Review Article

Incorporated herbal drugs in novel drug delivery system

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Abstract

Herbal drugs are considered as the natural products. These natural products are being used since ancient times to cure various disease. Many herbal products demonstrated low therapeutic action due to their solubility problems which finally resulted in low bioavailability shows their extraordinary potential. To overcome all these problems, novel drug delivery systems in form of carriers are being developed for phytomedicines. The herbal novel drug delivery systems include drug delivery such as liposomes, nanoparticles, phytosomes, ethosomes, transferosomes, solid-lipid nanoparticles, microemulsion/ nanoemulsion, microsphere. Many herbal drugs have been incorporated into these systems for improvement of stability, bioavailability and reduction of toxicity. The present review is based on the incorporation of herbal drugs in novel drug delivery systems, formulation and their application in therapy.

Keywords: Novel drug delivery systems, nanocarriers, transferosomes, phytosomes

Introduction

In Ayurveda Indian medical science is based on herbs, herbal minerals, including metal preparations (Garg, 2010; Pandey and Pandey, 2014). Today 75-80% of the world population, rely on traditional medicine due to better acceptability, compatibility and less side effects (Yadav et al., 2011; Peter and Smet, 1997). WHO has set precise guidelines for the evaluation of the safety, efficacy and quality of these herbal medicines (Atmakuri and Dathi, 2010; WHO Technical Report Series, 1996). The use of allopathic medicines has led to toxicity and side effects, thus there is rapid increase in use of herbal drug (Kumar et al., 2006). These have been taken as the OTC drugs (Harish, 2001).

Advantages of herbal medicines (Devi et al., 2006; Dhiman et al., 2012)

- Cost effective
- More productive in curing certain conditions.
- Offer long lasting benefits.
- Increases therapeutic activity, reduces toxicities and side effects.
- Has complete accessibility.
- Has enhanced tolerance and gives more protection.
- Has very high potency and efficiency.

Disadvantages of herbal medicines (Devi et al., 2006; Dhiman et al., 2012)

- Herbal medicines are taken without prescription.
- Curing period is longer.
- Can cause allergic reaction in some cases.
- The government does not approve any kind of herbal medication. It is usually consumed upon the persons own risk.
- Herbal medicine does not cure rapid sickness and accidents.
- They have risk with self medication.
- Herbal medicines have complexity in standardization.

Standardisation of herbal drugs

Standardisation of the drug relates to the identity confirmation, quantity and purity determination and also detection of nature of the adulterant using various parameters (morphological, microscopical, physical, chemical and biological observation).

Various tests performed under different parameters are as follows (Nikam and Jadhav, 2012; Patwekar and Suryawanshi, 2015; Kumari and Kotrcha, 2016;

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Shulammithi and Sharanya, 2016):

(a). Organoleptic characterization by color, odor, taste, texture and fracture.

(b). Botanical tests comprises qualitative/ quantitative estimation

(c). Physical characterization

(d). Chemical characterization

(e). Biological charcterization can be carried out by microbial contamination (total variable aerobic count, determination of pathogens, alfatoxins content, etc.)

Novel drug delivery system

Novel drug delivery system (NDDS) refers to the formulation system and technologies for the transporting a pharmaceutical compound in the body as it is needed to safety achieve its desired therapeutic effects. Some drugs have the optimum concentration range within which the maximum benefits is derived and the concentration above or below this range can be toxic or can produce no therapeutic benefits. On the other side, the very slow progress in the efficacy of the treatment of severe diseases has suggested a growing need of a multidisciplinary approach to the deliver of therapeutics to targets in tissues (Reddy and Swarnalatha, 2010).

To overcome all these problems new ideas on controlling the pharmacokinetics, pharmacodynamics, immunogenicity, non-specific toxicity, biorecognition and efficacy of drugs were generated. This aspect is called as Drug delivery systems (DDS) that are based on approaches which combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology. To prevent harmful side-effects, to minimize drug degradation and loss and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Controlled and novel drug delivery that was the only a dream or at best a possibility is now a reality.

Conventional drug delivery involves serious limitations in terms of higher dosage required, lower effectiveness, toxicity and adverse side effects. NDDS are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession. These systems can be characterised as controlled release systems and targeted drug delivery system (Bhagwat and Vaidhya, 2013).

Therapeutic benefits

- Increased efficacy and site specific delivery of drug
- Decreased toxicity/ side effects
- Viable treatments for previously incurable diseases
- Potential for prophylactic applications
- Better patient compliance

Need of herbal novel drug delivery system

NDDS has been widely used in pharmaceutical industry. The use of NDDS application has been reported as success drug delivery system for various herbal drug or plant extract. Drug Delivery system like nanostructured materials can enhance the stability, absorption and therapeutic concentration of the drug within the target tissue which is very effective to long-term release of the drug at the target site. Therefore, the active compound present in the plant extract can be transferred effectively to the target site and also results in the increased efficacy. The therapeutic and phytochemical importance of herbal medicine has been built for the improvement of human health, but its broader application is restricted due the low bioavailability, the problems come with poor lipid-soluble compounds due to limited membrane permeability (Yadav et al., 2014).

Many herbal products demonstrated low therapeutic action due to their solubility problems which finally resulted in low bioavailability shows their extraordinary potential, but there is large number of population that depends on traditional medicinal practices in order to fulfill their basic health needs. Generally to overcome these limitations of absorption profile is of great importance. In the past few years, considerable attention has been focused on the development of NDDS for herbal drugs. The novel carriers should ideally fulfil two requirements. First, it should deliver the drug at a rate directed by the needs of the body over the period of treatment and second it should channel the active ingredient of herbal drug to the site of action. In phyto-formulation research developing nano sized dosage forms like nanocapsules and polymeric nanoparticles, liposomes, solid-lipid nanoparticles, phytosomes and nanoemlusions have a number of advantages for herbal drugs like it enhances solubility, bioavailability, stability, pharmacological activity, helps in improving tissues macrophages distribution, sustained delivery and also helps in the protection from toxicity, physical and chemical degradation etc. Thus the nano sized novel drug delivery systems of herbal drugs have a potential future, for enhancing the activity and overcoming problems associated with the plant medicines (Bonifiacio et al., 2014).

There are some previous studies that used nanotechnology to optimize the properties of plant extracts had been using solid-lipid nanoparticles drug carrier for epidermal targeting of podophyllotoxin and the observed results had showed a good epidermal targeting effect. Solid lipid

nanoparticles are suitable carrier for topical delivery of podophyllotoxin used the methanol extract of *Ocimum sanctum* loaded nanoparticles on cotton fabrics to study about the antimicrobial activity and the final result shows the excellent antimicrobial activity along with good wash durability. The drug delivery system such as nanotechnology is needed to deliver the active constituent more effectively to the targeted area (Goyal et al., 2011; Mukharjee et al., 2010).

Carriers for herbal drug delivery

Nanoparticles

Nanoparticles are sub-nanosized colloidal structures which are composed of synthetic or natural polymers and varying in size from 1-1000nm. The drug which is dissolved /entrapped/ encapsulated or attached to the matrix of nanoparticles. Depending upon the method of preparation, nanoparticles can be prepared in the form of nanospheres or nanocapsules. In Nanocapsules the drug is confined to a cavity surrounded by a unique polymer membrane, while the nanospheres are based on the matrix systems in which the drug is physically and uniformly dispersed. The nanocarriers are made of safe materials, including synthetic biodegradable polymers, lipids and polysaccharides (Vyas and Khar, 2002).

A nanocarrier is a nanomaterial used as a carrier for another substance, such as a drug. Commonly used nanocarriers that include micelles, polymers, carbon- based materials, liposomes and other substances. Nanocarriers are currently used in drug delivery and their unique characteristics results their potential use in chemotherapy. Nanocarriers include polymer conjugates polymeric nanoparticles, lipid based carriers, dendrimers, carbon nanotubes and gold nanoparticles (Mamillapalli et al., 2016).

Types of nanoparticles

- *Polymeric nanoparticles*: Alginate, Chitosan, Gelatin etc.
- *Metallic nanoparticles*: Gold, Silver, Zinc, Platinum, oxides, sulfides etc.
- *Magnetic nanoparticles*: Cobalt, Iron, Nickel etc.
- *Ceramic nanoparticles*: Silica 30, Titania, aluminia etc.

Advantages (Mohanraj and Chen, 2006; Gupta et al., 2010)

- Site specific action
- Encapsulation within nanoparticles can improve the solubility and pharmacokinetics of drugs.
- Promote the drugs through the biological barriers and increase the bioavailability of drugs.

Disadvantages (Mohanraj and Chen, 2006; Gupta et al., 2010)

- Stability problem.
- Nanoparticles results in the aggregation and agglomeration called os ostwald ripening
- High cost

Liposomes

Liposomes are nanoparticles comprising lipid bilayer membranes surrounding any aqueous interior, as depicted in figure 1. These are micro-particulate or colloidal carriers, usually 0.05-5.0 um in diameter which forms spontaneously when certain lipids are hydrated in aqueous media. The liposomes are spherical particles that encapsulate a fabrication of the solvent in which they freely diffuse or float into their interior. They can also have one or multiple concentric membranes (Mukharjee et al., 2015). Liposomes are constructed of polar lipids which are characterized by having a liophilic and hydrophilic group on the same molecules. Upon interaction with polar lipids self-assemble and form self-organized colloidal particles. Liposome enhances the therapeutic index of anti-cancer agents by increasing the drug concentration in the tumor cells and decreasing the exposure to normal cells (Ajazuddin and Saraf, 2010; Kulkarni, 2011).

Advantages (Chari et al., 2001; Wen et al., 2010; Verma et al., 2013)

- Liposomes are used for drug delivery systems because

Table 1. Some herbal drugs used as nanoparticles

Sr. No	Herbal drugs	Indication	Applications	References
1.	Berberine	Anti-neoplastic	Inhibits the growth of *H. pylori*	(Chang et al., 2011)
2.	Ginseng	Antioxidant	Improves stability and action	(Leonard et al., 2011)
3.	*Radix salvia* miltiorrhiza	Anti-anginal	Improve bioavailability	(Fu et al., 2008)

Table 2. Example of herbal drugs as liposomes

Sr. No	Herbal drugs	Indication	Applications	References
1.	Silymarin	Hepatoprotective	Shows improvement in permeation and stability of silymarin	(Samaligy et al., 2006)
2.	Ampelopsin	Anticancer	Shows increase in efficiency	(He et al., 2008)
3.	Garlicin	Lungs disease	Increases the efficiency	(Sun et al., 2007)

of its unique structural properties.

- Can deliver drugs through the cell membrane as it is hydrophilic as well as hydrophobic in nature.
- Acts as a carrier for small cytotoxic molecules and as vehicle for macromolecules as gene.
- Can produce sustained and controlled release of formulation and enhances the drug solubility.

Disadvantages (Chari et al., 2001; Wen et al., 2010; Verma et al., 2013)

- Require high production cost.
- Chances of leakage and fusion of encapsulated drugs.
- Phospholipid present in liposomes may undergo oxidation and hydrolysis reaction.

Phytosomes

Phytosomes is consists of two words i.e phyto and some, "phyto" is related to plant while "some" related to cell-like. Phytosome are produced when the standardised extract and active ingredients of an herb are attached to the phospholipids on a molecular level. The structure of phytosome contains the active ingredients of the herb which is surrounded by phospholipids, as shown in the figure 1. The phospholipid structure of phytosomes has one water-soluble head and two fat-soluble tails, because of this dual nature of solubility, the phospholipid act as an effective emulsifier that is one of the chief components of the membranes in our cells (Bhanu et al., 2013). Phytosomes are advanced forms of herbal products which absorbs and utilizes in good manner, which produces better results than conventional herbal extracts (Sharma and Bhujbale, 2018).

Advantages (Raju et al., 2011; Kareparamban et al., 2012)

- It enhances the absorption of lipid insoluble hydrophillic polar phytoconstituents through oral as well as topical route and increases the bioavailability.
- It ensures appreciable drug entrapment.
- Reduces the dose requirement.
- Have better stability profile because chemical bonds are formed between phosphatidycholine molecule and phytoconstituent.
- Site specifc drug delivery is possible.

Disadvantages (Kareparamban et al., 2012)

- Phytoconstituent is rapidly eliminated from phytosomes.
- The duration of action is short.

Transferosomes

The transferosome name means “carrying body”, and is derived from the Latin word 'transferee', is 'to carry across', and the Greek word 'soma', is for a 'body'. A Transferosome carrier is an artificial vesicle which resembles the natural cell vesicle as mentioned in Figure 1. Thus it is suitable for targeted and controlled drug delivery. Transferosomes are vesicular system consisting of phospholipids as the main ingredient with 10-25% surfactant (like sodium cholate) and 3-10% ethanol. The surfactants work as “edge activators,” conferring ultra-deformability on the structure of transferosome, which helps them to squeeze through pores in the stratum corneum (Jain et al., 2010). The hypothesized mechanism of action of transferosome is by

Table 3. Example of herbal drugs as phytosomes

S. No.	Herbal drugs	Indication	Applications	References
1.	Ginkgo biloba	Cardioprotective and antioxidant.	Stabilizes Reactive Oxygen Species (ROS).	(Naik and Panda, 2008)
2.	Green tea	Nutraceutical, Antioxidant and Anticancer	Increases absorption	(Bhattacharya, 2009)
3.	Hawthron	Cardio-protective and Anti-hypertensive	Increases absorption and therapeutic efficacy	(Bhattacharya, 2009)

Table 4. Examples of herbal drugs as transferosomes

S. No	Herbal drugs	Indication	Applications	References
1.	Capsaicin	Analgesic	Increases skin penetration	(Xiao et al., 2006)
2.	Catharanthus roseus	Anticancer	Increases permeability	(Mishra et al. 2017)
3.	Colchicine	Anti-gout	Reduces GIT side effect	(Singh et al., 2009)

acting as a drug carrier and penetration enhancer for stratum corneum (Sharma et al., 2014). By using phospholipids Transferosomes are fabricated that act as vesicle forming material, surfactant that is used for providing flexibility, alcohol used as a solvent and buffering agent as the Hydrating medium (Venkatesh et al., 2014).

Advantages (Bhokare et al., 2016; Chauhan and Tyagi, 2018)

- Can accommodate drug molecules with wide range of solubility as it has both hydrophilic and lipophilic property.
- They are biocompatible and biodegradable.
- They have high entrapment efficiency, in case of lipophilic drug near to 90%.
- For releasing their contents slowly and gradually they act as a depot.
- For both systemic as well as topical delivery of drug they are used.
- Protects the encapsulated drug from metabolic degradation.

Disadvantages (Bhokare et al., 2016; Chauhan and Tyagi, 2018)

- Chemically unstable because of their predeposition to oxidative degradation
- Purity of natural phospholipids is another criteria militating against of transferosomes as drug delivery vehicles
- They are expensive

Ethosomes

Ethosomes are vesicles that are composed of phospholipids and high concentration of ethanol, as seen in figure 1. In ethosomes the high concentration of ethanol enhances their permeability through the skin by fluidising the skin lipids. Carriers of ethosomes can penetrate through the skin deeply which leads to improve drug delivery into deeper layers of skin and also into blood circulation (Tiwari et al., 2016). For topical delivery of the drug ethosomes of Triptolide were prepared. The ethosomal formulation resulted an increase in the bioavailability due to increase in the accumulation and reduction in erthema more rapidly as compared to the other formulations (Touitou and Godin, 2000).

Advantages (Navneet and Arvind, 2010; Chaturvedi et al., 2011)

- They enhances the transdermal permeation of drug through skin.
- Large amounts or the diverse groups of drug are delivered.
- They are administered in semisolid form resulting in improved patient compliance.
- Increases efficacy and therapeutic index.
- Reduction in toxicity of the encapsulated agent.

Disadvantages (Navneet and Arvind, 2010; Chaturvedi et al., 2011)

- Results in the very low yield so it not be made economical.
- Limited to potent drugs.
- Skin irritation or dermatitis may occur.
- Releases the product during transfer from organic to water media.

Microsphere

Microspheres are spherical particles having size range from 1-1000 μm, in which the drug is uniformly dispersed in polymer matrix (Figure 1) and releases following the first order kinetics (Jesindha and Kumar, 2014). Various natural and synthetic polymers used for microsphere preparation include albumin, gelatine, modified starches, polypropylene, dextran, polylactic acid and polylactide-co-glycolide etc

Table 5. Example of herbal drugs as Ethosomes

S. No.	Herbal drugs	Indication	Applications	References
1.	*Tripteygium wilford*	Anti-inflammatory and Anti-tumour	Increases percutaneous permeability	(Jin-Guang et al., 2010)
2.	*Sophora alopecuerides*	Anticancer and Anti-endotoxic	Increases permeability	(Zhou et al., 2010)
3.	*Curcuma longa*	Anti-inflammatory	Improves bioavailability	(Chen et al., 2013)

Table 6. Example of herbal drugs as microspheres

S. No	Herbal drugs	Indication	Applications	References
1.	Camptothecin	Anti cancer	Reduces dose	(Gupta et al., 2015)
2.	Silymarin	Treatment of Liver disease	Sustained release	(Garg and Gupta, 2010)
3.	Ginsenosides	Anti cancer	Improves solubility and stability	(Lee and Kim, 2014)

(Sarangi and Padhai, 2018). The microspheres and micropellets have large surface-to-volume ratio. The interfacial properties of microspheres often dictate their activity. These microspheres can be administered by oral route or either by injection (Verma et al., 2007; Meena et al., 2011).

Advantages (Kadam and Survana, 2015; Mohan and Sujtha, 2014)

- Microspheres can be ingested or injected and also used for site specific and organ targeted drug delivery.
- There is the easy release of the drug from the formulation.
- The specific function of drugs can be protected, and also releases the drugs into an outer phase for a long period.

Disadvantages (Mohan and Sujtha, 2014; Sree Giri et al., 2014)

- Higher in cost
- The fate of polymer matrix is observed which shows effect on the environment.
- Reproducibilty is less
- Process condition like change in temperature, pH, solvent addition and evaporation or agitation may influence the stability of core particles to be encapsulated
- The degradation of products of the polymer matrix are produced in response to heat, hydrolysis, oxidation, solar radiation or biological agents

Micro/Nanoemulsion

Emulsion is a biphasic system in which one phase is dispersed in the other phase in the form of minute droplets ranging in diameter from 0.1 μm to 100 μm. In emulsion there are two phases as it is the biphasic system, one phase is always water or aqueous phase, and the other phase is oily liquid or non aqueous as shown in figure 1. Its appearance is always from translucent to transparent liquid. Emulsion can be classified into ordinary emulsion (0.1–100 μm), micro-emulsion (10– 100 nm), sub-microemulsion (100–600 nm), etc. Among them, the microemulsion is also called nanoemulsion, and the sub–microemulsion is also called lipid emulsion (Yapar, 2017). The drug can be sustained release in a long time because the drug is packed in the inner phase and kept in direct touch with the body and tissue fluid. The oily drugs or lipophilic drugs being made into o/w or o/w/o emulsion, the oil droplets are phagocytosed by the macrophage and get a high concentration in the liver, spleen, and kidney where the amount of the dissolved drug is very large. While water soluble drug is produced into W/O or W/O/W emulsion, it can be easily concentrated in the lymphatic system by intramuscular or subcutaneous injection (Leiberman et al., 1998). Nanoemulsions allows the transparent appearance and also the different rheological behaviour. Microemulsion is a system which consists of oil, water and amphiphile that is optically isotropic and thermodynamically stable liquid solution. They can be administered through transdermal, parentral, pulmonary and ocular route (Lawrencea and Reesb, 2000; Thapa and Khan, 2013).

Advantages (Chi et al., 2009; Nazzal et al., 2002)

- Increase the rate of absorption
- It helps to solubilize Lipophilic drug
- It increases the bioavailability
- Increase the stability and improve the penetrability of

Table 7. Example of herbal drugs as Microemulsion/ Nanoemulsion

S. No	Herbal drugs	Indication	Applications	References
1.	Docetaxel	Anti tumor	Improves residence time	(Zhao et al., 2010)
2.	Matrine	Anti-bacterial, Anti-inflammtory and Anti-viral	Sustained release	(Ruan et al., 2010)
3.	Rhubarb	Cathartic and Laxative	Increases activity	(Sun and yeh, 2005)

Table 8. Example of herbal drugs as solid-lipid nanoparticles

S. No	Herbal drugs	Indication	Applications	References
1.	Curcumin	Anti-tumour, Antioxidant, anti-inflammatory	Increases stability	(Jourghanian and Ghaffari, 2016)
2.	Hibiscus	Anti-depressant	Activity increases	(Vijayananda and Jyothi, 2018)
3.	Podophyllotoxin	Anti-viral, Anti cancer	Reduces adverse effect of podophyllotoxin	(Chen and Chang, 2006)

drug into skin and mucous.

Disadvantages (Chi et al., 2009; Nazzal et al., 2002)

- Large concentration of surfactant and co-surfactant is necessary for stabilizing the droplets of microemulsion/ nanoemulsion.
- Limited solubilizing capacity for high melting substances used in the system.
- Stability is influenced by environmental parameters such as temperature and pH.

Solid-Lipid Nanoparticles

Solid lipid nanoparticles are nanoparticles that ranges from 50-1000nm which are made from lipids that remains in a solid state at room and body temperature, as depicted in figure 1. Lipids which are used include mono-, di-, or triglycerides, lipid acids, and glyceride mixtures or waxes that are stabilized with the help of biocompatible surfactants (Pople and Singh, 2006; Ekambaram and Sathali, 2012). The formulations incorporating herbal drugs in solid lipid nanoparticles include mouthwashes like peppermint oil, gargles like thymol and inhalations like eucalyptus oil (Kumar and Rai, 2012).

Advantages (Ramteke et al., 2012; Andrew, 2009)

- Have better stability and ease of upgradibility to production scale
- Decrease in the danger of acute and chronic toxicity.
- Has very high long-term stability.
- Easy to manufacture than biopolymeric nanoparticles.
- Release kinetics of encapsulated compound have been controlled in a better form.
- Enhances bioavailability of entrapped bioactive substances.
- Chemical protection of liable incorporated compound.
- Lyophilization is possible.

Disadvantages (Ramteke et al., 2012; Andrew, 2009)

- Poor drug loading capacity.
- Drug expulsion after polymeric transition during storage.
- The dispersions of water content is relatively high i.e about 70-99.9%.
- Low capacity to load hydrophilic drugs.

Conclusion

Herbal medicine is now globally accepted as a valid alternative system of therapy in the form of pharmaceuticals, functional foods etc., and recognized, advocated by World Health Organization (WHO). There are number of plant constituents that has showed enhanced therapeutic effect at

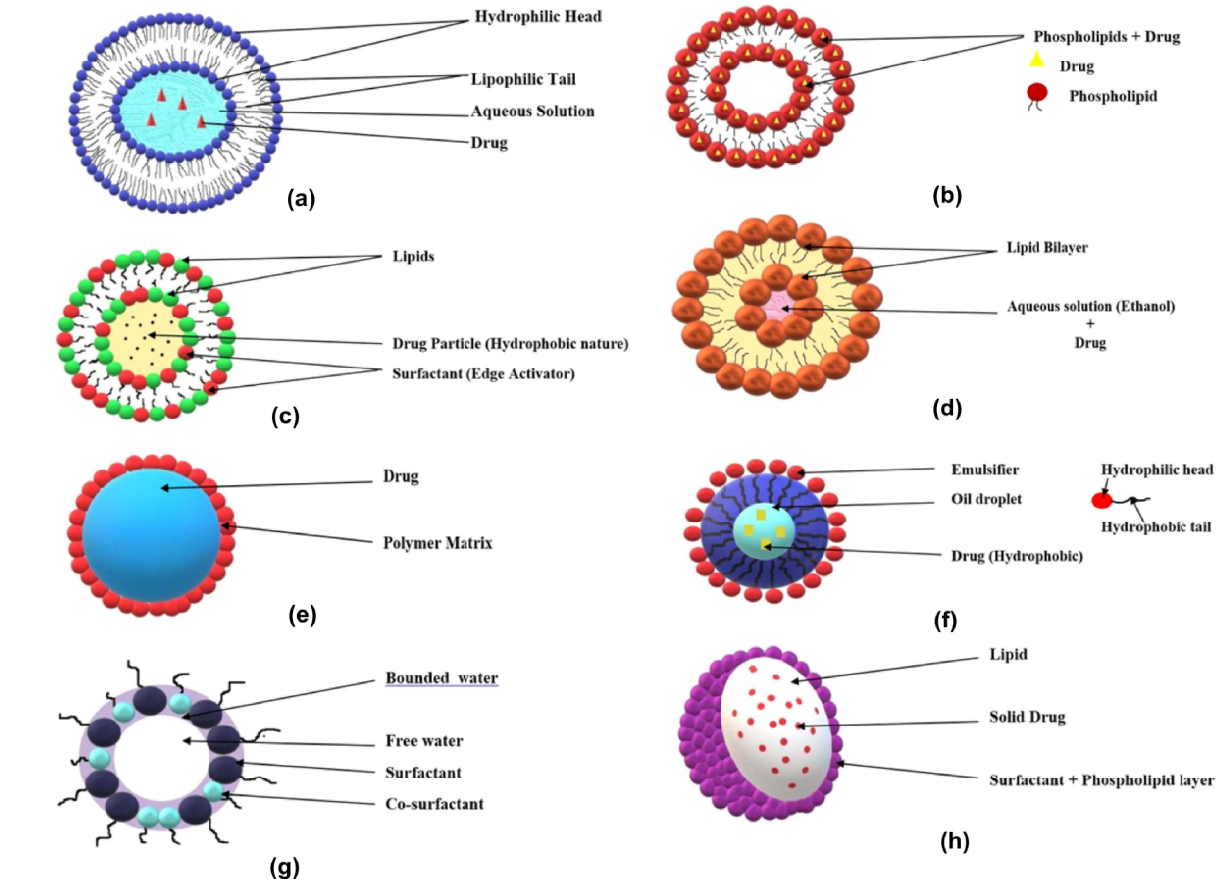

Figure 1. Schematic diagram of: (a) Liposomes (b) Phytosomes (c) Transferosomes (d) Ethosomes (e) Microsphere (f) Nanoemulsion (g) Microemulsion (h) Solid-lipid Nanoparticles

same or less dose when incorporated into novel drug delivery vesicles as compared to conventional plant extracts. Therefore, there is a great potential in development of the novel drug delivery system for valuable herbal drugs as they provides efficient and economical drug delivery. However, there are certain problems like poor bioavailability, low oral absorption, instability and unpredictable toxicity of herbal medicines results limitation in their use. In order to overcome such problems carriers including polymeric nanoparticles, liposomes, solid lipid nanoparticles, microemulsions, transferosome, Ethosomes, and microsphere shows potential utilization to deliver herbal medicines with better therapy.

Conflict of Interest

Not declared

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