Int. J. Chem. Sci.: 12(3), 2014, 797-814
ISSN 0972-768X
www.sadgurupublications.com

VESICULAR MODE OF DRUG DELIVERY : A PROMISING APPROACH FOR ANTI-INFECTIVE THERAPY

M. UDAYA SAKTHI, D. RAMYA DEVI and B. N. VEDHA HARI*

Department of Pharmaceutical Technology, School of Chemical and Biotechnology, SASTRA University, THANJAVUR – 613 401 (T.N.) INDIA

ABSTRACT

Infections are caused by several microorganisms, which are mostly affecting the mucosal surfaces such as gastrointestinal tract, respiratory tract, vaginal tract etc. These microorganisms are treated with anti-infective drugs based on their severity of action in the individuals. The conventional anti-infectives have short residence time at the site of application and poor bioavailability, which leads to incomplete elimination of organisms causing reoccurance and tolerance. Recently, vesicular mode of delivery of drugs has gained attraction because of its improved therapeutic efficacy and stability. Vesicles are bilayered structures formed by hydration of lipid molecules and can be used for incorporating both hydrophilic and lipophilic drugs. This paper focus on various vesicular systems such as liposomes, niosomes, ethosomes, transferosomes and their contribution towards overcoming the disadvantages of anti-infective drugs.

Key words: Vesicular systems, Anti-infectives, Bioavailability.

INTRODUCTION

Infection is the reaction of the host organism's body tissue to the disease causing microbes and the toxins, they produce. These infections are transmissible or communicable caused by infectious agents such as bacteria, fungi, viruses, nematodes, macro-parasites, which are eliminated from the body by the immune system. Severe infections can be treated with anti-microbial agents[1].

Antimicrobial agents

An agent that kills or inhibits the growth of the microorganisms is called antimicrobial agents. They can be classified according to their function and also based on the type of organism, they act upon. Agents that act against bacteria are called antibacterials and that acting against fungi are called antifungals.

*Author for correspondence; E-mail: vedhahari@scbt.sastra.edu

Antibacterial agents

Antibacterial agent kills or inhibits the growth of bacteria, and so called as antibiotics. Antibiotics denote a broader range of drugs and are classified by their mechanism of action, chemical structure and biological activity.

Based on the mechanism of action, they are classified by their ability to target the outer membrane of bacteria or that inhibit enzymes or nucleic acid and protein synthesis. Based on the biological activity they are classified as bactericidal (kills) and bacteriostatic (slows down) agents. Based on the chemical structure they are classified as beta lactums, cephalosporins and carbapenems. Other classes include aminoglycosides, quinolones, sulfonamides, macrolides, nitroimidazoles[2].

Antifungal agents

Antifungal agents are used to treat fungal infections and also to stop their development. They are used to treat mycoses such as *athlete's foot, candidiasis* and also some serious diseases like *crytococcal meningitis*. There are several classes of antifungals which are: polyene, imidazole, triazole, thiazole, allylamines, echinocandins etc. As fungal cells are similar to human cells (both are eukaryotes) targeting is difficult and so it may lead to some side effects[3].

These drugs discovered over the years do not have very good effectiveness due to factors such as drug resistance, their inability to reach target sites, short residence time, poor bioavailability, lack of penetration etc.[4] So to overcome these challenges novel delivery systems are being investigated for effective delivery of these drugs. One such approach is vesicular delivery systems; these include liposomes, niosomes, ethosomes, transferosomes, pharmacosomes, sphingosomes, herbosomes, cubosomes, aquasomes, virosomes, enzymosomes, bilosomes etc.[5]

Liposomes

Liposomes are bilayered structures composed of phospholipids and cholesterol that are used for the administration of nutrients and drugs. The core of liposomes entraps hydrophilic drugs and the membrane entraps hydrophobic drugs, which can be administered through oral, intravenous and topical delivery. The mechanism of delivering drugs is either by fusing with the cell membrane and releasing the drug or by endocytosis mechanism of the cells. The vesicles can be multilamellar, small unilamellar and large unilamellar depending on the method of preparation. For targeting, the surfaces of liposomes are attached with ligands specific to the target site[6].

Table 1: Types of liposomes used for different applications

Types	Uses
Conventional liposomes	Targeted delivery to macrophages and in vaccines
Cationic liposomes	Gene delivery
pH sensitive liposomes	Targeting tumours and in endocytosis
Temperature Sensitive liposomes	Site specific delivery of solid tumours
Stealth liposomes	Selective targeting to pathological areas
Immuno liposomes	Receptor mediated endocytosis
Magnetic liposomes	Targeting antibodies to brain[6]

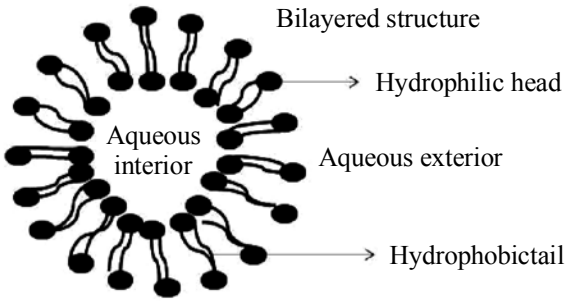

Fig. 1: Structure of vesicle

Antibacterial drugs in liposomes

Several antibacterial drugs were formulated as liposomes for increasing bioavailability, antibacterial activity, entrapment, prolonging release and permeation. Below Table 2 shows the drug, its composition and the method used for preparation.

These liposomes exhibit high antibacterial activity against *Mycobacterium avium, pneumonia, S. aureus* organisms and can be delivered through ocular, intravenous, topical and inhalation routes depending on the area infected.

Effect of surface charge

Shafaa et al.[7] reported that surface charge of the liposomes affects their activity against *S. aureus* infections. Negatively charged liposomes prepared by using Dicetyl

phosphate showed high antibacterial behaviour compared to the positively charged liposomes made with stearyl amine and the neutral liposomes.

Complexation with β-CD

Salem et al.[8] suggested that complexation of phospholipids with β-cyclodextrin and liposome encapsulation of Clarithromycin improved the solubility, which in turn may enhance the *in vivo* bioavailabiliy of the drug thus making it available to the macrophages infected with Mycobacterium avium complex (MAC).

Lung targetting

Zhang et al.[9] targetted lungs for treating pulmonary inflammation by injecting the liposomes loaded with Levofloxacin intravenously through caudal vein. High lung targeting efficiency was achieved reducing the side effects like hematotoxicity and neurotoxicity caused by direct injection of drug.

Long circulation half life and prolonged release

Sterically stabilized liposomes of Ciprofloxacin prepared by using polyethylene glycol (PEG) were not taken up by mononuclear phagocyte system (MPS) i.e., liver and spleen and thus showed high circulation half lives, which lead to localization of liposomes in the infected regions of *Klebsiella pneumonia.* But in rat models treatment with Ceftriaxone was found to be effective than the Ciprofloxacin encapsulated sterically stabilized liposomes[10].

Prolonged release of Chloramphenicol was obtained by incorporating the drug into liposome carrier and again incorporating it into a bioadhesive gel of carbapol 974P. This lead to prolonged release of drug for more than 24 hrs and also good stability of the formulation[11].

Antifungal drugs in liposomes

Antifungal drugs such as Clotrimazole, Miconazole, Itraconazole, Nystatin were formulated as liposomes and are used for treating infections caused by fungal organisms like *Candida albicans.*

Better permeation and retention on skin

Miconazole Liposomes prepared with saturated phospholipids showed better retention in the skin compared to unsaturated phospholipids. But the permeation of

liposomal formulations was high compared with non liposomal systems, which may be due to the dispersibility of the drug in the system in insoluble form[12].

Protecting erythrocytes with better antifungal activity

Nystatin is a polyene that is highly toxic when given intravenously. Liposomes of Nystatin displayed high spectrum of activity against *C. albicans* than amphotericin B. Also, encapsulation of drug with liposomal layer prevented the lysis of erythrocytes thus protecting the mammalian cells from damage[13].

Passive targetting

Itraconazole liposomes administered by intravenous injection showed high distribution of drug in lungs, brain and liver than the drug dissolved in cyclodextrin or polyethylene glycol 2000. Better efficacy of drug was observed under *in vivo* conditions. Hence, it was effective to treat systemic infections particularly in brain and lung[14].

Table 2: Liposome formulations of antibacterial and antifungal drugs

Drug	Composition	Method
Antibacterial drugs		
Cephalexin	L-α-dipalmitoyl phosphatidyl choline	Thin film hydration technique[7]
Clarithromycin	βCD-cyclodextrin, Egg yolk phosphatidylcholine	Thin film hydration technique and Complexation of drug with βCD[8]
Gentamicin (intra venous administration)	Egg phosphatidylcholine phosphatidylserine, stearylamine, and dipalmitoylphosphatidylcholine	Film hydration method and Sonication[15]
Chloramphenicol (gel for vaginosis)	Egg phosphatidylcholine/egg phosphatidylgycerol-sodium	Proliposome method and the polyol dilution method[11]
Levofloxacin (injection)	Soybean phosphatides	Ammonium sulphate gradient method[9]
Ticarcillin	Egg lecithin	Thin film hydration followed by sonication and extrusion[16]

Cont…

Drug	Composition	Method
Antifungal drugs		
Miconazole (Topical)	Phosphatidyl choline	Thin film hydration technique[12,14]
Itraconazole (intravenous)	Dipalmitoylphosphatidylcholine	
Nystatin	Dimyristoyl phosphatidylcholine (DMPC) and Dimyristoyl phosphatidylglycerol (DMPG)	Thin film hydration technique[13]

Niosomes

Niosomes are vesicular structures ranging from 10-1000 nm size, formed by incorporating non ionic surfactants, which can be used for delivering amphiphilic and lipophilic drugs. Niosomes are biodegradable, non-toxic, more stable and inexpensive. The chemical nature of the surfactants improves the stability of niosomes that makes them better than liposomes[17]. The stability is increased by incorporating cholesterol and little of anionic surfactants. Steric stabilization of niosomes is done for preventing aggregation of vesicles using compounds like dicetyl phosphate, stearyl amine that introduce electrostatic or repulsive steric forces. They can be administered through intramuscular, intravenous, transdermal and also oral.

The cholesterol in the mixture acts as fluidity buffer and intercalator, provides rigidity and stability to the vesicles, decreases the permeability coefficient of membranes[18].

Antibacterial drugs in niosomes

Penetration enhancement

Drugs such as Bacitracin, Benzoyl peroxide and Erythromycin are formulated as niosomal gel for topical use to overcome side effects such as irritation, redness, itching, edema. Encapsulation of drug into niosomal gel improved the penetration of drug into the layers of skin and also prolonged its release[19-21].

For ocular delivery without irritancy

Eye infections are treated by frequent administration of drugs or by directly injecting drugs on the site of infection, which have its own disadvantages like poor patient compliance,

slow residence time, lacrimal discharge. To overcome these limitations, niosomes of drugs such as Gentamicin, Levofloxacin, Chloramphenicol were prepared that gave sustained release for more than 10 hours without affecting vision. Ocular irritation was also not observed[22-24].

Effect of cholesterol and surfactant

Addition of cholesterol enhances the fluidity of niosomes that is essential for the rigidity of vesicles. In Norfloxacin niosomes, amount of cholesterol added had an effect on the release of the drug. Low surfactant and high cholesterol content lead to the formation of leaky vesicle. Hence amount of cholesterol added to the formulation was found to depend on the nature of the surfactant and its HLB (Hydrophilic Lipophilic Balance) value[25].

Effect of lipophilicity of surfactant

Niosomes of Rifampicin prepared by using different sorbitan esters (Span 20, 40, 60, 80, 85) showed difference in release rates, which may be due to the varying lipophilic nature of the surfactants. Least lipophilic nature eases the access of media to the drug but highly lipophilic nature hinders the permeation of media[26].

Lung targetting

Rifampicin niosomes were prepared and studied for its characteristics, which showed localization of 65% of drug in lungs for treating lung infections[27].

Effective against tuberculosis infections

Niosomes of Rifampicin and Gatifloxacin exhibited prolonged release of drug upto 16 hours, which could overcome the limitations such as frequent administration to patients, rheumatoid syndrome, allergy and hepatotoxic disorders. This also gave better bactericidal activity against *Mycobacterium tuberculosis* as that of the pure drug solutions[28].

Antifungal drugs in niosomes

Effect of cholesterol, surfactant and ethanol content on entrapment

The ratio of cholesterol: surfactant and the ethanol content in the formulation play significant role in the entrapment of drug into vesicle, which in turn altered the drug release. Itraconazole niosomes were formulated by varying the cholesterol: surfactant ratios and ethanol content. The entrapment of drug into vesicle increased with increase in ethanol content and decreased when cholesterol content was increased[29].

Overcoming nephrotoxicity

Amphotericin B, a polyene compound was effective against several mycoses but caused renal dysfunctions. Lipid based formulations could be used as an alternative for treating infections with amp B. Niosomes are best choice rather than liposomes, as the niosomes were not subjected to oxidation and withstand heat. Almost 85% of drug was found to be entrapped in the long alkyl chains of surfactant (sorbitan esters and polyoxylated sorbiatan esters) which gave slow and continuous delivery[30].

Effective for cancer treatment

Recently Ciclopirox, an antifungal agent has been proposed for cancer treatment. Cytotoxicity studies for liposomal and niosomal Ciclopirox were carried out on PC3 (prostate cancer), KB (oral cancer), Vero (kidney epithelial) and Siha (cervical cancer) cell lines by MTT assay. The IC50 (50% Inhibitory concentration) values were compared with the pure drug and standard doxorubicin to study the most efficient formulation. Niosomal formulation demonstrated cytotoxic effects at a much lower concentration than that of others, with signified pharmacological efficiency[31].

Enhanced cutaneous retention

Greater cutaneous accumulation of Fluconazole was achieved by loading the drug in niosomes. The vesicle size of formulations made with Span 40, Span 60, and Brij 72 were 0.378 ± 0.022 μm, 0.343 ± 0.063 μm, and 0.287 ± 0.012 μm, respectively. The small size of the vesicles and the nature of the surfactant affected the cutaneous accumulation and sustained delivery of drug[32].

Effective treatment for warts and corns

Penetration of drug into warts and corns was studied by preparing niosomal formulation of Salicylic acid with charged components such as veegum and cetylpyridium as it stabilizes the vesicle structure. The changes in molar and osmotic concentration of the release medium cause change in the entrapment efficiency. From the studies, it was concluded that niosomal formulation could be more successfully used for treating warts, corns and other inflammatory conditions[33].

Ethosomes

Ethosomes are soft, malleable lipid vesicles made of phospholipid, high concentration of alcohol (ethanol or isopropyl alcohol) and water. Ethanol (20 to 50%) acts as penetration enhancers and thus helps in delivering drugs to the deeper layers of the skin. High concentration of ethanol is said to be the reason for better penetration through the skin.

Ethanol increases the cell membrane fluidity and decrease the lipid density. Drugs including hormones, DNA, peptides can be incorporated in ethosomes. Ethosomes are prepared by 2 methods, namely Hot method and Cold method[41].

Table 3: Niosome formulations of antibacterial and antifungal drugs

Drug	Component	Method
Antibacterial drugs		
Bacitracin (Topical)		Thin film hydration technique[19]
Benzoyl peroxide (topical gel)	HPMC K15 gel	Thin film hydration technique[20]
Cefuroxime axetil	Span 40, 60, 80, Stearylamine	Hand shaking method[34]
Chloramphenicol	Polyoxyethylene alkyl esters (Brij 52,72,92)	Film hydration method[24]
Ciprofloxacin	Tween 40 Span 40	Film hydration and pH and ammonium sulphate gradient[35]
Erythromycin (Topical gel)	Span 20,60,80	Thin film hydration technique[21]
Gentamicin (Opthalmic)	Tween 60, 80, Brij 35, Dicetyl phosphate	Thin film hydration technique[22]
Levofloxacin (ophthalmic gel)	Span	Thin film hydration technique[23]
Norfloxacin (proniosomes)	Maltodextrin, Span	Slurry method[25]
Rifampicin and Gatifloxacin Rifampicin	Span, Tween, Dicetyl phosphate Span-20, Span-40, Span-60, Span-80 and Span-85	Lipid hydration method[28] Hand shaking method[26]
Sulfadiazine (Transdermal)	Pluronic L64 or Aerosol OT	Sonication[36]
Antifungal drugs		
Amphotericin B (iv infusion)	sorbitan esters (Spans), polyoxylated sorbitan esters (Tweens) and cetyltrimethyl ammoniumbromide (CTAB)	[30]

Cont…

Drug	Component	Method
Ciclopirox olamine	Span 60	Ethanol injection method[31]
Econazole (Transdermal)	Span 80	Thin film hydration technique[37]
Fluconazole (Cutaneous delivery)	Span and Brij	Film hydration method[32]
Griseofulvin(oral)	Span 20,40,60	Lipid film hydration and ether injection technique[38]
Itraconazole	Span 60	Hydration of proniosomes[29]
Ketoconazole (Niosomal gel)	Span, Tween	Thin film hydration technique[39]
Salicylic acid	Polysorbate-20	Lipid Film Hydration Technique[33]
Voriconazole	Span 80	Hand shaking method and Ether injection method[40]

Antibacterial drugs in ethosomes

Enhanced permeation

Bacitracin ethosomes labeled with fluorescein isothiocyanate (FITC) was prepared with 25% ethanol concentration and its permeation was studied in swiss albino mice fibroblasts, which showed more penetration of antibiotic into the cell membrane and releasing the drug into cells. Penetration of ethosomes into the skin layers was studied in human cadaver skin and rat skin, which demonstrated delivery of drug into deep layers up to 200 μm[42].

Effective against *S. aureus*

Skin infections with cellulites', erysipelas and trauma caused by *S. aureus* could lead to complication and sometimes morbidity and mortality. Systemic treatments of these infections lead to side effects, poor patient compliance and allergic reactions. To overcome these problems, topical treatment of deep skin infections was suggested which could be achieved by ethosomes. Erythromycin ethosomes healed the deeper skin infections more efficiently in mice induced with *S. aureus* infections, compared to the hydroethanolic solution[43].

Antifungal drugs in ethosomes

Overcoming the barrier function

Skin is the perfect barrier for all particles protecting the body from infections. For treating deep skin infections, most drugs could not pass through the skin layers to deliver its activity. To overcome this limitation, Cavamax (α, β, γ-cyclodextrin) was used for preparing Clotrimazole ethosomes with 30% ethanol and soya lecithin (0.3, 0.5, 0.8%). Ethosomes with 0.8% soya lecithin and cavamax W7 was found to be more stable and was incorporated in carbapol gel, which showed better antifungal activity by permeating through the fungal cells in deep skin layers[44].

Reduction in lesion diameter

Topical skin infections caused by *M. gypseum, M. canis, T. mentogrophytes, T. rubhum, C. albicans* can be treated with ethosomal gels of Econazole, Fluconazole, Griseofulvin. Deposition of drug in the skin was high, which contributed to the reduction of lesions[45-47].

Ethosomal gel was also used in treating dandruff. Griseofulvin ethosomal gel achieved complete healing within 8 days of treatment and initiated growth of hair within 5-6 days[47].

Reduction of dose frequency

Terbinafine hydrochloride gave severe side effects when administered orally. Lotions, creams and sprays of the drug have slow residence time and high dose frequency. For overcoming these problems, vesicular systems of reduced size was recommended topically. Ethosomes were prepared and sonicated for size reduction. Reduction in size gave high skin penetration and localization, which in turn reduced the dose frequency[48].

Transferosomes

Transferosomes are ultra-deformable vesicles with bilayered structure and are widely used for delivering high molecular weight peptides, hormones and several drugs. Biogenic molecules such as insulin, vaccines, which are degraded in the gastrointestinal tract can be administered through transferosomes. Due to their high flexibility, permeation becomes easy through the stratum corneum. Transferosomes squeeze through the intracellular lipid of the stratum corneum and penetrate into the skin layers overcoming their barrier function. Also the osmotic gradients in the skin layers help in the movement of vesicles from the dry stratum corneum (top layer) to the hydrated deeper layers of the skin.

Table 4: Ethosome and Transferosome formulations of antibacterial and antifungal drugs

Drug	Component	Method
Ethosomes		
Antibacterial drugs		
Bacitracin	Fluorescent phospholipids (rhodamine red dihexadecanoylglycero-phosphoethanolamine), Phospholipon 90	Cold method[42]
Erythromycin	Phospholipon 90, Ethanol	Cold method[43]
Antifungal drugs		
Clotrimazole	Soya lecithin, Cavamax W6, W7, and W8 (α-, β- and γ-cyclodextrin, respectively)	Cold method[44]
Econazole (topical gel)	Soya lecithin, ethanol (30%), Propelene glycol	Cold method[45]
Fluconazole	Soya Phosphatidyl choline, Ethanol	Hot method[46]
Griseofulvin	Phospholipon 90G, Ethanol	Cold method[47]
Ketoconazole	Phospholipid (1-3%), Ethanol (20-40%)	Cold method[49]
Terbinafine	Soya Phospholipid, Ethanol	Cold method followed by sonication[48]
Voriconazole (transethosomes)	Phosphatidylcholine (PC) from soybean lecithin, ethanol	Cold method [50]
Transferosomes		
Neomycin	Soya phosphatidylcholine (97.1%) (Phospholipone ®90G)	Rotary evaporation method[51]
Nystatin	Phospholipone H 100	Rotary evaporation-sonication method[52]

Stability of transferosomes is difficult to achieve because of its predisposition due to oxidative degradation. Natural phospholipids used for the preparation are not completely pure as its purification is a difficult process[51].

Antibacterial drug in transferosomes

Effective against staphylococcal infections

Neomycin elastic liposomes were prepared and incorporated into hydrogels for treating dermal infections of *S.aureus*. *In vivo* studies demonstrated high penetration of vesicles into the skin layers thus providing effective treatment for dermal infections[52].

Antifungal drug in transferosomes

Enhanced skin delivery

Surfactants in the formulation solubilised the lipids in the stratum corneum, which helped the vesicle to penetrate through the skin overcoming the barrier function. Nystatin transferosomes showed enhanced permeation through the skin lipid layer with improved anti-fungal activity than the liposomes[53].

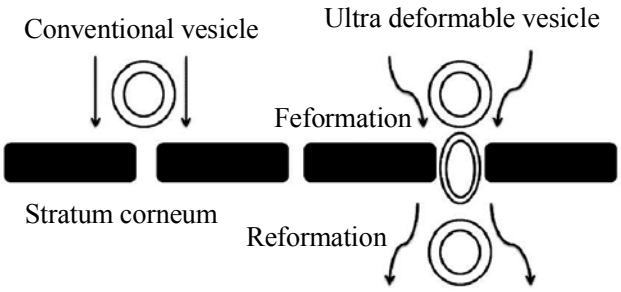

Fig. 2: Deformation of transferosomes through the stratum corneum

There are also other types of vesicular systems such as virosomes, pharmacosomes, emulosomes, enzymosomes, aquasomes that can be used for delivering drugs more effectively each having its own advantages.

CONCLUSION

This article outlines about liposomes, niosomes, ethosomes and transferosomes of anti-infective drugs and its merits over the conventional formulations. Vesicular systems can be prepared by different methods which influence the size and structure of vesicle and also the entrapment of the drug. The amount of cholesterol and surfactant added to the formulation also affect the characteristics of the vesicles. The vesicular delivery systems give many advantages such as increasing bioavailability, targeting and better stability in delivering drugs. Since, it has many advantages over the conventional medicine, vesicular

mode of delivery can be used for efficient administration of anti-infective drugs in near future.

REFERENCES

1. Bethesda (MD): National Institutes of Health (US); Biological Sciences Curriculum Study. NIH Curriculum Supplement Series [Internet]. National Institutes of Health (US) Understanding Emerging and Re-emerging Infectious Diseases. Available from: http://www.ncbi.nlm.nih.gov/books/NBK20370 (2007).

2. T. Saga and K. Yamaguchi, History of Antimicrobial Agents and Resistant Bacteria, Japan Medical Association, J. (JMAJ), **52(2)**, 103-108 (2009).

3. P. Vandeputte, S. Ferrari and A. T. Coste, Antifungal Resistance and New Strategies to Control Fungal Infections, Int. J. Microbiol., Article ID 713687, doi:10.1155/2012/713687 (2012).

4. D. B. Patel and J. K. Patel, Liposomal Drug Delivery of Metronidazole for Local Treatment of Vaginitis, Int. J. Pharm. Sci. Nanotech., **2(1)**, 421-427 (2009).

5. S. Bansal, C. P. Kashyap, G. Aggarwal and H. L. Harikumar, A Comparative Review on Vesicular Drug Delivery System and Stability Issues, Int. J. Res. Pharm. Chem., **2(3)**, 704-713 (2012).

6. S. Kamboj, V. Saini, N. Magon, S. Bala and V. Jhawat, Vesicular Drug Delivery Systems: A Novel Approach for Drug Targeting, Int. J. Drug Delivery, **5**, 121-130 (2013).

7. M. W. Shafaa, S. A. Dayem, W. M. Elshemey and H. M. Osman, *In Vitro* Antibacterial Activity of Liposomal Cephalexin against *Staphylococcus Aureus,* Romanian J. Biophys., **18(4)**, 293-300 (2008).

8. I. Ismail Salem and N. Du¨zgu¨nes, Efficacies of Cyclodextrin-Complexed and Liposome Encapsulated Clarithromycin against *Mycobacterium Avium* Complex Infection in Human Macrophages, Int. J. Pharm., **250**, 403-414 (2003).

9. X. Zhang, P. Sun, R. Bi, J. Wang, N. Zhang and G. Huang, Targeted Delivery of Levofloxacin-Liposomes for the Treatment of Pulmonary Inflammation, J. Drug Target., **17(5)**, 399-407 (2009).

10. H. E. Martin, M. O. Keith, M. J. G. Nielsen and L. C. Preheim, Efficacy of Liposome-Encapsulated Ciprofloxacin Compared with Ciprofloxacin and Ceftriaxone in a Rat Model of *Pneumococcal Pneumonia*, J. Antimicro. Chemother., **51**, 83-91 (2003).

11. Z. Pavelić, N. Skalko-Basnet and I. Jalsenjak, Liposomal Gel with Chloramphenicol: Characterisation and *In Vitro* release, Acta. Pharm., **54(4)**, 319-330 (2004).

12. R. Agarwal and O. P. Katare, Preparation and *In Vitro* Evaluation of Miconazole Nitrate–Loaded Topical Liposomes, Pharmaceutical Technology, 48-60 (2002).

13. R. T. Mehta, R. L. Hopfer, L. A. Gunner, R. L. Juliano and G. L. Berestein, Formulation, Toxicity, and Antifungal Activity *In Vitro* of Liposome-Encapsulated Nystatin as Therapeutic Agent for Systemic Candidiasis, Antimicrob. Agents Chemother., **31(12)**, 1897-1900 (1987).

14. P. L. Conte, V. Joly, L. S. Julien, M. Gillardin, C. Carbon and P. Yeni, Tissue Distribution and Antifungal Effect of Liposomal Itraconazole in Experimental Cryptococcosis and Pulmonary Aspergillosis, Am. Rev. Respir. Dis., **145(2)**, 424-429 (1992).

15. J. R. Morgan and K. E. Williams, Preparation and Properties of Liposome-Associated Gentamicin, Antimicrob. Agents Chemother., **17(4)**, 544-548 (1980).

16. A. Gharib, Z. Faezizadeh and M. Godarzee, *In Vitro* and *In Vivo* Activities of Ticarcillin-Loaded Nanoliposomes with Different Surface Charges against *Pseudomonas Aeruginosa* (ATCC 29248), DARU J. Pharm. Sci., **20**, 41 (2012).

17. A. Sankhyan and P. Pawar, Recent Trends in Niosome as Vesicular Drug Delivery System, J. Appl. Pharmaceut. Sci., **2(6)**, 20-32 (2012).

18. G. P. Kumar and P. Rajeshwarrao, Nonionic Surfactant Vesicular Systems for Effective Drug Delivery : An Overview, Acta Pharm. Sin B., **1(4)**, 208-219 (2011).

19. N. Kasliwal, Development, Characterization, and Evaluation of Liposomes and Niosomes of Bacitracin Zinc, J. Dispers. Sci. Technol., **9**, 1267-1273 (2012).

20. V. Jigar, V. Puja, R. Dhaval and P. Paresh, Development of Topical Niosomal Gel of Benzoyl Peroxide, ISRN Nanotechnology, doi:10.5402/2011/503158 (2011).

21. V. Jigar, V. Puja and S. Krutika, Formulation and Evaluation of Topical Niosomal Gel of Erythromycin, Int. J. Pharm. Pharm. Sci., **3(1)**, 123-126 (2010).

22. G. Abdelbary and N. El-gendy, Niosome-Encapsulated Gentamicin for Ophthalmic Controlled Delivery, AAPS Pharm. Sci. Tech., **9(3)**, 740-747 (2008).

23. N. Raghuwanshi, S. Dikshit, A. Sharma, N. Upamanyu, A. Dubey and A. Pathak, Formulation and Evaluation of Niosome-Encapsulated Levofloxacin for Ophthalmic Controlled Delivery, Int. J. Adv. Pharmaceut. Sci., **3(5)**, 901-906 (2012).

24. M. N. Yasin, S. Hussain, F. Malik, A. Hameed, T. Sultan, F. Qureshi, H. Riaz, G. Perveen and A. Wajid, Preparation and Characterization of Chloramphenicol Niosomes and Comparison with Chloramphenicol Eye Drops (0.5% w/v) in Experimental Conjunctivitis in Albino Rabbits, Pak. J. Pharm. Sci., **25(1)**, 117-21 (2012).

25. G. Hazel, D. Akhilesh, P. Prabhakara and K. V. Jagadish, Development and Evaluation of Norfloxacin Loaded Maltodextrin Based Proniosomes, Int. Res. J. Pharm., **3(6)**, 176-179 (2012).

26. V. S. Jatav, S. K. Singh, P. Khatri, A. K. Sharma and R. Singh, Formulation and *In Vitro* Evaluation of Rifampicin-Loaded Niosomes, J. Chem. Pharm. Res., **3(2)**, 199-203 (2011).

27. C. P. Jain and S. P. Vyas, Preparation and Characterization of Niosomes Containing Rifampicin for Lung Targeting, J. Microencapsul., **12(4)**, 401-407 (1995).

28. N. P. Rani, T. N. K. Suriyaprakash and R. Senthamarai, Formulation and Evaluation of Rifampicin and Gatifloxacin Niosomes on Logarithmic-Phase Cultures of *Mycobacterium Tuberculosis,* Int. J. Pharm. Bio. Sci., **1(4)**, 379-387 (2010).

29. V. D. Wagh and O. J. Deshmukh, Itraconazole Niosomes Drug Delivery System and Its Antimycotic Activity against *Candida Albicans*, ISRN Pharm, Article ID 653465, (2012).

30. A. Noormandi, A. Pardakhty and H. Torabifard, Formulation and *In Vitro* Characterization of Amphotericin B, Res. Pharm. Sci., **7(5)** (2012).

31. K. Shaikh, A. Pawar, S. Aphale and A. Moghe, Effect of Vesicular Encapsulation on *In Vitro* Cytotoxicity of Ciclopirox Olamine, Int. J. Drug Delivery, **4(2)**, 139 (2012).

32. M. Gupta, B. Vaidya, N. Mishra and S. P. Vyas, Effect of Surfactants on the Characteristics of Fluconazole Niosomes for Enhanced Cutaneous Delivery, Artif. Cells Nanomed. Biotechnol., **39(6)**, 376-384 (2011).

33. C. O. Esimone, N. C. Obitte, A. N. Onuora and V. I. Onyishi, *In Vitro* Evaluation of Polysorbate-20-Based Niosomal Formulations of Salicylic Acid, Niger. J. Pharm. Sci., **8(1)**, 218-228 (2010).

34. S. Sambhakar, B. Singh, S. K. Paliwal and P. R. Mishra, Niosomes as a Potential Carrier for Controlled Release of Cefuroxime Axetil, Asian J. Biochem. Pharmaceut. Res., **1(1)**, 126-136 (2011).

35. V. Akbari, D. Abedi, A. Pardakhty and H. S. Aliabadi, Ciprofloxacin Nano-Niosomes for Targeting Intracellular Infections: An *In Vitro* Evaluation, J. Nanopart. Res., 15, doi:10.1007/s11051-013-1556-y (2013).

36. L. Tavano, L Gentile, C. O. Rossi and R. Muzzalupo, Novel Gel-Niosomes Formulations as Multicomponent Systems for Transdermal Drug Delivery, Colloids Surf. B Biointerfaces, **110**, 281-288 (2013).

37. Y. P. Kumar, K. V. Kumar, R. R. Shekar, M. Ravi and V. S. Kishore, Formulation and Evaluation of Econazole Niosomes, Scholars Academic J. Pharm., **2(4)**, 315-318 (2013).

38. P. S. Jadon, V. Gajbhiye, R. S. Jadon, K. R. Gajbhiye and N. Ganesh, Enhanced Oral Bioavailability of Griseofulvin via Niosomes, AAPS Pharm. Sci. Tech., **10(4)**, 1186-1192 (2009).

39. S. B. Shirsand, M. S. Para, D. N. Kumar, K. M. Kanani and D. Keerthy, Formulation and Evaluation of Ketaconazole Niosomal Gel Drug Delivery System, Int. J. Pharm. Investig., **2(4)**, 201-207 (2012).

40. R. Parthibarajan, S. Pradeep Kumar, N. L. G. Shankar, L. Balakishan, B. Srinivas, B. V. Laxmi, A. Radha and K. Sheshma, Design and *In Vitro* Evaluation of Voriconazole Niosomes, Int. J. Pharm. Pharm. Sci., **5(3)**, 604-611 (2013).

41. T. Parashar, Soniya, R. Sachan, V. Singh, G. Singh, S. Tyagi, C. Patel and A. Gupta, Ethosomes: A Recent Vesicle of Transdermal Drug Delivery System, Int. J. Res. Development in Pharm. Life Sci., **2(2)**, 285-292 (2013).

42. B. Godin and E. Touitou, Mechanism of Bacitracin Permeation Enhancement through the Skin and Cellular Membranes from an Ethosomal Carrier, J. Control Release, **94**, 365-379 (2004).

43. B. Godin, E. Touitou, E. Rubinstein, A. Athamna and M. Athamna, A New Approach for Treatment of Deep Skin Infections by an Ethosomal Antibiotic Preparation: An *In Vivo* Study, J. Antimicrob. Chemother., **55**, 989-994 (2005).

44. N. Akhtar and K. Pathak, Cavamax W7 Composite Ethosomal Gel of Clotrimazole for Improved Topical Delivery: Development and Comparison with Ethosomal Gel, AAPS Pharm. Sci.Tech., **13(1)**, 344-355 (2012).

45. P. Verma and K. Pathak, Nanosized Ethanolic Vesicles Loaded with Econazole Nitrate for the Treatment of Deep Fungal Infections through Topical Gel Formulation, Nanomedicine: Nanotechnology, Biology, and Medicine, **8**, 489-496 (2012).

46. M. K. Bhalaria, S. Naik and A. N. Misra, Ethosomes: A Novel Delivery System for Anti-fungal Drugs in the Treatment of Topical Fungal Diseases, Indian J. Exp. Biol., **47**, 368-375 (2009).

47. N. Aggarwal and S. Goindi, Dermatopharmacokinetic and Pharmacodynamic Evaluation of Ethosomes of Griseofulvin Designed for Dermal Delivery, J. Nanopart. Res., **15**, 1983 (2013).

48. R. N. Charyulu, M. Satveek, N. M. Harish and A. B. Patil, A Comparative Study of Terbinafine Ethosomal Formulations : A Novel Approach, Nitte University J. Health Sci., **3(4)**, 23-29 (2013).

49. P. Reecha, Formulation and Evaluation of Ethosomes Containing Antifungal Agent, Inventi Impact: Ndds 2011 Article Id- " Inventi:pndds/230/11 " , Available From http://www.inventi.in/Article/pndds/230/11.aspx. 2011 [Cited 2013 Dec 20]

50. C. K. Song, P. Balakrishnan, C. K. Shim, S. J. Chung, S. Chong and D. D. Kim, Novel Vesicular Carrier, Transethosome, for Enhanced Skin Delivery of Voriconazole: Characterization and *In Vitro / In Vivo* Evaluation, Colloids Surf. B Biointerfaces., **92**, 299-304 (2012).

51. C. D. Modi and P. D. Bharadia, Transferosomes: New Dominants for Transdermal Delivery, Am. J. Pharm. Tech. Res., **2(3)**, 71-91 (2012).

52. G. Darwhekar, D. K. Jain and A. Choudhary, Elastic Liposomes for Delivery of Neomycin Sulphate in Deep Skin Infection, Asian J. Pharmaceut. Sci., **7(4)**, 230-240 (2012).

53. M. H. Abdallah, Transfersomes as a Transdermal Drug Delivery System for Enhancement the Antifungal Activity of Nystatin, Int. J. Pharm. Pharm. Sci., **5(4)**, 560-567 (2013).

Revised : 09.05.2014 *Accepted : 11.05.2014*