A comprehensive review on various Novel Drug Delivery Systems and their challenges in designing of Herbal drug Formulations

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Abstract:

From the traditional time onwards it has been attempt of the physician and the apothecary to provide patients with the best possible forms of medicines so that recovery from disease is faster and complete of the Treatment regimen. The drugs are designed and delivered in a suitable desired form of formulations keeping in view of patient's safety, efficacy and acceptability

among other biological factors like bioavailability, to avoid drug incompatibility, drug resistance etc. With the continues progress in all spheres of science and technology in the segment of pharmaceutical field, the dosage forms have evolved from simple dosage form like mixtures and pills to highly sophisticated technology like intensive drug delivery systems, which are pharmaceutically known as Novel Drug Delivery Systems (NDDS). The present study elaborately review the various Novel delivery systems like Phytosome, Liposomes, Nanoparticles, Niosomes, Proniosomes, Self emulsifyed drug delivery systems (SEDDS), Transdermal Drug Delivery System, Microspheres, Ethosomes, Transfereosomes, , Self nano emulsifyed drug delivery systems (SNEDDSs), Dendrimers and its applications in design and delivery of herbal formulations to improve the safety and efficacy .Also the review elaborated the retrospective research on novel drug formulations with herbs in various segments like Phytosome, Liposomes, Nanoparticles, Niosomes, Proniosomes, Transdermal Drug Delivery System, Microspheres, Ethosomes etc.,

Keywords: Herbo Formulations, Phytosome, Nanoparticles, Niosomes, Proniosomes, Liposomes

Introduction

From the traditional time onwards it has been attempt of the physician and the apothecary to provide patients with the best possible dosage forms of medicines so that recovery from disease is faster and complete of the Treatment regimen. The drugs are designed and delivered in a suitable desired forms of formulations keeping in view of patient's safety, efficacy and acceptability among other factors like bioavailability, to avoid drug incompatibility, drug resistance etc. With the continues progress in all spheres of science and technology, the dosage forms have evolved from simple dosage form like mixtures and pills to highly sophisticated technology like intensive drug delivery systems, which are pharmaceutically known as Novel Based Drug Delivery Systems (NDDS) [1]

In the past scenario, desirable attention given on the design and development of novel based drug delivery systems in the area of herbo drugs. [2] Herbo drugs are currently more popular in the recent world due to their enormous application to treat variety of diseases with high safety profile, minimal toxic effects and improvement of therapeutic efficacy when compare to modern medicine. However, some limitations of herbal extracts/herbal plant actives with respect to pharmacology aspects like instability in highly acidic pH, liver metabolism (first pass metabolism) etc. has led to drug levels below the therapeutic concentration in the blood level which results in minimal or very poor range of therapeutic effects in the body. As well as the Pharmaceutical aspects like stability of dosage and environmental instability as a challenges in herbal formulations. To overcome the above issues with the incorporation of novel drug delivery technology to herbal or plant actives minimizes the drug degradation, drug instability or pre systemic metabolism and serious side effects by accumulation of drugs to the non targeted

areas and improves the ease of administration especially in the paediatric and geriatric patients. [3]

Conventional based dosage forms are unable to meet the standard prerequisites of novel based carriers like ability to deliver of the drug at a rate directed by the necessity of the body as well as to the channel, the active entity of herbal drug at the required site of action

For improved Pharmacology activity like bioavailability, natural products must have a good balance between the hydrophilicity (for dissolving into the gastrointestinal fluids) and lipophilicity (to cross lipidic biological membranes). Many phyto constituents like polyphenolics have good water solubility, but are, nevertheless, poor absorption [4] Because of their multiple-ring larger molecules and this cannot be absorbed by simple process of diffusion, or due to their improper miscibility of oil and other lipids, which is severe limits their ability to cross the lipiodal –biological membranes of the enterocytes which is present in small intestine. [5]

Different drug delivery systems

1. Phytosome

The flavonoid and terpenoid constituents of phyto extracts have better binding capacity to phosphatidylcholine. Phytosomes to be derived by the reaction between stoichiometric quantity of the phospholipid (phosphatidylcholine) and the extract of standardized or polyphenolic derivatives (like flavonoids) in a non polar systemof solvent. [6]

Phosphatidylcholine is a bifunctional nature of compound, in which the phosphatidyl moiety to be on lipophilic and choline moiety as hydrophilic. Mechanism behind this the choline head of the phosphatidylcholine molecule which will binds to the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bounded material. The phytoconstituents which will produce a lipid compatible molecular complex adhere with phospholipids, and this is called as phyto-phospholipid complexation. Molecules are adhered through chemical bonds to the polar choline head of the phospholipids, and it can be studied special mechanism of spectroscopic studies. [7]

Chemical analysis study demonstrates phytosome is a combination of flavonoid molecule linked with at least one phosphatidylcholine molecule. In the form of little micro sphere based structure. The phytosome technology produces a little microspere like structure, in that the plant extracts or its active phytoconstituents is protected from the destruction of biological factors like gastric secretions and gut bacteria which results to gastro protective activity by the mechanism of phosphatidylcholine. [8]

Method of Preparation of phytosome

Phytosomes are novel method of complexation process which are derived by reacting from two to three moles but preferably with equal portion of natural or synthetic phospholipid, (Ex: phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine) with equal portion of flavanoid (Ex:flavolignanans), either alone or in combination of natural form of mixture in

suitable aprotic solvent (Ex:dioxane or acetone), in which complex to be isolated by precipitation based scientific mechanism with non polar solvent (Ex: aliphatic hydrocarbons) or lyophilization or by spray dried technology. In complexation process of phytosomes, the ratio between these two moieties is in the range start from 0.5 to 2.0 moles. The optimised ratio of phytosome combination of phospholipid to flavonoids is 1:1 from the Excising Research studies. [9]

In the phytosome based herbal formulations, phospholipids are selected from the group consisting of soya lecithin, from bovine or swine brain or dermis, phosphatidylcholine, phosphatidylethanolamine, phosphatidyiserine in which acyl group may be same or different and preferably derived from lipid serious like palmitic, stearic, oleic and linoleic acid. Selection of flavonoids are done from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3- rhamnoside, hyperoside, vitexine, diosmine, 3- rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolinglucoside, ginkgonetine, isoginkgonetine and bilobetine. Some liposomal based drug complex operates in the medium of the water or suitable pH dependent buffer solutions, where as phytosome formulations operate with the solvent having a reduced dielectric constant. Starting materials like flavonoids are insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming phytosome complex. This physiochemical property change is due to the formation and confirmation of a true stable phytosome based complex. [10]

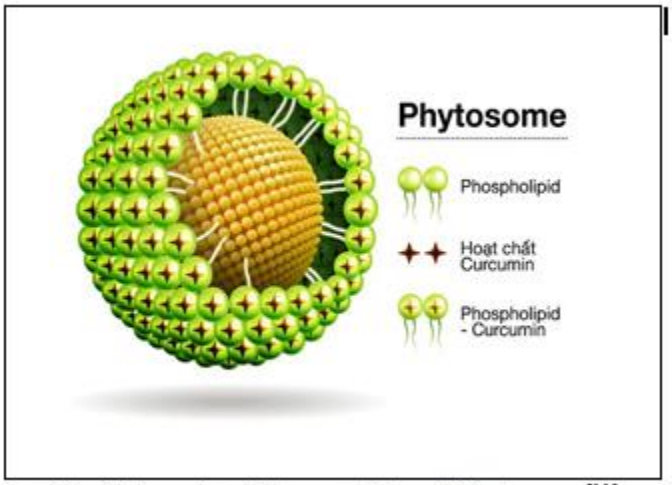

Fig: 1 Example of Curcumin based Phytosome [11]

Advantages of phytosomes

Phytosomes have the following advantages [12] [13] [14]

1. Improves the absorption of lipid insoluble polar phytoconstituents by oral route, topical/dermal shows improving bioavailability of herbal constituents and its formulations.

2. It enhances the absorption of active constituent(s) & reduces the frequency of dose requirements.

3. Phosphatidylcholine used in phytosome formulations, besides acting as a lipaidal carrier also in addition acts as a hepatoprotectiveagent, with synergistic effect.

4. The formation of Chemical bonds between phosphatidylcholine and phytoconstituent, so the stability of phytosome based formulations shows better formulation stability profile.

2. Liposomes

Liposomes are colloidal drug carriers or micro-particulate usually in the diameter of 0.05-5.0 μm which forms spontaneous process when certain lipids are hydrated in aqueous media. [15] These liposomes are spherical like particles that encapsulate a fraction of the solvent, in which they freely diffuse or float into their interior. They can have one, several or multiple concentric membranes. Liposomes are constructed of polar lipids which are characterized by having a lipophilic and hydrophilic group on the same molecules. Upon interaction with water, polar lipid molecules which will form self-assemble or self-organized colloidal shape Liposome particles. [16]

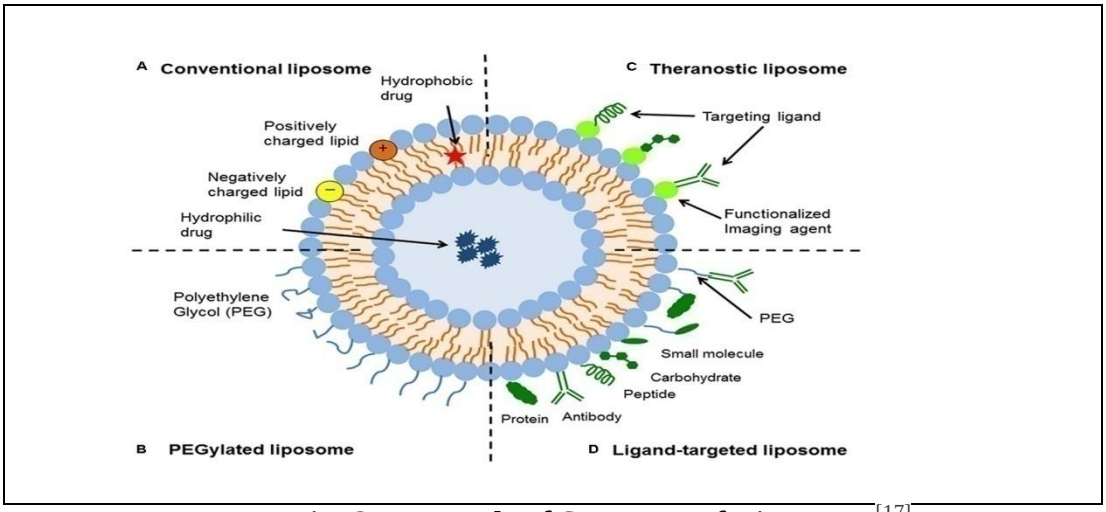

Fig: 2: Example of Structure of Liposome [17]

3. Nanoparticles

Nanoparticles are superior & efficacious delivery systems for the delivery of both hydrophilic and hydrophobic drug moieties. Nanoparticles are the submicron size particles having size range 10 to 1000 nm. [18] The major goal behind designing nanoparticle as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to

achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen. [19]

4. Niosomes

Niosomes are vesicles of multilamellar formed between non-ionic surfactants of the alkyl or dialkylpolyglycerol ether and cholesterol. [20] Niosomes are different from liposomes and niosomes have certain advantages compare to liposomes. Liposomes have certain issues like expensive, their ingredients like phospholipids which are chemically unstable due to their predisposition to oxidative degradation; they need special precautions like storage and Proper handling methods. A Niosomes formulation to be overcomes the above liposome based design issues. [21]

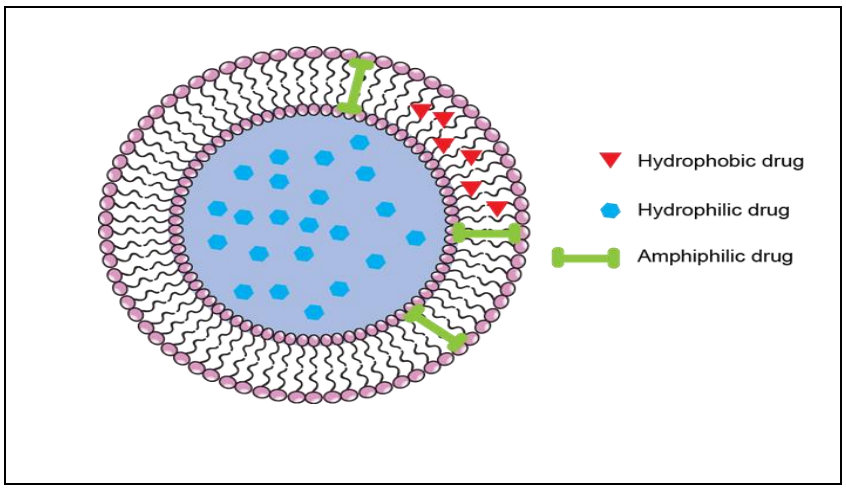

Fig: 3 Example of Structure of Niosomes [22]

5. Proniosomes

Proniosome gel have new generation when compare to niosome, which can be utilized for various drug delivery applications like delivery of actives at desired site of action. [23] Proniosomal are the drug formulations, which on *in situ* hydration with water available from the skin, then the pronisomes are changed into niosomes. [24]

6. Transdermal Drug Delivery System (TDDS)

TDDS has been an increased interest in the drug delivery via the skin for both local (topical delivery) as well as for systemic delivery of herbal based active constitutes. [25] However, they have limitation with certain kinds of drugs only due various factors related to skin biological barriers. [26] Transdermal delivery system provides the advantage of controlled delivery of drug with, enhanced bioavailability, minimization of side effects and easy of application. Transdermal formulations of boswellic acid and curcumins are certain examples for this TDDS category. [27]

7. Microspheres

Microspheres are discrete spherical particles ranging from 1 to 50 microns. Micro particulate drug delivery systems are considered and accepted as a reliable one to deliver the drug at the target site with specifically, to maintain the desired drug concentration in the aspect of therapeutic purpose. Micro encapsulation is a useful method, which increases the duration of drug effect significantly and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained during the therapeutic regimen. [28]

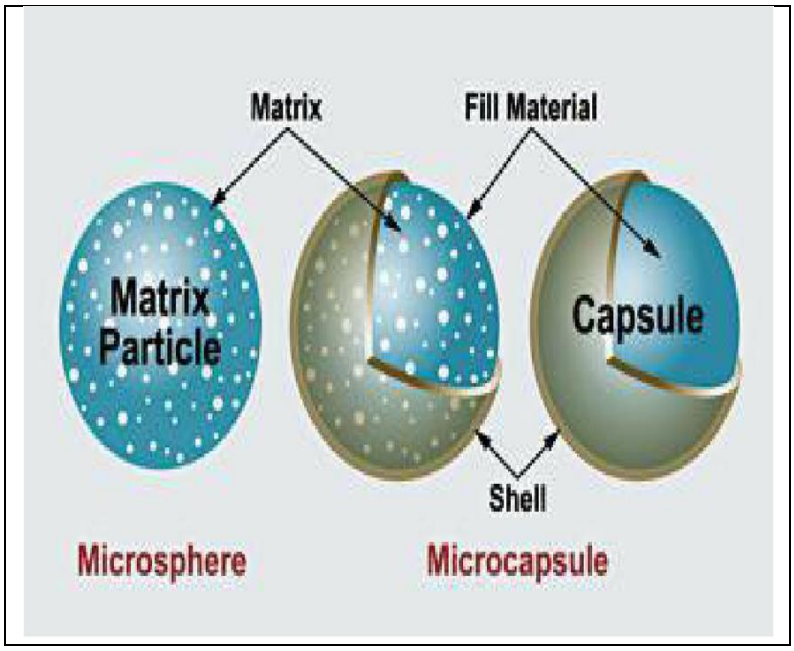

Fig: 4 Example of Structure of Microspheres [29]

8. Ethosomes

Newer advancements in the patch technology have lead to the development of ethosomal patch, which consists of drug in the form of ethosomes. Ethosomal systems are formulated with the combination of soyaphosphatidylcholine, ethanol and Water. They will form multilamellar vesicles and have a high entrapment efficient for molecules of various lipophilicities. The elastic vesicles and transferosomes have also been used as drug carriers for a range of small phyto molecules, peptides, proteins and vaccines. [30]

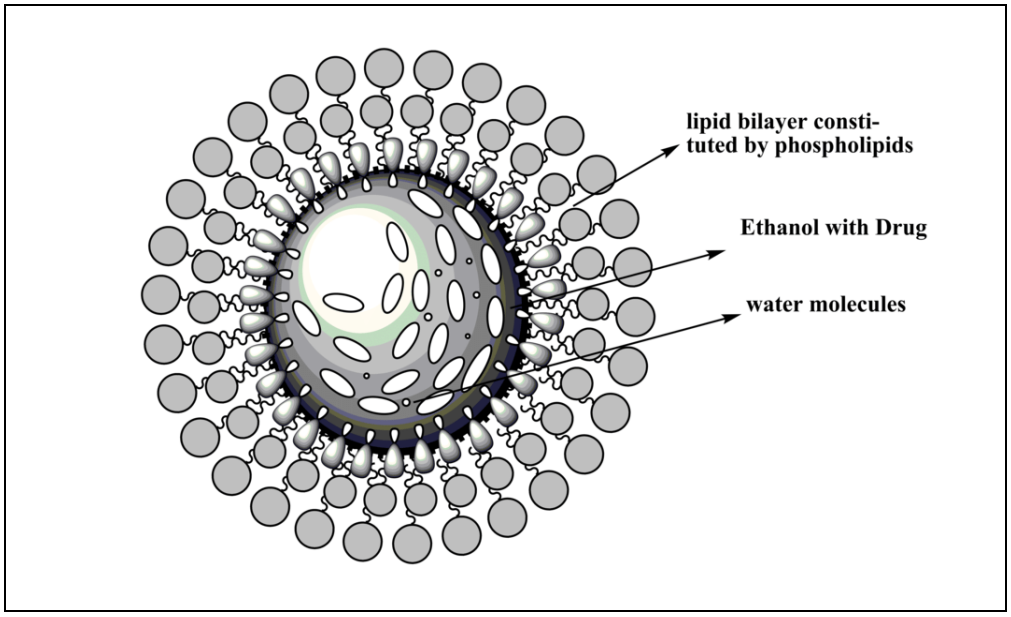

Fig: 5 Example of Structure of Ethosomes

9. Transfereosomes

Transfersomes are specially optimized particles or vesicles that can respond to an external stress by rapid and energetically inexpensive shape transformations. [31] The development of novel approaches like transferosomes have immensely contributed in resolving issues faced by transdermal drug delivery such as unable to transport larger molecules, penetration through the stratum corneum is the rate limiting step, physicochemical properties of drugs hinder their own transport through skin. These elastic vesicles can squeeze themselves through skin pores many times smaller than their own size and can transport larger phyto molecules. [32]

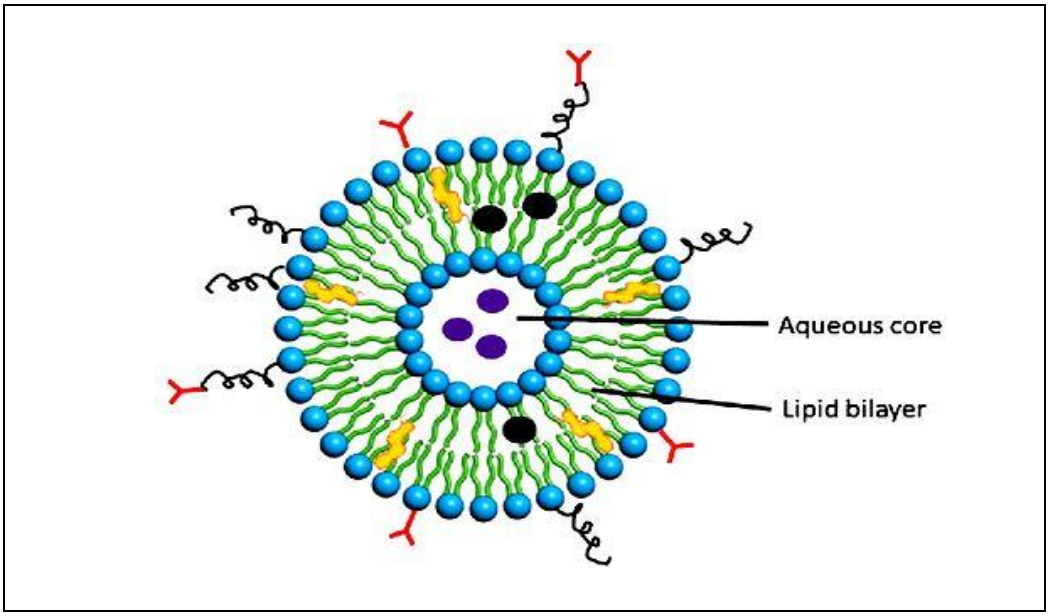

Fig: 6 Example of Structure of Transfereosomes [33]

10. Self emulsified drug delivery systems (SEDDS)

Self-emulsified drug delivery system (SEDDS) is a strategy that has drawn wide research interest, basically due to its distinct capacity to solubilise and prolong the bioavailability of hydrophobic drugs. [34] The presence of oil makes SEDDS unique and distinguishes them from ordinary surfactant dispersions of drugs. SEDDS are isotropic combination of drug, lipid/oil, co-solvents and surfactants. [35] On dilution by an aqueous phase which will form fine stable oil-in-water (o/w) emulsions or fine lipid droplets which is the characteristic feature of these systems. When such formulation is released into the lumen of the GIT, it disperses to form a fine emulsion generally o/w emulsion. SEDDS are generally formulated with triglyceride oils and ethoxylated non-ionic surfactants. In general, the concentration of surfactant is greater than 25% in the formulation. The size of droplets ranges approximately less than 100 nm. [36]

Advantages of SEDDS

SEDDS possess the following advantages among others

1. Improvement and reduction in the variability of GI absorption of poorly water soluble as well as lipophilic drugs.

2.Possible reduction in, or elimination of, a number of development and processing steps (e.g., salt selection or identification of a stable crystalline form of the drug, coating, taste masking, and reduced need for containment and clean-up requirements during manufacture of Highly-potent or cytotoxic drug products).

3. Food does not interfere with the absorption of drug by use of such SEDDS systems.

4. Relative ease of manufacture using readily available equipments.

5. The dose ranging from less than 25 mg to greater than 2000 mg can be administered by these drug delivery systems.

6. These systems enhance oral bioavailability due to bypass of hepatic metabolisms and delivers drug without hepatic degradations

7. Inhibition of p-glycoprotein mediated drug efflux and pre-absorptive metabolism by gut
Membrane bound cytochrome enzyme.

8. Protection of sensitive drug substances

9. High drug payloads.

10. Liquid or solid dosage forms.

11. Reduced energy requirement for emulsion formation.

12. Control of delivery profile

13. Promotion of lymphatic drug transport.

14. They enhance absorption of lipophilic drugs by stimulating pancreatic and biliary secretions and by prolongation of gastric residence time

Disadvantages of SEDDS

Lacuna of good predicative *invitro* models for assessment of the formulations.

1. Traditional dissolution methods do not work, because formulations are independent on Digestion prior to release of the drug.

2. *In vitro* model needs further development and validations.

3. Different lipid based prototype formulations needs to be developed and tested *invivo model*.

4. May irritate GIT due to chemical instabilities of drugs and high surfactant concentrations in formulations (approximately30-60%)

5. Volatile co solvents may migrate into the shells of soft or hard gelatine capsules which results in precipitation of the lipophilic drugs.

6. The precipitation tendency of the drug on dilution may be higher because of the dilution effect of the hydrophilic solvent.

7. Formulations containing several components become more challenging to validation

11. Self nano emulsifyed drug delivery systems (SNEDDSs)

Self-nano emulsifyed drug delivery systems are isotropic mixtures of oil, surfactant, Co-surfactant and drug that will form fine oil-in-water nanoemulsion, when introduced into aqueous

phases under gentle agitation process. SNEDDS spread immediately in the gastrointestinal segment, and digestive motility of the stomach and in intestine which will provide the agitation necessary for self-emulsification typically produce emulsions with turbid appearance, and droplet size in the range between 200 nm to 5 μm, while self micro emulsifying drug delivery systems forms translucent micro-emulsions less than 200 nm of droplet size. However, self nano-emulsifying drug delivery systems produce clear or transparent emulsion with droplets size less than 100 nm. [37]

Successful formulation of SNEDDS depends on the thorough understanding of the spontaneous nano-emulsification process and also on the physicochemical and biological properties of the components used for the fabrication of SNEDDS. The factors influencing the phenomenon of self nano-emulsification are:

1. The physicochemical nature and concentration of oily phase, surfactant and co-emulsifier
Or co surfactant or solubilizer (if included)

2. The ratio of the components, especially oil-surfactant ratio

3. The temperature and pH of the aqueous phase where nano-emulsification would occur

4. Physicochemical properties of the drug, such as hydrophilicity / lipophilicity, pKa and Polarity.

These factors should receive attention while formulating SNEDDS. In addition, the acceptability of the SNEDDS components for the desired route of administration is also very important while formulating SNEDDS

Advantages of SNEDDS

1. Protection of sensitive drug substances.

2. Selective targeting of drug(s) toward specific absorption window in GIT.

3. Enhanced oral bioavailability enabling reduction in dose level.

4. High drug payloads.

5. It can be easily stored since it belongs to a thermodynamics stable system.

6. Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GIT, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall in conventional dosages.

7. As compared with oily solutions, they provide a large interfacial area for partitioning of the drug between oil and water

Disadvantages of SNEDDS

1. Lacuna of good predicative *invitro* models for assessment of the formulations because traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug. To mimic this, an *in vitro* model simulating the digestive processes of the duodenum has been developed.

2. Need different lipid based prototype formulations to be developed and tested *invivo* in a suitable animal model

12. Dendrimers

Dendrimers are structural design of spheroid or globular based nanostructure with polymer based materials. These are more branches, monodisperse nanoparticles that bind the drug at the surface or entrap within their inner cores. There is a unique property of branching around the inner space that has huge effect on chemical and physical properties. Preparations of these particles are among any one of method like divergent or convergent. The size grows linearly depended on the number of surface groups. They have very low poly disparity index and dimension range from 1-10 nm. The performance and individual properties of dendrimers to be variance due to their linear complements**.** [38]

Advantages of Dendrimers [39]

1. Direct Medication to the affected part inside a patient's body.

2. Dendrimers applications in targeting solid tumours because of the due to increased level of permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumour cases (enhanced permeation rate). This is used to reduction in amount of drug used via targeted delivery (attaching site specific ligands at surface or magnetic guidance) and thus reduction in systemic toxicity.

3. Sustained release of drugs through this system.

4. Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation.

5. Bypassing the gastric medium and hence the eschewing the variation because of the effect of gastric secretions.

6.Therapeutic efficacy improvement , side effects reduction, decreased clearance of drug via altered distribution of drug in organs at site of localization and transportation because of the due to controlled and sustained release of the drug.

7. High drug loading Possibilities.

8. Preserves the drug activity: as drugs, can be incorporated into the systems without any chemical reaction.

At present, there are 3 different methods for dendrimers in drug delivery:

1. The drug is adhered to the periphery of the dendrimer to form dendrimerprodrugs,
2. The drug is coordinated to the outer functional groups via ionic interactions mechanisms.
3. Unimolecular micelle by encapsulating a pharmaceutical drug through the formation of a dendrimer drug (i.e., host–guest) supramolecular structure assembly. The novel approach is of interest for so many reasons and provides an opportunity to pharmacologically encapsulate active phyto compounds and also to study the supramolecular assembly's formation.
4. Dendrimers have several unique properties that make them a good nanoparticle based platform for antimicrobial drug delivery systems. [40]

Mechanism of Drug Delivery through Dendrimers

The 3D structure and many functional surface groups, drug molecules may be loaded both in the interior of the dendrimers as well as attached to the surface groups (as shown in the figure). The function of Dendrimers as drug carriers either by encapsulating drug moiety within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug) as shown in the fig 7.

There are broadly two mechanisms for drug delivery.

1. *Invivo* degradation of drug dendrimer conjugate (covalent bonding of drug to dendrimer), which depends on presence of suitable enzymes or an environment capable of degrading covalent bonds.

2. By releasing the drug due to changes in physical environment like pH, temperature etc. This approach is independent of the external factors and it will happen in cavities of the core (endo-receptor) or outer shell of receptor (exo-receptor)

There are two types of delivery; one is to a cell specific and other as a controlled release from a depot (which may be present in circulation or imbedded in some suitable tissue). Psivid as biosilicon which will allows drug molecules to be held in Nano-sized particles that release a tiny pulse of drug as the biosilicon dissolves. Biosilicon shows resistance to degradation in acid environment. A dendrimer of higher generations consists of shell and it consists of a central core and alternating two layers of monomers around the shell. Amines constitute the central core which may sometimes be replaced by alternative of sugar. All core molecules which will have multiple and identical reaction site. Amine is the simple core molecule which will present with three functional sites. The surface of all full generations consists of multiple amines, while the surface of the half generations consists of multiple acids. These two different amine and acid kinds of surfaces provide the means of attachment of multiple different functional components for the effective delivery. [41]

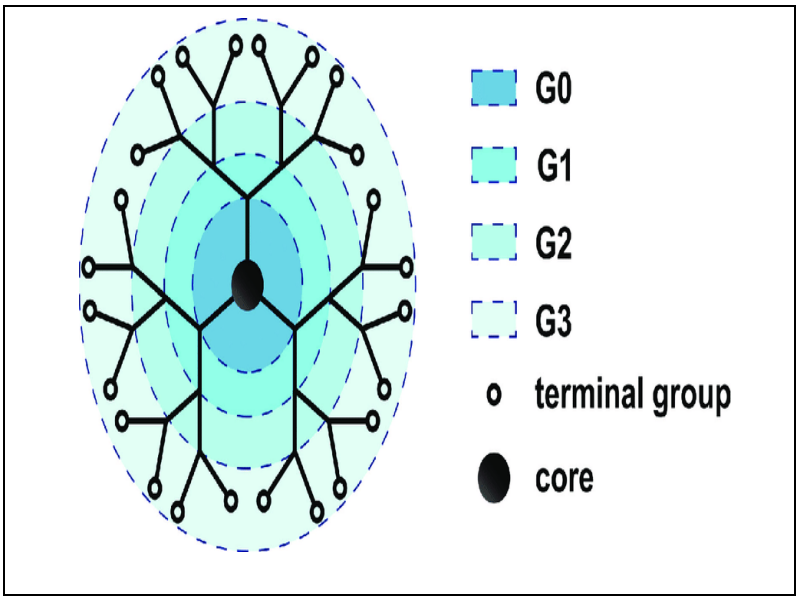

Fig: 7 Examples of Structures of Dendrimers [42]

Applications of Different drug delivery systems

1. APPLICATIONS OF PHYTOSOMES

Majority of phytosomal studies are focused to Silybummarianum, it contains premier liver-protectant flavonoid moiety. The milk thistle plant of fruit part (*S. marianum* Family *Steraceae*) contains flavonoids with the pharmacology for hepatoprotective effects. Silymarin

has positive effects in treating liver diseases which includes hepatitis, cirrhosis, fatty infiltration of the liver (chemical and alcohol induced fatty liver) and inflammation of the bile duct. The antioxidant capacity of silymarin substantially boosts the liver's resistance to toxic insults. Silymarin primarily contains three flavonoids of the flavonol subclass (having a fully saturated C-ring). Silybin predominates, followed by silydianin and silychristin. Silybin is actually a flavonolignan, probably produced within the plant by the combination of a flavonol with a coniferyl alcohol. It is now known that silybin is the most potent of the three Silybin protects the organ of liver by glutathione usage in the parenchymal cells, and this cells helps repair and replace cell membranes. These phytoconstituents to produce the synergistic effect of sparing liver cells from destruction. In its native form within the milk thistle fruit, silybin occurs primarily complexes with sugars, as a flavonyl glycoside or flavonolignan. Silybin has been extensively researched and found to have impressive bioactivity, albeit limited by poor bioavailability.

Mukerjee *et al.,* (2008) studied novel based hesperetin phytosome by complex formation between hesperetin and hydrogenated phosphatidyl choline. Further it was evaluated for antioxidant potential in CCl4 intoxicated rats for pharmacokinetic studies. These results revealed that sustained release property for over 24 h and improved antioxidant Property. Pharmacokinetic study showed that the phytosome dependent formulation has high level of relative bioavailability when compare to the than that of parent molecule with the condition of same dose level. [43]

Yanyu *et al.,* (2006) developed the silymarin phytosome and revealed its pharmacokinetic properties in the *invivo* animal model of rats. The bioavailability of silybin in rats showed increased remarkably after the oral form of prepared silybinphospholipid complex because of the impressive improvement of the lipophilic property of silybin-phospholipid complex as well as the effect of silybin. [44]

Busby *et al.,* (2002) studied that the use of a silymarin phytosome showed a better feto protectant activity in ethanol-induced behavioural deficits when compare to the uncomplexed silymarin. [45]

Bombardelli *et al.,* (1991) revealed Silymarin phytosomes,in that Silymarin (A standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) with phospholipids complex for higher specific activity and a longer lasting action when compare to single components, with respect to % reduction of odema, inhibition effect of myeloperoxidase activity, antioxidant and free radical scavenging properties etc.

Ravarotto *et al.,* (2004) reported silymarin phytosome revealed better anti hepato toxic activity than silymarin alone and also gives protection against the toxic effects of aflatoxin B1 on performance of broiler chicks. [46]

Maiti*et al.,* (2005) developed the quercetin–phospholipids complex by a simple, precise as well as reproducible method for better therapeutic efficacy in the rat for liver injury induced by using carbon tetrachloride as a model. [47]

Moscarella *et al.*, (1993) investigated in one of the case study with 232 patients in chronic hepatitis (viral, alcohol or drug induced) treated by silybin phytosome with the level at a dose of 120 mg by twice daily or thrice daily for 120 days duration and finally the, liver function returned to normal faster in patients treated with silybin phytosome when compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo). [48]

Barzaghi *et al.*, (1990) conducted a human based study assess the absorption of silybin when directly bound to phosphatadylcholine. Plasma silybin levels were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle. The results showed in healthy volunteers that the absorption of silybin from silybin phytosome formulation is approximately 7 times higher when compared to the absorption of silybin from regular milk thistle extract (70-80 % silymarin content).[49]

La Grange L *et al.*, (1999) studied on silymarin phytosome, which containing a standardized extract from the seeds of *S. marianum*, administered orally and found that it could protect the fetus from maternally ingested ethanol. [50]

Grape seed phytosome contains oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, Vitisvinifera) of varying molecular size, complexes with phospholipids. The main properties of procyanidin flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological antioxidant defences of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby produced marked protection for the cardiovascular system. [51]

The Extract of Green tea generally contains a totally standardized polyphenolic fraction obtained from leaves of green tea (*Theasinensis*) and mainly characterized by the presence of epigallocatechin 3-O-gallate, as the key phyto compound. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in majority of chronic-degenerative diseases such as cancer and atherosclerosis etc. Green tea has long term beneficial activities like antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardio-protective, antibacterial and anticariogenic effects. Despite such potential actions polyphenols of green tea have very poor oral bioavailability from conventional extracts. The complexation of polyphenols of green tea with phospholipids strongly improves their poor oral bioavailability. A study on oral absorption of phytosomal preparations was performed along with non complexed green tea extract in healthy human volunteers with the study period of 6 hours. The plasma concentration of total flavonoids was more than doubled in phytosomal versus the nonphytosomal extract. The Antioxidant capacity was measured as TRAP (Total Radical-trapping Antioxidant Parameter). The peak antioxidant effect was a 20% improvement and the study revealed that the phytosome formulation had about double the total antioxidant effect. [52] [53]

2. Applications of Nano emulsions for phytopharmaceuticals:

The effect of nanoemulsion on intestinal absorption of colchicines was demonstrated *in vivo* based Experiments. Colchicine nanoemulsion was prepared with isopropyl myristate,

eugenol, Tween 80, ethanol and water, with eugenol being the oil phase in the nano based formulation. Result obtained indicated that the intestinal absorption of colchicines was significantly enhanced by the Nano emulsified formulation. [54]

Genistein has been shown to possess anticancer activities in different experimental systems, yet the same effects could not be translated in the clinical setting due to its poor bioavailability. Researcher have tried various nano approaches including incorporation of genistein in topically derived nanoemulsion composed of egg lecithin, medium chain triglycerides/ octyldodecanol with water by spontaneous emulsification process with improved activity.[55]

O/w nanoemulsions has also showed increased anti-inflammatory activity in curcumin based formulation. [56]

Herbo formulations

Table 1 Herbo Liposomal Drug Delivery System (HLDDS)

Sr. no.	**Plant / Constituents**	**Biological activity**	**Application of Liposomal technology**
1	Ampelopsin	Anti cancer	Improved therapeutic outcomes
2	*Atractylodes macrocephala*	Digestive disorders and anti cancer	Enhancement of solubility and bioavailability
3	Capsaicin	Analgesic	Prolong action, permeation enhancement
4	Curcumin	Anti cancer	High entrapment efficiency
5	Garlicin	Lungs	Enhanced therapeutic outcomes
6	Magnolol	Vascular smooth muscle proliferation inhibition	Efficacy enhancement
7	*Myrtuscommunis*	Anti microbial and antioxidant	Activity enhancement
8	Nux vomica	Anti neoplastic, anti inflammatory and analgesic	Improved stability
9	*Origanumdictamnus*	Digestive disorders	Efficacy enhancement
10	Paclitaxel	Anti cancer	Sensitivity towards pH and improved entrapment

			efficiency
11	Puerarin	Antioxidant and antihypercholesterolemic	Enhanced efficacy
12	Quercetin	Anti congestion and antianxiety	Improved efficacy, improved bioavailability and side effect reduction
13	Quercetin and Rutin	Hemoglobin	Hemoglobin binding enhancement
14	*Tripterygiumwilfordi*	Anti cancer	Improved stability
15	Usnic acid	Anti mycobacterial	Prolong action and solubility
16	Wogonin	Anti cancer	Prolong duration of action

Table 2 Herbo Nanoparticle Drug Delivery System (HNDDS)

Sr	Plant/ Constituents	Biological activity	Application of Nanoparticulate technology
1	Artemisinin	Anti cancer	Bioavailability enhancement and sustained drug delivery
2	Berberine	Anti cancer	Inhibition of *Helicobacter pylori* growth
3	Breviscapin	Cerebrovascular and cardiovascular	Prolong half life
4	Camptothecin	Anti cancer	Prolong circulation and high density around tumor containing area
5	*Cuscutachinensis*	Anti oxidant and liver protective	Solubility enhancement
6	*Ginkgo biloba*	Brain activator	Metabolism and cerebral blood flow improvement
7	Ginseng	Anti oxidant	Improved Stability and pharmacological response
8	Glycyrrhizic acid	Anti hypertensive and anti inflammatory	Bioavailability enhancement
9	Hypocrellins	Anti viral	Improved efficacy hydrophilicity and stability

10	Paclitaxel	Anti cancer	Sustained action and minimization of side effects
11	Paclitaxel and doxorubicin	Anti cancer	Lesser chances of resistance development
12	Quercetin	Anti oxidant	Improved therapeutic outcome and release enhancement
13	*Radix Salvia Miltiorrhiza*	Anti anginal	Bioavailability enhancement
14	Silibinin	Hepatoprotective	Improved entrapment and stability
15	Silybinin	Hepatotoxicity treatment	Enhanced circulation
16	Tetrandrine	Lungs	Sustained release of drug
17	Naringenin	Hepatoprotective	Solubility enhancement and improved release of drug
18	Zedoary turmeric oil	Liver protective, Anti oxidant and anti neoplastic	Improved stability and improved loading of drug

Table 3 Herbo Phytosomal Drug Delivery Systems (HPDDS)

Sr.	Plant/ Constituent	Biological activity	Application of Phytosomal Technology
1	Curcumin	Anti cancer and Anti oxidant	Improved anti oxidant activity and bioavailability
2	Embelin	Anti fertility and anti Bacterial	Solubility enhancement
3	Epigallocatechins	Anti cancer and anti oxidant	Absorption enhancement
4	*Ginkgo biloba*	Anti asthmatic, anti diabetic and cardio protective	Improved efficacy
5	Ginsenosides	Immuno modulator and neutraceutical	Absorption enhancement
6	Hawthorn	Cardio protective and anti hypertensive	Improved efficacy and absorption

7	Marsupium	Anti viral	Bioavailability enhancement
8	Naringenin	Anti cancer and anti inflammatory	Prolong action and enhanced bioavailability
9	Oxymatrine	Anti viral	Bioavailability enhancement
10	Procyanidins	Cardio protective Anti oxidant	Increased total radical trapping antioxidant parameter (TRAP)

Table 4 Herbo Microsphere Drug Delivery Systems(HMDDS)

Sr. no.	Plant/ Constituent	Biological activity	Application of Microsphere Technology
1	Camptothecin	Anti cancer	Dose reduction
2	Ginsenosides	Anti cancer	Solubility and stability improvement
3	*Piper sarmentosumn*	Anti diabetic	Easy for industrial scale up
4	Quercetin	Anti inflammatory and anti oxidant	Permeation enhanced
5	Rutin	Anti oxidant	Specific delivery to heart and brain vascular systems
6	Silymarin	Treatment of Liver diseases	Sustained release of medicament Improved patient compliance

Table 5 Herbo Emulsion Systems (HES)

Sr.	Plant/ Constituents	Biological activity	Application of Technology
1	*Azadirachtaindica*	Acaricidal, anti bacterial And anti fungal	Reduction in associated adverse reactions
2	Berberine	Anti cancer	More residence time in the body
3	Curcumin	Anti cancer	Improved absorption
4	Docetaxel	Anti cancer	More residence time in the body

5	Matrine	Anti inflammatory and anti bacterial	Sustained release of medicament
6	Quercetin	Anti oxidant	Permeability enhancement
7	Rhubarb	Luxative and cathartic	Therapy improvement
8	Zedoary turmeric oil	Liver protective, anti cancer and anti Bacterial	Dispersibility, stability and bioavailability enhancement

Table 6 Herbo Transferosomal Drug Delivery Systems(HTDDS)

Sr.	Plant/ Constituent	Biological activity	Application of Transferosomal Technology
1	Colchicine	Anti gout	Reduction in associated GIT side effects
2	Curcumin	Anti cancer and anti oxidant	Permeation enhancement

Table 7 Herbo Ethosomal Drug Delivery Systems(HEDDS)

Sr.	Plant/ Constituent	Biological activity	Application of Ethosomal Technology
1	Matrine	Anti inflammatory , anti cancer, anti rheumatism and anti bacterial	Permeation enhancement and improved efficacy
2	*Sophoraalopencerides*	Anti cancer, Anti endotoxic	Permeation enhancement
3	Triptolide	Anti inflammatory	Bioavailability enhancement

Conclusion:

The present study elaborately review of Principle Mechanism of formulation and their pharmacology of various Novel delivery systems like Phytosome, Liposomes, Nanoparticles, Niosomes, Proniosomes, Transdermal Drug Delivery System, Microspheres, Ethosomes, Transfereosomes, Self emulsifyed drug delivery systems (SEDDS), Self nano emulsifyed drug delivery systems (SNEDDSs), Dendrimers etc. In addition the advantage and challenges of each new delivery system which emphasized to consider in designing of herbal drug formulations. The review retrospectively analyzed the research on this drug delivery on the various herbal

formulations which is already available to overcome the existing challenges. Hope this review will help to formulators to consider the challenges to design the herbal novel drug delivery for desired aspects and improve the safety and efficacy of herbal based Novel formulations.

DECLARATION

Acknowledgement:

The authors would like to thank Department of Pharmaceutics, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu DT, Tamilnadu, India for providing facilities and guidance to carry out the Review research.

Funding:

None.

Data Availability:

All datasets analyzed in the study are included in the manuscript and presented as tables.

Competing interests:

The authors declare that they have no competing interests

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