

## Review Article

# Lipid Based Vesicular Drug Delivery Systems

**Shikha Jain, Vikas Jain, and S. C. Mahajan**

*Mahakal Institute of Pharmaceutical Studies, Behind Air Strip, Datana, Dewas Road, Ujjain, Madhya Pradesh 456664, India*

Correspondence should be addressed to Vikas Jain; [vikasjain111180@gmail.com](mailto:vikasjain111180@gmail.com)

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Vesicular drug delivery system can be defined as highly ordered assemblies consisting of one or more concentric bilayers formed as a result of self-assembling of amphiphilic building blocks in presence of water. Vesicular drug delivery systems are particularly important for targeted delivery of drugs because of their ability to localize the activity of drug at the site or organ of action thereby lowering its concentration at the other sites in body. Vesicular drug delivery system sustains drug action at a predetermined rate, relatively constant (zero order kinetics), efficient drug level in the body, and simultaneously minimizes the undesirable side effects. It can also localize drug action in the diseased tissue or organ by targeted drug delivery using carriers or chemical derivatization. Different types of pharmaceutical carriers such as polymeric micelles, particulate systems, and macro- and micromolecules are presented in the form of novel drug delivery system for targeted delivery of drugs. Particulate type carrier also known as colloidal carrier system, includes lipid particles, micro- and nanoparticles, micro- and nanospheres, polymeric micelles and vesicular systems like liposomes, sphingosomes, niosomes, transfersomes, aquasomes, ufasomes, and so forth.

## 1. Introduction

In the past few decades, considerable attention has been paid to the development of novel drug delivery system. The novel drug delivery systems aim to fulfill two prerequisites; that is, it delivers the drug at a rate directed by the needs of the body, over the period of treatment, and it carries the drug directly to the inflamed tissues and/or organ. Conventional delivery systems including prolonged release dosage forms are unable to meet none of these. Novel drug delivery system sustains drug action at a predetermined rate, relatively constant (zero order kinetics), efficient drug level in the body, and simultaneously minimizes the undesirable side effects. It can also localize drug action in the diseased tissue or organ by targeted drug delivery using carriers or chemical derivatization. Different types of pharmaceutical carriers such as polymeric micelles, particulate systems, and macro- and micromolecules are presented in the form of novel drug delivery system for targeted delivery of drugs. Particulate type carrier, also known as colloidal carrier system, includes lipid particles, micro- and nanoparticles, micro- and nanospheres, polymeric micelles, and vesicular systems like liposomes,

sphingosomes, niosomes, transfersomes, aquasomes, ufasomes, and so forth.

*1.1. Lipid Based Vesicular Drug Delivery System.* Vesicular drug delivery system can be defined as highly ordered assemblies consisting of one or more concentric bilayers formed as a result of self-assembling of amphiphilic building blocks in presence of water. The biologic origin of lipid based vesicles was first reported by Bingham in 1965 and hence was named as Bingham Bodies. Vesicular drug delivery systems are particularly important for targeted delivery of drugs because of their ability to localize the activity of drug at the site or organ of action thereby lowering its concentration at the other sites in body.

### *1.1.1. Advantages of Vesicular Drug Delivery System*

- (i) Both hydrophilic and hydrophobic drugs can be easily encapsulated.
- (ii) Bioavailability of drugs can also be improved.

- (iii) Elimination of rapidly metabolizable drug can be delayed.
- (iv) Circulation life time of drugs in the body can be prolonged.
- (v) Targeted delivery of drugs can often be achieved.
- (vi) Stability issues of liable drugs can be resolved.
- (vii) Toxicity issues of certain drugs can often be resolved.

*1.2. Liposomes as Vesicular Drug Delivery System.* Liposomes are colloidal, concentric bilayered vesicles where aqueous compartment is entirely enclosed by a bilayer membrane, mainly composed of natural or synthetic lipids. The essential components of liposomal drug delivery system include phospholipids (mainly phosphatidylcholine) and cholesterol where cholesterol acts as a fluidity buffer. Although cholesterol do not participate in bilayer formation, it can be added to phosphatidylcholine up to 1:1 or even 2:1 molar ratio of cholesterol to phosphatidylcholine. Liposomes have gained much importance as potential drug carrier systems for targeted drug delivery [1]. Different researches on liposomes as vesicular drug delivery system are presented in Table 1.

#### *1.2.1. Advantages of Liposomes as Vesicular Drug Delivery System [2]*

- (i) Liposomes are suitable to deliver hydrophilic and lipophilic drugs.
- (ii) Improved stability, protects the encapsulated drug from environment.
- (iii) Reduced toxicity.
- (iv) Reduced exposure of sensitive tissues to toxic drugs and their metabolites.
- (v) Liposomes are suitable to deliver small molecular weight drugs as well as high molecular weight drugs.
- (vi) Target specific delivery can be achieved.
- (vii) Improved pharmacokinetic properties as reduced elimination and increased circulation life time.

#### *1.2.2. Disadvantages of Liposomes as Vesicular Drug Delivery System*

- (i) Liposomes are leaky in nature leading to premature drug release.
- (ii) Poor encapsulation efficiency for hydrophilic drug.
- (iii) Liposomes are expensive.
- (iv) Liposomes possess short half-life.

### *1.3. New Eras of Vesicular Drug Delivery Systems*

*1.3.1. Niosomes.* Requirement of cryogenic atmosphere for the handling of liposomes have prompted the use of nonionic surfactants for the preparation of vesicular drug delivery systems. This newly introduced vesicular drug delivery system

was termed as niosome which consist of unilamellar or multilamellar vesicles. Niosomes, that is, non-ionic surfactant vesicles, are microscopic lamellar vesicles formed when non-ionic surfactants (mainly of alkyl or dialkyl polyglycerol ether class) are added to cholesterol with subsequent hydration in aqueous media. Addition of cholesterol provides rigidity to the bilayer leading to the formation of less permeable niosomes. Addition of nonionic surfactants to niosomes increases the size of vesicles and provides charge to the vesicles and hence increases the entrapment efficiency of niosomes. Niosomes possess structure that is similar to liposomes and hence represent a promising drug delivery module. Niosomes are expected to be better drug carrier system than liposomes upon consideration of factors like cost, stability, entrapment efficiency, bioavailability, and so forth [3]. Different researches on niosomes as vesicular drug delivery system are presented in Table 2.

#### *(1) Advantages of Niosomes [4]*

- (i) Niosomes are relatively more stable.
- (ii) They do not require any special handling and storage condition.
- (iii) Niosomes are osmotically active.
- (iv) Niosomes can entrap drugs with wide range of solubility.
- (v) They can serve as a depot system to release the drug slowly as and when required.
- (vi) Niosomes are more flexible in design and structure than liposomes.
- (vii) They can increase oral, topical, and parenteral bioavailability of drugs.
- (viii) They improve the therapeutic performance of entrapped drug simply by restricting its effect to the target cells and by reducing the clearance of the drug.

*1.3.2. Transfersomes.* Because of the fact that liposomes and niosomes have poor skin permeability, their permeable nature, and their aggregation and fusion in skin tissues, they are not suitable for transdermal delivery of drugs and hence lead to the development of new type of carriers called transfersomes in 1991 by Gregor Cevc. Transfersomes means carrying body and is derived from Latin word "Transferre" (meaning to carry across) and a Greek word "some" (meaning body). Thus transfersomes can be defined as ultradeformable, stress responsive, complex vesicles possessing an aqueous core surrounded by complex bilayer of lipids. These artificial vesicles are composed of one natural amphiphilic lipid (e.g., phosphatidylcholine, dipalmitoylphosphatidylcholine) and are supplemented by a bilayer softener, that is, biocompatible surfactant (e.g., sodium cholate, span 80, and tween 80). Presence of amphiphilic surfactants allows transfersomes to modify their membrane composition reversibly so as to penetrate through narrow skin pores [5]. Different researches on

TABLE 1: Researches on liposomes as vesicular drug delivery system.

S. number	Name and year of researchers	Drug	Experiment	Reference
01	Moghimipour et al., 2013	Triamcinolone acetoneide	Liposomal gel of Triamcinolone acetoneide were prepared to increase the deposition of drugs within the skin at the site of action and reduce side effects of drug using carbomer 940 as gelling agent. Four different gel formulations including hydroalcoholic, multilamellar large vesicles (MLV), small unilamellar vesicles (SUV), and blank MLV gel containing free drug were prepared. The <i>in vitro</i> drug release studies were determined using dialysis membrane method. The results of drug release showed that SUV liposomal gel has the most regular and the least interaction between the drug and polymer.	[17]
02	Divakar et al., 2013	Metformin hydrochloride	Sustained release liposomes of Metformin hydrochloride were prepared using film hydration technique using varying concentrations of phosphatidylcholine and cholesterol. The results of <i>in vitro</i> drug release studies showed that release from liposomal formulation followed first order kinetics and sustained for >12 hrs. The release mechanism was non-Fickian diffusion from all the formulations.	[18]
03	Shivhare et al., 2012	Salbutamol sulfate	Sustained release liposomes of Salbutamol sulfate were prepared using soya lecithin and cholesterol for the treatment of asthma. The results of <i>in vitro</i> dissolution studies exhibited drug release 96.24% in 12 h and the total release pattern was very close to the theoretical release profile of sustained release system. No significant difference in drug release profile was observed during the stability study period of 2 months.	[19]
04	Manjunatha et al., 2009	Acyclovir	Liposomes of Acyclovir were prepared for enhanced oral bioavailability using various ratios of phosphatidylcholine with cholesterol and Cephalin (phosphatidylethanolamine) with cholesterol by reverse phase evaporation method. The % entrapped drug in soya lecithin liposomes was 60.51% and sustained the release and at the end of 12 hr the % drug release was 73.89%. The liposomes stored at 4 °C were found to be stable for duration of two months compared to other storage conditions.	[20]
05	Shivhare et al., 2009	Pentoxifylline	Liposomes of Pentoxifylline were prepared for enhanced oral bioavailability. The formulation showed release up to 8 h and above 90% of drug was released. The drug release kinetics was governed by Peppas model. It was concluded that as the percentage of cholesterol increased there was subsequent increase in the stability and rigidity of liposomes but at the same time percentage drug entrapment was reduced due to reduction in phosphatidylcholine and as the concentration of cholesterol increases, the particle size increases which was maybe due to formation of rigid bilayer structure.	[21]
06	Patel et al., 2009	Ketoconazole	Liposomes of Ketoconazole were prepared for topical application. The drug entrapment efficiency was found to be $54.41 \pm 0.19\%$ . The percentage cumulative drug release was determined by diffusion studies and found to be $34.96 \pm 0.86\%$ after 12 hours. Stability studies present percent drug retention at refrigerated temperature (2–8 °C).	[22]
07	Agarwal et al., 2001	Dianthrol	Dianthrol was entrapped in vesicles to help in the localized delivery of the drug and to improve availability of the drug at the site to reduce the dose and, in turn, the dose-dependent side effects like irritation and staining. The mean liposome and niosomes sizes were $4 \pm 1.25$ and $5 \pm 1.5 \mu\text{m}$ , respectively. The drug-leakage study carried out at different temperatures of 4–8, $25 \pm 2$ , and 37 °C for a period of two months affirms that the drug leakage increased at a higher temperature. The <i>in vitro</i> permeation study using mouse abdominal skin showed significantly enhanced permeation with vesicles as indicated by flux of Dianthrol from liposomes ( $23.13 \mu\text{g}/\text{cm}^2/\text{h}$ ) and niosomes ( $7.78 \mu\text{g}/\text{cm}^2/\text{h}$ ) as compared with the cream base ( $4.10 \mu\text{g}/\text{cm}^2/\text{h}$ ).	[23]

TABLE I: Continued.

S. number	Name and year of researchers	Drug	Experiment	Reference
08	Srinath et al., 2000	Indomethacin	The liposomes of the drug were prepared to reduce the toxic side effects such as ulceration of the kidney and central nervous system (CNS) toxicity. The drug release profile from the liposomes was biphasic, and the highest percentage drug release was observed with large unilamellar vesicles (LUVs) (100 nm). The anti-inflammatory activity was increased from the first to fifth hour PC : CH : PG (1 : 0.5 : 0.2) and PC : CH : SA (1 : 0.5 : 0.1) liposomes showed the highest percentage inhibition of edema. The ulcer index of the free drug was about three times more than the encapsulated drug when administered at the same dose intraperitoneally to arthritic rats consecutively for 21 days.	[24]
09	Glavas-Dodov et al., 2003	5-Flurouracil	Liposome gels bearing an antineoplastic agent, 5-Flurouracil, intended for topical application have been prepared. Liposomes were prepared by the film hydration method by varying the lipid phase composition (PL 90H/cholesterol mass ratio) and hydration conditions of dry lipid film (drug/aqueous phase mass ratio). Topical liposome gels were prepared by incorporation of lyophilized liposomes into a structured vehicle (1%, m/m, chitosan gel base). The rate of drug release from liposome gels was found to be dependent on the bilayer composition and the dry lipid film hydration conditions. The drug release obeyed the Higuchi diffusion model, while liposomes acted as reservoir systems for continuous delivery of the encapsulated drug.	[25]
10	Dubey et al., 2007	Melatonin	Melatonin loaded liposomes were prepared and were found to be spherical, unilamellar structures having low polydispersity ( $0.032 \pm 0.011$ ) and nanometric size range ( $122 \pm 3.5$ nm). % entrapment efficiency of drug in ethosomal carrier was found to be $70.71 \pm 1.4$ . Stability profile of prepared system assessed for 120 days revealed very low aggregation and growth in vesicular size ( $7.6 \pm 1.2\%$ ). MT loaded ethosomal carriers also provided an enhanced transdermal flux of $59.2 \pm 1.22 \mu\text{g}/\text{cm}^2/\text{h}$ and decreased lag time of 0.9 h across human cadaver skin	[26]

transfersomes as vesicular drug delivery system are presented in Table 3.

(1) *Advantages of Transfersomes* [6]. Since both hydrophilic and hydrophobic moieties are present in transfersomes, they can accommodate drugs with wide range of solubility.

- (i) They are so deformable that they can penetrate even through the narrow pores of skin without measurable loss.
- (ii) Both low and high molecular weight drugs can be entrapped efficiently.
- (iii) They protect the encapsulated drug from enzymatic, metabolic degradation.
- (iv) They can be used for topical as well as systemic delivery of drugs.
- (v) They can act as a depot formulation to release the contained drug in controlled manner.

(2) *Disadvantages of Transfersomes*

- (i) They are chemically unstable.

(ii) Purity of phospholipids is another important criterion to be considered.

(iii) They are expensive.

1.3.3. *Aquasomes*. Administration of bioactive molecules in their active state has been a challenge to the pharmaceutical as well as biotechnological industries. Drug associated challenges such as suitable route and site of drug delivery, chemical and physical instability, poor bioavailability, and potentially serious side effects of these bioengineered molecules (peptide, protein, hormones, antigens, and genes) are some potential limitations for successful formulation of these biomolecules. The combination of biotechnology and nanotechnology (i.e., nanobiotechnology) has proposed a new approach as a solution to their formulation problem in the form of aquasomes.

Aquasomes are like "bodies of water" and can be defined as trilayered self-assembled nanostructures comprising a solid phase nanocrystalline core which is coated with an oligomeric film (made up of carbohydrate) on which biochemically active molecules are adsorbed with or without modification. Aquasomes are also known as ceramic

TABLE 2: Researches on niosomes as vesicular drug delivery system.

S. number	Name and year of researchers	Drug	Experiment	Reference
01	Parthibarajan et al., 2013	Voriconazole	Voriconazole niosomes were prepared by hand shaking and ether injection method using span 80 and cholesterol. The niosomes size range was 0.5–5 $\mu$ and 0.5–2.5 $\mu$ by hand shaking method and ether injection method, respectively. The percent entrapment efficiency of niosomal formulation containing Voriconazole was determined by dialysis method. The drug entrapment efficiency was found to be more than 84.53% in case of niosomes prepared by hand shaking process. The <i>in vitro</i> release profile of drug indicated 70.06% drug release extended period of 24 hours for the formulation prepared by hand shaking method.	[27]
02	Allam et al., 2011	Acyclovir	Ophthalmic niosomes of Acyclovir were prepared using two different methods, that is, film hydration method (FHM) and reverse phase evaporation method (REV). Particle size distribution studies showed that particle size was the smallest in absence of cholesterol and as the amount of cholesterol was increased, subsequent increase in particle size was observed. Corneal permeation studies showed that the cumulative amount permeated from most niosomal formulations was lower than that from solution containing drug, except the formulations having cholesterol: surfactant molar ratio 1:1. No corneal damage was observed during corneal hydration studies. Prepared niosomes were more stable at 4°C than at 25°C.	[28]
03	Sathyavathi et al., 2012	Brimonidine tartrate	Niosomal <i>in-situ</i> gel of Brimonidine tartrate was developed using different ratios of span series and cholesterol for improved ocular bioavailability for the treatment of glaucoma. Small unilamellar vesicles were prepared in the size range of 50–100 nm. The niosomal formulation was transformed into gel when it was instilled into the eye. All the formulations exhibited pseudoplastic rheological behavior and slow drug release pattern. Antiglaucoma activity of the prepared gel formulations showed more significant and sustained effect in reducing intraocular pressure than marketed and niosomal drops.	[29]
04	Rani et al., 2010	Rifampicin and gatifloxacin	Niosomes of rifampicin and gatifloxacin were prepared by lipid hydration technique using rotary flash evaporator. The prepared niosomes showed a vesicle size in the range of 100–300 nm, the entrapment efficiency was 73% and 70%, respectively. The <i>in vitro</i> release study showed 98.98% and 97.74% of release of rifampicin and gatifloxacin niosomes, respectively. The bactericidal activities of prepared formulation were studied by BACTEC radiometric method using the resistant strains (RF 8554) and sensitive strains (H37Rv) of <i>Mycobacterium tuberculosis</i> which showed greater inhibition and reduced growth index.	[30]
05	Ning et al., 2005	Clotrimazole	Niosomes were evaluated as delivery vehicles to develop alternative formulation for the vaginal administration of clotrimazole, to provide sustained and controlled release of appropriate drug for local vaginal therapy. Niosomes were prepared by lipid hydration method and were incorporated into 2% carbopol gel, and the systems were evaluated for drug stability in phosphate-buffered saline (pH 7.4) and simulated vaginal fluid at 37 $\pm$ 1°C. Further, the vesicle gel system was evaluated by antifungal activity and tolerability on tissue level in rat.	[31]
06	Mura et al., 2007	Minoxidil	Minoxidil loaded niosomes were formulated to improve skin drug delivery. Multilamellar niosomes were prepared using soya phosphatidylcholine. Minoxidil skin penetration and permeation experiments were performed <i>in vitro</i> using vertical diffusion franz cells and human skin treated with either drug vesicular systems or propylene glycol-water-ethanol solution (control). Penetration of Minoxidil in epidermal and dermal layers was greater with liposomes than with niosomal formulations and the control solution. The greatest skin accumulation was always obtained with nondialyzed vesicular formulations. No permeation of Minoxidil through the whole skin thickness was detected in the present study. It was concluded that alcohol-free liposomal formulations would constitute a promising approach for the topical delivery of Minoxidil in hair loss treatment.	[32]

TABLE 2: Continued.

S. number	Name and year of researchers	Drug	Experiment	Reference
07	Guinedi et al., 2005	Acetazolamide	Niosomes were prepared by reverse-phase evaporation and thin film hydration method using Span 40 or Span 60 and cholesterol in the molar ratios of 7 : 4, 7 : 6 and 7 : 7. Stability studies were carried out to investigate the leaching of drug from niosomes during storage. It was observed that the type of surfactant, cholesterol content, and the method of preparation altered the entrapment efficiency and drug release rate from niosomes. Higher entrapment efficiency was obtained with multilamellar niosomes prepared from Span 60 and cholesterol in a 7 : 6 molar ratio. Niosomal formulations have shown a fairly high retention of Acetazolamide inside the vesicles (approximately 75%) at a refrigerated temperature up to a period of 3 months. Multilamellar Acetazolamide niosomes formulated with Span 60 and cholesterol in a 7 : 4 molar ratio were found to be the most effective and showed prolonged decrease in intraocular pressure.	[33]
08	Ruckmani et al., 2000	Cytarabine hydrochloride	Niosome vesicles of Cytarabine hydrochloride were prepared by a lipid hydration method that excluded dicetylphosphate. The sizes of the vesicles obtained ranged from 600 to 1000 nm, with the objective of producing more blood levels <i>in vivo</i> . The study of the release of drug from niosomes exhibited a prolonged release profile as studied over a period of 16 hr. The drug entrapment efficiency was about 80% with Tween 80, Span 60, and Tween 20; for Span 80, it was 67.5%. The physical stability profile of vesicular suspension was good as studied over a period of 4 weeks.	[34]

nanoparticles. The solid core provides the structural stability, at the same time as the products of carbohydrate coating against dehydration, and stabilizes the biochemically active molecules, and so forth. The nanocrystalline core comprises polymers such as albumin, gelatin, or acrylate or Ceramic such as diamond particles, brushite (calcium phosphate), and tin oxide. Coating materials commonly used are sucrose, cellobiose, trehalose, pyridoxal 5 phosphate, chitosan, citrate, and so forth. Aquasomes are widely utilized for the delivery of insulin, hemoglobin, and enzymes like serratiopeptidase [7]. Different researches on aquasomes as vesicular drug delivery system are presented in Table 4.

#### (1) Advantages of Aquasomes [8]

- (i) Aquasomes preserves the conformational integrity and biochemical stability of bioactive molecules.
- (ii) Because of their size and structure stability, aquasomes avoid reticuloendothelial clearance or degradation by other environmental challenges.
- (iii) Aquasomes exhibit physical properties of colloids.
- (iv) Since aquasomal suspension contains colloidal range biodegradable nanoparticles, they are more concentrated in liver and muscles.
- (v) Since the drug is absorbed on to the surface of the system without further surface modification as in case of insulin and antigen delivery, they may not find any difficulty in receptor recognition on the active site so that the pharmacological or biological activity can be achieved immediately.

1.3.4. *Colloidosomes*. Colloidosomes are the advanced drug delivery system for the efficient delivery of proteins, vitamins,

and food supplements. They are hollow shell microcapsules consisting of coagulated or fused particles at the interface of emulsion droplets. They can be prepared by introducing colloidal particles into the continuous phase of a water-in-oil emulsion where the particles self-assemble at the interface between the two immiscible liquid phases and form a colloidal shell structure. Subsequently, the colloidal shell structures, hydrated by the water droplets dispersed in the oil phase, are transferred to an aqueous phase either by centrifugation or repeated washing. This methodology has been used to create colloidosomes with particles ranging from 5 nm to several microns in diameter [9].

#### (1) Advantages of Colloidosomes [10]

- (i) Controlled size of colloidosomes provides flexibility in applications and choice of encapsulated material.
- (ii) They possess better potential in controlling the permeability of the entrapped species and allow the selective and time release.
- (iii) Colloidosomes are easy to construct.
- (iv) Colloidosomes have good mechanical strength so that yield stress can be adjusted to withstand mechanical load and to enable release by defined shear rates.
- (v) Fragile and sensitive materials such as biomolecules and cells can be easily encapsulated.

#### (2) Disadvantages of Colloidosomes

- (i) They have poor yield.
- (ii) When colloidosomes are transferred from organic to aqueous media, large proportion of colloidosomes is lost.

TABLE 3: Researches on transfersomes as vesicular drug delivery system.

S. number	Name and year of researchers	Drug	Experiment	Reference
01	Duangjit et al., 2013	Meloxicam (MX)	The aim of this study is to develop Meloxicam- (MX-) loaded cationic transfersomes as skin delivery carriers and to investigate the influence of formulation factors such as cholesterol and cationic surfactants on the physicochemical properties of transfersomes. Transfersomes provided greater MX skin permeation than conventional liposomes and MX suspensions. The skin permeation by the vesicles prepared in this study may be due to the vesicle adsorption to and/or fusion with the stratum corneum.	[35]
02	Irfan et al., 2012	Ibuprofen	Transfersomes of Ibuprofen were prepared using various ratios of soya phosphatidylcholine, span 80, and tween 80, using lipid film hydration by rotary evaporation method. The % entrapment efficiency of ibuprofen was $47.8 \pm 2.2$ and the elasticity of both increases with increase in surfactant conc. and were found to be $34.4 \pm 1.4$ and $26.5 \pm 1.6$ . Stability studies for transfersomes were carried out for 5 weeks at $45^\circ\text{C}$ . <i>In vitro</i> skin permeation studies were carried by human cadaver skin using franz diffusion cell, and release of the drug and flux was found to be 2.5824 and 1.9672 $\mu\text{g}/\text{cm}^2/\text{hr}$ , respectively, after 24 hrs.	[36]
03	Duangjit et al., 2011	Meloxicam (MX)	The goal of this study was to develop and evaluate the potential use of liposome and transfersome vesicles in the transdermal drug delivery of Meloxicam (MX). MX-loaded vesicles were prepared and evaluated for particle size, zeta potential, entrapment efficiency (%EE), loading efficiency, <i>in vitro</i> skin permeation study, and stability. The vesicles were spherical in structure, 90 to 140 nm in size, and negatively charged ( $-23$ to $-43$ mV). The %EE of MX in the vesicles ranged from 40 to 70%. It was concluded that transfersomes provided a significantly higher skin permeation of MX compared to liposomes.	[37]
04	Patel et al., 2009	Curcumin	The transfersomes were formulated by modified hand shaking method using surfactant such as Tween 80 and Span 80 in various concentrations. The entrapment efficiency of PC (Lecithin): Edge Activator (Tween 80 and Span 80) ratio dependent was determined. The average vesicle size for the optimized formula was found to be 339.9 nm and the entrapment efficiency was $89.6 \pm 0.049$ .	[38]
05	Jain et al., 2003	Dexamethasone	In the present study transfersomes were prepared by using dexamethasone as a model drug. The stability study was performed at $4^\circ\text{C}$ and $37^\circ\text{C}$ . An <i>in vitro</i> drug release study has shown a nearly zero order release of drug and no lag phase. The absence of lag phase in comparison to liposomes and ointment is attributed to the greater deformability, which may account for better skin permeability of transfersomes. <i>In vivo</i> studies of transfersomes showed better antiedema activity in comparison to liposomes and ointment, indicating better permeation through the penetration barrier of the skin.	[39]

(iii) Insufficient locking of shell leads to coalescence of colloidosomes.

**1.3.5. Cubosomes.** In presence of polar solvents, the hydrophobic region of amphiphilic molecules self-assembles into an array of thermodynamically stable liquid crystalline phases with lengths on nanometer scale. These liquid crystalline phases possess sufficient degree of molecular orientation and structural symmetry. One example is bicontinuous cubic liquid crystalline phase.

Bicontinuous cubic phases are extremely viscous, optically isotropic, and solid, similar to liquid crystalline substance with cubic crystallographic symmetry, and consist of two divided, continuous but nonintersecting hydrophilic regions divided by a lipid bilayer in to a periodic minimal surface with zero curvature. This bicontinuous nature of such cubic phases differentiates them from the micellar or

discontinuous cubic containing micelles packed in cubic symmetry. One of the important properties these cubic phases have is their ability to be dispersed in to particles, termed as cubosomes. They are typically produced by high-energy dispersion of bulk cubic phase, followed by colloidal stabilization using polymeric surfactants. After formation of the cubosomes, the dispersion can be formulated as a product and then applied to a bodily tissue. The term "cubosomes" was given by Larsson, which reflects the cubic molecular crystallography and similarity to liposomes [11]. Different researches on cubosomes as vesicular drug delivery system are presented in Table 5.

(1) *Advantages of Cubosomes* [12]

(i) Cubosomes have the potential for targeted release and controlled release of bioactive agents.

TABLE 4: Researches on aquasomes as vesicular drug delivery system.

S. number	Name and year of researchers	Drug	Experiment	Reference
01	Nanjwade et al., 2013	Etoposide	Etoposide aquasomes were obtained through the formation of an inorganic core of calcium phosphate covered with a lactose film and further adsorption of the Etoposide. The diameter of drug loaded aquasomes was found to be in the range of 150 to 250 nm. Entrapment efficiency was found to be 88.41%. The average targeting efficiency of drug loaded nanoparticles was found to be 42.54% of the injected dose in liver, 12.22% in lungs, 4.14% in kidney, and 25.12% in spleen. The results discovered that the nanoparticles bearing drug showed better drug targeting to liver followed by spleen, lungs, and kidney. Stability studies indicated that 4°C is the most suitable temperature for storage of Etoposide nanoparticles.	[40]
02	Vengala et al., 2013	Piroxicam	Ceramic nanoparticles of poorly aqueous soluble Piroxicam were prepared to explore the relationship between particle size and dissolution profile. The percent yield of ceramic nanoparticles was 66.7%. The dissolution profile of piroxicam aquasomes was obtained in 0.1 mol/L hydrochloric acid solution. The release of piroxicam from ceramic nanoparticles was linear and exhibited zero order kinetics. It was observed that the piroxicam ceramic nanoparticle formulations elicited release of piroxicam in 1 h and 15 min.	[41]
03	Tiwari et al., 2012	Dithranol	Aquasomes were prepared using colloidal precipitation method and then dispersed into a cream for the treatment of psoriasis. The drug loading efficiency was found to be 84.8% w/w. 55.93% drug release was observed in 7 hours. In <i>in vitro</i> drug release studies from both the creams revealed that aquasome loaded cream controlled the drug release as compared to plain cream.	[42]
04	Kommineni et al., 2012	Insulin	Insulin bearing aquasomes were prepared by the standard method employed for the preparation of aquasomes. The prepared systems were characterized for size, shape, size distribution, drug loading efficiency, and <i>in vivo</i> performance. The <i>in vivo</i> performance of the formulated aquasome was compared with standard porcine insulin solution, and better results were observed compared to insulin solution.	[43]
05	Cherian et al., 2000	Piroxicam	Ceramic nanoparticles were prepared using two techniques, namely, coprecipitation by refluxing and coprecipitation by sonication. Core preparation was finally done using sonication approach, based on the higher % yield ( $42.4 \pm 0.4\%$ ) and shorter duration (1 day) compared to the reflux method ( $27.4 \pm 2.05\%$ , 6 days). Morphological evaluation revealed spherical nanoparticles (size $56.56 \pm 5.93$ nm for lactose coated core and $184.75 \pm 13.78$ nm for piroxicam loaded aquasomes) confirming the nanometric dimensions.	[44]

- (ii) Hydrophilic, hydrophobic, and amphiphilic drugs can easily be encapsulated into cubosomes.
- (iii) Cubosomes are easy to be prepared.
- (iv) Since the lipids used in the formulation of cubosomes are biodegradable in nature, cubosomes are biodegradable.
- (v) Cubic crystalline structure and high internal surface area allow high drug payloads.
- (vi) Cubic phases are more bioadhesive in nature, so that they can be conveniently used in topical and mucosal delivery of drugs.

1.3.6. *Sphingosomes*. With liposomes, there are certain issues related with their stability including oxidation, hydrolysis, degradation, leaching, sedimentation, drug aggregation, and

so forth. Therefore, to improve stability the researchers have led us to the development of Sphingosomes [13, 14].

Sphingosomes can be defined as colloidal, concentric bilayered vesicles where aqueous compartment is entirely enclosed by a bilayer membrane, mainly composed of natural or synthetic sphingolipids; that is, sphingosomes are liposomes that are composed of sphingolipids. Sphingosomes consist of sphingolipid (sphingomyelin) and cholesterol at acidic intraliposomal pH ratio of sphingomyelin and cholesterol varying in the range of 75/25 mol%/mol% (55/45 mol%/mol% most preferably). Sphingosomes is more stable than the phospholipid liposome because of the following.

- (i) Sphingolipid are built up by only amide and ether linkage. They are more resistant to hydrolysis than ester linkage of lecithin.

TABLE 5: Researches cubosomes as vesicular drug delivery system.

S. number	Name and year of researchers	Drug	Experiment	Reference
01	Hundekar et al., 2014	Diclofenac sodium	Transdermal cubosomes of Diclofenac sodium were prepared to increase the percutaneous absorption with reduced systemic side effects. It was concluded that the Diclofenac sodium cubosome gel shows enhanced drug penetration through Wistar albino rat skin <i>in vitro</i> and <i>in vivo</i> and cubosome gel containing Diclofenac sodium may offer promise as an anti-inflammatory dosage form.	[45]
02	Yang et al., 2012	Amphotericin B (AmB)	Cubosomes of Amphotericin B (AmB) were prepared for enhanced oral bioavailability. AmB-loaded cubosomes were prepared by using the SolEmuls technology. The encapsulation efficiency and the results of <i>in vitro</i> release and stability studies in simulated gastrointestinal fluid further demonstrated that AmB was successfully encapsulated in cubosomes. Oral administration in rats did not show nephrotoxicity and its relative bioavailability was approximately 285% as compared to Fungizone.	[46]
03	Wu et al., 2011	Amphotericin B (AmB)	Oral formulation of Amphotericin B (AmB) using phytantriol- (PYT-) based cubosomes was prepared. Cubosomes with reproducible, narrow particle size distribution and a mean particle size of $256.9 \text{ nm} \pm 4.9 \text{ nm}$ were obtained. To overcome the poor drug solubility and increase the drug-loading rate, the encapsulation efficiency determined by HPLC assay was $87.8\% \pm 3.4\%$ , and stability studies in simulated gastric fluids further confirmed that AmB was successfully encapsulated in cubosomes.	[47]
04	Han et al., 2010	Flurbiprofen (FB)	Ophthalmic cubosomes of Flurbiprofen were prepared to reduce ocular irritancy and improve bioavailability. Cubosomes were prepared using hot and high-pressure homogenization. The particle size of each cubosome formulation was about 150 nm. Histological examination revealed that neither the structure nor the integrity of the cornea was visibly affected after incubation with cubosomes bearing Flurbiprofen. The AUC FB cubosome was $486.36 \pm 38.93 \text{ ng/mL}\cdot\text{min}/\mu\text{g}$ , which was significantly higher than that of FB Na eye drops ( $P < 0.01$ ). Compared with FB Na eye drops, the $T_{\text{max}}$ of FB cubosome was about 1.6-fold higher and the MRT was also significantly longer ( $P < 0.001$ ).	[48]
05	Morsi et al., 2013	Silver sulfadiazine	Cubosome dispersions were formulated by an emulsification technique using different concentrations of a lipid phase monoolein and the nonionic surfactant, Poloxamer 407, with or without polyvinyl alcohol. The optimum formulae were incorporated in a chitosan, carbopol 940 or chitosan/carbopol mixture based hydrogels, to form cubosomal hydrogels (cubogels). For the optimal cubogel formulae, an <i>in vivo</i> histopathological study was conducted on rats to predict the effectiveness of the newly prepared cubogels in comparison with the commercially available cream (Dermazin). <i>In vivo</i> histopathological study results showed that prepared cubogels were successful in the treatment of deep second degree burn which may result in better patient compliance and excellent healing results with least side effects in comparison with the commercially available product.	[49]
06	Tu et al., 2014	Curcumin	Curcumin was designed into the cubosome with piperine in order to improve oral bioavailability and tissue distribution of curcumin. The characteristic of the cubosome has demonstrated that the curcumin and piperine were encapsulated in the interior of the cubosome and the crystal form was Pn3m space. The pharmacokinetic test revealed that the cubosome could improve the oral bioavailability significantly compared to the suspension of curcumin with piperine and be mainly absorbed by the spleen.	[50]

- (ii) They also contain a smaller amount of double bonds than lecithin and thus less subjected to rancidity.
- (iii) They also absorb a smaller amount oil than lecithin that in consequence change in geometry and diameter.

The major sphingolipids that have been used in the formulation of sphingosomes include Sphinganines, Hexadecaphinganine, Lysosphingomyelins, and lysoglycosphingolipids, N-Acylsphingosines, Gangliosides, Glucuronosphingolipids, Phosphoglycosphingolipids, and so forth.

#### (1) Advantages of Sphingosomes [15]

- (i) Sphingosomes have better drug retention characteristics.
- (ii) They can be administered by subcutaneous, intravenous, intra-arterial, intramuscular, oral, and transdermal routes of drug administration and so forth.
- (iii) They provide selective passive targeting to tumor tissue.
- (iv) Sphingosomes increase efficacy and therapeutic index of the encapsulated drug.
- (v) Stability is increased via encapsulation.
- (vi) Toxicity of the encapsulated drug is reduced.
- (vii) Sphingosomes improve pharmacokinetics of the encapsulated drug simply by increasing the circulation time.
- (viii) Design of sphingosomes is so flexible to allow coupling with site specific ligands to achieve active targeting.

#### (2) Disadvantages of Sphingosomes

- (i) Since sphingolipids are expensive, sphingosomes are not economic.
- (ii) Sphingosomes have poor entrapment efficiency.

**1.3.7. Ufasomes [16].** Since topical route of administration has lower risk of systemic side effects, topical treatment appears to be most favorable route of administration, although the stratum corneum restricts the penetration of drugs into viable skin. Ufasomes have been developed to enhance penetration of drug into viable skin through stratumcorneum. Ufasomes containing lipid carriers that attached to the skin surface and allows lipid exchange between the outermost layers of the stratumcorneum. This carrier system appears to be promising for efficient delivery of drugs. Besides liposomes and niosomes, ufasomes have been developed for their potential for topical/transdermal delivery of drugs, proteins, peptides, hormones, and so forth. The formation of fatty acid vesicles was first reported by Gebicki and Hicks in 1973 and the vesicles formed were initially named "ufasomes," reflecting unsaturated fatty acid liposomes. Ufasomes, that is, unsaturated fatty acid vesicles, are suspensions of closed lipid bilayers that are composed of fatty acids and ionic surfactants. The pH range of ufasomal suspension varies from 7 to 9.

In ufasomes, fatty acid molecules assemble themselves in a manner that their hydrocarbon tails are directed toward the inner side of the membrane and the carboxyl groups remains in contact with water.

#### (1) Advantages of Ufasomes

- (i) Ufasomes are more stable than liposomes.
- (ii) They have better entrapment efficiency for both hydrophilic and hydrophobic drugs.
- (iii) Ufasomes are cheaper than liposomes.

## 2. Expert Opinion

Vesicular drug delivery systems are now useful in various scientific fields. In recent era these systems have become one of the vast and major delivery systems due to its efficient properties and functions like selective targeting. However, the pharmacokinetics of drugs is in research for making these drug delivery systems most valuable. Also the mechanism of action of this system is in its complete progress.

Sphingosomes are bilayered vesicles that have an aqueous volume completely covered by membrane lipid bilayer. This bilayer is formed of natural or synthetic sphingolipid. Due to their flexibility in size and composition, they have been developed for encapsulating chemotherapeutic agent, biological macromolecule, and diagnostics.

Aquasomes are responsible for preserving the structural integrity of proteins including hemoglobin and insulin, thus promoting a better therapeutic effect. They are the self-assembling surface-modified nanocrystalline ceramic cores. These preparations have been characterised for immunological response and may be used as immunoadjuvants.

Transfersomes have large molecules like peptides, hormones, and antibiotics. Because of these properties, they have their wide role in the drug delivery systems. Also for the drugs with poor penetration due to undesirable physiological characters and drugs for faster targeted actions, they have been widely used.

Colloidosomes have efficient results and properties for release of drugs, proteins, vitamins, and cosmetics and food supplements. Due to this property the colloidal drug delivery systems have changed the terms of treatment and diagnosis. They have wide control over size, permeability, mechanical strength, and compatibility.

Cubic liquid crystals are transparent and isotropic phases that are physically stable in excess water representing a unique system for the production of pharmaceutical dosage forms. Cubosome nanoparticles formed from cubic liquid crystalline phases are a unique and intriguing self-assembled material with enormous potential in areas as diverse as medicine, materials science, and consumer products.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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