Chapter

Drug Delivery through Targeted Approach with Special References to Phytosomes

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Abstract

Novel drug delivery is a great tool to deliver the drug at a specific site of action by the means of specific drug carrier like Solid-lipid Nanoparticles, Nano-structured lipid carriers, lipid vesicles, liposomes, phytosomes and ethosomes. Every carrier used in novel drug delivery system to deliver the drug at targeted site requires some special formulation techniques. These techniques help the drug carrier to deliver the active drug at targeted site, by reducing the side-effect, minimizing the dose, increasing the absorption and increasing the efficacy of the drug. There is a recent upsurge to move "back to nature" for healing body ailments because the report states that conventional treatment cause various side effects to the human body after prolonged used. Various novel drug delivery vesicles/'somes' are being used for the delivery of phytoconstitutents to the targeted site of action. Phytosome is one of the more reliable and best option for the delivery of herbal constituent to the targeted site. The combination of Novel drug delivery with the transdermal route may be a good idea having fast and targeted delivery of drug. Many health challenges like skin diseases, skin burns, migraine, allergies, cardiac problems, diabetes and trauma like bone fracture could be easily managed by the combination of novel drug delivery and the transdermal route in future.

Keywords: novel drug delivery, Phytosomes, herbal products, trauma, lipid vesicles, trandermal route

1. Background

With the advent of civilization Human beings have demonstrated their dependence on Nature and plant to fulfill all basic needs. In an eventuality of an infirmity, diseased situation or healing of body ailments the use the plant based remedies had been on the anvil. With the passing of time the knowledge of healing from natural resources developed into science of healing and was documented in India as Ayurveda. The other world event over had similar chronological developments that led to the validation of the traditional knowledge of healing, that strength of of herbal formulations for the treatment of disease and body ailments. Most of the herbal formulations are administered via oral route and are poorly absorbed due to hydrophobic behavior which leads to decreased bioavailability and increased systemic clearance. Repeated administration or dose increment is required to maintain the therapeutic efficacy thereby limiting the use of herbal medicines [1]. Commonly, the herbal medicines utilize crude powders, extracts be formulation

in accordance to the statutory compendia which might not be needed in large doses, limited route of drug administration but also could be less effective than the contemporary therapeutic formulations. The rapid progress of allopathic drug lead to its dominance in the therapeutic field. The various types of dosage form of allopathic drugs are available to treat the disease conditions i.e. solid dosage form (tablets, capsules, and powders), Liquid dosage form (syrup, suspension, and emulsion given by oral route and injectables given by parental route), and aerosols. Nausea, vomiting, and dizziness are some common side effects associated with these conventional dosage forms of allopathic system. Major complications have come forth after prolonged use of these formulations. There has been a continuous research on reducing side effects experienced by the patients resulting in some advancement to such conventional dosage form. Novel Drug delivery System (NDDS) is one such area of drug research that focuses on the target specific site of action and to minimize the side effects of the conventional dosage form. Nowadays, there has been a change in global trend from synthetic to natural medicine, which we can say "back to nature." The efficiency of medicinal plant species, or herbal medicine, depends on the active molecules present since they provide synergistic action and thus enhance the therapeutic effectiveness. Research is being continuously carried out for the amalgamation of Novel drug delivery and phytoconstituents to ward off any prevalent side effects of NDDS in allopathic system of treatment after prolonged used [2].

There are many kinds of herbal medicines and supplements used worldwide. The global market of phytomedicines currently stands at over $60 billion annually. The sale of herbal medicines was expected 6.4% on an average annual growth rate in 2012 [3, 4] (**Table 1**).

It is widely accepted that 70–80% of people globally rely on natural resources for their treatment. In the year 2017 the American Botanical council accepted that the sale of herbal supplements increased by 7.7% in US (on basis of turnover of herbal market in 2016). Europe leads the chart owing to extensive R&D for herbal medicine owing to considerable increase in funding for research on herbal medicinal plants. America stands on second position in the global herbal medicine market and held 16.2% of market share in 2017. The consumption of herbal supplements in US was majorly used for the conditions such as heart stroke (48.7%), Cancer (43.1%), and arthritis (43%) announced by National center for biotechnology information in 2017. Asia Pacific stands on third position having a growth rate of 5.99% due to the adoption of traditional medicine by pharmaceutical companies, researchers, and policy maker [5].

Global herbal market		
Market size	**(US$ billions)**	**Percentage**
European Union	28	45
Rest EU	2.4	4
ASEAN	10.8	19
Japan	9.8	16
North America	6.9	11
Others	4.1	7
Total	60	100

Source: http://www.markertresearchfuture.com/reports/herbal-medicine-market-325.

Table 1.
Segmentation of global herbal market in 2012.

The major players in global herbal medicine market are Arkopharma, Beovita, Hisimo Pharmaceuticals, Bayer AG, Schaper & Brummer Venus Pharma, and Arizona Natural products. Some key players in the industry involved in the production of herbal medicine and supplements include Bio-Botanica Inc., Dabur Ltd., Guangzhu Pharma Co., Nature's Answer, Inc., Sanjiu Medical & Pharmaceutical Co. Ltd. The high market demand and an upbeat market trend in favor of natural products are likely to boost the growth in the days to come [5].

Current drug market-mix contains numerous formulations based on medicinal plants and phytoconstituents. However the constant decree that the herbal formulations lack proper standardization protocols and is less efficacious or require larger dose to show its efficacy has deprived the impetus to become the alternative treatment regimen. Application of recent technological advancements such as amalgamation of novel drug delivery with herbal drugs would augment the efficacy of the traditional system.

Various approaches for improving bioavailability of novel herbals formulations followed as under [6–8]:

- Chemical derivatization to improve bioavailability which, however, generates a number of chemical analogs that need to be appropriately screened.
- Combination of the active molecules with other compounds as adjutants promoting the active molecule's absorption.
- Stabilizing natural molecules and promotion of intestinal absorption.
- Improving pharmacokinetic profile by formulating with dietary ingredients (soy lecithin).

Many herbal formulations are being developed with the help of novel technologies of incorporation the phytoconstituents in the vesicles of lipid bi-layers. These vesicles work as novel carriers to deliver the drug at its targeted site. Some advanced drug delivery techniques use novel vehicles "*somes*" as nanobiomedicine delivered by different route of drug delivery. The novel carrier should ideally fulfill two prerequisites. Firstly, it should deliver the drug at predefined period of time or according to the body requirements. Secondly, it should channel the active constituent to the site of action [9]. There are different types of novel drug vehicle as tabulated, use to deliver the drug molecules on the site of action (**Table 2**).

The nano-carrier used in novel drug delivery system of herbal drugs has a potential future, improving the activity and overcoming the problem associated with herbal constituents [10]. Any type of medicament could be delivered to its specific site of action with the help of novel drug delivery system. Researchers are

• Liposomes	• Nanoparticles and microspheres
• Niosomes	• Solid lipid nanoparticles
• Hydrogel nanoparticles	• Microparticles
• Resealed erythrocytes	• Supramolecular biovectors
• Lipoproteins	• Cyclodextrins
• Polymeric micelles	• Aquasomes
• Dendrimers	• Emulsions

Table 2.
Different types of novel drug delivery systems [10].

currently underway to develop an ideal drug delivery system which satisfies the need of targeted site of action. Biological membrane presents a barrier through which a drug must pass before it gets absorbed or excreted. Lipid solubility and molecular size of drug molecule pose two major limiting factors to pass the biological membrane by which drug can be absorbed systematically following oral or topical administration [11].

The conventional herbal dosage form has a problem of standardization and quality control which had relegated its usage in the in last few decades. When the side effects of allopathic drugs outweigh their risk to usage the focus for treatment shifts towards the natural components and herbal system of treatment. In herbal novel drug development polymeric nanoparticles and nanocapsules like liposomes, solid lipid nanoparticles, phytosomes and nanoemulsion are been formulated. NDDS provides many advantages for herbal drugs including enhancement of solubility and bioavailability, protection from toxicity, enhancement of stability, enhancement of pharmacological action, improving tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. The efficacy of herbal product (or medication) is dependent upon effective route of delivery and level of the active compounds [12].

Novel drug delivery systems deliver the drug components at a rate directed by the need of the body during the period of treatment and channelize the active entity onto the site of action. A number of novel drug delivery systems have been used to deliver herbal medicaments encompassing various routes of administration to achieve controlled and targeted drug delivery, for example, encapsulated vesicles can prolong the existence of the drug in systemic circulation and reduce the toxicity if selective uptake can be achieved through drug targeting, sustained or controlled release of conventional medicines [11, 12].

The novel drug delivery vehicles can be classified on the basis of their size, shape, and their composition (**Table 3**).

1.1 Liposomes

Liposomes are micro-sized spheres in which an aqueous core is surrounded by one or more lipid bi-layer. The lipid bi-layers are separated by water or aqueous buffer compartments, liposomes are simple microscopic vesicles in which aqueous volume is entirely enclosed by a membrane composed of lipid bilayers [13] (**Figure 1**).

Name of somes	Particle size/shape	Composition
Liposomes [13]	100–1000 nm(diameter)/ spherical	Phospholipids and cholesterol
Resealed erythrocytes [14]	6–9 μm (diameter)/oval	Plasma, protein and platelets
Niosomes [15]	100–140 nm (diameter)/ spherical	Non-ionic surfactants and cholesterol
Discomes [16]	16–20 μm/disc shaped vesicles	Cholesterol and niosomes
Transferosomes [17]	170–200 nm/oval	Soya phophatidylcholine surfactant and drug/antigen
Ethosomes [18]	50–100 nm/spherical	Phospholipid and ethanol
Phytosomes [19, 20]	10–100 nm/spherical	Phospholipid and herbal extract
Aquasome/hydrosomes	60–300 nm/circular	Ceramics, carbon [21]

Table 3.
Classification of herbal novel drug delivery approach on the basis of their size, shape, and composition.

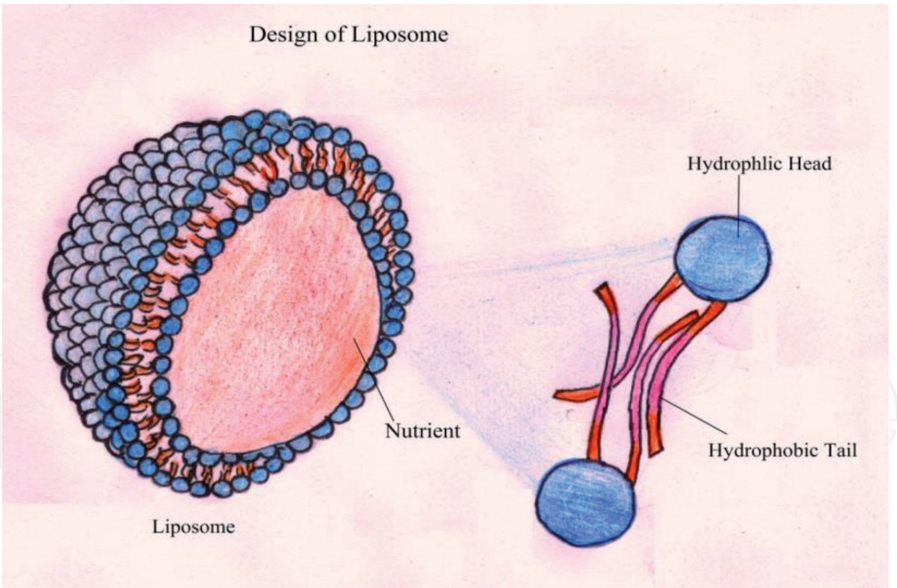

Figure 1.
Liposome (source: http://healthproductdistributor.com) [22].

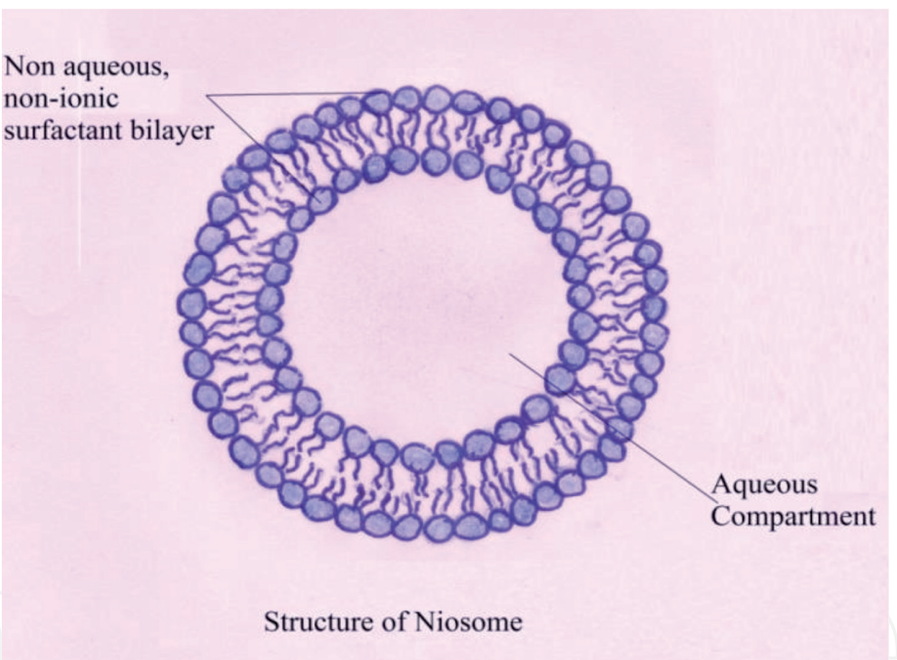

Figure 2.
Structure of niosome [24].

1.2 Niosomes

Niosomes are non-ionic surfactant-based liposomes. Niosomes can be obtained by hydration of liposomes. These are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class with cholesterol [15]. The stability of niosomes are affected by type of surfactant, nature of encapsulated drug, storage temperature, detergents, use of membrane spanning lipids, the interfacial polymerization of surfactant monomers in situ, inclusion of charged molecule. Niosomes have great penetrating capability [23] (**Figure 2**).

The sizes of Niosomes are microscopic and lie in nanometric scale. The particle size ranges from 10 to 100 nm [24].

1.3 Discomes

Discomes (disc shaped vesicles) are large (16–20 μm) sized vesicles structures capable of entrapping water soluble solutes, formed by solubilization of niosomes with a nonionic surfactant. They act as drug reservoirs in the field of drug delivery [16].

1.4 Transferesome

Transferosomes are complex vesicular aggregate optimized to attain extremely flexible and self-regulating membrane; this makes the vesicles very deformable. Transferosome have the property to cross microporous barrier very efficiently, even when available passage are much smaller than the average aggregate size. Transferosome consists of natural amphipathic compound suspended in water-based solution, something containing biocompatible surfactant. Transferosome also have lipid bilayer that surrounds an aqueous core and contain at least one component that soften the membrane and make skin more flexible. This allows an easy and rapid change in shape of transferosome [17].

1.5 Ethosomes

Ethosomes are lipid vesicles containing high amount of ethanol. They have the efficiency to penetrate the skin and enhance compound delivery both to deep skin strata and systemically. Ethanol fluidizes both lipid bilayers of the stratum corneum and intercellular lipid. The soft malleable vesicles then penetrate the disorganized lipid bilayer. This system consists of phospholipid, ethanol and water [18].

1.6 Resealed erythrocytes

The fluid portion of blood contains a large number of organic and inorganic substances in solution, which may diffusible (electrolyte, anabolic and catabolic substance formed during metabolism) and non-diffusible (proteins). The cellular portion of blood consists of erythrocytes (red blood cells), leukocytes (white blood cells) and thrombocytes (platelets). Erythrocytes have a solid content of about 35% (rest of being water) most of which is hemoglobin, which is remain tightly bound to the stroma of cell membrane [14]. Resealed erythrocytes are drug-loaded carrier erythrocytes, prepared simply by collecting blood samples from the organism of interest, separating erythrocytes from plasma, entrapping drug in the erythrocytes, and resealing the resultant cellular carriers. Hence, these carriers are called resealed erythrocytes [14].

1.7 Aquasomes

Aquasomes are the nano-structured biopharmaceutical vesicles based upon fundamental principle of self-assembling. It contains the particle core composed of nano-crystalline calcium phosphate or ceramic diamond, and is covered by a polyhydroxyl oligomeric film. Aquasomes are also called as “bodies of water”. The drug candidates/molecule delivered by Aquasomes represent better biological activity even in case of conformationally sensitive ones. Aquasome having properties like protection and preservation of fragile biological molecules, conformational integrity, and surface exposure made it as a successful carrier system for bioactive molecules like peptide, protein, hormones, antigens and genes to specific sites [21].

1.8 Phytosomes

Phytosomes is the combination of two words, the term "PHYTO" means plant while "SOME" means cell-like [25]. The formulation is developed by encapsulating the plant material or plant extract within the spherical cell like structure, which is an advanced nano-sphere or cell forms of herbal products that are better absorbed. Phytosomes produces better pharmacokinetic and pharmacodynamic profile of drug than conventional herbal formulations. It's a novel emerging technique that is applied to phytopharmaceuticals for the enhancement of bioavailability of natural plant extract for medicinal applications. Phytomedicines, complex chemical mixture prepared from plants, have been used in India and worldwide from the very beginning of human civilization and continue to have widespread popular use [26].

Phytosome is a patented process developed by Indena, a leading supplier of nutraceutical ingredients, to incorporate phospholipids into standardized extract and so vastly improve their absorption and utilization. Phytosome is one kind of herbal extracts delivery system that deliver natural values at target site in such manner. Certain of the water-soluble phytomolecules (mainly flavonoids and other polyphenols) can be converted into lipid-friendly complexes, by reacting herbal extract owing to their enhanced capacity to cross the lipid-rich biomembranes and finally reach the blood. They have improved pharmacokinetic and pharmacological parameters which are advantageous in the treatment of acute disease as well as in pharmaceutical and cosmetic compositions [19].

Phytosomes are better able making transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. The lipid- phase substances employed to make flavonoids lipid- compatible are phospholipids from soy, mainly phosphatidylcholine (PC). PC, the principal molecular building block of cell membranes, is miscible both in water and in oil/lipid environments and is well absorbed when taken by mouth. Precise chemical analysis indicates that a Phytosome is usually a hydrophilic herbal extract linked with at least one PC molecule. A bond is formed between the two molecules, creating a hybrid molecule. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte outer cell membrane [19].

2. Difference between phytosome and liposome

The fundamental difference between liposomes and Phytosomes is that in liposomes the active principle is dissolved in the medium contained in the cavity or in the layers of the membrane, whereas in the Phytosome it is an integral part of the membrane, being the molecules anchored through chemical bonds to the polar head of the phospholipid [20].

There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water soluble compound in Liposome. In contrast, the Phytosome contain Phosphatidylcholine and the individual plant components actually form a 1:1 or a 2:1 complex depending on the substance. This difference show that Phytosomes being much better absorbed than liposomes. Phytosomes are superior to liposomes in skin care products [27, 28] (**Figure 3**).

Phytosome (lower segment) liposome (upper segment).

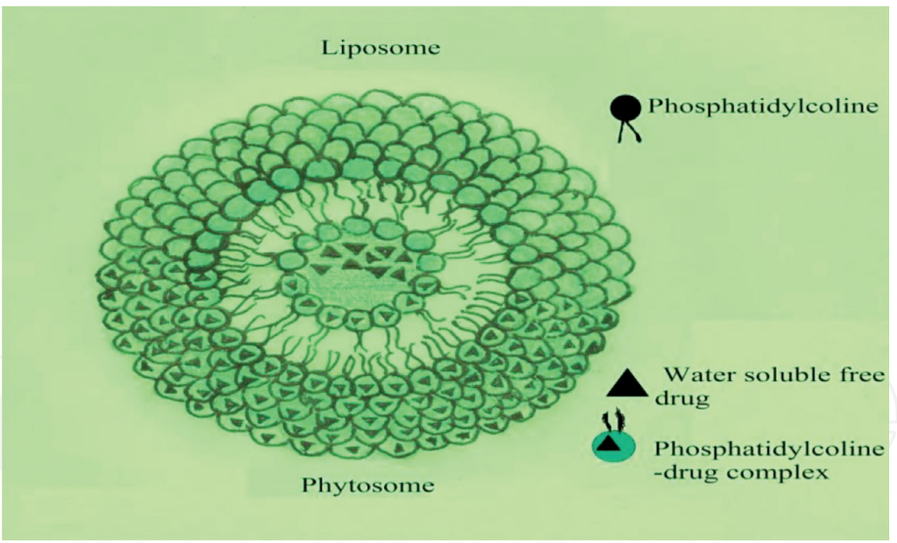

Figure 3.
Difference between phytosome and liposome [29].

3. Merits of phytosomes over conventional dosage forms

- The bioavailability of botanical extracts enhanced dramatically due to their complexation with phospholipids by which absorption of the constituent improved in the intestinal tract [27–30].

- Phytosme enhances the permeation of non- lipophilic botanical extract to allow better absorption from the intestinal lumen, which not possible by other carriers.

- The formulation aspect of phytosome is safe and all active components have been approved for pharmaceutical and cosmetics use.

- Due to high Bioavailability, Phytosome is being used to deliver liver protecting Flavonoids.

- This technology offers cost effective delivery of Phytoconstituents to various targeted site for pharmacological action. Phytosomes produce synergistic benefits when used as functional cosmetics, to protect the skin against exogenous or endogenous hazards in normal as well as stressful environment.

- They can be also used for enhancing permeation of drug, through skin in transdermal drug delivery system.

- They can be widely used in cosmetics due to their improved skin penetration and have a high lipid profile.

- Phosphatidylcholine, an essential part of the cell membrane and active components in phytome, act as a carrier and nourish the skin. There is no problem with drug entrapment during formulation development. The drug entrapment efficiency with phytsome is high and more over predetermined; because the drug itself forms vesicles after conjugation with lipid.

- They offer a better stability profile because chemical bonds are formed between the phosphatidylcholine molecules and phytoconstituents.

The phytosomal system is passive, non-invasive and can is suitable for immediate commercialization.

- The dose requirement is reduced due to improved absorption of the main constituent. They can also be given in smaller quantities to achieve the desired therapeutic values.

- Low risk profile: This technology has no risk since the toxicological profiles of the phytosomal components are well documented in the scientific literature. Highly attractive market profile for products with proprietary technology. It is easy to formulate because no complicated technical investment required for the production of phytosomes.

4. Pharmaceutical scope of phytosome

- It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, so it has wide therapeutic benefits [28, 30].

- Appreciable drug entrapment.

- Phytosomes help to improve the absorption of active constituents and reduces the dose requirements.

- Phosphatidylcholine used in preparation of Phytosomes, besides acting as a carrier also acts as a hepatoprotective agent. Hence produce the synergistic effect to the liver targeted drug.

- Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, this results better stability in Phytosome.

- Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as basic carrier for transdemal drug delivery.

5. Phospholipids: creating the structural framework for novel drug delivery systems

These are complex substance having chemical, biochemical and nutritional characteristics by which they can distinguish as placed in a unique nutritional category. They are complex lipid molecules important for life and are found in all human and the other known structure to make cell membranes. The biochemical importance of phospholipids is reflected in their extraordinary clinical benefits as dietary supplements. The phospholipids are readily compatible with the entire range of vitamins, minerals, metabolites and herbal preparations. The dietary phospholipids and omega-3 fatty acid works in functional synergy in cell membranes. Phosphatidylcholine is a bi-functional compound miscible both in water and in oil environments, and is well absorbed when taken by mouth. Phosphatidylcholine is not merely a passive "carrier" for the bioactive compounds, but is itself a bioactive nutrient with documented clinical efficacy for liver disease (including alcoholic hepatitis). Phosphatidylcholine is present in egg yolk, brain tissue and a wide

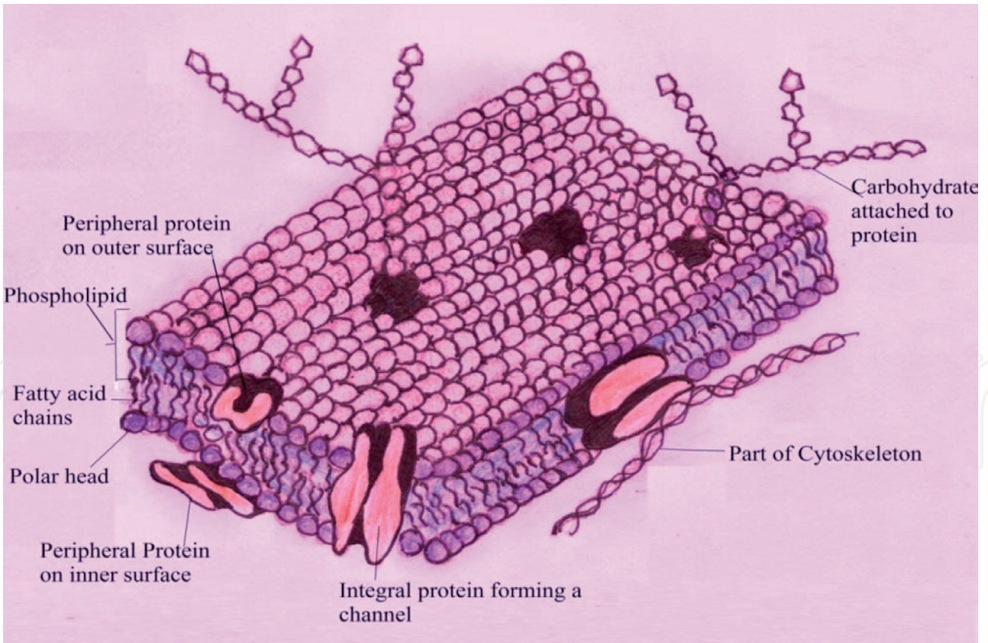

Figure 4.
Cell membranes are largely lipid phase. A double molecular layer consisting of PC and other phospholipids provides a continuous matrix into which the proteins insert [31].

variety of animal fat and plant oils. It is routinely present in the bile fluid, to help emulsify food ingredient for absorption [31] (**Figure 4**).

A number of drug delivery system is based entirely on Phosphatidylcholine such as liposomes, ethosomes, phytosomes, transferosomes, and nanocochhelates. The hydrophilic and hydrophobic domain/segment within the molecular geometry of amphiphilic lipids orient and self-organize in ordered supramolecular structure when confronted with solvents. Some commonly used synthetic phospholipids are dioleoyl-phosphatidyl-choline (DOPC), dioleoyl-phosphatidyl-ethanolamine (DOPE), distearoyl-phosphatidyl-choline (DSPC), and distearoyl-phosphatidyl-ethanolamine (DSPE) [31].

6. Conjugation of NDDS with transdermal route

Transdermal drug delivery systems (TDDS) are topically administered medications in the form of patches, which can deliver certain medication to systemic circulation in a more convenient and effective way than is possible with conventional dosage form. The potential of skin as a path of drug administration has been amply demonstrated by the acceptability of marketed therapeutic systems [32]. Administration of systemic drugs using a transdermal patch represents a noninvasive route, with improved patient compliance. This route of administration prevents passage through the gastrointestinal tract and maintains constant plasma levels for prolonged periods of time [33]. A transdermal patch is a medicated adhesive patch placed on the skin to deliver a time-released dose of medication through the skin for treating topical or systemic illness. Since early 1990, this dosage form of transdermal therapeutic system has been available in the pharmaceutical market. Such a system offers a variety of significant clinical benefits over others, such as tablet and injection [32, 33]. Transdermal route is a potential mode of delivery of lipophilic drugs in the systemic circulation. Some factors are responsible for transdermal drug delivery such as area of application, amount applied, release kinetics and prolongation of application time [34].

7. Feasibility of phytosome as novel vehicle for transdermal drug delivery

Lipophilic drugs could be easily transfused by transdemal route which enhance the bioavalibility of phytoconstitutent. Drug would be delivered into systemic circulation by transdermal route transdermal route. Drug has to pass three different skin layers before reaching to systemic circulation. The outermost layer, *Stratum corneum* provides hindrances to such type of drugs delivery due to its lipophilicity. The Phytosomal form of phytoconstituents can pass this barrier easily and helps to deliver the phytoconstituents in systemic circulation. The research studies from two decades show the phytosome technology has enough potency to be used as novel carrier of Phytoconstituents. Phytosomal carrier has enough potency to be used transdermally for increasing bioavailability of Phytoconstituents [34, 35].

8. Conclusion

Ever since the advent of human civilization, man is dependent on nature to fulfill all his need. Traditional system of healing human aliment was also derived from natural resources. In an era of development, devised various means of treatment primarily based on synthetic chemicals and popularly known as allopathic system of treatment. The inherent side effects of this system led to the shift in focus from contemporary to either conventional system of medication or to evolve the Novel drug delivery system. Novel drug delivery vehicles that can be used for the poorly soluble, pH sensitive and less potent drug to make them safe and target oriented. These novel drug delivery vehicles can also be utilized to deliver herbal formulations to its targeted site with lesser side effect. This phenomenon can be further augmented by conjugation of transdermal drug delivery system with novel drug delivery vehicle containing nanobiomedicine as herbal constituents. Phytosomes have shown the potential to be good carrier of herbal constituents for novel drug delivery systems. The combination of Transdermal route and Phytosomal drug delivery opens up an arena for better treatment for the patient suffering from skin diseases, Burn, allergies and bone fracture.

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Conflict of interest

There is no conflict of interest.

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