessory proteins.[32]

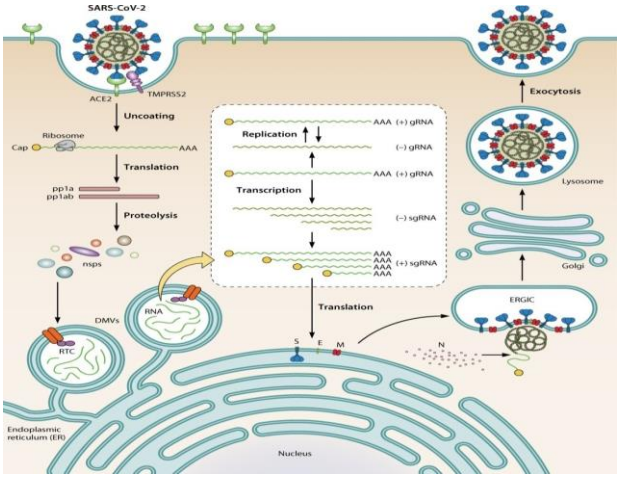


N encapsidates the positive-sense, single-stranded RNA genome (+ssRNA), while M and E make sure it is incorporated into the viral particle during assembly. S trimers provide selectivity for cellular entrance receptors and protrude from the host-derived viral envelope.[4] The 419 amino acid-long N protein is the only structural protein inside the virion. The replicase complex is made up of 16 non-structural proteins (Nsps 1–16), which are encoded by two big open reading frames (ORF1a and ORF1b) found at the 5′ end of the genomic RNA. These two huge open reading frames occupy two-thirds of the capped and polyadenylated genome.[6]

SARS-CoV-2 Life Cycle

SARS-CoV-2 can hijack the cell in two ways, either via endosomes or via plasma membrane fusion. Spike proteins (S1, S2) of SARS-CoV-2 mediate attachment to the membrane of a host cell and engage angiotensin-converting enzyme 2 (ACE2).[29] The spike proteins (S glycoprotein), which resemble spikes and are found on the transmembrane of the coronavirus, facilitate in the virus's entry into host cells.[30] The S protein binds to particular receptors on the exterior of the host cell to begin virus replication. The carcino-embryonic antigen-cell adhesion molecule (CEACAM) has been identified as the main receptor for MHV. Entry and uncoating of

the wild-type MHV are likely caused by direct fusion mediated by a fusion peptide in the S protein. This mechanism is pH independent.[28] The S1 component aids in binding the virion's N terminus to the host cell receptor. At the C terminus, the S2 subunit facilitates the fusion of the viral and cellular membranes.[1-3]



Clinical Manifestations

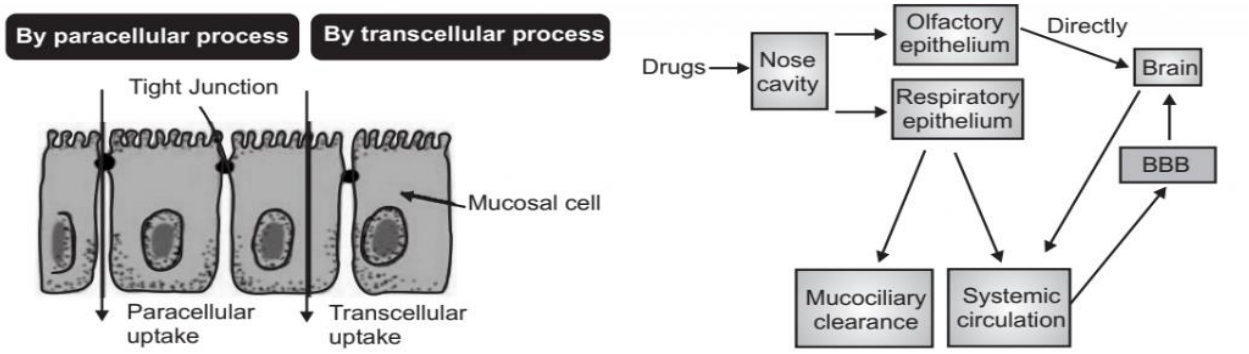
There are many different clinical characteristics of COVID-19, from asymptomatic condition to acute respiratory distress syndrome and multi-organ failure. The three main clinical stages are as follows. The first stage is the viral response phase. It normally lasts for four days by symptoms like fever, coughing, sore throats, and diarrhoea. The pulmonary phase is stage two, and lasts for five to thirteen days. At this stage, pulmonary symptoms occurs, later on hypoxia also occurs. Stage three is of systemic hyper-inflammation, which often begins on day 14. [39-40] Depending on their underlying medical conditions, such as cancer, diabetes, Parkinson's disease, kidney damage, or liver dysfunction, both elderly and youthful people may succumb to death. Within two to four weeks after therapy, healthy people may fully recover from the viral infection.

NASAL Anatomy and Development

The external nose has osseous, cartilaginous, epithelium, and neuro-epithelial components enclosed within its protuberance. Its external characteristics do not necessarily reflect its internal composition. The nasal tube is made up of two upward- and backward-directed channels that are separated by a cartilaginous and bony nasal septum, which is skin-lined horizontally. Strategically positioned air-warmer turbinates encircle the lateral nasal walls, configuring the air stream to fit their shapes and varying sizes. The auxiliary sinuses are located laterally in the maxilla, superiolaterally in the ethmoid bones, superiorly in the frontal bone, and posteriorly in the sphenoid bone. They are connected to the nasal chambers by their respective Ostia. In the upper part of the nasal chamber, the olfactory cleft is located.[11] The nasal cavity, which is a part of the nasopharynx, contains NALT (Nasopharynx associated lymphoid tissue). These nerve cells' principal axons enter the olfactory bulb through the cribriform plate of the ethmoid bone.[10]

Mechanism of Nasal Absorption

The mucus layer must be penetrated by the medications that are absorbed from the nasal cavity; this is the initial stage of absorption. This layer is easily penetrated by small, unmodified medications, but it is difficult to pass by large, charged drugs.[12] The mucus is the primary mechanism by which a medicine is delivered to and absorbed through the nasal passage. Mucin, a protein derived from mucus, is capable of binding to solutes and interfering with the diffusion process. Numerous mechanisms, including as paracellular and transcellular pathways, are available for nasal administration and absorption through the mucosa.[13] These include paracellular transport through cell-to-cell migration, transcytosis by vesicle carriers, transcellular, or simple membrane diffusion.[14]



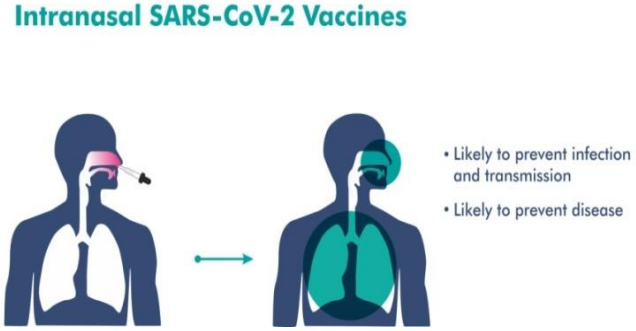
Despite the fact that other absorption processes have been developed over time, only two are primarily employed, including:

A. **First Mechanism**: The first mechanism involves an aqueous route of transport, which is also known as the paracellular route.[37] Intranasal absorption and the molecular weight of water-soluble substances have an inverse log-log relationship. The bioavailability of medicines with molecular weights more than 1000 Daltons is poor.[12]

B. **Second Mechanism**: The transcellular process, also known as the second method, which involves transport via a lipoidal pathway, is in charge of carrying out the rate-dependent transport of lipophilic medications. To promote the flow of drugs, for instance, the natural biopolymer chitosan, derived from shellfish, opens tight junctions between epithelial cells.[15]

Intranasal delivery of vaccines: The mucosal surfaces of our bodies are the primary route by which pathogenic bacteria, viruses, and parasites enter our bodies. Since it is natural, the majority of the immune system is either embedded within or in close proximity to mucosal membranes, acting as a "first line of defense" against potentially dangerous pathogens.[8] However, vaccines for the mucosa also cause a systemic reaction that is comparable to an injection, in addition to a robust local immune response. There are numerous sizes and formulations for nasal administration, including granular and spray delivery. When air is forced through the anterior surfaces of the nasal turbinate, the majority of particles larger than 5 mm in

diameter settle in the nasal cavity and a smaller number do so when the air flow moves to the posterior nasal cavity.[9] With the aid of readily available commercial broad distribution devices, it is a useful site for simple self-administration. Compared to the oral or occasionally parenteral method, nasal immunization often requires significantly smaller quantities of antigen. Nasal immunization protects antigens from low pH and digesting enzymes like nuclease and protease, while mucus barrier function prevents antigens from penetrating the mucosal epithelium. Strong immune responses may be primarily induced when vaccinations are administered orally.[10]



Comparison of Efficacy of various COVID-19 vaccines available in India

Vaccines available in INDIA: COVISHIELD, COVAXIN, SPUTNIK V [20]

COVISHIELD:

The serum Institute of India, which approved agreements with Oxford AstraZeneca, is providing the vaccine to the nation. It is producing the Oxford AstraZeneca-developed Adenovirus vector-based vaccine AZD1222, known as COVISHIELD in the nation. It was the first vaccination to be mass-administered, and as a result, more than 50 million doses have been given.[47] A preliminary evaluation of the safety and effectiveness of the Oxford-AstraZeneca chimpanzee adenovirus-vectored vaccine ChAdOx1 nCoV-19 (AZD1222) against COVID-19 in adults 18 years of age and older.[21] The regulatory bodies have collaborated to organize the Phase II/III trials. For the trials, plans were made for a randomized controlled review in healthy adults at different locations across the nation to compare the efficacy and safety of the locally produced COVISHIELD vaccine to the original ChAdOx1 vaccine developed by Oxford AstraZeneca in anticipation of COVID-19 infection. 1600 qualified participants who were at least 18 years old volunteered for the study were the basis for it. 400 participants were randomly assigned to receive either the COVISHIELD vaccination or the ChAdOx1 vaccine, individually, with the goal of investigating the immunogenicity of the vaccines. The remaining 1200 participants were randomly assigned to receive either the COVISHIELD vaccination or a placebo, each in a 3:1 ratio. The Oxford AstraZeneca ChAdOx1 regulated in two dosages 18 years or more established from clinical evaluations outside India revealed the viability to be 70.42%. The preliminary clinical trial data on immunogenicity and security were evaluated as being equivalent to the data from earlier preliminary studies conducted abroad.[20]

COVAXIN:

Any vaccine's main goals are to prevent disease and lessen disease severity.[22] At the time of writing, 327 million doses of Covaxin (BBV152) from Bharat Biotech had been provided in India, making it the second-most widely used vaccine. It is an inactivated vaccination with -propiolactone. A toll-like receptor 7/8 agonist molecule called imidazo-quinoline gallamide, which is adsorbed to alum, is added to the inactivated whole-virion structure as an adjuvant (Algel-IMDG). With little systemic spillage, the formulation enhances the homing of vaccination antigen onto draining lymph nodes. At the National Institute of Virology (NIV), Pune, a genetically stable strain NIV-2020-770 with the Asp614Gly mutation required for Covaxin production was identified from an asymptomatic SARS-CoV-2 positive patient. Th1-skewed responses were seen in the phase I studies. Comparable post-second dose seroconversion rates were obtained for the 3 g and 6 g Algel-IMDG adjuvant combos. Immunity that is mediated by cells and humour appeared to be suitably activated. Phase II trials were made possible by a remarkable safety profile with local and systemic adverse events in the range of 17%-21%. The 6 g + Algel-IMDG combination was discovered to have the highest immunogenicity in both the phase II trials and the follow-up to the phase I trials, and was ultimately chosen for phase III studies. These studies demonstrated a 93.4% efficacy against severe COVID-19, but only a 65.2% efficacy against the Delta variation. Little lot-to-lot differences existed, and the safety profile was comparable to that of a placebo.[23]

SPUTNIK V:

Instead of using a pre-fusion "locked" S34, the Sputnik V vaccine, developed by AstraZeneca, is based on adenovirus vectored production of a native S sequence. While the interim analysis of Phase 3 trials conducted in Russia showing that the Sputnik V vaccine had a claimed vaccination effectiveness of 91.6%, neither the independent lineages with the E484K mutation nor any of the preceding VOC were common in Russia at the time. It is crucial to evaluate the neutralizing activity of Sputnik vaccine elicited antibody responses against these cognate VOC and mutant spikes because the Sputnik vaccine is now used not only in Russia but also in nations like Argentina, Mexico, and Hungary where some of the emerging lineages bearing the E484K mutation are more prevalent.[24] A randomized controlled research was conducted for the phase III trials, in which 14,964 adults were randomly chosen and received two doses of the vaccine, while the remaining 4,902 were given a placebo.[40] The experiment discovered that just 16 of the vaccine recipients went on to develop symptoms, whereas 62 of the placebo recipients did. As a result, the trial came to the conclusion that the vaccine had a 91.6% efficacy rate. Also, it was highlighted that while there were no cases of moderate to severe disease reported in those who received the vaccination, 20 people who received the placebo experienced moderate to severe disease.[41]

iNCOVACC

India's first intranasal Covid-19 vaccine, known as iNCOVACC (BBV154), delivers quick and painless coronavirus immunization. Bharat Biotech, the product's inventor, claims that by inducing a robust immune response, iNCOVACC prevents coronavirus infection as well as transmission.[25] Recombinant adenoviral vector vaccines are used in the nasal vaccine and restricted to adults (18+ age group) only.Those who have already had two doses of the vaccination will only now receive the new nasal vaccine as a booster dose.[26] Intranasal vaccinations are thought to be more effective because of this. With the dose supplied through the nose, which is where the virus enters our bodies for the first time, India's new nasal vaccine, iNCOVACC is hailed as having the power to break the cycle of transmission, stop infection, prevent lung damage, as well as other negative effects. The intranasal vaccines can also activate immune cells that remain near mucosal tissues in addition to T cells and B cells. Another form of antibody, known as IgA, is produced by the B cells found in the mucosal tissues and is crucial in the elimination of airway infections. Also, the nearby T cells have the ability to memorize the diseases they have encountered and will keep scouting the area where they were first discovered.[26]

Conclusion:

Recent research has shown that immunizing against COVID-19 with several vaccine types led to strong protective immunity in animal models. The encouraging outcomes greatly encouraged the assessment of them in clinical trials. Unfortunately, little is yet known about how IN vaccination with various vaccines affects the mucosal and systemic immune responses. To effectively deliver the intact forms of antigens towards target cells, significant effort must also be put into developing suitable mucosal adjuants and delivery vehicles with high efficacy and tolerability. Given that IN vaccinations have many advantages over IM vaccines, as was stated in the previous section, we should educate the public about the characteristics and immunological mechanisms of IN vaccines and give them a choice of immunization techniques. To put it simply, the IN-immunization method can produce sterile mucosal immunity and systemic immunity, significantly reducing the risk of virus infection and transmission. The use of IN vaccines should aid in the future management of the COVID-19 pandemic and other possible viral infectious diseases.

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PRECISION MEDICINE IN GYNECOLOGICAL CANCERS: ADVANCING PERSONALIZED THERAPEUTICS FOR IMPROVED OUTCOMES

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Abstract:
Precision medicine has revolutionized the landscape of oncology by shifting the paradigm from a one-size-fits-all approach to individualized, targeted treatment strategies. This chapter explores the evolving role of precision medicine in the management of gynecological cancers, with a focus on ovarian, endometrial, cervical, vaginal, and vulvar malignancies. It delves into the genomic and molecular underpinnings of these cancers, highlighting the significance of key mutations such as *BRCA1/2*, *TP53*, *PTEN*, *ARID1A*, and HPV-related genetic alterations. The integration of next-generation sequencing (NGS), liquid biopsy technologies, and molecular profiling has paved the way for the identification of actionable mutations and predictive biomarkers, enabling the application of targeted therapies and immunotherapies. The chapter also reviews the clinical impact of therapies such as PARP inhibitors, HER2-targeted agents, PI3K/AKT/mTOR inhibitors, and immune checkpoint inhibitors in various gynecologic malignancies. Furthermore, the application of artificial intelligence (AI) and big data analytics in precision oncology is discussed, showcasing how machine learning models are enhancing treatment response predictions and personalized care planning. The chapter also addresses ethical and socioeconomic challenges related to the accessibility, affordability, and equity of precision medicine, particularly in low-resource settings. Looking ahead, the future of gynecologic oncology lies in the integration of multi-omics data, gene editing technologies like CRISPR, and the development of personalized nanomedicine. By harnessing these innovations, precision medicine promises to redefine diagnosis, treatment, and survival outcomes for women affected by gynecological cancers.

Keywords: Precision Medicine, Gynecological Nursing, Targeted/Tailored Therapy, Personalised Cancer Treatment

Introduction:

Gynecological cancers, including ovarian, cervical, endometrial, vaginal, and vulvar cancers, account for a significant burden of morbidity and mortality worldwide. Traditional treatment strategies, such as surgery, chemotherapy, and radiation, have been the cornerstone of management. However, these approaches often lead to variable responses due to genetic, molecular, and environmental differences among patients. Precision medicine has revolutionized

cancer care by offering personalized therapeutic strategies based on an individual's genetic profile, tumor characteristics, and molecular biomarkers. By leveraging advancements in genomics, transcriptomics, and proteomics, precision medicine allows for targeted therapies, immunotherapy, and individualized treatment regimens. This approach not only enhances treatment efficacy but also minimizes adverse effects, improving overall patient outcomes.

This chapter explores the principles of precision medicine in gynecological cancers, current advancements, diagnostic approaches, targeted therapies, and the future landscape of personalized oncology in women's health.

Overview of Gynecological Cancers

Gynecological cancers refer to malignancies that originate in the female reproductive organs, including the ovaries, cervix, endometrium (uterus), vagina, and vulva. These cancers collectively contribute to a significant portion of cancer-related morbidity and mortality among women worldwide. Understanding their classification, epidemiology, risk factors, and treatment modalities is crucial for early detection, effective management, and the advancement of precision medicine approaches.

1. Classification, Prevalence and Risk Factors of Gynecological Cancers: Gynecological cancers are classified based on the organ of origin. The major types, prevalence and risk factors include:

Cancer Type	Description	Prevalence	Risk Factors
Cervical Cancer	Cancer of the cervix, the lower part of the uterus that opens into the vagina.	4th most common cancer in women globally	HPV infection, smoking, multiple sexual partners, weakened immune system
Endometrial Cancer	Cancer of the endometrium, the lining of the uterus.	Most common Gynecological cancer in developed countries	Obesity, diabetes, high blood pressure, history of breast cancer, hormone therapy
Ovarian Cancer	Cancer of the ovaries, the female reproductive organs that produce eggs.	7th most common cancer in women globally	Age, family history of ovarian, breast, or colorectal cancer, obesity, infertility
Vulvar Cancer	Cancer of the vulva, the external female genitalia.	Rare, accounting for about 5% of gynecological cancers	HPV infection, smoking, lichen sclerosus, history of cervical cancer
Vaginal Cancer	Cancer of the vagina, the muscular canal that leads from the cervix to the external genitalia.	Very rare, accounting for about 1% of gynecological cancers	HPV infection, smoking, history of cervical cancer, diethylstilbestrol (DES) exposure

2. Current Treatment Modalities and Their Limitations

2.1 Surgery: Standard treatment for early-stage gynecological cancers (e.g., hysterectomy for endometrial cancer, radical hysterectomy for cervical cancer).

- Limitations:
  - Invasive and associated with post-surgical complications.
  - Often not effective for advanced-stage cancers.

2.2 Chemotherapy:

- Common regimens:
  - Platinum-based chemotherapy (e.g., carboplatin, cisplatin) for ovarian and cervical cancers.
  - Paclitaxel and doxorubicin for advanced and recurrent cases.
- Limitations:
  - Non-specific cytotoxic effects lead to significant side effects (nausea, fatigue, myelosuppression).
  - Development of resistance in recurrent cancers.

2.3 Radiation Therapy:

- Widely used for cervical and vaginal cancers and in palliative settings.
- Limitations:
  - Side effects include radiation cystitis, bowel toxicity, and secondary malignancies.
  - Not always effective for metastatic disease.

2.4 Hormonal Therapy:

- Used in hormone receptor-positive endometrial cancers (e.g., progestins, aromatase inhibitors).
- Limitations:
  - Resistance can develop over time.

2.5 Targeted Therapy and Immunotherapy:

- PARP inhibitors (e.g., Olaparib, Niraparib) for BRCA-mutated ovarian cancer.
- Immune checkpoint inhibitors (Pembrolizumab, Atezolizumab) for MSI-high and PD-L1-positive tumors.
- Limitations**:**
  - Expensive and not universally accessible.
  - Not all patients respond to targeted agents.

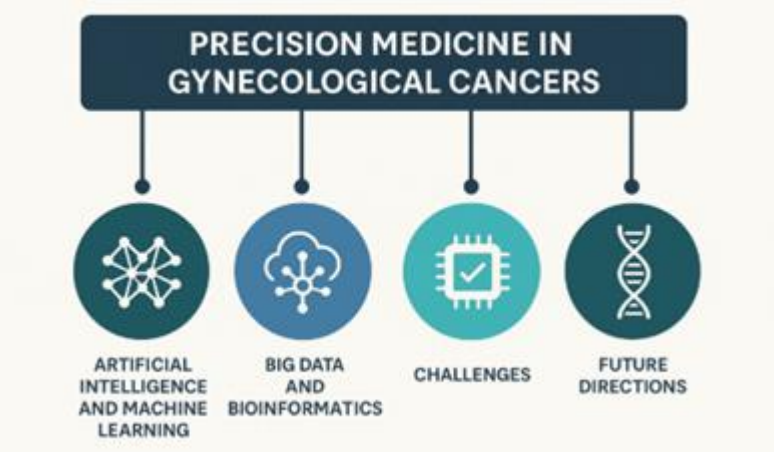
The Role of Precision Medicine in Oncology

1.1 Definition and Principles of Precision Medicine

Precision medicine is a modern approach to disease treatment and prevention that considers an individual's genetic makeup, lifestyle, and environmental factors. Unlike the traditional "one-

size-fits-all" approach, precision medicine tailors treatment strategies based on a patient's molecular and genetic profile.

In oncology, this means identifying specific genetic mutations or biomarkers in cancer cells to develop targeted therapies that improve efficacy and reduce adverse effects.



Key Principles of Precision Medicine

1. **Genomic Profiling:**
   - Identifies genetic mutations and molecular alterations in tumors.
   - Enables the selection of targeted therapies.
2. **Biomarker-Driven Treatment:**
   - Uses predictive and prognostic biomarkers to guide therapy choices.
   - Examples: HER2 status in breast cancer, BRCA mutations in ovarian cancer.
3. **Targeted Therapies:**
   - Designed to attack specific genetic mutations or signaling pathways.
   - Examples: PARP inhibitors for BRCA-mutated ovarian cancer.
4. **Immunotherapy:**
   - Utilizes the patient's immune system to recognize and attack cancer cells.
   - Examples: PD-1/PD-L1 inhibitors for cervical and endometrial cancers.
5. **Comprehensive Data Integration:**
   - Combines genomic, proteomic, and clinical data for personalized treatment decisions.

1.2 Evolution of Precision Medicine in Cancer Treatment

- **Early Approaches to Cancer Treatment:** Traditionally, cancer treatment relied on surgery, chemotherapy, and radiation therapy, with protocols based on tumor location and stage. Many patients received non-specific therapies, leading to variable responses and significant side effects.
- **Advances in Molecular Oncology and Genomics**
  - **1990s:** The discovery of oncogenes (e.g., BRCA1, BRCA2, HER2) revolutionized cancer classification.

- **2000s:** Completion of the Human Genome Project and advancements in next-generation sequencing (NGS) enabled detailed tumor profiling.
- **2010s - Present:** Introduction of targeted therapies, immunotherapies, and liquid biopsy techniques.

- **Landmark Developments in Precision Oncology**
  - HER2-targeted therapy (Trastuzumab) revolutionized breast cancer treatment.
  - BRCA-targeted therapy (PARP inhibitors) improved ovarian cancer survival.
  - Mismatch repair (MMR) deficiency testing led to immunotherapy advancements in endometrial cancer
- **Current Innovations**
  - Artificial intelligence (AI) and machine learning aid in treatment selection.
  - Organoid models and 3D cell cultures allow personalized drug testing.
  - CRISPR gene editing holds promise for future precision oncology interventions.

1.3 How Precision Medicine is Reshaping Gynecological Cancer Care: Precision medicine is transforming the management of gynecological cancers (ovarian, endometrial, and cervical) through advanced diagnostics, targeted therapies, and immunotherapies.

- **Ovarian Cancer**
  - **BRCA1/BRCA2 Mutation Testing:** Identifies patients for **PARP inhibitors** (e.g., olaparib, niraparib).
  - **Homologous Recombination Deficiency (HRD) Testing:** Helps select patients for platinum-based chemotherapy and maintenance therapy.
  - **Angiogenesis Inhibitors (Bevacizumab):**Targets VEGF to prevent tumor blood supply.
- **Endometrial Cancer**
  - **Molecular Subtyping (The Cancer Genome Atlas – TCGA Classification):** POLE-ultramutated (good prognosis), MSI-H (immune-responsive, benefits from PD-1 inhibitors like pembrolizumab) and Copy-number high (p53-mutated, aggressive).
  - **Immunotherapy for Mismatch Repair Deficiency (dMMR):** dMMR tumors respond well to **immune checkpoint inhibitors** (e.g., nivolumab).
- **Cervical Cancer**
  - **HPV-Driven Precision Strategies:** HPV vaccines (Gardasil, Cervarix) prevent infection and associated cancers and HPV genotyping identifies high-risk strains.
  - **Immunotherapy (PD-1 Inhibitors):** Pembrolizumab (approved for advanced cervical cancer).

Genomic and Molecular Basis of Gynecological Cancers

Gynecological cancers, including ovarian, endometrial, and cervical cancers, are driven by various genetic mutations and molecular alterations. Understanding these changes is crucial for developing targeted therapies and improving treatment outcomes.

- **Role of Genetic Mutations in Gynecological Cancers**

  Genetic mutations play a key role in the development and progression of gynecological malignancies. These mutations can be inherited (germline) or acquired (somatic). Advances in genomic sequencing have identified key oncogenes and tumor suppressor genes involved in these cancers, leading to better classification and personalized treatment strategies.
- **BRCA1 and BRCA2 in Ovarian Cancer**
  - **BRCA1 and BRCA2** are tumor suppressor genes involved in DNA repair via homologous recombination.
  - Mutations in these genes significantly increase the lifetime risk of ovarian and breast cancers.
  - **BRCA-mutated ovarian cancers** are often sensitive to platinum-based chemotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib and niraparib.
  - **Genetic Testing:** BRCA mutation testing is recommended for ovarian cancer patients to guide treatment and preventive strategies, such as risk-reducing surgery.
- **TP53, PTEN, and ARID1A in Endometrial Cancer**
  - **TP53 Mutations:** Found in Type II endometrial cancers (serous carcinoma), leading to aggressive tumor behavior and poor prognosis.
  - **PTEN Mutations:** Frequently seen in Type I endometrial cancers (endometrioid carcinoma), PTEN loss results in uncontrolled cell proliferation.
  - **ARID1A Mutations:** Associated with defects in chromatin remodeling, found in 20–40% of endometrial and ovarian clear cell carcinomas.
- **Implications for Treatment:**
  - PI3K/AKT/mTOR pathway inhibitors are being explored for PTEN-deficient endometrial cancers.
  - Immune checkpoint inhibitors (PD-1/PD-L1 blockade) show promise in mismatch repair-deficient (dMMR) endometrial cancers.
- **HPV-Related Genetic Changes in Cervical Cancer**
  - **High-risk HPV types (16, 18, 31, 33, etc.)** integrate their viral DNA into the host genome, causing oncogenic changes.
  - **Key Genetic Alterations:**
    - **E6 protein:** Degrades p53, preventing apoptosis.

- **E7 protein:** Inactivates RB1 (retinoblastoma protein), leading to uncontrolled cell proliferation.

- **Clinical Implications:**
  - **HPV testing and vaccination** (Gardasil, Cervarix) are effective in preventing cervical cancer.
  - **Immunotherapy (PD-1 inhibitors)** is emerging as a promising treatment option for recurrent/metastatic cervical cancer.

- **Importance of Molecular Subtyping in Treatment Selection**

  Advancements in molecular profiling have led to improved subtyping of gynecological cancers, allowing for personalized treatment strategies:

  1. **Endometrial Cancer (TCGA Classification):**
     - POLE-ultramutated
     - MSI-H (Mismatch Repair Deficient)
     - Copy-number low (Endometrioid, PTEN-mutated)
     - Copy-number high (Serous, TP53-mutated)
  2. **Ovarian Cancer Subtypes:**
     - High-grade serous (p53 mutations, BRCA-associated)
     - Low-grade serous (KRAS, BRAF mutations)
     - Endometrioid (ARID1A, PTEN mutations)
     - Clear cell (HNF1B, ARID1A mutations)
  3. **Cervical Cancer:**
     - HPV-positive squamous cell carcinoma
     - HPV-negative adenocarcinoma
     - Neuroendocrine small cell carcinoma (rare, aggressive)

- **Clinical Significance:**
  - **Molecular classification** guides the use of targeted therapies, immunotherapies, and chemotherapy regimens.
  - **Liquid biopsy and next-generation sequencing (NGS)** are emerging tools to detect genetic mutations for real-time monitoring and treatment adjustments.

Diagnostic and Predictive Biomarkers in Gynecological Cancers

Biomarkers play a crucial role in the early detection, prognosis, and treatment selection for gynecological cancers, including ovarian, endometrial, and cervical cancers. Advances in molecular diagnostics, including next-generation sequencing (NGS), liquid biopsy, and immunohistochemistry (IHC), have significantly improved precision oncology.

1. Role of Next-Generation Sequencing (NGS) in Identifying Actionable Mutations

What is NGS?

Next-generation sequencing (NGS) is a high-throughput technology that enables comprehensive genomic profiling by analyzing multiple genes simultaneously. It is widely used to detect mutations, copy number variations, and gene fusions in cancer.

Applications of NGS in Gynecological Cancers

- **Ovarian Cancer:**
    - Detects BRCA1/BRCA2 mutations for selecting PARP inhibitors.
    - Identifies homologous recombination deficiency (HRD) status.
- **Endometrial Cancer:**
    - Determines POLE, PTEN, and PIK3CA mutations for molecular subtyping.
    - Assesses microsatellite instability (MSI) and mismatch repair deficiency (dMMR) for immunotherapy response.
- **Cervical Cancer:**
    - Identifies HPV genotypes and mutations in PIK3CA, TP53, and EGFR for targeted therapy selection.

Clinical Impact of NGS

- **Personalized Treatment:** Identifies specific mutations that guide targeted therapy.
- **Prognostic Insights:** Determines tumor aggressiveness and potential resistance to therapy.
- **Therapeutic Resistance Monitoring:** Detects emerging mutations associated with drug resistance.

2. Liquid Biopsy and Circulating Tumor DNA (ctDNA)

What is Liquid Biopsy?

Liquid biopsy is a minimally invasive technique that detects circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles from a patient's blood sample. It allows real-time monitoring of tumor dynamics.

Benefits of Liquid Biopsy

- Early Cancer Detection: Identifies genetic alterations before tumor progression.
- Real-Time Treatment Monitoring: Tracks tumor evolution and therapy response.
- Minimal Invasiveness: Eliminates the need for repeated tissue biopsies.

Applications in Gynecological Cancers

- **Ovarian Cancer:**
    - Detects BRCA mutations and HRD-associated genetic alterations.
    - Monitors resistance to PARP inhibitors and platinum-based chemotherapy.

- **Endometrial Cancer:**
  - Identifies ctDNA mutations (e.g., PTEN, PIK3CA, and ARID1A).
  - Monitors tumor recurrence and progression.
- **Cervical Cancer:**
  - Detects HPV DNA for early-stage diagnosis and post-treatment surveillance.
  - Monitors response to immunotherapy and chemotherapy.

Clinical Significance of ctDNA

- Predicts Disease Progression: Increased ctDNA levels correlate with tumor burden.
- Guides Targeted Therapy: Identifies emerging mutations for adaptive treatment strategies.
- Assesses Minimal Residual Disease (MRD): Helps in post-treatment surveillance to detect relapse.

3. Immunohistochemistry (IHC) and Molecular Profiling for Targeted Therapy Selection

What is IHC?

Immunohistochemistry (IHC) is a laboratory technique that uses antibody-based staining to detect specific protein biomarkers in tumor tissue. It is widely used to guide targeted therapies in gynecological cancers.

Key IHC Markers in Gynecological Cancers

Cancer Type	Biomarker	Targeted Therapy
Ovarian Cancer	BRCA1/2	PARP inhibitors (Olaparib, Niraparib)
Ovarian Cancer	p53	Prognostic indicator
Endometrial Cancer	ER/PR	Hormonal therapy (Progestins, Tamoxifen)
Endometrial Cancer	HER2	Trastuzumab (HER2+ aggressive tumors)
Cervical Cancer	PD-L1	Immune checkpoint inhibitors (Pembrolizumab)
Cervical Cancer	HPV E6/E7	Prognostic marker for HPV-driven cancers

Molecular Profiling in Gynecological Cancers

Molecular profiling integrates **IHC, NGS, and RNA sequencing** to categorize tumors based on genetic and protein expression patterns.

- **Helps in Classifying Tumors:**
  - Endometrial cancer: POLE-mutated, MSI-H, Copy-number high (p53-mutated).
- **Identifies Drug Sensitivities:**
  - Ovarian cancer: HRD-positive tumors benefit from PARP inhibitors.
- **Predicts Treatment Response:**
  - PD-L1 expression in cervical cancer predicts immunotherapy efficacy.

4. Microsatellite Instability (MSI) and Mismatch Repair Deficiency (dMMR) in Endometrial Cancer

What is MSI and dMMR?

- Microsatellite instability (MSI) refers to the accumulation of mutations in repetitive DNA sequences due to defective DNA repair mechanisms.
- Mismatch repair deficiency (dMMR) results from mutations in genes like MLH1, MSH2, MSH6, and PMS2, leading to MSI.

Significance of MSI/dMMR in Endometrial Cancer

- MSI-High (MSI-H) tumors respond well to immunotherapy.
- MSI status determines prognosis:
  - MSI-H tumors have a better response to immune checkpoint inhibitors (Pembrolizumab, Nivolumab).
  - dMMR tumors are more aggressive but immunotherapy-sensitive.

Clinical Testing for MSI/dMMR

- IHC Analysis: Detects loss of MMR protein expression.
- PCR-based MSI Testing: Identifies microsatellite instability.
- NGS-based Testing: Detects MSI along with other mutations.

Impact on Treatment Decisions

- MSI-H/dMMR tumors are resistant to conventional chemotherapy but respond well to immunotherapy.
- Non-MSI-H tumors may benefit more from hormonal therapy or targeted agents.

5. Targeted Therapies and Immunotherapy in Gynecological Cancers

Precision medicine in gynecological oncology is increasingly focusing on molecular-targeted treatments and immunotherapy. These therapeutic strategies aim to inhibit cancer growth by specifically interfering with molecular pathways involved in tumor progression, while minimizing harm to normal cells.

5.1 Targeted Therapies

Targeted therapies are drugs designed to interact with specific molecules or pathways that are overactive or mutated in cancer cells. These include inhibitors of DNA repair enzymes, cell signaling pathways, and angiogenesis factors.

a. Poly (ADP-ribose) Polymerase (PARP) Inhibitors: PARP inhibitors block the PARP enzyme, which helps repair single-strand DNA breaks. In cancer cells with BRCA1/2 mutations or homologous recombination deficiency (HRD), this results in accumulation of DNA damage and cell death—a concept known as synthetic lethality.

- **Olaparib**: FDA-approved for maintenance therapy in BRCA-mutated ovarian cancer and as a first-line maintenance in combination with bevacizumab for HRD-positive cases.

- **Niraparib**: Approved for all patients (regardless of BRCA status) as maintenance therapy following platinum-based chemotherapy response.
- **Rucaparib**: Used in relapsed ovarian cancer and for maintenance therapy in BRCA-mutant tumors.

Clinical Relevance:

- Improves progression-free survival in high-grade serous ovarian cancer.
- Can delay or prevent recurrence in platinum-sensitive disease.

b. HER2-Targeted Therapy: HER2 (human epidermal growth factor receptor 2) is overexpressed in a subset of serous endometrial and clear cell carcinomas. HER2 amplification leads to increased tumor growth and poor prognosis.

- **Trastuzumab**: A monoclonal antibody that targets the HER2 receptor.
    - Approved for HER2-positive endometrial cancer, particularly in combination with carboplatin and paclitaxel.
    - Shows promise in serous uterine carcinoma with HER2 amplification.

c. PI3K/AKT/mTOR Inhibitors: The PI3K/AKT/mTOR pathway is often dysregulated in endometrial cancer, especially with PTEN mutations and PIK3CA alterations.

- **Alpelisib**: A PI3K-alpha inhibitor showing activity in PTEN-deficient or PIK3CA-mutated tumors.
- Other investigational agents include everolimus and temsirolimus, targeting mTOR.

Clinical Potential:

- Under investigation in recurrent or advanced endometrial cancer.
- Combination with hormonal therapy or ICIs is showing encouraging outcomes.

d. Anti-Angiogenic Therapy: Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis. VEGF (vascular endothelial growth factor) is a key target in this process.

- **Bevacizumab**: A monoclonal antibody that inhibits VEGF-A.
    - Approved for use in platinum-resistant ovarian cancer.
    - Shows benefit in advanced cervical cancer, especially in combination with chemotherapy.

5.2 Immunotherapy

Immunotherapy aims to stimulate the patient's immune system to recognize and attack tumor cells. Immune checkpoint inhibitors (ICIs) and cancer vaccines have changed the treatment paradigm for several gynecological cancers.

a. Immune Checkpoint Inhibitors (ICIs)

Immune checkpoints such as **PD-1/PD-L1 and CTLA-4** are regulatory molecules that prevent overactivation of T-cells. Many tumors exploit these checkpoints to evade immune detection.

- **Pembrolizumab**: FDA-approved for MSI-high (MSI-H) or mismatch repair-deficient (dMMR) tumors in endometrial cancer and also used in PD-L1 positive cervical cancer, often in combination with chemotherapy (KEYNOTE-826 trial).
- **Atezolizumab**: A PD-L1 inhibitor showing activity in recurrent or metastatic cervical cancer. Being evaluated in combination with bevacizumab and other agents.

b. Cancer Vaccines: Cancer vaccines either prevent infection-associated cancers or stimulate immune responses against tumor-specific antigens.

- **HPV Vaccines**: Prevent cervical, vaginal, vulvar, and some anal cancers by protecting against high-risk HPV types (e.g., 16 and 18). Widely recommended as a primary prevention strategy in adolescents and young adults.
- **Personalized Tumor Vaccines**: Experimental approach using patient-specific tumor antigens. Tailored to individual's tumor neoantigen profile. Currently in early-phase clinical trials for recurrent gynecologic cancers.

6. Role of Artificial Intelligence and Big Data in Precision Oncology

The convergence of artificial intelligence (AI), big data, and bioinformatics has become a transformative force in precision oncology, enabling more accurate, efficient, and individualized care in gynecological cancers.

6.1 Application of AI and Machine Learning in Predicting Treatment Responses

AI algorithms, particularly machine learning (ML) models, are being trained to:

- Analyze large genomic datasets to identify mutation patterns.
- Predict therapeutic outcomes based on tumor genetics, histopathology, and clinical parameters.
- Identify resistance markers to chemotherapy and immunotherapy.

For example:

- ML models can predict BRCA mutation status or MSI status from histology slides.
- Deep learning tools assist in automated image analysis, improving diagnostic accuracy and reducing pathologist workload.

6.2 Role of Big Data and Bioinformatics in Personalized Treatment Plans

Big data in oncology includes Genomic sequences, Electronic Health Records (EHRs), Imaging data and Lifestyle and environmental exposures. Through bioinformatics pipelines, this data is processed to:

- Match patients with targeted therapies.
- Stratify patients into molecular subtypes.
- Develop real-time clinical decision support tools.

Case example: Databases like The Cancer Genome Atlas (TCGA) and AACR GENIE help clinicians select targeted agents based on tumor mutational profiles.

6.3 Enhancing Clinical Decision-Making with AI-Driven Predictive Models

AI-based clinical decision support systems (CDSS) use predictive analytics to:

- Recommend individualized treatment regimens.
- Assess recurrence risks and survival probabilities.
- Flag patients for clinical trials based on eligibility criteria.

These tools reduce clinical uncertainty, especially in complex cases where treatment options depend on a multitude of biological and clinical variables.

7. Challenges and Ethical Considerations in Precision Medicine

While precision medicine holds immense promise, several practical and ethical challenges hinder its equitable and widespread implementation.

7.1 Accessibility and Cost-Effectiveness of Precision Medicine

- Genomic sequencing and targeted therapies remain expensive and are often unavailable in low-resource settings.
- Insurance coverage is limited in many regions, preventing widespread uptake.
- High cost of companion diagnostics, such as NGS panels or biomarker assays, further limits access.

7.2 Ethical Issues in Genetic Testing and Patient Privacy

- Informed consent is crucial when performing genomic testing due to implications for family members.
- Concerns over data security and potential misuse of genetic information (e.g., by insurers or employers).
- Patients must be educated on the potential for incidental findings, such as predispositions to other hereditary conditions.

7.3 Addressing Racial and Socioeconomic Disparities

- Ethnic minorities are underrepresented in genomic research and clinical trials.
- Many reference genomes and datasets lack diversity, leading to biased treatment outcomes.
- Socioeconomic factors limit access to advanced diagnostics and personalized treatments, perpetuating health inequities.

Efforts are needed to build inclusive genomic databases and ensure fair access to innovations in precision oncology.

8. Future Directions in Precision Medicine for Gynecological Cancers

The future of gynecologic oncology lies in the integration of next-generation technologies, multimodal data, and personalized therapeutic approaches.

8.1 Emerging Trends in Gene Editing (CRISPR) for Targeted Cancer Therapy

- CRISPR-Cas9 allows for precise editing of cancer-related genes such as TP53, BRCA, or PTEN.
- Promising applications in:
  - Silencing oncogenes
  - Enhancing T-cell therapies
  - Sensitizing tumors to chemotherapy

While still largely in preclinical or early clinical stages, gene editing could revolutionize cancer therapy.

8.2 Integration of Multi-Omics Data (Genomics, Proteomics, Metabolomics)

- Combining genomic (DNA), transcriptomic (RNA), proteomic (proteins), and metabolomic (metabolites) data offers a comprehensive view of tumor biology.
- Enables:
  - More accurate tumor classification
  - Identification of new therapeutic targets
  - Better understanding of drug resistance mechanisms

Advanced AI tools are being developed to handle this multi-dimensional data and extract actionable insights.

8.3 Advances in Personalized Nanomedicine for Drug Delivery

- Nanoparticles can be engineered to deliver drugs specifically to tumor cells, bypass biological barriers and reduce off-target toxicity
- Emerging nanotherapies are being designed for BRCA-mutated ovarian cancer, HER2-positive endometrial cancer, and more.

8.4 Expanding Clinical Trials for Precision Oncology in Gynecological Cancers

- Rise of basket trials (targeting specific mutations across cancer types) and umbrella trials (different treatments for subtypes within one cancer).
- Increasing focus on adaptive trial designs, which evolve based on interim results.
- Global efforts to ensure diverse patient inclusion and real-world applicability of findings.

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Advances in Pharma and Health Science Research Volume I

ISBN: 978-93-48620-46-0

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Bhumi Publishing

ISBN 978-93-48620-46-0

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