PHARMACEUTICAL PRONIOSOMAL DRUG DELIVERY: A COMPLETE REVIEW OF NEW DELIVERY SYSTEM

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ABSTRACT:

Numerous issues arise in the field of solubility augmentation. Pharmacosomes, a revolutionary method based on lipid medication delivery, have emerged. Pharmacosomes are covalently bound, colloidal, nanometric-size micelles, vesicles, or hexagonal assemblies of colloidal drug dispersions to the phospholipid. Due to their special qualities such tiny size, amphiphilicity, active drug loading, high entrapment efficiency, and stability, they serve as suitable carriers for drug administration fairly accurately. In addition to lowering therapy costs, drug leakage and toxicity, increasing the bioavailability of poorly soluble medications, and having restorative benefits, they aid in the regulated release of pharmaceuticals at the site of action. This medication delivery system's capabilities have expanded to accommodate more medicines.

KEY WORDS: *Pharmacosomes, lipid based drug delivery systems, hydrophilic and lipophilic drugs Amphiphilic. , vesicular drug delivery system.*

INTRODUCTION:

Part of the innovative medicine delivery method are pharmacosomes. In 1968, Vaizoglu and Speriser initially presented them. Over the last few decades, A pharmacological substance is scientifically categorised using the Biopharmaceutics Classification System (BCS) based on its intestinal permeability and water solubility. A substance taken orally first dissolves into the stomach fluid (hydrophilic), then permeates across biological membranes (lipophilic), and eventually enters the blood (lipophilic). Many synthetic and natural medications suffer from the issue of either poor absorption or poor penetration across the biological membrane, limiting their total availability to the body system and their capacity to be absorbed.

Poor permeation may be caused by poor miscibility with the lipids, whereas poor absorption may be caused by their poor water solubility, severely restricting their capacity to traverse the lipid-rich outer membranes of the small intestine. Therefore, a wide range of techniques have been researched to enhance the absorption and penetration of biologically active molecules[1-3], including soluble pro-drugs, solid dispersions, cyclodextrin and phospholipids, and vesicular drug delivery systems.

Vesicular drug delivery systems (VDDS) are crucial techniques for stabilizing, improving, and targeting medication absorption. These systems typically have an aqueous core encircled by a lipid bilayer. The device serves as a fantastic delivery mechanism for both hydrophilic and hydrophobic medication kinds. While lipophilic medications are enclosed in a lipid bilayer, hydrophilic drugs are confined in the inner watery core. High drug entrapment, long retention period, tissue targeting, less side effects, and enhanced bioavailability are just a few of the benefits provided by VDDS. Additionally, a medicine can be delivered to the target location by the system at a predefined rate[4-6].

PHARMACOSOME:

The drug is covalently bonded to lipid in pharmacosomes, which are colloidal dispersions that result in an amphiphilic block. According to the chemical makeup of the drug lipid complex, they occur as micelles, hexagonal, and ultrafine vesicular aggregates. Drug and lipid interactions at the surface and in bulk lead to the formation of vesicular pharmacosomes. Prodrugs are created when a drug with the active functional groups (-COOH, -OH, and -NH2) is covalently attached to lipids with or without a spacer chain via esterification or another effective conjugation method. In interaction with the aqueous media, these prodrugs behave like amphiphilic molecules and self-assemble in one or more layers. These layers then continued to self-assemble into vesicles, producing pharmacosomes. The drug molecules function as the polar head and the associated lipids as the non-polar tail in pharmacosomes.

With pharmacosomes, issues including medication leakage, drug incorporation, and shortened shelf life are avoided. Due to the decreased interfacial tension and greater area of contact, they can boost medication bioavailability. The physical and chemical properties of the conjugate system determine how stable pharmacosomes are. It functions as an alternative to these vesicular systems since it has a number of benefits over others including transferosomes, niosomes, and liposomesP[7].

Pharmacosomes are essential for improving how well medications dissolve in gastrointestinal fluid and how well they pass across lipophilic membranes. Additionally, they can boost a drug's bioavailability if it has a low lipid or water solubility. The prodrug method effectively inhibits burst release and vesicle leakage while providing excellent drug entrapment effectiveness.

Pharmacosomes possess higher biopharmaceutical properties of the drug leading to improved bioavailability[.8]
As a result, one of liposomes' major drawbacks—removing the medication from the formulation process once it is liberated or unentrapped—can be avoided. The physiochemical characteristics of the drug-phospholipid conjugate, such as solubility, melting point, phase transition temperature, and lipid composition, have a major impact on the stability of pharmacosomes[9,10].

Fig.1

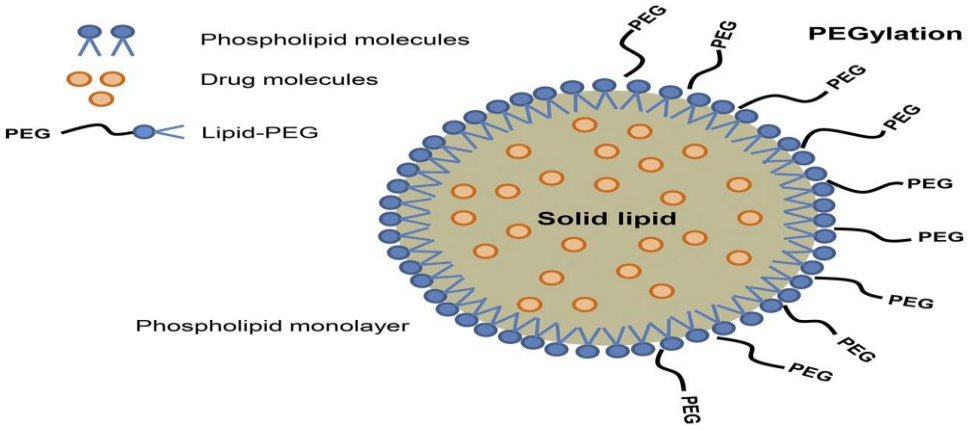


Fig.1 Pharmacosomes

PHARMACOSOME LIMITATIONS [11,12,13]

a) The drug's hydrophilic and lipophilic characteristics can both affect how this molecule is synthesised.
b) It calls for both surface-level and systemic drug-lipid interaction.
c) The covalent bond type that is necessary to prevent medication leakage.
d) Because of their vulnerability, pharmacosomes fuse, and chemicals stored in containers either aggregate or hydrolyze.

SALIENT FEATURES OF PHARMACOSOMES:

• Drugs that are lipophilic and hydrophilic can both be included in pharmacosomes.
• The complex's physical and chemical bonding properties, which regulate the formulation's overall stability.
• They are able to pass through tissue, cell walls, and cell membranes.
• Proper drug incorporation into lipid; • The covalent bond between the drug and the phospholipid can limit drug leakage.
• Administered by a variety of methods, including intravascular, extravascular, rectal, topical, or oral; and • Having a predefined entrapment efficiency.
The drug-lipid complex's phase transition temperature affects the fluidity of membranes.
• The extent of size and functional group contained in the drug molecule, as well as the length of the fatty acid chain in the lipid, determine the rate of their breakdown to the active drug molecule at the time of administration.

METHOD OF PREPARARTION

1. Ether injection technique: In this procedure, a correctly prepared solution containing a drug-lipid combination is slowly injected into a heated aqueous medium using a gauze needle, where vesicles readily form[14]
This approach involves dissolving the medication lipoid advanced with an organic solvent. When this combination is gradually fed into the heated liquid agents, the vesicles are formed. Because of the inflated concentration, several shapes of structures, such as spherical cylindrical, disc, cubic, or hexagonal type, may be seen. The concentration shows the nature of amphiphilies introduced in a chemical compound condition while it is at low concentration. Then compare the effects of the prodrug of diglyceride and a common wetting agent, dodecylamine hydrochloride, on the interfacial surface tension. [15] When it was fully completed, it was greater than the critical micellar concentration, the hexagonal organisation was confirmed by lengthy cylinders, and the drug displayed a liquid crystalline component with large molecular structures

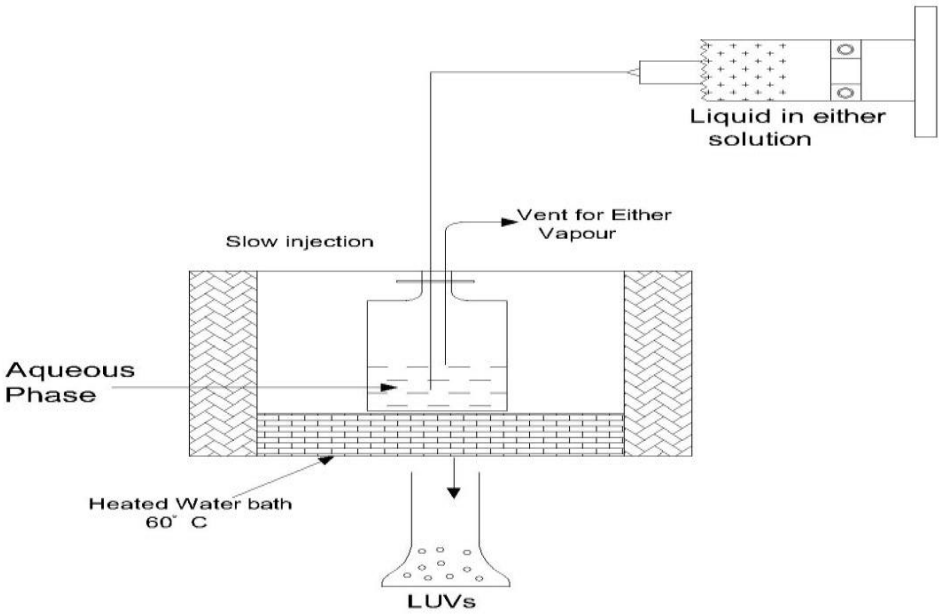


Fig.2: Ether injection technique

2. Method involving hand shaking or solvent evaporation: A volatile organic solvent is used to dissolve a medication and lipid mixture. A thin layer of the solid mixture is then placed on the flask walls after the solvent is evaporated using a rotatory evaporator in the round-bottom flask. The dry film easily produces a vesicular suspension when hydrated with aqueous medium[16]. In this method, the drug lipid complex dried film (either with or without egg lecithin) is placed in a bottom flask with a spherical shape, and upon contact with an aqueous medium, a vesicular suspension quickly develops. The drug lipid complex is slowly injected using the ether injection technique, resulting in the rapid formation of vesicles in a heated liquid injection media. The chemical compound occurs in an amphiphilic form at lower concentrations.[17] When the monomers are multiplied further, they may produce certain structures, such as micelles that are shaped like spherical rods, discs, or other shapes. In this study, the effects of a common detergent, dodecylamine hydrochloride, and the medication diglycerides on the interfacial surface tension are studied. Both of these data show a reduction in surface tension. The prodrug has a mesomorphic lyotropic character and forms supramolecular structures when its particle concentration exceeds the threshold level[18,19]

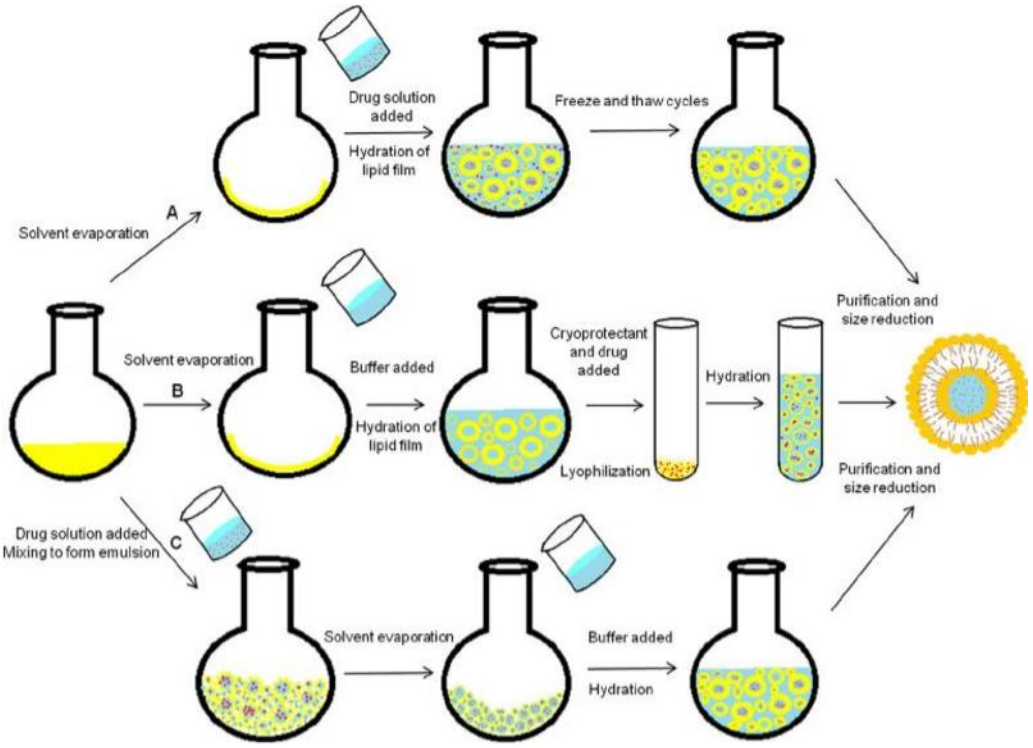
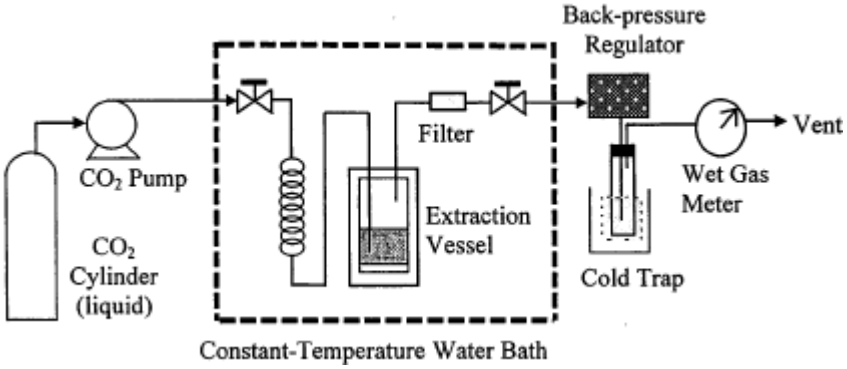


Fig.3: Hand shaking method

3. Anhydrous co-solvent lyophilization method: The medication and phospholipids are first dissolved in a solution of glacial acetic acid and dimethyl sulfoxide. After stirring the mixture to get a clear liquid, it is overnight freeze-dried at condenser temperature. The resulting complex is kept at 4oC[16] after being nitrogen flushe.

4. **the use of supercritical fluids** : In a supercritical fluid containing CO2, the drug and lipid complex are dissolved, then combined in a nozzle mixing chamber.**Fig.4**



5.solvent evaporation:

- To make the active hydrogen potentially accessible for complexation, the medication is first acidified.
- The drug acid is then recrystallized after being chloroform extracted.
- In a 100ml round-bottom flask, the precisely weighed PC and drug acid are added. A appropriate amount of dichloromethane is then used to dissolve the mixture.
- The mixture is refluxed for one hour, after which the solvent is evaporated in a rotating vacuum evaporator at 40°C under vacuum.
- After that, the dried residues are gathered and put in a vacuum desiccator to finish drying [20] [21].

ADVANTAGES OF PHARMACOSOMES:

- Since the medicine is covalently bonded to the lipid, there won't be any leaching.
- Deliver drugs to the designated location.
- By hydrolyzing the lipid polymer, the medication is released.
- The functional group, drug size, lipid chain length, and spacer all affect how a medication is metabolised.
- They are appropriate for both hydrophilic and lipophilic medications.
- Due to the covalent bonding between the dugs and carrier, entrapment efficiency is excellent.

- Increase bioavailability when a drug's solubility is inadequate.
- Lessen the toxicity and negative effects.
- Incorporating drugs is not a concern.
- Lower the price of therapy[22] r.

DISADVANTAGES OF PHARMACOSOM

- Pharmacosome storage involves fusion, aggregation, as well as chemical hydrolysis.
- The amphiphilic character of a molecule affects how it is synthesised.
- It necessitates drug and lipid surface and bulk interaction.
- Covalent bonding is necessary to prevent medication leakage[22]
- suffer chemical hydrolysis, fusion, and aggregation while stored.[23]

APPLICATIONS

- The method has effectively enhanced the therapeutic efficacy of several medications, including taxol, acyclovir, pindolol maleate, and bupranolol hydrochloride. Pharmacosomes' interactions with membranes may be significantly impacted by the phase transition temperature of the vesicular and micellar states. Bimembranes and pharmacosomes can cooperate to improve the transport of the active component. Bimembranes' phase transition temperature changes as a result of this interaction, which also improves the fluidity of the membrane and increases permeations. [24,25]
- The pharmacokinetic and pharmacodynamic effects of phytoconstituents such flavanoids, glycosides, and xanthones have increased.
- The strategy has been beneficial in enhancing the therapeutic efficacy of several medications. Specifically, acyclovir, taxol, and pindolomate.
- Pharmacosomes' interaction with membranes should be significantly influenced by the temperature at which they transition between their vesicular and micellar states.
- Pharmacosomes are more selective in their ability to operate on particular target cells.
- Pharmacosomes and biomembranes can interact to improve the transfer of active ingredients. A result of this interaction is change.

Table 1: Outcomes of Various Drugs After Incorporation InPharmacosomes

Drugs	**Outcomes**
Etodolac	Increased solubility, entrapment efficiency and sustained release
Aceclofenac	Enhancement ofsolubility, dissolution profile and improved bioavailability
Diclofenac	Improved solubility and drug loading.
Ketoprofen	Improved solubility, dissolutionprofile
Cytrabin	Biological activity was enhanced.
Bupranolohydrochloride	Augmented lymphatic transport and affect intraocular pressure
Pindolodiglyceride	Plasma concentreation impoved up tp three to five folds
Carbamezapine	Carbamezapins include dizziness,drowsiness,ataxia,nausea
Mefenamic acid	Upset stomach ,nausea,heartbeat,diarrhea
Levodopa	Headache,unsual dearms,loss of appetite
Felodipine	Dose dependent decrease in systolic and diastolic blood pressure
Dexamethasone	Infammatroy and function change airway
Intraconazole	Bioavalable intraconazole better as compared toconventional intraconazole

Table 2: Comparison between Liposomes and Pharmacosomes [26]:

Liposomes		**Pharmacosomes**
Principle	Including a drug in an aqueous or lipid phase of a mixture of lipids, where the physicochemical characteristics of the carrier and drug release will depend on the specific lipids employed.	Covalent drug-lipid binding in which the resultant molecule serves as both the carrier and the active ingredient. The physicochemical characteristics are influenced by the lipid and the medication.
Loss of drug	Through leakage	No leakage, since drug is covalently bound but loss of drug by hydrolysis is possible.
Manufacturing	Cast fill technique Extrusion/sonication injectable approach such as reverse phase evaporation	Self dispersion by sonication and modest mixing.
Separation of free drug	via dialysis, ultrafiltration, ultracentrifugation, and gel filtration.	Not necessary since the drug covalently linked
Volume of inclusion	Decisive in incorporation of drug molecules	Irrelevant, since the drug is covalently bound.
Surface charge	Achieved through lipid combination	Depends on the physicochemical structure of the drug lipid complex
Membrane fluidity	Depends on lipid combination and presence of cholesterol fluidity influences the rate of drug release and physical stability of system.	Depends on phase transition temperature of drug lipid complex. No effect on release rate since the drug is covalently bound
Release of drug	Bilayer-level diffusion and desorption fromthe surface or release as a result ofliposomes.	Hydrolysis (including enzymatic).
Physical stability	Aggregation with a double-valenced cation is quite good.	Double valenced cations allow for rather excellent agglomeration.

EVALUATION STUDIES OF PHARMACOSOMAL GEL:

1. Physical appearance and Homogeneity:

After the produced gels were placed in the container, ocular observations were made to determine their physical appearance and homogeneity. They had examinations to check for aggregates and to see how they looked.

2. Clarity:

By visual inspection against a black and white backdrop, the clarity of several formulations was assessed and scored as follows: Clear: ++, very clear (glassy): +++, and turbid: + [27]

3. pH Determination:

In 100 ml of sterile water, 1.0 g of gel was precisely weighed and distributed.A digital pH metre was used to measure the dispersion's pH; it was calibrated with standard buffer solution at pH values of 4.0, 7.0, and 9.0 before to use. The pH measurements were made three times, and the average results were determined**.**

4. Viscosity.

The viscosity and rheological characteristics of the Naproxen pharmacosomal gel were measured using a Brookfield digital viscometer with spindle noT-96. At a temperature of 37°C, the viscosity of gel was tested at various angular velocities. Changing the angular velocity from 0.3 to 2.5 rpm was normal for a run. The viscosity was calculated using the averages of two measurements [28]

5. Spread ability:

A circle of one centimetre in diameter was pre-marked on a glass plate, and 0.5g of gel was placed inside of it to test the spreadability of the formulation. A second glass plate was then placed on top of the first. 500 g of weight was placed on the upper glass plate and left there for five minutes. It was observed that the gels' spreading caused the diameter to grow**.**

6. Extrudability:

A closed, collapsible tube carrying a formulation was forcibly squeezed at the crimped end to ascertain its extrudability. Formula extruded once the cap was taken off until the pressure subsided. It was calculated the weight in grammes needed to extrude a 0.5 cm ribbon of the formulation in 10 seconds. [27] stated the average extrusion pressure in g.

7. Nuclear magnetic resonance:

Nuclear magnetic resonance (NMR) is the name given to a physical resonance phenomenon involving the observation of specific quantum mechanical magnetic properties of an atomic nucleus in the presence of an applied, external magnetic field.

The principle of NMR usually involves two sequential steps:

The alignment (polarization) of the magnetic nuclear spins

- in an applied, constant magnetic field H0. The perturbation of this alignment of the nuclear spins
- employing an electro-magnetic, usually radio frequency (RF) pulse.

The required perturbing frequency is dependent upon the static magnetic field (H0) and the nuclei of observation. NMR spectroscopy is one of the principal techniques used to obtain physical, chemical, electronic and structural information about molecules due to either the chemical shift Zeeman Effect, or the Knight Shift effect, or a combination of both, on the resonant frequencies of the nuclei present in the sample. It is a powerful technique that can provide detailed information on the topology, dynamics and three-dimensional structure of molecules in solution and the solid state.

8. surface morphology:

The surface of the sample is imaged by the scanning electron microscope (SEM), a form of electron microscope, using a high-energy electron beam in a raster scan pattern. The sample's atoms and electrons interact to produce signals that provide details about the sample's surface topography, chemical composition, and other characteristics like electrical conductivity.

An SEM can generate secondary electrons, back scattered electrons (BSE), distinctive x-rays, light (cathodoluminescence), specimen current, and transmitted electrons, among other forms of signals. The signals are the consequence of interactions between the electron beam and atoms on or near the sample surface. From around x 25 (roughly similar to that of a strong hand-lens) to approximately x 250,000, a broad variety of magnifications are achievable.

9. In vitro release rate:

Emulsion is added within the dialysis bag in the bulk equilibrium reverse dialysis bag procedure that is detailed here and outside is where the continuous (receiver) phase is situated. The donor phase (diluted emulsion) is suspended in a jar holding the continuous phase (receiver phase) alone, and the system is agitated. Each dialysis bag is taken out and its contents are examined for released drugs at predefined intervals. The increased membrane surface area that is accessible for transfer from the donor to the receiver phases is a benefit of this method. A further benefit of this approach is the improved personnel effectiveness brought about by the elimination of extra stages.

IMPORTANCE OF PHARMACOSOMES:

- The physicochemical stability of the pharmacosome depends upon the physicochemical properties of the drug-lipid complex. [29,30]
- Pharmacosomes are useful in avoiding the time-consuming process of taking the medication out of the formulation free and unentrapped**.**
- Pharmacosomes provide a productive means ofdirect medicine delivery to the infection site,resulting in a decrease in medication toxicity with no negative effectseffects and lowers the price of treatment byincreased drug bioavailability, particularly inscenario of illiquid digs.
- Drug-bilayer interactions and collected volume do not affect entrapment effectiveness in the case of Pharmacosomes

CONCLUSION:

Pharmacosomes are thought to be a cutting-edge medication delivery system. The medication performs well.Entrapment effectiveness and low medication loss via leaking. They benefit specifically.over liposomes because they increase the stability of the drug delivery mechanism and prevent drug leakage. CellularPharmacosomes can be used to accomplish targeting. However, study is required to lessen fusion. as well as chemical hydrolysis during storage.Pharmacosomes are superior to many cutting-edge medication delivery technologies in a number of ways. Due to its ability to mix with lipids and form vesicles, it has a high entrapment potency. It is important for medication targeting for many disorders as well. Since the medicine is mixed with lipids to create vesicles in pharmacosomes, the timing of drug administration may be predetermined. Therefore, it can be said that pharmacosomes have a great deal of promise to enhance medication delivery for both synthetic and natural active ingredients. In the pharmaceutical sector, vesicular systems are the developing carrier systems. Although they have the drawbacks of being fused and aggregated, they are nonetheless an essential tool for medication targeting and prolonged release. Further drug destiny and biological activity may be

altered with improved spacer groups and connections. However, more work has to be put into figuring out the mechanism of action and studying nonbilayer phases. Pharmacosomes therefore offer enormous potential to enhance medication delivery for both natural and manufactured active ingredients. Cellular targeting employing various techniques, such as PEGylation, Biotinylation, and so on, is a current research trend.

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