JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON : NOVEL HERBAL DRUG DELIVERY SYSTEM

Rani M Londhe*, Shital R Kurumkar[1] ,Pooja J Lashkare[2], Pooja M Lande[3], Ganesh D Nalge[4]
H.S.B.P.V.T's GOI COLLEGE OF PHARMACY KASHTI, Ahmednagar, Maharashtra, India, 414701
Email: ranilondhe1999@gmail.com

ABSTRACT

The distribution of phytoactives at an effective level determines the strength of any herbal formulation. This constraint can be overcome by developing innovative drug delivery systems that ensure optimal medication distribution, increased bioavailability, and improved stability of phyto components for improved therapeutic benefits. Several novel herbal delivery systems, such as liposomes, phytosomes, solid-lipid nanoparticles, ethosomes, microemulsions, and other vesicular systems, have been effectively created in recent years. Transfersomes are vesicular drug delivery systems that are similar to liposomes in structure but have higher skin penetration capabilities, allowing medicines to reach deeper skin tissues. Because of their ultradeformable shape, transfersomes are excellent drug delivery agents. Transfersomes are pliable, allowing them to deform and squeeze as an unbroken vesicle through tiny holes that are substantially smaller than their size.

The goal of this paper is to explain the concept of transfersomes, the mechanism of action, various techniques of manufacture and characterization, and factors affecting transfersome features, as well as their latest uses in transdermal drug delivery.

KEYWORDS: herbal, new medication delivery method, Lipsome, Niosome, Transferosomes, Phytosome

Introduction :

According to recent research, more than 70% of newly designed medications have low water solubility, which represents a limiting factor in drug absorption following oral administration. The bioavailability of natural compounds is limited.Low solubility of the active substance, as well as poor stability due to acidity in the

stomach and intestines, poor metabolism due to gut bacteria, and poor digestion absorption across the intestinal wall, a faulty active efflux system, and firstpass absorption are all factors to consider.Clinical trial failure is caused by a variety of variables, including metabolic consequences.In this regard, we created a unique herbal drug delivery method and carriers.Some prerequisites, such as proper delivery of the medicine, should be in the ideal case over a period of time, according on the body's demands.(1)

Liposomes and niosomes are vesicular carrier systems that have get a lot of attention in recent decades as a way to deliver drugs transdermally. The features of vesicles architectures have been studied in order to improve medication administration within their cavities, as well as to tag the vesicles for cell selectivity. Vesicles are used in transdermal drug administration because they operate as drug carriers, delivering entrapped drug molecules over the skin, and because of their composition, they also act as penetration enhancers. Furthermore, in the case of topical preparations, these vesicles function as a depot for the sustained release of active substances, as well as a rate-limiting membrane barrier for the control of systemic absorption.

Novel herbal medication carriers treat a specific ailment by targeting and conveying the drug to the afflicted area within a patient's body. NDDS has the advantage of releasing the herbal medication at a controlled rate and delivering the drug at the site of action, reducing adverse effects and increasing drug bioavailability.

Controlling drug dispersion is achieved in new drug delivery technology by integrating the drug into a carrier system or altering the drug's social organisation at the molecular level. Increased solubility, improved stability, protection from toxicity, increased pharmacological activity, improved tissue macrophage distribution, prolonged delivery, and protection from physical and chemical damage are all benefits of including herbal medications into the delivery system. (2)

Types of novel herbal drug delivery system :

Plant actives and extracts have made significant progress in the development of new drug delivery systems (NDDS) in recent years. Bioactive and plant extracts have been used to create a number of unique herbal formulations, including polymeric nanoparticles, nanocapsules, liposomes, phytosomes, nanoemulsions, microspheres, transferosomes, and ethosomes. The novel formulations are said to have significant advantages over traditional formulations of plant actives and extracts, including improved solubility, bioavailability, toxicity protection, pharmacological activity enhancement, stability enhancement, improved tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation.

1.Liposomes

Liposomes are small vesicles made up of one or more lipid bilayers that are concentric. An aqueous medium separates them. Adsorbed lipophiles are in one compartment, whereas adsorbed lipophiles are in another.Liposomes membrane inserted into the kind of lipid. A variety of animals have been categorised according on their size surface charge and lamellae In terms of the surface .Liposomes are classed as anionic

because of their charge cationic or neutral Drug delivery through liposomes.systems have the potential to improve the therapeutic efficacy of natural medicines Liposomes encase the proteins.0.05-5.0 m spherical vesicles are used as solvents which are allowed to float around in the interior.Liposomes improve component solubility and bioavailability invitro and in-vivo distribution, bioavailability ,stability and pharmacokinetics changes.Formulations of herbal drugs are accessible in the market .

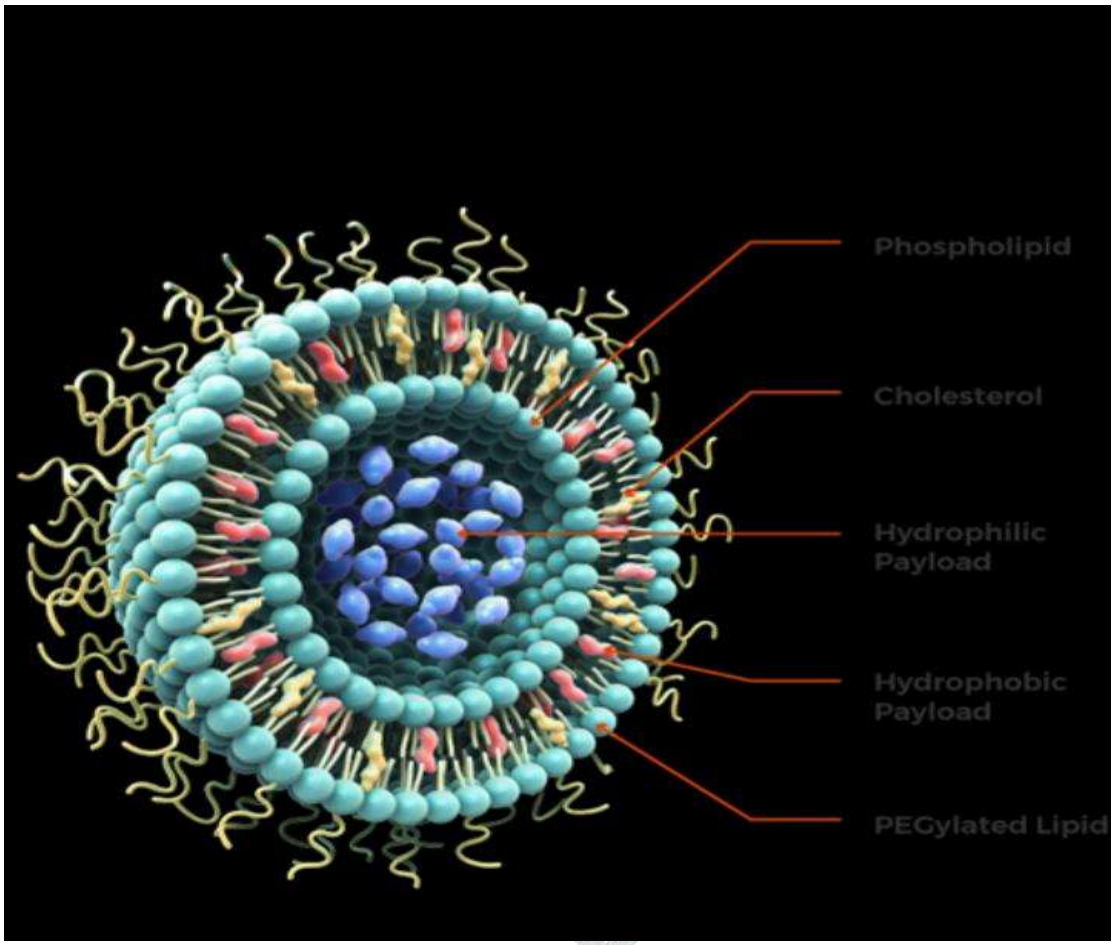


Fig. Structure of Liposome

2.Phytosomes

'Phyto' refers to a plant, and'some' refers to a cell-like structure . Phytosomes are tiny cell-like structures. Phytosome is a new type of plant compositions including physiologically active ingredients herb extract active phytoconstituents complexed with phospholipids, resulting in molecular complexes that are compatible with lipids. It is a newly created and patented product .a method for incorporating water-soluble materials standardised plant extracts or phytoconstituents phospholipids to make lipidcompatible lipids .

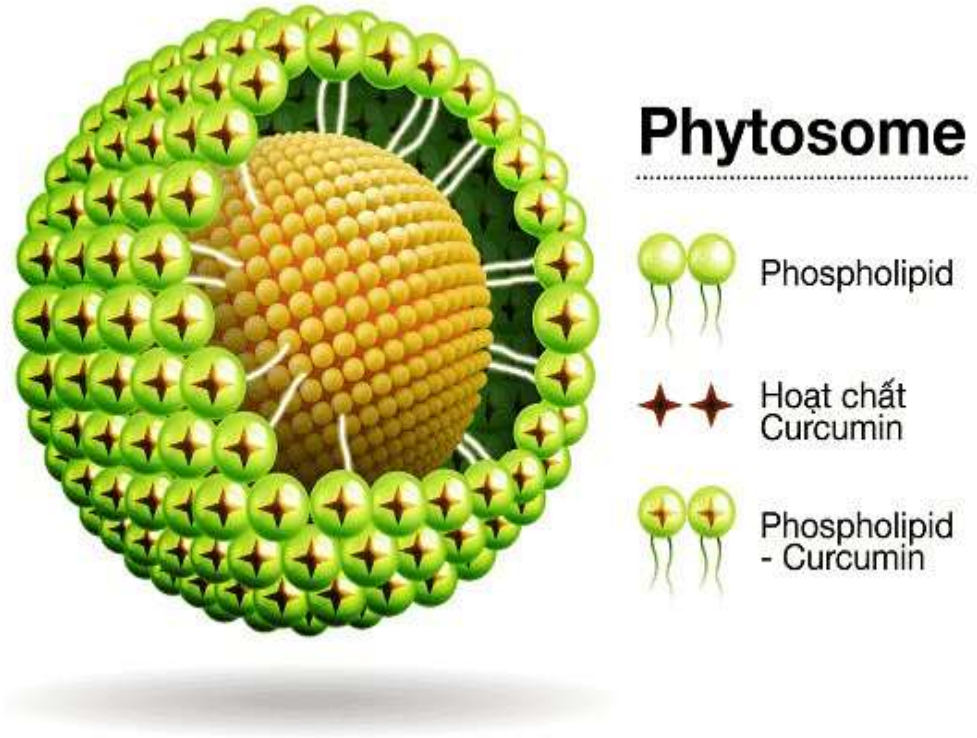


Fig structure of. Phytosome

3.Niosomes

It has a higher level of stability as a result of the chemical connections are formed between Phosphatidylcholine and phytoconstituent. Molecules. Non-ionic surfactant of the alkyl or dialkyl polyglycerol and non-ionic surfactant of the alkyl or dialkyl polyglycerol produce niosomes Can be employed as a possible medication carrier.Liposomes are a type of nanoparticle that is comparable to nanoparticles. Niosomes have a number of advantages.It has a number of advantages over liposomes, including the fact that it is more stable. It is capable of encapsulating a variety of medications .They are less expensive than liposomes and have a distinct structure. Several herbal formulations based on niosome.

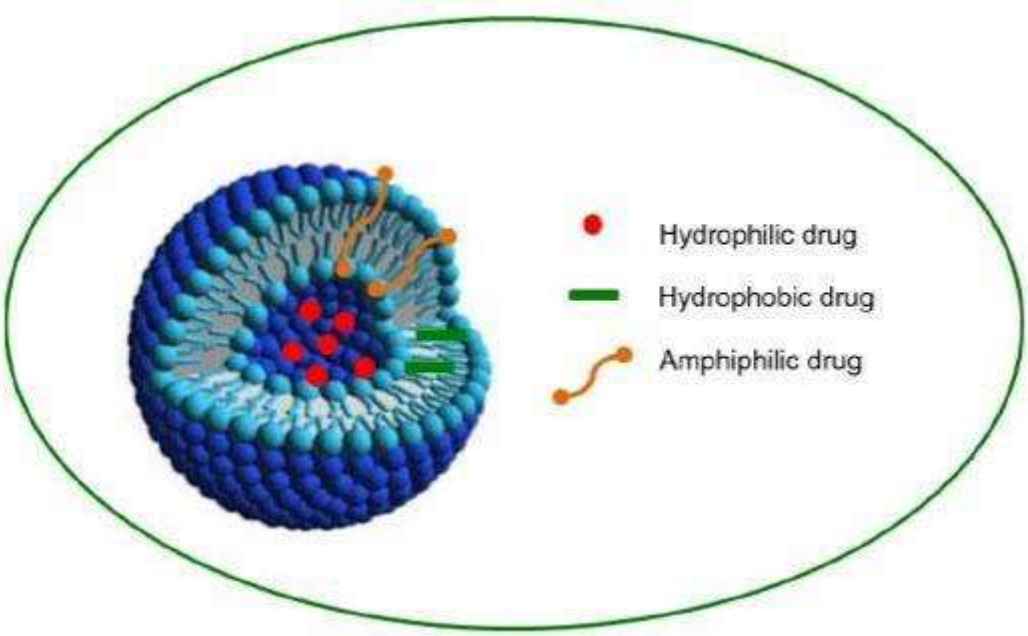


Fig. Structure of Niosomes

4.Ethosomes

Ethosomes are sac-like structures that contain a high concentration of ethanol and phospholipids. Ethanol content in the sac is high improves the permeability of their through the medicine was administered in the form of an ethosome for patient comfort, use a cream or gel.

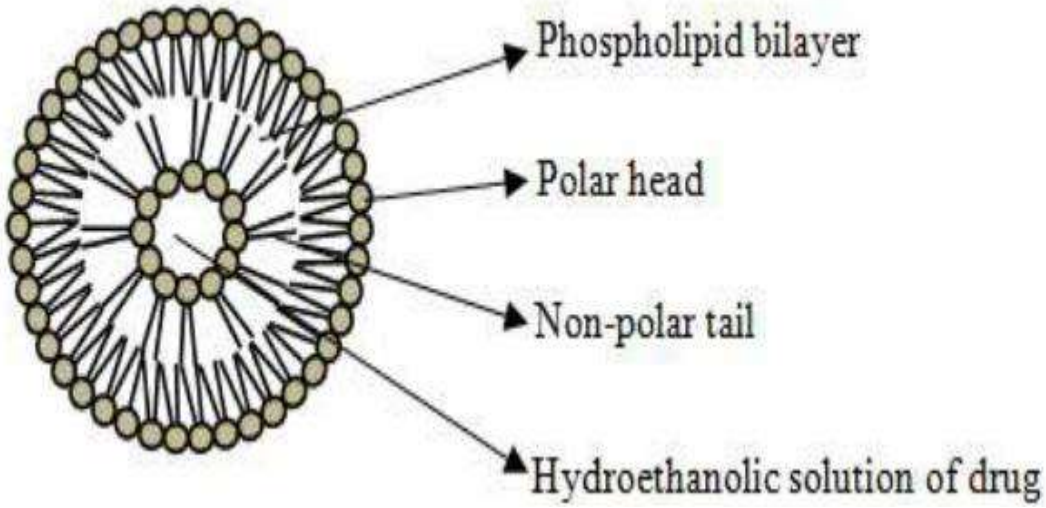


Fig. Structure of Ethosome

5.Microsphere

In microspheres, drug is dispersed in the polymer within a matrix and released follow first order kinetics. It is a spherical shaped particle having size ideally 1-300 μm. At first, the dissolution media diffuse the matrix which makes the dispersed drug to solubilize in media and drug released. In another type microsphere, polymer show surface erosion behavior where the surface dissolved layer by layer and the release of drug occurs. Degradation and dissolution of the matrix control the release of drug from microsphere, polymer show surface erosion behavior where the surface dissolved layer by layer and the release of drug occurs. Degradation and dissolution of the matrix control the release of drug from microsphere.The release of drug is affected by the type of matrix, size, and polymer concentration etc.

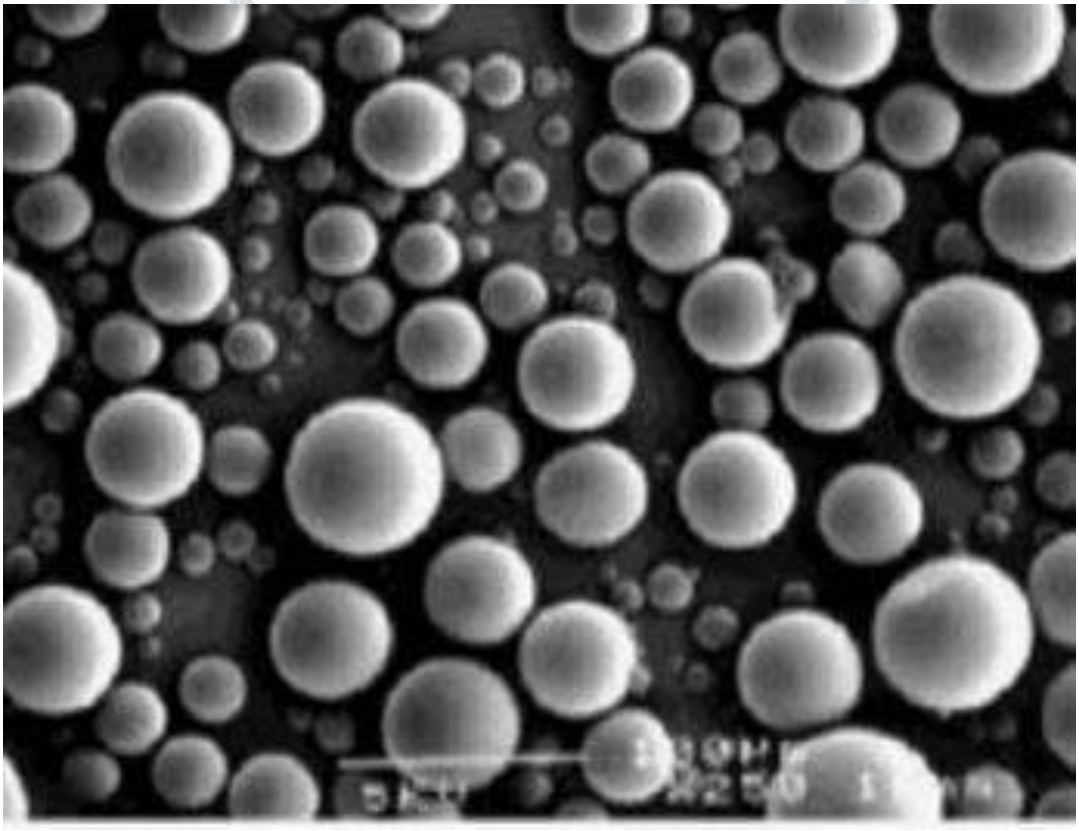


Fig. Structure of microsphere

6.Dendrimer :

A dendrimer is a tree-like synthetic polymer with a single central core and numerous branches of variably armed macromolecules (external capping and multifunctional groups) to improve targeting to specific spots. Sugars, nucleotides, and amino acids are common components, which might be natural or manufactured.(26)

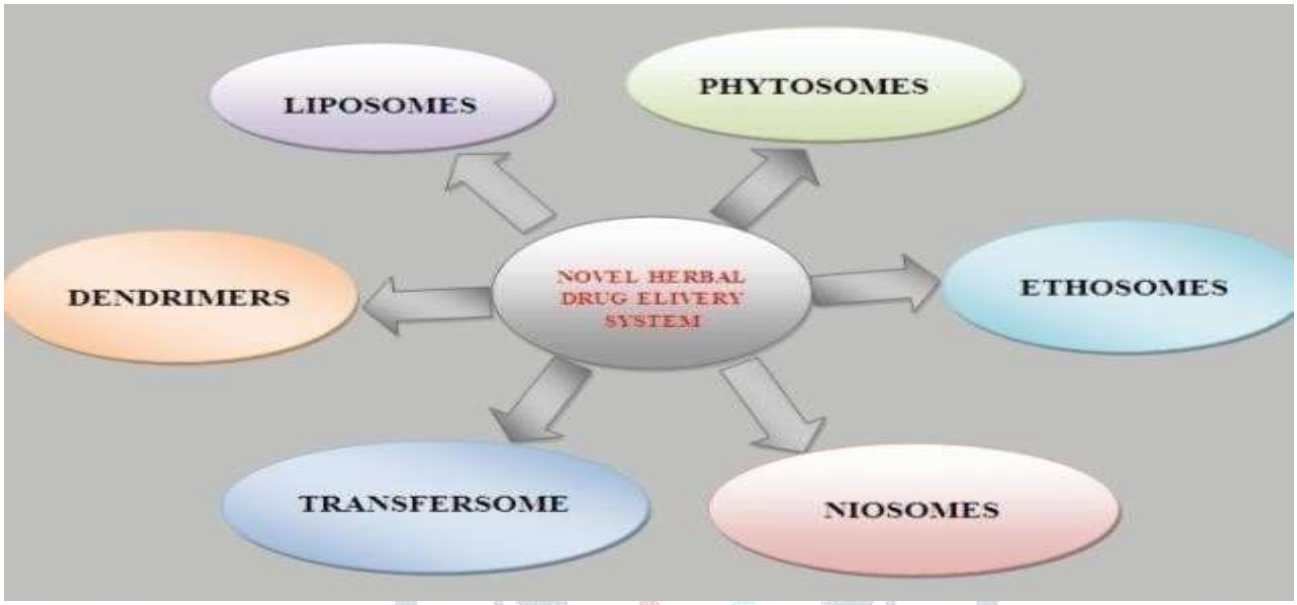


Fig-1. types of novel herbal drug delivery system

Advantages of novel herbal drug delivery system

1.risk of side effects: Herbal drugs are generally well tolerated by patients, with fewer unintended consequences and side effects than traditional medicine, and may be more effective.It is safer to use.

2.Greater Efficacy: Herbal medicines are more effective for long-term health problems. That do not react well to conventional treatment Herbs and alternative medicine

Example ;Arthritis medicines are utilised to treat the disease. Vioxx, a well-known prescription

medicine used to treat arthritis, has been linked to a number of deaths. Due to an

increased risk of cardiovascular complications, it was recalled. Treatments using herbs for On the other hand, arthritis has less adverse effects. Dietary modifications are one of these treatments. Such as adding simple herbs, avoiding vegetables from the nightshade family, and lowering sodium intake consumption of white sugar.

3. Lower cost: Compared to prescription medications, herbal drugs are much less expensive. The cost of prescription drugs is significantly increased by research, testing, and marketing. In comparison to

pharmaceuticals, herbs are usually less expensive. Herbs are widely available and do not require a prescription. Herbs that are easy to grow, like basil can be grown at home, such as peppermint and chamomile (3)

Importantance:

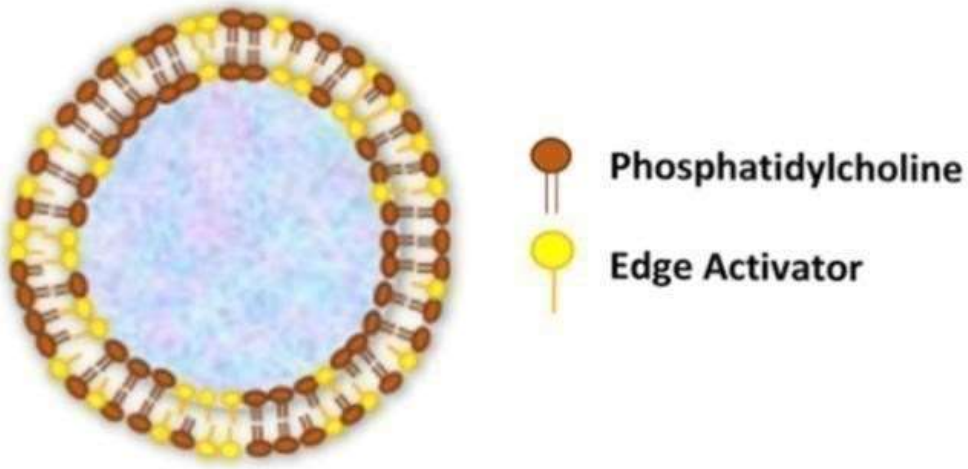
The term "novel drug delivery system" refers to a new technique to drug distribution that overcomes the constraints of established drug administration methods. Our country has a large Ayurvedic knowledge base whose full potential has just recently been revealed. The drug delivery method, on the other hand, is problematic. Traditional and out-of-date methods of giving herbal medication to patients are used. As a result, the drug's efficacy is reduced. If the novel drug delivery technology is used in a clinical setting, Herbal medication has the potential to improve efficacy while lowering negative effects. Herbal compounds and plants come in a variety of forms. This is the fundamental concept behind adopting innovative ideas. In herbal treatments, there is a way of drug delivery that is used. As a result, it's critical to incorporate new drug developments. To combine this, a delivery system and Indian Ayurvedic medicines for modern phytopharmaceutical research can solve the scientific needs (such as determination of Pharmacokinetics, mechanism of action, site of action, accurate dose required etc.) of herbal .To tackle more serious disorders, it is critical to combine innovative medication delivery systems with Indian Ayurvedic therapies. Herbal medications were not regarded for development as innovative formulations for a long time due to a number of factors. processing challenges, such as standardisation and extraction, and a lack of scientific explanation .

Individual medication components in complicated poly herbal systems, as well as their identification. However,Modern phytopharmaceutical research can meet scientific needs (such as determining the presence or absence of a substance). Herbal pharmacokinetics (pharmacokinetics, mechanism of action, location of action, precise dose required, etc.)

Nanoparticles, micro emulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticle, and other new drug delivery systems . Various drug delivery and drug targeting systems are being developed at the moment. to reduce medication degradation and loss, to avoid undesirable side effects, and to improve drug efficacybioavailability and the percentage of medication that accumulates in the necessary zone.(4)

7. Transferosomes:

Transferosomes are vesicular carrier systems with at least one inner aqueous compartment and an edge activator enclosed by a lipid bilayer.



Structure of transfersomes.

This aqueous core is enclosed by a lipid bilayer, resulting in ultra-deformable vesicles that may self-optimize and regulate themselves . (5) As a result, transferosomes are elastomeric in nature and may bend and squeeze themselves as whole vesicles without discernible loss via skin constrictions or pores that are substantially smaller than the vesicle size.(6)

Unlike conventional liposomes, which are made up of natural (egg phosphatidylcholine—EPC) or synthetic (dimyristoyl phosphatidylcholine—DPPC, and dipalmitoyl phosphatidyl glycerol— DPPG) phospholipids, the modified liposomal vesicular system (transfersomes) is made up of the phospholipid component and a single-chain surfactant Edge activators (EAs) are membranedestabilizing factors that increase the deformability of vesicle membranes. When combined in the right ratio with the right lipid, they create the ideal mixture, allowing transfersomes to become deformable and ultra-flexible, resulting in increased permeation capability.

As a result, transfersomes overcome the major disadvantages of traditional liposomes by penetrating pores much smaller than their own diameters. Furthermore, even after passing through the narrower pores, the transfersomes maintained their diameters against fragmentation. The use of EAs in the transfersomal formulation has resulted in improved performance when compared to traditional liposomes . EAs in transfersomal formulations can also aid in the solubilization of hydrophobic pharmaceuticals, enhancing the formulations' drug entrapment efficiency . Furthermore, EAs have the ability to solubilize and fluidize skin lipids, resulting in improved skin permeability .The effect of EAs on skin permeations is dependent on the kind and concentration of the EAs.(10,11)

Phospholipid vesicles are also used as a transdermal medication carrier in this technique. It can pass through the stratum corneum either intracellularly or transcellularly by creating a "osmotic gradient."

Transferosomes have a wide variety of solubilities, are better at penetrating, are biocompatible and biodegradable, and so forth. Transferosomes have several advantages, including oxidative breakdown, high cost, and so forth. Using the traditional rotary evaporation sonication process, the transfersomes were created. It was prepared using phospholipids, surfactant, and the medication. Vesicle size distribution and zeta potential are two transferosome evaluation metrics. Entrapment efficiency, vesicle shape, number of vesicles per cubic mm Penetration ability, drug content, turbidity measurement, degree of deformability or permeability measurement Effect of occlusion Charge on the surface as well as charge density, Physical stability, in-vitro drug release, and invitro skin permeation studies Transferosomes can be used for a variety of applications, including controlled release, transfer of big molecules, target delivery to peripheral subcutaneous tissues, and transdermal immunisation.(12)

Methods of transfersomes preparation

Phospholipids, surfactants, dyes, alcohol, buffering agents, and other substances are employed in the formulation of transfersomes.

Table- various ingredients and their role for synthesis of transfersomes

Ingredients	Chemical	Role
Phospholipids	Phosphatidyl choline, soya phosphatidyl choline, Dipalmitoyl phosphatidyl choline	Formation of vesicles
Surface active agents (edge activator)	Sodium cholate, sodium deoxycholate, tween 80, span 80	Flexibility improvement

Primary alcohol	Ethanol Methanol	Solvent
Buffering agents	PH 6.4 phosphate saline	Hydration medium

Thin film hydration method

In this approach, phospholipids and surfactants are dissolved in a suitable organic medium, such as chloroform-methanol, and a thin film is formed using a rotary evaporator. At 50C, the organic solvent evaporated at a temperature exceeding the lipid transition point.

A saline phosphate buffer with a pH of 6.4 is added to the hydrate stack of the film and then rotated at 60rpm for 1 hour. The film is then kept at room temperature for 2 hours, until the swelling of the vesicle is complete. The dispersion is then sonicated to get the appropriate size.
(12)

Modified hand shaking lipid film hydration method

In a chloroform-ethanol mixture, phytoconstituents, phosphatidyl choline (lecithin), and other additions, such as edge activators (sodium cholate), are dissolved (1:1). The organic solvent combination is removed by evaporation using a rotary evaporator or by hand shaking at 43°C. Over the inner wall of the flask, a stack of thin lipid film is created. The obtained stack on the inner wall is vacuumed overnight to ensure that all solvent traces are removed. The phosphate buffer (pH 4) is applied to rehydrate the film for 15 minutes at the specified temperature with hand shaking. Sonication can be used to create a vesicle of the required size.
(12)

Vortexing -Sonication Method

In a phosphate buffer, the phospholipids, edge activator, and medication are combined. After that, the mixture is vortexed till it forms a milky transfersomal suspension. It's then sonicated for a set amount of time at room temperature in a bath sonicator before being extruded through polycarbonate membranes (example: 450 and 220 nm)(20,21)

The Centrifugation Method

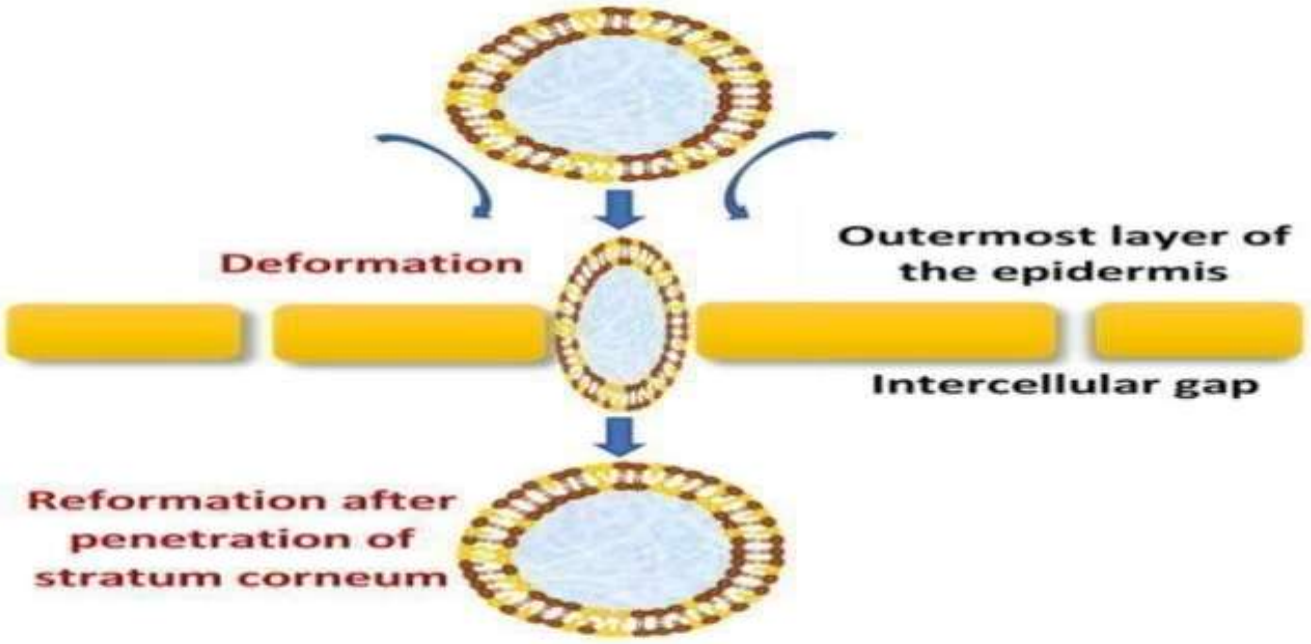
The organic solvent is used to dissolve the phospholipids, edge activator, and lipophilic drug. The solvent is then extracted using a rotary evaporator at the appropriate temperature and under reduced pressure. Under vacuum, any leftover residues of solvent are eliminated. By centrifuging at room temperature, the deposited lipid layer is hydrated with the suitable buffer solution. This is the time to include the hydrophilic medication. At room temperature, the resultant vesicles are enlarged. At room temperature, the resulting multilamellar lipid vesicles are sonicated (22)

Mechanism of action :

Colloidal particles, often known as vesicles, are aqueous compartments surrounded by a concentric bilayer of amphiphilic molecules.

They're great for vesicular drug delivery because hydrophilic pharmaceuticals are contained in the inner aqueous compartment, while hydrophobic drugs are confined in the lipid bilayer.(13)

Transfersomes are extremely deformable (ultra-flexible) and self-optimizing new drug carrier vesicles, with membrane flexibility, hydrophilicity, and the ability to retain the vesicle's integrity being the most important factors in their passage over the skin. (14,15) The transdermal water activity differential, which is caused by the natural transdermal gradient, exerts a large force on the skin via transfersome vesicles, which drive the widening of intercellular connections with the lowest resistance, resulting in transcutaneous channels 20–30 nm wide. These channels allow ultra-deformable, slimed transfersomes to move across the skin in relation to the moisture gradient.(18)



The mechanism of action of transfersomes.

According to Cevc and Blume's research, hydrotaxis (xerophobia) is the permeation mechanism of transfersomes, which is defined as the transferosome's moistureseeking tendency towards deeper skin layers rather than the dry outer background due to moisture evaporation from the transfersomal formulation after application on the skin (nonocclusive condition) (16)

Transfersomes can pass through the stratum corneum and reach the dermis and blood circulation, among other places. The deformability of the transfersomal membrane, which can be linked to vesicle compositions, determines their ability to penetrate [17]. As a result, the best vesicle compositions must be determined by executing specially designed experimental procedures for each therapeutic agent in order to generate the best carriers with the best deformability, drug carrying capacity, and stability.

Advantages of Transfersomes as Vesicle-based Transdermal Drug Delivery Systems :

• Transfersome carriers are made up of hydrophilic and hydrophobic moieties, resulting in a one-of-a-kind drug delivery system that can handle a wide range of solubility.

• Because of their ultra-deformability and elastic qualities, transfersomes can squeeze themselves through skin barrier constrictions that are 5 to 10 times smaller than the vesicle diameter.

• High vesicle deformability allows medications to be transported across the skin without causing significant vesicle loss, and it can be employed for both topical and systemic treatments.

• Transfersome carriers are extremely adaptable and efficient at accepting a wide range of agents, regardless of size, structure, molecular weight, or polarity.

• Transfersomes are an obvious alternative for establishing a consistent and longlasting medication release.

• They have the ability to increase transdermal flow and improve bioactive agent site specificity.

• By avoiding first-pass metabolism, which is a significant limitation in oral medication administration, the drug's bioavailability is improved.

• Reduce the drug's unpleasant side effects and preserve it against metabolic breakdown, as well as the utility of short-half-life medications.(19)

• **Transfersome limitations:**

• Because of their proclivity for oxidative destruction, transfersomes are classified as chemically unstable. When the aqueous media is degassed and purged with inert gases like nitrogen and argon, the oxidation of transfersomes can be considerably reduced .

• Another barrier to using transfersomes as a medication delivery mechanism is the difficulty in obtaining natural phospholipid purity. Synthetic phospholipids could thus be employed as a substitute

• The high cost of transfersomal formulations is due to the high cost of the raw ingredients used in lipid excipients, as well as the high cost of the equipment required.(23,24)

Applications of transferosomes :

Transferosomes have a wide range of uses in the transdermal delivery of drugs and other molecules.

1. Delivery of protein :

it is extremely difficult to move large biogenic molecules such as body proteins and peptides into the body. When given orally, such a chemical degrades in the gastrointestinal tract .

Transfersomes are the most effective method for delivering all types of proteins into the body. The bioavailability of molecules delivered by transfersomes is comparable to that of drugs administered via subcutaneous injections Protein preparations, such as bovine serum albumin (immunogenic adjuvent) applied repeatedly in the preparation of transfersomes via epicutaneous route, elicited a strong immunogenic response. Transfersomes have been shown to penetrate the skin intact, present the antigen to dendritic cells, and elicit a specific immune response to the antigen. . Antigenspecific antibody titers elicited by gap junction proteins loaded in transfersomes were comparable to those elicited by the subcutaneous route. Encoding DNA in Plasmids Hepatitis-B surface antigen (HBs-Ag)-loaded cationic transfersomes were also used for topical vaccination, and the HBs-Ag antibody titer and cytokinin levels were significantly higher .

2.Delivery of anticancer drugs:

Transfersomes are utilised as carriers for anti-cancer medications, and they're very good at treating skin cancers. The use of methotraxate-loaded transfersomes in the treatment of skin cancer was investigated. Tamoxifen (TAM), an anti-breast cancer drug, is transferred through the skin by transfersomes and accelerates the formation of murine uteri, where it acts as an anti-oestrogen, even at low doses.

3.delivery of interferon:

Interferon- nd interleukines-2 (IL-2)-loaded transfersomes were successfully manufactured, and it was discovered that both molecules kept their biological activity and could be efficiently enclosed in carrier.

4. Insulin delivery :

Orally administered polypeptidic or proteinaceous medicines are practically inactive therapeutically because they are digested in the gastro-intestinal tract. Transfersomes have the ability to transfer their associated medications, including subcutaneously given insulin, into the body on their own. This occurs despite the fact that insulin's large molecular weight of 5808 Da ordinarily prevents it from penetrating the skin. The selfregulating membrane deformability of transfersomes is strongly related to the selfreparation capability of the associated vesicles, with the latter being required for transfersome stability and practical utility. Insulin is thought to be delivered into the body via intact skin cells, with a bio efficiency of at least 50% of the subcutaneous dosage activity.(12)

Conclusion :

Transfersomes are ultra-deformable carriers that allow for more effective distribution of a wide range of drug compounds through the skin barrier than traditional vesicular systems. The fundamental driving mechanism for transfersome movement into the deeper epidermal layers is the osmotic gradient. Importantly, transferosomes are custom-designed vesicular systems that must be tuned for specific cases of pharmaceuticals of interest in order to get the most effective formulations and pharmacological reactions. Further research into transfersomes could lead to unique and potential therapeutic options for a variety of disorders. (25)

Reference :

1. Rahman HS, Othman HH, Hammadi NI, Yeap SK, Amin KM, Samad NA, Alitheen NB. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. International journal of nanomedicine. 2020;15:2439.

2. Sarangi MK, Padhi S. Novel herbal drug delivery system: An overview. Archives of Medicine and Health Sciences. 2018 Jan 1;6(1):171.

3. Rai S, Pandey V, Rai G. Transfersomes as versatile and flexible nano-vesicular carriers in skin cancer therapy: The state of the art. Nano reviews & experiments. 2017 Jan 1;8(1):1325708.

4. Sivannarayana P, Rani AP, Saikishore V, VenuBabu C, SriRekha V. Transfersomes: Ultra deformable vesicular carrier systems in transdermal drug delivery system. Research Journal of Pharmaceutical Dosage Forms and Technology. 2012 Sep 1;4(5):1.

5. Sachan R, Parashar T, Soniya SV, Singh G, Tyagi S, Patel C, Gupta A. Drug carrier transfersomes: a novel tool for transdermal drug delivery system. International Journal of Research and Development in Pharmacy and Life Sciences. 2013 Feb;2(2):309-16.

6. Lei W, Yu C, Lin H, Zhou X. Development of tacrolimus-loaded transfersomes for deeper skin penetration enhancement and therapeutic effect improvement in vivo. Asian journal of pharmaceutical sciences. 2013 Dec 1;8(6):336-45.

7. Anushree P, Mittal A, Chauhan N, Alam S. Role of surfactants as penetration enhancer in transdermal drug delivery system. Journal of Molecular Pharmaceutics & Organic Process Research. 2014 May 15.

8. Solanki D, Kushwah L, Motiwale M, Chouhan V. Transferosomes-a review. World Journal of Pharmacy and Pharmaceutical Sciences. 2016 Aug 12;5:435-49.

9. Jadupati M, Amites G, Kumar NA. Transferosomes: an opportunistic carrier for Transdermal drug delivery system. International Journal of Pharmacy IRJP. 2012;3(3):35-8.

10. Cevc G, Blume G, Schätzlein A, Gebauer D, Paul A. The skin: a pathway for systemic treatment with patches and lipid-based agent carriers. Advanced drug delivery reviews. 1996 Feb 8;18(3):349-78.

11. Mahmood S, Taher M, Mandal UK. Experimental design and optimization of raloxifene hydrochloride loaded nanotransfersomes for transdermal application. International journal of nanomedicine. 2014;9:4331.

12. Cipolla D, Wu H, Gonda I, Eastman S, Redelmeier T, Chan HK. Modifying the release properties of liposomes toward personalized medicine. Journal of pharmaceutical sciences. 2014 Jun 1;103(6):1851-62.

13. Dudhipala N, Phasha Mohammed R, Adel Ali Youssef A, Banala N. Effect of lipid and edge activator concentration on development of aceclofenac-loaded transfersomes gel for transdermal application: In vitro and ex vivo skin permeation. Drug development and industrial pharmacy. 2020 Aug 2;46(8):1334-44.

14. Cevc G, Schätzlein A, Richardsen H. Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2002 Aug 19;1564(1):21-30.

15. Opatha SA, Titapiwatanakun V, Chutoprapat R. Transfersomes: A promising nanoencapsulation technique for transdermal drug delivery. Pharmaceutics. 2020 Sep;12(9):855.

16. Yusuf M, Sharma V, Pathak K. Nanovesicles for transdermal delivery of felodipine: development, characterization, and pharmacokinetics. International journal of pharmaceutical investigation. 2014 Jul;4(3):119.

17. Chaurasiya P, Ganju E, Upmanyu N, Ray SK, Jain P. Transfersomes: a novel technique for transdermal drug delivery. Journal of Drug Delivery and Therapeutics. 2019 Jan 15;9(1):279-85.

18. Rahmi AD, Pangesti DM. Comparison of the Characteristics of Transfersomes and Protransfersomes Containing Azelaic Acid. Journal of Young Pharmacists. 2018 Apr 2;10.

19. Van Hoogevest P, Wendel A. The use of natural and synthetic phospholipids as pharmaceutical excipients. European journal of lipid science and technology. 2014 Sep;116(9):1088-107.

20. Afrin S, Jahan I, Hasan AH, Deepa KN. Novel approaches of herbal drug delivery. J Pharm Res Int. 2018 Jan 1;21(5):1-1.

21. Rahman HS, Othman HH, Hammadi NI, Yeap SK, Amin KM, Samad NA, Alitheen NB. Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. International journal of nanomedicine. 2020;15:2439.