National Journal of Pharmaceutical Sciences

E-ISSN: 2788-9270
P-ISSN: 2788-9262
www.pharmajournal.net
NJPS 2022; 2(2): 177-190
Received: 10-06-2022
Accepted: 15-08-2022

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Dosage forms in novel drug delivery system

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Abstract
Novel Drug Delivery System an existing drug molecule can get a new life. An appropriately designed Novel Drug Delivery System can be a major advance for solving the problems related towards the release of the drug at specific site with specific rate. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. This article covers the basic information regarding Novel Drug Delivery Systems and also different types of the same.
Now-a-days, recent advances in the understanding of pharmacokinetic pharmacodynamic behaviour of drug have offer a more rational approach to the development of optimal drug delivery system. Now it's appreciable that future success in Drug delivery research will largely be result of multidisciplinary efforts. If any therapeutic agent that can be the more efficacious and safe using and improved drug delivery system represent both lucrative marketing opportunities for pharmaceutical company and advancement in the treatment of diseases of mindkind. An ideally design drug delivery system delivers a specified amount of drug to target particular site at an appropriate time and rate as dictated or desired by the etiological and physiological needs of the body. Conventional Pharmaceutical Dosage forms are incapable of controlling the rate of drug delivery to target site. As a result the distribution of drug in non- target tissue and body fluids necessitate therapeutic doses that could far exceed the amount required in target cells, the higher doses often lead to serious adverse during treatment thus, the novel drug delivery systems (NDDS) are carriers which maintain the drug concentration in therapeutic range for longer period of time and also, in addition, may deliver the content to the site of action if so desired as per requirements.

Keywords: Novel drug delivery system, nano particle, therapeutic agent, phytopharmaceuticals, herbal medicine

Introduction
Novel drug delivery system
Definition and Brief View
Since ancient times, complex chemical concoctions made from plants, or phytomedicines, have been utilised to maintain health. However, many phytomedicines' efficiency is constrained due to their poor oral absorption. Phyto denotes a plant, and some implies something that resembles a cell. Phytosomes are tiny structures that resemble cells [1]. A lipid surrounds and binds the bioactive phytoconstituents of the herb extract in this sophisticated form of herbal preparation. Water-soluble substances like flavonoids, glycosides, and terpenoids of which flavonoids are a significant class-make up the majority of the bioactive components of phytomedicines.
Plants are nature’s remedies and have been used by human beings on earth since ancient times for food and medicine. Today there are global movements towards finding of herbal medicaments in plants to bring them in market via a suitable drug delivery system for mankind. The basic thought behind it is treatment of each disease is hidden in nature. However, delivery of herbal drugs also requires modification with the purpose to achieve sustain release, to increase patient compliance etc. previously herbal drugs could not attract scientists towards the modifications of novel drug delivery systems due to processing, standardizing, extracting and identification difficulties. But now days with the advancement in the technology, novel drug delivery systems (NDDS) open the door towards the development of herbal novel drug delivery system. With use of advance techniques protection from toxicity, enhancement in stability, improved bioavailability of herbal formulations, protection from physical and chemical degradation can be achieve. Novel drug delivery technologies have gained the importance to achieve modified delivery of herbal drugs their by increasing the therapeutic value as well as reducing toxicity.

The present reviews gives information regarding various novel techniques used for improving safety and efficacy of phytomedicines and application of novel formulation [2].

Novel drug delivery systems will present an opportunity for formulation scientists to overcome the many challenges associated with current antihypertensive drug therapy, thereby improving the management of patients with hypertension in future. Evolution of an existing drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety and efficacy. In the form of a Novel Drug Delivery System an existing drug molecule can get a new life. An appropriately designed Novel Drug Delivery System can be a major advance for solving the problems related towards the release of the drug at specific site with specific rate. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery system. This article covers the basic information regarding Novel Drug Delivery Systems and also different types of the same.

Phytosome drug delivery system

Introduction

By combining standardised plant extracts or water-soluble phytoconstituents with phospholipids to form lipid-compatible molecular complexes, a new patented technology known as herbosomes significantly improves absorption and bioavailability. Cells and plants are referred to as "Phyto" and "some", respectively. Based on recent advancements and the findings of various research investigations, transdermal distribution of phytoconstituents has been recognised as a potential technique. Plant-derived products or plant extracts are gaining popularity as dietary supplements for the homeostatic regulation of inflammation, toxins, malignancies, weight loss, and other chronic or acute degenerative disorders. However, these drugs frequently have stability and bioavailability problems [3, 4, 5].

Plant products become unstable when isolated and might not be suitable for usage across international borders. The actual biological membrane. These tasks are substantially easier using the phytosome technique. The phytosome or herbosome technique increases the hydrophilicity of highly lipophilic medicines, enabling them to be used for drug delivery, and improves the lipophilicity of hydrophilic phytoconstituents sufficiently to penetrate biological membranes. The ability of phytosomes to be used topically for cosmetic purposes has already been proven. This article contains a comparison of phytosomes with liposomes with an emphasis on transdermal drug delivery, along with recent advancements in phytosome technology [6, 7]. The poor oral bioavailability of polyphenolic substances can be improved by incorporating them into phospholipid-based self-assembled delivery vehicles known as phytosomes. There are several things with available phytosomal compounds. Examples of natural drug delivery methods include Ginkgo biloba, Silybum marianum and Camellia sinensis.

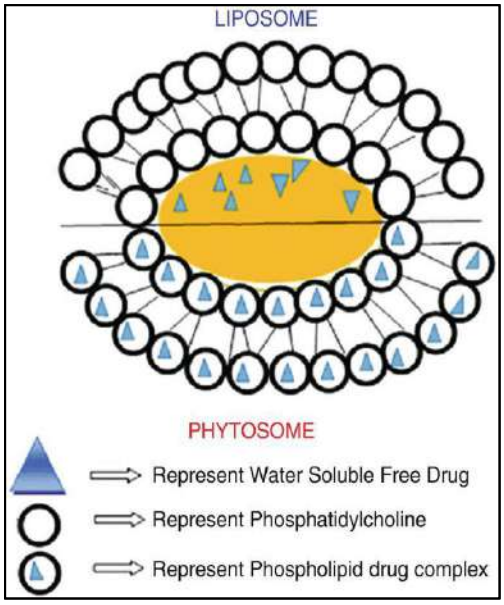

Fig 1: Structure of Phytosomes

Table 1: Some marketed formulation of phytosomes

Product	Indication	Dosage form
Ginkgo Select phytosomes	Improve memory, brain function circulation and blood flow	Capsule
Grape seed	Promotes adaptogenic function and resistance to stress	Capsule
Green Tea phytosome	Natural antioxidant protection	Capsule

Method of preparation

Typically, phytosomes can be produced using the solvent evaporation method. Drop by drop, phytoconstituents such bioflavonoids, flavonolignan and polyphenolic compounds react with phospholipid-based phosphatidylcholine (PC), a solution of natural or synthetic phospholipids, to generate phytosomes. In this manner, ginsenoside, puerarin and kushenin phytosomes are created.

Another illustration is the Curcumin phospholipid complexes, which are produced by mixing the phospholipids with the hydro-alcoholic extract of turmeric rhizomes in an ethanol solution and letting it reflux. Phytosomes produced by non-solvent methods such as freeze drying and spray [8].

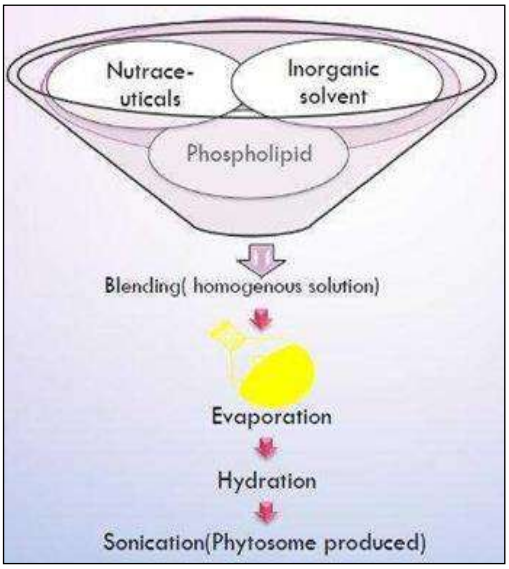

Fig 2: Representation of Phytosome Preparation

Properties of phytosomes

1) Physico chemical properties

A natural substance and organic phospholipids, such as soy phospholipids, come together to form phytosomes. A stoichiometric reaction between the substrate and phospholipids in the proper solvent results in the formation of this complex. Based on spectroscopic evidence, it has been demonstrated that the primary interaction between phospholipids and their substrate is caused by the formation of hydrogen bonds between the polar head of phospholipids (i.e., the phosphate and ammonium groups) and the polar functionalities of the substrate. Phytosomes take on a micellar shape after being exposed to water, generating structures that resemble liposomes. The active ingredient in liposomes is either dissolved in the internal pocket or floats in the layer membrane. In contrast, the active ingredient in phytosomes is tethered to the polar head of phospholipids and becomes a structural component of the membrane. The phenolic hydroxyl terminals of the flavones moiety and the phosphate ion on the phosphatidylcholine moiety, for instance, form H-bonds in the case of the catechin distearoyl phosphatidylcholine complex [9, 10]. The complex's 1H and 13C NMR spectra can be compared to those of the pure precursors to determine the presence of phosphatidyl choline. The signals of the fatty chain are mostly unaltered. By generating a lipophilic envelope that protects the polar head of the phospholipid and flavonoid molecules and enables the complex to dissolve in low polarity liquids, the too-long aliphatic chains are thought to be wrapped around the active principle. This was inferred from the evidence [11].

Biological properties: In comparison to traditional herbal extracts, phytosomes are more advanced herbal products that are better absorbed, used and hence offer greater effects. Pharmacokinetic investigations or pharmacodynamic tests on experimental animals and humans have shown that the phytosome has a higher bioavailability than the non-complexed botanical derivatives.

Advantages: The Italian company Indena S.P.A. created the phytosome technology, which significantly increases the bioavailability of specific phytomedicines by integrating phospholipids into standardised plant extract, which enhances their absorption and utilisation. Both in water and lipids, the polyphenols have a limited solubility. Through hydrogen bonding and polar interactions with the charged phosphate head of phospholipids, the polar functions of the lipophilic guest interact to generate a distinctive structure that may be demonstrated by spectroscopy8. Due to the fact that phosphatidylcholine is a bifunctional molecule with a hydrophilic choline and a hydrophobic phosphatidyl group, the chemical binds to the choline group head while the phosphatidyl section envelops the bounded area [12].

To meet contemporary food criteria, the phytosome generations have recently been produced employing hydro-ethanolic solvent instead of the first generation's method of mixing chosen polyphenolic extract with phospholipids in a nonpolar solvent.

1. Increase the bioavailability and improve lipid-insoluble polar phytoconstituent absorption.
2. Considerable drug entrapment that is advantageous.
3. Due to improved absorption, lower the dose.
4. Because phosphatidylcholine also has hepatoprotective properties, it exhibits synergistic effects.
5. Because of the chemical connection between the phytoconstituents and the carrier, phosphatidylcholine, phytosomes are more stable.
6. Successful in cosmetics.

Disadvantages

Phytosomes have a lot of benefits, but there are some drawbacks to this technology, such as the quick removal of phytoconstituents from the Phytosome.

Liposomal drug delivery system

Introduction

Liposomes are vesicular structures made of bilayers that spontaneously develop when phospholipids are spread in water. They are a new drug delivery system (NDDS). They are microscopic vesicles that completely surround an aqueous volume with a membrane made of lipid bilayers. The goal of NDDS is to give the medication at a pace determined by the body's demands during the course of treatment and to target the site of action. Liposomes, also known as vesicles or colloidal spheres, are composed of cholesterol, non-toxic surfactants, sphingolipids, glycolipids, long-chain fatty acids, even membrane proteins, and medicinal molecules. It varies in size, composition, and charge and is a drug carrier that is loaded with a range of molecules, including proteins, nucleotides, plasmids, and tiny drug molecules. To increase their therapeutic index, only a small number of medicines are created as liposomes. As a result, several vesicular drug delivery systems, including liposomes, niosomes, transfersomes and pharmacosomes, are being developed. This chapter focuses on different preparation techniques, liposome characterisation, benefits and applications, among other things [13].

Drug delivery systems called liposomes have been hailed as promising and adaptable. Site-targeting, sustained or controlled release, protection of pharmaceuticals from degradation and clearance, improved therapeutic benefits, and fewer harmful side effects are just a few of the advantages liposomes have over conventional drug delivery methods. These advantages have led to the successful approval and usage of a number of liposomal medicinal

products in clinics during the past couple of decades [14, 15]. The liposomal pharmaceutical products that have been approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) are reviewed in this overview. Based on the FDA's and EMA's published clearance packages, crucial chemistry data, and established pharmaceutical technologies used in commercially available liposomal products, such as the lipid excipient, manufacturing processes, nanosizing methodology, and drug loading are introduced, along with critical quality attributions (CQAs) of items. Also outlined are the existing regulatory guidelines and anticipated developments for liposomal products. This information can be applied to the development of potential liposomal drugs at many stages of the pipelines, including on the lab bench, in pilot plants and during mass production [16].

Liposomes are self-assembling (phospho) lipid-based drug vesicles with a core aqueous compartment enclosed by a single bilayer (uni-lamellar) or a concentric series of multiple bilayers (multi-lamellar). The phospholipid bilayer of liposomes, which range in size from 30 nm to the micrometre scale, is 4-5 nm thick. In the middle of the 1960s, British scientist Alec Bangham and colleagues at Babraham Cambridge established the science of liposomology. In 1964, they released the first study describing the structure of liposomes. Since then, a lot of research has been done on the use of liposomes as carriers for small-molecule medicines, proteins, nucleic acids, and imaging agents [17]. To increase treatment efficacy and patient compliance, various delivery routes, including parenteral, pulmonary, oral, transdermal, ocular and nasal routes, have been devised. Additionally, liposomes have been used extensively in a variety of fields of cosmetics and food.

Liposomes are exceptional drug delivery systems because they preserve the encapsulated materials from physiological deterioration, increase the drug's half-life, regulate drug molecule release and have great biocompatibility and safety. Furthermore, by passively or actively directing their payload to the sick location, liposomes can reduce systemic side effects, increase the maximum tolerated dose, and enhance therapeutic effects [18, 19].

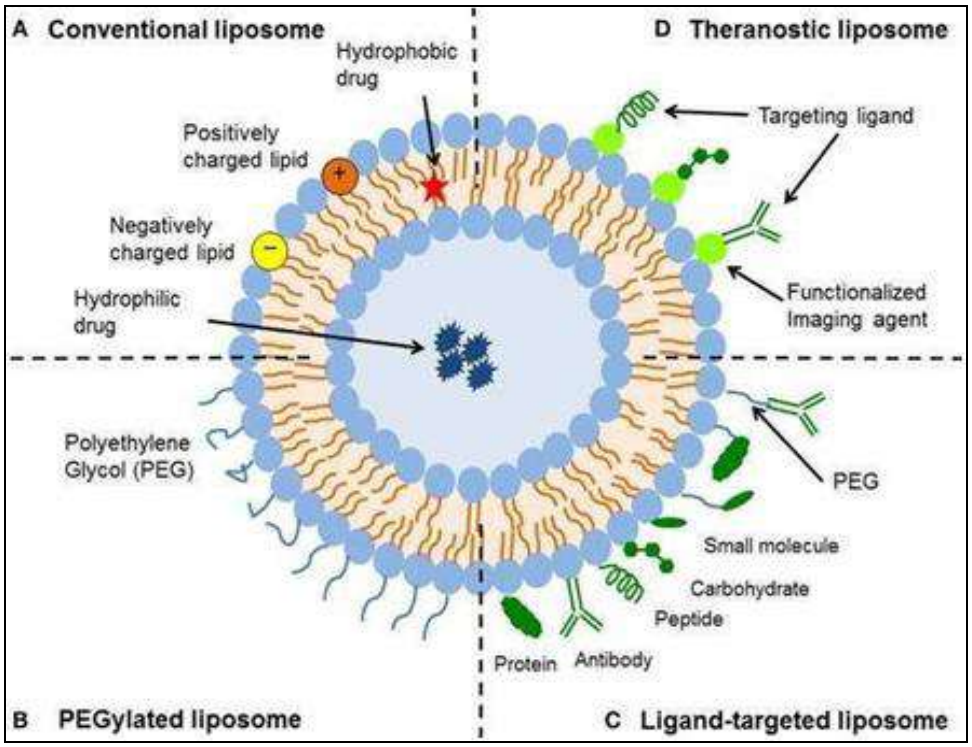

Fig 3: Structure of Liposomal

Advantages

1. Improved pharmacokinetic and pharmacodynamic management.
2. Reduction in toxicity.
3. Increased medication effectiveness against intracellular infections.
4. Target-specific usage of liposomes.
5. Increased action against infections that are extracellular.

Disadvantages

The expense of making lipid-based drug delivery systems is considerable, which drives up production costs. The price is high because producing more fatty excipients requires expensive machinery and raw materials, both of which are expensive [20, 21].

Microemulsion drug delivery system

Introduction

Almost all administrative channels have been used to exploit the novel carriers. With the development of technology and the need for tailored delivery methods like microemulsions, several innovative carriers are currently emerging. A co-surfactant is routinely added to clear, stable, isotropic solutions of oil, water, and surfactant to create microemulsions. One or more surfactants, a co-surfactant, and a medication are dissolved in oil to create the microemulsion formulations. Oils create a unique core inside the surfactant aggregate, which improves the oils' ability to dissolve other substances and the microemulsion ability to load more drugs. Recent research suggests that microemulsions [o/w or w/o] have enormous potential to improve the bioavailability of medications [22]. The focus of

the current review was on microemulsion formulation, benefits, and applications. A thorough understanding of the micro-emulsion structure, phase behaviour, factors contributing to its thermodynamic stability, factors influencing drug release from the formulation, requirements for ideal microemulsion excipients, and potential uses and limitations of the microemulsion are necessary for creating a pharmaceutically acceptable dosage form.

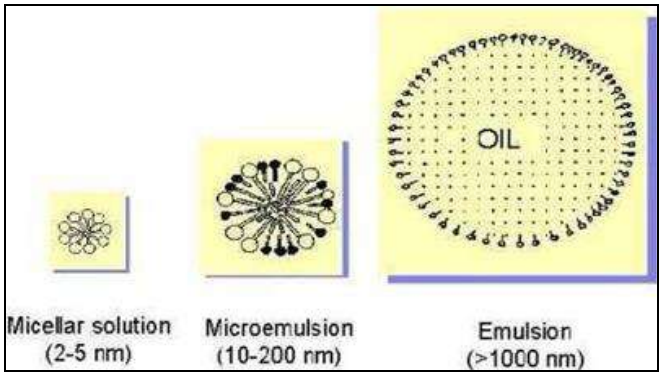

Fig 4: Structure of Microemulsion

Pharmaceutical research is constantly developing new drug delivery systems with the goal of improving the efficacy of already available medications. Given the variety of drug delivery methods that have been created, colloidal drug delivery systems in particular have a great deal of promise to help with drug targeting [23]. A thermodynamically stable, isotropically transparent dispersion of two immiscible liquids, such as oil and water, stabilised by an interfacial coating of surfactant molecules is referred to as a "microemulsion". A polar and an apolar group are both present in the molecules of surfactants. As a result, they display some extremely odd behaviour. To start, they become adsorbed at the interface, where they can satisfy their dual affinity for hydrophilic groups situated in hydrophobic groups in oil or the watery phase. Second, they use the Micellization Process to lessen solvent mismatching. The oil/water interfacial tension is extremely low in the dispersed phase, which typically consists of minute particles or droplets with a size range of 5 nm-200 nm. Microemulsions are transparent because the droplet size is less than 25% of the wavelength of visible light. The microemulsion forms easily and occasionally on its own, usually without the use of much energy. In addition to the surfactant, the oil phase, and the water phase, a cosurfactant or cosolvent is frequently utilised. Hoar and Schulman first proposed the idea of a microemulsion in 1943. To create the first microemulsions, they dispersed oil in an aqueous surfactant solution and added alcohol as a co-surfactant, resulting in a clear, stable formulation. A microemulsion is a system of water, oil, and amphiphilic chemicals (surfactant and co-surfactant), which is a transparent, single optically isotropic, and thermodynamically stable liquid. The existence of this theoretical structure was later proved by use of multiple technologies [24, 25].

Advantages

1. Quicken the absorption rate.
2. Does away with variations in absorption.
3. Aids in the solubilization of lipophilic medications.
4. Offers aqueous dose forms for medications that are not water soluble.
5. Enhances bioavailability in.
6. The medicine can be delivered via a number of different ways, including oral, intravenous, and tropical.
7. The drug moiety is penetrated quickly and effectively.
8. Effective at disguising flavour.
9. Offers defence against hydrolysis and oxidation since the medicine in the oil phase of the o/w microemulsion is not exposed to water and air, which can both cause damage.
10. Patient compliance is improved by liquid dosage forms.
11. Lower energy requirements [26, 27, 28].

Disadvantages of microemulsion based systems

1. The stabilisation of nano droplets requires the use of co-surfactants and surfactants at high concentrations.
2. Limited ability to dissolve materials with high melting points.
3. The surfactant used in pharmaceutical applications must not be harmful.
4. Environmental factors like pH and temperature might affect how stable a microemulsion is. When patients get microemulsions, these parameters change.
5. It may have a softening or hardening impact on the capsule shell when a special dosage is prepared in gelatin capsules, making it unattractive for long-term storage [29].

Applications

Pharmaceutical microemulsion parenteral administration: Due to the extremely low concentration of drug that is actually delivered to a targeted site, parenteral administration (particularly via the intravenous route) of medicines with restricted solubility is a significant issue in the pharmaceutical industry. When administered parenterally, microemulsion formulations have unique advantages over macroemulsion systems because the small particles in the former are eliminated more slowly than the latter and so have a longer residence time in the body. For parenteral administration, O/W and W/O microemulsions are both acceptable [30].

Pharmaceutical peptide and protein medications have very strong physiological effects and are very targeted. The majority, though, are challenging to provide orally. They are typically not therapeutically active when taken orally since their conventional (i.e., non-microemulsion based) formulation has an oral bioavailability of less than 10%. Most protein medicines are only offered as parenteral formulations due to their poor oral bioavailability. Peptide medications must be dosed numerous times since they have a very short biological half-life when given by parenteral route [31].

Topical administration: There are a number of reasons why topical administration of medications is preferable to other approaches, one of which being the avoidance of the drug's hepatic first pass metabolism and associated adverse consequences. Another is the drug's capacity to distribute itself directly to the skin or eyes that is impacted.

Ocular and pulmonary delivery: Drugs are mostly administered topically during ocular and pulmonary delivery for the treatment of eye illnesses. O/W microemulsions have been studied for use in ocular

delivery, to break down poorly soluble medications, to improve absorption and to achieve a prolonged release profile [32, 33].

Microsphere drug delivery system

Introduction: Microspheres are typically free-flowing powders made of proteins or synthetic polymers, with particle sizes ranging from 1-1000.

In order to increase bioavailability, stability, and activity at the specified site to a predetermined pace, microspheres are utilised in drug delivery systems designed to achieve prolonged or controlled drug delivery. Since microspheres are spherical, the therapeutic effectiveness of microspheres carrying drugs depends on their properties, which can be changed as needed by changing the materials, processes, polymers or techniques utilised. In comparison to traditional dosage forms, these delivery systems provide a number of benefits, including increased efficacy, decreased toxicity, better patient compliance, and convenience. Glass, polymers and ceramic are just a few of the materials that can be used to make microspheres [34].

There are many different types of microspheres, including bioadhesive microspheres, magnetic microspheres, floating microspheres, radioactive microspheres, polymeric microspheres, biodegradable polymeric microspheres, and synthetic polymeric microspheres. They are made using a variety of techniques, including spray drying, solvent extraction, quasi emulsion solvent diff, single-emulsion technique, double-emulsion technique, phase separation coacervation technique and spray drying Microspheres regulated and prolonged release makes them suitable for a variety of uses.

According to one definition, microspheres are chemicals or compounds with a free-flowing quality (powders). Proteins or synthetic polymers that are biodegradable in nature make up microspheres, which should ideally have particles between 1 and 1000 m in size.

Microparticles is another name for microspheres. Glass, polymers and ceramic microspheres are just a few of the materials that can be used to make microspheres. Depending on the material and particle size utilised in construction, they are employed in a variety of applications. Microspheres come in two varieties: microcapsules and micrometrics. Micro-capsules are those in which the material that is being contained is clearly enclosed by a distinct capsule wall. The entrapped substance in micrometrics is spread throughout the matrix (see figure 1). The use of microspheres can reduce adverse effects and increase the bioavailability of traditional medications [35, 36, 37].

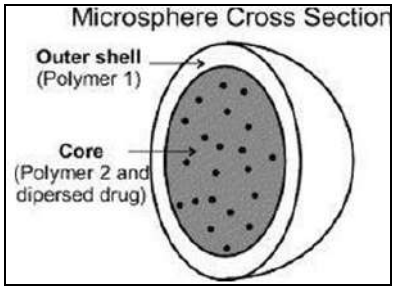

Fig 5: Structure of Microsphere

Advantage

1. The poorly soluble medication becomes more soluble after particle size reduction.
2. The therapeutic impact of microsphere is continuous and lasting.
3. Maintain a steady drug level in the blood to improve patient compliance.
4. Reduce toxicity and dosage.
5. They are excellent for drug distribution because they prevent enzymatic and photolytic cleavage of the medication.
6. Decrease the dosage frequency to increase patient compliance.
7. More effective medicine use will increase bioavailability and lessen the frequency or severity of side effects.
8. Guards against the drug's irritating effects on the GIT.
9. Compared to big polymer implants, biodegradable microspheres offer the benefit of not requiring surgery for installation or removal.
10. Biodegradable microspheres are utilised in controlled release drug delivery to regulate drug release rates, which reduces harmful side effects and the issues associated with repeated injections.
11. Masking of taste and odour.
12. The solidification of oils and other liquids for handling.
13. Drugs that protect the environment (moisture, light etc.).
14. Powder flow has been improved.
15. Assists or facilitates the dispersion of compounds that are insoluble in water in aqueous media [38].

Disadvantage

1. Compared to ordinary formulations, the prices of the components and processing for the controlled release preparation are significantly greater.
2. How polymer matrix decays and how it affects the environment.
3. What happens to polymer additives such fillers, stabilisers, antioxidants and plasticizers.
4. There is less reproducibility.
5. Process variables such as temperature variation, pH changes, solvent addition, and agitation/evaporation may have an impact on the stability of the core particles to be encapsulated.
6. The impact on the environment of the polymer matrix breakdown products created in reaction to heat, hydrolysis, oxidation, solar radiation, or biological agents [39].

Ideal properties of microspheres

1. The capability of incorporating medication concentrations that are reasonably high.
2. After synthesis, the preparation must be stable and have a shelf life that is therapeutically acceptable.
3. Particle size and dispersibility in aqueous injection vehicles are controlled.
4. Controlled release of the active reagent over a broad time frame. Biodegradability that is manageable while maintaining biocompatibility.
5. Chemically modifiable susceptibility [40].

Evaluation parameters of microsphere

1. Size and form of the particles SEM and conventional light microscopy (LM) are the two most popular techniques for observing microparticles (SEM).
2. **Electron spectroscopy for chemical analysis:** This technique can be used to determine the surface chemistry of the microspheres (ESCA).

3. **Determining density:** A multi volume pycnometer can be used to estimate the density of the microspheres.
4. **Isoelectric point:** By measuring the electrophoretic mobility of microspheres using micro electrophoresis, the isoelectric point can be ascertained.
5. **Angle of contact:** The angle of contact is assessed to ascertain a microparticulate carrier's wetting characteristic.
6. **Methods used *in vitro*:** Rotating paddle apparatus (USP/BP) is the most common dissolution media used for release investigations on various types of microspheres.
7. The effectiveness of drug entrapment can be determined using the formula: % Entrapment = Actual content/Theoretical content x 100.
8. **Swelling index:** The formula used to compute the swelling index of the microsphere was: Swelling index = (mass of swollen microspheres-mass of dry microspheres/mass of dried microspheres) [41].

Application of microspheres

1. Vaccine distribution.
2. Monoclonal antibodies.
3. Imaging.
4. Topical microspheres with pores.
5. Nasal medication administration.
6. Oral medication administration.
7. Specializing in medicine delivery.
8. Controlled delivery system that is gastroretentive.
9. Use in biomedicine.
10. Application in medicine [42].

Table 2: Other application of microspheres

Category	Drug	Uses
NSAID	Aceclofenac 25	Anti-inflammatory
Antibiotic	Amoxic	For helicobacter pylorl infection
Anti-inflammatory	Indomethacin 28	Anti-inflammatory
Steroidal	Progesterone 34	Steroid
Antidiabetic agents	Insulin	Antihyperglycemic

Table 3: Marketing formulation of Microspheres

Brand name	Drug	Treatment
Pantoprazole	Pantoprazole	Gastric ulcer
Altinac, Avita	Tretinoin	Skin renew
Optician	Human albumin microspheres	Ultrasound imaging procedure

Transferase drug delivery system

Introduction

Due to the ongoing advancements in the industry, transdermal drug delivery strives to develop a reliable and efficient technique of delivering medications through the skin. Almost identical in structure to liposomes but with stronger skin penetration capabilities, transferosomes are flexible or malleable vesicles that were first discovered in the early 1990s.

The Latin word "Transferee," which means "to carry through" and the Greek word "soma," which means "body" were combined to form the moniker "transporting bodies" or transferosomes. In contrast to conventional herbal extracts, phytosomes (Transferosomes) are made by joining particular herbal extracts to phosphatidylcholine. This results in a formulation with improved pharmacokinetic and pharmacodynamic properties of the entrapped drugs due to the formulation's increased solubility and better absorption. As we have standardised vesicular administration of herbal medications through skin, we are referring to phytosomes and transferosomes interchangeably. With a focus on phytosomes (Transferosomes), a particular lipid-based nanocarrier for transdermal medication delivery, we have highlighted in this mini-review the immense potential of developing nanotechnology to deliver bioactive phytochemicals.

The transdermal drug delivery system (TDDS) is a viable substitute for hypodermic injection and an appealing alternative to taking medications orally. For therapeutic purposes, people have applied chemicals and herbal extracts to their skin for thousands of years. In the modern era, a wide variety of topical formulations have been developed to treat local indications. Transdermal administration offers a number of advantages over oral delivery. It is used especially when the liver has a significant first-pass effect that could result in drugs being digested too quickly. Additionally, transdermal administration has benefits over hypodermic injections, which are uncomfortably painful, generate hazardous medical waste, and pose a danger of disease transmission through the reuse of needles, especially in underdeveloped countries [43].

The delivery of medicinal phytochemicals externally can change with the development of transfersomes (phytosome) nanotechnology. Their incredibly low absorption rate is the main barrier preventing phytochemicals from releasing their therapeutic potential in a clinical setting a critical function in enhancing the pharmacokinetic and pharmacodynamic properties of polyphenolic compounds obtained from herbs, making this nanotechnology a potential tool for the development of innovative topical formulations. With the use of this nanosized vesicular drug delivery technique, phytochemicals may be better able to cross biological barriers due to their unique physicochemical features, thus increasing their bioavailability. Phytochemicals found in medicinal plants are now being numerous illnesses are treated using it on a regular basis. However, their lack of selectivity and limited bioavailability may limit their therapeutic utility.

Because of this, bioavailability is viewed as a major obstacle to enhancing the bio- efficacy of transporting dietary phytochemicals. However, the fundamental structure of a transfersomes is a suitable method for transdermal phytochemical transport for local and systemic therapeutic action due to its improved membrane flexibility, ultra-deformability and soft nature Because of this, bioavailability is viewed as a major obstacle to enhancing the bio-efficacy of transporting dietary phytochemicals. However, the fundamental structure of a transfersomes is a suitable method for transdermal phytochemical transport for local and systemic therapeutic action due to its improved membrane flexibility, ultra-deformability, and soft nature Because of this, bioavailability is viewed as a major obstacle to enhancing the bio-efficacy of transporting dietary phytochemicals. However, the fundamental structure of a transfersomes is a suitable method for transdermal phytochemical transport for local and systemic therapeutic action due to its improved membrane flexibility, ultra-deformability, and soft nature Because of this,

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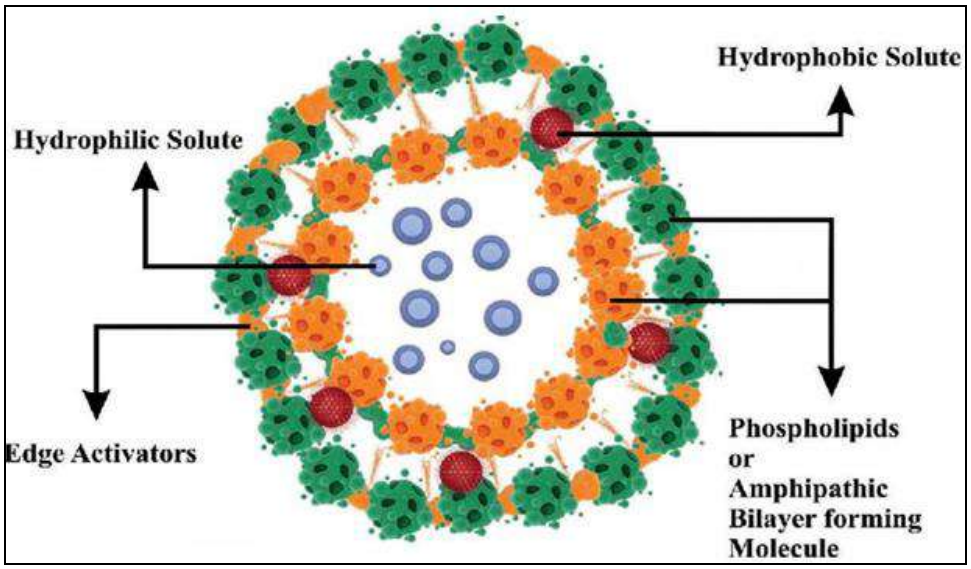

Fig 6: Structure of Microsphere

Because of this, bioavailability is viewed as a major obstacle to enhancing the bio-efficacy of transporting dietary phytochemicals (Barani *et al*., 2021). However, the fundamental structure of a transfersomes is a suitable method for transdermal phytochemical transport for local and systemic therapeutic action due to its improved membrane flexibility, ultra-deformability, and soft nature. The configuration of an H- bond between the polar head of the phospholipid and the polar functions of the phytochemical contents, however, is how phospholipid interacts with phytochemicals. Surfactants, an edge activator, are incorporated into the cholesterol-phospholipid bilayers to create flexibility. Transfersomes are particularly useful for delivering medications through the epidermis that have a low solubility.

Advantages

1. Transfersomes can accommodate medicinal molecules with a wide range of solubilities since their architecture is made up of both hydrophobic and hydrophilic moieties. They can flex and squeeze through spaces that are five to ten times smaller than their own diameter without suffering serious damage.
2. This system's high deformability allows intact vesicles to be penetrated more effectively. Drugs of both low and high molecular weights, such as analgesics, anaesthetics, corticosteroids, sex hormone, anticancer, insulin and albumin, can be transported via them.
3. Due to the fact that they are created from organic phospholipids, much like liposomes, they are biocompatible and biodegradable. They have a high entrapment efficiency, up to 90% in the case of lipophilic drugs. For instance, proteins and peptides shield the medication from metabolic breakdown.
4. They serve as depots, slowly and gradually releasing their contents, and can be employed for both systemic and topical medication delivery. As the process is straightforward and avoids needless use of pharmaceutically inappropriate ingredients, they are simple to scale up.
5. At first look, transfersomes resemble liposomes, which are lipid bilayered vesicles. However, in terms of functionality, transfersomes are far more malleable and flexible than routinely employed liposomes.
6. Because of the membrane's remarkable flexibility, transfersomes can squeeze through pores that are much smaller than their own diameter.
7. Transfersomes can accommodate medicinal molecules with a wide range of solubilities since their infrastructure is made up of both hydrophobic and hydrophilic moieties.
8. Transfersomes are capable of deforming and navigating tiny constriction (between 5 and 10 times smaller than their own diameter) without suffering appreciable damage. Due to this great deformability, intact vesicles can penetrate tight junctions more effectively.
9. They may transport both low-and high-molecular-weight medications, including as analgesics, anaesthetics, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin. Due to the fact that they are created from natural phospholipids, much like liposomes, they are biocompatible and biodegradable. They have a high entrapment efficiency, up to 90% in the case of lipophilic drugs.
10. They prevent metabolic breakdown of the medication that is encapsulated. They serve as depots, slowly and gradually discharging their contents. They can be utilised for both topical and systemic medication delivery. They can be utilised for both topical and systemic medication

delivery. Simple procedures that don't require arduous usage of extra resources or pharmaceutically inappropriate additions are simple to scale up [46].

Disadvantage

1. Due to their propensity for oxidative destruction, transfersomes are chemically unstable.
2. The natural phospholipids' purity is another factor that works against the use of transfersomes as drug delivery systems.
3. Formulations for transfersomes are pricey.

Application of Transferosomes

1. Due to the integration of phospholipids, transferosomes have the potential to increase the stability of labile pharmaceuticals and allow for the regulated release of delivered medications.
2. With the aid of transferosomes, heavy molecules can be easily carried through the skin. For instance, mammalian skin can be used to transmit insulin and interferons like leukocytic generated interferon (INF). They have long been employed as a means of transport for various proteins and peptides. Proteins and peptides are huge biogenic molecules that are challenging to enter the body, breakdown in the GI tract, and suffer from transdermal problems because of their size.
3. Because the bioavailability of transferosomes is comparable to that of subcutaneous injection. When administered via a transdermal method and contained in Transferosomes, human serum albumin has been demonstrated to be effective in eliciting an immunological response.
4. **Peripheral drug targeting:** Transferosomes' capacity to target peripheral subcutaneous tissues is a result of the minimal drug clearance that occurs through the subcutaneous tissue's blood arteries as a result of their associated carrier proteins.
5. **Transdermal immunisation:** Hepatitis-B vaccinations administered transcutaneously have shown promising outcomes. Zidovudine was administered with a 12 times higher AUC than usual control medication. Additionally, there was an increase in the selectivity of deposition in RES, which is where HIV often resides.
6. There are numerous GI adverse effects linked to NSAIDS. Transdermal delivery employing extremely deformable vesicles can get over these problems.
7. Proteins and peptides have been transported via transferosomes on a large scale. When taken orally, proteins and peptides are totally broken down in the GI tract and are therefore exceedingly difficult to transfer into the body. These are the explanations for why injections of these peptides and proteins are still necessary. To make these circumstances better, several strategies have been devised. Transferosomes' increased bioavailability is relatively comparable to subcutaneous injection of the same protein suspension.
8. As an example, the adjuvant immunogenic bovine serum albumin in transferosomes, after several dermal challenges, is as immunologically active as is the corresponding injected proteo-transferosomes preparations. The transferosomal preparations of this protein also induced a strong immune response after the repeated epicutaneous application.
9. The successful method for non-invasive therapeutic application of such large molecular weight medicines on the skin is insulin delivery by transferosomes. Insulin is often given through an uncomfortable subcutaneous method. These issues are all solved by encapsulating insulin in transferosomes (transfersulin). Depending on the particular carrier composition, the first signs of systemic hypoglycemia are visible 90 to 180 minutes after transfersulin administration on undamaged skin.
10. Interferons, like as INF-, have also been transported via transferosomes. INF-is a naturally occurring protein with antiviral, antiproliferative, and some immunomodulatory properties. Transferosomes as drug delivery systems have the potential to increase the stability of labile pharmaceuticals and provide controlled release of the medication delivered [47].

Ethosomal drug delivery system

Introduction: Ethosomes are brand-new lipid vesicular carriers with a reasonably high ethanol content that are used as a transdermal drug delivery system to test the effectiveness of a targeted medication at the site of action. There are several applications in the creation of formulations for enhanced systemic circulation release. The amount of medicine in the formulation and the amount released to the site of action can both be observed, and this allows us to determine how these formulations will behave therapeutically. The hydroalcoholic or hydroalcoholic/glycolic phospholipid that makes up ethosomes is a vesicular carrier with a relatively high concentration of alcohols or their combination. Drug molecules with different physicochemical properties, such as hydrophilic, lipophilic, or amphiphilic, can be captured by ethosomes. For individuals who cannot take medications orally, these formulations are a superior choice.

The main disadvantage of TDDS is that it encounters the barrier properties of the Stratum Corneum, which means that only the lipophilic drugs with a molecular weight of less than 500 Dacan pass through it. Transdermal drug delivery system (TDDS) has shown promising results when compared to oral drug delivery system because it eliminates gastrointestinal interferences and first pass metabolism of the drug. Ethosomes can range in size from tens of nanometers to microns (). The discovery that some modified vesicles had characteristics that made it possible for them to successfully carry medications in deeper layers of skin was one of the key developments in vesicle research [48, 49].

Transdermal medicine distribution is crucial because it is a non-invasive process. Additionally, the issue of medication breakdown by digestive enzymes following oral delivery and the discomfort Several strategies have been researched to increase drug absorption through the skin, including the use of chemical or physical enhancers, such as iontophoresis, sonophoresis, etc.

Drug permeability across the stratum corneum has also been found to be improved by liposomes, niosomes, transferosomes, and ethosomes. Drugs can easily pass through the skin thanks to permeation enhancers, which make the skin more permeable. Ethosomes can improve permeability through the stratum corneum barrier, in contrast to conventional liposomes, which are recognised primarily for delivering medications to the skin's outer layers [50]. Ethosomes have a substantially higher transdermal flow and penetrate the epidermal layers more

quickly than regular liposomes. Ethosomes are lipid vesicles that contain water, phospholipids, and relatively high concentrations of alcohol (ethanol and isopropyl alcohol). Ethosomes are soft vesicles composed primarily of water, phospholipids, and ethanol (in larger amounts). Medication administration via parenteral routes can be avoided. It is the most used method for delivering medications systemically to pediatric, geriatric and patients having dysphasia.

Numerous strategies have been researched to break through the stratum corneum barrier, including the use of chemical or physical enhancers such iontophoresis, sonophoresis, etc. As found to increase drug permeability across the stratum corneum barrier, liposomes, niosomes, transferosomes and ethosomes may also be able to penetrate the skin barrier.

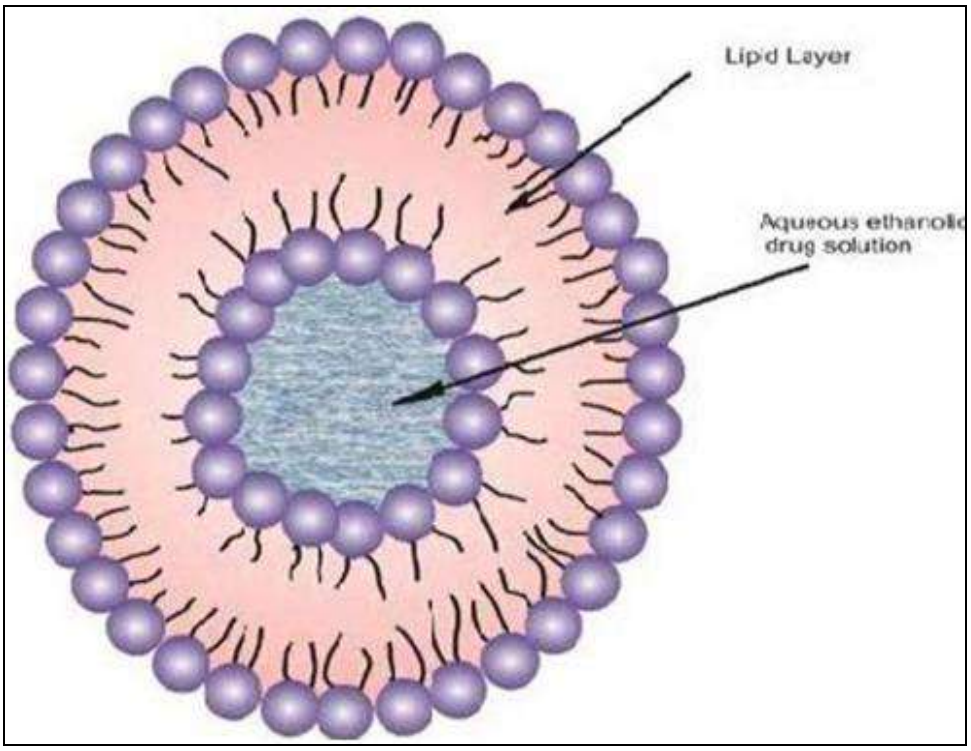

Fig 7: Structure of Ethosomal

Advantages

1. Large molecules, such as peptides and protein molecules, can be delivered.
2. Its formulation uses non-toxic raw materials.
3. Improved.
4. The pharmaceutical, veterinary and cosmetic industries can all benefit from ethosomal drug penetration of drug via skin for transdermal drug delivery system.
5. **High patient compliance:** Because the ethosomal medication is administered as a semisolid (gel or cream), high patient compliance is the result.
6. A straightforward drug delivery technology as opposed to complex ones like phonophoresis and iontophoresis.
7. The ethosomal system may be immediately commercialised and is passive and non-invasive. Comparing the ethosomal drug delivery technique to other transdermal and dermal administration technologies reveals significant advantages. These benefits include improved medication penetration through skin for transdermal drug delivery; ethosomes offer a platform for the transport of a wide range of medicines (peptides, protein molecules) across the skin; Ethosomes are made of non-toxic ingredients and are supplied as semisolid gel or cream drugs, which results in good patient compliance. The ethosomal drug delivery technology is broadly applicable to the veterinary, cosmetic and pharmaceutical industries; the ethosomal system is passive, non-intrusive, and immediately marketable; Comparing ethosomal drug delivery to iontophoresis, phonophoresis, and other complex procedures, it is incredibly straightforward [51, 52].

Applications of ethosomes

1. Antiviral drug delivery a powerful antiviral drug that targets the AIDS virus is zidovudine. Zidovudine is an oral drug that can have serious side effects.

To maintain the anticipated anti-AIDS impact, an adequate zero order delivery of zidovudine is desired. Concluded that ethosomes could boost transdermal flow, extend release, and offer a convenient way to distribute zidovudine over the long term. Another anti-viral medication that is frequently applied topically to treat Herpes labialis is acyclovir. The hydrophilic acyclovir used in the conventionally marketed external formulation of acyclovir is known to have low skin absorption and minimal therapeutic effectiveness. According to reports, the basal dermis is where virus replication occurs. To resolve the issue with the standard topical preparation of acyclovir. The acyclovir ethosomal formulation for topical administration was created by Horwitz *et al*. The findings revealed that when acyclovir was loaded into ethosomes, a higher percentage of abortive lesions and a shorter healing time were seen [53].

Ethosome composition

The hydroalcoholic or hydro/alcoholic/glycolic phospholipid that makes up ethosomes is a vesicular carrier with a relatively high concentration of alcohols or their

combination. 4-9 many kinds of chemicals utilised in ethosomes.

Table 4: Different additives employed in formulation

Additives	Uses	Examples
Phospholipid	Vesicles forming component	Soya phosphatidyl choline, Egg Phosphatidylcholine, Dipalmitoyl, Phosphatidyl choline, Distearly phosphatidyl choline
Polyglycol	Skin penetration enhancer	Propylene glycol, Transcutol
Cholesterol	Stabilizer	Cholesterol
Vehicle	As a gel former	Carbopol 934
Dye	For characterization study	6-Carboxy Fluorescence, Rhodamine-123, Rhodamine red, Fluorescence

Method of preparation: The formulation and preparation of ethosomes can be done in one of two ways. Both of them are incredibly easy to do and convenient because they don't require any sophisticated equipment or laborious procedures.

Hot Method

By heating phospholipid in a water bath at 400C until a colloidal solution is formed, phospholipid is dispersed in water using this approach. Propylene glycol and ethanol are combined and heated to 400 °C in a different vessel. The organic phase is introduced to the aqueous phase once both combinations have reached 400 °C. Depending on whether the medication is hydrophilic or hydrophobic, it dissolves in either water or ethanol. Using the probe sonication or extrusion approach, the vesicle size of the ethosomal formulation can be reduced to the desired extent. Using the probe sonication or extrusion approach, the ethosomal formulation's vesicle size can be reduced to the desired degree.

Cold method

This approach involves vigorously swirling with the use of a mixer to dissolve phospholipid, drug and other lipid components in ethanol in a covered vessel at room temperature. While stirring, propylene glycol or another polyol is added. In a water bath, this mixture is heated to 300 °C. The mixture is then agitated for 5 minutes in a covered vessel while the water heated to 300 °C in a different pot is added. Using the sonication or extrusion process, the ethosomal formulation's vesicle size can be reduced to the desired extent. The formulation is then placed in a refrigerator for storage [54, 55].

Solid liquid nano particle drug delivery system

Introduction: An alternate carrier system to conventional colloidal carriers such emulsions, liposomes, and polymeric micro-and nanoparticles is the solid lipid nanoparticle (SLN), which was first presented in 1991 [56, 57, 58].

As an innovative colloidal drug carrier for intravenous applications, nanoparticles synthesised from solid lipids are gaining significant attention. They have been suggested as an alternate particulate carrier system. SLN are physiological lipid-based sub-micron colloidal carriers with a size range of 50 to 1000 nm that are distributed in water or an aqueous surfactant solution [59, 60]. Because of their potential to enhance the efficacy of pharmaceuticals, SLN are appealing due to their distinctive qualities, which include their tiny size, vast surface area, high drug loading, and phase interaction at the interface [61].

Solid lipid nanoparticles (SLN) have a number of potential uses in research and drug delivery and are at the forefront of the quickly evolving field of nanotechnology. Lipid nanoparticles present a chance to create novel therapies because of their special size-dependent characteristics. Drug targeting is made possible by the ability to combine pharmaceuticals into nanocarriers, which gives a new drug delivery concept [62].

Thus, solid lipid nanoparticles have garnered a lot of interest from researchers due to their significant potential for achieving the goal of regulated and site-specific drug delivery. This review covers a wide range of solid lipid nanoparticles, outlining the objectives, methods of manufacture, benefits, drawbacks, and potential solutions [63]. The proper analytical methods for characterizing SLN, such as differential scanning calorimetry, scanning electron microscopy and photon correlation spectroscopy, are highlighted. Discussions also include the *in vivo* destiny of the carriers and the route of delivery of the SLN [64, 65].

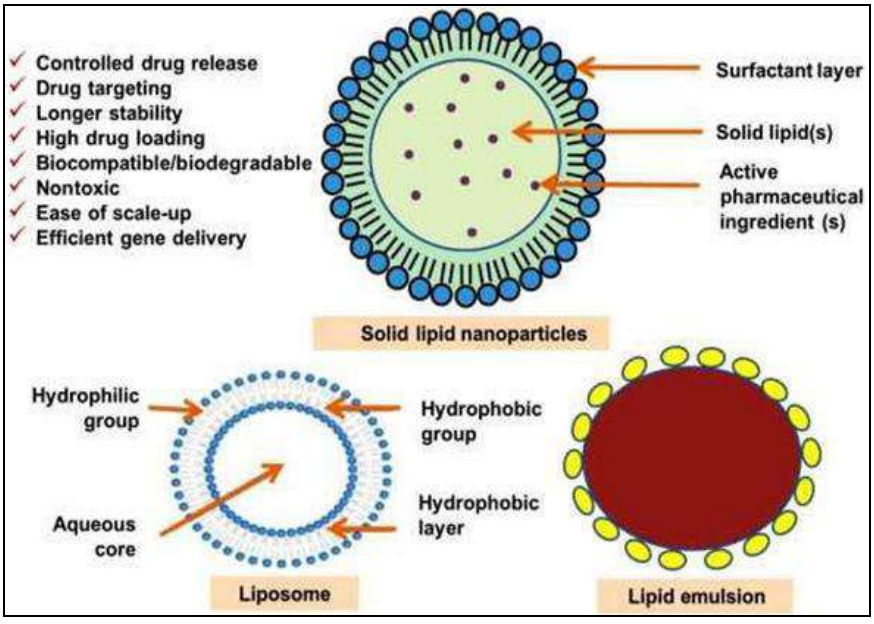

Fig 8: Structure of Solid liquid nano particle

For many years, the pharmaceutical industry has used lipid materials that are solid at room temperature to create a variety of formulations, including emulsions, lotions, ointments, and suppositories. Lipids (both solid and liquid at room temperature) are also regular constituents of other enteral and parenteral formulations, like soft/hard capsules or parenteral emulsions, but they have historically been used most frequently as inert ingredients in topical medications due to the high affinity of the lipid-rich intercellular space of the stratum corneum for these kinds of materials [66, 67, 68].

Method of preparation of solid lipid nanoparticles

1. High pressure homogenization
A. Hot homogenization.
B. Cold homogenization.
2. High-speed homogenization and ultrasonication.
A. Ultrasonication a probe.
B. Ultrasonic bathing.
3. The method of solvent evaporation.
4. The solvent emulsion-diffusion technique.
5. The use of supercritical fluid.
6. A approach based on microemulsions.
7. Spraying technique.
8. The dual-emulsion technique.
9. The method of precipitation.
10. Dispersion of film ultrasonics Advantages
1. Regulate and/or focus drug release.
2. Outstanding biocompatibility.
3. Enhance medication stability.
4. Significantly increased drug content.
5. Simple to sterilize and scale up.
6. Better control over the kinetics of chemical release from capsules.
7. Improved bioavailability of bioactive substances that have been trapped.
8. Chemical safeguards for incorporated labile chemicals.
9. Can be produced much more easily than bio polymeric nanoparticles.
10. No unique solvent is needed.
11. The use of traditional emulsion manufacturing techniques.
12. Raw materials are just as important in emulsions.
13. Outstanding long-term stability
14. Flexibility in application.
15. May be sterilised using commercial techniques [69]. Disadvantages.
1. Particle growth.
2. Unpredictable gelation tendency.
3. Unexpected dynamics of polymeric transitions [71, 72].

Conclusion

Novel drug delivery systems serve to boost therapeutic value by decreasing toxicity, enhancing bioavailability and other factors. They also lessen the need for repeated administration to overcome non-compliance. Herbal medicines are the subject of extensive study to include them in new drug delivery methods. Through the use of these cutting-edge methods, natural medicines will exhibit improved bioavailability, decreased toxicity, sustained release action, and protection from GI degradation. Which cannot be obtained through conventional drug delivery system due to large molecular size, poor solubility, degradation of herbal medicine in gastrointestinal media.

The performance of an existing medicinal molecule in terms of patient compliance, safety, and efficacy can be greatly enhanced by evolving it from a traditional form to a unique delivery mechanism. An old medication molecule can be given new life as a Novel Drug Delivery System. A significant improvement in the ability to release a drug at a specified spot and rate is possible with a novel drug delivery system that is properly developed. Pharmaceutical companies are working to create novel drug delivery systems in order to give medications to patients effectively and with fewer side effects. This article discusses the fundamentals of novel drug delivery systems as well as their various varieties.

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