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Review Article

Novel Strategies in Drug Delivery System: A Review

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ABSTRACT

This review article illustrates the various ways that various drugs can be administered. The mechanism via which a medication enters the body to treat a variety of illnesses or conditions is referred to in pharmacology as the route of administration. The different ways of delivery affect the drug's bioavailability. The classification of administration routes, along with their key characteristics, benefits, drawbacks, and illustrations, are included in this article. There has also been discussion of the latest developments in medication preparations administered using these methods. NDDS defines a method of drug delivery that differs from the traditional drug delivery system. It blends state-of-the-art methodology with novel dosage forms that outperform customary dosage forms. In the field of pharmaceutical sciences, the creation of innovative medication delivery methods has drawn more attention lately. By administering medications to specified targets in a regulated and targeted manner, these systems hope to increase the effectiveness and safety of pharmaceuticals. A medication's performance can be significantly improved by changing from a standard form to a unique delivery mechanism in terms of patient adherence, safety, and efficacy. It is possible to revitalize an existing pharmaceutical chemical by creating a novel therapeutic delivery system. A well-designed innovative drug delivery system can significantly lessen the difficulties associated with releasing a medication at a certain location and tempo. Pharmaceutical firms are striving to create novel drug delivery methods in response to the need to provide patients their drugs efficiently and with the fewest possible negative effects. This article discusses the principles of innovative drug delivery systems and the various types of these systems.

INTRODUCTION

The effectiveness of a medication can be greatly impacted by how it is given. Certain drugs have an ideal concentration range where the greatest benefit is received; concentrations above or below this range may be dangerous or fail to produce any therapeutic benefit On the other hand, the very

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modest progress in the efficacy of treating serious diseases has shown that a multidisciplinary approach to medicine delivery to targets in tissues is becoming more and more necessary. As a result, novel ideas for controlling the pharmacokinetics, pharmacodynamics, immunogenicity, bioavailability, and efficacy of drugs were developed. These novel techniques—often referred to as drug delivery systems. Drug delivery and targeting systems are now being developed in a variety of ways to lower drug loss and degradation, avoid adverse effects, increase medication bioavailability, and increase the amount of the drug that accumulates in the required zone[1]. The novel dose forms and advanced technology known as NDDS are considerably superior than traditional dosage forms. For almost two decades, scientists have acknowledged the potential benefits of nanotechnology in bringing about substantial improvements in drug delivery and targeting. Other drug delivery strategies concentrate on finding safe and effective ways to deliver protein drugs outside of the gastrointestinal tract, where they may degrade, or on overcoming particular delivery barriers, such as the blood-brain barrier (BBB), to better target the drug and increase its efficacy. The term Novel Drug Delivery System refers to a method of administering medication that differs from traditional drug delivery systems. It blends state-of-the-art methodology with novel dosage forms that outperform customary dosage forms. NDDS leads to methodologies, formulations, technologies, and systems that are used for this purpose. In any case, it might also entail supporting systematic pharmacokinetics. It usually has to do with how much and how long the medication has been present. It also contains the body's particular scientific site targeting. The efficacy of the medication may be significantly impacted by these novel methods for drug delivery. New methods for controlling a drug's pharmacokinetics, pharmacodynamics, toxicity, immunological response, biorecognition, and efficacy have therefore appeared[2].

There are several advantages of novel drug delivery systems over conventional drug delivery.

1. Optimum therapeutic- drug concentration in the blood or tissue maintained over a prolonged period of time.
2. Pre- determined release rates of extended period of time may be achieved.
3. Duration for short half- life drug may be increased
4. By targeting the site of action, side effects may be eliminated.
5. Frequent dosing and wastage of the drug may be reduced or excluded.
6. Better patient compliance may be ensured.

Need of NDDS

Unlike conventional dosing forms, it does not result in fluctuations in the drug level in the blood. NDDS is a sophisticated drug delivery technology that has shown promise in terms of drug effectiveness, regulated drug release for a long-lasting effect, and targeting specific tissues in ants. To reduce unwanted effects and optimize therapeutic benefits, it keeps the drug's concentration within a therapeutic window. Some medications, like vaccines, proteins, and antibodies, may not be absorbed through the regular channels due to poor bioavailability and enzymatic breakdown. These flaws have been addressed by NDDS[3].

DIFFERENT ROUTES OF DRUG ADMINISTRATION.

The route of administration of a medication directly affects the drug bioavailability, which

determines both the start and the duration of the pharmacological effect. Some considerations must be taken into account when designing a drug dosage form:

1. Intended route of administration.
2. Amount or dose to be administered.
3. Anatomical and physiological characteristics (membrane permeability, blood flow) of the site of absorption
4. Physicochemical properties of the site, such as pH and osmotic pressure of physiological fluids.
5. Potential effect of the medication over the site of administration.

A medication administration route is often classified by the location at which the drug is administered, such as oral or intravenous. The choice of routes in which the medication is given depends not only on convenience and compliance but also on the drug's pharmacokinetics and pharmacodynamic profile. Each medication administration route has unique contraindications. Therefore, it is crucial to understand the characteristics of the various routes and associated techniques. When the systemic absorption of a drug is desired, medications are usually administered by two main routes: the parental route (through skin by injection, avoiding the digestive system) and the enteral route (directly at some point of the gastrointestinal tract). To a lesser extent, the pulmonary (or respiratory) and nasal routes are employed. Other routes of administration, such as ophthalmic and vaginal, are not included here because their application is almost exclusive for local (not systemic) drug administration.

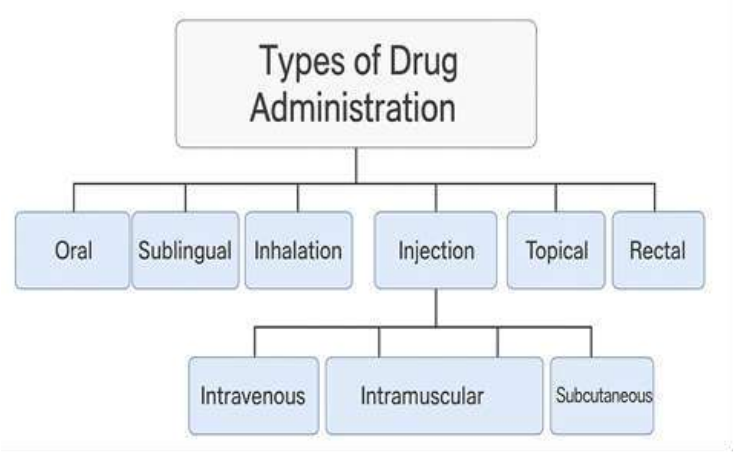

Figure 1: Different routes of drug administration

Enteral Routes of Medication

Oral

This is convenient and indicated for patients who can ingest and tolerate oral medication. Medication given orally has a slower onset, typically about 30-60 minutes. Some medications with short half-lives are administered orally as timed-release or sustained-release forms that get absorbed over several hours. If the patient has difficulty swallowing (dysphagia), tablets are typically crushed and placed in a substance like applesauce or pudding for easier swallowing (based on the patient's prescribed diet). However, it is important to verify that a tablet may be crushed by consulting a drug reference or a pharmacist. For example, medications such as enteric-coated tablets, capsules, and sustained-release or long-acting drugs should never be crushed because doing so will affect the intended

action of the medication. In this event, the provider must be contacted for a change in route.

Advantages:

- Ease of administration
- Widespread acceptance by the patients
- Absorption takes place along the whole length of GI tract.
- Economical as compared with other parenteral route.

Disadvantages:

- Variable absorption rates
- Degradation of some drugs before reaching the site of absorption into the bloodstream
- The inability of many compounds to effectively traverse the intestinal epithelial membrane cells to reach the bloodstream.
- Irritation of the mucous lining of the gastrointestinal tract.

Sublingual and Buccal Routes

These are indicated for medications with high first-pass metabolism that need to avoid clearance by the liver.

Sublingual route :- In this route of administration the drug is placed under the tongue. And it is taken without the use of water. When it is placed under the tongue it disintegrates there and then absorption occurs in mouth. The tablets are small in size which is to be used through the sublingual route. Example of Sublingual tablet is Nitroglycerine tablets (nitroglycerin is cleared more than 90% during a single pass through the liver)

Buccal Route :- In this route of administration the drug is kept in the buccal cavity where it disintegrates and absorption occurs in the mouth[4].

Advantages:

- Rapid absorption is due to the abundant mucosal network of systemic veins and lymphatics, thereby leading to a rapid onset of action.
- If there is any untoward event, the tablet can be removed.
- Avoids first-pass hepatic metabolism.
- This route is useful in patients having swallowing difficulties.
- Convenience

Disadvantages:

- The tablet must be kept in the buccal cavity and neither chewed nor swallowed.
- Excessive salivation may cause quick dissolution and absorption of the tablet.
- Patients may find it difficult to accept an unpalatable tablet. Hence some drugs are applied as a patch or a spray[5].

Rectal Route

This route is useful for patients with gastrointestinal motility problems such as dysphagia or ileus that can interfere with delivering the drug to the intestinal tract. The rectal route is also often utilized in patients near the end of life undergoing hospice care.

Advantages:

- A relatively large amount of the drug can be administered.
- Those drugs destroyed by the acidic medium in the stomach and those metabolized by pancreatic enzymes can be administered effectively.
- Safe and convenient for infants and the elderly.

- It can be used in emergency situations, such as in infants having seizures when the intravenous route is unavailable.
- The rate of absorption is uninfluenced by the ingestion of food or the rate of gastric emptying.
- Bypasses hepatic metabolism
- Less degradation of drugs compared to that in the upper gastrointestinal tract.

Disadvantages:

- Some hydrophilic drugs like antibiotics and peptide drugs are unsuitable for rectal administration as they are not readily absorbed.
- Some drugs can cause rectal irritation and proctitis, leading to ulceration and bleeding.

Parenteral Routes of Medication

Intravenous Route

This directly administers the medications to the systemic circulation. It is indicated when a rapid drug effect is desired, a precise serum drug level is needed, or when drugs are unstable or poorly absorbed in the gastrointestinal tract. It is also the route utilized in patients with altered mental status or severe nausea or vomiting, unable to tolerate oral medications[5].

Advantages:

- Rapid onset of action
- Predictable way of action and almost complete bioavailability
- The problems of oral drug administration can be eliminated by avoiding the gastrointestinal tract
- The best way of administration in very ill and comatose patients who cannot ingest anything orally

Disadvantages:

- Causes pain
- Chance of infection
- The delivery of protein products that require sustained levels can be difficult.

Intramuscular Route

This can be utilized when oral drug absorption occurs in an erratic or incomplete pattern, the drug has high first-pass metabolism, or the patient is not compliant. A depot preparation of the drug can be given intramuscularly, and the medication dissolves slowly into the circulation to provide a sustained dose over a more extended time. An example includes haloperidol decanoate. Vaccines are also administered via the intramuscular route[6].

Disadvantages:

- Injection site pain
- The amount of drug administered has to be adjusted according to the mass of the muscle available.
- Peptides get degraded locally.
- Complications - hematoma, abscess, peripheral nerve injury, puncture of a blood vessel leading to inadvertent intravascular administration.

Subcutaneous Route

In this route of administration the drug is given into the subcutaneous layer with the help of injection. Drug once reaches to the subcutaneous layer crosses the membrane and absorbs into the blood. This is used when the drug's molecular size is too large to be effectively absorbed in the intestinal tract or when better bioavailability or a faster absorption rate is needed than the oral route. It is easy to administer and requires minimal skills, so patients can often self-administer the

medication. Common medications administered subcutaneously include insulin, heparin, and monoclonal antibodies. The rate of absorption of drugs through this route can be enhanced by infiltration with the enzyme hyaluronidase. The major factors that affect the rate of absorption by this route include the size of the molecules (large molecules having slow penetration), viscosity, and the anatomical characteristics of the site of injection (vascularity and amount of fatty tissue).

Disadvantages:

- The rate of absorption is difficult to control.
- Local complications - irritation and pain.
- Injection sites must be changed frequently to prevent the build-up of unabsorbed medication, which could lead to tissue injury[7].

Other Routes of Medication

Intranasal Route

This can be utilized in administering nasal decongestants for cold or allergy treatment. Other uses include desmopressin for the treatment of diabetes insipidus or intranasal calcitonin for the treatment of osteoporosis[5]

Factors that affect the rate of absorption of drugs via the nasal route are:

- The rate of nasal secretion - The rate of secretion is inversely proportional to bioavailability of drug.
- Ciliary movement - The speed of ciliary movement is inversely proportional to the bioavailability of the drug.
- Vascularity of the nose - The volume of blood flow is directly proportional to the rate of drug absorption.
- Metabolism of drugs in the nasal cavity - The enzymes present in the nasal tissues alter the absorption of some compounds, especially peptides that are disintegrated by aminopeptidases.
- Diseases affecting nasal mucous membrane. Common colds can affect nasal drug absorption.

Enhancement of nasal drug delivery:

Rapid mucociliary clearance can lead to poor bioavailability of the drug. This can be overcome by in situ gelling drug delivery. Chitosan is a natural bioadhesive polysaccharide obtained from crustacean shells that can be used as an absorption enhancer. Chitosan binds to the nasal mucosal membrane and facilitates drug absorption through paracellular transport and other mechanisms.

Advantages:

- Increased permeability of the nasal mucosa compared to the gastrointestinal mucosa.
- Highly vascularized sub epithelial tissue.
- Quick absorption, usually within thirty minutes
- Avoids the first-pass effect.
- Ease of administration.
- Higher bioavailability of the drugs than in the case of the enteral route or inhalational route.

Disadvantages:

- Nasal cavity diseases and conditions may result in impaired absorption.
- The dose is limited due to the small area available for absorption.
- The time available for absorption is limited.
- This route does not apply to all drugs.

Inhalational Route

The structure of the airways, with rich capillary bed of the alveoli, allows air to come in close

contact with the blood. This makes drug administration through the airways, in the form of inhalation or aerosol, a useful route. Inhalation therapies have been used successfully for years, providing rapid relief for respiratory illnesses such as asthma and chronic obstructive pulmonary disease (COPD)

Advantages:

- Large surface area
- Proximity to blood flow
- Avoids first-pass hepatic metabolism
- Only smaller doses are enough to achieve equivalent therapeutic effects as the oral route
- There is greater protection against drug degradation by oxygen and moisture, so stability is increased.

Disadvantages:

- The transport of drug to the site of action is not guaranteed.
- There may be drug irritation and toxicity.
- Drug retention and drug clearance may be a problem.
- Only 10–40% of the drug from a conventional inhalation device is actually deposited in the lungs.
- Targeting specificity is questionable[8].

Transdermal Route

Transdermal therapeutic systems are defined as a type of dosage form which when applied to the intact skin; deliver the drug through the skin at a controlled rate to the systemic circulation. The drug enters the systemic circulation through a process known as Percutaneous Absorption which involves the passive diffusion of substances across the skin. This permeation of drug can take place through:

1. Passage through epidermis itself (Trans epidermal)
2. Diffusion through widely distributed hair follicles and sweat glands (Trans follicular)[9,10]

Advantages

- Provides smooth plasma concentrations of the drug without fluctuations, for a long period.
- Minimizes inter-individual variations as drug is subjected to little first pass metabolism
- Fewer side effects thereby increasing the therapeutic value of many drugs.
- Equivalent therapeutic effect can be elicited with less amount of dose if given as a transdermal patch.
- Drug intake can be stopped at any point by simply removing the transdermal patch.
- Self- administration is possible.
- Patient compliance is better as many patients prefer transdermal patches to oral tablets of same drug[11]

Disadvantages

- Only lipophilic drugs can effectively cross the stratum corneum and hence the drugs must have some desirable physicochemical properties for penetration. Hydrophilic drugs will not be able to reach the systemic circulation unless modified to some suitable form.
- Doses of only 5mg or less can be administered in a day.
- Large numbers of excipients used may cause rashes, local irritation, erythema or contact dermatitis. E.g.: Scopolamine patches used to

treat motion sickness or to prevent nausea and vomiting. However, excessive uptakes through the skin and rubbing of the patch on the eye have resulted in mydriasis

- The patch may be uncomfortable to wear as adhesives may not adhere well to all types of skin.
- High cost of product.

DRUG DELIVERY CARRIERS

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.

❖ Carrier based Drug Delivery System:

- ❖ Liposomes
- ❖ Dendrimers
- ❖ Nanoparticles
- ❖ Microspheres
- ❖ Niosomes
- ❖ Phytosomes
- ❖ Ethosomes

A) Carrier based Drug Delivery System:

LIPOSOMES

Liposomes are spherical artificial vesicles that can be synthesized from natural harmless phospholipids and cholesterol. Because of their size and unique hydrophobic and hydrophilic properties, liposomes hold great promise as drug delivery vehicles. The manufacturing process, size, surface charge, and lipid composition all have a significant impact on liposome capabilities. Phospholipids have been shown to spontaneously form closed structures upon hydration in aqueous solutions. These vesicles with one or more phospholipid bilayer membranes can carry either lipid or aqueous medications. Lipids' thermodynamic phase qualities and self-assembling traits affect the entropically focused arrangement of their hydro-phobic sections into spherical bilayers because they are amphipathic in watery conditions. Lamellae are the names for those layers. Generally, liposomes are definite as spherical vesicles with particle sizes ranging from 30 nm to several micrometers. They consist of one or more lipid bilayers surrounding aqueous units, where the polar head groups are oriented in the pathway of the interior and exterior aqueous phases. On the other hand, self-aggregation of polar lipids is not limited to conventional bilayer structures which rely on molecular shape, temperature, and environmental and preparation conditions but may self-assemble into various types of colloidal particles[12]

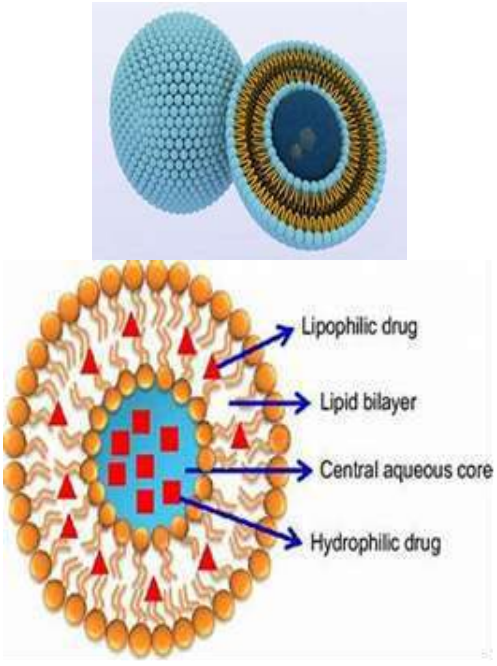

Figure 2: Structure of Liposomes[64].

Advantages:-

- Provides selective passive targeting to tumor tissues (Liposomal doxorubicin).
- Increased efficacy and therapeutic index.
- Increased stability via encapsulation.
- Reduction in toxicity of the encapsulated agents.
- Site avoidance effect
- Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
- Flexibility to couple with site specific ligands to achieve active targeting[12]

General method of Liposomes preparation.

Reverse phase evaporation technique-

Inverted micelles or water-in-oil emulsions, in which the organic phase is made up of lipids to form liposomal bilayers and the aqueous phase contains the pharmaceuticals of interest, are the basis of the reverse phase evaporation technique. (To obtain lipid films, we add this lipid mixture to a flask and evaporate the solvents. The lipid films are then dissolved once more using an organic phase that is primarily made of isopropyl ether and/or diethyl ether. A two-phase system is created by the addition of the water phase, and a homogenous dispersion is the outcome of the next sonication. As the organic solvent gradually evaporated, the mixture changed into a thick gel that created an aqueous suspension containing liposomes. Higher internal aqueous loading is one advantage of the reverse phase evaporation technique over the thin-film hydration method. While some organic solvent may remain and be able to interact further with the lipids or the drugs, techniques like centrifugation and dialysis can be used to remove the remaining solvent.)[13].

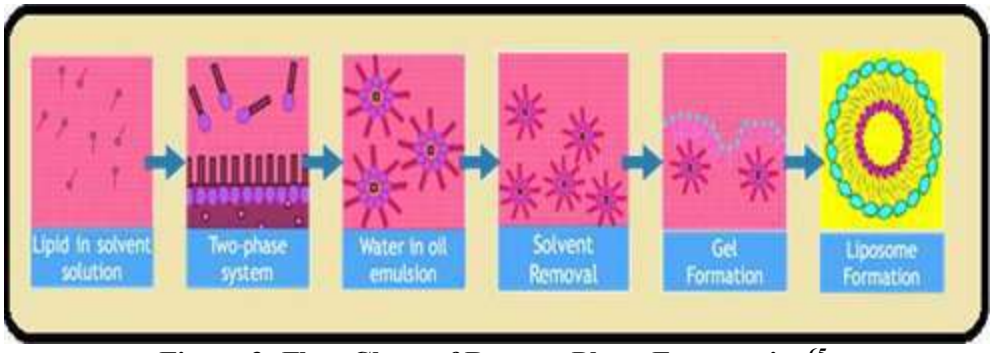

Figure 3: Flow Chart of Reverse Phase Evaporation[65].

DENDRIMERS

Dendrimers are symmetrical macromolecules with nanometer-sized, highly branching, monodisperse structures. A central core, branching units, and terminal functional groupings make them up. The environment of the Nano cavities and, subsequently, their solubilizing capabilities are determined by the core together with the internal units, whilst the solubility and chemical behavior of these polymers are determined by the exterior groups. Attaching targeting ligands to the dendrimers' exterior surfaces influences the efficiency of targeting, and functionalizing the dendrimers with polyethylene glycol chains increases their stability and protects them from the Mononuclear Phagocyte System. The characteristics of both the liquid and solid states are combined in liquid crystals. They are capable of taking on various geometries and can incorporate aqueous medicinal solutions in alternative polar and non-polar layers[14].

NANOPARTICLES

Nanoparticles are in the solid form and can be either amorphous or crystalline, with sizes ranging from 10 to 200 nm for Nano spheres and Nano capsules. They have the capacity to adsorb and/or encapsulate a medication, shielding it from enzymatic and chemical deterioration. Given their uses in the controlled release of drugs, the ability to target specific organs or tissues, the ability to carry DNA in gene therapy, and the ability to deliver proteins, peptides, and genes orally, biodegradable polymeric nanoparticles have received a lot of attention recently as potential drug delivery devices[15].

Method of Preparation

The preparation techniques for nanoparticles can be broadly divided into two groups i.e, dispersion of preformed polymers and polymerization of monomers. Among the techniques for dispersing preformed polymers are:

1. Solvent evaporation method
2. Spontaneous emulsification method
3. Salting out/emulsion diffusion method
4. Non aqueous phase separation method

Solvent evaporation method

Using an organic solvent like chloroform, acetone, or ethyl acetate, preformed polymers like polylactic acid or poly (d,l-lactic co-glycolic acid) are dissolved. In order to create an oil-in-water emulsion, the payload medication is typically dissolved in the polymer solution and then transferred to an aqueous phase containing a surfactant, such as polyvinyl alcohol. If the homogenization process is carried out for a long enough duration, it can help the organic solvent evaporate. Ultracentrifugation is used to gather the nanoparticles at the conclusion of the homogenization process. To obtain the required particle size, process variables can be changed, including the ratio of polymer to organic solvent, the kind of organic solvent, and the speed and duration of homogenization[16]

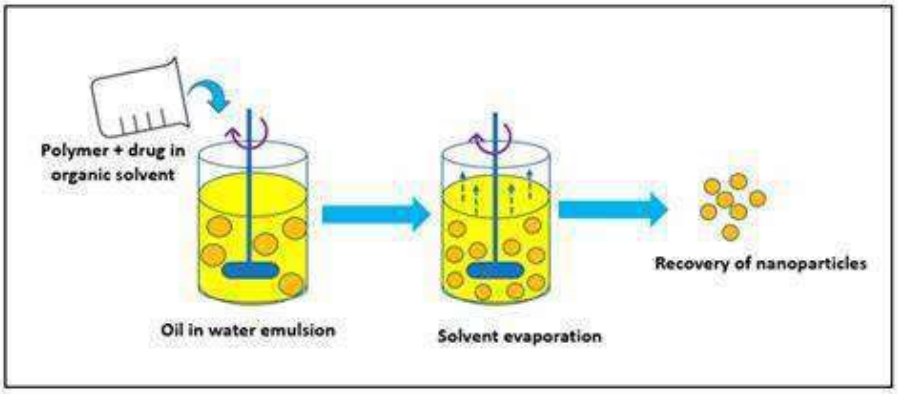

Figure 4: Flow Chart of Solvent Evaporation Method[66]

NIOSOMES

A unique vesicular drug delivery technology called niosomes makes it possible to distribute medications in a focused, regulated, and long-lasting way. Liposomes were the first vesicular drug delivery technology, but they have a lot of disadvantages, such as toxicity, cheap cost, and pH stability issues. The disadvantages of liposomes have raised interest in niosome research. It is feasible to form unilamellar, oligolamellar, and multilamellar niosomes. The reason niosomes are non-toxic is that they are made of non-ionic surfactants, which is how they got their name. In addition to non-ionic surfactants, they might also comprise charged molecules and cholesterol or its derivatives. The charged molecule in the cholesterol, which gives the structure stiffness,

keeps the preparation stable. Niosomes are created when non-ionic surface-active substances self-assemble. They can be used to load and deliver both hydrophilic and hydrophobic drugs due to their structure[17]

Method of preparation

To prepare niosomes, a lipid mixture and surfactant are hydrated at high temperatures. Niosome size reduction is then optionally performed to produce a colloidal suspension. Niosome preparation can be done using a number of well-researched conventional techniques. Examples include sonication, hand shaking, ether injection, and micro fluidization technique. Then, by centrifugation, gel filtration, or dialysis, the unentrapped drug is separated from the entrapped drug

Reverse-phase evaporation method

In addition to ether and chloroform, the reverse-phase evaporation method employs a combination that includes cholesterol and surfactant in a 1:1 ratio. The target drug-containing aqueous phase is added to the mixture, and it is then sonicated at a temperature of 4-5°C. A tiny quantity of phosphate-buffered saline is added to the mixture, and then the sonication process is resumed. Phosphate-buffered saline is used to dilute the residual suspension after the organic solvent is extracted at 40°C while operating at low pressure. The final product, niosomes, is formed by heating the mixture at 60°C for 10 minutes[18].

MICROSPHERES

Another name for the microspheres is micro-particles. They are made to improve a drug's therapeutic efficacy and address some of the issues with traditional therapy. To achieve the intended effect, the drug must deliver the maximum therapeutic effect and the least amount of side effects to the target tissue at the right time. The prolonged release of the anticancer drugs and their ability to target the tumor with the microspheres attracted a lot of attention. The spherical micro particles known as microspheres are utilized in applications where a consistent and predictable particle surface area is crucial. The medication is contained in the center of the microspheres, where it is protected by a special polymeric membrane[19].

Method of Preparation

Wax coating and hot melt

Wax used to encapsulate the main components, by dissolving or dispersing the product in melted wax. The waxy paste or mixture, such as frozen liquid paraffin, is released by high intensity blending with cold water. The water is heated up for at least an hour. The substance is stirred up for at least 1 hour. Then the external layer (liquid paraffin) is decanted and the microspheres are immersed in a non-miscible solvent and dry air is required to dry. For the surface ingredients, carnauba wax and beeswax can be used and both should be combined to obtain desirable characteristics.

Spray drying technique

This was used to prepare polymer microsphere mixed charged with drug. This requires dispersing the raw substance into liquefied coating liquid, and then spraying the mixture into the air for surface solidification accompanied by rapid solvent evaporation. Organic solvent and polymer solution are formulated and sprayed in various weight ratios and drug in specific laboratory conditions producing microspheres filled with medications. This is fast but may lose crystalinity due to rapid drying.

Coacervation

This method is a straight forward separation of macromolecular fluid into two immiscible types of material, a thick coacervate layer, comparatively condensed in macromolecules, and a distilled layer of equilibria. This method is referred to as basic coacervation, in the presence of just one macromolecule. If two or more opposite-charge macromolecules are involved, they are considered complex coacervation. The former is caused by specific factors including temperature shift,Using non-solvent or micro-ions contributing to dehydration in macromolecules, since they facilitate interactions between polymer and polymer through polymer solvent interactions. This can be engineered to generate different properties on microsphere

Freeze Drying

Freeze-drying is effectively used in protein API microspheres praparation. The method is freezing, sublimation, main drying, and secondary drying. At the freezing step, account is taken of the eutectic point of the components. During the process, lyoprotectants or cryoprotectants will stabilise API molecules by removing water, creating a glass matrix, lowering intermolecular interaction by forming hydrogen bonds between the molecules or dipole - dipole interactions. It's a beneficial cycle for heat tolerant molecules, given its high expense. Freeze-drying produces solidification and then enables the reconstitution of particles in an aqueous media.

Ionic gelation method

Ionotropic gelation is depend on the tendency of polyelectrolytes to cross connect to develop hydrogel beads often called gelispheres in the existence of counter ions. Gelispheres are Circular cross linked polymeric hydrophilic agent capable of substantial gelation and thickening in model biological fluids and drug release regulated by polymer relaxation via it. The hydrogel beads are formed by dumping a drug-laden polymeric solution into the polyvalent cations aqueous solution. The cations migrate through the drug-laden hydrophilic compounds, creating a three-dimensional lattice the moiety is ionically crosslinked. Biomolecules may also be placed into these gelispheres to maintain their three-dimensional form under moderate conditions.

Emulsion Solvent Evaporation Technique

This method involves dissolving the medication in a polymer that has already been dissolved in chloroform, and then adding the resultant solution to an aqueous phase that contains 0.2 percent sodium PVP as an emulsifying agent. After 500 rpm of agitation, the drug and polymer (eudragit) were separated into fine droplets, which were then collected by filtration, cleaned with demineralized water, and dried at room temperature for a full day. The solidified microspheres were formed by solvent evaporation[20].

PHYTOSOMES

Phytosomes means herbal drug loaded in vesicles, which is available in the Nano form. The phytosome provide an envelope, like coating around the active constituent of drug and due to this the chief constituent of herbal extract remains safe from degradation by digestive secretion and bacteria. Phytosome is effectively able to absorb from a water loving environment into lipid loving environment of the cell membrane and finally reaching to blood circulation. The current review highlights the future scope and emerging technologies in the field of NDDS for the benefit of herbal and traditional medicines prepared from plant origins. The term “Phyto” means plant and “some” means cell like. It is also mentioned as herbosomes. This is a new patented technology, where standardized plant extracts or water soluble

phytoconstituents are complexed with phospholipids to produce lipid compatible molecular complexes, there by greatly increasing absorption and bioavailability. Phospholipids are complex molecules which are used in the formation of cell membranes Phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol are the phospholipids used, but phosphatidylcholine obtained from soya bean are widely used because of their certain therapeutic value in case of liver diseases, alcoholic steatosis, drug induced liver damage and hepatitis. Phospholipids are also employed as natural digestive aids and as carriers for both fat miscible and water miscible nutrients. Phytosomes can easily traverse the lipophilic path of the enterohepatic cell membranes and also stratum corneum layer of the skin[21].

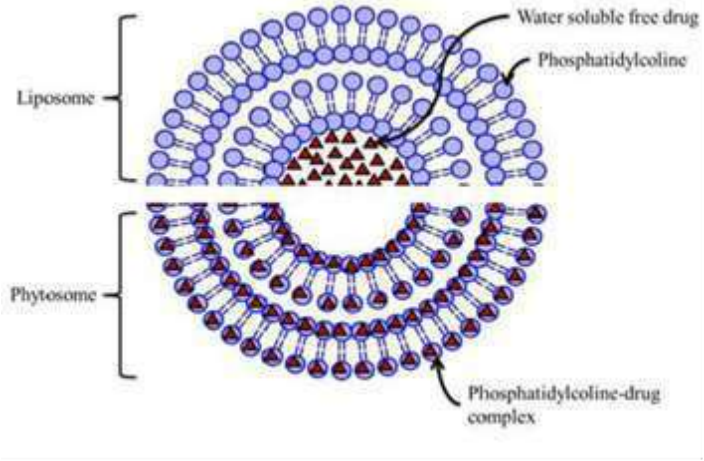

Figure 5: Structure of phytosomes[67].

ADVANTAGES OF PHYTOSOMES:

1. Phytosomes have better stability due to formation of chemical bonds between phytoconstituents and the phosphatidylcholine molecules.
2. Phytosomes produces a little cell where the active components of herbal extracts are protected from destruction by gut and digestive secretions.
3. Small dose can produce desired results, as the absorption of active component is improved.
4. Formulation of phytosomes is easy and it shows better drug entrapment efficiency.
5. Phytosomes increases the solubility of bile to herbal constituents.
6. Duration of action of phytosomes is increased.
7. Phosphatidylcholine is not only a carrier, also having hepatoprotective activity and nutritional value.
8. Cosmetic and other topical use of herbal constituents can be done by phytosome formulations

PREPRATION OF PHYTOSOMES:-

Solvent evaporation method

The solvent evaporation methods involves integration of the phytoconstituents and PC during a flask containing organic solvent. This reaction mixture is kept at an optimum temperature usually 40°C for specific interval of 1 hr to achieve maximum drug entrapment within the phytosomes formed. Thin film phytosomes are seprated by 100 mesh sieves and stored in desiccators for overnight[22].

Mechanical Dispersion method

In the experiments, the lipids dissolved in organic solvent are brought be in contact with aqueous phase containing the drug (Sikarwar MS et al., 2008). the next removal of the organic solvent under reduced pressure results in the formation of phyto-phospholipid complex. Recently methods for the phospholipid involute preparation includes super critical fluids (SCF), which include gas anti-solvent technique (GAS) compressed anti-solvent process (PCA), supercritical anti-solvent method (SAS)[23].

Lyophilization method

The lyophilization technique DSN was plenarily dissolved in DMSO. The resulting DSN solution (2.5% weight/volume) was added to the answer of SPC dissolved in t-butylalcohal (1.5% weight/volume) followed by stirring for 3 hours on a magnetic stirrer until complex formation. The complex was then isolated by lyophilization. After abstracting the samples from the freeze drier, the resultant DSN:SPC involute (yield 90.4%, weight/weight) was placed during a desiccator over P2O5 at 4°C until testing. For the culled developing technique the influence of variable formulation factors was assessed including SPC type (Lipoid® S100, Lipoid® S75 and Lipoid® S PC-3), drug phospholipid ratio (1:1, 1:2, and 1:4) and co-solvent type of chemical (methanol, ethanol, chloroform, acetone, and TBA). Non-conventional methods are customarily employed in construction of phytosome complexes. Modernistic herbal complexes are composed by reaction between equilar amalgamation of natural or synthetic phospholipid and active constituents or herbal extract in acrostic organic solvents

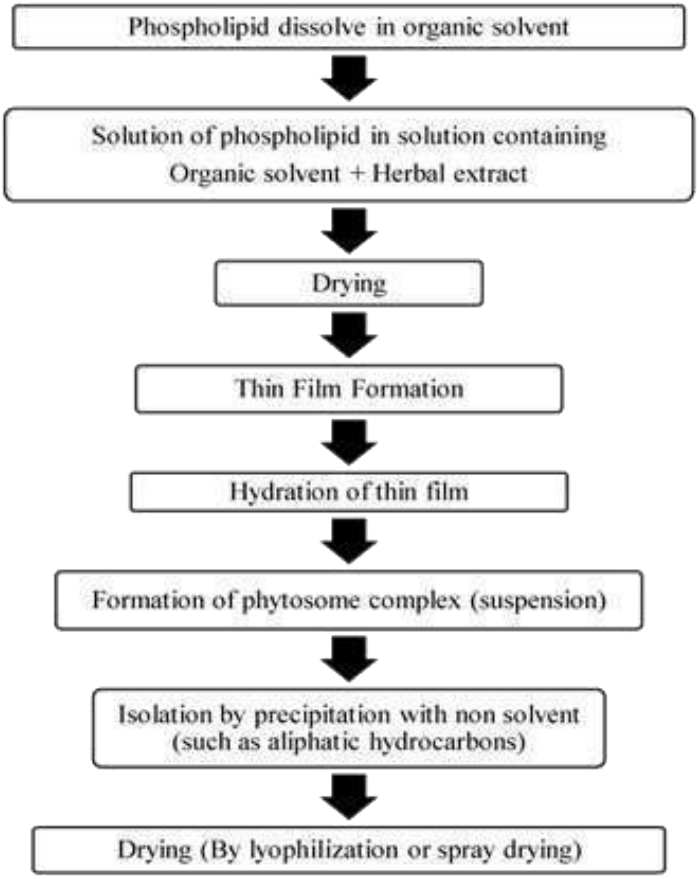

Figure 6: General method of phytosomes preparation[68]

ETHOSOMES

Ethosomes were developed by Touitou et al.,1997, as additional novel lipid carriers composed of ethanol, phospholipids, and water. They are reported to improve the skin delivery of various drugs. Ethanol is an efficient permeation enhancer that is believed to act by affecting the intercellular region of the stratum corneum. Ethosomes are soft malleable vesicles composed mainly of phospholipids, ethanol (relatively high concentration), and water. These soft vesicles represent novel vesicles carriers for enhanced delivery through the skin. The size of the ethosomes vesicles can be modulated from tens of nanometers to microns. Ethosomes are non-invasive delivery carriers that enable drugs to reach the deep skin layers and / or the systemic circulation. The high concentration of ethanol makes the ethosomes unique, as ethanol is known for its disturbance of skin lipid bilayer organization. Therefore, when integrated into a vesicles membrane; it gives the vesicle the ability to penetrate the stratum corneum. Also, because of their high ethanol concentration, the lipid membrane is packed less tightly than the conventional vesicles, although it has equivalent stability, allowing a more malleable structure and improves the drug distribution ability in the stratum corneum lipids[24].

Methods of Preparation of Ethosomes [25,26,27]

a) Hot method

The drug is dissolved in a mixture of ethanol and propyleneglycol and the mixture is added to the phospholipid dispersion in water at 40°C. After mixing for five minutes the preparation is sonicated at 4°C for three cycles of five minutes, with a rest of five minutes between each cycle, using the Probe Sonicator. The formulation is then homogenized at 15,000 psi pressure, in three cycles, using a high-pressure homogenizer to get nano-sized ethosomes

b) Cold method

This is one of the most widely used techniques for preparation of ethosomes, which consists of two basic and simple setups. In the first setup, phospholipid and other lipid material is dissolved in ethanol at room temperature by vigorous stirring with the use of mixer such as Heidolph mixer with continuous addition of polyols such as propylene glycol etc. with constant stirring followed by heating at 30 °C in water bath. In the second setup, water is to be heated at 30 °C in a separate vessel, both mixtures (obtained from first and second setup) are to be blended together following 5 min stirring in a covered vessel. The vesicle size of ethosomal formulation can be decreased to desire extend using sonication or extrusion method. Finally, the formulation is stored under refrigeration

Mechanism of Action

The stratum corneum and pilosebaceous pathways are involved in a number of related processes that occur when the ethosomal system is applied to the skin. These processes involve the disruption of the stratum corneum lipid bilayer's organization by ethanol, followed by an increase in the lipid bilayer's fluidity. Due to their particle nature, stretchable ethosomes vesicles can even mimic a passage through the skin by penetrating disrupted stratum corneum bilayers. The fusion of ethosomes with skin lipids and drug release at different locations along the penetration pathway may also result in the release of the medication into the deep layers of the skin and its transdermal absorption. Skin lipids, ethanol, and vesicles work together to support ethosome function. Ethamomes increase the dispersion of active substances over liposomes because they interact

better with skin lipids. The transition temperature of the lipids in the stratum corneum is lowered when ethanol interacts with the lipid molecules in the polar head group region. They reduce the density of the lipid multilayer and increase fluidity, which allows the medicine to be absorbed into theskin's deeper layers. Moreover, ethanol gives vesicles a smoother, more flexible texture, which promotes deeper penetration into the epidermal layer[28].

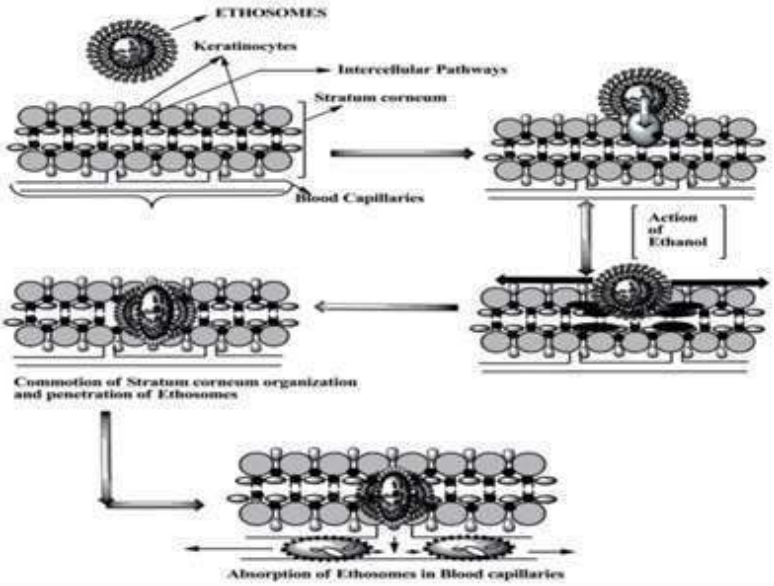

Figure 7: Projected model presenting mechanism of action of ethosomes for skin delivery[69].

AQUASOMES

Aquasomes are nanoparticulate carrier system but instead of being simple nanoparticle these are three layered self-assembled structures, comprised of a solid phase nanocrystalline core coated with oligomeric film on which biochemically active molecules are adsorbed with or without modification Aquasomes are like “bodies of water" and their water like properties protect and preserve fragile biological molecules, and this property of maintaining conformational integrity as well as high degree of surface exposure is exploited in targeting of bio-active molecules like peptide and protein hormones, enzymes, antigens and genes to specific sites. These three-layered structures are self-assembled by non-covalent and ionic bonds. These carbohydrates stabilize nanoparticles of ceramic are known as “aquasomes”. The pharmacologically active molecule incorporated by co-polymerization, diffusion or adsorption to carbohydrate surface of pre formed nanoparticles. Aquasomes discovery comprises a principle from microbiology, food chemistry, biophysics and many discoveries including solid phase synthesis, supramolecular chemistry, molecular shape change and self assembly[29].

METHOD OF PREPARATION OF AQUASOMES

By using the principle of self assembly, the aquasomes are prepared in three steps i.e., preparation of core, coating of core, and immobilization of drug molecule.

Preparation of the core:

The first step of aquasome preparation is the fabrication of the ceramic core. The process of ceramic core preparation depends on the selection

of the materials for core. These ceramic cores can be fabricated by colloidal precipitation and sonication, inverted magnetron sputtering, plasma condensation and other processes. The precipitated cores are centrifuged and then washed with enough distilled water to remove sodium chloride formed during the action. The precipitates are resuspended in distilled water and passed through a fine membrane, filter to collect the particles of desired size. Two ceramic cores that are most often used are diamond and calcium phosphate.

Carbohydrate coatings:

The second step involves coating carbohydrate on the surface of ceramic cores. There are number of processes to enable the carbohydrate (polyhydroxy oligomers) coating to adsorb epitaxially on to the surface of the nano-crystalline ceramic cores. The processes generally entail the addition of polyhydroxy oligomer to a dispersion of meticulously cleaned ceramics in ultra pure water, sonication and then lyophilization to promote the largely irreversible adsorption of carbohydrates on to the surfaces. Excess and readily desorbing carbohydrate is removed by by stir cell ultra-filtration17. The commonly used coating materials are cellobiose, citrate, pyridoxal-5-phosphate, sucrose and trehalose.

Immobilization of drugs: The surface modified nano-crystalline cores provide the solid phase for the subsequent non-denaturing self assembly for broad range of biochemically active molecules. The drug can be loaded by partial adsorption[30,31].

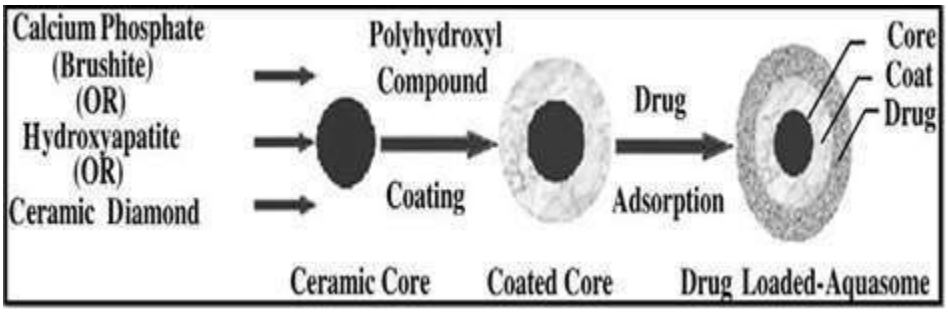

Figure 8: Preparation of Aquasomes[70]

Table 1: Comparative evaluation of Phytosome, Liposomes, Niosomes, and Ethosomes[71]

Characteristics	Phytosome	Liposome	Niosome	Ethosome
Composition	Phospholipids and polyphenolic phytoconstituents	Phospholipids and cholesterol	Non-ionic surfactant and cholesterol	Phospholipid, alcohol, polyglycol and water
Flexibility	Rigid	Rigid	Rigid	Elasticity
Main application	Phyto-delivery	Drug and gene delivery	Drug delivery and cosmetics	Skin delivery
Administration	Oral, parenteral topical, transdermal	Oral, parenteral topical, transdermal	Oral, parenteral topical, transdermal	Topical and transdermal
Key features	High entrapment efficiency along with a depot formation which releases the contents slowly	Biocompatibility, capacity for self-assembly, ability to carry large drug payloads	Improved dispersion of compounds with solubility issues, high stability, low-cost materials	Enhance permeation of drugs across/ through the skin in an efficient manner

Limitation	Leaching of the phytoconstituents which reduces the desired drug concentration ndicating their unstable nature	Low skin penetration, low stability	Low skin penetration and toxicity of surfactant	Poor yield, coalescence and fall apart on transfer into water, Loss of product during transfer form organic to water media
Marketed product	Leucoselect, Greenselect, Panax ginseng, Sabalselect, etc.	Doxil, Abelcet, Visudyne, DepoDur, etc.	Lancome and L'Oreal	MaccabiCARE, Nanominox, Trima, etc.

MICROENCAPSULATION

Through the process of microencapsulation, thin wall material coatings are formed around solids, liquids, or even gases, enclosing them in microscopic particles. A variety of microencapsulated materials, including medications, were developed as a result of the breakthrough invention of replication paper and ribbons in the 1950s that contained dyes in microscopic gelatine capsules that were released upon hit by a typewriter key or the pressure of a pen or pencil. And the technique is also known as "microencapsulation "which involves coating or encircling minuscule liquid or solid droplets with a continuous polymeric layer. Bioencapsulation, which is more limited to enclosing a biologically active material (such as DNA or a complete cell or group of cells) in order to increase its performance and/or prolong its shelf life, is a subset of microencapsulation. Through microencapsulation, liquids may be turned into solids, surface and colloidal properties can be changed, the environment can be protected, and the release characteristics or availability of coated materials can be managed[32]. Three processes are typically involved in coacervation-phase separation microencapsulation, which is done under continuous agitation: (a) production of three immiscible chemical phases; (b) coating deposition; and (c) coating rigidization. There are two types of coacervation-phase separation: simple coacervation and complicated coacervation. The former suggests incorporating a very hydrophilic material into a colloid solution. Two phases are created as a result of this additional material. The process of complicated corrosion is primarily pH dependent. Microcapsules are created by manipulating the system's basic or acidic composition. Depending on how basic or acidic the system is, it may form microcapsules over a particular threshold pH value. They won't develop at pH values lower than that. Complex coacervation typically addresses the system containing more than one colloid[33].

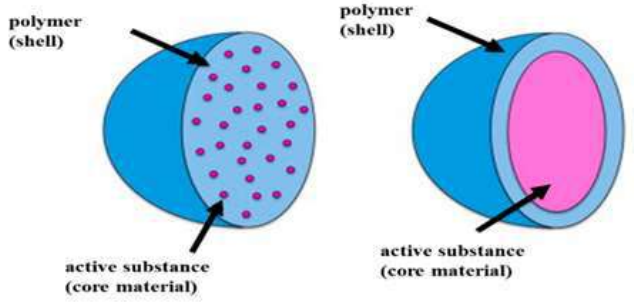

Figure 10: Microencapsulation[66].

MICROSPONGES

Microsponges are patented polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents Like a true sponge, each microsphere consists of a myriad of interconnecting voids within a non-collapsible structure, with a large porous surface. The size of the microsponges can be varied, usually from 5 – 300 µm in diameter, depending upon the degree of smoothness or after-feel required for the end formula. Although the microsponge size may vary, a typical 25 µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 ft in length, providing a total pore volume of about 1 ml/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent. The microsponge particles themselves are too large to be absorbed into the skin and this adds a measure of safety to these microsponge materials. Another safety concern is the potential bacterial contamination of the materials entrapped in the microsponge. As the size of the pore diameter is smaller, the bacteria ranging from 0.007 to 0.2 µm cannot penetrate into the tunnel structure of the microsponges[34,35].

Characteristics of microsponges [36,37]

1. Microsponge formulations are stable over range of pH 1 to 11 and temperature upto 130^0C.
2. Compatible with most vehicles and ingredients.
3. Self- sterilizing as their average pore size is about 0.25µm where the bacteria cannot penetrate the pores.
4. Formulations have high entrapment upto 50 to 60%.
5. Microsponge formulations are free flowing and can be cost effective.
6. Microsponge particles themselves are too large so they are difficult to be absorbed into the skin and this adds a measure of safety to these microsponge materials by avoiding the side effects of the microsponge adjutants.
7. Microsponges can absorb oil up to 6 times its weight without drying.
8. It provides continuous action up to 12 hours i.e. extended release.
9. They have superior formulation flexibility.

METHODS OF PREPARATION

Quasi-emulsion solvent diffusion method

Quasi-emulsion solvent diffusion method is a two-step process and increases the sensitivity of the drug release. This method uses different amounts of polymer. This consists of two phases i.e., internal phase and external phase.The internal phase consists of polymer such as Eudragit RS-100 (low permeability). This polymer is cationic and non-biodegradable and entrapment efficiency was found to increase with increased amount of Eudragit RS-100. The external phase consists of polyvinyl alcohol (PVA) with distilled waterInternal phase containing Eudragit RS-100 is dissolved in a solvent like ethyl alcohol at 35 °C under ultrasonication so that the internal phase is dispersed in the external phase containing PVA solution in water. The solution is stirred and 1 hour andis filtered to obtain the solid microsponges. This solid microsponge is dried in an oven at 35 °C- 40 °C for 12 hours before use[38,39].

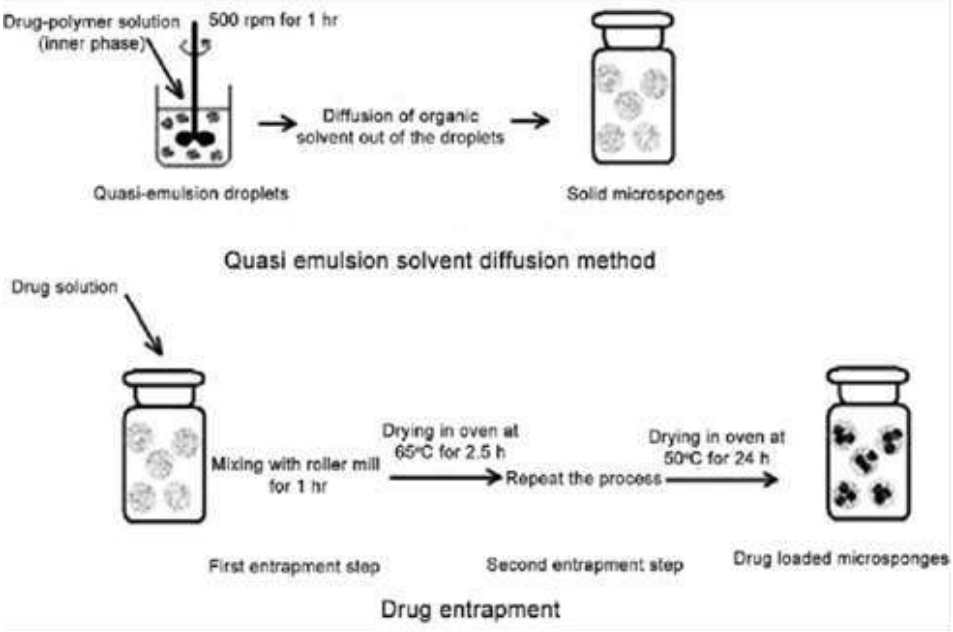

Figure 11: Quasi-emulsion solvent diffusion method[72].

Hypothetical mechanism of action

The active ingredient is added to the vehicle in an entrapped form. As the microsponge particles have an open structure (i.e., they do not have a continuous membrane surrounding them), the active ingredient is free to move in and out from the particles and into the vehicle until equilibrium is reached, when the vehicle becomes saturated. Once the finished product is applied to the skin, the active ingredient that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore, disturbing the equilibrium. This will start a flow of the active from the microsponge particle into the vehicle, and from it to the skin, until the vehicle is either dried or absorbed. Even after that the microsponge particles retained on the surface of the stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time. If the active is too soluble in the desired vehicle during compounding of the finished products, the products will not provide the desired benefits of gradual release[39].

B.) Other Approaches of Novel drug delivery

SONOPHORESIS

It is a method that uses ultrasonic radiation to dramatically accelerate the absorption of topical chemicals (transdermal administration) into the skin's dermis, epidermis, and appendages. One quick, easy, non-invasive, targeted way to transfer macromolecules and low molecular weight medications to the skin are using sonophoresis.Sonophoresis is thought to improve medication delivery mechanistically by altering skin tissue through a mix of chemical, mechanical, and thermal changes. Sonophoresis has been achieved using ultrasound at different frequencies between 20 kHz and 16 MHz, with intensities up to 3 W/cm. Percutaneous absorption is known to be impacted by ultrasound parameters, with frequency, intensity, and length of treatment being the most significant. Sonophoresis happens when ultrasonic waves raise the total kinetic energy of the molecules that make up topical medicines and induce micro-vibrations beneath the skin's epidermis. Drug distribution is likely improved by ultrasound by cavitation, microstreaming, and heating.[40,41,42].

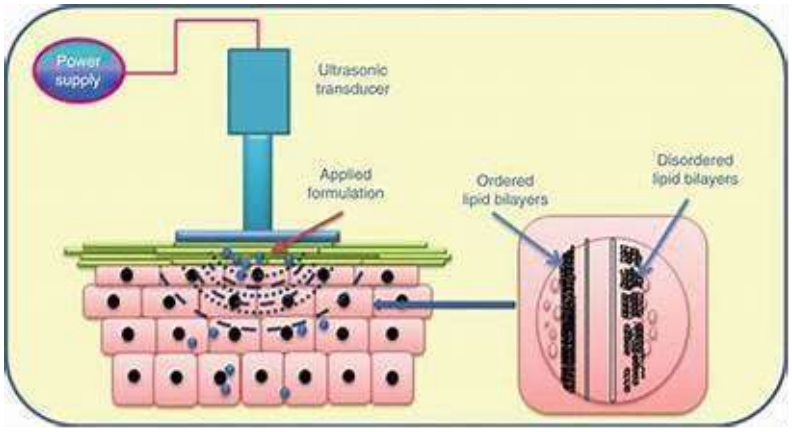

Figure 9: Mechanism of sonophoresis[73]

OSMOTIC PUMP

Osmogen and a drug-filled core make up the majority of osmotic delivery devices, also known as osmotic pumps. These are covered with a semi-permeable membrane with one or more drug delivery pores, allowing the medication to be delivered gradually as a suspension or solution[59]. The heart of an oral osmotic system is a compressed tablet covered in a semi-permeable membrane, through which delivery orifices are drilled using a mechanical drill or a laser beam. These regulated systems are not affected by different gastrointestinal variables and are based on osmosis and osmotic pressure. Nonetheless, it is important to remember that a number of crucial elements, such as drug solubility, delivery orifices, osmotic pressure, semi-permeable membrane, and others, affect how osmotically controlled drug delivery systems are designed its membrane thickness, plasticizer type and quantity, and polymer type and nature. The next breakthrough was the implanted pump, a gadget that was meant to be inserted beneath the skin in order to avoid using a catheter. Drug release is continuous with these devices[43,44].

HYDROGELS

Hydrogels are polymeric material that exhibits its ability to swell and retain a significant fraction of water within its structure, but will not dissolve in water. They possess a degree of flexibility very similar to natural tissue due to their large water content. The ability of hydrogel to absorb water arises from hydrophilic functional group attached to polymeric backbone, while their resistant to dissolution arises from crosslinks between network chains. During last two decades, natural hydrogels were replaced by synthetic hydrogels which has long service life, high capacity of water absorption and high gel strength. Synthetic polymers usually well-defined structure that can modify to yield tail or able degradability and functionality. They are polymers of carboxylic acids. The acid groups ionise in water, leaving the polymer with several negative charges along its length. This increases the viscosity of the resulting mixture because the polymer chain now takes up more space and resists the flow of solvent molecules around it. The polymer is in equilibrium with the water around it, but the equilibrium can be disturbed in a number of ways. If the ionic concentration of the solution is increased, for example by adding salt, the positive ions attach themselves to the negative sites on the polymer, effectively neutralizing the charges. This causes the polymer to collapse in on itself again. Adding alkali removes the acid ions and causes the position of equilibrium to move to the right; adding acid has the opposite effect. There are a large number of hydrogels and they expand and contract at different pH values, temperatures and

ionic concentrations. By using a mixture of monomers to create the polymer these characteristics can be fine-tuned[45].

Properties of Hydrogel

1. Swelling Properties: A small change in environmental condition may trigger fast and reversible changes in hydrogel. The alteration in environmental parameters like electric signal, pH, temperature, and presence of enzyme or other ionic species may lead to a change in physical texture of the hydrogel.
2. Mechanical properties: The mechanical properties can vary and be tuned depending on the purpose of the material. It is possible to obtain a gel with higher stiffness increasing the crosslinking degree or lowering it by heating the material. The changes in mechanical properties link to a wide range of variables and causes and different analysis must be made according to the material.
3. Polymers used in hydrogels: Hydrogels are prepared from natural and synthetic polymers.
4. Natural polymers: - Chitosan, gelatin, alginates, fibrin.
5. Synthetic polymers: - Vinyl acetate, acryolic acid, methacrylate-vinyl 2 pyrrolidine.
6. Biocompatible properties: Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility consists basically of two elements: (a) bio-functionality i.e. the ability of material to perform the specific task for which it is intended. (b) bio-safety i.e. appropriate host response not only systemic but also local (the surrounding tissue), the absence of mutagenesis, cytotoxicity[46].

HYDROGEL PREPARATION METHODS

Hydrogels are polymer networks having hydrophilic properties. While hydrogels are generally prepared based on hydrophilic monomers, hydrophobic monomers are sometimes used in hydrogel preparation. In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger compared to natural polymers. Their mechanical strength results in slow degradation rate, but on the other hand, mechanical strength provides the durability as well. These two opposite properties should be balanced through optimal design. Also, it can be applied to preparation of hydrogels based on natural polymers provided that these polymers have suitable functional groups or have been functionalized with radically polymerizable groups. The polymerization techniques have been described below:

a) **Bulk polymerization**

Bulk hydrogels can be formed with one or more types of monomers mainly include vinyl monomers for the productions of hydrogels. Usually, a small amount of cross-linking agent is added in any hydrogel formulation. Radiation, ultraviolet, or chemical catalysts is used for the initiation of the polymerization reaction. The initiator is chosen which depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including rods, particles, films and membranes, and emulsions.

b) **Free radical polymerization**

The main monomers which are used in this method for the preparation of hydrogels are such as acrylates, vinyl lactams and amides. These polymers have suitable functional groups or have been functionalized with radically polymerizable

groups. This method involves the chemistry of typical free-radical polymerizations, which includes propagation, chain transfer, initiation, and termination steps. For the radical generation in the initiation step a wide variety of thermal, ultraviolet, visible, and redox initiators can be utilized, the radicals react with the monomers which convert them into active forms[46,47].

ORAL FAST DISSOLVING FILM

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens[48,49]. Fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. Oral fast dissolving film (OFDF) is one such novel approach to increase consumer acceptance by virtue of rapid dissolution, self administration without water or chewing. The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administer, maintains a simple and convenient packaging, alleviates unpleasant taste, and is straightforward to manufacture. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The development of a fast-dissolving film also provides an opportunity for a line extension in the market place, a wide range of drugs (e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered candidates for this dosage form.

A large number of drugs can be formulated as mouth dissolving films. Innovative products may increase the therapeutic possibilities in the following indications[50].

1. Pediatrics (Antitussives, Expectorants, Antiasthamatics)
2. Geriatrics (Antiepileptic, Expectorants)
3. Gastrointestinal diseases
4. Nausea (due to Cytostatic therapy)
5. Pain (Migraine)
6. CNS (Antiparkinsonism therapy)

Special features of fast dissolving films.

1. Film should be thin and elegant.
2. Available in various size and shapes.
3. Unobstructive.
4. It should adhere to the oral cavity easily.
5. Should processes fast disintegration without water.
6. Rapid release.

Advantages of fast dissolving films.

1. Convenient dosing.
2. No risk of chocking.
3. Taste masking.
4. Enhanced stability.
5. Improved patient compliance.
6. The drug enters the systemic circulation with reduced hepatic first pass effect.
7. Site specific and local action.

8. Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.

Disadvantages of Fast Dissolving Oral Films[52,53]

1. Drugs which are unstable at buccal pH cannot be administered.
2. Drugs which irritate the mucosa cannot be administered by this route.
3. Drug with small dose requirement can only be administered.
4. Taste masking- Most drugs have bitter taste, and need taste masking.
5. Special packaging- OFDFs are fragile and must be protected from water so it needs special packaging.
6. Dose uniformity is a technical challenge
7. Expensive packaging of oral film

Ideal characteristics of a suitable drug candidate[54,55]

1. The drug should have pleasant taste.
2. The drug to be incorporated should have low dose up to 40 mg.
3. The drug should have smaller and moderate molecular weight.
4. The drug should have good stability and solubility in water as well as saliva.
5. It should be partially unionized at the pH of oral cavity.
6. It should have ability to permeate the oral mucosal tissue

APPROACHES USED FOR FORMULATION OF FAST DISSOLVING FILMS [56-59]

Conventional approaches:-

Solvent casting method

In this method, firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size.

Hot-melt extrusion

In hot melt extrusion method, the initial mass is formed with the help of carriers. To form initial mass, the drug is mixed with carriers and a solid mass is obtained and dried. Then dried granular material is introduced into the extruder. The extruder is divided into four zones having following degrees of temperature: 800°C (zone 1), 1150°C (zone 2), 1000°C (zone 3), and 650°C (zone 4). The speed of extruder screw speed should be set at 15 rpm in order to process the granules inside the barrel of extruder for approximately 3-4 min so that mass should be properly melted. The extrudate obtained is then pressed into a cylindrical calendar in order to obtain a film. There are certain benefits of hot melt extrusion: Fewer operation units, minimum product wastage, possibility to scale up, an anhydrous process, absence of organic solvents, include shorter temperature and shorter residence time of the drug carrier mix, and better content uniformity.

Semi-solid casting

This method is mostly preferred when film ingredient involves acid insoluble polymer. In this firstly, the water soluble polymers are dissolved in water. The obtained solution is added to the acid insoluble polymer solution which is separately formed. Both the solutions are mixed properly. After mixing the two solutions, appropriate

amount of plasticizer is added to the obtained final solution so that gel's mass can be obtained. At last, the gel mass is casted onto the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015-0.05". The ratio of the acid insoluble polymer to film forming polymer should be 1:4. Examples of acid insoluble polymers are cellulose acetate phthalate and cellulose acetate butyrate.

Solid dispersion extrusion

Method involves the solid dispersion of drug incorporated in melted polymer solution so that drug can be loaded. The drug is dissolved in suitable liquid solvent and obtained solution is added to the melt of suitable polymer, obtainable below 70°C without removing the liquid solvent to obtain the solid dispersion. Finally the obtained solid dispersions are shaped into films by means of dyes.

Rolling method

In rolling method, both the drug solution and film forming polymer solution are mixed thoroughly and the resultant solution or suspension is subjected to the roller. The solution or suspension should have specific rheological consideration. The film is dried on rollers and cut into desired shapes and sizes.

FLOATING *IN SITU* GEL

Floating *in situ* gels are novel gastroretentive drug delivery systems designed to prolong the residence time of a drug in the stomach, thereby enhancing its absorption and therapeutic efficacy. These systems are administered in a liquid form and undergo sol-to-gel transition under physiological conditions, such as changes in pH, temperature, or ionic concentration, after oral administration. The floating property of these gels allows them to remain buoyant on gastric fluids, preventing premature passage through the pylorus. This is typically achieved by incorporating gas-generating agents (such as sodium bicarbonate or calcium carbonate), which release CO_2 in the acidic environment of the stomach, or by using low-density polymers that help the formulation remain afloat [60,61]

DIFFERENT APPROACHES FOR *IN SITU* GELLING SYSTEM:[62]

The various mechanisms for triggering the in situ gelling formation are :-

A. *In situ* gel formation due to physiological stimuli:

- Temperature triggered in situ gel systems
- pH triggered in situ gelling systems

B. *In situ* gel formation due to ion-activated system

C. *In situ* gel formation due to physical mechanism

- Swelling
- Diffusion

D. *In situ* gel formation due to chemical reactions

- Ionic cross-linking
- Enzymatically cross linking
- Photo-polymerization

Advantages and disadvantages of Floating *in situ* gel [61-63]

Advantages

1. Increases the bioavailability of medications with a stomach absorption window.
2. Reduces the negative impact of medications on the colon.

3. Increases medicine efficacy by lowering the body's counteractivity.
4. Beneficial for medications that are absorbed in the small intestine's proximal region.
5. Beneficial for medications that operate locally in the stomach.
6. Enhances gastrointestinal residence time, which enhances medication absorption.

Disadvantages

1. For treatment to be effective, enough stomach fluid is needed.
2. Drugs with a high first-pass metabolism are not a good fit for this use.
3. It is not appropriate to take medications that cause stomach irritation.
4. Additionally, medications with poor aqueous solubility and GI tract stability issues are not good candidates for this delivery system.
5. Unstable medicine ingredients in the stomach's acidic environment are not good choices.

CONCLUSION:

In this review the differences in routes of administration of various medications and the regional differences in routes of use, have implications for the provision of preventive and treatment services. Furthermore, it has emphasized the significance of novel drug delivery systems (NDDS) in addressing the shortcomings of conventional methods. There are several administrative routes, primarily systemic and local. The enteral route, also known as the oral route, is the most widely used mode of administration for systemic routes. In contrast, the parenteral route should always be used in an emergency. There is also the local route, which involves applying the drug to a specific area of the body. This route determines the medication's bioavailability and time of effect. Drug delivery techniques that are new help to direct the medication to the location of action, hence minimizing side effects that are localized Such approaches include microspheres, liposomes, niosomes, nanoparticles.

Using an Innovative Drug Delivery Method The innovative dosage forms in NDDS combine cutting-edge technology with superiority over conventional dosage forms. The innovative drug delivery system offers advantages to patients, better therapy, reduced manufacturing costs, efficient use of expensive pharmaceuticals and excipients, ideal dosage at the right time and location, improved comfort and quality of life, and benefits to patients. Among the fundamental novel drug delivery system modalities are targeted and controlled drug delivery systems, among others. Pharmaceutical science focuses on the administration of medications, vaccinations, gene therapy, and the commercial development of new carriers, among other innovative methods for drug transport and targeting**.** The continued evolution and innovation in drug delivery technologies present promising opportunities for optimizing patient care and revitalizing existing pharmaceutical agents. As research and development in this area progress, the future of drug administration is poised to become more precise, effective, and patient-centric.

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REFERENCES

1. Reddy PD, Swarnalatha D. Recent advances in novel drug delivery systems. International Journal of PharmTech Research., 2010; 2(3):2025-2027.
2. Kharat A.and Pawar P. Novel Drug Delivery Systems In Herbals's International Journal Of Pharmaceutical, Chemical And Biological

Sciences 2014, 4(4), 910-930 ISSN: 2249-9504
3. Patwardhan B, Vaidya DB and Chorghade M. Ayurveda and natural Products drug discovery. Current Science 2004;86(6):789-799.
4. Lewis S, Subramanian G, Pandey S and Udupa N, Design, evaluation and pharmacokinetic study of mucoadhesive buccal tablets of nicotine for smoking cessation, 2006: 68:6: 829- 831.
5. Jain KK. An Overview of Drug Delivery Systems. Methods Mol Biol. 2020;2059:1-54.
6. Nicoll LH, Hesby A. Intramuscular injection: an integrative research review and guideline for evidence-based practice. Appl Nurs Res. 2002 Aug;15 (3):149-62
7. P. Verma , A.S. Thakur, K. Deshmukh, Dr. A.K. Jha, S. Verma, Routes Of Drug Administration, International Journal of Pharmaceutical Studies and Research E-ISSN 2229-4619
8. Sciarra J, Anthony J. Cutie. Pharmaceutical Aerosols. The Theory and Practice of Industrial Pharmacy. 2nd ed., Bombay, Varghese Publishing House, 1991: 589-618.
9. Pimple A, Kudal V, Murkute P, Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy,Aurangabad, Maharashtra, India, A Review: Routes Of Drug Administration With Their Recent Advances, International Journal Of Creative Research Thoughts, vol. 10, Issue 2, Feb 2022, ISSN: 2320-2882.
10. N.K. Jain. Controlled and novel drug delivery, first edition, CBS publishers and distributors, New Delhi, 1997.
11. D.M. Brahmankar, S.B. Jaiswal. Biopharmaceutics and pharmacokinetics A Treatise. Vallabh Prakashan, Delhi, 1995: 335-371.
12. Kagalkar A. A, Nitave S. A. Review: Approach On Novel Drug Delivery System World Journal Of Pharmacy And Pharmaceutical Sciences Volume 2,, Issue 5,, 3449-3461.. Review Article ISSN 2278 – 4357
13. Kalhapure R.S, et al. Nanoengineered Drug Delivery Systems for Enhancing Antibiotic Therapy. Journal of Pharmaceutical Sciences, 2015;104(3):872-905
14. Verma RK, Garg S, Current status of drug delivery technologies and future directions. Pharm Tech On-Line. 2001; 25(2):1-14.
15. Torchilin VP. Structure and design of polymeric surfactant-based drug delivery systems. J Control Release. 2001; 73:137-72.
16. Rajashekar K, Nandita G. D , Sudip K. Das, Emerging Nanotechnologies for Diagnostics, Drug Delivery and Medical Devices, 2017;105-144
17. Bhardwaj P, Tripathi P, Gupta R, Pandey S,.Niosomes: A review on niosomal research in the last decade , Journal of Drug Delivery Science and Technology,2020;56:101581 https://doi.org/10.1016/j.jddst.2020.101581
18. Kumar GP, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery-an overview. Acta Pharm Sin B. 2011;1:208. https://doi.org/10.1016/j.apsb.2011.09.002
19. Patil NV, Wadd NV, Thorat SS, Upadhye Shashikant Sudarshan, Microspheres: A Novel Drug Delivery System. American Journal of PharmTech Research 2020:20(10). ISSN: 2249-3387
20. Dhadde GS, Mali HS., Raut ID., Nitalikar MM., Bhutkar M A., A Review on Microspheres: Types, Method of Preparation, Characterization and Application, Asian Journal of Pharmacy and Technology. 11(2):2021, 1-5
21. Kumar R, Chandra A, Gautam PK and Shrivastava A: Resealed Erythrocytes as A Novel Carrier For Drug Delivery: A Review.

22. Kalita B., Das K.M., Sharma K.A., "Novel phytosome formulation making herbal extract more effective" J Pharm Technol 2013, 6 (11), 1295.
23. A.Vaishnavi1, Swarupa Arvapalli2, Ps.Rishika3, Syeda Jabeen4, B.Karunakar5, Dr.J.V.C Sharma6. A Review on Phytosomes: Promising Approach for Drug Delivery of Herbal Phytochemicals International Journal of Pharmaceutical Research and Applications Volume 6, Issue 1 Jan-Feb 2021, pp: 289-296 www.ijprajournal.com ISSN: 2249-7781
24. Barzaghi N, Crema F, Gatti G, Pifferi G, Perucca E: Pharmacokinetic Studies on Idb 1016, A Silybin Phosphatidylcholine Complex in Healthy Human Subjects, Eur J Drug Metab Pharmacokinetics 1990; 15: 333-38.
25. Bendas ER, Tadros MI. Enhanced transdermal delivery of sulbutamol sulfate via ethosomes. AAPS Pharm Sci Tech 2007;8:1-7.
26. Verma P, Pathak K, Therapeutic and cosmeceutical potential of ethosomes: An overview Journal of Advanced Pharmaceutical Technology & Research | Jul-Sep 2010 | Vol 1 | Issue 3 DOI: 10.4103/0110-5558.72415
27. Bhalaria MK, Naik S, Mishra AN. Ethosomes: A novel system for antifungal drugs in the treatment of topical fungal disease. Ind J Exp Biol 2009;47:368-75.
28. Pandey V, Golhani D, Shukla R, (2015) Ethosomes: versatile vesicular carriers for efficient transdermal delivery of therapeutic agents, Drug Delivery, 22:8, 988-1002, DOI: 10.3109/10717544.2014.889777
29. Jain, S.S. & Jagtap, Pramod & Dand, Neha & Jadhav, Kisan & Kadam, V.J.. (2012). Aquasomes: A novel drug carrier. Journal of Applied Pharmaceutical Science. 2. 184-192.
30. Rao S et al., Aquasomes: A Nanoparticulate Drug Carrier System . American Journal of PharmTech Research 2018.
31. Vyas S.P., Goyal A.K., Khatri K., Mishra N., Mehta A., Vaidya, B., et al. Aquasomes a nanoparticulate approach for the delivery of antigen. Drug Dev Ind Pharm. 2008; 34:1297-1305.
32. Alagusundaram M, Chetty MS, Umashankari C. Microspheres as a Novel drug delivery system - A review. Int J Chem. Tech. 2009;12: 526-534.
33. Kiyoyama S, Shiomori K, Kawano Y, Hatate Y. Preparation of microcapsules and control of their morphology. J Microencapsulation. 2003;20:497. https://doi.org/10.1080/02652040310000930 96
34. Kumari N, Verma S, Kumar, Sokindra. Microsponge: An advanced drug delivery system. Journal of Clinical and Scientific Research 2021,10(2):p 108-111
35. Nacht S, Kantz M. The microsponge: A novel topical programmable delivery system. Top Drug Deliv Syst 1992;42:299-325.
36. Aritomi H., Yamasaki Y., Yamada K., Honda H, Koshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method. Journal of Pharmaceutical Sciences and Technology. 1996; 68(1): 49-56.
37. D"souza J.I., Masvekar R.R., Pattekari P.P., Pudi S.R , More H.N. Microspongic delivery of fluconazole for topical application. Indo-Japanese Int. Conference on Adv. Pharm. Res. and Tech. 2004;76.
38. Parthiban K.G., Manivannan R., Krishnarajan D., Chandra S., Nidhin R. Microsponge role in novel drug delivery system. Intl. J. Pharm. Res. Devel., 2011; 3(4): 117-125.

39. Kaity S, Maiti S, Ghosh A, Banerje S, Microsponges: A novel strategy for drug delivery system, Journal of Advanced Pharmaceutical Technology & Research | Jul-Sep 2010 | Vol 1 | Issue 3 DOI: 10.4103/0110-5558.72416
40. Pahade A, Jadhav VM, Kadam VJ. Sonophoresis: an overview. International Journal of Pharmaceutical Sciences Review and Research 2010; 3 Suppl 2:24-32.
41. Mitragotri S, Blankschtein D, and Langer R. Transdermal drug delivery using low-frequency sonophoresis. Pharmaceutical research 1996; 13 Suppl 3:411-420. https://doi.org/10.1023/A:1016096626810 PMid:8692734
42. Allen LV, Popovich NG, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems. Transdermal drug delivey systems. 8th ed. India: Gopsons papers ltd.; 2006;298-315.
43. Sahoo C.K., Rao S.R., Sudhakar M. Evaluation of controlled porosity osmotic pump tablets: A Review. Res. J. Pharm. Technol. 2015;8:1340. https://doi.org/10.5958/0974-360X.2015.00312.1
44. Sareen R., Jain N., Kumar D.J. An insight to osmotic drug delivery. Curr. Drug Deliv. 2012; 9:285-296. https://doi.org/10.2174/156720112800389106 PMid:22452403
45. Malpure PS et al., A Review On- Hydrogel. American Journal of PharmTech Research 2018
46. Sing SK, Juyal D. Hydrogels: Preparation, characterization and Applications. The Pharma Innovation journal. 2017; 6(6): 25-32.
47. Sherbiny IM, Yacoub MH. Hydrogel scaffolds for tissue engineering: Progress and challenges. Global Cardiology Science and Practice. 2013; 38.
48. Vondrak B, Barnhart, Scott. Dissolvable films: Dissolvable films for flex product format in drug delivery. Pharm rechnol 2008. P. 1-5.
49. Bhyan B, Jangra S, Kaur M, Singh H;Orally Fast Dissolving films: Innovation in formulation and technology. International journal of pharmaceutical science review and research, Vol. 9, Issue 2, Aug 2010.
50. Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Int J Pharm Sci Rev Res 2011;9:50-6.
51. Bhura N, Sanghivi K, Patel U, Parmar B. A review on fast dissolving film. Int J Res Bio Sci 2012;3:66-90
52. K.Sunil Kumar Reddy et al. A Detailed Review on Fast Dissolving Oral Films. Indo American Journal of Pharmaceutical Research.2018:8(06).
53. Siegel, I.A. and H.P. Gordon, 1985. Surfactant- induced increase of permeability of rat oral mucosa to non-electolytes in vivo. Archives of Oral Biol., 30: 43-47.
54. Fulzele SV, Satturwar PM, Dorle AK. Polymerized rosin:Novel film forming polymer for drug delivery. Int J Pharm 2002;249:175-84.
55. Bala R, Pawar P, Khanna S, Arora S. Orally dissolving strips: A new approach to oral drug delivery system. Int J Pharma Investig 2013;3:67-76.
56. Khairnar A, Jain P, Bhaviskar D, Jain D. Development of mucoadhesive buccal patches containing aceclofenac: In vitro evaluation. Int J Pharm Sci 2009;1:91-5.
57. Shinde AJ, Garala KC, More HN. Development and characterization of transdermal therapeutics system of tramadol hydrochloride. Asian J Pharm 2008;2:265-9.

58. S. Lydzinski, T. Manegold, D. Solarek, J. Tsai, C. Puglisi, Film containing starch, U.S.Patent 2003/0099692, May 29, 2003.
59. Hypromellose, Ethylcellulose and Polyethylene oxide used in hot melt extrusion. Coppens, K.A., M.J. Hall, S.A. Mitchell and M.D. Read, 2005. Pharmaceutical Technol., pp: 1-6
60. Devasani S. Dev A. Rathod S. Deshmukh G, An overview of in situ gelling systems, Pharmaceutical and Biological Evaluations 2016; vol. 3 (1): 60-69. ISSN: 2394-0859.
61. Patial K, Dua JS, Menra M and Prasad DN., A review: Floating drug delivery system. World Journal of Pharmaceutical Research,2016; 6 ; 614-633.
62. Vijayakumar A, Senthilnathan B, Ravichandiran V., A Review Article on Different Types of Floating Drug Delivery Systems. International Journal of Pharmacy and Pharmaceutical Sciences,2012;4(1); 45-50.
63. Kataria S, Middha A, Bhardwaj S, Singh P, Floating Drug Delivery System: A Review. International Research Journal of Pharmacy,2011;2(9);18-24.
64. https://hello100.com/what-is-the-liposome-and-the-liposomal-drug-delivery/
65. Dhiman J, Novel Drug Delivery System: Brief Review. Journal of Drug Delivery and Therapeutics. 2023, 13. 188-196. 10.22270/jddt.v13i11.6023.
66. Ahlawat, J.; Henriquez, G.; Narayan, M. Enhancing the Delivery of Chemotherapeutics: Role of Biodegradable Polymeric Nanoparticles. Molecules 2018, 23, 2157. https://doi.org/10.3390/molecules23092157
67. Awasthi, R, Kulkarni, G, Pawar, V. Phytosomes: An Approach to Increase The Bioavailability of Plant Extracts. International Journal of Pharmacy and Pharmaceutical Sciences. 2021, 3. 1-3.
68. https://www.omicsonline.org/articles-images/JBABM-07-006-g001.html
69. Pandey V, Golhani, D, Shukla R. Ethosomes: Versatile vesicular carriers for efficient transdermal delivery of therapeutic agents. Drug delivery.2014, 22. 10.3109/10717544.2014.889777.
70. Kumar R, Gulati M. Aquasomes- A promising carrier for protein and peptides.. Nanomedicine: Nanotech. Biol. Med.. 2010, 6. 419-426.
71. Barani M, Sangiovanni E, Angarano M, Rajizadeh MA, Mehrabani M, Piazza S, Gangadharappa HV, Pardakhty A, Mehrbani M, Dell'Agli M, Nematollahi MH. Phytosomes as Innovative Delivery Systems for Phytochemicals: A Comprehensive Review of Literature. Int J Nanomedicine. 2021;16:6983-7022 https://doi.org/10.2147/IJN.S318416
72. Kulkarni A, Ingale D, Patil, R.A. Microsponges as Innovative Drug Delivery Systems. Int J Pharm Sci Nanotechnol. 5. 2012, 10.37285/ijpsn.2012.5.1.2.
73. https://plasticsurgerykey.com/therapeutic-applications-of-sonophoresis-and-sonophoretic-devices/

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