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INCORPORATION OF NOVEL DRUG DELIVERY IN HERBAL SYSTEM - A REVIEW

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ABSTRACT

The basic thought behind it is treatment of each disease is hidden in nature. However, delivery of herbal drugs also requires modifications with the purpose to achieve sustained release, to increase patient compliance etc. Previously herbal drugs could not attract scientists towards the development 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) opens the door towards the development of herbal drug delivery systems. Novel drug delivery technologies have gained the importance to achieve modified delivery of herbal drugs thereby increasing the therapeutic value as well as reducing toxicity. For last one decade many novel carriers such as liposomes, nanoparticles, phytosomes and ethosomes, implants have been reported for successful modified delivery of various herbal drugs. The objective of this review article is to summarize various novel drug delivery technologies which have been developed for delivery of herbal drugs, to achieve better therapeutic response.

KEYWORDS: liposomes, ethosomes, herbal, novel drug delivery system (NDDS).

INTRODUCTION

In the past few decades, considerable attention has been focused on the development of novel drug delivery system for herbal drugs. Herbal drugs are becoming more popular in the modern world for their application to cure variety of diseases with less toxic effects and better therapeutic effects. Novel herbal drug carriers cure particular disease by targeting exactly the affected zone inside a patient's body and transporting the drug to that area. Novel

drug delivery system is advantageous in delivering the herbal drug at predetermined rate and delivery of drug at the site of action which minimizes the toxic effects with increase in bioavailability of drugs. In novel drug delivery technology, control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. Incorporation of herbal drugs in the delivery system also aids to increase in solubility, enhanced stability, protection from toxicity, enhanced pharmacological activity, improved tissue macrophage distribution, sustained delivery and protection from physical and chemical degradation. For example, liposomes act as potential vehicles to carry anti-cancer agents by increasing amount of drug in tumor area and decrease the exposure or accumulation of drug in normal cells/tissues thereby preventing tissue toxicity effects. The phytosomal carriers have been studied for effective delivery of herbal extracts of ginseng (*Ginkgo biloba*),lyvopene(*Solanum lycopersicum)*etc. Direct binding of phosphatidylcholine to herbal extract components led to better absorption characteristics as compared to conventional delivery of herbal extracts. Other vesicular assemblies like microspheres, nanoemulsions, polymeric nanoparticles etc. have been proved beneficial to carry herbal components. The present review article is aimed to provide an overview of different types of drug delivery systems incorporating active ingredients and potential advantages of such systems. In the present article, an attempt has been made to touch upon various aspects and applications related to novel herbal drug formulations.[1]

Advantages of herbal Extracts

1. **Low risk of side effects:** Mostly herbal drugs are well tolerated by the patient, having fewer unintended consequences and fewer side effects than traditional medicine, and may be safer to use.

2. **More Effectiveness:** Herbal drugs are more effective for long-standing health complaints that don't respond well to traditional medicine. One example is the herbs and alternative remedies used to treat arthritis. Vioxx, a well-known prescription drug used to treat arthritis, was recalled due to increased risk of cardiovascular complications. Herbal treatments for arthritis, on the other hand, have lesser side effects. Such treatments include dietary changes like adding simple herbs, eliminating vegetables from the nightshade family and reducing white sugar consumption.

3. **Lower cost:** Cost of herbal drugs is much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.

4. **Widespread availability:** Herbs are available without a prescription. Simple herbs, such as peppermint and chamomile, can be cultivated at home.[2]

- **Active constituents which can be used in NDDS**

1. **Lycopene**
2. **Capsicin**
3. **Bromalein etc**

- **Importance of novel drug delivery systems in herbal medicines**

Novel drug delivery system is a novel approach to drug delivery that addresses the limitations of the traditional drug delivery systems. Our country has a vast knowledge base of Ayurveda whose potential is only being realized in the recent years. However, the drug delivery system used for administering the herbal medicine to the patient is traditional and out-of-date, resulting in reduced efficacy of the drug. If the novel drug delivery technology is applied in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal compounds and herbs. This is the basic idea behind incorporating novel method of drug delivery in herbal medicines. Thus it is important to integrate novel drug delivery system and Indian Ayurvedic medicines to combat more serious diseases. For a long time, herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and processing difficulties, such as standardization, extraction and identification of individual drug components in complex poly herbal systems. However, 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 medicines to be incorporated in novel drug delivery system, such as nanoparticles, micro emulsions, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on.[3] Various drug delivery and drug targeting systems are currently under development to minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone.[2]

- **Advantages of novel drug delivery systems**

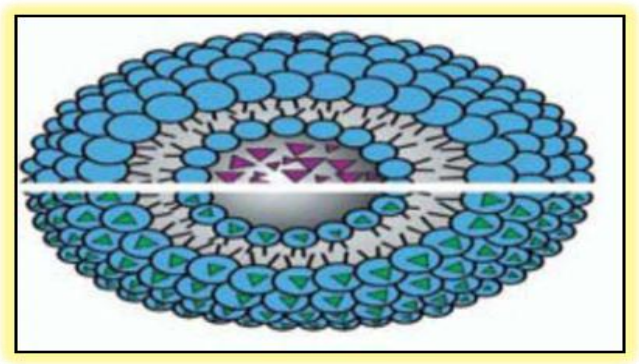
1. Enhancement of solubility.

2. Increased bioavailability.
3. Protection from toxicity.
4. Enhancement of pharmacological activity.
5. Enhancement of stability.
6. Improved tissue macrophages distribution.
7. Sustained delivery.
8. Protection from physical and chemical degradation.

- **Types of Novel Herbal Drug Delivery Systems**

Various approaches in case of novel herbal drug delivery system include different types of formulations as shown in the fig 1. such as liposomes, phytosomes, niosomes, transferosomes, ethosomes, and dendrimers etc. are discussed below.[1]

1. PHYTOSOME The term 'Phyto' means plant while 'Some' means cell-like. Phytosome is vesicular drug delivery system in which phyto constituents of herb extract surround and bound by lipid (one phyto-constituent molecule linked with at least one phospholipid molecule). Phytosome protect valuable component of herbal extract from destruction by digestive secretion and gut bacteria and because of which they show better absorption which produces better bioavailability and improved pharmacological and pharmacokinetic parameters than conventional herbal extract.[4] and the difference between phytosomes and liposome shown in fig 2.



Water soluble free drug

Phosphatidylcholine

Phosphatidylcholine-drug complex

Fig.1: Major difference between liposome and Phytosome

- **Advantages of Phytosomes**

1. Increased bioavailability due to phospholipid complex.
2. Improved absorption in GIT.
3. Increased bioavailability causes improved therapeutic effect.
4. Less dose requirement due to high bioavailability.
5. Higher stability.
6. High lipophilicity causes high penetrability, hence forth used in cosmetics over liposomes
7. Greater clinical benefits.
8. Phosphatidylcholine acts as liver protective other than a carrier.[5]

Table 1. Commercially available Phytosome products [7]

Sr.no	Phytosome product	Phytoconstituent complexed with phosphatidylcholine	Dose	Indication
1.	Silybin Phytosome	Silybin from *Silybum marianum*	120 mg	Hepatoprotective, antioxidant for liver and skin.
2.	Hawthorn Phytosome	Flavonoids from *Crataegus* sp.	100 mg	Nutraceutical .Best choice in heart disease or high blood pressure
3.	Ginseng Phytosome	37.5 % ginsenosides from immuno modulat or *Panax* 150 mg *ginseng*		Nutraceutical,Immunomodulator
4.	Green Tea Phytosome	Epigallocatechin from *Thea sinensis*	50 - 100 mg	Nutraceutical, Systemic antioxidant. Best choice for protection against cancer and damage to cholesterol.
5.	Ginkgo Biloba Phytosome	24 %Ginkgo flavonglycosides from *Ginkgo biloba*	120 mg	Protects brain and vascular lining; Anti-skin ageing agent. Best choice most people over the age of 50.
6.	Grape Seed Phytosome	Procyanidins from *Vitis vinifera*	50-100 mg	Nutraceutical, systemic antioxidant. Best choice for most people under age of fifty. Also specific for, lungs, diabetes, varicose veins, and protects against heart disease.
7.	Bilberry Phytosomes	Extract of *Bilberry* which provides anthocyanosides	-	Improve capillary tone, reduce abnormal permeability, and are potent antioxidants
8.	Super Milk thistle	Silybin from *Silymarin* Food Product	150 mg	Antioxidant for liver and skin
9.	Olive oil Phytosomes	Polyphenols from *Olea europaea* oil	-	Inhibit oxidation of LDL cholesterol, and also have anti-inflammatory activity
10.	Visnadine Phytosome	Visnadine from *Ammi visnaga*	-	Circulation Improver

2. LIPOSOME

Liposomes are concentric bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. A liposome can be formed at a variety of sizes as uni-lamellar or multi-lamellar construction, and its name relates to its structural building blocks, phospholipids, and not to its size. A liposome does not necessarily have lipophobic contents, such as water, although it usually does. Liposomes are artificially prepared vesicles made of lipid bilayer. Liposomes can be filled with drugs, and used to deliver drugs for cancer and other diseases. Liposomes can be prepared by disrupting biological membranes, for example by sonication. Liposomes are micro particulate or colloidal carriers, usually 0.05- 5.0 µm in diameter which form spontaneously when certain lipids are hydrated in aqueous media. Liposomes are composed of relatively biocompatible and biodegradable material, and they consist of an aqueous volume entrapped by one or more bilayer of natural and/or synthetic lipids. Drug with widely varying lipophilicity can be encapsulated in liposomes, either in the phospholipids bilayer, in the entrapped aqueous volume or at the bilayer interface.[8]and the drug encapsulated in liposomes shown in fig.2.

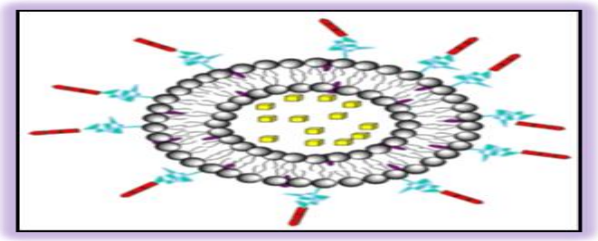


Fig.2: Drug encapsulation in Liposomes

- **Liposome classification based on structural features** [9]

1. MLV - Multilamellar large vesicles
2. OLV - Oligolamellar vesicles
3. UV - Unilamellar vesicles
4. SUV- Small unilamellar vesicles
5. MUV - sized unilamellar vesicles
6. LUV - Large unilamellar vesicles
7. GUV - Giant unilamellar vesicles
8. MVV -Multivesicular vesicles

- **Liposome classification based on method of liposome preparation.**[9]

1. REV -Single or oligolamellar vesicle made by reverse phase evaporation method.
2. MLV / REV -Multilamellar vesicles made by reverse phase evaporation method.
3. SPLV -Stable plurilamellar vesicles.
4. FAT-MLV Frozen and thawed MLV
5. VET- Vesicles prepared by extrusion method.
6. FUV-Vesicles prepared by fusion
7. FPV -Vesicles prepared by French press
8. DRV- Dehydration- rehydration vesicles
9. BSV- Bubblesomes

- **Advantages of Liposome**[10]

1. Provides selective passive targeting to tumor tissues (Liposomal doxorubicin).
2. Increased efficacy and therapeutic index.
3. Increased stability via encapsulation.
4. Reduction in toxicity of the encapsulated agents.
5. Site avoidance effect.
6. Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
7. Flexibility to couple with site specific ligands to achieve active targeting
8. Biodegradable and flexible
9. Can incorporate micro and macro molecules
10. Can carry both water and lipid soluble drugs

Table 2: Liposome Herbal Formulations[11]

Sr.no	Herbal medicine	Chemical classification	Pharmacological activity	Benefit of formulation
1.	**Curcumin**	Natural polyphenol isolated from the root of *Curcuma longa*	Antitumor, antioxidant, antiamylodin, antiplatelet aggregation and anti-inflammatory.	Improved intravenous delivery of curcumin to tissue macrophages
2.	**Catechins**	Polyphenolic plant metabolites abundant in teas derived from the tea plant *Camellia sinensis*	Chemopreventive, anticarcinogenic, antiviral, antioxidative, anti-obesity, anti-inflammatory, antidiabetic, antimutagenic, antiangiogenic, antibacterial, antiageing activities	Improved loading and in vivo deposition of catechins

3.	**Silymarin**	Flavonol glycoside obtained from dried fruits of *Silybus marianum*	Hepatoprotective agent	Improved permeation and stability of silymarin

3. NIOSOMES are microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and a charge inducing agent with subsequent hydration in aqueous media. Niosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubility's. Niosomes have been evaluated in many pharmaceutical applications. In such therapeutic applications, important advantages of using niosomes include their ability to reduce systemic toxicity by encapsulation of treatment agents and minimize clearance of such agents from the body by slow drug release.[12] and the structure of niosome shown in the fig 3.[13]

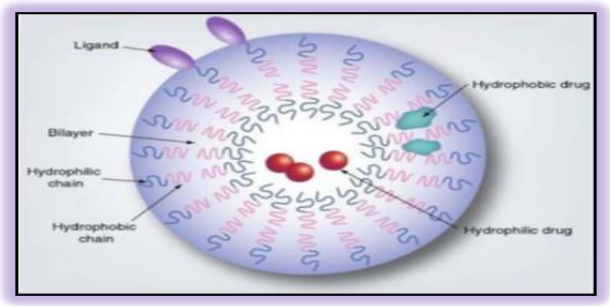


Fig.3: Structure of Niosome

- **Types of Niosomes[13]**

1. Niosomes are classified based on number of bilayer, size
2. and method of preparation.
3. Mulitlamellar- 0.5µm to 10µm in diameter.
4. Larger unilamellar- 0.1µm to 1µm in diameter
5. Small unilamellar – 25-500nm in diameter

- **Advantages of Niosome[14]**

1. Niosomes are biodegradable, biocompatible, non-toxic and non-immunogenic.
2. Niosomes are able to encapsulate large amount of materials in a small volume of vesicles.
3. Niosomes have better patient adherence and satisfaction and also better effectiveness than conventional oily formulations.
4. Niosomes can entrap wide range of chemicals (hydrophilic, lipophilic and amphiphilic drugs) due to its unique structure.

5. The characteristics of niosome such as shape, fluidity and size can be easily controlled by changing in structural composition and method of production.
6. Niosomes can be prescribed via different administration routes such as oral, parenteral and topical, etc. with different dosage forms such as semisolids, powders, suspensions.
7. Due to chemical stability of structural composition, the storage of the niosome is easy.

Table 3: Applications of Niosomal Formulations

Sr.no.	Drugs	Applications of Niosomal Formulations	Biological activity
1.	Colchicine	Prolonged release profile	reat rheumatic complaints
2.	Silymarin	Increase drug bioavailability	Treat liver and gallbladder disorders

4. TRANSFERSOME

The term and concept of Transfersome were introduced in 1991 by Gregor Cevc. The name means “carrying body”, and is derived from the Latin word 'transferre',meaning ‘to carry across’, and the Greek word ‘soma’, fora ‘body’. A Transfersome carrier is an artificial vesicle which resembles the natural cell vesicle. Thus it is suitable for targeted and controlled drug delivery. Transfersome is a highly adaptable and stress-responsive, complex aggregate. It is an ultra-deformable vesicle which possesses an aqueous core surrounded by the complex lipid bilayer. Interdependency of local composition and shape of the bilayer makes the vesicle both self-regulating and self-optimising. This enables the Transfersome to cross various transport barriers efficiently, and then act as a drug carrier for non-invasive targeted drug delivery and sustained release of therapeutic agents. These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. These vesicular transfersome are several orders of magnitudes more elastic than the standard liposome and thus well suited for the skin penetration. Transfersomes over come the skin penetration difficulty by squeezing them selves along the intracellular sealing lipid of the stratum corneum. Flexibility of transfersome membrane is achieved by mixing suitable surface-active components in the proper ratios.[15]. structure as shown in the fig.3.[17] List of drugs used for Transfersomes shown in table 4.[15,18]

Fig.3: Undeformable Vesicle (Transferosome)

- **Advantages of Transfersomes**[16]

1. Transfersomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
2. They have high entrapment efficiency, in case of lipophilic drug near to 90%.
3. This high deformability gives better penetration of intact vesicles.
4. They can act as a carrier for low as well as high molecular weight drugs e.g. analgesic, anesthetic, corticosteroids, sex hormone, anticancer, insulin, gap junction protein, and albumin.
5. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
6. They act as depot, releasing their contents slowly and gradually.
7. They can be used for both systemic as well as topical delivery of drug.
8. They are biocompatible and biodegradable as they are made from natural phospholipids similar to liposomes.
9. They protect the encapsulated drug from metabolic degradation.
10. Easy to scale up, as procedure is simple, do not involve lengthy procedure and unnecessary use or pharmaceutically unacceptable additives.

Table 4. List of drugs used for Transfersomes

Sr. No	Name of drug	Biological source	Inference
1.	Curcumin	Curcuma longa	Better permeation for anti-inflammatory activity
2.	Capsaicin 6	Capsicum annum	Increase skin penetration
4.	Vincristine	Catharanthus roseus	Increase entrapment efficiency and skin permeation
5	Colchicine	Colchicum automnale	Reduction in GIT side effects
6	Lycopene	Solanum lycopersicum	Anticancer activity

6. DENDRIMERS

Dendrimers are spheroid or globular nanostructures of polymeric materials. They are highly branched, monodisperse nanoparticles that bind the drug at the surface or entrap within their inner cores. There is a unique property of branching around the inner space that has huge effect on physical and chemical properties. Preparations of these particles are either by divergent or convergent methods. The size grows linearly while the number of surface groups put in. They have very low poly disparity index and ranging dimension increment by stepwise from 1-10 nm. The performance and individual properties of dendrimers can be at

variance deeply from their linear complements. Due to very low polydispersity of Dendrimers, they contribute to their efficacy as drug delivery strategy.[19] structure of the Dendrimers as shown in fig.4.[20]

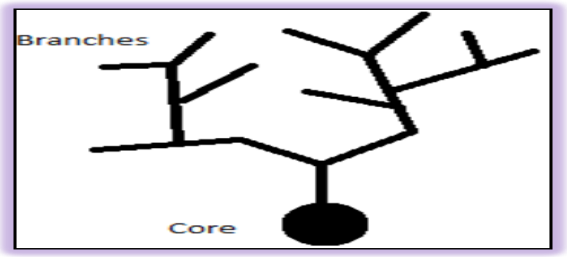


Fig.4: Structure of a Dendrimer

- **Advantages of Dendrimer** [20]

1. Medication to the affected part inside a patient's body directly.
2. In target drug delivery: Dendrimers are suitable for targeting solid tumors due to increased permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumor (enhanced permeation rate). There is also reduction in amount of drug used via targeted delivery (attaching site specific ligands at surface or magnetic guidance) and thus reduction in systemic toxicity.
3. Controlled and sustained release of drugs can also be obtained.
4. Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation.
5. Bypassing the gastric medium and hence the eschewing the variation due to effect of gastric secretions.
6. Increase in therapeutic efficacy, decrease in side effects: decreased clearance of drug via altered distribution of drug in organs at site of localization and transportation due to controlled and sustained release of the drug.
7. Relatively high drug loading.
8. Preservation of drug activity: as drugs can be incorporated into the systems without any chemical reaction.

- **Currently, there are three methods for using dendrimers in drug delivery**

a) The drug is attached to the periphery of the dendrimer to form dendrimer prodrugs,
b) The drug is coordinated to the outer functional groups via ionic interactions, or
c) The dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer drug (i.e., host–guest) supramolecular assembly. The latter

approach is of interest for multiple reasons and provides an opportunity to encapsulate pharmacologically active compounds and to study the supramolecular assemblies formed in these systems. [21]

d) Dendrimers possess several unique properties that make them a good nanoparticle platform for antimicrobial drug delivery.[22]

- **Mechanism of Drug Delivery Through Dendrimers**

The well defined 3D structure and many functional surface groups, drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups (as shown in the figure). Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug).as shown in the fig.5.

There are broadly two mechanisms for drug delivery.

A) First, is by in vivo degradation of drug dendrimer conjugate (covalent bonding of drug to dendrimer), which depends on presence of suitable enzymes or an environment capable of degrading bonds.

B) The second one is by releasing the drug due to changes in physical environment such as pH, temperature. This approach is independent of the external factors and takes place in cavities of the core (endo-receptor) or outer shell of receptor (exo-receptor)

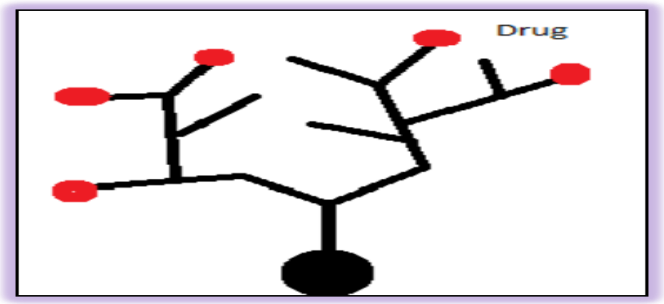


Fig.5: A Dendrimer molecule with drug molecules loaded at terminal surface of branches

There are two types of delivery, one is to a specific type of cell and other as a controlled release from a depot (which may be present in circulation or imbedded in some suitable tissue) 1. Psividas biosilicon allows drug molecules to be held in Nano-sized particles that release a tiny pulse of drug as the biosilicon dissolves. Biosilicon shows resistance to degradation in acid environment. A dendrimer of higher generations consists of shell. A shell

consists of a central core and alternating two layers of monomers around it. Amines constitute the central core which may sometimes be replaced by sugar. All core molecules have multiple and identical reaction site. Amine is the simplest core molecule present with three functional sites. The surface of all full generations consists of multiple amines, while the surface of the half generations consists of multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components.[22]

6. ETHOSOMES

Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers (nm) to microns (μ) ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux.[23] as shown in the fig.6.[25]

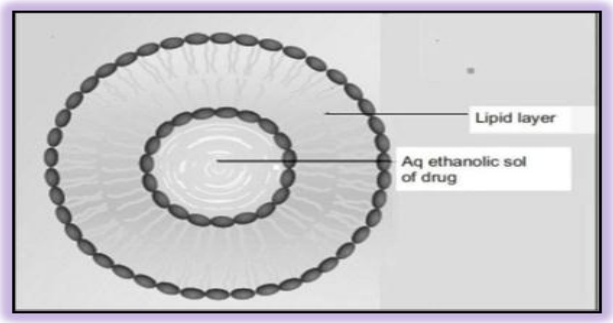


Fig.6: Diagram of Ethosomes

- **Advantages of Ethosomes**[24]

1. Delivery of large molecules (peptides, protein molecules) is possible.
2. It contains non-toxic raw material in formulation.
3. Enhanced permeation of drug through skin for transdermal drug delivery.
4. Ethosomal drug delivery system can be applied widely in Pharmaceutical, Veterinary, Cosmetic fields.
5. High patient compliance: The ethosomal drug is administrated in semisolid form (gel or cream) hence producing high patient compliance.
6. Simple method for drug delivery in comparison to Iontophoresis and Phonophoresis and other complicated methods
7. The Ethosomal system is passive, non-invasive and is available for immediate commercialization.

Table 5. System Application of Ethosomal formulations[25]

Sr.no.	Botanical	Active ingredients	Biological activity	Application of ethosomal formulations
1.	*Sophora alopecuroides*	Sophora Alopecuroides ethosomes	Anti-endotoxic, anti-cancer and anti-inflammatory	Ethosome enhances delivery of drugs through the stratum corneum barrier into the deep layer of the skin
2.	*Sophora flavescens*	Matrine	Antibacterial, anti-inflammatory, anti-rheumatism and anti-tumour	Increase the per cutaneous permeation and improve anti-inflammatory effect
3.	*Sesbania grandiflora*	Sesbania ethosome	Anti-microbial	Enhance Transdermal permeation
4.	*Glycyrrhiza glabra*	Amonium Glycyrrhizinate Ethosomes	Anti inflammatory	Increases of *in vitro* percutaneous permeation and significantly enhanced anti inflammatory activity
5.	*Podophyllum hexandrum*	Podophyllotoxin	Purgative, antirheumatic, antiviral and antitumor	Higher entrapment efficiency and enhance its therapeutic effect
6.	*Tripterygium wilfordi*	Triptolide	Anti inflammatory	high entrapment efficiency, good percutaneous permeability

- **Future Prospects and Opportunities in India**

India is one of the most strategic regions for the pharmaceutical market. Therefore many multinational giants have been keen to invest and grow preferentially in this sector. Developments in the new and advanced techniques in the field of NDDS will create huge demand for variety of excipients usage and development. India is well known for its quick adaptability to new excipients and associated technologies. So market for excipients in India will grow on two aspects; one is in the form of exporting new organic excipients and the second one in the form of employing new excipients in various advanced delivery technologies. Majority of the pharmaceutical companies in the country have been applying and receiving new patents in the field of the Novel drug delivery systems. This eventually, in the near future derives huge demand for the products and services offered by pharmaceutical and allied businesses. Nanotechnology offers various modern applications in novel drug delivery systems that potentially improve the diagnosis, treatment and help monitoring of post-administration transformation of drug composition within the body systems. Another important milestone to be mentioned here is Computer aided Drug Design, which offers a lot of scope for the development of this kind of novel and advanced systems. Computer aided Drug Design helps in designing and developing the drugs and delivery systems consuming less time and resources with more accuracy and quality compared to traditional methods.[26]

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