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REVIEW ARTICLE

Colloidal and vesicular delivery system for herbal bioactive constituents

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Abstract

Objectives The main objective of the present review is to explore and examine the effectiveness of currently developed novel techniques to resolve the issues which are associated with the herbal constituents/extract.

Methods A systematic thorough search and collection of reviewed information from Science direct, PubMed and Google Scholar databases based on various sets of key phrases have been performed. All the findings from these data have been studied and briefed based on their relevant and irrelevant information.

Result Herbal drugs are gaining more popularity in the modern world due to their applications in curing various ailments with minimum toxic effects, side effect or adverse effect. However, various challenges exist with herbal extracts/plant actives such as poor solubility (water/lipid), poor permeation, lack of targeting specificity, instability in highly acidic pH, and liver metabolism, etc. Nowadays with the expansion in the technology, novel drug delivery system provides avenues and newer opportunity towards the delivery of herbal drugs with improved physical chemical properties, pharmacokinetic and pharmacodynamic. Developing nano-strategies like Polymeric nanoparticles, Liposomes, Niosomes, Microspheres, Phytosomes, Nanoemulsion and Self Nano Emulsifying Drug Delivery System, etc. imparts benefits for delivery of phyto formulation and herbal bioactives. Nano formulation of phytoconstituents/ herbal extract could lead to enhancement of aqueous solubility, dissolution, bioavailability, stability, reduce toxicity, permeation, sustained delivery, protection from enzymatic degradation, etc.

Conclusion Based on the above findings, the conclusion can be drawn that the nano sized novel drug delivery systems of herbal and herbal bioactives have a potential future for upgrading the pharmacological action and defeating or overcoming the issues related with these constituents. The aims of the present review was to summarize and critically analyze the recent development of nano sized strategies for promising phytochemicals delivery systems along with their therapeutic applications supported by experimental evidence and discussing the opportunities for further aspects.

Keywords Herbal medicine · Nano-strategies · Vesicular carriers · Drug delivery system

Introduction

Since ancient times humans rely on plants for their livelihood. Nature has furnished a complete storehouse of remedies in the form of herbs [1]. The knowledge of herbal medicines encompassed over thousands of years so that most of the phytoconstituents are utilized for ensuring health care. In twentieth century, bioactive compounds are explored due to their therapeutic potential to treat several diseases such as cancer, cardiovascular, neurodegenerative diseases and many more [2]. These phytoconstituents/bioactive compounds are reported to posses pharmacological activity but due to their poor physicochemical, pharmacokinetic (solubility and bioavailability) and pharmacodynamics properties, they are unable to meet the desired delivery [3–5].

Herbal extracts/plant actives have various hurdles like physicochemical considerations that may result in poor and/or variable solubility, chemical instability in the acidic pH and metabolism, poor permeation through the intestinal wall [5]. Many herbal extracts containing phytoconstituents like flavonoids, tannins, terpenoids and polyphenolics are highly soluble in water but are nevertheless poorly absorbed either due to their multiple-ring large size molecules (500–4000 Da), which

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cannot be absorbed by diffusion or due to poor absorption through lipid-rich membranes of the small intestine. [3, 6] Similarly, some phytoconstituents like Silybin, Triterpenes, Ginkgolides, Bilobalide, Curcuminoids etc. have low aqueous solubility and minimum absorptivity, leading to drug levels below therapeutic concentration in the blood. Taken as a whole, these findings lead to the conclusion that phyto-formulations must have a good balance between hydrophilicity and lipophilicity.

Therefore, recent research is more focused on the designing of novel carrier systems, including surfactant and polymer/lipid-based systems for the effective delivery of phytoconstituents. However, there is still lack information about the physicochemical stability as well as the targeted delivery of these herbal drugs [1, 2, 5]. The physicochemical properties depend on various factors like pKa of the compound, log *P* value, gastrointestinal pH, size of the particle and surface area. The process of absorption also depends on the surface area, gastro intestinal track length and blood flow [7–9].

Nano-sized particulate, colloidal, and vesicular carrier drug delivery systems are emerging trends that have grained potential to address these associated limitations. Novel drug delivery system (NDDS) refers to a combined approach that is based on various streams like biological science, physical science, biotechnology, polymer science, applied chemistry and pharmaceutical sciences; thus the nano-sized drug delivery systems (ranging from 1 to 100 nm) for bioactive compounds have great future for overcoming the limitation associated with them thereby enhancing the utilization of herbal molecules [5, 8]. Pharmaceutical nanomedicine can deliver bioactive compounds or plant extracts into the body with their desired therapeutic efficacy. These modern approaches are termed as novel drug delivery systems (NDDS), which contain polymeric/lipidic nanoparticles, nanoemulsions, liposomes, niosomes, phytosomes, transferosomes, microspheres, self-emulsifying drug delivery system, hydrogel and cyclodextrin complexation [3, 5]. Thus, the encapsulation of herbal extracts or plant actives into novel carrier systems reduces the metabolic degradation and accumulation of drugs at the non-specific target site which improves their efficacy. This also contributes towards the patients' compliance in case of pediatrics and geriatrics [9].

In the past few years, considerable attention has been focused on the expansion of novel nanomedicine [10–12]. These techniques have reported remarkable advantages over the conventional formulation. Modern drug delivery systems led to an enhancement of solubility and stability, improved bioavailability and reduced toxicity along with the improved kinetics and dynamics of the herbal formulation [3, 5, 13]. In the present review emphasis on various aspects like recent advancement in novel strategies for phyto-formulations, their limitations and applications in drug delivery are covered. This review aims to provide exhaustive information about the findings related to such systems which will be beneficial for pharmaceutical researchers, academics and industrialist. The novelty being focusing on those many bioactive compounds which are yet to be explored for their physical, chemical, kinetics, dynamics and therapeutic effect. The overall finding report use of liposomes and self-emulsifying drug delivery system as the most preferred system for delivery of herbal compounds.

Novel strategies for delivery of herbal extract/bioactive

Vesicular nano-carrier drug delivery system

In the current scenario drug targeting and desired (sustained/controlled) delivery are key requirements to improve the quality of therapy. Researchers have focused on formulation studies of vesicular nanocarrier systems like Phytosomes, Liposomes, Niosomes, Transferosomes as these are promising materials to overcome the shortcomings associated with conventional medicines [14, 15].

Colloidal particulate drug delivery system

Nanotechnology deals with the size range of one thousand millionths of a particular unit i.e.,

1 nm = 10^9 m, which offers an advanced drug delivery system for preventing and treating various diseases [10]. The different types of colloidal particulate drug delivery systems like Solid lipid nanoparticles, Metal nanoparticles, Microspheres and Emulsions are discussed below [3, 10].

Other drug delivery system

Besides vesicular and colloidal systems hydrogels and cyclodextrin contributes as another drug delivery system [16, 17].

Vesicular nano-carrier drug delivery system

Phytosome

Definition Phytosome is a patented technology developed by INDENA which is a leading Italian manufacturing company of pharmaceuticals and nutraceuticals [3]. This technology has emerged as an advanced herbal drug delivery system with improved stability, bioavailability and target specificity of active plant constituents. According to the known definition, it consists of two words "Phyto" and "Some" here "Phyto" means plant and "Some" means cell-like structure [18].

Description Phytosomes are reported as ideal vesicular drug delivery systems (VDDS) capable of delivering both water-soluble (like flavonoids, tannins, terpenoids, etc.) and lipid-soluble (polyphenols-sparingly soluble in both water and lipids) compounds along with phospholipid [19]. Phosphatidylcholine a bifunctional moiety with hydrophilic choline and lipophilic phosphatidyl part is important characteristic of phytosomes [20]. The phospholipid and phytoconstituent exist in specific stoichiometric proportion of 2:1 or 1:2. The average phospholipid complexes have particle size range 50 nm to 100 μm [21, 22]. The Phyto-phospholipid complex structure by micelle formation is depicted in Fig. 1 [2, 3]. Improved stability and solubility due to the chemical linkage, improved membrane permeation ability as well as improved bioavailability with the desired therapeutic effect are the advantages of phytosomes, which prove it as most acceptable system for delivery of herbal bioactives [23, 24].

Method of preparation In phytosome formulation therapeutic agents, carrier material and solvent are the most important components. The selection of standardized herbal extract or an active phytoconstituent depends on its hydrophilicity or lipophilicity. The choice of carrier phospholipid depends on its chemical stability. The phospholipids commonly used are phosphatidylserine/ phosphatidylcholine/ phosphatidylethanolamine [3, 21]. In phospholipid complexation strategy the choice of solvent depends on the solubility of both herbal bioactive and phospholipids. Several types of research suggest that the use of either aprotic or protic solvents as well as a mixture of solvents for better dissolution of compounds. Aprotic solvents like dichloromethane, diethyl ether, dichloromethane, dioxane, chloroform and n-hexane are replaced with alcohol (ethanol) which is considered safe. In the first step of phytosome preparation 2–3 mol of natural or synthetic phospholipid is mixed with 1 mol of herbal extract/phytoconstituent and then dissolved in organic solvent like dioxane, acetone, methylene chloride, hexane and ethyl acetate. The organic solvent is then removed completely along with the aqueous content by a rotary vacuum evaporator. Phytosomes are isolated by precipitation with non-solvent, lyophilization, spray drying or vacuum drying. The diagrammatic representation is depicted in fig. 2 [18, 21, 24, 25].

Applications Phytochemicals such as polyphenols, flavonoids, tannins, terpenoids, nitrogen/sulphur-containing compounds delivered as phytosomes which posses antimicrobial, antioxidant and anti-inflammatory properties [15]. Recently curcumin,

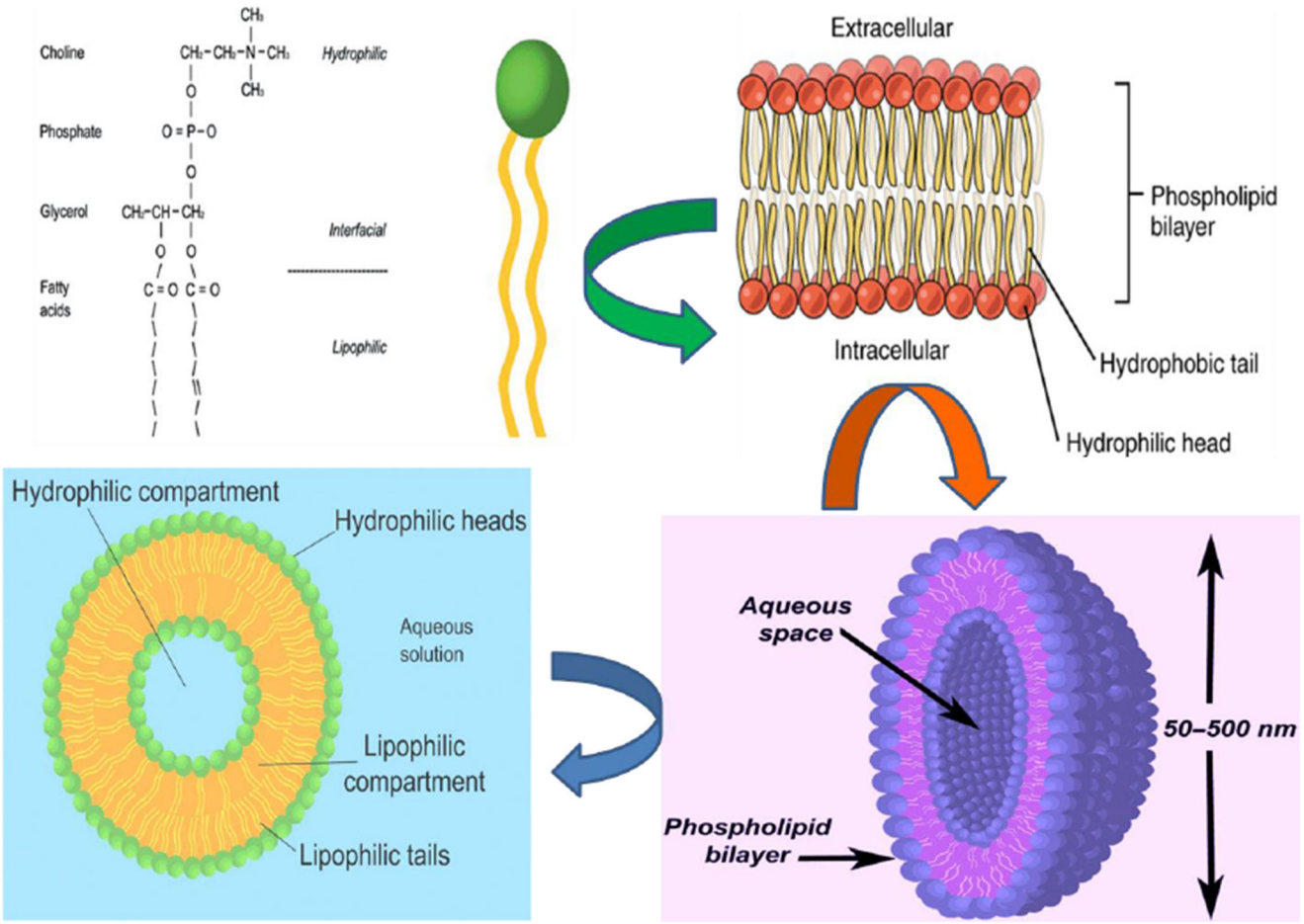

Fig. 1 Phyto phospholipid complex structure by micelle formation (Phytosome) [3] [2]

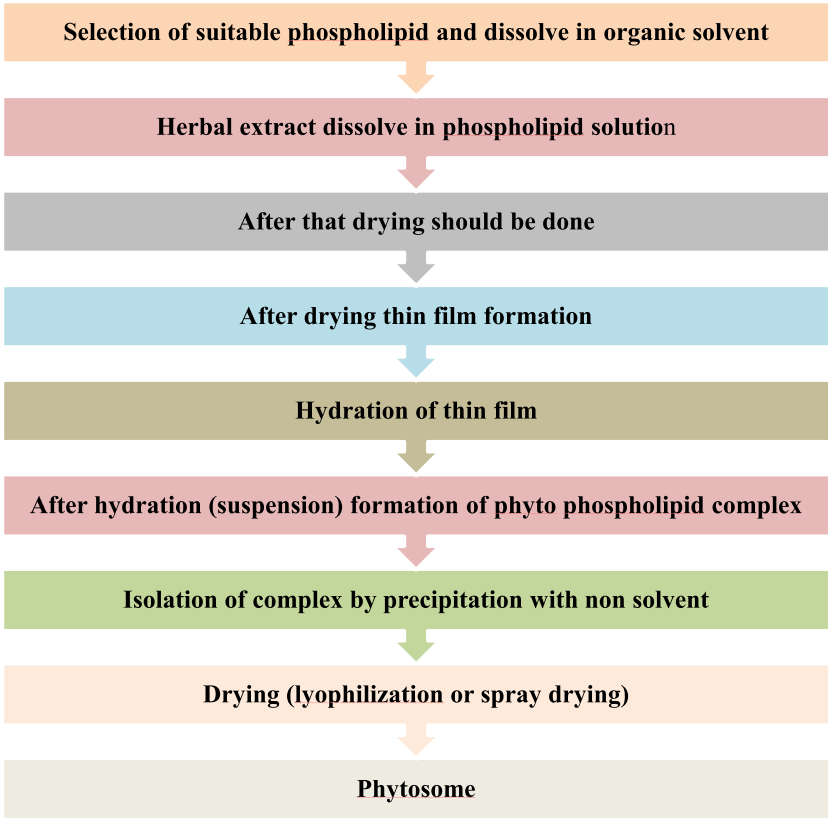

Fig. 2 Processing steps for preparation of phytosomes [18, 21, 24, 25]

resveratrol and many other polyphenolic compounds have been investigated for their use in preventive of cancer and cardiovascular diseases [7]. Research evidence suggests that phytosome tailored drug delivery system helps to overcome the limitations associated with herbal extract/bio-actives [10, 18]. Commercial products of phytosomes along with their pharmaceutical applications are listed in Table No.1-(1.1.1-a) & the recent findings of herbal constituents by phytosomal delivery system is enlisted in (1.1.1-b) [31–40].

Liposome

Definition Liposomes are spherical shaped vesicular drug delivery systems comprising of concentric bilayers capable of encapsulating both hydrophilic and lipophilic material in a single structure [3]. They are self-assembled lipid bilayer membranes vesicles which are formed by phospholipids and cholesterol [10, 18]. This colloidal system is designed with a unique framework by interaction with water, polar lipids and form self-organized colloidal particles. As drug carriers, liposomes are extremely versatile [2, 41]. They can carry hydrophobic drugs within the non-polar lipid membrane core and hydrophilic drugs in the aqueous interior pocket consequently; the water-soluble compounds are entrapped in the aqueous compartment and lipid-soluble compounds aggregate in the lipid section. The size of the liposomes ranges from 50 nm to more than 1 μm, depending upon their respective composition and preparation method [42].

Description Liposomes are bilayer lipidic vesicular carrier system which can be prepared using various phospholipids like phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, phosphatidylglycerol and other molecules such as cholesterol. There are various types of liposomal vesicles like small unilamellar vehicles (SUV-100 nm), large unilamellar vesicles (LUV-200 to 800 nm), multilamellar vesicles (MLV-500 to 5000 nm), long-circulating liposomes (usually surface-grafted with certain polymers), immunoliposomes (carrying antibodies) [18, 43, 44]. Various types of liposomal vesicles are depicted in Fig. 3.

The conventional liposomes have certain limitations (leakage and fusion, short half-life, less stability, etc.) so these liposomes are tailored into advanced carrier systems as new generation liposomes. These spherical vesicular systems effectively provide improved sustained/controlled release, longer stability, drug loading efficacy, target selectivity, prolonged action and higher drug entrapment efficiency of bioactive components [5, 45].

Method of preparation The synthesis of the liposome is complex process due to complications in attaining nano size, stability and effective encapsulation efficiency. The methods for

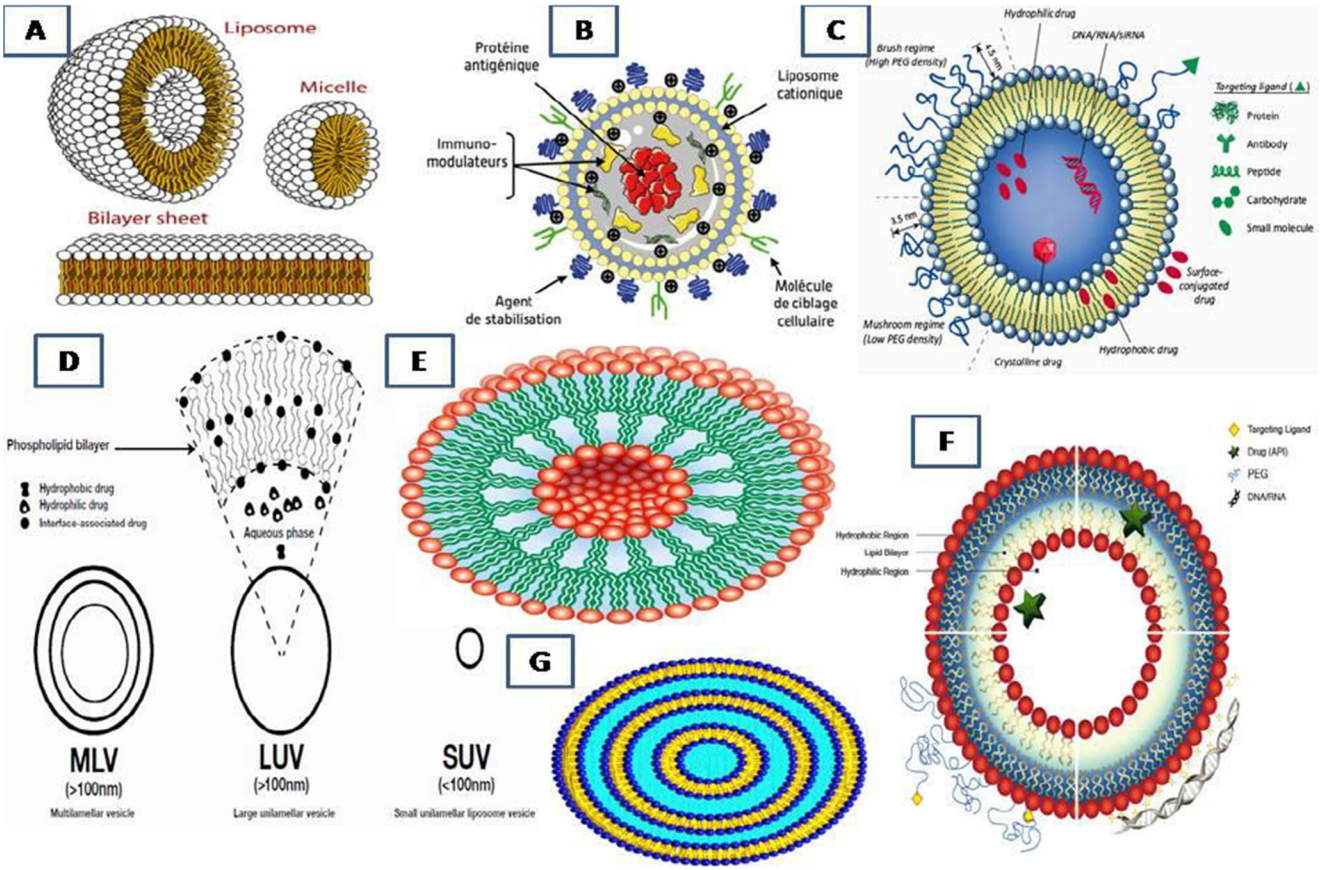

Fig. 3 Structure of new generation liposome carrier system. (**A**) Conventional liposome (**B**) Cellular membrane coated liposome (antibody) (**C**) Polymer functionalized liposome (**D**) Different lamellar vesicles liposome (**E**) Core- shell lipid polymer liposome (**F**) Surface modified immuno liposome (**G**) Multi lamellar liposome. [18, 43, 44]

synthesis of liposomes are classified based on mechanical methods, organic solvent replacement method and fusion method.

- Mechanical methods -
- Film method and
- Ultrasonic method [3, 10]
- Organic solvent replacement method
- Reverse-phase evaporation and
- Ether vaporization method [18, 41, 46]
- The fusion of prepared vesicles or size transformation method
- Freeze-thaw extrusion method and
- Dehydration–rehydration method [32, 47, 48].

New generation liposome - PEGylated Liposomes.

In PEGylation of liposomes has gained much attention as compared to the conventional and targeted liposomes. Poly-(ethylene glycol) (PEG) has been widely used as a polymeric steric stabilizer to improve the blood circulation time of liposomes. It can be incorporated on the liposomal surface in different ways, but the most widely used method is to anchor the polymer in the liposomal membrane via a cross-linked lipid (i. e, PEG- distearoyl-phosphatidylethanolamine [DSPE] [3, 43].

PEG is a linear polyether diol with advantages of biocompatibility, solubility in aqueous and organic media, lack of toxicity, very low immunogenicity, antigenicity and good excretion kinetics. For example, when liposomes are covalently bound to PEG for reducing the identification by macrophages, the stability and circulation half-lives were increased. Daniel Bobo et al., reported, several liposomal formulations which had been approved by the USFDA like Doxil, DaunoXome, and Abraxane etc. and some of nano-liposomal formulations like CPT-11, SPI-077, and CPX-35 are in different clinical trial phases [49].

Long circulating liposomes are composed of poly (ethylene glycol) (PEG). This PEG is grafted on the exterior surface of liposome. The circulation time of the vesicles can be prolonged depending upon both the amount of grafted PEG and the length or molecular weight of the polymer. For example, Marcel B. Bally et al., reported that 1,2-distearoyl-sn-glycero-3-phosphatidylethanolamine (DSPE) when modified with PEG(DSPE-PEG 2000) showed increased plasma circulation longevity as compared to 1,2-distearoyl-sn-glycero-3-phosphatidylcholine (DSPC). Similarly, longer-chain PEGs

(i.e., PEG 1900 and PEG 5000) have maximum blood residence time as compared to short-chain PEG (i.e., PEG 750 and PEG 120). PEG 2000 containing liposome exhibit increased blood circulation time compared to formulations containing PEG 350 to 750 [50, 51].

Surface modification of liposomes with PEG can be achieved in several ways: -

- by physically adsorbing the polymer into the surface of the vesicles,
- by incorporating PEG-lipid conjugate during liposome preparation, or
- by covalently attaching reactive groups on the surface of the preformed liposome.

Liposomes can serve as the carriers system for antitumor drugs, anti-fungal drugs, analgesic drugs, gene therapy and vaccines. Surface modification of liposomes with PEG is illustrated in Fig. 4 [43].

Applications Liposomes are increasingly used to deliver several herbal products for the prevention or treatment diseases [29]. Presently, the liposomal delivery system finds wide application in food processing, cosmetic formulation and pharmaceutical industries [15]. Liposomal phytoconstituents delivery can help in achieving consistent stability, bioavailability, and therapeutic effects of herbal products. The list of phytoconstituents liposomal delivery system is summarized in Table No.1- (1.1.2) [52–60].

Niosome

Definition Niosomes are bilayer amphipathic vesicular carriers similar to liposomes, in which phospholipids are replaced with nonionic surfactants. Niosomes can entrap hydrophilic, amphiphilic, and lipophilic molecules and can exhibit longer circulation time compared to liposomes [3, 14, 61].

Description Niosomes are bi-layered structure, hydrophilic and hydrophobic ends of their surfactant tend to arrange into external and internal sites, respectively [2, 10]. These vesicular carriers are compatible with intracellular tissues, non-toxic, biodegradable, non-immunogenic and can deliver various therapeutic agents, including proteins, herbal extract and bio-actives to their target site of action [61]. Niosomes have structural similarities with liposomes; however, liposomes have some limitations like leaking, fusion, less economic and stability issues [52]. Niosomes formulations can successfully overcome these disadvantages and are widely acceptable systems. Niosomes as delivery system offers several

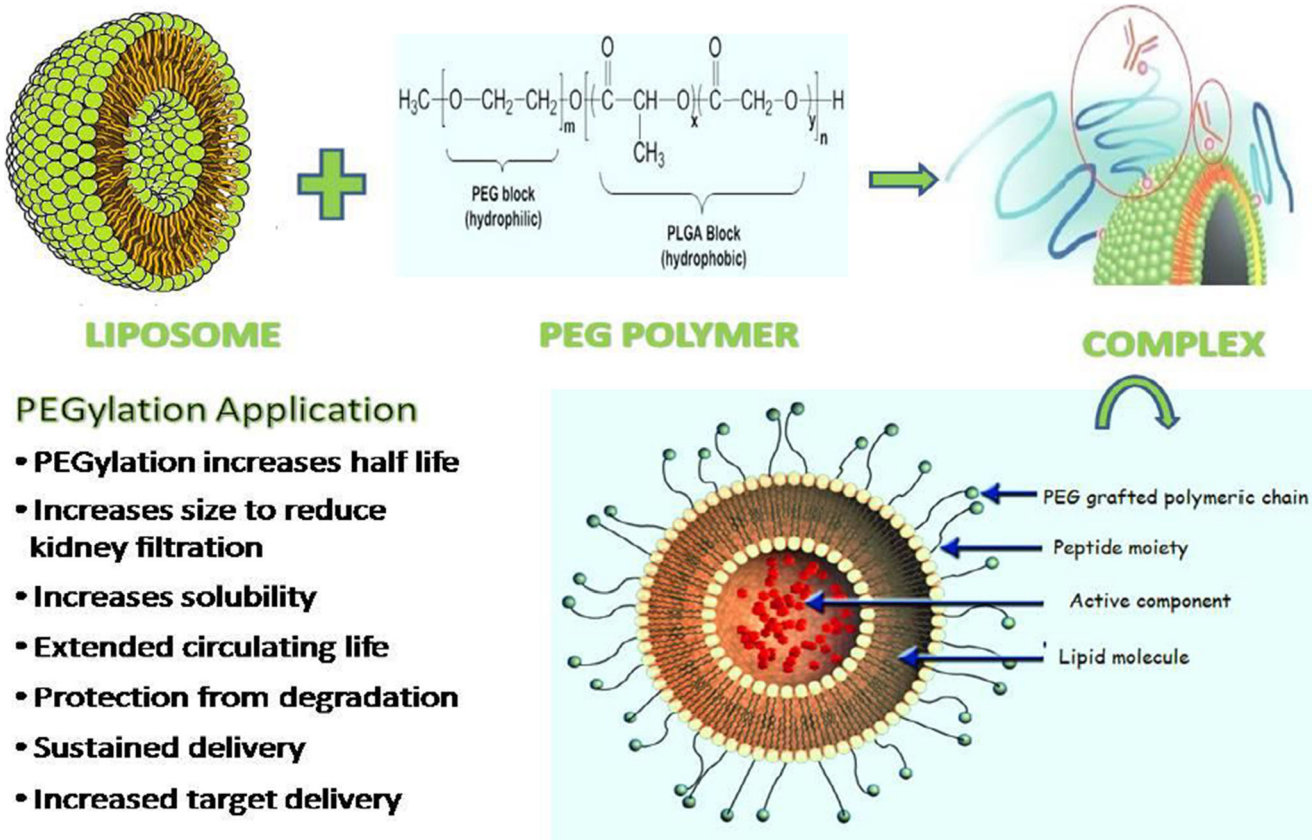

Fig. 4 Systemic presentation of modification of convention liposome into PEG coated liposome for specific target delivery of active component.. [3] [43]

advantages like reduced dose, highly stable in varying pH, targeted drug delivery, reduced side effects, increased efficacy and osmotically active [61]. Delivery of active drug substance by noisome is represented in Fig. 5 [3, 14, 61].

Method of preparation Niosomes are formulated by the non-ionic surfactant, cholesterol and di-ethyl ether with successive hydration in the appropriate media. This vesicular system can deliver hydrophilic/lipophilic and synthetic drugs as a unilamellar or multilamellar vesicle [61–63]. The different methods for preparation of niosomes are represented in Fig. 6. Thin-film hydration method and reverse phase evaporation method are discussed below-.

Thin-film hydration method This method is suitable for multilamellar niosomes. In this method, the surfactants, cholesterol, and additives are dissolved in an organic solvent. Excess of solvent is removed by rotatory vacuum evaporator to obtain a thin film. Dried surfactant film could be rehydrated by the aqueous phase. After hydration, multilamellar niosomes vesicles are obtained [61].

Reverse phase evaporation method This method is applied for large unilamellar vesicles of niosomes. For this, all ingredients are dissolved in a mixture of ether and chloroform and added to the aqueous phase containing the drug. The mixture is sonicated for emulsification and evaporated to get unilamellar vesicles [42].

Applications Niosomes have a wide range of biological applications such as target specificity, maximum stability and retention of drugs in blood circulation, sustain/controlled release of drugs and as diagnostic imaging agents. In addition to the pharmaceutical application, noisome also act as an excellent carrier for anti-inflammatory drugs, anticancer drugs, hormones and natural compounds such as plant extracts or their active components [61]. The term phyto-niosomes describes niosomes containing various herbal drug extracts such as *Ginkgo biloba* extract, marigold extract etc. [63, 64]. Pereira M.C. et al. introduced a novel vesicular carrier system for cancer by formulating coated niosomes which provides long circulation time and uniform bio distribution throughout the entire tumor cells. Rinaldi F. et al. studied and investigated the better anti-inflammatory activity of ibuprofen and lidocaine containing noisome as compared to the free drug. Some of the reported work on niosome delivery system is summarized in Table No.1-(1.1.3) [63–71].

Transfersomes

Definition Transfersomes are defined as specially designed highly deformable vesicles, consisting of at least one inner aqueous compartment enclosed by lipid vesicles. They are like liposomes in morphology, but, functionally, they are suitably deformable to go through membrane pores [3]. Transferosome is a trademarked technology of the German company IDEA AG. It consists of two words "transferred" and "some" where "transferred" means carrying and "some" means body [5, 10, 72, 73].

Description Transfersomes consist of phospholipid, surfactant, and water [1, 3]. They are elastic and extremely adaptable aggregates and this property assist in their quick penetration through the intercellular lipid pathway of the subcutaneous tissue. They have a diameter of approx. 100 nm [18, 22]. Tranferosomes can encapsulate both hydrophilic and hydrophobic moieties (herbal/synthetic) in their structural framework are highly biocompatible, sustained release and

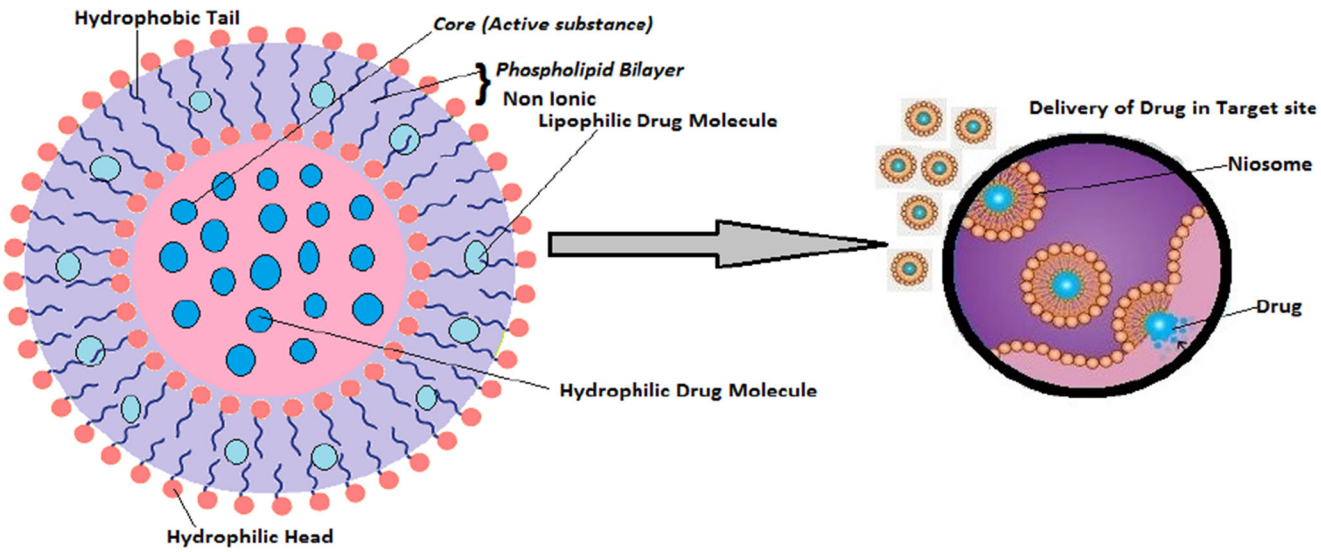

Fig. 5 Delivery of active drug substance by Niosome. [3, 14] [61]

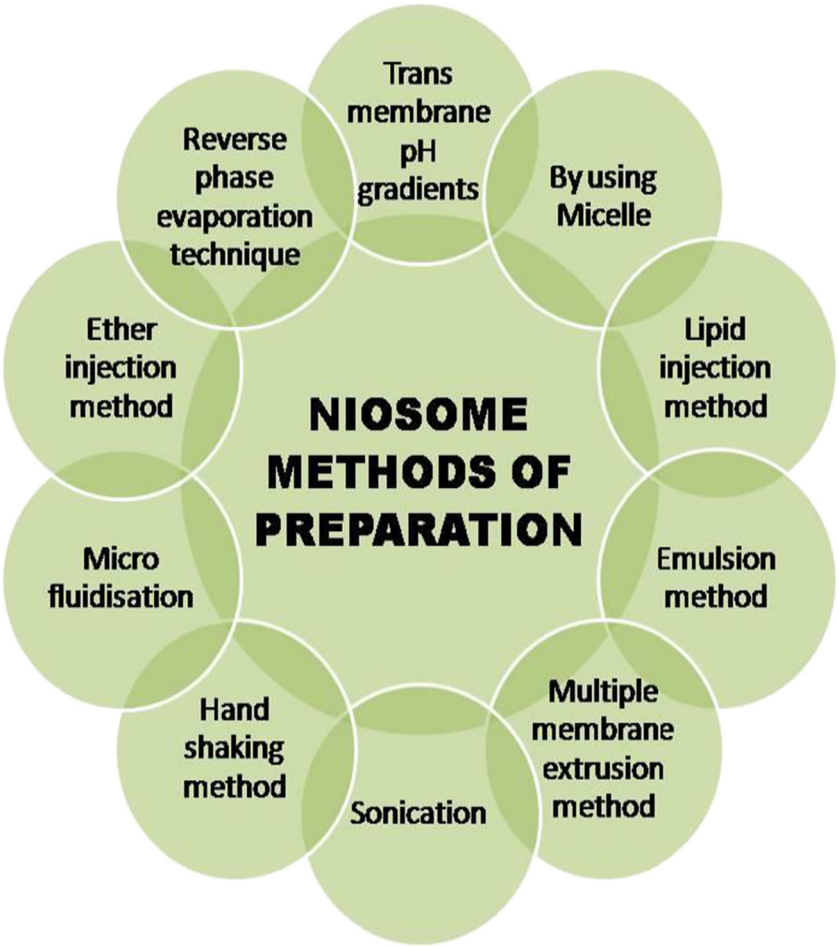

Fig. 6 Methods of Preparation for Niosomes. [42] [61] [63] [64]

effectively used in topical application [3, 10]. The technologies (Freeze-thaw method, Ethanol injection method, Vortexing sonication method, Reverse-phase evaporation method and Rotary film evaporation method) are popular for the preparation of transfersomes. [61, 72]. Rotary film evaporation method and reverse-phase evaporation method are discussed below-.

Method of preparation Rotary film evaporation method

This method was invented by Bangham. It is also known as the hand-shaking method. For the preparation of transferosomes all ingredients phospholipids and surfactants are dissolved in a mixture of solvent (chloroform and methanol) into a round bottom flask. After constant rotation film is prepared on the walls of the flask. This film is then hydrated using aqueous media containing drug resulting in formation of bilayer vesicles due to the swelling of lipid [72].

Reverse-phase evaporation method In this method, surfactant-containing aqueous media and lipids containing organic solvents are collected in a round-bottomed flask. Then drug is added to the lipid or aqueous medium based on its solubility. The mixture is sonicated fallowed by removal of solvent under low pressure [72, 73].

Applications Transfersomes have been used as carriers for delivery of different therapeutic agents, including proteins, nutraceuticals, insulin, antigens, peptides, albumin, analgesics, sex hormones, anticancer drugs and phytoconstituents/ herbal extracts. The example of drugs delivered as transfersomes are mention in Table 1-(1.1.4) [74–78].

Colloidal particulate drug delivery system

Polymeric nanoparticles

Definition Nanonization deals with several issues like low oral bioavailability, low solvency, poor ingestion etc. [3, 10]. Polymeric nanoparticles are the structure of solid colloidal particles with a size dimension of 10 to 1000 nm (1 μm). There are several types of nanomaterials such as polymeric nanoparticles, solid lipid nanoparticles, metal nanoparticles, etc. which if investigated could be an interesting approach in drug delivery systems. Usually, these nanoparticles are coupled with nonionic surfactants to reduce the interaction

Table 1 Listing of recent work on vesicular nano-carrier drug delivery system to solve the hurdles related with herbal drug

VESICULAR NANO-CARRIER DRUG DELIVERY SYSTEM

1.1.1 PHYTOSOME – a. Phytosome commercial products and their pharmaceutical applications

S.No.	Phytosome Trade Name	Phytoconstituents complex	Daily dose	Pharmacological action	Bioactive compound
1.	18β-glycyrrhetinic acid phytosome®	18-β glycyrrhetinic acid from *Glycyrrhizaglabra* Root	–	Anti-inflammatory,Soothing	18- βGlycyrrhetinic acid [26]
2.	Bosexil® Phytosome®	Triterpenoid acid *Boswelliaserrata*Roxb. Ex Colebr. – Resin	–	Soothing, Anti-photo ageing	β -boswellic acid [26]
3.	Centellaasiatica selected triterpenes phytosome®	Terpens from *Centella Asitica*	–	Used in treatment of Skin and Vein Disorder, Brain tonic, increased permeability	Asiaticoside [26]
4.	*Ginkgo biloba* dimeric flavonoids phytosome®	Flavonoids from *Ginkobiloba leaves.*	120 mg	Anti-aging, Protects Brain & Vascular Liling	Quercetin, kaempferol and isorhamnetin [26]
5.	Greenselect® phytosome®	Epigallocatechin from *Thea Sinensis*	150 mg twice a day,	Anti-cancer, Antioxidant	Epigallocatechin [26]
7.	Silybinphytosome	Silybin from *Silibium Marianum*	120 mg	Hepatoprotective, Antioxidant.	Silybin [3]
8.	Curbilenephytosome	Curbilene from *Curcurbitapeposeeds*	–	Skin care, Matting Agent	Curbilene [3]
9.	Ruscogeninphytosome	Steroid saponins from *Ruscusaculeatus*	–	Anti-inflammatory, Improve Skin Circulation	Steroid saponins [3]
10.	Gallic acid phytosome®	Gallic acid from *Terminalia belerica*Roxb	45 mg/kg	Antibacterial, antiviral, analgesic	Gallic acid [27]
11.	Quercetin phytosome	Quercetin	10 mg/kg	dietary flavonol phytoestrogen increased absorption	Quercetin [28]
12.	Bacopa Extractphytosome	*Bacopa monnieri*	–	improved permeation- treatment of anxiety, memory enhancement, neuroprotection, and hepato-protection	*Bacopa monnieri* extract [29]
13.	Naringeninphytosomes®	Naringenin	100 mg/kg	Antioxidant	Naringenin [30]
14.	Ginseng phytosome®	*panax ginseng*Ginsenosides	150 mg	Used as Skin elesticity improver and Immunomodulator,	Panaxdiols, Panaxtriols [26]
15.	Hawthorn phytosome®	Flavonoids from *crataegus Species*	100 mg	Cardiovascular health, Antioxidant	Quercetin, kaempferol [26]

PHYTOSOME – b. Recent reported work of herbal constituents by phytosome delivery system

S.No.	Problem associated with phytoconstituents	Methodology	Modification	Reference
1.	Rapid metabolism and elimination of Gallic acid	Phospholipid complex with gallic Acid	Complex significantly reduced the hepatic marker enzymes and the complex improved the pharmacokinetics of Gallic acid	Sauvik Bhattacharyya et al. [31]
2.	Poor absorption and oral bioavailability of Boerhaviadiffusa L. (Nyctaginaceae)	Phospholipid complex (Rotenoid-rich fraction)	Increased anti-inflammatory activity and increases plasma level of boeravinone B	Khemraj Birwa and Sanjay MadhukarJachak [32]
3.	Low solubility, poor dissolution profiles and reduced skin permeation abilities of Propolis (caffeic acid, quercetin and kaempferol	Complexation of L-α-Phosphatidylcholine (PC-egg yolk) with propolis	Complex showed increased dissolution profile	Andi Dian Permanaa et al., [33]
4.	Poor bioavailability of Sinigrin	Phosphatidylcholine complex with pure Sinigrin [ratio of 1:1 (*w*/w)]	Improved bioavailability and effective wound healing effects (sinigrin–phytosome complex completely cured the wound.	AnishaMazumder et al., [34]

Table 1 (continued)

VESICULAR NANO-CARRIER DRUG DELIVERY SYSTEM

5.	Silybin low bioavailability	Silybin–phospholipid complex	Phospholipid complex [Phosphatidylcholine (PC, 30–33%), phosphatidylethanolamine (PE, 12–15%), phosphatidylinositol (PI, 13–16%) and phosphatidic acid (PA, 3–6%)]	Ruggero Angelico et al., [35]
6.	Poor solubility of boswellic acids	Poor solubility of boswellic acids	Poor solubility of boswellic acids	Poor solubility of boswellic acids [36]
7.	Poor solubility of *Centellaasiatica*extrctcontaingasiatic acid and madecassic acid	*Centellaasiatica*phytosome anti-solvent precipitation (phosphatidylcholine, phophatidylethanolamine or phosphatidylserine)	Improved bioavailability	Ju Ho Park [37]
8.	Poor aqueous solubility and limited gastrointestinal absorption	Silybin-phospholipid complex	Increased bioavailability and better hepatoprotection efficacy.	Cheng Chi et al., [38]
9.	Poor aqueous solubility and chemical instability of (Polyphenolic) Rosmarinic Acid	Rosmarinic Acid phytosome	improved solubility andstability profile	Abhishek Singh,et al., [39]
10.	Poor aqueous solubility and chemical instability of vitamin C and E	Ascorbic acid and α-tocopherol complex with milk phospholipid	improved solubility and stability profile	Zhiguang Huang at el, [40]

1.1.2 LIPOSOME -Current literature on phyto-constituents by liposomal delivery system

S.No.	**Problem associated with phytoconstituents**	**Modification**	**Employed Method**	**Application and Result**
1.	Ginseng Liposomes	Ginsenoside-based multifunctional liposomal with Egg yolk lecithin and cholesterol used in 10:3 mass ratio	Thin film hydration fallowed by high pressure homogenization	longer blood circulation time active targeting abilities [52]
2.	Poor solubility of Fisetin	Fisetin Liposomes are shown high conc. In-vivo administration,	Probe sonication method	Applicable as antioxidant, anti-inflammatory and anti-carcinogenic and fisetin encapsulation (73%) [53]
3.	Poor solubility of Quercetin	Polymeric complexation of Quercetin result multilamellar liposomes formation	Rotary evaporation	Satisfactory entrapment and improved penetrate lipid bilayers [54]
4.	Low permeability of Quercetin	Quercetin deformable liposome for skin protection by UV radiation, antioxidant activity was increased	Ethanol injection technique	80.41±4.22% and penetration rate was 3.8 fold greater [55]
5.	Low permeability of berberine and palmatine	Berberine and palmatine liposome shown Antioxidant activity	Rotatory evaporation	Well encapsulated [56]
6.	Madecassoside liposomes	Madecassoside liposomes [(poly(ethylene glycol)-poly(ε-caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG, PECE)]	Double emulsion method	Excellent therapeutic effects in wound healing 213.43±4.68 nm(size) [57]
7.	PEGylated iposomalberberine (PEG-BBR) (low bioavailability)	Goniodiol loaded in PEGylated liposomes with PEG, 2-Distearoyl-Sn-glycero-3-phosphocholine(DSPC)cholesterol (CHO)	Thin-film hydration method	DSPC, CHOL, PEG and BBR at a molar ratio of (60: 35:2.5:2.5) and solvent used chloroform: methanol=2: 1 (v/v) Enhanced cellular uptake of (PEG-BBR) liposomes [58]
8.	Poor doxorubicin delivery in brain	Glutathione PEGylated liposomal doxorubicins were developed to enhance safe delivery of drug into brain tumors.	Cerebral open flow microperfusion technique was used. In combination with cOFM sampling, sodium fluorescein (NaF) is used as tool in blood brain barrier. ONE one intravenous dose (7 mg/kg) SHOW enhanced doxorubicin concentration.	4.8 fold increased concentration [59]
9.	Glutathione pegylated liposomal methylprednisolone	Glutathione pegylated liposomal methylprednisolone are used for pediatric epilepsy Syndromes treatment.	Rats were treated with glutathione pegylated liposome. Methylprednisolone.	Treatment regimen that was administered beyond the acute status epilepticus phase does not reduce brain inflammation and development of temporal lobe epilepsy. [60]

Table 1 (continued)

VESICULAR NANO-CARRIER DRUG DELIVERY SYSTEM

10.	Low bioavailability of doxorubicin	PEGylated liposomal doxorubicin by PEGylated doxorubicin in thermosensitive liposomes and nonthermosensitive PEGylated doxorubicin liposomes	PEGylated doxorubicin liposomes (PLDs), having a slow and continuous drug release, longer circulation time of doxorubicin from PLD than from PLDTS may be beneficial in many therapeutic instances	Glutathione coated were 58% and 75%. (management of ischemic stroke) [61]
1.1.3 NOISOME - Recent reported work on niosome delivery system.				
S.No.	**Drug**	**Problem associated with active constituents and their modification**	**Biological activity and Route of administration**	**Method of Preparation**
1.	Marigold extract (*Calendula L.*,) Poor bioavailability	Poor bioavailability of Marigold extract(*C. officinalis)* which significantly increased aftermethanolic extract entrapment into a Tween 60 niosome.	antifungal, anti-bacterial, antiviral, antioxidant, anti-inflammatory, anti-mutagenic, hepato-protective activities.	Film hydration method [63]
2.	Ginkgo biloba extract (GbE)	Poor oral bioavailability of conventional GbE tablets. After noisome formulation -improved oral bioavailability.	entrapment efficiency between the spray-drying method (about 77.5%) and the freeze-drying method (about 50.1%) and prolong release. Application as antitumor and protective effects in the central nervous system	film dispersion-homogenization method [64]
3.	Rice bran Bioactive compounds. *(Oryza sativa L.)*-ferulic acid (F), γ-oryzanol (O), and phytic acid (P)	-Poor bioavailability rice - bran extracts containing the bioactive compounds F, O, and P entrapped in niosomes (Gel nio, Cream nio, and Cream RBO) for skin anti-aging.	Anti-aging efficacy and chemical stability of the bioactive compounds in the extracts was also enhanced by entrapping in niosomes	$scCO_2$ technique on SFE-500 MR-2-C50 system [66]
	Colchicine- 5 fluorouracil	Low bioavailability enhance by polymeric modification and improve Prolonged release profile	Used in the treatment of rheumatic disorder and treatment of cancer	Evaporation-Sonication method [67]
1.	Colchicine	Gastric degradation	Antigout Activity	Sonication [68]
2.	Niosomal gel of benzoyl peroxide	Poor solubility	treatment against acne	thin film hydration method [69]
3.	Rosmarinicacid containing antiacneniosomal gel. Poor bioavalibility and release	cholesterol and surfactants (1:1) dissolved in chloroform for sustained delivery.	antibacterial and anti-inflammatory potential of rosemarinic acid	Reverse phase evaporation technique [70]
4.	Hypericumperforatum (flavonoids) -Stability issues	80% of drug entrapment and extent of drug release (78.8±1% after 180 min) and	Used in wounds, ulcers, sunburns and hemorrhoids	Reverse phase evaporation technique [71]
1.1.4. TRANSFEROSOMES - Recent reported work on niosome delivery system.				
S.No.	**Drug**	**Problem associated with active constituents and their modification**	**Biological activity and Route of administration**	**Method of Preparation**
1.	-Sinomenine alkaloid from *Sinomeniumacutum*, -Monoterpenes-containing PEGylated transfersomes	Cholesterol (CH), egg phosphatidylcholine (EPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and DSPE-PEG2000 aare used for modification	An anti-inflammation drug.	Ethanol injection process [74]
2.	Ginsenoside- triterpenoid saponins	Poor penetration and low bioavailability alter by Transfersomes	Used to treat tumor, inflammation, diabetes, stress and acquired immunodeficiency syndrome in	Emulsification method [75]
3.	Sildenafil citrate loaded transfersomes	Poor penetration and bioavailability improved bytransfersomes	Sildenafil Citrate loaded nano vesicles ranged from 69.08 nm to 265.80 nm, the encapsulation efficiencies ranged from 59.90% to 92.49% and the in vitro drug release	Thin film hydration and sonication technique [76]
4.	Vitamin C-Enriched Adapalene-Loaded Transfersome Gel	Increased topically applicable	Management of acne vulgaris	Reverse-phase evaporation method [77]
5.	Miconazole Nitrate	Increased topically applicable	Increase antifungal activity. Candidiasis	film hydration technique [78]

with the immunological system and the functional groups attached with them. Based on the structure, nanoparticles are broadly known as nanospheres and nanocapsules. The system in which the drug is enclosed into a cavity surrounded by a unique polymer membrane is known as nanospheres, whereas the matrix systems in which the drug molecule is dispersed are nanocapsules [17, 22].

Description Nanoparticles are an effective delivery system which requires synthetic polymer, proteins, lipid and carbohydrates for the delivery of drug component. Several herbal compounds such as curcuminoids, praziquantel and paclitaxel are delivered as polymeric nanoparticles with 400 nm size range. Polymeric nanoparticles are synthesized by using biocompatible polymers that facilitate controlled drug delivery with target specificity and prolong stability [3, 81]. Nowadays various advanced polymers are extensively used in polymeric nanoparticles such as poly-L-lactic acid (PLA) and copolymers with glycolic acid (PLGA). Besides there, the other widely used polymers are poly (ε-caprolactone) (PCL), methacrylic acid copolymers, and acrylic or methacrylic esters, triglycerides, lecithin natural or synthetic lipids are used [79, 80]. Bisht et al. synthesized curcumin-loaded polymeric nanoparticles using copolymers of N-isopropyl acrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly(ethylene glycol)monoacrylate (PEG-A). Solvent evaporation and electrospinning method are discussed for the preparation of polymeric nanoparticles [82, 83].

Method of preparation Solvent evaporation

In this method, the polymer is first dissolved in ethyl acetate (better toxicological profile in comparison to Dichloromethane and chloroform), therefore the resulting solution is emulsified with an aqueous phase. Then the mixture is typically processed using a surfactant and high-speed homogenization or ultra-sonication, to obtained dispersion of nanodroplets. By using a continuous magnetic stirring solvent is completely evaporated. After the solvent has evaporated, the solidified nanoparticles can be washed and collected by centrifuging, followed by freeze-drying for long term storage.

Electrospinning This technique is highly versatile for fabrication of nanofibrous materials. It is one of the widely adopted encapsulation technique for thermosensitive bioactive agents. The electrostatic force is used to draw a fine nanofiber out of polymer solution droplet, which flies toward the nearest lower electrical potential target. The electrospinning apparatus consist of three main components: a high voltage power supply, a polymer solution reservoir (e.g., a syringe) with or without a flow control pump, and a metal collecting screen. The concentration of polymer, molecular weight, and fiber morphology (low viscosity), electrical conductivity (higher molecular weight polymer) and effect of solvents are the critical parameter to be considered in the preparation of nanofibres containing bioactive components.

The three stages of method includes –

- The polymeric solution is kept in a reservoir and connected to a power supply to establish a charged polymer jet.
- Charging the polymer solution could be done either with a syringe with a metal needle or a capillary with a metal tip in the polymer solution.
- The fiber collecting screen is expected to be conductive and it can either be a stationary plate or a rotating platform or substrate. The plate can produce non-woven fibers, whereas a rotating platform can produce both nonwoven and aligned fibres. [84, 85].

Applications To improve the nanosize range and specificity several metal ions have been used for the preparation of nanoparticles such as gold, silver, zinc and platinum. Recently the phyto extracts of *Cucurbita pepo, Malvacrispa, Acalyphaindica, Zingiberoffcinale, Syzygiumcumini leaf extract Cymbopogon citrate, Abelmoschusesculentus, Pelargonium graveolens, Cassia auriculata* and *Punicagranutum* were successfully delivered as gold nanoparticles. Similarly several phytoconstituents such as *Acoruscalamus, Boerhaaviadiffusa Tea extract, Tribulusterrestris, Cocousnucifera, Abutilon indicum, Pistaciaatlantica, Ziziphoratenuior, Cymbopogancitratus, Acalyphaindica, Premnaherbacea, Calotropisprocera, Centellaasiatica, Argyreia nervosa, Psoraleacorylifolia, Brassica rapa, Cocciniaindica, Vitexnegundo* were delivered as silver nanoparticles [5, 27, 45].

Dube, A. et al., formulated chitosan nanoparticles for enhanced intestinal absorption of both (+)-catechinand(−)-epigallocatechin gallate. The cumulative amounts transported after encapsulation were significantly ($p < 0.05$) higher, i.e. 302.1 ± 46.1 vs 206.8 ± 12.6 ng/cm2 and 102.7 ± 12.4 vs 57.9 ± 7.9 ng/cm2 for catechin and epigallocatechin gallate, respectively. The mechanism by which absorption was enhanced was stabilization of catechins after encapsulation (99.7 ± 0.7 vs 94.9% ± 3.8% and 56.9 ± 3.0 vs 1.3% ± 1.7% of the initial catechin and epigallocatechin gallate concentration respectively) [86]. Konecsni, K., et al., formulated rutin loaded chitosan (CH)-tripolyphosphate (TPP) nanoparticles. Theses nanoparticles are prepared by using 4.0:1.0 of CH:TPP mass ratio. The particles carried a high positive charge which promoted mucoadhesion. These are some examples of polymeric nanoparticles loaded with herbal bioactive [87]. The polymeric particles for herbal constituents are listed in Table 2-(2.1.1) [82, 86–94].

Table 2 Listing of recent work on colloidal particulate drug delivery system to solve the hurdles related with herbal drug

COLLOIDAL PARTICULATE DRUG DELIVERY SYSTEM

2.1.1 POLYMERIC NANOPARTICLES– recent literature on nanoparticle delivery system

S.No	**Nanoparticle formulations and Bioactive compound**	**Modification and Method of preparation**	**Biological activity**	**Size and application**
1.	Iron oxide magnetic nanoparticles of *Argemone Mexicana L.* extract (Alkaloids)	Co-precipitation method used for nanoparticle synthesis, Nanoparticles show improved target delivery	Diuretic, purgative and also useful to cure bacterial diseases.	10 and 30 nm [88]
2.	Silver nanoparticles of Vincarosea(Alkaloids)	Prepared nanoparticle show improved drug pharmacokinetic and pharmacodynamics	Improved Antimicrobial activity	27 nm and 30 nm [89]
3.	Silver Nanoparticles of *Eucalyptus globulus* Leaf Extract	Nanoaprticle Microwave Accelerated method used for	Improved Antimicrobial activity	1.9–4.3 nm and 5–25 nm, [90]
4.	B-sitosterol (Flavonoids) and green tea extract loaded nanoparticle	Low bioavailability improved by sustained released	Improved Antioxidant activity	less than 200 nm [91]
5.	Silver Nanoparticles of extracts of *Trachyspermumammi* and *Papaver somniferum* (essential oil and alkaloid)	Improved target specificity	Antispasmodic	3.2 and 7.6 μm [92]
6.	Gold nanoparticles of *Euphorbia hirta L.*	Improved antimicrobial activity by nanoparticle	Anti-bacterial and anti-fungal	6 nm to 71 nm [93]
7.	Polymeric nanoparticle of Curcumin, *(Curcuma longa),*	aqueous solubility and bioavailability enhanced by polymeric nanoparticle	Poor aqueous solubility and bioavailability.	50 nm
8.	Rutin loaded Chitosan–tripolyphosphate sub-micron particles	Particles are ionic gelling techniques	antioxidants	(2.0:1.0–5.0:1.0) – size 814 nm (2.0:1:0)size 528 nm 4.0:1.0 size 322 nm [87]
9.	Chitosan nanoparticles containing catechins (+)-catechin and (−)-epigallocatechin gallate	Encapsulation of catechins in Chitosan nanoparticlesenhances their intestinal absorption and bioavailability	*Camellia sinensis* used in myocardial infarction, hypertension, atherosclerosis), neurodegenerative diseases (e.g. Parkinson's and Alzheimer's disease), and certain cancers (e.g. gastric, breast and cervical cancer)	432±37 nm [86]
10.	silver nanoparticles ofaqueous aloe leaf extract	Capping silver nitrate was used for synthesis of nanoparticle	Antimicrobial and Carcinogenic activity	15.2 nm ± 4.2 nm [94]

2.1.2 MICROSPHERES -Some of the recent literature on microspheres drug delivery

S.No	Active component	**Modification and application**	**Method of preparation**	**Size of microsphere**
1.	Microspheres containing zedoary turmeric oil with Hepatoprotective	Poor release patter and less bioavailability improved by the microsphere	Emulsion solvent diffusion method	100–600 μm [96]
2.	Locust bean gum microsphere	Applied as thickening and gelling agent in food technology, hypo cholesterolaemic activity	Water in oil emulsion crosslinking method	734.18 μm to 293.17 μm [98]
3.	Rutin microsphere	Improved antioxidant activity	Coprecipitation method,	Small and uniform [99]
4.	Soy protein isolate Micro particle have pharmacological activity Estrogen beta agonist (decreases serum testosterone levels)	Used as gelling agent, as good binding agent, emulsifying agent and fat absorbing agent.	Spray drying	5.5 to 9.3 μm [100]
5.	Chelerythrineloaded O-carboxymethyl chitosan Microspheres	Improved drug delivery with Antimicrobial, anti-inflammatory, antitumor, and anti-plaque effect	Emulsion cross-linking method	12.18 μm [101]

Table 2 (continued)

COLLOIDAL PARTICULATE DRUG DELIVERY SYSTEM				
6.	Rosemary extract Microspheres	Anti-proliferative	Solvent evaporation method	254.5 nm [102]
7	Essential oil Microspheres with Thymol (5-methyl-2 isopropyl phenol), clove, origanum, and camphor white oil	Larvicidal activity and used as Applied for use in pest control	Hot-melt Procedure	5 μm to over 300 μm [103]
8.	Delivery of hydrophobic bioactive compound, microsphere contain Oxidized Starch	Improved activity	Double emulsion method	Small in size [104]
9.	Microspheres containing extract of *Crataegusmonogyna Jacq.* (hawthorn)	Improved therapeutic efficacy	Spray drying technique	Small in size [105]
10.	Quercetin polycaprolactone microspheres	Effective in the management of arthritis	Solvent evaporation method	In micro rang -[106]
2.1.3 EMULSION -Recent reported work on phyto constituent micro emulsion delivery system				
S.No	**Bioactive compound**	**Formulations**	**Modification and application**	**Work done by**
1.	Ampelopsin isolated from *Ampelopsisgrossedentata*	Microemulsioncontaining active component	Bioavailability Enhancement of Ampelopsin, micro emulsion prepared by water titration method	Shailendra Singh Solanki et al. [111]
2.	Zedoary turmeric oil extracted from the dry rhizome of *Curcuma zedoaria*	Self nanoemulsifying drug delivery system for Zedoary turmeric oil	Improves oral absorption and reduced loading of drug	Zhao Y et al. [112]
3.	Extract of *Hibiscus Rosa Sinensis* and *murrayakoenigii*	Microemulsion containing *Hibiscus Rosa Sinensis* and *murrayakoenigii*	Extract contain steroids, alkaloids and essential oil	NaliniS.Kurup [113]
4.	Extract of *Sonchusoleraceus Linn*	Self-nano-emulsifying formulation of *Sonchusoleraceus Linn*	antioxidant antibacterial, anxiolytic good droplet size (< 200 nm) of PEG400	Lei Chen et al. [114]
5.	Rutin which was neither water-soluble nor oil--soluble.	Non-aqueous self-double-emulsifying drug delivery system of rutin	Poor solubility enhance by emulsification Rutin-loaded N-SDEDDS displayed sustained release profile (53.79% in 12 h)	QiangWang et al. [115]
6.	Papain loaded mucolytic self-emulsifying drug delivery system (SEDDS)	Self-emulsifying drug delivery system for improved mucus permeation	Prolonged mucosal residence confirmed	Andreas Bernkop-Schnürch et al., [116]
5.	Nano emulsifying drug delivery systems of cannabinoids	Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD)BCS class II, extremely lipophilic compounds (logP of ~7 and~6 respectively)	.Lipophilic drugs such as THC and CBD are poorly soluble in the aqueous environment of the GI tract are effectively delivered.	Amnon Hoffman et al., [117]
8.	Self-microemulsifying drug delivery system for apigenin	To improve the solubility and dissolution of apigenin	Increased the solubility of apigenin in water for about 7500 folds.	Lili Zhao et al., [118]
9.	Binary mixed micelles systemsystem for apigenin	Copolymers of Soluplus® and Pluronic used to improve the efficacy of apigenin	apigenin -loaded mixed micelles (AP-M) were prepared by ethanol thin-film hydration	Zhenhai Zhang et al., [119]
10.	Curcumin-loaded self-assembled micelles	Ethanol solvent evaporation method was used.	Solubility of curcumin in self-assembled micelles was dramatically increased by 4200 times as compared to free curcumin.	Lu-Lu Wang et al., [120].

Microspheres

Definition Microspheres are spherical shaped micro sized particles with diameter 1–1000 μm protecting the drugs efficiently [3]. Microparticles are classified into two types; microcapsules (distinct capsule wall) and microspheres (dispersed throughout the matrix) [5]. The natural and synthetic polymers used for formulation of microspheres are polylactide-co-glycolide, albumin, polypropylene, gelatine, dextran, modified starches, polylactic acid. This delivery system is capable of controlling the release pattern of herbal components for a longer period i.e. can provide prolong release(sustain/control) [15, 61].

Description Microspheres are classified as biodegradable and non-biodegradable. Syringeability and target specificity made this delivery system more popular for bio-actives delivery of bioactives. In the last few decades, many herbal extract/ phytoconstituents are such as zedoary oil, tetrandrine, quercetin and Cynarascolymus extract are delivered as microspheres [80].

Method of preparation The following methods are used for the preparation of the microspheres. Some of them are discussed below-

- Solvent evaporation
- Single emulsion technique –

– Thermal cross-linking
– Chemical cross-linking agent

- Double emulsion technique
- Polymerization technique –

– Normal phase polymerization- Bulk, Suspension, Emulsion.
– Interfacial polymerization

- Spray-drying technique
- Wet inversion technique
- Complex coacervation
- Hot melt microencapsulation
- Extrusion spheronization
- Quasi-emulsion solvent diffusion method [95–97].

Solvent evaporation technique This is the most popular and commonly used technique. It utilizes both microencapsulation and the o/w emulsion, system for the preparation of microspheres. This method is used for the formulation of microparticles with low drug loading capacity [95, 97].

Double emulsion technique This method is also called the hydrous technique and is applicable for water-soluble drugs. This technique is carried out in fallowing steps-

1. Formation of primary emulsion (drug + aqueous solution of polymer)
2. Formation of double emulsion (addition of aqueous solution of polyvinyl alcohol)
3. Formation of multiple emulsion (addition of large aqueous phase (w/o/w))
4. Solvent evaporation (microsphere in solution)
5. Separation, washing and drying. (Collection of microspheres)

Wet inversion technique This technique is carried out in the following steps –

a. Addition of polymeric solution (dropwise through the small-sized nozzle) with acetic acid in an aqueous solution of a counterion such as sodium tripolyphosphate.
b. After the formation of microsphere addition of cross-linking agent (ethylene glycol di glycidyl ether)
c. Microspheres are then washed and freeze-dried [97].

Applications Novel carrier drug delivery systems are specially designed to achieve increase drug concentration at the target site, to reduce side effects and to improve bioavailability. The microspheres are promising carriers for the effective delivery of various herb extract/bioactive as well as synthetic drugs [75]. Zeng H. et al., prepared microspheres of locust bean gum (LBG) and poly(vinyl alcohol) (PVA) was developed for oral controlled release of buflomedil hydrochloride (BH) by emulsion crosslinking method using glutaraldehyde as crosslinker. Hence, microspheres of LBG and PVA can be used as a potential carrier for controlled oral delivery of highly water-soluble drugs like BH. Some of the recent literature is mentioned in Table 2- (2.1.2) [96, 98–106].

Emulsion

Definition As per the known definitions, Emulsion refers to isotropic dispersed systems of two immiscible liquids [1, 3]. They consist of an oily system dispersed in an aqueous system or vice-versa. One of them is internal phase and the other is continuous phase. In o/w emulsion water in the continuous phase whereas in w/o emulsion oil in the continuous phase. The emulsion is composed of natural/synthetic oils, solid/ liquid surfactants, and/or one or more hydrophilic solvents and co-solvents/ surfactants [3]. Its appearance is translucent to transparent liquid. Emulsions are generally classified ordinary

emulsion (0.1–100 μm), microemulsion (10–100 nm), sub-micro-emulsion (100–600 nm), etc. [107].

Description As a vesicular drug delivery system emulsion have a greater affinity towards lymphatic fluids. Hence nano-diametric vesicles can easily cross membrane barriers and enhance the efficacy of drug. Now-a-day's research is being focused to reduce the size of the globules to make the delivery system more stable for desired and improved pharmacokinetics of the drug. Various surfactants including polysorbate 20, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 60 castor oil, and PEG 300 caprylic and co-surfactants like ethanol, glycerine, poloxamer 407 and propylene glycol are widely used for micro-emulsion preparation.

The small droplet size of emulsion facilitated maximum surface area for the better penetration of herbal extract/poor aqueous soluble drug. The lipophilic drugs being delivered by o/w or o/w/o emulsion, while water-soluble drugs are delivered by w/o or w/o/w emulsion [107, 108].

Multiple emulsion Multiple emulsion are also known as "emulsions of emulsions" in which w/o/w emulsions consist of water droplets dispersed within larger oil droplets, which are dispersed in an aqueous continuous phase while o/w/o emulsion consists of larger water droplets enclosing smaller oil droplets, which are dispersed in a continuous oil phase [6].

Various advancements in emulsifying drug delivery systems were done in the last decade as microemulsion/nanoemulsion, self-emulsifying drug delivery system, etc. [109]. Various herbal extract and phytoconstituents are effectively delivered by emulsion drug delivery. Most of the phytoconstituents like bruceajavanica oil, silybin, wurenchun, *Ginkgo biloba* extracts, curcumin, apigenin, camptothecinlutein, kaempferiaparviflora, honokiol, wurenchun, ligusticum chuanxiong oil and zedoary oil are delivered as emulsion. The mechanism of drug absorption by emulsifying drug delivery is represented in fig.7 [5, 20, 110].

Self-emulsifying drug delivery system (SEDDS) SEDDS are defined as lipid-based drug delivery systems having drug, oil, surfactant, co-surfactant, co-solvent as main components. SEDDS is classified into self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS). Pouton C.W. et al., explained the successful absorption of the drug by SMEDDS from the gastrointestinal fluid. Droplet size that provides a larger surface area for rapid absorption, greater solubility and thus prevents from enzymatic degradation (prevent the first-pass metabolism). [107, 108] The ability to formulate SMEDDS depends on the solubility of the drugs in the excipients. The optimal solubility parameter (log p) of the poor water-soluble compounds lies in the range of 2 to 4. Majority of drugs are lipophilic with poor bioavailability which needs a smart carrier system for their effectiveness. Hence SEDDS acts as a promising carrier for effective drug delivery [62].

Method of preparation Various emulsification methods are used for the preparation of SEDDS. The key components which facilitate the effective penetration of drug at their target site –

1. Oils [Labrafaclipophile WL139, Oleic acid, Captex 200],
2. Surfactants [carboxyl (RCOO-) sulfate (ROSO3-), polyoxyethylene (Tweens)]
3. Co-solvents [propylene glycol, and polyethylene glycol]
4. Co-surfactant [Ethanol] [108].

Applications Emulsifying drug delivery has wide applications as transdermal, parenteral, pulmonary and ocular drug delivery for the alternative tool of oral drug delivery. As stated in the literature, the emulsifying drug delivery system is a better approach to delivery systems for low solubility and/or low permeability drugs, to facilitate their dissolution and absorption [45]. Several approved formulations available in the market are Neoral (Cyclosporine A), Norvir (Ritonavir) are Fortovase (Saquinavir). Wenli Liu et al. developed a self-micro emulsifying drug delivery system of baicalein to improve its oral bioavailability and solubility. S. hanmugam S et al. developed Solid Self Nano Emulsifying Drug Delivery System (SSNEDDS) in which bioactive carotenoid lutein incorporated with phosphatidylcholine enhanced bioavailability and solubility [79]. Amnon Hoffman et al., reported that high lipophilic compounds such as with higher log *p* value (about ~7and ~ 6) were also effectively delivered by nano emulsifying drug delivery systems such as cannabinoids Δ9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). Recent research work reported work of phytoconstituent by emulsifying drug delivery system is summarized in of Table 2-(2.1.3) [111–120].

Other drug delivery system

Hydrogel

Definition Hydrogel are cross linked water swollen hydrophilic polymeric network which can hold a large amount of water in their three-dimensional structure. It is also known as "Biomacromolecular hydrogels." They have wide range of applications in case of phytoconstituents delivery, synthetic drug delivery, diagnosis, cellular immobilization, separation of molecules and regulation of the barrier material for better absorption. Furthermore, they have been also applied in various fields like food industries, tissue engineering (artificial muscles), wound dressing, chemical valves, contact lenses and biomedical implant devices [3, 107, 121].

Description In the last few decades, hydrogels have been successfully investigated as a high mechanical strength

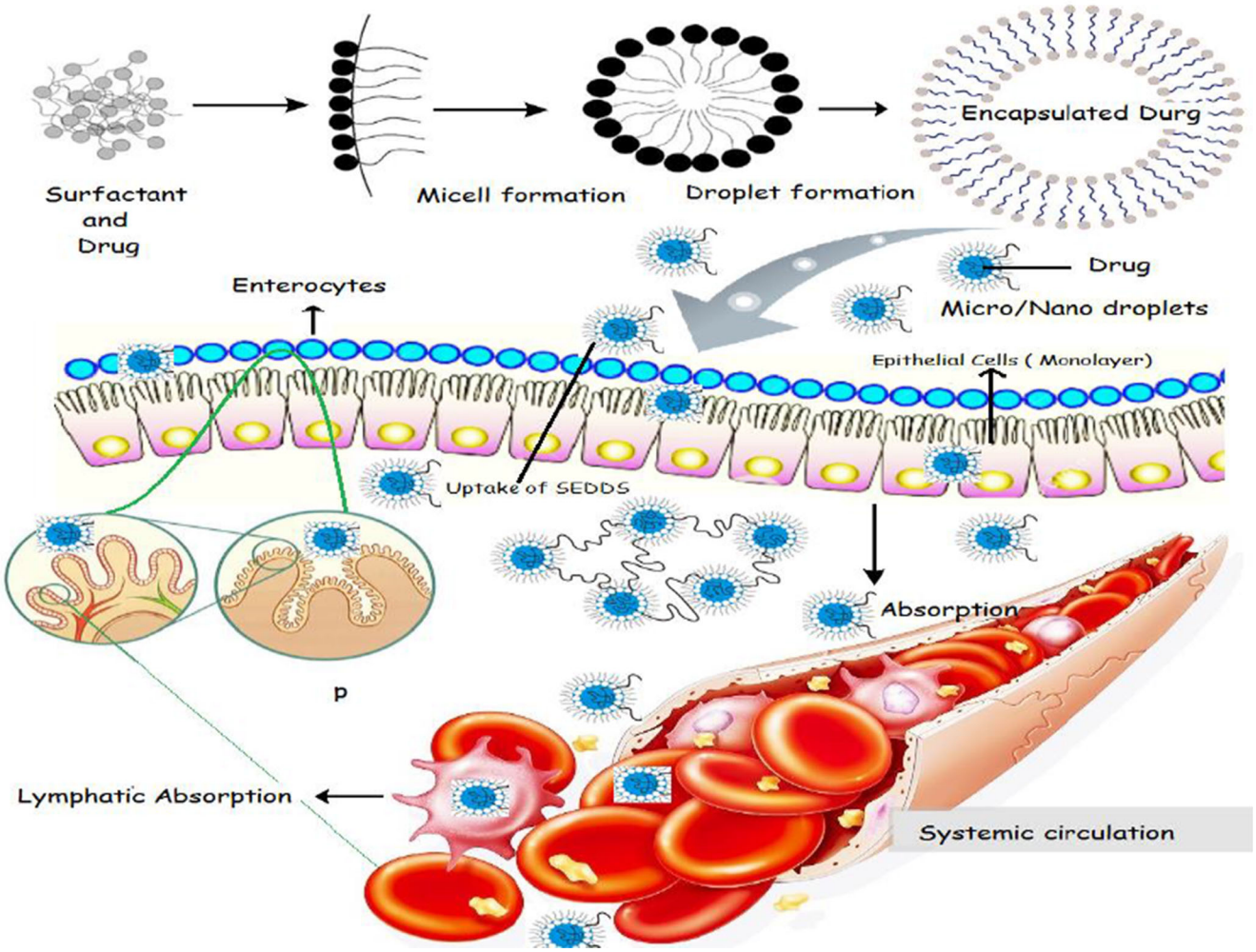

Fig. 7 The mechanism of drug absorption by emulsifying drug delivery. [5] [20, 110]

framework system. Ionic interaction and hydrogen bonding of cross-linking agents also assist insolubility improving in water. Varieties of natural and synthetic polymers like polysaccharides (e.g., alginate chitosan, hyaluronic acid, dextran, synthetic polymers such as polyethylene glycol, polyethylene oxide, polyacrylic acid, polyvinyl alcohol (PVA), poly-dimethyl aminoethyl methacrylate, poly lactic-co-glycolic acid, polycaprolactone, polypeptides and polyurethane, etc. Polymers are cross-linked using glutaraldehyde, N,N′-Methylenebisacrylamide, ethylene glycol di-methacrylate etc. are used in formulation of hydrogel. PVA chains cross-linked using glyoxal, glutaraldehyde, or borate. Poly(ethylene oxide) (PEO) and poly(ethylene glycol) (PEG) have gained attention recently for biomedical applications because of the nontoxic behavior of PEG, and its wide use in PEGylation of nanoscale drug carriers. Absorption of the active component through hydrogen is shown in Fig. 8 [122, 123].

Classification of hydrogels Depending on their method of preparation -

Homopolymer hydrogels;
Copolymer hydrogels;
Multipolymer hydrogels; and
Interpenetrating network (IPN) hydrogels.

Ionic hydrogels-

Neutral hydrogels (uncharged);
Anionic hydrogels (having negative charges only);
Cationic hydrogels (having positive charges only); or.
Ampholytic hydrogels (having both positive and negative charges).
Based on physicochemical structural features of the network, hydrogels.
Amorphous hydrogels (having covalent cross-links); or
Semicrystalline hydrogels (may or may not have covalent cross-links) [3, 121, 123, 124].

Applications Hydrogels are used for delivery of chemotherapeutic agents, herbal bioactive, tissue engineering, diagnosis,

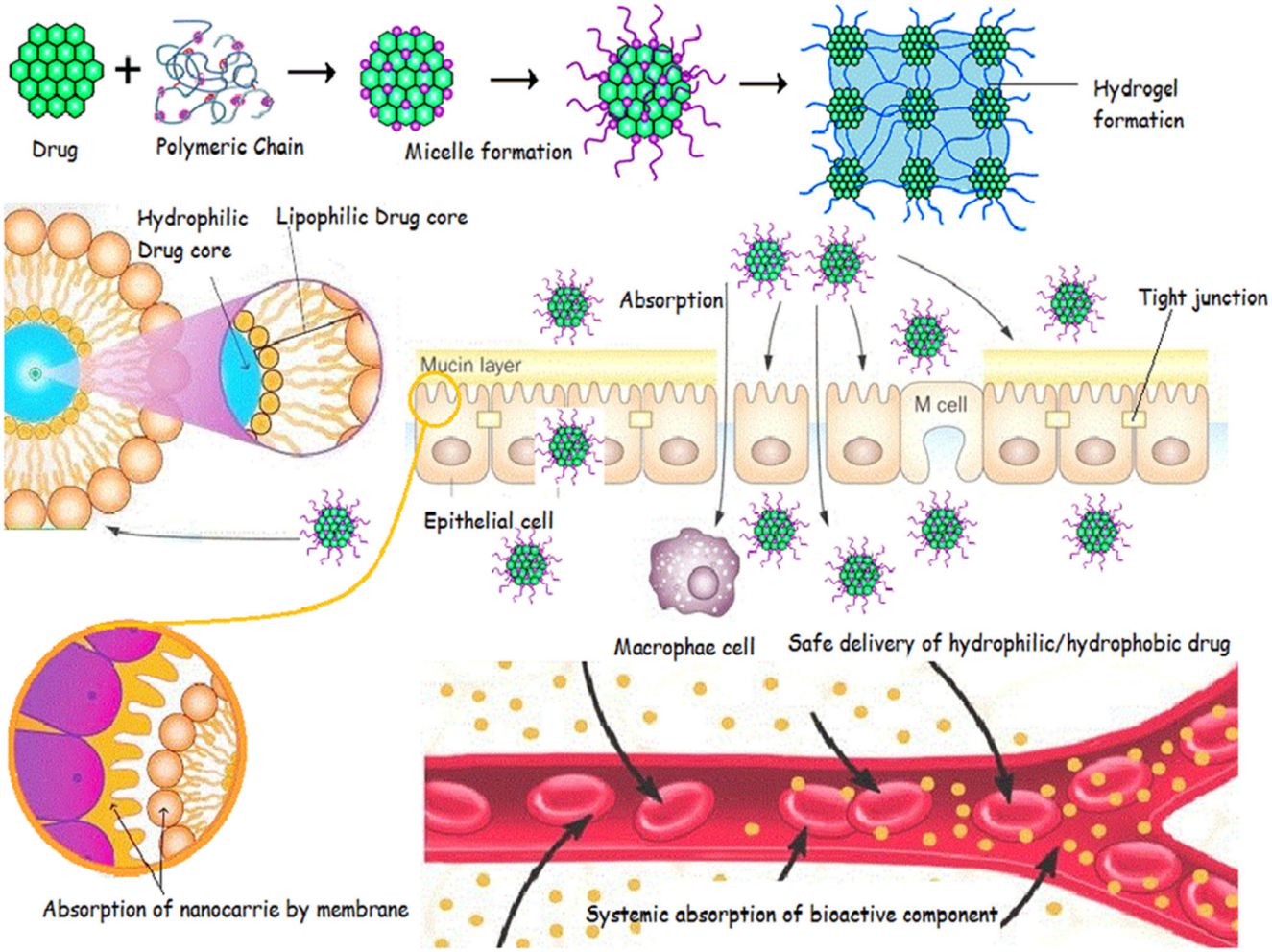

Fig. 8 Absorption of active component through hydrogen drug delivery system [122] [123]

cellular immobilization, separation of molecules [107]. Some of the examples are enlisted in Table 3-(3.1.1) [16, 125–133].

Cyclodextrins

Definition Cyclodextrins (CDs) are a family of cyclic oligosaccharides, obtained by enzymatic degradation of starch, composed of α (1–4)-linked D-glucopyranose units. They have cyclic structure, with hydrophilic outer core and hydrophobic inner cavity. They can effective encapsulate or supra molecular complex guest molecule with proper dimensions, leading to the formation of "inclusion complex". [3, 17, 134].

Description CDs have truncated cone structure with the ability to self-assemble and form aggregates in aqueous media. Formation of water-soluble drug/CD complexes can increase drug permeation through biological membranes. The stoichiometry of drug/CD complexes is most frequently 1:1. Natural CDs that is αCD, βCD and γCD have somewhat limited solubility in water so that verities of polymeric materials are used to modify natural CDs to obtain water-soluble CD derivatives. For example, hydroxypropylated CD derivatives (e.g., HPβCD and HPγCD-propylene oxide), carboxymethylated CDs (e.g., CMβCD-monochloroacetic acid), randomly methylated CDs (e.g., RMβCD- methyl iodide) and sulfobutylether CDs (e.g., SBEβCD and SBEγCD-4-butane sultone). These tailored CDs derivatives are currently applied in academic researches and industries. Presently researchers are focusing on use of CD polymers, inclusion complexes and other CD-based materials for solubility enhancement of poorly water-soluble drugs/ herbal bioactive as well as for drug stabilization, protection from light, thermal and oxidative stress, taste masking of drugs, and reduced dermal, ocular or gastrointestinal irritation etc. [135, 136].

Applications Cyclodextrins have versatile applications in the field of research, a large number of phytoconstituents and synthetic drugs are successfully delivered with the help of inclusion complex. Cyclic oligosaccharides have a great ability to enhance the effective delivery of bioactive components in the physiological system. Most of the isolated phytoconstituents are having such problems enzymatic degradation, poor aqueous solubility and bioavailability; these all issues are effectively resolved by

Table 3 Listing some of other drug delivery system to solve the hurdles related with herbal drug

OTHER NOVEL DRUG DELIVERY SYSTEM FOR HERBAL DRUG DELIVERY

3.1.1 HYDROGEL– recent literature on hydrogeldelivery system

S.No.	Bioactive compound	Modification and Method of preparation	**Polymer**	**Application**
1.	Epigallocatechin Gallate(EGCG) from *Camellia sinensis*	epigallocatechin gallate poor stability and permeability across intestine which improved by hydrogel formation	gelatin and γ-polyglutamic acid (γ-PGA),	anti-cancer, anti-inflammatory, antioxidant, anti-viral, cardio-protective and neuro-protective.. [125]
2.	Green tea catechin extract	Stability and long lasting effect	Pluronic F-127	Used for the treatment of periodontal diseases [126]
3.	Modified polymeric system of hydrogel for the delivery of Theophylline	Effective delivery of Theophylline by modified polymer in with Controlled release profile	Interpenetrating polymer network	asthma, chronic bronchitis, emphysema, [127]
4.	Naringenincontaining Hydrogel	-enhanced transdermaldelivery -used in atopic dermatitis	carboxymethyl cellulose/2-hydroxyethyl acrylate	antioxidant, antiinflammatory, anticancer, and anti-proliferative effects [128]
5.	Phytoconstituent containing Hydrogel (curcumin)	N,-Ocarboxymethyl chitosan/oxidized alginate hydrogel for improved stability and similar antioxidant efficiency	methoxy poly(ethylene glycol)bpoly(εcaprolactone) copolymer (MPEGPCL)	wound healing [129]
6.	Naringenin	Naringenin-loaded submicron emulsion improves topical effect	Isopropyl myristate Tween 80, Span 20	anti-inflammatory, antioxidant, free radical scavenger, antimutagenic and antiproliferative properties [130]
7.	Locust bean gum	Controllable drug	divinyl sulfone (DVS) crosslinking in a surfactant free cyclohexane	Immunomodulatory effect [131]
8.	Topical hydrogel containing *Fumaria vaillantiiloisel.* Extract	To improve topical administration	HPMC (Hydroxypropyl methylcellulose) 4000 cP, HPMC 15 cP and Carbomer 940,	Wound healing [132]
9.	quercetin and rutin-loaded ceramide liposomes containing hydrogel	enhance transdermal permeation of quercetin and its glycoside rutin	L-a-phosphatidylcholine	An antioxidant [133]
10.	Venlafaxine HCl	Drug release was increased by increasing acrylic acid concentration and decreasing cross-linker concentration	Polyethylene glycol-co-acrylic acid	an anti-depressant

3.1.2 CYCLODEXTRINS- Recent reported work on cyclodextrins for phytoconstituents delivery

S.No.	**Active component**	**Description about modification by cyclodextrine**	**Application**
1.	Myricetin	Solubility Enhancement by Complexation withHeptakis-O-(2-Hydroxypropyl) β-Cyclodextrin	Myricetin, a natural flavonol used in treatment of glycaemia [136]
2.	Piroxicam-Cyclodextrin Complexes	cyclodextrins (β -cyclodextrin (β -CD), methylated-βcyclodextrin (Me-βCD), andhydroxypropyl-βcyclodextrin (HP- β-CD)) used for complexsation by co-evaporation method.	Improved Buccal Delivery [137]
3.	Formononetinpermeation/retention	Hydroxypropyl- β -cyclodextrin	hydroxypropyl- β-cyclodextrin that enhanced its permeation [138]
4.	Quercetin and 3-O-methylquercetin	Complexation with β –cyclodextrin and hydrogel drug delivery	Natural antiviral and antioxidant agent, [139]
5.	Naringenin	Improvement of water solubility and dissolution profile	antiinflammatory, [140]
6.	Curcumin	cyclodextrin inclusion complex with Curcumin	Improved solubility and stability [141]
7.	*Curcuma longa* polyphenol	poor solubility improved by Complex formation with β-cyclodextrin	Pharmaceutical application [142]
8.	Red bell pepper carotenoids	2-hydroxypropyl βcyclodextrin complexed withcarotenoids to improve solubility	Used as natural pigment and important bioactive component used in food industry. [143]
9.	Carvacrol and thymol	Carvacrol and thymol have poor aqueous solubility which enhanced by inclusion with cyclodextrins	Antimicrobial and antioxidant activity [144]
10.	Piceatannol	Piceatannolencapsulation by natural and modified cyclodextrins	Solubility enhancement [145]

using cyclodextrins. Polymeric CDs are not only used in medical technology they are also applicable for food engineering, environmental pollution control technologies and oilfields industries [17, 135]. Recently reported work on cyclodextrins for phytoconstituents delivery is given in Table 3-(3.1.2) [136–145].

Conclusion

Numerous attempts have been made in the creation of powerful nanotechnologies which have been an essential part to tackle worldwide difficulties related to food processing, drug targeting, strength and adequacy of natural nutraceutical and pharmaceutical segments. These specialized developments have numerous applications in farming, food processing, sustenance bundling, nutraceutical supplements delivery of active constituents, etc. at present the enormous therapeutic efficacy of phytoconstituents is being explored by encapsulating them into the novel micro or nano-sized carrier system. The phytoconstituents have certain limitations like low solubilization, poor absorption, low bioavailability such hurdles can be effectively overcome by using an advanced delivery system. In the present article, we have summarized some of the recently reported research works of several phytoconstituent categories such as flavonoids, terpenoids, tannins, glycoside, alkaloids sugars, and xanthones, which have been successfully delivered to the target site. The efficacy of phytoconstituents at the desired target site such as liver, brain, heart, kidney and tumor cells was improved as reported in the literature. The nanotechnology delivery system improves the utilization of phytoconstituents in various fields like food industries, cosmetic industries, agriculture sector and especially highlights the increased utilization in pharmaceutical industries.

Nowadays, several advance strategies have been developed by researchers for the effective delivery of phytoconstituents into the physiological system which have produced better pharmacokinetic properties, bioavailability profile and subsequently desired pharmacological action is obtained. Researchers have worked for the development of better drug delivery tools for the phytoconstituents which are capable of overcoming the limitations of conventional therapy. In this review article, we have discussed several novel strategies for the delivery of phytoconstituents using Liposomes, Niosomes, Phytosomes, Transferosomes, Nanoparticles, Microemulsion, Microspheres, Hydrogel, and Cyclodextrins. An attempt to feature the fundamental application of phytoconstituents has been made successfully. Novel medication delivery has improved the problems of phytoconstituents associated with their properties. Here, the attempt to address a novel drug delivery system as a promising tool for the better and effective delivery of nutraceuticals and pharmaceutical components will help the readers, researchers and academicians to overcome the limitations issues. Effectiveness, stability studies, and shelf life of herbal drugs can be extensively improved by formulation development. Therefore, it can be hoped that the special structural features and properties of the novel carriers will contribute in the coming years for maximum efficacy of phytoconstituents and the benefit of humanity at large scale.

Future prospects

In the era of a novel drug delivery system plant, constituent delivery is extremely encouraging for further research to improve the carrier materials. Some of the Modern tailored delivery approaches have proved appropriate carrier system which can easily reduce the toxicity of drugs and boost up their activity thus, improve the overall quality of the isolated phytoconstituents. Herbal drug designing has a huge therapeutic prospective which needs to be investigated through novel approaches to have high efficacy of poor soluble bioactive/ drug (hydrophilic/lipophilic). They need to be evaluating for the short term and long term effects of their products. Current advancement should be focused on the commercial development of the bioactive phyto molecules. The cost of the delivery system needs to be minimized which will render the formulation as economic. The current market and research status of the novel delivery development system for phytoconstituents need to be explored for several therapeutic agents. The development of phytoconstituent delivery can help in achieving consistent quality, bioavailability, and therapeutic effects of herbal drugs and products. In the future, these phytoconstituents can be isolated and investigated for pharmacological and therapeutic activity through in-vivo models. However, the conventional available herbal products or phyto formulation can be redesigned into vesicular carrier drug delivery systems with improved physicochemical properties, pharmacokinetics and pharmacodynamics aspects.

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