

Vesicular drug delivery systems: A novel approach for drug targeting

Sunil Kamboj^{1*}, Vipin Saini¹, Nancy Magon¹, Suman Bala¹, Vikas Jhawat¹

*Corresponding author:

Sunil Kamboj

¹Department of Pharmaceutics, M.M. College of Pharmacy, M.M. University, Mullana, Ambala (Haryana), 133203

Abstract

The objective of the study is to evaluate the potential of novel vesicular drug delivery systems for drug targeting. Novel vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action. Vesicular drug delivery systems have been used to improve the therapeutic index, solubility, stability and rapid degradation of drug molecule. Thus a number of novel vesicular drug delivery systems have been developed that allow drug targeting and sustained or controlled release of drug. The focus of this review is to discuss various lipoidal and non-lipoidal vesicles with special emphasis on targeting of drugs.

Keywords: Vesicular drug delivery systems, drug targeting, bioavailability enhancement, lipoidal and non-lipoidal biocarriers.

Introduction

Novel vesicular drug delivery systems aim to deliver the drug at a rate directed by need of body during the period of treatment, and channel the active entity to the site of action. Biologic origin of these vesicles was first reported in 1965 by 'Bingham' and has been given the name 'Bingham bodies'. A number of novel vesicular drug delivery systems have been emerged encompassing various routes of administration, to achieve targeted and controlled drug delivery [1]. Targeted drug delivery is a mode of delivering the therapeutic agent to the tissues of interest while reducing the relative concentration of therapeutic agent in remaining tissues which improves the therapeutic efficacy and reduces the side effects. Drug targeting means the delivery of drugs to receptor, organs or any other specific part of body to which one wishes to deliver the entire drug [2]. The targeted drug delivery system was developed by Paul Ehrlich, in 1909, which delivered the therapeutic agent directly to diseased cells. Since then, numbers of carriers were utilized to deliver the drug at target site; these include immunoglobulins, serum proteins, synthetic polymers, microspheres, liposomes, niosomes, erythrocytes etc. Among different carriers, vesicular drug delivery systems are found to be well renowned [3]. These systems have also been used to improve the therapeutic index, solubility, stability and rapid degradation of drug molecules [1-4]. In this article, an attempt has been made to discuss various types of vesicular drug delivery systems with special emphasis on their drug targeting application.

Types

The targeted vesicles are classified on the basis of their composition (5):

- Lipoidal biocarriers
- Non-lipoidal biocarriers

Table 1: Types of vesicles for site specific targeting

| Lipoidal biocarriers for site specific targeting | |
|---|-------------------|
| 1. Liposomes | 2. Emulsomes |
| 3. Enzymosomes | 4. Ethosomes |
| 5. Sphingosomes | 6. Transferosomes |
| 7. Pharmacosomes | 8. Virosomes |
| Non-lipoidal biocarriers for site-specific targeting: | |
| 1. Niosomes | 2. Bilosomes |
| 3. Aquasomes | |

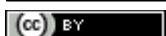
Lipoidal Biocarriers for Site Specific Targeting

Liposomes

Liposomes are simple microscopic lipid vesicles ranging from 20 nanometers to several micrometers in size. They have lipid bilayer structures, which is present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecules in such a way that both hydrophilic and lipophilic drugs can be successfully entrapped [1,6,7]. The lipophilic drugs get entrapped within bilayer membrane whereas hydrophilic drugs get entrapped in the central aqueous core of the vesicles[6]. Liposomes can be used for both oral as well as topical drug targeting. They act by the following mechanisms [8].

They attach to cellular membrane and appear to fuse with them, releasing their content into the cell.

Sometimes they are taken up by the cell and their phospholipids are incorporated into the cell membrane by which the drug trapped inside is released.



In the case of phagocytic cell, liposomes are taken up, the phospholipid walls are acted upon by organelles called lysosomes and entrapped drug is released.

A number of components are present in liposomes, with phospholipid and cholesterol being the main ingredients[1]. The most commonly used natural phospholipid is phosphatidylcholine (PC). Some other phospholipids such as phosphatidyl ethanolamine (PE), phosphatidyl serine (PS), phosphatidyl inositol (PI) and phosphatidyl glycerol (PG) can also be used[9]. Cholesterol is added to the bilayer mixture for the following purposes[1,8].

It acts as a fluidity buffer.

Provides rigidity and orientational order

Acts as intercalator with phospholipid molecules

Decreases the permeability coefficient of negative, neutral as well as positively charged membranes to Na⁺, K⁺, Cl⁻ and glucose.

Stabilizes the membrane against temperature changes, leading to lower permeability at elevated temperature and impart better stability.

Table 2: Several types of liposomes with composition and applications

| S. No. | Type | Composition | Applications | Reference |
|--------|--|---|--|-----------|
| 1 | Conventional liposomes (CL) | Neutral or negatively charged phospholipids with cholesterol | Targeted delivery of antimicrobial agent to macrophages, vaccination | [1,10] |
| 2 | pH sensitive liposomes | Phospholipids such as phosphatidyl ethanolamine, dioleoylphosphatidylethanolamine | Tumourtargeting, coated pit endocytosis | [1] |
| 3 | Cationic liposomes | Positively charged cationic lipids | Gene delivery | [1,8,10] |
| 4 | Long circulatory (stealth) liposomes (LCL) | Neutral high transition temperature, lipid, cholesterol and 5-10% of PEG (polyethylene glycol) | Selective targeting to pathological areas | [1,10] |
| 5 | Immuno-liposomes | Conventional or long circulatory liposomes with attached antibody or recognition sequence | Subject to receptor mediated endocytosis, specific targeting | [1] |
| 6 | Magnetic liposomes | Phosphatidylcholine, cholesterol, small amounts of linear chain aldehyde and colloidal particles of magnetic iron oxide | Specific targeting of antibodies to brain | [1,11] |
| 7 | Temperature or heat sensitive liposomes | Dipalmitoylphosphatidyl choline | Site specific delivery of drugs for the treatment of solid tumours | [1,7,12] |

The loading of drugs into liposomes offer an efficient means of drug targeting to mononuclear phagocytic system (MPS) cells. As particulate carriers, liposomes naturally target cells of the MPS, particularly macrophages to treat a number of diseases including infectious diseases, inflammatory diseases, cancer and atherosclerosis. To achieve targeting of liposomes to monocytes, macrophages and dendritic cells, the physicochemical properties of liposomes has been modified by addition of surface ligands such as proteins, peptides, antibodies, polysaccharides, glycolipids, glycoproteins and lectins [11]. Epidermal growth factor receptor (EGFR) targeted doxorubicin immunoliposomes have been prepared to increase drug delivery to tumours such as breast, colon, pancreatic, lungs and ovarian cancers [13]. Doijad Rajindra C et al prepared zidovudine, loaded liposomes for targeting to liver followed by lungs, kidney and spleen against human immunodeficiency virus (HIV) [14]. Amphotericin-B loaded aerosolized liposomes coated with o-palmitoyl mannan were prepared by Vyas et al for their selective targeting to lungs (alveolar macrophages) for the treatment of fungal diseases in

lungs [15]. Targeted chemotherapy of brain tumor using polysaccharide-anchored liposomes loaded with cisplatin has been attempted by Ochi et al [16].

Emulsomes

Emulsome is a lipid based drug delivery system, especially designed for parenteral delivery of drugs having poor aqueous solubility [17]. In emulsomes, the internal core is made up of fats and triglycerides, which are stabilized in form of o/w emulsion by addition of high concentration of lecithin. Emulsomes have the characteristics of both liposomes and emulsions. By virtue of solidified or semisolidified internal oily core, it provides better opportunity to load lipophilic drugs in high concentration, simultaneously a controlled release can also be expected and these also have the ability to encapsulate water soluble medicaments in aqueous compartments of surrounding phospholipids layers. The solvent-free and surfactant-free emulsome technologies have demonstrated high encapsulation



capacity for water insoluble antifungal and anticancer drugs, showed enhanced drug delivery and improved preclinical efficacy for oral route [5]. Senthil et al prepared amphotericin B (an effective antifungal and anti-leishmanial agent) loaded emulsomes for the treatment of visceral leishmaniasis. This study focus on preparing macrophage (liver, spleen and bone marrow) targeted emulsomes to reduce the adverse effects of conventional treatments [18]. Raza et al prepared dithranol loaded emulsomes with enhanced biocompatibility, efficacy and stability in treatment of psoriasis [19]. Vyas et al developed zidovudine emulsomes for sustained and targeted drug delivery to liver for the treatment of life-threatening viral infections like hepatitis, HIV and Epstein-Barr virus infection [20].

Enzymosomes

The therapeutic proteins like enzymes can be delivered through several approaches such as using polymeric carriers; aqueous space of lipid and bilayered vesicles but their delivery by attachment on surface of liposomes has shown the prominent response for the development of antibodies at the target site. Enzymes upon complexing with lipids generate enzymosomes. Superoxide Dismutase (a therapeutic agent for oxidative stress related diseases like rheumatoid arthritis and ischaemia/reperfusion situations) loaded enzymosomes have been developed with long circulation time in the blood, in order to accumulate at inflamed target sites, while maintaining enzymatic activity in its intact form [21,22].

Ethosomes

Ethosomes have also been developed for delivering the drugs having low penetration power through skin. Ethosomes are soft lipid vesicles of size range from tens of nanometers to microns, containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water [23,24]. Ethanol acts as penetration enhancer and fluidizes the ethosomal lipids and stratum corneum bilayer, thus allowing the soft, malleable vesicles to penetrate the disorganized lipid bilayer. The high concentration of ethanol (20-50%) is the main reason for better skin permeation ability. Ethanol confers a surface negative net charge to ethosomes due to which size of vesicles decreases. Hence, size of ethosomal vesicles increases with decrease in concentration of ethanol [25]. Ethosomes can also be used for delivery of various antifungal agents (fluconazole) antiviral agents (zidovudine, lamivudine, stavudine, and acyclovir), NSAIDS (diclofenac, aceclofenac), antibiotics (erythromycin, cannabidol) and various other drugs like ammonium glycyrrhizinate, salbutamol sulfate, propranolol, testosterone, finasteride, bacitracin, and methotrexate. These have shown the enhancement of pharmacological efficacy in drug targeting to transdermal and dermal sites for the treatment of various skin diseases [25-28].

Sphingosomes

Sphingosomes were introduced to overcome the stability problems of liposomes. These are so called due to the presence of

sphingolipids instead of phospholipids present in liposomes. Phospholipids used in liposomes are prone to undergo chemical degradation such as oxidation and hydrolysis of ester linkage. The ether or amide linkage containing sphingolipids are found to be more stable than phospholipids as these are resistant to the chemical degradation [29]. Sphingosomes are efficient carrier for targeting of the drug to the site of action, because of being biodegradable, innocuous nature and identical to biological membrane. Sphingosomes provide selective passive targeting to tumour tissues and flexibly couple with site-specific ligands to achieve active targeting [30]. Sphingosomes are much more stable to acid hydrolysis and have better drug retention characteristics [29]. Sphingosomal products e.g., Marqibo^(TM) (vincristine loaded sphingosomes) are loaded with active, cell cycle-specific anticancer agents that are benefited from increased targeting and long duration of drug exposure at the tumor site. Vincristine, vinorelbine and topotecan are approved cancer therapies which have been selected for sphingosomal formulation specifically for their ability to benefit from this novel encapsulation [30].

Transferosomes

The term transferosome was introduced in 1991 by Gregor Cevc. Transferosome means carrying body and is derived from Latin word 'transfere' means 'to carry across' and the Greek word 'soma' means 'body' [31]. Transferosomes are such novel vesicular drug delivery systems whose uniqueness is an ultra deformable vesicle. It can squeeze itself through a pore, many times smaller than its size owing to its elasticity, designed to enhance the skin penetration and deliver the drug non-invasively through the skin barrier without measurable loss [31,32].

Transferosomes have been widely used as carrier for the controlled and targeted delivery of proteins, peptides, hormones and several drugs [33,34]. The oral delivery of peptides such as insulin and interferons, is impossible due to their instability and rapid degradation in the harsh environment of gastro intestinal tract. These are also difficult to diffuse through skin due to their large molecular weight, but these can be transported easily across the skin with the help of transferosomes. Transferosomes have also been used in transdermal immunization of tetanus toxoid and transcutaneous delivery of hepatitis-B vaccine [31]. Diclofenac loaded ultra-deformable vesicles have shown longer effect and reached in 10 times higher concentration in tissues under skin when compared with drug from commercial hydrogel [35]. Drugs can be readily targeted to peripheral tissues through transferosomes. Transferosomal formulations have been prepared for anti-HIV agents like zidovudine, indinavir and have been shown enhanced permeation through skin [31]. The ultra-deformable vesicles of ethinylestradiol have shown better anti-ovulatory effect as compared to plain drug for oral administration. Transferosomal formulation of local anaesthetics e.g. lidocaine and tetracaine induces topical anesthesia with less than 10 min with pain insensitivity as strong (80%) as that comparable with subcutaneous bolus injection, but the effect of transferosomal anaesthetic lasted for longer time [31,33].



Table 3: Components used for the preparation of transferosomes

| S.No. | Type of material | Example | Uses |
|-------|------------------|--|---|
| 1. | Phospholipids | Soya phosphatidyl choline, Dipalmitoylphosphatidyl choline, Distearoylphosphatidyl choline | Vesicles forming component |
| 2. | Surfactants | Sodium cholate, Sodiumdeoxycholate, Span-80, Tween-80 | For providing flexibility |
| 3. | Alcohol | Ethanol, Methanol | As a solvent |
| 4. | Buffering agent | Saline Phosphate buffer(6.4) | As a hydrating medium |
| 5. | Dye | Rhodamine-123, Fluorescein, Nile red | For CSLM (confocal scanning laser microscopy) study |

Pharmacosomes

Pharmacosomes are novel vesicular drug delivery systems having unique advantages over other drug delivery systems [36]. Pharmacosomes are amphiphilic lipoidal colloidal dispersions of drugs, covalently bound to lipids with potential to improve bioavailability of poorly water soluble as well as poorly lipophilic drugs [37]. Any drug possessing a free carboxyl group or an active hydrogen atom (-OH, -NH₂) can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. An amphiphilic prodrug is then converted to pharmacosomes upon dilution with water. The prodrug conjoins hydrophilic and lipophilic properties (thereby acquiring amphiphilic characteristics), reduces interfacial tension, and at higher concentration exhibits mesomorphic behavior. Because of decrease in interfacial tension, the contact area increases, therefore bioavailability also increases [36]. As the drug is covalently conjugated with lipids, loss due to leakage of drug does not occur. Hence, provides maximum entrapment efficiency. The three main components for the preparation of pharmacosomes are drug, solvent and lipid. Drug should contain active hydrogen atom (-COOH, OH, NH₂), can be esterified with lipid and form amphiphilic complexes, which facilitate membrane transfer. The solvent should have high purity, volatility and intermediate polarity (between the polarity of phospholipid and drug) for the preparation of pharmacosomes. The most commonly used lipid for the preparation of pharmacosomes is phosphatidylcholine. The pharmacosomes can be prepared by hand-shaking and ether-injection methods. These have been prepared for various non-steroidal anti-inflammatory drugs, proteins, cardiovascular and antineoplastic drugs [36,38]. Ajay Semalty et al successfully prepared and evaluated diclofenac loaded pharmacosomes to enhance the bioavailability and reduce the GI toxicity of drug [37]. Al Ping et al prepared didanosine loaded pharmacosomes for targeting to liver. They determined their *in vivo* behavior including liver targeting and sustained release at target site, in rats [39]. Zhang and Wang prepared 3,5-dioctanoyl-5-fluoro-2-deoxyuridine loaded pharmacosomes by central composite design showed good targeting efficiency *in vivo* and improved the ability of drug to cross the blood brain barrier [40].

Virosomes

Virosomes are reconstituted viral envelopes that are composed of a lipid bilayer in which inserted viral glycoproteins can be derived from different enveloped viruses. Virosomes are described as liposomes with influenza virus hemagglutinin (HA) and neuraminidase (NA) spikes on their surface. Virosomes closely mimic the intact virus except that they do not contain virus replication machineries. They retain the cell entry and membrane fusion characteristics of the virus derived from. The two pathways by which reconstituted vesicles are able to enter the cells and deliver their contents into the cytoplasm are plasma membrane fusion (Sendai virus) and acid-induced fusion from within endosomes (Influenza virus). As a result, foreign substances encapsulated within the lumen of virosomes are effectively delivered to the cytosol of target cells. Virosomes can be used in vaccination for the efficient induction of antibody responses against the virus they are derived from [5].

Non-Lipoidal Biocarriers for Site-Specific Targeting

Niosomes

Handjanivila et al first reported the formation of vesicles on hydration of mixture of cholesterol and a single alkyl chain non-ionic and non-toxic surfactant. Since then a number of non-ionic surfactants have been used to prepare vesicles e.g., polyglycerol alkyl ethers, glucosyldialkyl ethers, crown ethers, polyoxyethylene alkyl ethers, ester linked surfactants, steroid linked surfactant, brij and a series of spans and tweens. The resulting vesicles are termed as niosomes [41,42]. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structure of size range 10-1000nm consisting of spherical, uni or multilamellar and polyhedral vesicles in aqueous media. These also consist of inverse structures which appear only in non-aqueous media, formed by self-assembly of non-ionic surfactant and cholesterol with subsequent hydration [42-44]. The first report of non-ionic surfactant vesicles came from the cosmetic application devised by L'Oreal. Non-ionic surfactants are preferred due to less irritation power which decreases in the order of cationic, anionic, ampholytic and non-ionic surfactants respectively [45].



Niosomes as novel vesicular drug delivery system offer various advantages:

Better patient compliance and better therapeutic effect in comparison to oily formulations [46].

Can be used to deliver hydrophilic, lipophilic as well as amphiphilic drugs and can accommodate drugs with wide range of solubility [47].

Controlled and sustained release of drugs due to depot formation [46].

Enhance the oral bioavailability of drugs [48].

Osmotically active and stable [48].

Biocompatible, biodegradable, non-toxic and non-immunogenic [44,48].

Protect the drug from enzymatic metabolism thus increases the stability of drug [44,46].

Drug targeting to various organs [46].

Enhance the skin permeation of drugs [46].

Easy to handle, store and transport [46].

Administered by various routes via oral, parenteral, topical etc. [46]

The shape, size, composition and fluidity of niosomes can be controlled as and when required [46].

Vanlerbeghe et al first reported the niosomes as an aspect of cosmetic industry [3]. Jain et al developed the niosomal gel for site specific sustained delivery of celecoxib. They found that the niosomal gel provided better skin permeation of drug as compared to carbopol gel [49]. Pei et al developed hydroxycamptothecin loaded PEGylated niosomes modified with transferrin for efficient tumour targeting [50]. Yong et al formulated and evaluated minoxidil niosomes for drug cutaneous targeting in treatment of skin diseases [51]. Lakshmi et al formulated salbutamol sulphate niosomes for lung targeting in the treatment of asthma [52]. Sathali et al formulated and evaluated terbinafine hydrochloride niosomes for targeting to fungal affected cells [53]. Hashim et al prepared and evaluated ribavirin niosomes for liver targeting for the treatment of chronic hepatitis C infection [54]. Malay K Das et al prepared rofecoxib niosomes for skin targeting for its sustained anti-inflammatory action [55]. The various other applications of niosomes for internal drug delivery and external drug delivery are discussed in table 4 and 5 respectively.

Bilosomes

Bilosomes are the novel innovative drug delivery carriers consist of deoxycholic acid incorporated into the membrane of niosomes [5]. As conventional vesicles (liposomes and niosomes) can cause dissolution and undergo enzymatic degradation in gastro intestinal

tract but incorporation of bile salts (commonly used penetration enhancers) in niosomal formulation could stabilize the membrane against the detrimental effects of bile acids in GI tract [5,81]. These bile salt stabilized vesicles are known as bilosomes. These are highly biocompatible and have been found to improve the therapeutic efficacy of drugs due to their stability in gastro intestinal tract. Bilosomes have been found to increase the bioavailability of drugs as they can readily absorbed through small intestine to the portal circulation (hepatocirculation). Through this circulation they approach to liver and release the drug, so found to be an effective tool in drug targeting to liver [5,82]. Shukla et al showed that HBsAg loaded bilosomes produced both systemic as well as mucosal antibody responses upon oral administration [83]. For extended humoral, cell-mediated and mucosal immune responses, additional coating carrier system provided better protection against disease for longer period of time. Optimum mannan coating was found to stabilize the vesicles in gastrointestinal environment and also act as a targeting ligand for mannose receptors expressed on macrophages and dendritic cells [81].

Aquasomes

Aquasomes firstly developed by Kossovsky, are one of the most recently developed delivery system for bioactive molecules [84]. Aquasomes are three layered structures (i.e. core, coating and drug) that are self-assembled through non covalent bonds, ionic bonds and vander waals forces [85]. They consist of tin oxide, nanocrystalline carbon ceramic (diamonds) or brushite (calcium phosphate dihydrate) core coated with oligomeric film to which biochemically active molecules are adsorbed by copolymerization, diffusion or adsorption with or without modification [86,88]. The solid core provides the structural stability, while the carbohydrate coating protects against dehydration and stabilizes the biochemically active molecules. Aquasomes are spherical 60-300nm size particles called 'bodies of water'. Their water like properties protects and preserves fragile biological molecules [86]. Mechanism of action of aquasomes is controlled by their surface chemistry, which deliver contents through combination of specific targeting, molecular shielding and slow and sustained release process. Due to their size and structural stability, these avoid clearance by reticuloendothelial system and degradation by other environmental changes [87]. Aquasomes can be used as red blood cell substitutes for the release of oxygen by haemoglobin. Aquasomes can be used as vaccines for delivery of viral antigen, for targeted intracellular gene therapy, for delivery of insulin and enzymes like DNAase and pigments/dyes [88].



Table 4: For internal drug delivery by niosomes

| S.No. | Application | Drug used | Non-ionic surfactant used | Method | Reference |
|-------|--|---------------------|------------------------------------|---|-----------|
| 1. | Oral bioavailability enhancement | Aceclofenac | Span 20, 60 | Ether injection technique | [56] |
| | | Acyclovir | Span 60 | Thin film hydration method | [57] |
| | | Cefuroxime axetil | Span 40, 60, 80 | Hand shaking method | [58] |
| | | Gliclazide | Span 60 | Thin film hydration method | [59] |
| | | Griseofulvin | Span 20, 40, 60 | Thin film hydration method, ether injection technique | [60] |
| 2. | Cancer and atherosclerosis treatment | β -carotene | Tween 20, 60 | Thin film hydration method | [61] |
| | | | Span 20, 40, 60 Brij 72, 76, 78 | | |
| 3. | Reduce toxicity | Cefpodoximeproxetil | Span 40, 60, 80 | Thin film hydration method | [62] |
| 4. | Stability improvement | Fluconazole | Span 20, 40, 80 | Ether injection technique | [63] |
| 5. | Tumour targeting | Hydroxycamptothecin | Span 60 | Thin film hydration method, ultrasound method | [64] |
| 6. | Treatment of tuberculosis | Adiramycin | Monoalkyltriglycerol ether | Hand shaking technique, ether injection technique | [55] |
| | | Isoniazid | Span 60 | Ether injection method | [66] |
| 7. | Antacid and antiulcer agent | Isoniazid | Span 20, 60 | Reverse phase evaporation method | [67] |
| | | | Span 60 | Reverse phase evaporation technique | [68] |
| 8. | Anti-inflammatory activity | Lansoprazole | Span 20, 40, 60 | Thin film hydration method and ether injection method | [69] |
| 9. | Oral delivery of peptides | Insulin | Brij 35, 52, 58, 72, 76, 92, 97 | Thin film hydration method | [70] |
| 10. | Treatment of tuberculosis along lymphatic system to prolong the release time | Rifampicin | Span 20, 40, 60, 80, 85 | Reverse phase evaporation method | [71] |
| 11. | Liver targeting | Ribavirin | Span 60 | Thin film hydration method | [54] |
| 12. | Lung targeting | Salbutamol sulphate | Span 60 | Thin film hydration method, Trans membrane pH gradient method | [52] |



Table 5: For external drug delivery by niosomes

| S.No. | Application | Drug used | Non-ionic surfactant used | Method | Reference |
|-------|--|---------------------|---------------------------|--|-----------|
| 1. | Ocular delivery to improve the low corneal penetration and bioavailability | Acetazolamide | Span 40, 60 | Reverse phase evaporation, thin film hydration technique | [72] |
| | | Ofloxacin | Span 60 | Thin film hydration technique | [73] |
| 2. | Prolong the drug release | Acyclovir | Sorbitan monostearate | Thin film hydration technique | [74] |
| 3. | Ocular drug delivery for glaucoma treatment | Brimonidinetartrate | Span 20, 40, 60, 80 | Thin film hydration technique | [75] |
| 4. | Site specific sustained delivery in treatment of arthritis | Celecoxib | Span 60, 80 | Thin film hydration technique | [49] |
| 5. | Localized psoriasis treatment | Dithranol | Span 60 | Thin film hydration technique | [77] |
| 6. | Topical drug delivery carrier for treatment of cancer | 5-fluorouracil | Bola surfactant, Span 80 | Thin film evaporation technique | [78] |
| 7. | Transdermal drug delivery system | Gallidermin | Tween 61 | Freeze dried method | [79] |
| | | Capsaicin | Span 80, Tween 80 | Thin film hydration technique | [76] |
| 8. | Anti-inflammatory activity | Meloxicam | Span 60, 80 Tween 60, 80 | Thin film hydration technique | [80] |
| 9. | Improve skin permeation and bioavailability | Minoxidil | Brij 52, 76 | Thin film hydration technique | [51] |
| 10. | Sustained therapeutic action | Rofecoxib | Span 20, 40, 60, 80 | Thin film hydration technique | [55] |

Conclusion

Because of the site specific targeting of drugs and lots of other advantages, vesicular drug delivery system is gaining popularity in present scenario. Drugs can be directly targeted to their site of action to prevent toxic and undesired effects to other sites, further these can be used for bioavailability enhancement of the drugs, having poor bioavailability, to reduce the dose of drug administered and to enhance pharmacological action of drug. Vesicular system is valuable for drugs having narrow therapeutic index because targeting of drug to their site of action improves the overall

pharmacokinetic and pharmacodynamic profile of drug and hence improvement in the overall therapy of the disease. Drugs can be successfully delivered using lipoidal biocarriers such as liposomes, enzymosomes, ethosomes, transferosomes, pharmacosomes, sphingosomes, virosomes, emulsomes and non lipoidal biocarriers such as niosomes, bilosomes and aquasomes as per the convenience of therapy. All these biocarriers have been reported for their successfully site specific targeting.

References

- [1]. Biju SS, Talegaonkar S, Mishra PR, Khar RK. Vesicular systems: an overview. *Indian J Pharm Sci.* 2006; 68(2):141-153.
- [2]. Manish G, Vimukta S. Targeted drug delivery system: a review. *Res J Chem Sci.* 2011; 1(2):135-138.
- [3]. Mujoriya R, Bodla RB, Dhamande K, Singh D, Patle L. Niosomal drug delivery system: the magic bullet. *J Appl Pharm Sci.* 2011; 01(09):20-23.
- [4]. Kumar R, Kumar S, Jha SS, Jha AK. Vesicular system-carrier for drug delivery. *Der Pharmacia Sinica.* 2011; 2(4):192-202.
- [5]. Kumar D, Sharma D, Singh G, Singh M, Rathore MS. Lipoidal soft hybrid biocarriers of supramolecular construction for drug delivery. *Int*



- Scholar Res Network Pharm. 2012; 2012:1-14.
- [6]. Anwekar H, Patel S, Singhai AK. Liposome-as drug carrier. *Int J Pharm Life Sci.* 2011; 2(7): 945-951.
- [7]. Wagner A, Uhl KV. Liposome technology for industrial purposes. *J Drug Deliv.* 2011; 2011:1-9.
- [8]. Samad A, Sultana Y, Aqil M. Liposomal systems: an update review. *Curr Drug Deliv.* 2007; 4:297-305.
- [9]. Sivasankar M, Katyayani T. Liposomes-the future of formulations. *Int J Res Pharm Chem.* 2011; 1(2):259-267.
- [10]. Storm G, Crommelin DJA. Liposomes: quo vadis. *Pharm Sci Technol Today.* 1988; 1(1):19-31.
- [11]. Kelly C, Jefferies C, Cryan SA. Targeted liposomal drug delivery to monocytes and macrophages. *J Drug Deliv.* 2011; 2011:1-11.
- [12]. Shao P, Wang B, Wang Y, Li J, Zhang Y. The application of thermosensitive nanocarriers in controlled drug delivery. *J Nanomater.* 2011; 2011:1-12.
- [13]. Lehtinen J, Raki M, Bergstrom KA, Uutela P, Lehtinen K, Hiltunen A, Pikkarainen J, Liang H, Pitkanen S, Maatta AM, Ketola RA, Yliperttula M, Wirth T, Urtti A. Pre-targeting and direct immunotargeting of liposomal drug carriers to ovarian carcinoma. *Plosone.* 2012; 7(7):1-10.
- [14]. Doijad RC, Bhambere DS, Manvi FV, Deshmukh NV. Formulation and characterization of vesicular drug delivery system for anti-HIV drug. *J Global Pharm Technol.* 2009; 1(1):94-100.
- [15]. Vyas SP, Khatri K, Goyal AK. Functionalized nanocarriers to image and target fungi infected cells. *J Med Mycol.* 2009, 47 (Suppl 1):s362-s368.
- [16]. Ochi A, Shibata S, Mori K, Sato T, Sunamoto J. Targeting chemotherapy of brain tumor using liposome encapsulated cisplatin. Part 2. Pullulan anchored liposomes to target brain tumor. *J Drug Deliv.* 1990; 5:261-271.
- [17]. Bhatt DA, Pethe AM. Lipoidal technology-a promising drug delivery for poorly water soluble drugs. *Int J Pharm Res Dev.* 2010; 2(7):1-11.
- [18]. Gill V, Kumar MS, Khurana B, Arora D, Mahadevan N. Development of amphotericin B loaded modified emulsomes for visceral leishmaniasis: in vitro. *Int J Recent Adv Pharm Res* 2011; 2:14-20.
- [19]. Raza K, Katare OP, Setia A, Bhatia A, Singh B. Improved therapeutic performance of dithranol against psoriasis employing systematically optimized nanoemulsomes. *J Microencapsul.* 2012:1-12.
- [20]. Vyas SP, Subhedar R, Jain S. Development and characterization of emulsomes for sustained and targeted delivery of an antiviral agent to liver. *J Pharm Pharmacol.* 2006; 58:321-326.
- [21]. Vale CA, Corvo ML, Martins LCD, Marques CR, Storm G, Cruz MEM, Martins MBF. Construction of enzymosomes: optimization of coupling parameters. *NSTI-Nanotech.* 2006; 2: 396-397.
- [22]. Gaspar MM, Martins MB, Corvo ML, Cruz MEM. Design and characterization of enzymosomes with surface-exposed superoxide dismutase. *Biochimica Biophysica Acta.* 2003; 1609:211-217.
- [23]. Vijayakumar MR, Sathalia AH, Arun K. Formulation and evaluation of diclofenac potassium ethosomes. *Int J Pharm Pharm Sci.* 2010; 2(4):82-86.
- [24]. Gangwar S, Singh S, Garg G. Ethosomes: a novel tool for drug delivery through skin. *J Pharm Res.* 2010; 3(4):688-691.
- [25]. Nikalje AP, Tiwari S. Ethosomes: a novel tool for transdermal drug delivery. *Int J Res Pharm Sci.* 2012; 2(1):1-20.
- [26]. Bhalaria MK, Naik S, Misra AN. Ethosomes: a novel delivery system for antifungal drugs in the treatment of topical fungal diseases. *Indian J Exp Biol.* 2009; 47:368-375.
- [27]. Jain S, Tiwary AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. *AAPS Pharm Sci Tech.* 2007; 8(4):E1-E9.
- [28]. Presa PDL, Rueda T, Morales MDP, Chichon JF, Arranz R, Valpuesta JM, Hernando A. Gold nanoparticles generated in ethosome bilayers as revealed by cryo-electron-tomography. *J PhyChem B.* 2009; 113:1-30.
- [29]. Lankaldapalli S, Damuluri M. Sphingosomes: applications in targeted drug delivery. *Int J Pharm Chem Biol Sci.* 2012; 2(4):507-516.
- [30]. Saraf S, Paliwal S, Saraf S. Sphingosomes a novel approach to vesicular drug delivery. *Int J Curr Sci Res.* 2011; 1(2):63-68.
- [31]. Malakar J, Gangopadhyay A, Nayak AK. Transferosome: an opportunistic carrier for transdermal drug delivery system. *Int Res J Pharm.* 2012; 3(3):35-38.
- [32]. Ambarish G, Prajapati SK, Anand JP, Akhtar A, Aviral. Ultradeformable vesicle as a novel drug delivery system. *Int Res J Pharm.* 2012; 3(8):116-120.
- [33]. Kaushik A, Dwivedi A, Sunda M. Transferosome: the drug loaded ultradeformable vesicles for transdermal drug delivery. *Int Res J Pharm.* 2011; 2(11):40-42.
- [34]. Prajapati ST, Patel CG, Patel CN. Transferosomes: a vesicular carrier system for transdermal drug delivery. *Asian J Biochem Pharm Res.* 2011; 1(2):507-524.
- [35]. Cevc G, Blume G. New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable carriers, transferosomes. *Biochimica et Biophysica Acta.* 2001; 781:37:1-15.
- [36]. Patel JL, Bharadia PD. A review on: pharmacosomes as a novel vesicular drug delivery system. *World J Pharm Res.* 2012; 1(3):456-469.



- [37]. Semalty A, Semalty M, Singh D, Rawat MSM. Development and physicochemical evaluation of pharmacosomes of diclofenac. *Acta Pharm.* 2009; 59:335-344.
- [38]. Kumar DP, Arnab De. Pharmacosomes: A potential vesicular drug delivery system. *Int Res J Pharm.* 2012; 3(3):102-105.
- [39]. Ping A, Yi guang J, Da wei C. Preparation and in vivo behavior of didanosinepharmacosomes in rats. *Chin J Pharm.* 2005; 3(4):227-235.
- [40]. Zhang ZR, Wang JX, Lu J. Optimization of the preparation of 3',5'-dioctanoyl-5-fluoro-2'-deoxyuridine pharmacosomes using central composite design. *ActaPharmaceuticaSinica.* 2001; 36(6):456-461.
- [41]. Namdeo A, Jain NK. Niosomes as drug Carriers. *Indian J Pharm Sci.* 1996; 58(2):41-46.
- [42]. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F. Vesicles of non-ionic surfactants (niosomes) and drug delivery potential. *Int J Pharm Sci Nanotechnol.* 2008; 1(1):1-8.
- [43]. Jadhav SM, Morey P, Karpe M, Kadam V. Novel vesicular system: an overview. *J Appl Pharm Sci.* 2012; 02(01):193-202.
- [44]. Khan A, Sharma PK, Visht S, Malviya R. Niosomes as colloidal drug delivery system: a review. *J Chronother drug deliv.* 2011; 2(1):15-21.
- [45]. Mahale NB, Thakkar PD, Mali RG, Walnuj DR, Chaudhari SR. Niosomes: novel sustained release nonionic stable vesicular systems-an overview. *Adv Colloid Interfac Sci.* 2012; 183-184:46-54.
- [46]. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: a controlled and novel drug delivery system. *Biol. Pharm. Bull.* 2011; 34(7): 945-953.
- [47]. Sankhyan A, Pawar P. Recent trends in niosomes as vesicular drug delivery system. *J Appl Pharm Sci.* 2012; 02(06):20-32.
- [48]. Diljyot K. Niosomes: A new approach to targeted drug delivery. *Int J Pharm Phytopharmacol Res.* 2012; 2(1):53-59.
- [49]. Kaur K, Jain S, Sapra B, Tiwary AK. Niosomal gel for site-specific delivery of anti-arthritis drug: in vitro-in vivo evaluation. *Curr Drug Deliv.* 2007; 4:276-282.
- [50]. Hong M, Zhu S, Jiang Y, Tang G, Pei Y. Efficient tumor targeting of hydroxycamptothecin loaded PEGylated niosomes modified with transferring. *J Control Release.* 2009; 133:96-102.
- [51]. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, Kim DD, Kim JS, Yoo BK, Choi HG, Woo JS, Yong CS. Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. *Int J Pharm.* 2009; 377:1-8.
- [52]. Bhaskaran S, Lakshmi PK. Comparative Evaluation of niosomes formulations prepared by different techniques. *ActaPharmaceuticaScientia.* 2009; 51:27-32.
- [53]. Sathali AAH, Rajalakshmi G. Evaluation of transdermal targeted niosomal drug delivery of terbinafine hydrochloride. *Int J Pharm Tech Res.* 2010; 2(3): 2081-2089.
- [54]. Hashim F, Ridy MEI, Nasr M, Abdallah Y. Preparation and characterization of niosomes containing ribavirin for liver targeting. *J Drug Deliv.* 2010; 17(5): 282-287.
- [55]. Das MK, Palei NN. Sorbitan ester niosomes for topical delivery of rofecoxib. *Indian J Exp Biol.* 2011; 49:438-445.
- [56]. Srinivas S, Kumar YA, Hemanth A, Anitha M. Preparation and evaluation of niosomes containing aceclofenac. *Dig J nanomaterbiostr.* 2010; 5(1):249-254.
- [57]. Attia IA, El GizawySanaa, Fouda MA, Donia AM. Influence of a niosomal formulation on the oral bioavailability of acyclovir in rabbits. *AAPS Pharm Sci Tech.* 2007; 8(4):E1-E7.
- [58]. Sambhakar S, Singh B, Paliwal SK, Mishra PR. Niosomes as a potential carrier for controlled release of cefuroxime axetil. *Asian J Biochem Pharm Res.* 2011; 1(1):126-136.
- [59]. Tamizharasi S, Dubey A, Rathi V, Rathi JC. Development and characterization of niosomal drug delivery of gliclazide. *J Young Pharm.* 2009; 1(3):205-209.
- [60]. Jadon PS, Gajbhiye V, Jadon RS, Gaybhiye KR, Narayanan G. Enhanced oral bioavailability of griseofulvin via niosomes. *AAPS Pharm Sci Tech.* 2009; 10(4):1186-1192.
- [61]. Bayindir ZS, Yuksel N. Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. *J Pharm Sci.* 2010; 99(4):2049-2060.
- [62]. Palozza P, Muzzalupo R, Trombino S, Valdannini A, Picci N. Solubilization and stabilization of b-carotene in niosomes: delivery to cultured cells. *ChemPhy Lipid.* 2006; 139: 32-42.
- [63]. Shivanand P. Development and characterization of cefpodoximeproxetil niosomes. *Int J Pharm World Res.* 2010; 1(3):1-11.
- [64]. Sharma SK, Chauhan M, Pillay N, Kumar A. Span-60 niosomal oral suspension of fluconazole: formulation and in vitro evaluation. *J Pharm Res Health care.* 2009; 1(2):142-156.
- [65]. Kerr DJ, Rogerson A, Morrison GJ, Florence AT, Kaye SB. Antitumor activity and pharmacokinetics of niosome encapsulated adiramycin in monolayer, spheroid and xenograft. *Br J Cancer.* 1988; 58:432-436.
- [66]. Karki R, Mamatha GC, Subramanya G, Udupa N. Preparation, characterization and tissue disposition of niosomes containing isoniazid. *Rasayan J Chem.* 2008; 1(2):224-227.
- [67]. Singh G, Dwivedi H, Saraf SK, Saraf SA. Niosomal delivery of isoniazid-development and characterization. *Trop J Pharm Res.* 2011; 10(2):203-210.
- [68]. Ahuja N, Saini V, Bishnoi VK, Garg A, Hisoria M, Sharma J, Nepali K. Formulation and evaluation of



- lansoprazoleniosome. *Rasayan J. Chem.* 2008; 1(3):561-563.
- [69]. Singh CH, Jain CP, Bairwa NK. Formulation, characterization, stability and in vitro evaluation of nimesulide niosomes. *Pharmacophore.* 2011; 2(3):168-185.
- [70]. Pardakhty A, Varshosaz J, Rouholamini A. In vitro study of polyoxyethylene alkyl ether niosomes for delivery of insulin. *Int J Pharm.* 2007; 328:130-141.
- [71]. Jain CP, Vyas SP, Dixit VK. Niosomal system for delivery of rifampicin to lymphatics. *Indian J Pharm Sci.* 2006; 68(5):575-578.
- [72]. Guinedi AS, Mortada ND, Mansour S, Hathout RM. Preparation and evaluation of revers-phase evaporation and multilamellar niosomes as ophthalmic carriers of acetazolamide. *Int J Pharm.* 2005; 306:71-82.
- [73]. Gupta N, Shrivastava V, Saxena S, Pandey A. Formulation and evaluation of non-ionic surfactant vesicles (niosomes) for ocular delivery of ofloxacin. *Int J Pharm life Sci.* 2010; 1(7): 413-418.
- [74]. Modi KA, Shelat PK. Formulation and development of topical niosomal gel of BCS class-3 anti-viral drug for better efficacy as herpes treatment. *Int Res J Pharm.* 2012; 3(3):271-276.
- [75]. Sathyavathi V, Hasansathali AA, Ilavarasan R, Sangeetha T. Formulation and evaluation of niosomal in situ gel ocular delivery system of brimonidinetartrate. *Int J Life Sci Pharm Res.* 2012; 2(1):L-82- L-95.
- [76]. Tavano L, Alfano P, Muzzalupo R, Cindio BD. Niosomes vs microemulsions: new carriers for topical delivery of capsaicin. *Colloid Surf B: Biointerface.* 2011:1-7.
- [77]. Agarwal R, Katare OP, Vyas SP. Preparation and in vitro evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. *Int J Pharm.* 2001; 228:43-52.
- [78]. Paolino D, Cosco D, Muzzalupo R, Trapasso E, Picci N, Fresta M. Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer. *Int J Pharm.* 2008; 353:233-242.
- [79]. Manosroi A, Khanrin P, Lohcharoenkal W, Werner RG, Götz F, Manosroi W, Manosroi J. Transdermal absorption enhancement through rat skin of gallidermin loaded in niosomes. *Int J Pharm.* 2010; 392:304-310.
- [80]. Gupta KS, Nappinnai M, Gupta VRM. Formulation and evaluation of topical meloxicam niosomal gel. *Int J Biopharm.* 1; 2010:7-13.
- [81]. Arora D, Khurana B, Kumar MS, Vyas SP. Oral immunization against hepatitis B virus using mannosylated bilosomes. *Int J Recent Adv Pharm Res.* 2011; 1:45-51.
- [82]. Schiff ER, Dietschy JM. Current concepts of bile acid absorption. *Am J Clin Nutr.* 1969; 22(3):273-278.
- [83]. Shukla A, Khatri K, Gupta PN, Goyal AK, Mehta A and Vyas SP. Oral immunization against hepatitis B using bile salt stabilized vesicles (bilosomes). *J Pharm Pharm Sci.* 2008; 11(1):59-66.
- [84]. Chaudhari MJ, Pandya DP, Thakkar PP, Soni AM, Modi DA. Aquasomes: a novel drug delivery system. *Int J Pharm Res Scholar.* 2012; 1(2):485-489.
- [85]. Umashankar MS, Sachdeva RK, Gulati M. Aquasomes: a promising carrier for peptides and protein delivery. *Nanomed Nanotechnol Biol Med.* 2010; 6:419-426.
- [86]. Sutariya V, Patel P. Aquasomes: a novel carrier for drug delivery. *Int J Pharm Sci Res.* 2012; 3(3):688-694.
- [87]. Vengala P, Dintakurthi S, Aslam S, Gollagudem R, Kumaraswamy P. Aquasomes: a novel drug carrier system. *Int Res J Pharm.* 2012; 3(4):123-127.
- [88]. Sethi P, Sharma A, Patel SN, Singhai AK. Aquasome-a novel carrier system. *Int J Pharm Life Sci.* 2010; 1(4):222-225.

