ejpmr, 2021,8(6), 520-529

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

AN OVERVIEW OF PHARMACOSOMES AS NOVEL VESICULAR DRUG DELIVERY SYSTEM

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Article Received on 20/04/2021 **Article Revised on 10/05/2021** **Article Accepted on 30/05/2021**

ABSTRACT

Novel drug delivery systems mainly focus on attaining the desired concentration of drug at the target site for the intended period of time using various carrier systems. Pharmacosomes are amphiphilic phospholipid complexes of drugs bearing active hydrogen that bind to phospholipid. The evaluation of pharmacosome is done on basis of different parameters such as size, surface morphology and *in vitro* release. Pharmacosomes are used as potential alternative for conventional vesicles like liposomes and nisomes because they produce a unique advantage over these conventional vesicle. They act by making an amphiphilic phospholipid complex with drug bearing active hydrogen atom covalently that bind to phospholipids. Pharmacosomes are also useful for maintaining low toxicity level of drug by minimizing the side effects. Pharmacosomes are used to achieve grater shelf life and better stability of drug. Bioavailability of poorly soluble drug increased by pharmacosomes and they also help to minimize the degradation of the drug. Using pharmacosomes as vesicular drug delivery system is economical compared to other technique. The drug releaseof pharmacosome is controlled by the process of enzymatic reaction and acid hydrolysis. Pharmacosomes are used for drug targeting in cancer and brain by using 3,5 – dioctanoyl – 5 – fluro – 2 – deoxyuridine. Pharmacosomes are capable of incorporating both hydrophilic and lipophilic drugs.

KEYWORDS: Pharmacosomes, amphiphilic, Drug targeting, novel drug delivery system, phospholipids, bioavailability.

INTRODUCTION

There are so many research works done on novel drug delivery system over the past few decades for fulfilling the purpose of developingthis system. The development of novel drug delivery systems is done to explain the clinical advantages and economical aspects of these systems. The two must-have qualities of being an ideal novel drug delivery system are: firstly, it should deliver the drug at a rate directed by the body required, secondly; it should channel the active entity at the targeted site of action.[1] At present, there is no such novel drug delivery system which behaves ideally, but few appropriate attempts has been done to achieve those ideal characteristics through various novel approaches in drug delivery. Approaches are being made to accomplish this goal, by giving essential attention either to control the distribution of drug by incorporating it in a carrier system or by reforming the structure of the drug at the molecular level or by limiting the input of the drug into bio- environment to ensure a preferable profile of distribution. Novel drug delivery system mainly aims at offering some control, either this is temporal or spatial nature, or both, of drug release in the body. The Bulk of drugs, especially chemotherapeutic agents, had shown to have narrow therapeutic window and their clinical use is partial and compromised by dose limiting toxic effect. So, the therapeutic effectiveness of the present drugs is developed by formulating them in a rewarding way. Novel drug delivery system has some advantages over conventional drug delivery system.[3]

Those advantages are as follow

- Ideal dose at the certain time and certain location.
- Effective use of costly drugs and experiment.
- A low cost systems and effectiveness of drug is alsoimproved.
- Known to maintain drug concentration at a particularrange.
- Reduce adverse or toxic effect.
- Preferable therapy and improved comfort and simplelife of patient.

There are different modes of novel drug delivery system and targeted drug delivery system is one of them. Vesicular drug delivery systems are considered as one of the main targeted drug delivery system. Owing to the fact that these systems have the potential to localize the activity of drug at the site or organ of

the action there by reducing its concentration at the other sites of the body. Several variant categories of pharmaceutical carriers are put into service to localize drug action in the diseased tissue or organ in vesicular drug delivery system. Some of those pharmaceutical carriers are polymer micelles, macro- and micro molecules, micro- and nano spheres, polymeric micelles. Some example of vesicular systems are liposomes, niosomes, transferosomes, pharmacosomes etc. Pharmacosomes is a type of vesicular drug deliverysystem because of their ability to release the drug at the targeted site ordisease tissue. Pharmacosomes are also useful for maintaining lowtoxicity level of drug by reducing side effects. Pharmacosomes arecapable of incorporating both hydrophilic and lipophilic drugs. Using pharmacosomes as vesicular drug delivery system cost less amount of money than other technique.

Background of Drug Targeting

The idea of inventing a newly design specific delivery system to accomplish selective drug targeting has been developed from the perception of Paul Ehrlich, who introduce drug delivery as "magic bullet". The foremost published report of Paul Ehrlich in 1902 on drug targetinghad narrated that the targeted drug delivery as a phenomenon where a drug carrier conjugate delivers drug independently to the preselected target cell in specific manner. In later years Bangham had done some observation on hexagonal liquid crystals to develop targeted drug delivery system. That observation yields the information that hexagonal liquid crystals are permselective to the ions in same way to bio-membrane, lead to discovery of artificial vesicular system based on phospholipids" amphiphiles, Gregoriodis, 1981 explained drug targetingusing npvel drug delivery systems as "old drugs in new cloths" .[4]

Concept of Drug Targeting

In the conventional way of drug delivery system such as oral ingestion, intravascular injection etc. the drug administrated to the non- healthy tissue of the body through the systemic circulation. Because of this reason the targeted drug delivery system become very important. In targeted drug delivery system the dose of drug can be specifically released at the desired site of action or deceased tissue. For the above reason the therapeutic efficiency of targeted drug delivery system is better than conventional way of drug delivery system. For designing the targeted drug delivery system, several vitalaspects should be considered such as target, carrier, ligands and physically modulated components. Drug targeting applies for specific and successive localization of medicament at desired targets in therapeutic concentration, simultaneously inhibiting its access to non-target tissue. Hence, drug targeting causes less toxic effects and less therapeutic index. Drug targeting affects distinctive therapeutic benefits in pre-existing accessible domains e.g. intercellular sites, virus, bacteria and parasites offers distinctive benefits. Drug targeting can be done through various approaches of vectoring the drug to the target site.[4] Those approaches can be classified as below:

- Passive targeting
- Active targeting
- Inverse targeting
- Duel targeting
- Double targeting
- Combination targeting

Vesicular Drug Delivery System

In the past few decades, vesicular systems have been applied as drug delivery carriers. In the year of 1965 Bingham was the first to report the biologic origin oflipid based vesicles and at that time those were named as "Bingham Bodies"[1]. Vesicles are water-filled colloidal particles. The valves of this particles consist ofamphiphilic molecules in a bilayer composition. When the water level increase, these amphiphilic molecules can form one unilamellar vesicles or more that is multilamellar vesicles. Hydrophilic drug can be entrapped into the internal aqueous compartment. On theother hand, amphiphilic, lipophilic and charged hydrophilic drugs can be associate with the vesicle bilayer by hydrophobic or electrostatic interactions. Capsulation of a drug in vesicular structure can be predicted to prolong the exitance of drug in systemic circulation and perhaps reduces the toxicity, if selective uptake can be achieved. The composition of vesicle influences their physiochemical characteristics such as size, charge, lamellarity, thermodynamic phase and bilayer clasticity. Most commonly used material for the formation of vesicles are phospholipid, cholesterol andnon-ionic surfactants.[1]

A very important role is played by lipid based vesicles in modeling biological membrane and in the targeting and transporting of medicament. At present, vesicles in some of the fields such as immunology, membrane biology, diagnostics and genetic engineering are getting system. Some problems of conventional drug delivery system such as drug insolubility, instability and rapid degradation can be solved by applying vesicular drug delivery system.

The toxicity of drug is less in vesicular drug delivery system than other drug delivery system, because in this system drug can be released at a slow rate in the of action.[5]

***Definition*:** Vesicular drug delivery system can be defined as highly ordered assemblies consisting of one or more concentric bilayers formed as a result of self-assembling of amphiphilic building blocks in presence ofwater.

Advantages of Vesicular Drug Delivery System[15]

- Increases bioavailability and biocompatibility of thedrugs in case of poorly aqueous soluble drug.
- Low toxicity of the drug.
- They can trap both hydrophilic and hydrophobic compounds.
- The drug can stay in systemic circulation for a long period of time.
- Controlled drug delivery rate and extent could be produced.
- Can act as a depot formation to sustain release of drug.
- Increased permeation of drugs through the skin.
- This system penetration enhancer because of their unique concentration.

But, some drugs carriers like particulates (e.g. liposomes, nanoparticles, microemulsions) and externally triggered carriers (e.g. temperature, pH, or magnetic sensitive) load drugs passively in vesicular drug delivery system may cause drug leakage in preparation, preservation and transport *in-vivo*. Some examples of vesicular drug delivery system are liposomes, niosomes, transferosomes, pharmacosomes etc.

Pharmacosomes

Pharmacosomes are part of the vesicular drug delivery system. Vaizoglu and Speriser were the first to introduce pharmacosomes in 1968.[16] Pharmacosomes were first prepared in 1982 by Macoss. Pharmacosomes are also known as "Vesicular constructs". The appropriate elaboration of pharmacosomes which is the lipid based drugdelivery system can be done as colloidal dispersions of drugs having a covalent electrostatic or hydrogen bonding with lipid. Pharmacosomes are considered of having more advantages over liposomal, transferosomal, and niosomal drug delivery system due to some limitations like drug leakage or insufficient shelf life ofdrug can be avoided by pharmacosomes.

"Pharmacosomes" the word is derived from two Greek words, one is "Pharmakon" which means "drug" and another one is "Soma" which means „carrier". So, we can say that pharmacosomes is a drug delivery system in which the drug is linked to a carrier. Hence, pharmacosomes can be defined as "the colloidal dispersion of drugs covalently bound to lipids, and may exist as an ultrafine vesicular, micelle or hexagonal aggregates depending upon the chemical structure of drug-lipid complex."

The evaluation of pharmacosomes is done on the basis of different parameters such as size, surface, morphology, and *in vitro* release. Pharmacosomes are amphiphilic phospholipid complexes of drugs bearing an active hydrogen that bound to phospholipid. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2 etc.) can be esterified to the lipid with or without spacer chain. Synthesis of such compounds may be guided in such a way that strongly amphiphilic compound results, which will facilitate membrane, tissue or cell wall transfer in the organism.

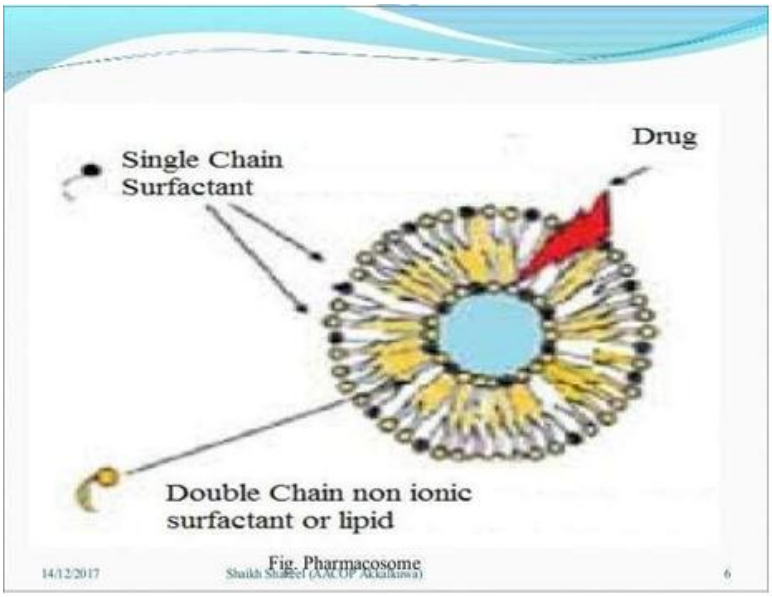

Figure 1: Diagram of pharmacosomes.

Principle of Pharmacosomes

The principle of pharmacosomes is that the drug binds covalently toa lipid where the resulting compound is the carrier and the active compound at the same time. Physiochemical properties depend on drug as well as lipid. Pharmacosomes are neutral molecule having both negative as well as positive charge, means having both hydrophilic and lipophilic properties at the same time. It means that pharmacosomes can incorporate both lipophilic and hydrophilic drugs. Pharmacosomes have optimal concentration and optimal proportion of poly phenols and phospholipids and these drugs are bonded with the lipids with a hydrogen bond[14]

Salient Features of Pharmacosomes[27]

- Pharmacosomes can administrated through several routes such as topical routes, oral route, intravascular route etc.
- Pharmacosomes can pass through the cell membrane, walls, or tissue with ease as they are made of both water-loving and fat- loving properties.
- The stability of the whole system is always affected by chemical and physical properties of conjugate.
- Some factors such as size, nature of functional group present in the drug molecule, length of the fatty acid chain in lipid, presence or absence of spacer decide the rate of degradation. For the improvisation of *in- vivo* pharmacokinetic behavior, all these factors can fluctuate.

Components of Pharmacosomes

There are three essential components for pharmacosomes" preparation. Those are as mentioned below –

a) Drugs

Active hydrogen atom (-COOH, -OH, -NH_2 etc.) possessing any drug can be esterified to the lipid, with or without spacer chain. These synthesized amphiphilic complexes facilitate membrane, tissue or cell wall transfer in the organism.[9]

b) Solvent

As per the requirement for the preparation of pharmacosomes, an analytical grade organic solvent is important ingredient. That solvent must be of high purityand volatile in nature. Either by addition or by refluxing the selected solvent must dissolve the drug and lipid.

c) Lipid

Phospholipids are considered as the main building component for biological membrane. These membranes are consist of two types of phospholipids. Those two phospholipids are phosphoglycerides and spingolipids for the most of the time. Phosphatidylcholine, which is the most common type of phospholipid, is an amphipathic molecule. There is a glycerol bridge that links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group, phosphocholine in phosphatidylcholine.

Preparation of Pharmacosomes

A number of methods are used for the preparation of pharmacosomes. Those are

The Hand-Shaking Method

- Inthis technique, firstly the mixture of drug and lipidwill be poured in the round bottom flask.
- Next step will be the evaporation of the organic solvent by using rotary vacuum evaporator at room temperature. This process yields a thin film of deposition on the walls.
- Now, the dried film is hydrated with buffer and rotated in one direction with hand which leads to theformation of vesicular suspension.[3]

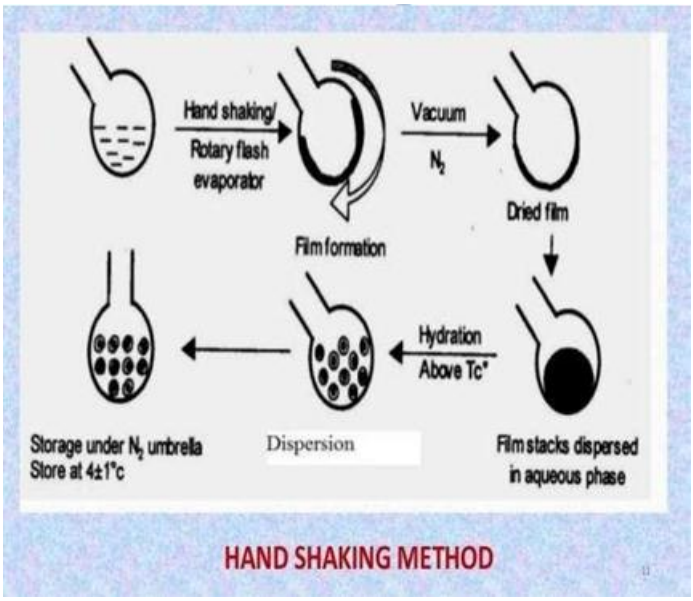

Figure 2: Hand Shaking Method.

Ether Injection Method

- In this method, at first we need to dissolve the complex of drug-lipid in specific volume of ether.
- Now, the above mixture is slowly injected into a heated buffer solution. This process leads to the formation of vesicles.
- The concentration controls the shape of natural vesicles.
- The amphiphilic state causes the formation of different structure such as round, cylindrical, disc, cubic, or hexagonal.

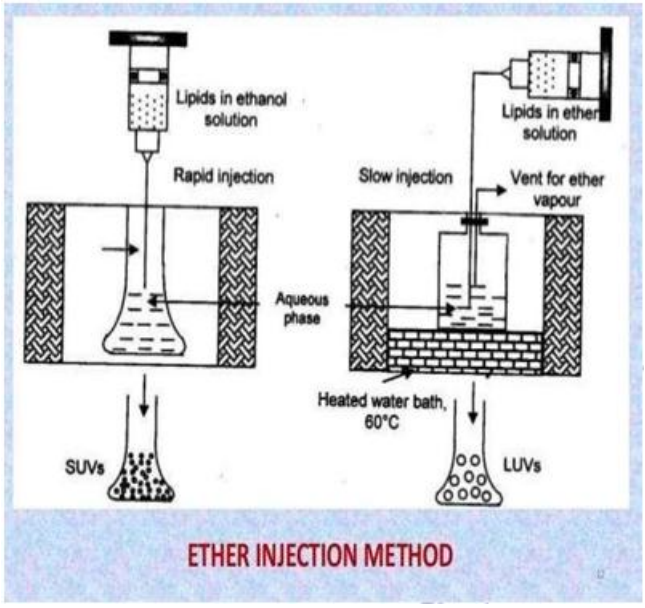

Figure 3: Ether Injection Method.

Anhydrous co-solvent lyophilization method

- First, the mixture of the drugs and phospholipids is dissolved in solution of dimethyl sulfoxide containing glacial acetic acid.
- Now, the new mixture is agitated to get clear liquid and then freeze-dried at condenser temperature of - 40^0C for a whole night.
- In the next step, the obtained complex is flushed with nitrogen and stored at 4^0C.

Supercritical Fluid Process

- The another name of this technique is solution enhanced dispersion by complex supercritical fluid.
- First, the mixture of drug and lipid complex are mixed with supercritical fluid of carbon dioxide, and then high super saturation is obtained by passing through nozzle mixture.
- Now, fast mixing of dispersion take place due to the turbulent flow of solvent and carbon dioxide which results in the formation of pharmacosome.

Other Recent Approaches

- Synthesis of a biodegradable micelle forming drug conjugate is done from the polymer consisting of poly xyethylene glycol and polyasportic acid with a adriamycin which is hydrophobic in nature.
- The micelle is diluted in absence of the active constituent getting precipitated in the monomeric drug conjugate.
- Muller-Goymann and Hamann have diluted lyotropic liquid crystals of amphiphilic drug for the preparation of pharmacosome.[17]

Chracterization of Pharmacosomes Complex Determination

The formation of the complex or the conjugate can be determined by observing the correlating spectrum in complex sample with that of discrete constituents and also with their mixture using fourier transform infrared spectroscopy (FTIR).[21]

Surface Morphology

The study of surface morphology of pharmacosomes is done by the scanning electro microscopy (SEM) or transmission electron microscopy (TEM). The purity grade of lipid are being used in this technique and also a few variables are observed during operation (method of preparation, vacuum assigned, and rotational speed).

Drug-Lipid Compatibility

The compatibility of drug-lipid complex can be determined by the help of differential scanning colorimetry which is a thermoanalytical technique. The thermal response examined by the use of separate samples and by heating them in a sample pan which is closed. The nitrogen is purged, and the temperature is maintained in a specific range with required heating rate. If, any interaction is done between drug-lipid complex can also be determined by the above technique.[21]

Crystalline State Measurement
X-ray power diffraction (XRPD) technique is used for the determination of the crystalline nature of the drug. The tube voltage and tube current are used in X-ray generator and the source of the radiation is copper lines. The scan angle may be regulated. The intensity of all refection peaks are combined and projected by area under curve of XRPD pattern that specifies the specimen attributes.

Dissolution Studies
Various models are used to know the information about dissolution studies. The assessment of the outcome is carried on the basis of apprehended activity of the active constituents therapeutically.[13]

Evaluation of Pharmacosomes
A instrument called Zetasizer XS used for the measurement of the size of pharmacosomes. The instrument works on a principle that is based on scattering of light. First, solution containing vesicles is made. Then, light ray is passed through it. Now, on the basis of scattered light, the size of the vesicle is measured. Pharmacosomes are less than 200 nanometers.

Solubility of Pharmacosomes
With the help of shake-flask technique, the solubility can be determined and the modification of solubility occurs due to complexation. Organic and aqueous phase are two phases that take part in this technique. The organic phase is 1-octanol and the aqueous phase is buffer solution at specific pH consisting of drug-phospholipid conjugate. Now, these two phases are consorted and constantly stirred by maintaining the equilibrium and then it was left alone at temperature of 37^0C for one day. Then the aqueous phase is separated and concentration is determined by using UV or HPLC technique.[30]

Stability of Pharmacosomes
After completion of the lyophilization of the product, the correlation between the spectrum of complex at various points of time in the solid state and spectrum of dispersion in water consisting of small particles is used to evaluate the stability of the system.

Drug Content
For the determination of the quantity of drug present in pharmacosomes, estimated amount of pharmacosomes were weighed and taken to a volumetric flask containing known volume of solvent in which drug is soluble. Then, the mixture of the above contents was stirred continuously on magnetic stirrer and after that it was left alone for 24 hours. Then, desired dilution took place and measurement of drug content was done by using UV spectroscopy or HPLC.

Nuclear Magnetic Resonance (NMR)
Nuclear magnetic resonance spectroscopy is considered as one of the main techniques for the determination of physical, chemical, electronical, electronic and structural information about molecule.

Advantages of Pharmacosomes[32]
- In case of pharmacosomes system, there is no need for a time consuming step like tedious step which is done to remove the unentrapped drug compared to liposomes system.
- Pharmacosomes offer an effective process that can deliver the drug to the desired site of action with no adverse effect. For this reason the system cause less amount of drug toxicity. The cost of the therapy for this type of drug delivery system is less due to improve bio-availability of drug, especially in case of poorly soluble drug.
- Pharmacosomes can in corporate both hydrophilic and lipophilic drugs.
- In this drug delivery system, the drug itself can conjugate with lipids from vesicles. So, entrapment efficiency can be predetermined and is higher than other system.
- In case of pharmacosomes, drug leakage does not take place as the drug is covalently linked.
- Drug incorporation does not have any drawbacks.
- Entrapment efficiency is not affected by encaptured volume and drug-bilayer interactions, regarding pharmacosomes.
- Physiochemical properties of the drug-lipid complex are controlled by physiochemical stability of pharmacosomes.

Disadvantages of Pharmacosomes
- Both hydrophilic and lipophilic nature of drugs can affect the synthesis of this compound.[15]
- Both superficial and mass drug-lipid interaction are necessary.
- If pharmacosomes are stored for a duration of time, they can undergo fusion and aggregation as well as chemical hydrolysis.
- In this system, water insoluble drugs can not be encapsulated relatively in a large hydrophobic region within membrane bilayer.
- The bond between drug and lipid should be a covalent bond.
- Surface and bulk interaction of lipids with drug is essential due to their susceptibility and chemicals.

Advantages of Pharmacosomes Over Other Vesicular Drug Delivery System
- Pharmacosomes system is less time consuming than niosomes system. Pharmacosomes are more stable and efficient than niosomes because of no leaching of drug.[19]
- Pharmacosomes system costs lesser amount of money than liposomes system. In liposomes system drug entrapment is dependent, but in pharmacosomes system it is independent.

- Transferosomes system is more expensive than pharmacosomes system. Pharmacosomes system is not dependent on the availability of phospholipids like transferosomes system. Pharmacosomes system can resist oxidation, not like transferosomes system.

Applications of Pharmacosomes

- Pharmacosomes are applied to get better stability and shelf life compared to other vesicular drug delivery system.
- The ability of absorption and permeation of drug can be enhancedby formulating them to pharmacosomes.[29]
- Drugs like Pindolol diglyceride, Amoxicillin, Taxol, Crystabine, Dermalansulfate, Bupranololor hydrochloride etc. showed more pharmacological action when they are formulated to pharmacosomes.
- Pharmacosomes are applied due to their capability todeliver the drug in the targeted site of action.
- Pharmacosomes can enhance the rate of permeation by improving the membrane fluidity. The transition temperature of vesicle in the form of vesicle and micelles pose an affect on vesicular interaction with biomembrane, hence improving the transfer of drug across membrane.
- With the help of pharmacosomes, we can study the mechanism of action of drug and non-bilayer phases.
- Bioavailability of aspirin is improved and gastrointestinal toxicity of aspirin decreased due to the synthesis of aspirin phospholipid complex.[31]
- Solubility and permeability of drugs like Diclofenac and Acelofenac are more when they are formulated in pharmacosome than conventional dosage form.[30]
- The drug 3,5 – dioctanoyl – 5 – fluro – 2 – deoxyuridine is formulated to pharmacosome for targeting the desired diseased tissue or site of action to achieve better therapeutic efficiency of drug in cancer treatment.[26]
- Pharmacosomes has the ability to transport biological components such as proteins, amino acidsetc.

CONCLUSION

Pharmacosomes can overcome the limitations of the conventional vesicular drug delivery system such as liposomes, niosomes, transferosomes. So, pharmacosomes system is a potential alternative for other vesicular systems. In case of pharmacosomes, theentrapment efficiency is excellent and also minimal amount of drug is wasted due to leakage of drug. This is also more economical than other vesicular system. Pharmacosomes also comes with some limitations like if they are stored for a duration of time, they can undergo fusion and aggregation and as well as chemical hydrolysis. In this system the bond between drug and lipid should be a covalent bond. In spite of all these limitations, pharmacosomes still play an important role in selective drug targeting and the controlled delivery of various drugs. Hence, pharmacosomes have significant capability to improve drug delivery in case of both natural and synthetic active constituents. Current research are basically based on utilization of different approaches such as pegylation, biotinyzation etc. for cellular targeting.

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