Review Article

Pharmacosomes: A Novel Vesicular Approach for Targeted Drug Delivery

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ABSTRACT

Novel drug delivery attempts to either sustain drug action at a predetermined rate, or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, when certain amphiphillic building blocks are confronted with water. The vesicular system such as liposome, niosomes, sphingosomes, ethosomes, transferosomes and pharmacosomes are used to improve the therapeutic index of both existing and new drug molecules by encapsulating an active medicament inside vesicular structure in one such system. It prolongs the existence of the drug in systemic circulation and finally reduces the toxicity. Such different systems are widely used in gene delivery, tumor targeting, oral formulations, in stability and permeability problems of drugs. Now a day's vesicle as a carrier system have become the vehicle of choice in drug delivery and lipid vesicles were found to be of value in immunology, membrane biology and diagnostic technique and most recently in genetic engineering.

Keywords: Vesicular drug delivery systems, drug targeting, bioavailability enhancement, controlled drug delivery, stability.

INTRODUCTION

In recent era researchers throughout the world engaged in the development of novel vesicular systems such as liposomes, niosomes, transfersomes etc. After development each has some of the advantages and disadvantages. Newer systems developed with an aim to overcome previous system disadvantage, so pharmacosome came in market with the new scientific approach. Oxidative degradation occurred in case of transfersome which can be overcome in case of pharmacosome[1-3].

Definition

Pharmacosomes are colloidal dispersion of drugs covalently bound to lipids and may exist as an ultrafine vesicular, micellar or aggregates depending on chemical structure of drug lipid complexes. Pharmacosomes are amphillic phospholipid complexes hexagonal of drug bearing active hydrogen that bind to complex phospholipid. Pharmacosomes impart better biopharmaceutical properties to the drugs, resulting in improved bioavailability. Pharmacosomes have been prepared for various NSAIDS, proteins, cardiovascular, anti neoplastic drugs. Developing the pharmacosomes drugs have been found to improve the absorption and minimize GI toxicity[1, 3, 4]. Example of hydrogen bearing compounds: Chloroform ($CHCl_3$), Ammonia (NH_3), Alcohol, etc.

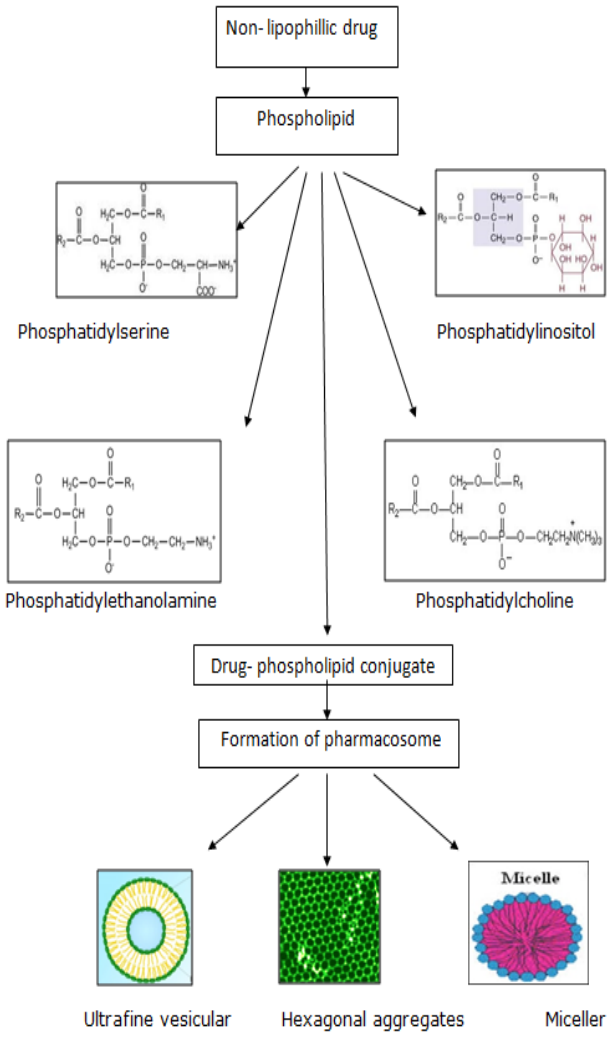

Figure 1: Targeting of drug and formation of pharmacosome

Advantages of Pharmacosomes[6]

1. Pharmacosomes provide an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects and also reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs.
2. Pharmacosomes are suitable for incorporating both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependent aggregation.
3. Entrapment efficiency is not only high but also predetermined, because drug itself in conjugation with lipids forms vesicles and covalently linked together.
4. Unlike liposome, there is no need of following the tedious, time-consuming step for removing the free, unentrapped drug from the formulation.
5. Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis.
6. No problem of drug incorporation.
7. Encaptured volume and drug-bilayer interactions do not influence entrapment efficiency, in case of pharmacosome. These factors on the other hand have great influence on entrapment efficiency in case of liposomes.
8. The lipid composition in liposome decides its membrane fluidity, which in turn influences the rate of drug release, and physical stability of the system. However, in pharmacosomes, membrane fluidity depends upon the phase transition temperature of the drug lipid complex, butit does not affect release rate since the drug is covalently bound. The drug is released from pharmacosome by hydrolysis (including enzymatic).

Limitations of Pharmacosome[7]

1. For the synthesis of compound the amphiphilic nature is required.
2. The basic principle for pharmacosomes are surface and bulk interaction of lipid with drug
3. The pharmacosomes undergo fusion, aggregation as well as hydrolysis when they set on storage.
4. Required covalent bonding to protect the leakage of drugs.

Rationale behind Selection of Pharmacosomes[8]

1. Since the drug is covalently linked, loss due to leakage of drug, does not take place.
2. Encaptured volume and drug bilayered interactions do not influence entrapment efficiency, in case of pharmacosomes.
3. The drug is release from pharmaosome by hydrolysis (including enzymatic).
4. The physicochemical stability of pharmacosome depends upon physicochemical properties of drug lipid complex.
5. They can be given orally, topically, extra or intra vascularly.

COMPONENTS OF PHARMACOSOMES[9]

For a delivery system three components are Drugs, solvent and carriers (lipid).

1. Drugs

Any drug processing an active hydrogen atom (-COOH, -OH,-NH_2 etc) can be esterifies to the lipid, with or without spacer chain resulting into amphiphilic complexes. These synthesized amphiphilic complexes (pharmacosome), facilitate membrane, tissue, or cell wall transfer, in the organism.

2. Solvent

An analytical grade organic solvent is required for the preparation of pharmacosome. It must be of high purity and volatile in nature. The Phospholipids and the drug must be dissolved in the selected solvent either simply by its addition or by refluxing. The selection of solvent depends on polarity of the drug and the lipid. A solvent with intermediate polarity is selected for pharmacosome preparation.

3. Lipids

Lipid or lecithin is the principal molecular building block of cell membranes. It is miscible both in water and in oil / lipid environment and well absorbed orally. Lecithin is a dietary supplement in two forms: as granular lecithin and a capsule, containing dispersion in oil. Comparison by weight of unrefined and refined soy lecithin is given in **Table 1**.

Table 1: Composition by weight of unrefined and refined soya lecithin

S. no.	Oil free compound	Un refined lecithin	Refined leithin
1	Phospatidyl choline	17.5	23
2	Phospatidylethanolamone	15	20
3	Phospatidyl inositol	10	14
4	Other phospholipids	14-18	-
5	Unrefined soya oil	31-34	0-3
6	Glycolipids	13-16	13-16
7	Neutral lipids (Mostly triglycerides)	2-4	-

Salient Features of Pharmacosomes[10-12]

1. Entrapment efficiency is not only high but predetermined, because drug itself in conjugation with lipids forms vesicles.

2. Unlike liposomes, there is no need of following the tedious, time-consuming step for removing the free, unentrapped drug from the formulation.
3. Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis.
4. No problem of drug incorporation into the lipids.
5. In pharmacosome, the encaptured volume and drug-bilayer interactions do not influence on entrapment efficiency. However, these factors have great influence on entrapment efficiency in case of liposomes.
6. The lipid composition in liposomes decides its membrane fluidity, which in turn influences the rate of drug release, and physical stability of the system. However, in pharmacosomes, membrane fluidity depends upon the phase transition temperature of the drug lipid complex, but it does not affect release rate since the drug is covalently bound to lipids.
7. Phospholipid transfer/exchange is reduced, and solubilization by HDL is low.
8. The physicochemical stability of the pharmacosomes depends upon the physicochemical properties of the drug-lipid complex.
9. Following absorption, their degradation velocity into active drug molecule depends to a great extent on the size and functional groups of drug molecule, the chain length of the lipids, and the spacer. These can be varied relatively precisely for optimized *in vivo* pharmacokinetics.
10. They can be given orally, topically, extra or intravascularly.

Method of Preparation

Ether injection method

This method was reported in 1976 by Deamer and Bangham. Take sufficient quantity of lipid and dissolve in di-ethyl ether to form lipid solution. This prepared solution is now slowly introduced into warm water by using syringe type infusion pump at 55-65^{0}C and under reduced pressure. Vaporization of ether leads to the formation of single layered vesicles (SLVs) depending upon the conditions used, the diameter of vesicles varies.

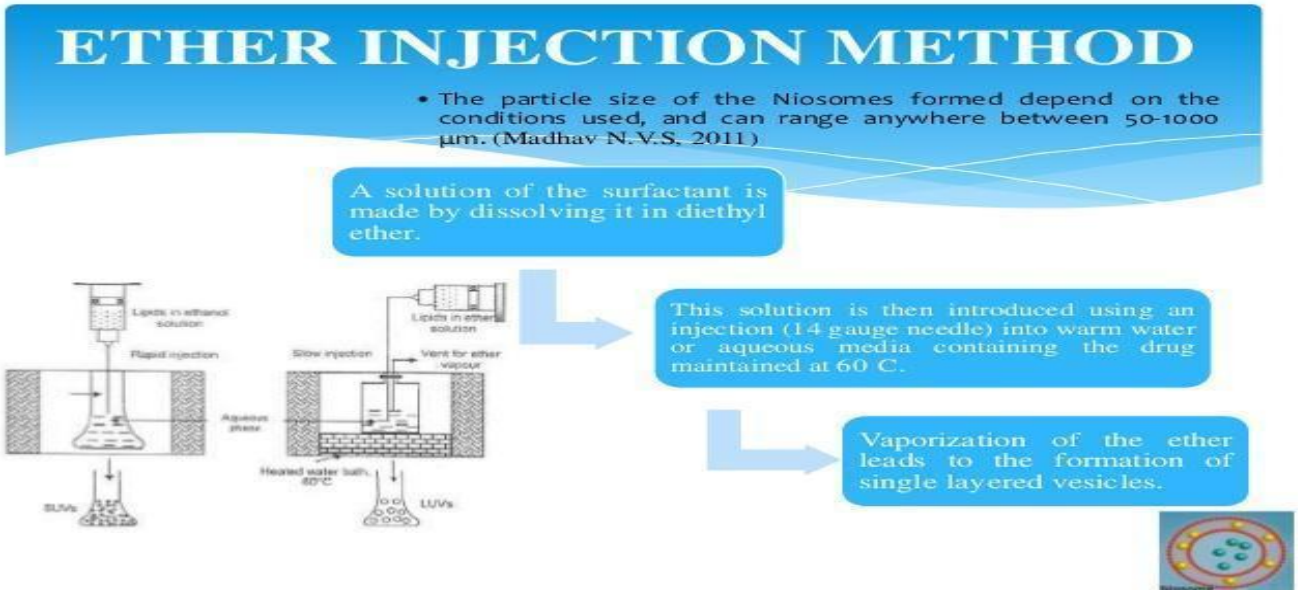

Figure 2: Ether Injection Method

Lipid film formation (Hand shaking method)

Lipid, drug and other excipients mixture is dissolve in organic solvent such as di-ethyl ether in a round bottom flask. Ether is removed at room temperature under reduced pressure by gentle shaking of round bottom flask or by using rotary evaporator. The dried film is hydrated with aqueous phase at 50-60°C with gentle agitation; this method produces multilamellar vesicles (MLVs) with large diameter.

Sonication method

Aqueous phase of drug is added into the lipid solution and mixture is kept for sonication by using probe sonicator or bath sonicator at 60°C for 3 minutes to produce pharmacosomes.

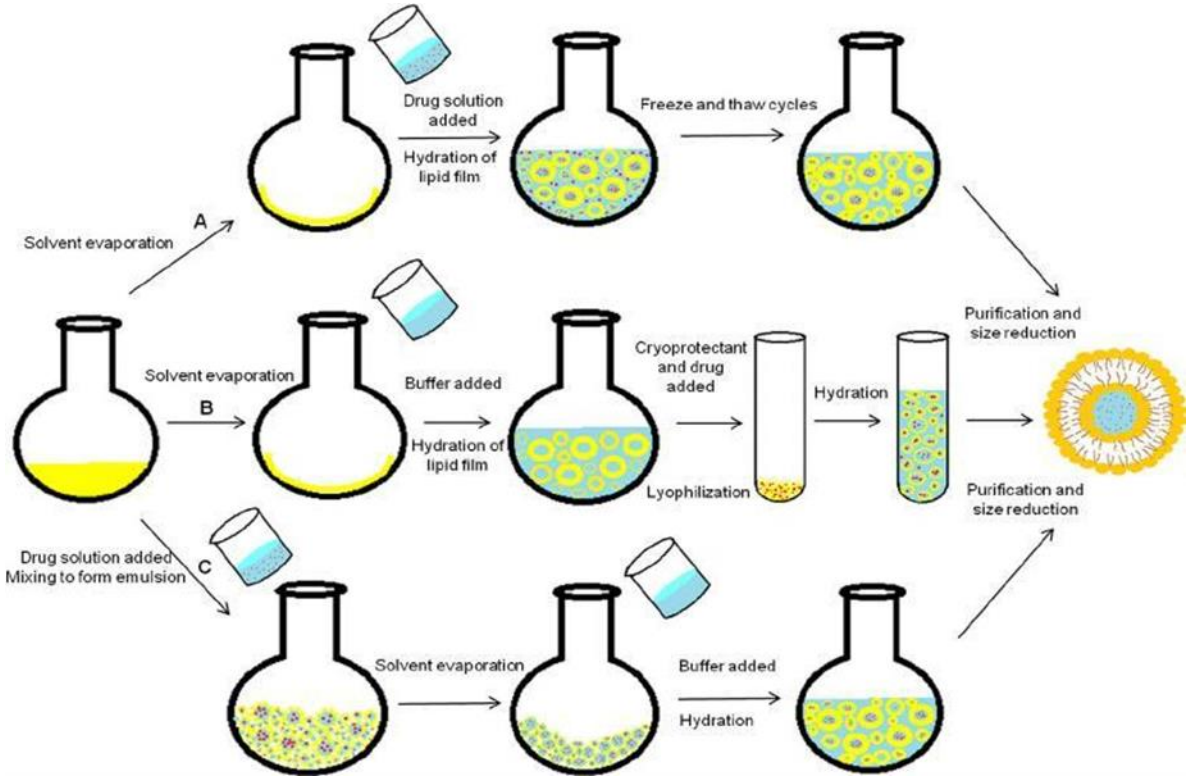

Figure 3: Hand Shaking Method

Micro fluidization

This is a recent technique to prepare small MLVS. A Micro fluidizer is used to pump the fluid at a very high pressure (10,000psi) through a screen. Thereafter; it is forced along defined micro channels, which direct two streams of fluid to collide together at right angles, thereby affecting a very efficient transfer of energy. The lipids can be introduced into the fluidizer. The fluid collected can be recycled through the pump until vesicles of spherical dimensions are obtained. This results in greater uniformity, small size and better reproducible pharmacosomes[1-3,10-15].

Reverse phase separation

The novel key in this method is the removal of solvent from an emulsion by evaporation. Water in oil emulsion is formed by bath sonication of a mixture of two phases, and then the emulsion is dried to a semi-solid gel in a rotary evaporator under reduced pressure. The next step is to bring about the collapse of certain portion of water droplets by vigorous mechanical shaking with a vortex mixture. In these circumstances, the lipid monolayer, which encloses the collapse vesicles, is contributed to adjacent intact vesicles to form the outer leaflet of the bilayer of large unilamellar pharmacosomes. The vesicles formed are unilamellar and have a diameter of 0.5 µm.

Anhydrous co solvent lyophilisation method

In this method drug powder and phospholipids dissolved with addition of 1 ml Dimethyl sulfoxide containing 5% of glacial acetic acid. Clear mixture is form by uniform gentle agitation. Next step involves freeze drying at overnight, resulting complex flushed with nitrogen and stored at 4^0C temperature.

Modified method

Amphiphillic drug and lipids are dissolved in organic solvent. Then organic solvent is evaporated leading to formation of thin solid film .film is hydrated to form vesicular suspension.

Supercritical fluid process

Method is explained in figure

Characterization of Pharmacosomes[7-9, 12]

Complex Determination

The formation of complex and conjugate can be determined by the correlation spectrum observed in complex sample with that of discrete constituents and also with their mixture will be determined in the help of FTIR spectrum.

Solubility

With the help of shake –flask Techniques the determination of change in solubility due to complexation can be evaluated. In this techniques solubility of drug acid and drug PC- complex was determined in phosphate buffer 6.8 and n-octanol was also determined. In this technique, the drug acid and n-octanol i.e. phosphate buffer at pH OF drug-phospholipids conjugated are mixed after constant shaking, equilibrium is maintained with the temperature of 37 °C for 24 hrs. The separation of

aqueous phase is occurring and concentration is determined using UV or HPLC techniques.

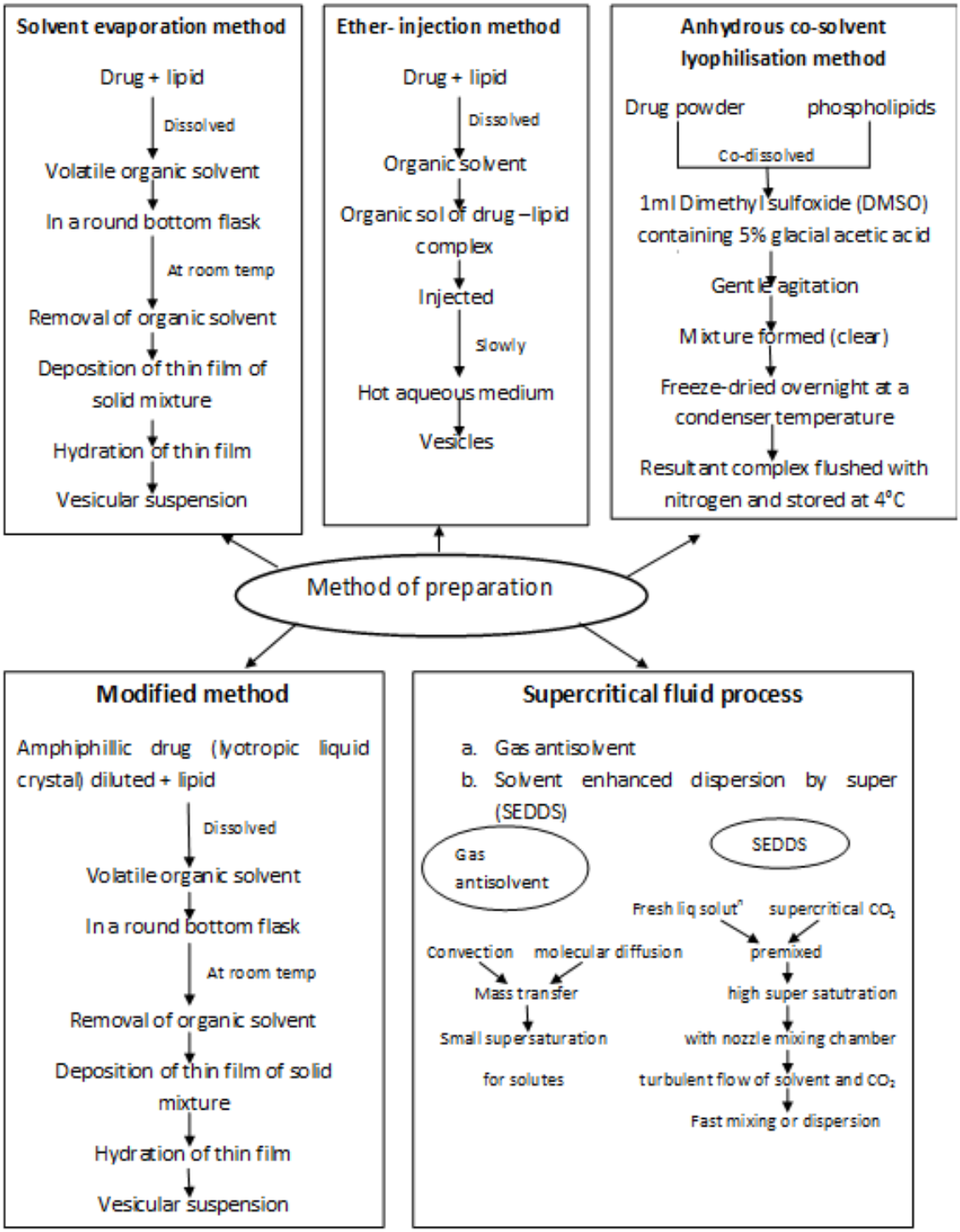

Figure 4: Various methods for preparation of pharmacosome

Scanning electron microscopy

Scanning electron microscopy detects the surface morphology of pharmacosome.

Drug content

To determine the drug content in drug – pc complex, complex is equivalent to drug was weighed and added into volumetric flask with Ph 6.8 Phosphate buffer. Then volumetric flask was stirred for 24 hrs on magnetic stirrer. After 24 hrs suitable dilution were made and measured for the drug content at 276nm UV spectrophotometrically.

Differential scanning calorimetry

This thermo analtyical techniqueis used to determine the drug–excipient compatibility interactions were recorded using a 2910 Modulated Differential Scanning Calorimeter V4.4E.The thermal behavior was studied by heating 2.0+ 0.2 mg of each individual sample in a covered sample pan under nitrogen gas flow. The investigations were carried out over the temperature range 25-250 °C at a heating

rate of 10°C min– 1. The interaction can be concludes by the elimination endothermic peaks, appearance of peaks and change in peak shape and its onset , peak temperature/melting point and relative peaks area or enthalpy.

X-ray power diffraction (XRPD)

It is performed to determine the degree of crystalline by using the relative integrated intensity of reflection peaks. The integrated intensity is given by the area under curves of the XRPD patterns and it represents the specimen characteristics.

Fourier transform infrared spectroscopy (FTIR)

With the help of IR spectroscopy the formation of complex can be confirmed by comparing the spectrum of complex with the spectrum of individual components and their mechanical mixture. In different time interval the stability can be determined by comparing the spectrum of complex in solid form with the spectrum of micro dispersion in water after lyophilization techniques.

***In –Vitro* Study**

Depending upon the expected therapeutic activity of biologically active constituents, model of in –vivo and in-vitro evaluation have been carried out.

Surface Morphology

With the help of scanning electron microscopy (SEM) or transmission electron microscopy (TEM), the surface morphology can be observed. Purity grades of Phospholipid affected to shape and size of pharmacosome and the process variables such as speed of rotation,vacuum applied or the method used.

Application of Pharmacosome[11-14,16]

1. Pharmacosomes demonstrate a wider stability profile and greater shelf-life.

2. Pharmacosomes have the capacity to augment drug absorption and its transport. Using response surface design, Yueand colleagues optimized the formulated geniposide pharmacosomes and examined their attributes. The ratio of phospholipid to drug, temperature of reaction mixture and concentration of drug were found to be 3, 50^{0}C and 5.5mg/mL, respectively.

3. Pharmacosomes can improve the rate of permeation by improving the membrane fluidity. The transition temperature of vesicles in the form of vesicles and micelles might pose an evident effect on vesicular interaction with biomembrane, hence improving the transfer of drug across membrane.

4. Khare demonstrated the prominent effect of cascade fusion system of pharmacosomes at appropriate temperature on drug targeting in an organism by applying heating and cooling phenomenon on tissues.

5. Pharmacosomes have achieved a new level by enhancing therapeutic effects of several drugs (Table No.2) like pindolol derivative, taxol, bupranolol acid derivative, cytarabin, amoxicillin, dermatansulphate, and so forth.

6. Pharmacosomes, the amphiphilic lipid vesicular system, can be used for the development of novel ophthalmic dosage forms. Amphiphilicpro drug forms pharmacosomes, when diluted with tear, and modify corneal drug transport and release profile.

7. Pharmacosomes have greater degree of selectivity for action on specific target cells. Raikhman described pharmacosomes as building particles capable in the transport of biologically active substances including nucleic acids and proteins.

Table 2: Therapeutic application of drugs after incorporation with pharmacosomes

Sr.No	Drugs	Effect after Incorporation in Pharmacosomes.
1.	Pindololdiglyceride	Three to five fold increase in plasma concentration Lower renal clearance.
2.	Amoxicillin	Improved cytoprotection and treatment of H.pylori infections in male rats.
3.	Taxol	Improved biological activity.
4.	Cytarabin	Improved biological activity.
5.	Dermatan sulfate	Improved biological activity.
6.	Bupranolol hydrochloride	Enhanced effect on intraocular pressure Enhance lymph transport.
7.	ketoprofen	Increase solubility enhancement Increase permeation of drug using dioeylphosphatidylcholine
8.	fenoprofen	Increase solubility
9.	Acyclovir	Stability from heat, absorbed by plasma protein in blood decrease hemolytic reaction
10.	Insulin phospholipids	Improve lipophillicity, improved oral absorption

Marketed Preparations

Human Iron Dextran is manufactured as low molecular weight Iron Dextran by Pharmacosmos. As the only injectable iron product, CosmoFer® offers the flexibility of iron repletion by total dose iron infusion, intravenous and intramuscular iron injection. Veterinary Iron Dextran is used as iron supplement for prevention of iron deficiency anemia in piglets. Uniferon® Iron Dextran drug products are marketed in several countries. Dextran polymers from Pharmacosmos are manufactured according to Good Manufacturing Practice (GMP). Our Dextran products include clinical and reagent grade Dextran and GPC Standards for GPC chromatography[15].

Future Prospective

The drugs are delivered in a suitable formulation keeping in view the safety, efficacy and acceptability among other factors, and the formulation is usually known as dosage form or drug delivery system. With the progress in all spheres of science and technology, the dosage forms have evolved from simple mixtures and pills to the highly sophisticated technology intensive drug delivery systems, which are known as Novel Drug Delivery Systems (NDDS)

New Drug Delivery System (NDDS) has got new inspiration since early eighties to have improved therapeutic outcome from the same drug, because the NDDS have several advantages over the conventional dosage form. Since then several NDDS have been developed and it constitute a sizable portion of the global market. Indian researchers have shifted their interest towards NDDS since early eighties.

The driving force behind the development of NDDS has been two-fold, first, the obvious clinical advantages of these systems and second, their economic aspects. The NDDS are being developed in order to attain greater control over a drug's pharmacokinetics and pharmacodynamics after administration so that the dosage forms thus produced would be highly effective, safe and better than the conventional products. Often, reformulation of an old drug in a NDDS rejuvenates clinical interest in the drug, thus adding to its effective market life. This brings us to the economic aspects of NDDS.

With NDDS, relatively lesser investment of time and money could lead to higher margins of profit taking the advantages of patent cover. It is easier to develop a NDDS rather than a new molecule and a company can file an Abbreviated New Drug Application (ANDA) to USFDA more easily. Some of the Indian companies have already been succeeded in this arena.

CONCLUSION

The limitations of liposomes, niosomes, transferosomes like oxidation, instability, lack of purity respectively can be minimize by Pharmacosome. Pharmacosomes could be used to improve aqueous solubility and permeability of liphophilic and hydrophilic drug respectively by forming a Drug-Lipid complex. Pharmacosomes is not only having high entrapment efficiency but it can be predetermined, because drug itself in conjugation with lipids forms vesicles. The approach of pharmacosomal drug delivery possesses many advantages over conventional vesicular systems. In case of Pharmacosomes the encaptured volume of drug-bilayer interactions do not influence entrapment efficiency.

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