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Vesicular System-Carrier for Drug Delivery

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ABSTRACT

The application of vesicular system in drug delivery has changed the definitions of diagnosis and treatment in different aspects of biomedical field. The vesicular system as liposomes, niosomes, sphinosomes, transferosomes and pharmacosomes are used to improve the therapeutic index of both existing and new drug molecules by encapsulating an active medicament inside vesicular structure in one such system. It prolong the existence of the drug in systemic circulation and finally reduce the toxicity. Such different systems are widely used in gene delivery, tumor targeting to brain, oral formulations, in stability and permeability problems of drugs. In this review we really focused on different aspects of vesicular system in terms of its advantages, limitation, application and different marketed product of vesicular system as novel drug delivery.

Key words: Vesicular drug delivery, Application, limitation, Marketed product.

INTRODUCTION

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfill two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms, are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery [1]. Recently different carrier systems and technologies have been extensively studied with the aim of controlling the drug release and improving the efficacy and selectivity of formulation. Now a days vesicles as a carrier system have become the vehicle of choice in drug delivery and lipid vesicles were found to be of value

in immunology, membrane biology and diagnostic technique and most recently in genetic engineering [2]. Vesicular delivery system provides an efficient method for delivery to the site of infection, leading to reduce of drug toxicity with no adverse effects. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both by hydrophilic and liophilic drugs [3]. Different novel approaches used for delivering the drugs by vesicular system include liposomes, niosomes.,sphinosomes,transferosomes and pharmacosomes Thus a main aim to design this review article is to introduce different vesicular drug delivery system with their marketed formulation and limitation for a student, guide or researcher or who might keen to know about vesicular drug delivery system.

Vesicular system-Carrier for Drug Delivery:

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayer formed, when certain amphiphillic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphillic building blocks. Biologic origin of these vesicles was first reported in 1965 by Bingham, and was given the name Bingham bodies [4]. Drug carrier can be engineered to slowly degrade, react to stimuli and be site-specific. The ultimate aim is to control degradation of drug and loss, prevention of harmful side effects and increase the availability of the drug at the disease site [5]. Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved [6].Lipid vesicles are one type of many experimental models of biomembranes which evolved successfully, as vehicles for controlled delivery. For the treatment of intracellular infections, conventional chemotherapy is not effective, due to limited permeation of drugs into cells. This can overcome by the use of vesicular drug delivery systems. Vesicular drug delivery system has some of the advantages like:

1. Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
2. Improves the bioavailability especially in the case of poorly soluble drugs.
3. Both hydrophilic and lipophilic drugs can be incorporated.
4. Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems [4].

These vesicular systems are accompanied with some problems like drug carriers and externally triggered (eg., temperature, pH, or magnetic sensitive) carriers load drugs passively, which may lead to low drug loading efficiency and drug leakage in preparation, preservation and transport in vivo[7].

Liposomes:

The liposomes have emerged as most practically useful carriers for in-vivo drug delivery as majority of reports has concentrated on the use of phospholipid vesicles or liposomes as potential drug carrier systems [8]. Liposomes or lipid based vesicles are microscopic (unilamellar or multilamellar) vesicles that are formed as a result of self-assembly of phospholipids in an aqueous media resulting in closed bilayered structures [9]. The assembly into closed bilayered structures is a spontaneous process and usually needs some input of energy in the form of physical agitation, sonication, heat etc [10]. Since lipid bilayered membrane encloses an aqueous core, both water and lipid soluble drugs can be successfully entrapped into the liposomes. The

lipid soluble or lipophilic drugs get entrapped within the bilayered membrane whereas water soluble or hydrophilic drugs get entrapped in the central aqueous core of the vesicles [11]. Liposomes are potential carrier for controlled drug release of tumours therapeutic agents and antibiotic, for gene and antisense therapy through nucleic acid sequence delivery, immunization through antigen delivery and for anti-Parkinson's. In last one decade, pharmaceutical researchers use the tools of biophysics in evaluating liposomal dosage forms. Liposomes have covered predominantly medical, albeit some non-medical areas like bioreactors, catalysts, cosmetics and ecology [12-16].

Advantage:

1. Liposomes supply both a lipophilic environment and aqueous "milieu interne" in one system and are therefore suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs and agents.
2. Liposomes could encapsulate not only small molecules but also macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2 and interferon-g.
3. Liposomes reduced toxicity and increased stability of entrapped drug via encapsulation (eg.Amphotericin B, Taxol).
4. Liposomes help to reduce exposure of sensitive tissues to toxic drugs.
5. Alter the pharmacokinetic and pharmacodynamic property of drugs (reduced elimination, increased circulation life time).

Limitation:

1. High production cost
2. Leakage and fusion of encapsulated drug / molecules.
3. Sometimes phospholipid undergoes oxidation and hydrolysis
4. Short half-life
5. Low solubility
6. Less stability [17].

Table-1: Therapeutic Applications of Liposomes [18]

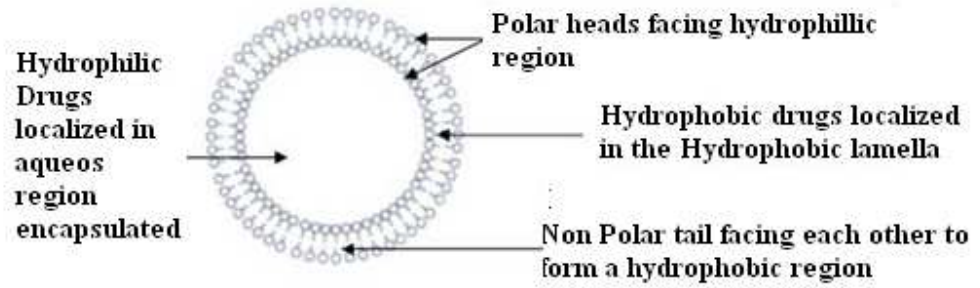
Drugs	Route of Administration	Application	Targeted Disease
Amphotericin-B	Oral delivery	Ergosterol membrane	Mycotic infection
Insulin	Oral,Ocular,Pulmonary and Transdermal delivery	Decrease Glucose Level	Diabetic Mellitus
Ketoprofen	Ocular delivery	Cyclo-oxygenase enzyme inhibitor	Pain muscle condition
Pentoxyfylline	Pulmonary delivery	Phosphodiesterase	Asthma
Tobramycin	Pulmonary delivery	Protein synthesis inhibitor	Pseudomonas infection,aeruginosa
Salbutamol	Pulmonary delivery	Adrenoceptor Antagonist	Asthma
Ketoconazole	Transdermal delivery	Inhibit ergosterol membrane	Candida-albicans
Levonogesterol	Transdermal	Rhamnose receptor	Skin disorder
Ibuprofen	Oral delivery	Chemoreceptor,free nerve ending	Rheumatoid Arthritis
Idoxiuridine	Ocular delivery	DNA-synthesis,Protein sysnthesis	Herpex-Simplex Keratitis
Adrenalin	Ocular delivery	Decrease Intra-ocular pressure	Glucoma Conjuctivitis
Triamcinolone	Ocular delivery Transdermal delivery	Inhibiton of Prostaglandin	Anti-inflammatory

Table-2: Marketed Formulation of Liposome [19]

Various Marketed Formulations of Liopomes Product	Drugs	Company
Ambisome™	Amphotericin B	NeXstar Pharmceuticals,Inc.,Co
Abelcet™	Amphotericin B	liposome Company NJ,USA
Amphocil™	Amphotericin B	Sequus Pharmaceuticals,Inc.,C.A
Doxil™	Doxorubicin	Sequus Pharmaceuticals,Inc.,C.A
DaunoXome™	Daunorubicin	NeXstar Pharmceuticals,Inc.,Co
MiKasome™	Amikacin	NeXstar Pharmceuticals,Inc.,Co
DC99™	Doxorubicin	liposome Company NJ,USA
Epaxel™	Hepatitis A Vaccine	Swiss SerumInstitute,Switzerland
ELA-MAX™	Lidocaine	Biozone Labs,CA,USA

Niosomes:

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale. Although structurally similar to liposomes, they offer several advantages over them. Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery [20],[21].The figure below will give a better idea of what a niosome looks like and where the drug is located within the vesicals [22].



In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides this, niosome have been used to solve the problem of insolubility, instability and rapid degradation of drugs [23].

Advantages associated with Niosomes:

1) Niosomes are biodegradable, biocompatible and non immunogenic to the body[24].
2) Niosomes can be utilized in the delivery of wide variety of drugs as it has capability to entrap hydrophilic, lipophilic as well as amphiphilic drugs [25, 26].
3) Niosomes shows controlled and sustained release of drugs due to depot formation [26]
4) Niosomes show a greater bioavailability than conventional dosage forms [27].
5) Shape, size, composition, fluidity of niosomes drug can be controlled as and when required.
6) Niosomes had been effectively used in targeting drugs to various organs [28].

Limitation:
Physical instability in niosomal dispersion during storage occurs due to vesicles aggregations,fusion and leaking. This may leads to hydrolysis of encapsulated drugs which affects the shelf life of the dispersion.

Table-3: Therapeutic Application of Niosomes[29]

Application	Drugs Encapsulated in Niosomes	Mechanism of Action
Anticancer	Doxorubicin HCl	Destroy Daltons ascetic Lymphoma cell
	Methotrexate	Increase AUC ,than the plain drug
	Bleomycin	Less accumulation of drug
	Vincristine	Higher tumoridal efficacy in s-180
Antiinfective Agent	Sodium Stibogluconate	Increase level of antimony for treatment of Visceral leshminiasis
Antiinflammatory Agent	Diclofenac	Increases inflammatory Action than that of Plain Drug
	Nimesulide	
	Flurbiprofen	
Opthalmic Drug Delivery	Acetazolamide Gentamycin	Reduce intraocular Pressure
Transdermal Drug Delivery	Keterolac with Span 60	Increases Bioavailability and Therapeutic effect
Niosomal in Oral Drug Delivery	Insulin prepared with Niosomes	Increases gastro intestinal tract absorption
Brain Targeted Delivery Sytem for the Vasoactive Instestinal peptide	Radio labeled I 125VIP loaded glucose bearing niosomes	Higher VIP brain uptake

Sphinosomes:
Liposome stability problems are of course much more severe so it is very important task to improve the liposomal stability. Liposomal phospholipid can undergo chemical degradation such as oxidation and hydrolysis either as a result of these changes or otherwise liposome maintained in aqueous suspension may aggregate, fuse, or leak their content. Hydrolysis of ester linkage will slow at pH value close to neutral. The hydrolysis may be avoided altogether by use of lipid which contains ether or amide linkage instead of ester linkage (such are found in sphingolipid) or phospholipid derivatives with the 2- ester linkage replaced by carbomoyloxy function [30]**.** Thus sphingolipid are been nowadays used for the preparation of stable liposomes known as sphingosomes. Sphingosome may be defined as “concentric, bilayered vesicle in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic sphingolipid.

Sphingosomes are administered in many ways these include parentral route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial. Generally it will be administered intravenous or some cases by inhalation. Often it will be administered into a large central vein, such as the superior vena cava and inferior vena cava to allow highly concentrated solution to be administered into large volume and flow vessels. Sphingosomes may be administered orally or transdermally [31][32]. In simple way we can say sphingosome is liposome which is composed of sphingolipid [33].

Advantage:

1. Provide selective passive targeting to tumor tissue.
2. Increase efficacy and therapeutic index.
3. Increase stability via encapsulation.
4. Reduction in toxicity of the encapsulated agent.
5. Improve pharmacokinetic effect (increase circulation time).
6. Flexibility to couple with site specific ligands to achieve active targeting[34].

Limitation:

1. Higher cost of sphingolipid hinders the preparation and use of these vesicular systems.
2. Low entrapment efficacy [35].

Table -4: Therapeutic Application of Sphinosomes

Drugs	Action	Application	Targeted disease	Reference
Vinorelbine	Kill tumor cells by interfering with mitosis	In tumor therapy	Tumor site /Cancerous cell	[36]
Prostaglandins and Other steroids	Act as a Vehicle	As a drug delivery vehicles	For the treatment of prostaglandin disease,immune diseaseand infectious disease	[37]
Beclomethasone	By enhancing the penetration of drugs	In Cosmetic Industry	Skin/Dermal therapy	[30]
Idoxuridine	Drugs entrapped inside sphinosomes which posess optimum corneal and increase contact time	Occular drug delivery	Acute/Chronic herpatitics keatitis	
Streptokinase Urokinase	Proceed by sysnthesis of ester,peptide and sugar	Enzyme Delivery	Treatment of malnutrition	[38] [39]

Table-5: Marketed Products of Niosomes and Sphinosomes

Various Marketed Formulation	Drugs	Company	Application	Vesicular Drug Delivery Sytem
Prototype#37-C Lancome L-oreal	Fibrelastine D-contraxol	Elldia Laboratories L'Oreals Group	Anti Aging Agent	Niosomes
Dorzox	Dorzolamide Acetazolamide	Cipla	Anti-Glaucoma Dermal	
Margibo(TM) Oncovin(R)	Vincristine Vincristine	Eli Lilly Company	Hematologic Malignancies and acute Lymphoblastic leukemia	Sphinosomes
Navelbine(R)	Vinorelbine	Glaskosmith Kline	First line treatment of non small cell lung cancer	
Hycumtin(R)	Topotecan	Glaskosmith kline	Small cell lung cancer and Ovarian Cancer	

Pharmacosomes:
Pharmacosomes bearing unique advantages over liposome and niosome vesicles, have come up as potential alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as pharmacosomes. They are an effective tool to achieve desired therapeutic goals such as drug targeting and controlled release. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids with drug. Any drug possessing an active hydrogen atom (- COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism. The prodrug conjoins hydrophilic and lipophilic properties, thus acquires amphiphilc characters, and therefore found to reduce interfacial tension, and at higher concentrations exhibits mesomorphic behavior [35] [40].

Advantage:
1. As drug is covalently bound, membrane fluidity has no effect on release rate, but in turn depends upon the phase-transition temperature of the drug-lipid complex.
2. No leakage of drug take place as the drug is covalently linked to the carrier.
3. Drug can be delivered directly to the site of infection.
4. Drug release from pharmacosomes is by hydrolysis (including enzymatic).
5. Their degradation velocity into active drug molecule, after absorption depends very much on the size and functional groups of the drug molecule, the chain length of the lipids, and the spacer.
6. Reduced cost of therapy **[**41].

Limitation:
1. Synthesis of a compound depends upon its ampiphilic nature.
2. Required surface and bulk interaction of lipids with drugs.
3. Required covalent bonding to protect the leakage of drugs.
4. Pharmacosomes, on storage, undergo fusion and aggregation, as well chemical hydrolysis [42].

Table- 6: Therapeutic Application of Drugs After incorporation with Pharmacosomes

Drug	Efffect after Incorporation in Pharmacosomes	Reference
Pindolol diglyceride	Three to five fold increase in plasma concentration Lower renal clearance	[43]
Amoxicillin	Improved cytoprotection and treatment of H.pylori infections in male rats	[44]
Taxol	Improved biological activity	[45]
Cytarbin	Improved biological activity	[46]
Dermatan sulfate	Improved biological activity	[46]
Bupranolol hydrochloride	Enhanced effect on intraocular pressure Enhance lymph transport	[47] [48]

Transferosomes:
Transferosomes was introduced for the effective transdermal delivery of number of low and high molecular weight drugs. Transfersomes can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties [49]. It consist of both hydrophilic and hydrophobic properties, high deformablity gives better penetration of intact

vesicles [50].These vesicular transfersomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of transfersomes membrane is achieved by mixing suitable surface-active components in the proper ratios. Transferosome based formulations of local anesthetics- lidocaine and tetracaine showed permeation equivalent to subcutaneous injections. Anti cancer drugs like methotrexate were tried for transdermal delivery using transferosome technology. This provided a new approach for treatment especially of skin cancer.

Advantage:

1. Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with wide range of solubility.
2. Transferosomes can deform and pass through narrow constriction (from 5 to 10 times less than their own diameter) without measurable loss.
3. Posess high entrapment efficiency, in case of lipophilic drug near to 90%.
4. Used for both systemic as well as topical delivery of drug.

Limitation:

1. Transferosomes are chemically unstable because of their predisposition to oxidative degradation.
2. Purity of natural phospholipids is another criteria militating against adoption of transfersomes as drug delivery vehicles.
3. Transferosomes formulations are expensive.[51]

Table-7: Therapeutic Application of Drugs after incorporation with Transferosomes

Drugs	Effects after incorporation of drugs in Transferosomes	Application	Reference
Insulin	Transferulin	Delivery of insulin by Dermal Route	[52]
Zidovudine	Increases the level of IgA Higher AUC	Transdermal immunization	[53] [54]
NSAIDS Ketoprofen Transferosomes	Increases Bioavailability		

Future Perspective:

Vesicular drug delivery systems are emerging with the diverse application in Pharmaceutics, Cosmetics and food industries. Their delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. It also reduces the cost of therapy by imparting better biopharmaceutical properties to the drug, resulting in improved bioavailability, especially in case of poorly soluble drugs. Now a day's various non-steroidal anti inflammatory drugs, proteins, cardiovascular, antineoplastic, antiglucoma, antidiabetic drugs that are incorporated with vesicular system are available in a commercial market that are playing a vital role to cure from a disease, hence improving the health of human kinds. Some of the emerging vesicular drug delivery system are listed below.

Table-8: Emerging Vesicular Drug Delivery System

Vesicular System	Description	Application	Reference
Aquasomes	Three layered self assembly compositions with ceramics carbon nanocrystalline particulate core coated with glassy cellobiose	Specific Targeting, molecular shielding.	55
Cryptosmes	Lipid vesicles with a surface coat composed of pc and of suitable polyoxoyethylene derivative of phosphotidyl ethanolamine.	Ligand mediated drug targeting	56
Discomes	Niosomes solublized with non ionic surfactant solutions (polyoxyethylene cetyl ether class)	Ligand mediated drug targeting	57
Emulsomes	Nanosize Lipid particles (bioadhesives nanoemulsion) consisted of microscopic lipid assembly with apolar core.	Parenteral delivery of poorly water soluble drugs.	58
Enzymosomes	Liposomal constructs engineered to provide a mini bioenvironmental in which enzymes are covalently immobilized or coupled to the surface of liposomes.	Targeted delivery to tumor cell	59
Ethosomes	Ethosomes are lipid “Soft malleablevesicles”embodying a permeation enhancer and composed of phospholipid, ethanol and water.	Targeted delivery to deep skin layer	60
Genosomes	Artificial macromolecular complexes for functional gene transfer .Cationic lipids are most suitable because they posess high biodegradability and stability in the blood stream.	Cell specific gene transfer	61
Photosomes	Photolysase encapsulated in liposomes ,which release the content photo-triggered charges in membrane permeability characteristics.	Photodynamic Therapy	62
Virosomes	Liposomes spiked with virus glycoprotein, incorporated into the liposomal bilayers based on retro viruses derived lipids.	Immunological adjuvants	63
Vesosomes	Nested bilayer compartment in vitro via the interdigested bilayer phase formed by adding ethanol to a variety of saturated phospholipids.	Multiple compartment of the vesosomes give better protection to the interior contents in serum.	64
Proteosomes	High molecular weight multi-submit enzyme complexes with catalytic activity, which is specifically due to the assembly pattern of enzymes.	Better catalytic activity turnover than non associated enzymes.	65

CONCLUSION

The forgoing review shows different aspects related with the vesicular system approaching a vital role to deliver a drug by different route to achieve better therapeutic action.Inspite of certain drawbacks, the vesicular delivery systems still play an important role in the selective targeting and controlled delivery of various drugs. Researcher are implementing their efforts in improving the design of vesicular system by making them steady in nature,inorder to prevent leaching of contents, oxidation and their uptake by natural defense mechanism. As their flexibility in design posses a wide range of potential, its application must be explored throughout the world by encouraging the participation of researcher in the field of vesicular drug delivery system.

REFERENCES

[1] V.H.K.Li, J.R.Robinson, V.H.L.Lee; Controlled Drug Delivery: Fundamentals and Applications, Marcel Dekker Inc, NY, **1987**.
[2] N.K.Dhaiya, R.Rao, S.Nanda, *J.Pharm.Biomedical.Sci*., **2011,** 5, 20,1-8.
[3] S.Saraf, R.Rathi, C.D.Kaur, S.Saraf, *Asian.J. Scient.Res.*, **2011,** 4, 1,1-15.
[4] A.D. Bangha, M.M .Standish, J.G.Watkins,*J. Mol. Biol.*, **1965**, 13,238.
[5] D.P. Rao, S.K.Srivastav, C. Prasad, R.Saxena, S.Asthana,*Int.J.Nanotech.Application.*,**2010**, 1,45-49.
[6] J. A. Todd, E. J. Modest, P. W. Rossow, Z. A. Tokes,*Biochem. Pharmacol.*, **1982**, 34, 54.
[7] U.Ogihara, T.Sasaki, H.Toyama, M.Sneha, H.Nishigori,*Cancer Detect Prev.*, **1997**, 21, 6, 490.
[8] A.Sharma, U.S.Sharma, *Int. J. Pharm.*, **1997,**154, 123-140.
[9] A.D Bangham, R.W Horne, *J.Mol. Bi.*, **1964**, 8, 660-668.
[10] D.D. Lasic, *J. Colloid Interface Sci.*,**1990**, 140, 302-304.
[11] G. Gregoriadis, A.T.Florence, *Drugs Review*., **1993**,45, 15-28.
[12] M.C. Woddle, D. Papahadjopoulos, *Enzymol.*,**1989**, 171, 193-217.
[13**]** I.F.Uchegbu, S.P.Vyas, *Int. J. Pharm.*, **1998**,172, 33-70.
[14] A. Namdeo, N.K.Jain, *Indian J. Pharm. Sci.*,**1985**, 58, 2, 41-46.
[15] A.J. Baillie, A.T. Florence, I.R. Hume, G.T. Muirhead, A. Rogerson, *J. Pharm. Pharmcol*., **1985**, 37, 863-868.
[16] G.Parthasarthi, N. Udupa, G.K. Pillai,*Indian J. Pharm. Sci.*,**1994**, 56,7, 90-94.
[17] C. Hu, D.G. Rhodes, *Int. J. Pharm.*, **1999**, 185, 23-25.
[18] S.S Patel, *Pharmainfo.net*, **2009**.
[19] V.K.Sharma, D.N.Mishra, A.K.Sharma, B.Srivastava, *Int.J.Curr.Pharm.Rev.Res*, **2010,** 1, 2,6-1
[20] R.A. RajaNaresh,G. Chandrashekhar, G.K. Pillai,N.Udupa, *Ind.J.Pharmacol.*, **1994,**2,46-48.
[21] S .Chauhan,M.J.Luorence,*J. Pharm. Pharmacol*., **1989**, 41, 6.
[22] G.Buckton; International Phenomenom in Drug Delivery and Targeting, Academic Publishers, Switzerland, **1995**.
[23] H .Kiwada, H.Niimura, Y.Fujisaki, S. Yamada, Y. Kato, *Chem. Pharm. Bull*.,**1985**, 33, 753–759.
[24] http://www.pharmainfo.net/reviews/niosome-unique-drug-delivery-system.
[25] S.Verma, S. K.Singh, N. Syan, P. Mathur, V.J Valecha, *Chem. Pharm. Res*.,**2010**,2,2, 496-509.
[26] A. A. Ismail, A. Sanaa, E. Gizawy, M. A. Fouda, M.A. Donia, *AAPS Pharm Sci Tech*.,**2007**,8,4.
[27] G. Haran, R. Coben, L.K. Bar, Y. Barenholz, *Biophys. Acta.*, **1993,**1151,201.
[28] M.N. Azmin, A.T. Florence, R.M. Handjani-Vila, J.F.B. Stuart, G. Vanlerberghe, J.S. Whittaker, *J. Pharm. Pharmacol*.,**1985**, 37, 237–242.
[29] S. Biswal, P.N.Murthy, J.Sahu, P.Sahoo, F.Amir, *Int.J.Phar.Sci and Nanotechnology.*, **2008,**1,1,1-8.
[30] N.K. Jain; Controlled and novel drug delivery,CBS publishers and distributors, New Delhi, **2001**.
[31] Inex Pharmaceutical Corporation Sphingosome for enhanced drug delivery:M.S. Webb, M.B Bally, L.D. Mayor, US Patent 5543152, **1996**.

[32] Inex Pharmaceutical Corporation. Sphingosomes for enhanced drug delivery: M.S.Webb, M.B. Bally, L.D Mayor, World Patent 035094, **1995**.
[33] R.A. Brunke; Sphingosomes: Properties and Potential (liposomes based on sphingolipid), Drug and Cosmetic industry,**1991**.
[34] S.P Vyas, R.K .Khar; Targeted and controlled drug delivery, CBS publisher and Distributor, New Delhi,**2001**.
[35] S.S Biju, S. Talegaonkar, P.R Mishra,*Indian. J. Pharm. Sci*., **2006**, 68,141-153.
[36] Hana biosciences,Businesswire **2006**, http://findarticles.com/p/articles.
[37] Vectron therapeutic AG. Drug delivery vehicles and uses theirof:R.Mueller, T .Hilka, T.Nahde, European Patent 1537858, **2005**.
[38] S. Erdogan, Y. Ozer, H. Bilgili, *Int J Phar.*, **2005**, 295, 1-6.
[39] S. Erdogan, Y. Ozer, H Bilgili, *Drug Delivery*, **2006,** 13, 4,303-309.
[40] M. Kanwar, *Drug Dev. Ind. Pharm.*, **2002**, 28, 5, 473–493.
[41] M.O. Vaizoglu, P.P. Speiser, *Acta Pharm. Suec.*,**1986,** 23, 163–172.
[42] F. Volkering, *App. Environ. Micro***, 1995**, 61, 5, 1699–1705.
[43] Nilesh, Pharmacosomes –FarmavitaR Regulatory affairs network, 11 December **2007**.
[44] M. Gulati, *Int. J. Pharm.*, **1998**, 165**,** 129–168.
[45] Targeted Vesicular Constructs For Cytoprotection and Treatment of *H. Pylori* Infections: A. Singh, R. Jain,US Patent 6576,625, **2003**.
[46] (C1 S14-25,A61K31/70):A. Steve, US Patent S534499, **1996**.
[47] N.K. Jain;Advances In Controlled and Novel Drug Delivery,CBS Publishers and Distributor, New Delhi, India, **2003**.
[48] J.S. Valentino,N.C. William, *Lymphatic Transport of Drugs*., **1992**, 205.
[49] A.Schatzlein,G.Ceve,In;G. Cevc.E.Paltauf(Ed.),Phospholipid Characterization,metabolism and novel biological applications,AOCS press,Champaign, **1995**,191.
[50] G.Cevc, *Chem. Phys. Lipids*.,**1991,** 57,293-299.
[51] S.Pandey, M.Goyal, V.Devmurari, J.Fakir, *Der Pharmacia Lettre.*, **2009**, 1, 2,143-150.
[52] G. Cevc,*Anesthesia and Analgesia*, **1992**, 75,615-621.
[53] Y.K. Song, C.K Kim, *Biomaterials*, **2006**, 27, 271-280.
[54] Y.K. Oh, M.Y. Kim, J.Y. Shin, T.W. Kim, M.O. Yun, S.J. Yang, S.S. Choi, W.W. Jung, J.A Kim, H.G. Choi, *J. Pharm. Pharmacol.*, **2006**, 58,161-166.
[55]. B.Godin,E.Touitou,*Crit.Rev.Ther.Drug Carrier Syst*,**2003**,20,63
[56].M.Kretschmar,S.Amselem,E.Zawoznik,K.Mosbach,H.A.Hof,T.Nichterlein,*Mycoses*,**2001**,44,281
[57].A.J .Khopade,S.Jain,N.K.Jain,*Int J Pharm.*,**2002**,241,145
[58].S.P.Vyas,V.Jaitley,P.Kanuja,*Indian J.Exp.Biology.*,**1997**,35,212.
[59].A.Huckriede,L.Bungener,T.Daemen,J.Wilschut,*Methods Enzymol.*,**2003**,373,74
[60].R.I. Zhdanov,O.V. Podobed ,V.V. Vlassov,*Biochemistry.*,**2002**,58,53
[61].C.Petit-Free,P.H.Clingen,C.F.Arlett,M.H.Green,*J.Invest.Dermatol*.,**1998**,111,354.
[62].J.Cuppoletti,E.Mayhew,C.R.Zobel,C.Y.Jung,*Proc.Natil.Acad.Sci.USA*,**1981**,78,3786
[63].M.A. Babizhayev, *Arch.Biochem.Biophys*,**1988**, 266,446.
[64].E.T.Kisak,B.Coldren,C.A.Evans,J.A.Zasadzinski,*Curr.Med.Chem.*,**2004**,279,11696
[65].L.Krishnan,S.Patil, G.B.Patil,G.D.Sprott,*J.Immunol.*,**2001**,166,1885.