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PHARMACOSOMES: A DEVELOPING NOVEL VESICULAR DRUG DELIVERY SYSTEM

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ABSTRACT

Pharmacosomes are colloidal dispersions in which the drug is covalently bound to lipids and may persist as vesicular, hexagonal aggregates, or micellar relying on the atom arrangement of the drug-lipid complex. Pharmacosomes are a likely substitute for conventional vesicle methods. The encapsulation of the drug in the vesicle of small size and amphiphilic nature both enhances the retention of the drug in the systemic circulation of the body. The pharmacosomes enhance the cell wall transfer, improves the poorly water-soluble molecule's solubility by ameliorating bioavailability and also reduces the toxicity of the drug. Pharmacosomes have successfully been prepared for numerous drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs and antineoplastic drugs. This review dealt with all facets of pharmacosomes such as composition, method of preparation, method of characterization/evaluations and their therapeutic application. The pharmacosomes containing the herbal drugs are referred to as phytosomes. Pharmacosomes offers emerging challenges and opportunities to improve novel vesicular drug delivery system for the superior efficacy of the administered drug.

KEYWORDS: Pharmacosomes, Novel drug delivery system (NDDS), vesicular drug delivery system, phospholipids, phytosomes.

INTRODUCTION

Novel drug delivery system (NDDS) majorly focuses on the formulation, designing technologies and systems for transporting pharmaceutical compounds to effectively accomplish their desired therapeutic effects in the body. NDDS endeavors to either withstand drug action at a predefined rate or by maintaining an approximately constant and efficacious drug concentration extent in the body with minimization of associated side effects.[1] The selective drug delivery to the target tissues will enhance the therapeutic effectiveness of the drug and lowers its undesirable impact on non-target tissues and hence reduces the toxicity of the drug.[2] The updated version of NDDS is a vesicular drug delivery system. Biological origins of the vesicles were initially described by Bingham in the year 1965, thus they are termed as "Bingham bodies". Vesicular drug delivery system is widely used in immunological, genetic engineering, membrane and diagnostic techniques. The vesicular drug delivery system plays an indispensable role in the targeting and delivery of the therapeutic drug molecule. The word pharmacosomes is obtained from the word "Pharmakon" which means drug and "soma" means carrier thus the vesicular system pharmacosomes means the drug is linked with the carrier.

Drug carriers are the substances which used in the process of drug delivery and it facilitates administration of a drug by ameliorating the drug effectiveness, safety and selectivity. Drug carriers are used to augment pharmacokinetics and bioavailability.[1] Pharmacosomes are amphiphilic complexes of drugs (comprising of an active hydrogen atom) with lipids as shown in figure 1. The drugs are bound either covalently, electrostatically or by hydrogen bonds to lipids.[3] Pharmacosomes as novel drug delivery systems were first discussed by Vaizoglu et al 1986.[4] Moreover, pharmacosomes may additionally be interpreted as a neutral molecule containing both positive and negative charges, hydrophilic and hydrophobic properties and acceptable polyphenol to phospholipids ratio in the complex form.[5] These are also defined as colloidal dispersions of drugs covalently bound to lipids and may exist as ultrafine vesicular, micellar or hexagonal aggregates, relying on the atom arrangement of the drug-lipid complex.[6] The drugs are linked with lipids by forming a hydrogen bond or by electron pair sharing and electrostatic forces and are present in a dispersion form in these lipoidal drug delivery systems. The concept for the development of the vesicular pharmacosomes is centered on the surface and bulk interactions of lipids with drugs.[7]

These lipid conjugated vesicles may exist as colloidal or nanometric size micelles in which it arranges itself as hexagonal assembly, in which a functional hydrogen atom is supported on the architecture of the complex (Fig. 1). The drug molecule with a free carboxylic or functional hydrogen atom-like amino, hydroxyl groups are altered to an ester with the aid of the hydroxyl moiety of the lipid, leads to the formation of a prodrug. A spacer chain may or may not be taken into account for this purpose.[3] Synthesis of these types of compounds may be guided in such a way that strongly results in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism.[8] The amphiphilic character helps pharmacosomes to decrease the interfacial tension and at elevated concentrations exhibit mesomorphic behavior.[9] The pharmacosomes prepared with herbal drugs are called phytosomes. As the name suggests phytosomes especially contain plant-based drugs (having poor-solubility).[10]

The prodrugs possess both hydrophilic and lipophilic properties. Prodrugs also can decrease interfacial tension, increase the area of contact and thus enhance the bioavailability of the drug. These prodrugs assemble into single or multiple layers for the formation of pharmacosomes on contact with water. The development of this type of system depends upon the surface properties and bulk properties of the drug-lipid conjugate.[3]

Characteristics of pharmacosomes

Pharmacosomes can easily incorporate both hydrophilic and lipophilic drugs.[11] The drug is covalently linked in pharmacosomes, thus in contrast to liposomes, loss because of leakage of drug doesn't take place, however, hydrolysis may be the reason of loss to occur in the case of pharmacosomes. There's no problem with drug incorporation in the body of the patient.[12] As the drug itself forms vesicles in conjugation with lipids, entrapment efficiency is high and predetermined. Drug-bilayer interactions and encaptured volume do not influence entrapment efficiency in pharmacosomes whereas these have a magnificent effect on the entrapment efficiency of liposomes. Membrane fluidity which has an impact on the rate of drug release and physical stability depends upon the lipid composition in liposomes. On the other hand, membrane fluidity in pharmacosomes doesn't affect the rate of drug release because the drug is covalently bound, moreover, it depends upon the phase transition temperature of the drug lipid complex. The physicochemical stability of the pharmacosomes is based on the physicochemical properties of the drug-lipid complex. Amphiphilicity in pharmacosomes ameliorates the bioavailability of poorly lipid and water-soluble drugs. Multiple transfers through the lipophilic membrane system occur in pharmacosomes because of the amphiphilic behavior of pharmacosomes and also the transport mechanisms such as endocytosis and exocytosis involve in transport through cellular walls. The system is stable and efficient because of covalent linkage. The degradation velocity into active drug molecule after absorption depends upon the size (dimensions), functional groups (drug molecule), chain length (lipids) and spacer. The stability of the entire system is regulated by the physical and chemical properties of the conjugate.[13-15] To obtain optimum *in vivo* pharmacokinetics, these factors are often varied within the suitable limit. Unlike liposomes, pharmacosomes don't require monotonous, laborious, time-wasting steps for separating the free drug (remaining to entrap) from the formulation. Pharmacosomes are often administered topically, orally, extra-or intravascularly. Adverse effects and toxicity are often reduced as drugs deliver on to the location of infection by pharmacosomes. This approach has successfully been employed to improve the therapeutic efficiency of various drugs such as amoxicillin, bupranolol hydrochloride, pindolol maleate, taxol and cytarabine.

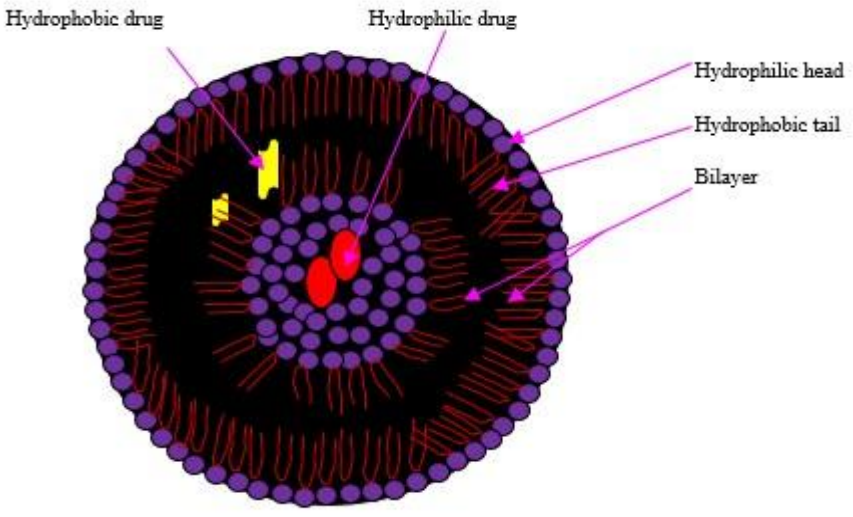

Figure 1: Structure of pharmacosomes.

Limitations of pharmacosomes

Despite having a larger area, the water-insoluble drugs encapsulated in the pharmacosomes in relatively small hydrophobic regions within the membrane bilayer.[14] The amphiphilic character of the pharmacosomes is necessary for the synthesis of a compound. To prevent the leakage of medication from the conjugate, pharmacosomes require a surface or bulk interaction and covalent bonding of lipids with drugs. Upon prolong storage, pharmacosomes may get affected by fusion, aggregation and chemical hydrolysis.[6]

Formulation of pharmacosomes

There are mainly three components required to formulate pharmacosomes viz. drug, solvent and carrier (lipid). These components and their requirements for preparation of pharmacosomes are described in Fig. 2.

Drug

The requirement of the drug to formulate pharmacosomes should meet the following written facet. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2) which may be esterified to the lipid, with or without spacer chain leading to the formulation of amphiphilic complexes may be employed to prepare pharmacosomes. Membrane, tissue, or cell membrane transfer of medication in the organism is facilitated by these synthesized amphiphilic complexes (pharmacosomes).[1]

Lipid

Phospholipids are the most important constituent of cell membranes. Phospholipids commonly employed to prepare pharmacosomes are phosphoglycerides, phosphatidylcholine and sphingolipids. Phosphatidylcholine, the foremost common molecule used, is an amphiphilic molecule within which glycerol bridges are present because of the linkage of a pair of hydrophobic acyl hydrocarbon chains with the hydrophilic polar head group. Phosphatidylcholine plays an important role within the basic biological process and in supporting cell wall integrity. Pharmacosomes can also manage liver disorders and act as hepatoprotective agents as it provides choline from phospholipids. Pharmacosomes due to the presence of phospholipids can even promote the breakdown of collagen and can prevent fibrosis and cirrhosis. It also exhibits protection against infectious hepatitis A, B and C, and supplements presenile dementia-like maladies.

Solvent

The organic solvents of analytical grade are utilized in the preparation of pharmacosomes. High purity and volatility are the primary requirements of solvent. The solvent media must dissolve phospholipids and the drug in it. The choice of solvent is based on the polarity of the drug and also of the lipid.[1,15]

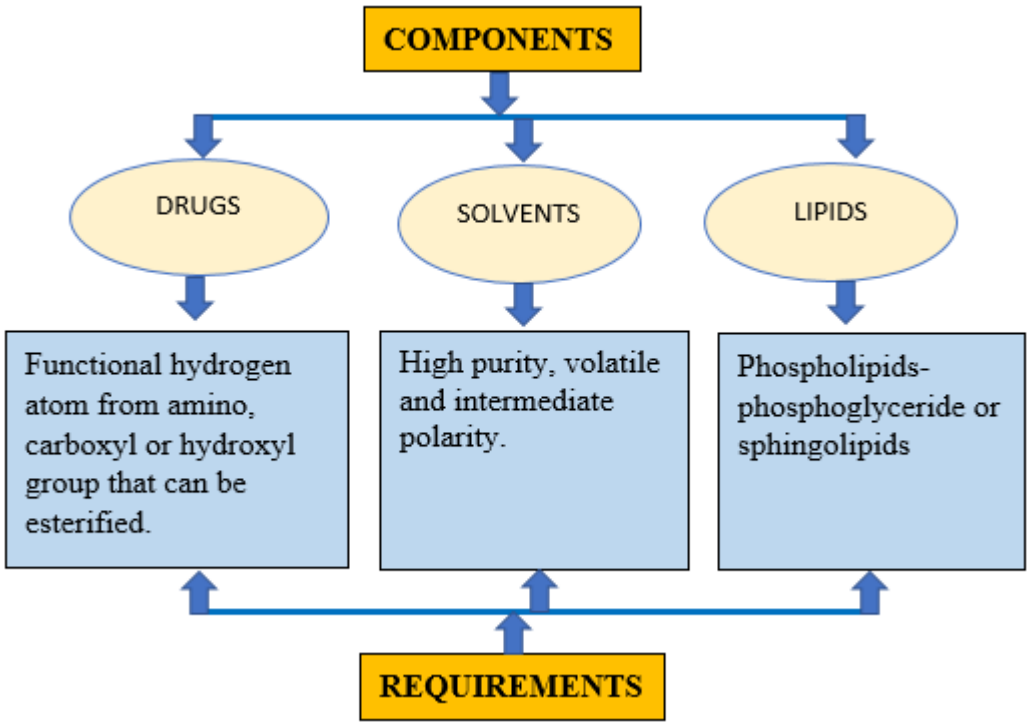

Figure 2: Components and their requirements for preparation of pharmacosomes.

METHODS OF PREPARATION

Ether injection method

In this method, ether acts as a solvent in which a solution containing a drug-lipid complex is mixed thoroughly. With the help of a gauze needle, the solution prepared is slowly injected into a hot aqueous medium which will lead to the production of vesicles.[14] Based on the amphiphilic nature, a variety of structures such as round,

cylindrical, disc, cubic, or hexagonal type may be formed.[1]

Ping et al. (2005)[15] prepared didanosine pharmacosomes with the help of the injection method by employing solvent tetrahydrofuran (cyclic ether). The *in vivo* behavior of the formulation was studied in rats. The prolonged effect in targeting organs demonstrates that the pharmacosomes are also a possible delivery system for the said objectives.

Solvent evaporation method / Hand-shaking method

The selected volatile organic solvent is employed to dissolve the mixture of the drug and the lipid, which will lead to the formation of the solution mixture. In a Round Bottom Flask (RBF) of a rotatory evaporator, the solution mixture is now transferred. The solvent evaporates and a skinny film of the solid mixture is left deposited on the walls of the RBF. Vesicular suspension is prepared by the hydration of this dried solid mixture film with the help of an aqueous medium.[16,17]

Jiang et al. (2001)[18] prepared flavonoid phytosomes (pharmacosomes) employing the solvent evaporation technique.

Yanyu et al. (2006)[19] used ethanol as a solvent to prepare a silybin-phospholipid complex and employed the solvent evaporation method for the complex preparation.

Semalty et al. (2010)[20] used the solvent evaporation method to prepare aspirin-phospholipid complex and determined enhancement in the bioavailability of aspirin and thus retardation in the gastrointestinal toxicity.

Anhydrous co-solvent lyophilization method

The drug and phospholipids are dissolved in a solution of dimethyl sulfoxide containing glacial ethanoic acid. Then the transparent liquid is obtained by stirring this mixture. The clear liquid is further kept all night at condenser temperature for freeze-drying. The consequent complex mixture is subjected to nitrogen (as it is an inert gas, which is used to extend the shelf life and to ensure the quality of the final drug product) and then stored at 4 degrees Celsius.[1]

Shi et al. (2006)[21] employed an anhydrous co-solvent lyophilization method to auspiciously prepare a novel insulin-phospholipid complex.

Supercritical fluid process

In this process, the supercritical fluid of CO_2 is employed to dissolve the drug and lipid complex and then mixed into a nozzle mixing chamber.[16] In current years, the Supercritical Antisolvent precipitation (SAS) method which is one amongst the Supercritical Fluid (SCF) technology, is employed to form micronic and submicronic particles having a manageable size and size distribution. As compared to the general industrial comminution techniques like jet milling, liquid antisolvent precipitation, SAS utilizes very delicate conditions of temperature to obtain smaller particles based on the drug and process conditions.[3]

Li et al.(2008)[22] prepared phospholipids complexes of Puerarin (isoflavone) by employing two different SCF technologies viz. Gas Antisolvent (GAS) and Solution Enhanced Dispersion by Supercritical fluid (SEDS) which was associated with the SAS process.

Patents pertaining to pharmacosomes

The patents related to pharmacosomes are compiled in Table 1.

Table 1: Patents related to pharmacosomes.[23]

Research	Innovation	Patent number	Year of publication	Inventor(s)	Reference
Saponin phospholipid along with cosmeceutical and pharmaceutical compositions in them	High lipophilicity, improve bioavailability, pharmaceutical, dermatologic and cosmetic advantages	EPO283713	1992	Bombardelli, Patri	[24]
A herbal plant extract	Antioxidants, cure of circulatory problems	EP1214084	2004	Merizzi, Gianfranco	[25]
Thymosinß-4	For the treatment and repair of wound	2007/0015698	2007	Kleinman, Hynda K., Goldstein, Allan L.	[26]
Gingko biloba derivatives	Asthma and allergy treated	EP1813280	2007	Di pierro francesco	[27]
Olive extracted from leaves or fruits	Improved bioavailability	EP/1844785	2010	Giori, Andrea, Franceschi,	[28]

complexed with phospholipids				Federico	
Isoflavone characteristic	Solubility, color, taste and textural attributes improved	WO/2004/045541	2015	Prakash, Indra, Dubois, Grant E.	[29]
Cosmetic and dermatological composition	For the treatment of aging or photo damaged skin	EP1640041	2016	Jones, Stevan David, Gujraty	[30]

Evaluations of pharmacosomes

Shape and Surface morphology

Electron microscopy techniques like Scanning Electron microscopy (SEM) and Transmission Electron microscopy (TEM) are utilized to find out the overall shape and morphology of pharmacosomes. It allows the determination of particle size and distribution. SEM generates an image by recognizing reflected or knocked-off electrons while TEM generates an image using transmitted electrons (electrons that are specifically passing through the sample).[31] The purity of phospholipids, process variables such as speed of rotation, vacuum applied or techniques for the preparation of pharmacosomes may affect the shape and size of the pharmacosomes. Phospholipids of about 80% purity are used for desirable pharmacosomes products because low purity grades yield greasy products while high purity grades are vulnerable to oxidative degradation of the pharmacosomes products.[1]

Stability studies

FTIR spectroscopy (Fourier Transform Infrared Spectroscopy) and AFM (Atomic Force Microscopy) provides conformation of the formed complex in pharmacosomes formulations by comparing the spectrum of the complex with the spectrum of individual components (drug, phospholipids and solvent) and their mixture. To determine the stability of pharmacosomes, the comparison between the spectrum of the complex in solid form and the spectrum of its microdispersion in water after lyophilization, at different time intervals is examined.[6]

Solubility studies

In order to achieve desired aspects of absorption and bioavailability, the solubility considerations of the drug, phospholipids, their physical mixture and therefore the pharmacosomes are taken into account. The apparent partition coefficient can be calculated by the shake flask method in which two phases (aqueous and oil phases) are mutually saturated before use.

Method

Both the phases in equal volume viz aqueous phase as buffer solutions (having pH range from 2.0 to 7.4)and oily phase as 1- octanol containing phospholipids complex are mixed thoroughly in a separating funnel and equilibrated at 37ºC for 24h with constant shaking. After separating each phase, the concentration of the drug can be determined by an appropriate method like HPLC or UV spectrophotometry.[16]

Drug-excipient compatibility

Drug-excipient compatibility and feasible interactions can be detected with the help of differential scanning calorimetry (DSC).The terminating of an endothermic peak, the advent of a new peak, alteration in peak shape and its origin, peak temperature/ melting point and relative peak area or enthalpy-like facets helps in the detection of possible interactions.

Degree of crystallinity

The degree of crystallinity can be determined with the help of the X-ray powder diffraction analytical technique. The relative integrated intensity of the reflection peak is used to detect the degree of crystallinity.

***In vitro* and *in vivo* evaluations**

The *in vitro* and *in vivo* evaluations are conducted by taking into account the estimated therapeutic activity of the drug.[6] Different dissolution apparatuses are available to conduct dissolution studies because no single equipment is adequate for all drugs and dosage forms.[32] *In vitro* dissolution studies of drug-phosphatidylcholine complex and plain drug are conducted using media of various pH in standard dissolution apparatus (USP I basket type) to figure out the pH-dependent dissolution profile.[16] Factors associated with dissolution apparatus, dissolution fluid and process parameters are the several factors to be considered in the design of dissolution test.[33] The reverse dialysis bag technique can also be employed for *in vitro* determination of the release of the drug. In this method, the nanoparticulate systems are precisely poured into the release medium which is placed externally the dialysis sacs and the system is agitated constantly. After certain time intervals, samples of the release medium within dialysis sacs are withdrawn and studied at various time intervals for released drug content. An expansion in the membrane surface area to carry out the transport across the membrane and an increase in the efficiency due to less intricated steps are the major promising characteristics of this method.[14] Various evaluation parameters and instrument required are compiled in Table 2.

Table 2: Evaluation parameters and their techniques/instruments.

Parameters	Techniques/Instruments
Shape and Surface morphology	Electron microscopy techniques-Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM)
Stability studies	Fourier Transform Infrared Spectroscopy (FTIR spectroscopy)
Confirmation of complex formation	Atomic Force Microscopy (AFM), Fourier Transform Infrared Spectroscopy (FTIR spectroscopy)
Solubility studies	Shake flask method (partition coefficient determination)
Drug concentration	UV- Visible spectrophotometer, High Performance/Pressure Liquid Chromatography (HPLC)
Drug-excipient compatibility	Differential Scanning Calorimetry (DSC)
In vitro dissolution studies	Dissolution test apparatus, Reverse dialysis bag technique

Applications of pharmacosomes

Pharmacosomes may enhance drug dissolution, absorption, features a greater stability profile and shelf life as compared to liposomes.[6,14]

Increase lipophilicity of drug

Yue et al. (2012)[34] prepared geniposide pharmacosomes in tetrahydrofuran as a reaction mixture. Yue et al. and colleagues honed the formulated geniposide pharmacosomes and analyzed their characteristics with the help of response surface design. A higher concentration of geniposide was observed in the blood after administration as pharmacosomes because of an increase in the lipophilicity of the drug. The rate of permeation of pharmacosomes is enhanced due to ameliorating of membrane fluidity. A clear effect on vesicular interaction with biomembrane is observed due to the transition temperature of vesicles in the form of vesicles and micelles, which may lead to the improvement in the transfer of drug across the membrane.[14]

Khare (2004)[35] demonstrated the noticeable outcome of the cascade fusion system of pharmacosomes by applying heating and cooling phenomena on tissues at a relevant temperature, on drug targeting in an organism. Pharmacosomes helps in the enhancement of the therapeutic effects of various drugs such as cytarabine, bupranolol acid derivative, taxol, amoxicillin, pindolol derivative and dermatan sulfate, which let the novel drug delivery systems like pharmacosomes to propel forward in the field of nanoparticulate drug delivery systems. The evolution of novel ophthalmic dosage forms can also be achieved by the amphiphilic lipid vesicular systems like pharmacosomes. Modification of corneal drug transport and release profile can be accomplished when amphiphilic prodrug forms pharmacosomes diluted subsequently after coming in contact with tears.

Enhancement of dissolution of the drug

Raikhman et al. (1978)[36] demonstrated pharmacosomes as building particles that may efficiently conveyance the biologically active substances such as nucleic acids and proteins.

Semalty et al. (2010)[37] formulated pharmacosomes of aceclofenac and solubility of aceclofenac pharmacosomes was observed more than aceclofenac. The drug release profile at 4 hrs of dissolution study was found to be 68.69% and 79.78% for aceclofenac and aceclofenac pharmacosomes (1:1 ratio of drug and lipid) respectively.

Semalty et al. (2009)[38] formulated pharmacosomes of diclofenac and enhanced solubility was noticed. The diclofenac pharmacosomes solubility was found more i.e, 22.1 µg/ml in contrast to diclofenac i.e, 10.5 µg/ml. After 10 hours of the dissolution study, it was concluded that the cumulative drug release was ameliorated with pharmacosomes of diclofenac i.e, 87.8%as compared to diclofenac i.e, 60.4%.

Pharmacosomes enhance the dissolution and permeation of the drug. Several poorly soluble non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, aceclofenac, fenoprofen, diclofenac, were studied and enhanced dissolution was observed. The advent of pharmacosomes has significantly boosted the therapeutic performance of various drugs as mentioned in Table 3.[13]

Increase stability

Han et al. (2010)[39] formulated pharmacosomes of 20(S)-protopanaxadiol (Ppd) by thin-film dispersion method, and its stability was studied *in vitro*. The increase in encapsulation efficiency of the pharmacosomes was observed.

Selectivity for specific target cells

Zhang et al. (2010)[40] prepared as well as optimized the pharmacosomes of 3′,5′-dioctanoyl-5-fluoro-2′-deoxyuridine. The thin layer ultrasonic techniques were used to prepare pharmacosomes and the central composite design was used to optimize the pharmacosomes. *In vivo*, better targeting efficiency of pharmacosomes was observed due to enhanced drug potential to cross the blood-brain barrier.

Yi-Guang et al. (2005)[41] formulated the negatively charged nanometric acyclovir succinyl glyceryl monostearate pharmacosomes using tetrahydrofuran (THF) injection method. The *in vivo* study revealed that pharmacosomes of acyclovir were absorbed by the plasma proteins in the blood thus lowering the extent of hemolytic reaction.

Drugs used in the form of pharmacosomes are tabulated in Table 3.

Table 3: Drugs used in the form of pharmacosomes.

Drugs	Class	Result
Taxol	Plant alkaloids	Biological potency improved
Pindolol diglyceride	Non – selective beta-blocker	Plasma concentration reached 3 to 5 times
Cytarabine	Antimetabolite	Biological potency increased
Bupranolol hydrochloride	Non – selective beta-blocker	Augmented lymphatic transport and affects intraocular pressure
Amoxicillin	Aminopenicillins	Enhanced the safety of cells, cures peptic ulcer in male rats

CONCLUSIONS

Pharmacosomes play a significant role in enhancing drug absorption, dissolution ability and permeation of drug. Pharmacosomes provide safety, long-term stability, efficacy and better patient compliance. Pharmacosomes have various applications which include asthma and allergy treatment, antioxidants and topical skin treatment. The approaches have remarkably ameliorated the therapeutic capabilities of various drugs such astaxol, cytarabine, pindolol diglyceride, dermatan sulfate, amoxicillin and bupranolol hydrochloride. Pharmacosomes may be formulated into various dosage forms like pharmacosomes gels, dry powder pharmacosomes, or loaded with drugs or bioactive agents. Pharmacosomes may become a promising drug carrier for enhancing the performance of various drugs systematically and topically.

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