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A REVIEW ON PHARMACOSOMES: A NOVEL VESICULAR APPROACH FOR ENHANCEMENT OF SOLUBILITY AND PERMEABILITY OF DRUGS.

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ABSTRACT
Novel drug delivery system mainly consents about achieving the targeted concentration to release the drug at targeted site by using carrier system, altering the structure and microenvironment around the drug. Especially drugs which are having narrow therapeutic window are difficult to formulate, with the advantage of novel drug delivery systems like particulate, polymeric carrier, macromolecular and cellular carriers. In vesicular drug delivery system drug binds covalently to the lipid molecule by which the drug release is in a controlled manner and also drugs which are of hydrophilic or lipophilic nature can be delivered by using vesicular drug delivery systems. Both synthetic and natural drugs which are facing difficulties like low solubility and low permeability can be effectively formulated and can achieve required pharmacokinetic and pharmacodynamic parameters. In the arena of solubility enhancement, several problems are encountered. A novel approach based on lipid drug delivery system has evolved, pharmacosomes. Pharmacosomes are colloidal, nanometric size micelles, vesicles or may be in the form of hexagonal assembly of colloidal drug dispersions attached covalently to the phospholipid. Pharmacosomes are prepared by hand shaking method, ether injection, solvent evaporation method, anhydrous co-solvent lyophilyzation, supercritical fluid approach and other alternative methods they are characterized by complex determination, surface morphology, drug entrapment, solubility, drug lipid compatibility, crystal state measurement, dissolution studies and *in vitro* drug release rate.

KEYWORDS: phospholipid, permeability, drug phospholipid complex, covalent bond, pharmacosomes, preparation, characterization.

1. INTRODUCTION

Novel drug delivery system (NDDS) primarily focuses on formulation, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects.

There are number of novel carriers which have been established and known to be useful for controlled and targeted drug delivery. Some of the types of novel drug delivery systems are, Sustained- or controlled- drug delivery systems provide drug action at a pre determined

- Sustained- or controlled- drug delivery systems provide drug action at a pre- determined rate by providing a prolonged drug (Zero-order) release respectively, at the therapeutically effective levels in the blood stream.
- Localized drug delivery systems provide drug action through temporal control of drug molecules release (usually rate- limiting) within the vicinity of the target site.
- Rate- pre-programmed drug delivery systems achieves therapeutic action by manipulating the drug release which control diffusion of drug molecules into blood stream.
- Targeted drug delivery provides drug action by using carries either for passive or active targeting, it is usually favored by suitable sensory devices, which recognize the receptors at the target site2,3,4.The two ideal requirements for a system to be novel are,

1. drug delivery at a predetermined rate and for predetermined period of time;
2. Carrying the active moiety to the target site.[5]

Novel drug delivery attempts to minimize the side effects and maintain potent levels of drug molecules in the body. The nanocarriers may help to localize the drug action spatially in diseased tissue or organ or any other site where it is required. Among the different pharmaceutical carriers, the vesicular carriers are extremely organized assemblies of lipid bilayers that may be single or concentric in nature formed when the building blocks (amphipathic) of these bilayers encounter water.

Safely novel drug delivery is far better than the conventional dosage form. Novel drug delivery system should full fill the following requirements. Firstly, it delivers specific amount of drug at a rate directed by the needs of the body, over the period of treatment.[1,2,3]

Advantages of novel drug delivery system

- Incorporation of therapeutic dose at controlled rate,
- Sustaining drug concentration within an optimal range,
- Optimum dose at right time and at right location,
- Efficient use of expensive drugs and excipients,
- Minimizes adverse or toxic effects,
- Freedom from frequent dose intake,
- Improved patient compliance.[4,5]

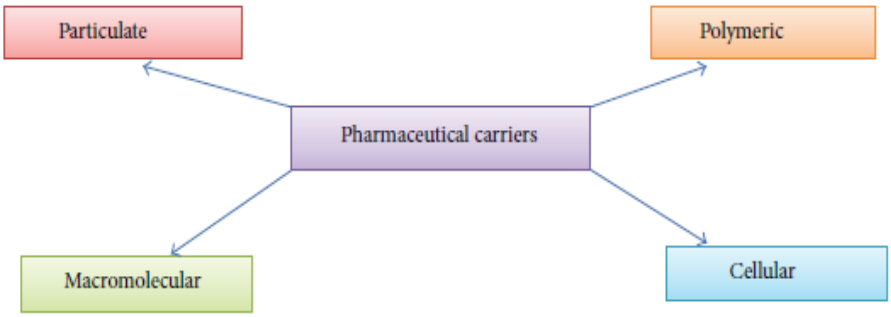

Figure 1: Different types of Pharmaceutical Carriers.

2. VESICULAR DRUG DELIVERY SYSTEM

Vesicular drug delivery systems are the systems that can improve the bioavailability of the drug and the reduction in toxicity by drug targeting to the specific site. Bingham pioneered the biologic origin of vesicular systems in 1965, and hence named them Bingham bodies. As a consequence, a large account of vesicular systems like liposome, noisome, and pharmacosome came into existence Drug carriers release the drug in systemic circulation in a controlled manner. This can be attained either by slow release of drug over a long period of time or by actuated release at the drug target by some stimulants such as changes in pH, application of heat, and activation by light.

Especially, in the case of drugs with poor water solubility and/or membrane permeability, drug carriers are used to improve their pharmacokinetic and the bioavailability. The pharmaceutical carriers are classified as particulate type, polymeric, macromolecular and cellular carriers. The different methods present in binding the drug with carrier include adsorption, encapsulation and covalent bonding. Different type drug carriers utilize different type of attachment methods.[6,7,8]

3. ADVANTAGES OF VESICULAR DRUG DELIVERY SYSTEM

- They extend the presence of the drug in systemic circulation.
- Vesicular drug delivery is an efficacious method for reducing the drug toxicity and targeting to the site of action.
- This system improves the bioavailability principally in case of the poorly aqueous soluble drugs.
- In this systems both the hydrophilic and lipophilic drugs are embodied.
- It sustains the release of drugs by delaying the time of elimination through they are rapidly metabolizable.
- They overcoming the problems regarding stability, solubility and degradation of the drug.
- It acts as drug reservoir by encapsulating the drug and overcoming the problems of conventional dosage forms.
- These carriers correspond to the structure and function of biomolecules and hence are biocompatible and biodegradable.
- The vesicular carrier systems have observed a number of applications in various fields.[9]

4. PHARMACOSOMES

Pharmacosomes are part of the novel drug delivery system. They were first introduced by vaizoglu and Speriser in 1968. 10 Pharmacosomes are determined as the colloidal dispersions, drugs covalently bound to the lipids, and may exists as ultra fine vesicular, micellar, or hexagonal aggregates, on the basis of the chemical structure of the drug-lipid complex. The system is composed by linking a drug (pharmakon) to a carrier (soma), so they termed as “Pharmacosomes”. The drugs are present in a dispersion form in these lipoidal drug delivery system conjugated by electron pair sharings and electrostatic hydroxyl groups, is converted to an ester with the help ofthe hydroxyl moiety of the lipid, resulting in the formation of a prodrug. A spacer chain may or may not be used for this purpose. The prodrug possesses both hydrophilic and lipophilic properties. Despite these properties, prodrugs have the capability to reduce interfacial tension, increase the area of contact, and hence improve bioavailability. They aid the deportation through the cell membrane, cell wall, and tissues. If the concentration is increased beyond a level, it may exist in an intermediate state between liquid and crystal. On contact with water, these prodrugs assemble into a single or multiple layers resulting in the formation of pharmacosomes.[10,11,12,13]

5. SALIENT FEATURES OF PHARMACOSOMES

- The physical and chemical traits of the conjugate control the stability of the whole system.
- As they consist of both water-loving and fat-loving properties, they have an ease of passing through the cell membrane, walls, or tissues either by the action of endocytosis or exocytosis.
- The rate of degradation relies on size, nature of functional group present in the drug molecule, fatty acid chain length in lipids, presence, or absence of spacer. All these factors can be varied to optimize *invivo* pharmacokinetic behaviour.
- They can be administered via topical, oral, extra- or intravascular route.[14,15,16,17]

6. ADVANTAGES OF PHARMACOSOMES OVER CONVENTIONAL VESICULAR SYSTEMS

- When compared with other categories of lipid based delivery systems, pharmacosomes exhibit better results in many ways.
- The drug-lipid complex depends upon the phase transition temperature but independent on rate of release as it is covalently bounded to the lipid.
- No leaching will occur as drug is bounded to the lipid by covalent bonding.
- Delivers drug at the specific site and site targeted.
- By enzymatic methods like hydrolysis drug is released from the lipid polymer.
- The metabolism of the drug depends on the spacer, length of chain in lipid, functional groups and size of the drug during its absorption.
- They reduce the cost of therapy.
- They are suitable for the both lipophilic and hydrophilic drugs.
- The aqueous solution of the amphiphiles exhibits concentration dependant aggregation.
- The drug and carrier are covalently linked together so, entrapment efficiency is high and predetermined.
- Drug release of pharmacosomes is by hydrolysis.
- They improves the bioavailability majorly incase of poorly soluble drugs.
- They reduce the adverse effects and toxicity.
- In pharmacosomes, there is no need to remove the unentrapped drug when compared to liposomes where the free drug should be removed.
- Drugs like bupranolol hydrochloride, pindolol maleate, acyclovir, taxol, etc by using of pharmacosomes drug delivery has therapeutic performance has been improved.[18,19,20]
- Entrapment efficiency of these complexes is independent of inclusion volume and drug bilayer interactions, covalent type of bonding prevents drug leakage from the complexes, oxidation resistance. Whereas in liposomes the drug is degraded by oxidation, sedimentation, and leaching.
- Phospholipids that are less expensive, more resistant to oxidation can be used and use of pure and natural phospholipids is not required.
- More robust and efficient

7. DISADVANTAGES OF PHARMACOSOMES

- Water insoluble drugs are encapsulated relatively in a less hydrophobic region within membrane bilayer rather than relatively large surface area.
- The storage of pharmacosomes undergoes fusion and aggregation as well as chemical hydrolysis.[21,22,23,24]

8. COMPONENTS OF PHARMACOSOMES

Drugs

Any drug containing active hydrogen atom (-COOH, -OH, -NH2, etc) can be esterified with the lipid, with or without spacer chain. Facilitates membrane, tissue, cell wall transfer in the organisms is due to its amphiphilic nature.

Solvents

They should be high pure and volatile in nature, and should be selected based on the intermediate polarity for their preparations.

Lipids

Phospholipids are the major components of biological membrane; majorly two types of phospholipids are used namely phosphoglycerides and sphingolipids.

The most common type of phospholipids is Phosphotidylecholine moiety.

Phosphotidylecholine is an amphiphilic molecule in which a glycerol bridges links a pair of hydrophobic acylhydrocarbon chains with hydrophilic polar head group phosphocholine.[25,26]

9. IDEAL DRUG CANDIDATES FOR PREPARATION OF PHARMACOSOMES

BCS class II and IV drugs can be successfully loaded into pharmacosomes so as to increase their solubility and permeability.

10. APPLICATIONS OF PHARMACOSOMES

1. Pharmacosomes provides a wider stability profile and greater shelf life.

2. Pharmacosomes have the capacity to augment drug absorption and its transport. Using response surface design, Yue et al. and 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 0C and 5.5mg/mL, respectively.

3. Pharmacosomes can enhances 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 like pindolol derivative, taxol, bupranolol acid derivative, cytarabin, amoxicillin, dermatan sulphate.
6. Pharmacosomes are the amphiphilic lipid vesicular system, can be used for the development of novel ophthalmic dosage forms. Amphiphilic prodrug 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 et al. described pharmacosomes as building particles capable in the transport of biologically active substances including nucleic acids and proteins.[27]

11. PERMEABILITY ENHANCEMENT USING VESICULAR DRUG DELIVERY SYSTEMS PHARMACOSOMES

Poor aqueous solubility (dissolution) or permeability (across the biomembranes) of drugs are the major factors which govern bioavailability of drugs. During the course of drug discovery and development of dosage form the solubility and permeability are the key issue and for the same the drugs are classified in different classes on the same basis in Biopharmaceutical Classification System (BCS). The phytoconstituents may have the solubility (dissolution in aqueous media/gastro intestinal fluid)) rate limited or the permeation rate limited absorption from the oral route and topical route. For improving solubility various techniques like solvent deposition, micronization, solid dispersion, supercritical fluid process, use of surfactants, use of salt forms, complexation etc. have been investigated. Out of these, the complexation technique has been studied exhaustively to improve the solubility and the dissolution of poor water soluble drugs. In particular the lipid complexation improves the solubility as well as the permeability, due to the formation of an amphiphilic drug-lipid complex. Moreover, by virtue of their ability to form a protective coat over the mucosa, the lipid complexes have also been reported to reduce the gastric and hepatic toxicities of drug molecule 6- 8. The lipid complexes are prepared with phosphatidylcholine. PC is an integral part of the cell membrane and exists in zwitterionic form. PC is not only a passive carrier for drug delivery but is itself a natural component with well investigated and reported clinical efficacy for various liver diseases. These amphiphilic drug-lipid complexes are stable and more bioavailable drug delivery systems with low interfacial tension between the system and the GI fluid thereby improving the permeation of drugs across the biomembranes.[28,29]

12. PREPARATION OF PHARMACOSOMES

Initially for the formation of pharmacosomes, there is a need of drug-lipid conjugate. For this purpose, the salt form of the drug is converted into the acidic form to expose the functional hydrogen atom to form a complex. The aqueous solution of the drug is acidified, extracted using chloroform, and subsequently recrystallised. Then equimolar phospholipid concentration is taken and dissolved in an organic solvent, which is then evaporated under vacuum at a definite temperature. The complex is then collected as a dry residue after placing it in a dessicator overnight.

1. Solvent Evaporation Technique

a. Hand-shaking method

→ In the hand-shaking method, both the drug and lipid shell be mixed in the round bottomed flask.
→ The organic solvent is evaporated by using rotary vaccum evaporator at room temperature, results in formation of a thin film of deposition on the walls.
→ The dried film is then hydrated with buffer and rotated in one direction with hand which results in the formation of vesicular suspension.

b. Rotary evaporator (Figure 5)

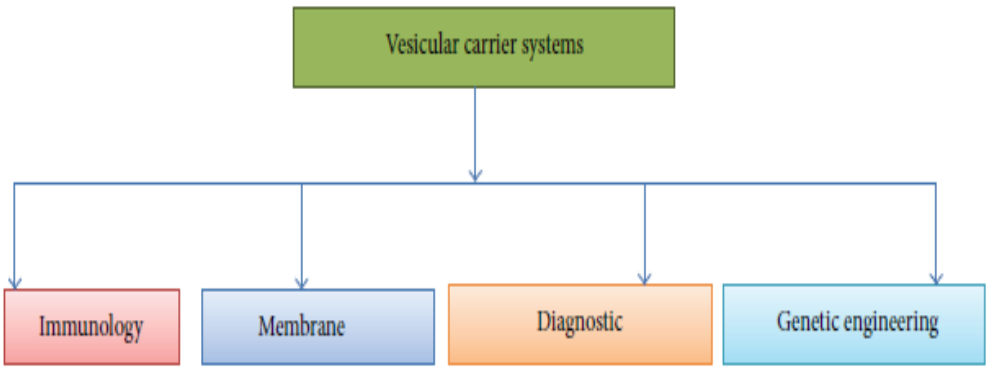

Figure 2: Applications of vesicular carrier systems..

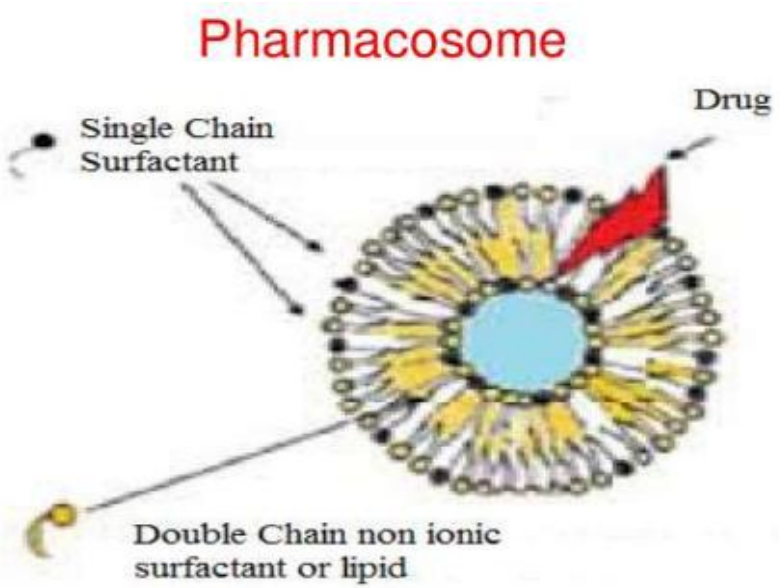

Figure 3: Structure of Pharmacosome.

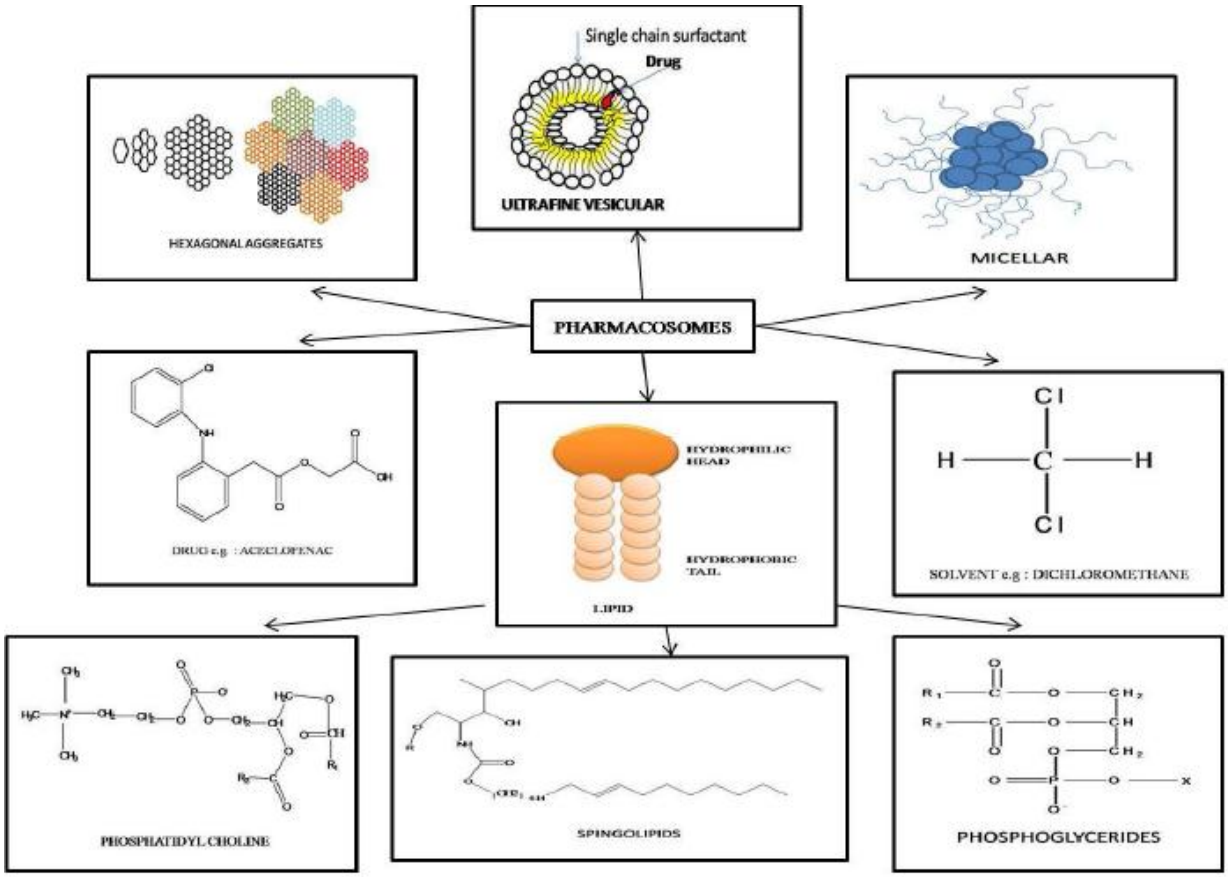

Figure 4: Forms and Components of Pharmacosomes.

2. Ether Injection Method

→ The drug-lipid complex is dissolved in specified volume of ether.

→ Then the above mixture is slowly injected into a heated buffer solution, resulting in the formation of the vesicles.

→ The nature of vesicle especially the shape depends on the concentration.

→ The variety of structures may be formed that are, round, cylindrical, disc, cubic, or hexagonal type depending on the amphiphilic state.

3. Anhydrous Co-Solvent Lyophilyzation Method

→ Drug and phospholipids are dissolved in solution of dimethyle sulfoxide containing glacial acetic acid.

→ Then the above mixture is agitated to get clear liquid and then freeze-dried overnight at condenser temperature.
→ The complex obtained is flushed with nitrogen and stored at 4˚c.

4. Supercritical Fluid Process

→ This method is known as solution enhanced dispersion by complex supercritical fluid.
→ Drug and lipid complex are premixed in a supercritical fluid of carbon dioxide, then high super saturation is obtained by passing through the nozzle mixture chamber.
→ The turbulent flow of solvent and carbon dioxide results in fast mixing of dispersion leading to the formation of pharmacosome.

5. Solvent Evaporation Method

→ In the solvent evaporation method of preparing the pharmacosomes, the drug is first acidified so that the active hydrogen might be available for complexation.
→ The drug acid is then extracted into chloroform and subsequently recrystallized. The drug-PC complex is prepared by associating drug acid with PC in various molar ratios.
→ The accurately weighed PC and drug acid are placed in a 100 ml round bottom flask and dissolved in sufficient amount of dichloromethane.
→ The mixture is refluxed for one hour. Then the solvent is evaporated off under vacuum at 40 ° C in a rotary vacuum evaporator.
→ The dried residues are then collected and placed in vacuum desiccator for complete drying.

6. Recent Approaches

→ A biodegradable micelle forming drug conjugate was synthesized from the polymer consisting of polyxyethylene glycol and polyaspartic acid with a Adriamycin which is hydrophobic in nature.
→ Diluting the micelle without the active constituent getting precipitated in the monomeric drug conjugate.
→ Diluting lyotropic liquid crystals of amphiphilic drug by Muller-Goymann and Hamann.17
→ Phosphotidylethanolamine with various molar ratios of Phosphotidylecholine and cholesterol which significantly enhanced cytoprotection by encapsulating amoxicilin Singh et al. formulated "vesicular constructs" using aqueous domain.[30,31,32,33]

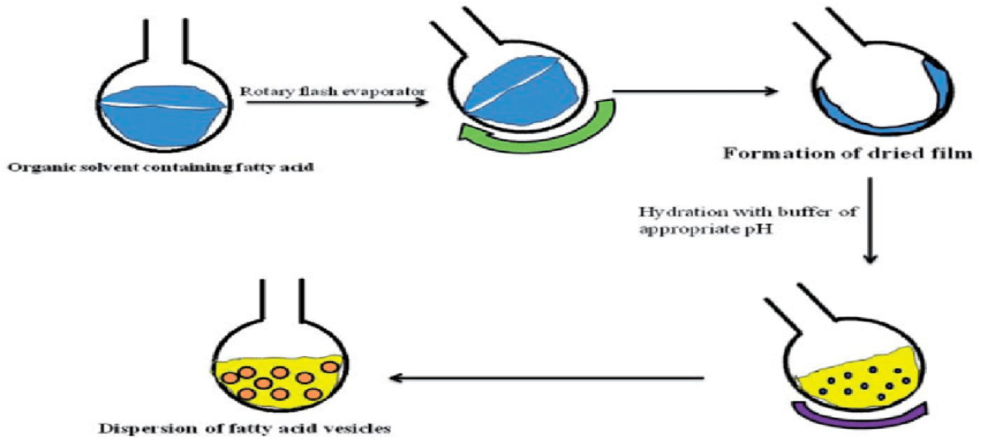

Figure 5: Rotary Evaporator Method.

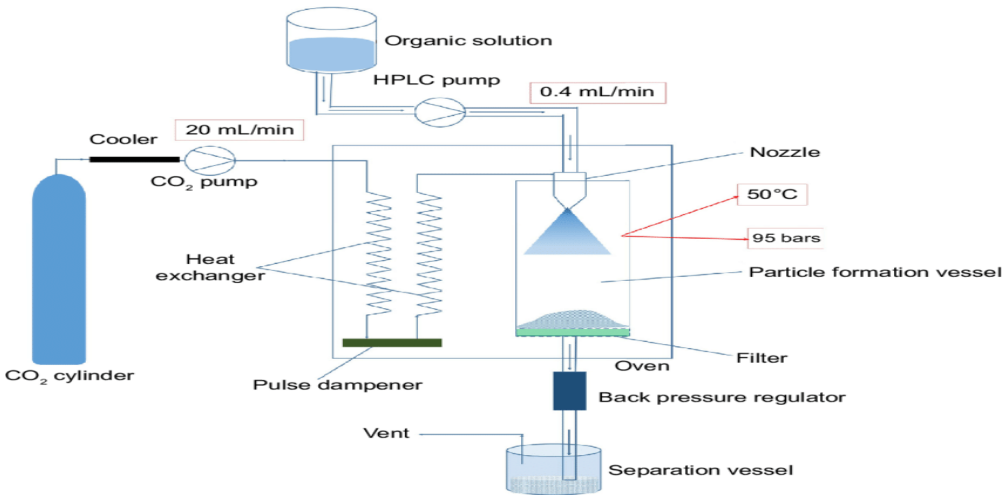

Figure 6: Supercritical Fluid Process.

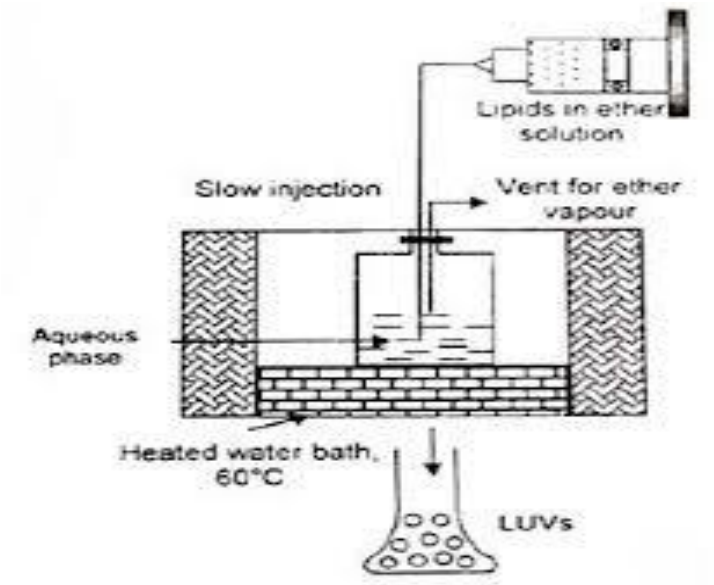

Figure 7: Ether Injection Method.

12. Characterization of pharmacosomes

1) Complex determination

Using correlation spectrum the formation of both conjugate and complex can be contingent upon inspecting with that of discrete constituents and also with their mixture using FTIR spectrum.

2) Surface morphology

The surface morphology can be predicted using Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM). The shape and size of pharmacosomes are prone to variations by some variables such as rotation speed, vaccum applied, Purity grade of phospholipids or the method used.

3) Entrapment Efficiency

The entrapment efficiency of Pharmacosomes are measured using the centrifugation method. In a laboratory centrifuge, an aliquot of Pharmacosomal suspension is centrifuged at 5000 rpm for 35 minutes at 4°C. The unentrapped drug is carefully separated from the clear supernatant, and the absorbance is measured. The sediment in the centrifuge tube is washed three times with a suitable solvent and then diluted to 5 mL with the same solvent before being tested for absorbance. To generate a calibration curve, different concentrations of appropriate solvents (1 g/mL-10 /10 mL) are used. The supernatant and sediment are used to calculate the total quantity of drug in a 1 mL suspension60.

Entrapment efficiency **%** Total drug ˍ free drug/ Total Drug (100)

4) The Yield of drug "Present as a Complex" (%)

The prepared pharmacosomes are dispersed insufficient dichloromethane (5 ml/mg furosemide–SPC). The complex and phospholipids both were easily checked up in the dichloromethane or any other solvent in which drug is insoluble. The drug non-complexes is sedimented and separated to assay. The yield of drug "present as a complex (%) is defined using following formula equation,

$$The\ yield = \frac{a-b}{a} \times 100\%$$

Where a is the content of drug "present as a complex", b is the content of drug "no-present as a complex" in the complex.

5) Determination of the Content of drug in Phospholipids Complex

The contents of drug in the complex are determined spectrophotometrically. A powder of 10 mg of the complex equivalent to the drug is dissolved in 10 ml of acetone and stirred for 2 h on a magnetic stirrer. The absorption of drug in the complex is determined by making suitable dilution and, measuring the absorbance at specified wavelength.

6) Solubility

Solubility is determined by placing the known amount of phospholipid complex in a screw caped penicillin bottle containing aqueous phase buffer solution of varying pH (2-7.4) and organic phase like 1- Octonol with continuous shaking at a temperature of 37oc for 24hrs. Then both the layers will be separated and samples were analyzed using HPLC or UV spectrophotometer.

7) Solubility of Pharmacosomes Complexes

Pharmacosomes complexes solubility was found out by preparing saturated solutions in various buffers at 37°C ± 0.5°C and continually shaken into mechanical orbital shaker (Remi mechanical shaking incubator, Bombay) up to 24 hrs.

Samples are to be withdrawn and filtered through a 0.45 µm membrane filter (Millipore, India) followed by dilution and analyzed spectrophotometrically.

8) Partition Coefficient

Partition Coefficient determination of pharmacosomes was carried out by adding required quantity of pharmacosomes equivalent to dug, to a series of 10mL water solutions in sealed glass containers at 25°C, respectively. Each experiment is then executed in triplicate for each term. All the liquids are agitated for 24 h and centrifuged to remove excessive residues (15 min, 8000 rpm), respectively. Each liquid is added 10mL n-octanol and agitated for 24 h. And so they are centrifuged at 8000 RPM for 15 min, respectively. The water phase and n-octanol phase are separated. The water phase and n-octanol phase are filtrated through a 0.45µm membrane, respectively. Suitable dilution are made, the concentrations of drug is measured.

8) Drug lipid compatibility

Differential scanning electron microscopy is a thermo analytical technique used to determine drug-lipid compatibility and their interactions. Thermal response is studied by using separate sample and heating them in a sample pan, which is closed. The nitrogen gas is plugged, and the temperature is maintained in a definite range with a specific heating rate.

9) Crystal state measurement

The crystal nature of the drug can be determined by using X-ray diffraction technique. The tube voltage and tube current can be regulated in the X-ray generator. Copper lines may be used as the source of radiations. The overall integrated intensity of all reflection peaks are projected by area under curve of X-ray diffraction pattern that specifies the specimen characteristics.

10) Dissolution studies

Dissolution studies *in vitro* are done by using various models available using different buffers, then the results obtained are estimated on the basis of activity of the drug.

11) *In vitro* drug release rate

The *in vitro* drug release rate is estimated by reverse dialysis bag technique. In this method pharmacosomes are introduced inside the dialysis bag and the receiver phase is placed outside. Dialysis bag containing the continuous phase and they are suspended in a vessel containing the donor phase and stirred at predetermined time intervals, each dialysis bag is removed and the contents are analyzed for drug release. An advantage of this technique is increase in the membrane surface area available for transport from the donor to receptor compartment. Another advantage of this technique is the increased efficiency in terms of staffing as a consequence of reduction in number of step.

12) Stability of pharmacosomes

Although pharmacosomes do not undergo destabilisation of lipid bilayer membrane as that of liposomes beause the drug is covalently bound to the phospholipid but the two major degradation pathway i.e. oxidation and hydrolysis results in reduction of shelf life of phospholipid based vesicles. In comparison to saturated fatty acids, unsaturated fatty acyl chains are more susceptible to oxidation. Phospholipid peroxidation can be reduced by utilizing pure form of phospholipids, storing them at a lesser temperature, protecting them from exposure to light and oxygen, and adding antioxidants. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), liquid chromatography mass spectrometry (LCMS), and HPLC were used to study the degradation of the drug-phospholipid combination. The appearance phospholipid due to hydrolysis of prodrug indicates that the prodrug has been subjected to enzymatic degradation.[34,35,36,37,38]

Table 1: Comparision of various methods of pharmacosomes preparation of various drugs and their outcomes.

S. no	Drug	Polymer	Solvent	Bonding	Technique used	Results	Final Product
1	Geniposide	Phospholipids	Tetrahydrofuran	Hydrog, van der waal forces	Vaccum evaporation method	Lipid solubility character of Geniposide was increased	Dry powdered pharmacosomes
2	Naproxen	Soya lecithin	Diethyl ether, ethanol, acetone	Covalent bond	Ether injection method	Solubility enhanced and achieved controlled drug release	Pharmacosomes gel
3	Aspirin	Soya phosphotidylcholine	Dichloromethane	Covalent bond	Solvent evaporation	Improved drug delivery controlled drug delivery	Pharmacosomes
4	Furosemide	Soya phosphotidylcholine	Methyl alcohol	Hydrogen bond	Vaccum evaporation	Release and permeation increased	Pharmacosomes
5	Ketoprofen	Soya phosphotidylcholine	Dichloromethane	-	Solvent evaporation	Improved solubility, dissolution profile	Pharmacosomes
6	Etodolac	Soya lecithin	Acetone,	-	Thin film	Increased solubility,	Pharmacosomes gel

			dichloromethane, methanol		hydration	entrapment efficiency and sustained relaese	
7	Rosuvastatin	Soya lecithin	Chloroform, dichloromethane	-	Solvent evaporation	Sustained drug release and improved bioavailability	Pharmacosomes
8	Ibuprofen	Phosphotidylec holine	Dichloromethane, chloroform	-	-	Increased bioavailability	Pharmacosomes
9	Bupranolol	Soya lecithin		Covalent bond		Enhanced effect on intraocular pressure and enhance lymph transport.	Pharmacosomes
10	Levodopa	Soya lecithin	Tetrahydrofuran	Covalent bond	Solvent evaporation	Enhanced brain uptake	Pharmacosomes
11	Diclofenac	Phosphotidylec holine	Dichloromethane	Covalent bond	Solvent evaporation	Improved solubility and drug loading	Pharmacosomes
12	Didanosine	Soya lecithin	Chloroform, acetone, methanol		Tetrahydrofur an injection method	Increased solubility, dissolution profile and bioavailability	Pharmacosomes

Table 2: Comparison of various vesicular drug delivery systems.

S.no	Type	Ingredients	Method	Advantages	Disadvantages
1	Pharmacosomes	Solvents, phospholipids	Sonication, Hand shaking method, Ether injection, Anhydrous co-solvent lyophilyzation.	No leaching will occur as drug bounded to the lipid by covalent bonding, Delivers the drug at the site specific and site targeted, They reduces the cost therapy, Reduces the adverse effects and toxicity	The storage of pharmacosomes undergoes fusion, aggregation and hydrolysis, Water insoluble drugs are encapsulated relatively in a less hydrophobic region within membrane bilayer or relatively large surface area
2	Liposomes	Phosphotidylech oline, cholesterol, sphingolipids, steroids, polymeric materials.	Sonication method, French pressure cell, Freeze-thawed liposomes, Lipid film hydration by hand shaking or freeze drying.	Suitable for delivery of hydrophilic, hydrophobic drugs. Biocompatible, suitable for controlled drug delivery, localized action in particular tissue.	High production cost, leakage (or) fusion of encapsulated drug phospholipid undergo hydrolysis (or) oxidation reaction, short half life and low solubility
3	Niosomes	Solvents, phospholipids	Sonication, Microfluididation, Hand shaking, Ether injection , Reverse phase evaporation, Bubble method, Active transport.	Stable, increase the stability of entrapment drug , Improved oral bioavailability of poorly absorbed drugs, PEG-glucose conjugates on the surface of niosomes significantly improved tumor targeting of an encapsulated paramagnetic agent	Time consuming, In efficient drug loading, Requires specialized equipments.
4	Transferosomes	Phospholipids, surfactants, alcohols, dye, buffering agents	Thin film hydration method,Modified hand shaking method, Vortexing-sonication method, Suspension, homogenization process, Aqueous lipid, suspension process, Centrifugation process.	High entrapment efficiency in case of lipophilic drugs, They protect the encapsulated drug from metabolic degradation.	They are chemically unstable because of predisposition to oxidative degradation, Their formulation and manufacturing expensive.
5	Aquasomes	Polymers, ceramic core	Preparation of core, Carbohydrate coating, Immobilization of drugs	Aquasomes preserves the conformational integrity and biochemical stability of	-

				bioactive molecules, Aquasomes exhibit physical properties of colloids, Aquasomes avoids reticuloendothelial clearance or degradation by other environmental challenges, Aquasomes suspensions contain colloidal range biodegradable nanoparticles, they are more concentrated	
6	Phytosomes	Phospholipids, commercial products, flavonoids	Solvent evaporation, Salting out, lyophilyzation,, Rotary evaporation , Anti solvent precipitation .	As the efficacy increases the dosage requirement is also reduced They have better stability, By increasing solubility of bile to herbal origin Phytoconstituents, Phytosomes enhance the liver targeting, Time period of action is increased	Duration of action is short, Phytoconstituents is rapidly eliminated from Phytosomes.

CONCLUSION

In pharmacosomes drug is bound to the polymer by covalent, van der Waal and hydrogen bonding. The drug will be released will by hydrogen bonding. Both the lipophilic and hydrophilic drugs can be suitable candidates, by covalent bonding with the polymer shows increase in entrapment efficiency. Pharmacosomes reduce toxicity and can improve therapeutic performance of drug. A biodegradable micelle forming drug conjugates increasing hydrophilicity of drug, Whereas change in the ratio of polymers show enhance cytoprotection by formulation of "vesicular constructs "using aqueous domain. Despite having disadvantages of getting fused, aggregated, they still serve as a vital tool for targeting and sustained drug release. Hence, pharmacosomes have immense potential in improving the drug delivery in case of both natural and synthetic active constituents.

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