Review article

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EMERGING TRENDS OF NANOVESICLES DRUG DELIVERY SYSTEM IN NANOTECHNOLOGY: PRONIOSOMES

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ABSTRACT

Nanotechnology has brought revolutionary changes and helps in preparing newer formulations, which is proniosomes. Proniosomes are water soluble carrier particles that are coated with surfactant and can undergo hydration to form niosomes. Proniosomes can overcome the problems involved with niosomal and liposomal drug delivery systems by reducing niosomes physical stability such as fusion, aggregation, leaking and provide additional convenience in transportation, distribution, storage and dosing. Proniosomes-derived niosomes show better results than conventional niosomes. The aim of this review is to focus on different aspects of proniosomes such as classification, method of preparation, evaluation, in-vitro drug release, in-vitro permeation studies, stability studies and different formulations of proniosomes.

Keywords: Dry granular proniosomes, Sorbitol based proniosomes, Maltodextrin based proniosomes

INTRODUCTION

Proniosomes are dry solid colloidal carrier particles that are surfactant-coated, which can be measured out and dehydrated to form niosomal dispersion right before use on brief agitation in hot water within minutes [1-2]. Proniosomes minimize problems of nonionic surfactant vesicles i.e., niosomes physical stability such as leaking, fusion, aggregation and provided additional convenience in dosing, storage, distribution and transportation.[3] Proniosome-derived niosomes are superior to conventional niosomes in ease of storage, transport and dosing. These carriers can act as drug reservoirs and can control the rate of drug release by modifying their composition. These carriers are able to entrap both hydrophilic and lipophilic drugs and so they are known as drug reservoir. Ease of measuring, transfer, distribution, and storage make proniosomes a good delivery system with potential for use in drug delivery applications due to their capability to carry a variety of drugs [4], drug targeting [5], controlled release [6] and permeation enhancement of drugs [7]. The current review deals with the trends, different aspects and the future perspective in the development of proniosomal drug delivery systems. In the stability point of view, the stability of dry proniosomes is supposed to be more stable than a pre-manufactured niosomal formulation. In release studies, proniosomes appear to be same to conventional niosomes. Size distributions of proniosome-derived niosomes are much greater than conventional niosomes, so the release performance is also better. Proniosomes are dry powder which provides excellent flexibility, unit dosing, easy processing and packaging, thus the proniosome powder could be dispensed in capsule form [11]. A type of proniosome based on maltodextrin was recently developed that has potential to be used in delivery amphiphilic and hydrophobic drugs. These proniosomes used a hollow particle with extraordinary high surface area. The main advantage of this formulation was high mass ratios of surfactant to carrier proniosomes can be perpared and was easy to adjust the amount of carrier required to support the surfactant. We can study the hydration of surfactant from proniosomes due to the ease of production of proniosomes using the maltodextrin, which is by slurry method [8 – 10].

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CLASSIFICATION OF PRONIOSOMES

Dry granular proniosomes:

Dry granular type of proniosomes involves the coating of water-soluble carrier such as sorbitol and maltodextrin with surfactant. The result is a dry formulation in which thin film of surfactant covers each water-soluble particle. It is necessary to

prepare vesicles at a temperature above the transition temperature of the non-ionic surfactant which is used in the formulation. These are further categorized as follows:

Sorbitol based proniosomes:

Sorbital base proniosomes are dry formulation which consist sorbitol as carrier, then further coated with non-ionic surfactant and are used as niosomes within a minute by adding hot water and agitation. These are usually made by spraying the surfactant mixture prepared in organic solvent on to the sorbitol powder then evaporate the solvent. The process must be repeated until the desired surfactant coating is achieved since the sorbitol carrier is soluble in organic solvent. In sorbitol based proniosomes size distribution is uniform. It is useful in case where the active ingredient is susceptible to hydrolysis. Thin layer of surfactant is coated on the carrier and undergoes hydration. This allows multilamellar vesicles to form when the carrier dissolves. The residual sorbitol decreases entrappment efficiency to less than one half of that observed with sorbitol. This necessiate reduction in proportion of carrier in final niosome suspension. The difficulty lies in testing of sorbitol particles because sorbitol is soluable in chloroform and other organic solvent. Its prepared by slow spraying method [12][14-16].

Maltodextrin based proniosomes:

It is prepared by fast slurry method. Time needed to produce proniosomes is independent of the ratio of surfactant solution. Proniosomes of high surface to carrier ratio can be carried out. The method of obtaining niosomes from such a proniosomes for the drug delivery is very simple. The process with sorbital gives a solid, sorbitol/surfactant cake. Maltodextrin is a polysaccharide which easily soluble in water and is used as a carrier. Since maltodextrin morphology is preserved, hollow blown maltodextrin particles show significant gain in surface area. The higher surface area results in thinner surface coating, which makes the rehydration process much easier [8-10].

Liquid crystalline proniosomes:

When the surfactant molecule is contact with water, there are three ways through which lipophilic chains of surfactant can be changed into a disordered liquid state, called lyotrpoic liquid crystalline state(neat phase). The three ways are addition of solvent which dissolve lipids, increasing the Kraft temperature (Tc) and also using both temperature and solvent. Neat phase also known as lamellar phase contains bilayer arranged in a sheet over one another within intervening aqueous layer. This type of structure gives typical x-ray diffraction and thread like bi-refrigerant structure under polarized microscope. The lamellar crystalline phase is converted into niosomes at higher concentration. The liquid crystalline proniosomes and proniosomal gel acts as reservoir for transdermal drug delivery [13][17-21].

Liquid crystalline proniosomes shows few advantages:

- As a penetration enhancer
- Stability
- High entrapment efficiency
- Easy to scale up as not involve in lengthy process
- Avoid using pharmaceutically unacceptable additives.

METHOD OF PREPARATION OF PRONIOSOMES

Proniosome preparation mainly consists of coating carriers, non-ionic surfactants, and membrane stabilizers. Proniosome may be prepared by few methods.

Slurry method:

Proniosomes can be prepared by adding the carrier and surfactant solution into a round bottomed flask which is fitted to rotary flash evaporator. Vacuum is aslo applied to form a dry and free flowing powder. The proniosomal powder formed is collected and sealed in containers and stored at 4°C. Proniosomes are prepared by developed slurry method using Maltodextrin as a carrier. The required volume of surfactant and cholesterol stock solution per gram of carrier and drug should be dissolved in the solvent in 100 ml round bottom flask containing the carrier (Maltodextrin, Sorbitol). Chloroform can be added to form slurry if the surfactant loading is low. The flask is attached to a rotary flash evaporator to evaporate solvent at 45°C with the speed of 50-60rpm and a reduced pressure of 600 mmHg. Lastly, the formulation is stored in a tightly closed container under refrigeration in light. This method is advantageous due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation [22, 24].

Slow spray coating method:

Proniosomes can be prepared by spraying surfactant onto the carrier and then evaporate the solvent. A rotary flash evaporator is attached to a 100 ml round bottom flask containing desired amount of carrier. Cholesterol and surfactant are prepared and inserted into round bottom flask by sequential spray onto carrier's surface. The evaporator must be evacuated and rotating flask can be rotated in water bath under vacuum for 15-20 minutes at 65-70°C. This process is repeated until all of the surfactant solution had been used. The evaporation must continue until the powder becomes totally dry. This method is advantageous because it can be used to formulate hydrophobic drugs in a lipid suspension with or without problem with instability of the suspension or susceptibility of active ingredient to hydrolysis [22, 24].

Co-acervation phase separation method:

In this method, surfactant, lipid and drug are placed in a 5ml wide mouthed glass vial awith some alcohol in it. A glass rod is used to mix the ingredients and a glass lid is placed on top of the open end of the glass bottle to prevent the loss of solvent. The mixture is then warmed by water bath for 5 minutes at 60-70°C until the mixture is dissolved completely. Aqueous phase is then added to the glass vial and warmed again until a clear solution is formed. The mixture is then allowed to cooled at room temperature till the dispersion converts to a proniosome [22, 23]. They are converted to uniformly sized niosomes after the hydration of proniosomes. (Fig.1)

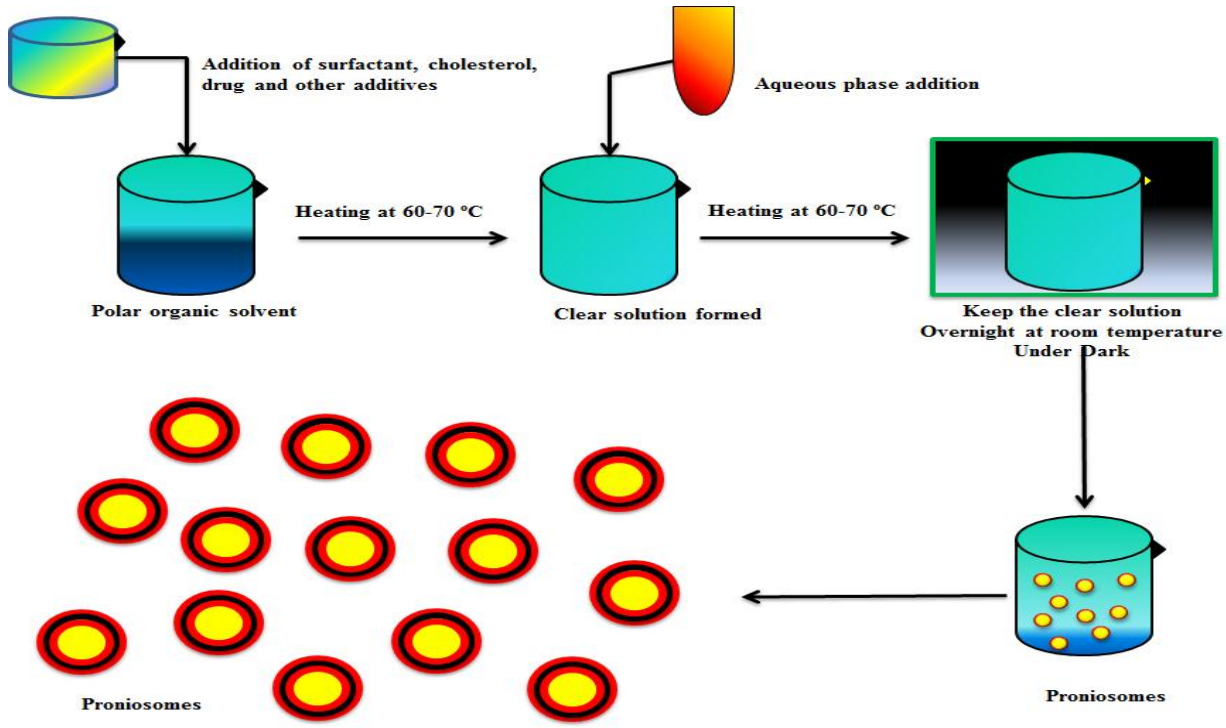

Figure-1: Coacervation phase separation method

EVALUATION OF PRONIOSOMES

Drug entrapment efficiency:

DEE of the proniosomes can be evaluated by separating the unentrapped drug by centrifugation [26], dialysis [25-26] or gel filtration [28, 27] while the drug which entrapped in niosomes is determined by vesicle disruption using 0.1% Triton X-100 or 50 % n-propanol. The resultant solution is analyzed by suitable assay method for the drug [29, 30]. The DEE can be calculated as follows:

DEE (%) = [Entrapped drug / Total drug] × 100

Angle of repose:

The angle of repose of dry proniosome powder is measured by funnel method. The funnel is fixed at a position so that the 13 mm outlet orifice of the funnel is 10 cm above the black surface. The powder is poured through the funnel to form a cone on the surface. The angle of repose is then calculated by measuring the height of the cone and the diameter of its base.

Vesicle size and vesicle size distribution:

Drug permeability depends on vesicle size. To

determine the average vesicle size and vesicle size distribution, instruments used mainly are: a) Malvern Mastersizer [31]; b) Optical microscopy[32]; c)Laser diffraction particle size analyzer [33]; d) Coulter submicron size analyzer [34].

Vesicle shape and surface characterization:

To determine vesicle shape and surface characterization, instruments used are: a) Optical microscopy [32]; b) Transmission electron microscopy (TEM) [31]; c) Scanning electron microscopy (SEM) [35].

Rate of hydration:

To determine the rate of hydration, Neubaur's chamber is used [36].

Zeta potential:

Zeta potential value determination is necessary to analyze the colloidal properties of proniosomal formulations. It can be determined by Malvern Zetasizer [31].

In-vitro Drug release:

Dialysis Tubing:

First, the proniosome is placed in prewashed dialysis tubing which can be hermetically sealed. It is then dialyzed through dialysis sac by using a suitable dissolution medium at room temperature. The samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable analytical method. The study requires a maintained sink condition [36].

Reverse Dialysis:

In this technique a number of small dialysis bags containing 1 ml of dissolution medium are kept in proniosomes. The proniosomes are then displaced into the dissolution medium. The drug release can be quantified with direct dilution of proniosome [37].

Franz diffusion cell:

The in vitro diffusion studies are generally performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with dialysis membrane or biological membrane. The entrapped drugs get permeated through the dialysis membrane from donor chamber to receptor chamber containing a suitable dissolution medium at room temperature. The samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable analytical methods [38].

In-vitro permeation study:

The rate of permeation of drugs from proniosomes can be determined by using Keshary Chien diffusion cell, while the drug content can be determined by suitable analytical method. The interaction between skin and proniosomes plays an important role to improve transdermal drug delivery. One of the possible ways to improve the niosomal permeability is by modifying the structure of stratum corneum. Both non-ionic surfactants and phospholipids are used in proniosomes as penetration enhancers, which is to increase the permeation of many other drugs. The permeation of haloperidol from proniosome was determined by flow through diffusion cell [54]. Adherence of vesicles and direct contact with skin surface is important for the drug to penetrate and partition between the formulation and the stratum corneum.

In vitro drug release kinetics and mechanism:

In order to understand the kinetic and mechanism of drug release, the result of in-vitro drug release study were fitted with various kinetic equations like: zero order, first order, Higuchi's model and Koresmeyer-Peppas Model.

Zero-order Kinetics: $F = Ko\ t$; where, F represents the fraction of drug released in time t, and Ko is the zero-order release constant.

First-order Kinetics: $\ln (1-F) = - K1\ t$; where, F represents the fraction of drug released in time t, and K1 is the first-order release constant.

Higuch Model: $F = KH\ t1/2$; where, F represents the fraction of drug released in time t, and KH is the Higuchi dissolution constant.

Koresmeyer-Peppas Model: $F = Kp\ tn$; where, F represents the fraction of drug released in time t, and Kp is the Koresmeyer-Peppas release rate constant and n is the diffusion exponent.

The Korsmeyer-Peppas model was employed to determine the mechanism of drug release from the formulation. Type of diffusion can be categorized on the basis of diffusion exponent like: Fickian (non-steady) diffusional when $n \leq 0.5$ and a case-II transport (zero-order) when $n \geq 1$. And the in between 0.5 and 1 are indicative of non-Fickian, 'anomalous' release [39-40].

Osmotic shock:

Osmotic shock study is important to monitor the change in vesicle size viewed under optical microscope after incubation with isotonic or hypotonic solutions for 3 hours [41].

Stability studies:

Stability studies of proniosomes were carried out by keeping the formulations at various temperature conditions like refrigeration temperature (2-8°C), room temperature (25 ± 0.5°C) and elevated temperature (45 ± 0.5°C) from one month to three months. Variation in the average vesicle diameter and drug content were monitored [42, 32, 36].

ICH guidelines suggests that stability studies for the dry proniosome powders should include the studies for accelerated stability at 40°C/75 % RH (relative humidity) as per international climatic zones and climatic conditions (WHO, 1996). According to ICH guidelines, for long term stability studies the temperature is 25°C/60 % RH for the countries in zone I and II and for the countries in zone III and IV the temperature is 30°C/65 % RH. Product should be evaluated for colour, assay, pH, appearance, sterility, pyrogenicity, preservative content and particulate matter.

Table-1: Different formulations of proniosomes

Drug	Property of drug	Application	Therapeutic category
Tenoxicam[43]	Sparingly soluble	Proniosome gel	NSAID
Piroxicam[44]	Lipophilic	Proniosome gel, patch	NSAID
Flurbiprofe[45]	Lipophilic	Proniosome gel	NSAID
Ketorolac[46]	Lipophilic	Proniosome gel	NSAID
Frusemide[47]		Proniosome gel, patch	Antihypertensive
Losartan Potassium[48]	Hydrophilic	Proniosome gel, patch	Antihypertensive
Captopril[49]	Hydrophilic	Proniosome gel	Antihypertensive
Chlorphenir Amine Maleate[50]	Hydrophilic	Proniosome gel	Skin Disorder
Estradiol[51]	Lipophilic	Proniosome gel	Hormone
Levonorgesterol[52]	Lipophilic	Proniosome gel, patch	contraceptive agent
Vinpocetine[53]	Poorly water soluble	Proniosome gel	Cerebrovascular and cerebral degenerative diseases

CONCLUSION

Proniosomes are representing a promising drug delivery module for the future. Proniosomes are found to be having greater physical, chemical stability and potentially scalable for commercial viability than niosomes. Proniosome is a better way for delivering drug through transdermal route, due to the advantages like non-toxicity, penetration enhancing effect of surfactants and effective modification of drug release. Proniosome is also more suitable for preparing beads, tablets and capsules due to its dry poweder form. Hence, proniosomes are widely used as drug carriers due to all these advantages.

Many different types of drug deliveries are possible by using proniosomes based niosomes like ophthalmic, topical, targeting, parenteral and peroral vaccine. More researches can be carry out to investigate new carrier material for proniosomes preparation and also to know the exact potential of proniosomes in drug delivery system to full extent.

REFERENCES

[1] AB Solanki, JR Parikh, RH Parikh. Formulation and optimization of Piroxicam proniosomes by 3-Factor, 3-Level Box-Behnken Design. *AAPS PharmSciTech*. 8(4): E1-E7(2007).

[2] V Sankar, K Ruckmani, S Durga, S Jailani. Proniosomes as drug carriers. *Pak J Pharm Sci*. 23: 103-107(2010).

[3] F Ijeoma, S Uchegbu, P V yas. Non-ionic surfactant based vesicles (niosomes) in drug delivery. *Int J Pharm*. 172: 33–70(1998).

[4] C Puglia, D Trombetta, V Venuti, A Saija, F

Bonina. Evaluation of in vivo topical anti-inflammatory activity of indometacin from liposomal vesicles. *J Pharm Pharmacol*. 56: 1225-1232(2004).

[5] PN Gupta, V Mishra, P Singh, A Rawat, P Dubey, S Mahor, SP Vyas. Tetanus toxoid loaded transfersomes for topical immunization. *J Pharm Pharmacol*. 57: 295-301(2005).

[6] R Barber, P Shek. In: Pharmaceutical Particulate Carriers. *Rolland A, ed. Marcel Dekker, New York.* 1–20(1993).

[7] DD V erma, S V erma, G Blume, A Fahr. Liposomes increase skin penetration of entrapped and non-entrapped hydrophilic substances into human skin: a skin penetration and confocal laser scanning microscopy study. *Eur J Pharm Biopharm*. 55: 271-277(2003).

[8] I Almira, Blazek-Welsh, DG Rhodes. Maltodextrin-Based Proniosomes. *AAPS PharmSciTech 3* (1) article 1(2001).

[9] Blazek-Walsh AI and DG Rhodes. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes. *Pharm Res*. 18: 656-661(2001).

[10] Mahdi, Jufri, Effionora, Anwar, Joshita, 24. Djajadisastra, 2004. Preparation of Maltodextrin DE 5-10 based Ibuprofen Proniosomes. *Majalah Ilmu Kefarmasian I.* 1, 10–20(2004).

[11] T Sudhamani, N Priyadarisini, Radhakrishnan. Proniosomes – A Promising Drug Carriers. *International Journal of PharmTech Research CODEN (USA): IJPRIF ISSN : 0974-4304 27. Vol.2, No.2.* 1446-1454(April-June 2010).

[12] C Hu and DG Rhodes. Proniosomes: a novel drug carrier preparation. *International Journal Pharmaceutical Technology*. 185: 23-35(1999).

[13] AL Blazek –Welsh, DG Rhodes. Maltodextrin based proniosomes. *AAPS Pharmacist.* 3: 1-8(2001).

[14] P Arunotharyanun, MS Bernard, DQH Craig, TF Uchegbu, AT Florenace. The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. *Int. J. Pharm.* 201, 7(2000).

[15] AB Welesh, DG Rhodes. Maltodextrin based proniosomes. *Pharm. Sci*. 3, 1(2001).

[16] AB Welesh, DG Rhodes. SEM imaging predicts quality of niosomes from maltodextrin based proniosomes. *Pharm. Res*. 18, 656(2001).

[17] JY Fang, CT Hong, WT Chiu and YY Wang. Effect of liposomes and niosomes on skin permeation of enoxacin. *Int. J. Pharm*. 219, 61(2001).

[18] JY Fang, YU, SY, WU, PC and YB Huang. In-vitro skin permeation of estradiol from various proniosome formulations. *Int. J. Pharm*. 215, 91(2001).

[19] S Friberg, K Larsson, GH Brown (Ed.). Advances in crystals. *Academics Press.* 2, 173(1976).

[20] S Perrett, M Golding, WP Williams. A simple method for the preparation of liposomes for pharmaceutical applications: Characterization of liposomes. *J. Pharm. Pharmacol*. 43, 154(1991).

[21] B Vora, AJ Khopade, NK Jain. Proniosome based transdermal delivery of levonogesterol for effective contraception. *J. Control. Rel*. 54, 149(1998).

[22] JR Walve, BR Rane, NA Gujrathi, SR Bakaliwal, SP Pawar. Proniosomes: A Surrogated Carrier for Improved Transdermal Drug Delivery System. *IJRAP*. 2(3): 743 -750(2011).

[23] R Jukanti , D Annakula, MR Errabelli, S Bandari. Provesicular drug delivery systems: An overview and appraisal. *Arch. Appl.Sci.Res*. 2(4): 135-146(2010).

[24] D Akhilesh, G Hazel, JV Kamath. Proniosomes – A Propitious Provesicular Drug Carrier. *Int. J. Pharm PharmSciRes.* 1(3): 98-103(2011).

[25] S Chauhan, MJ Luorence. The preparation of polyoxyethylene containing non-ionic surfactant. vesicles. *J Pharm Pharmacol*. 41: 6(1989).

[26] S Ajay, P Jolly, P Rajesh. Preparation, characterization, optimization, and stability studies of aceclofenac proniosomes. *Iranian J Pharm Res*. 7(4): 237-246(2008).

[27] SG Devi, P Venkatesh, N Udupa. Niosomal sumatriptan succinate for nasal administration. *Int J Pharm Sci.* 62(6): 479-481(2000).

[28] T Yoshioka, B Sternberg, AT Florence. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (span- 20, span-40, span- 60, span-80) and a sorbitan triester (span-85). *Int J Pharm*. 105: 1-6(1994).

[29] C Hu, DG Rhodes. Proniosomes: A novel drug carrier preparation. *Int J Pharm*. 185:

23-35(1999).

[30] KS Chandraprakash, N Udupa, P Umadevi, GK Pillai. Pharmacokinetic evaluation ofsurfactant vesicles containing methotrexate in tumor bearing mice. *Int J Pharm*. 61: R1-R3(1990).

[31] A Abd-Elbary, MI El-laithy, HM Tadros. Sucrose stearate- based proniosome- derived niosomes for the nebulisable delivery of cromolyn sodium. *Int J Pharm*. 357:189-198(2008).

[32] A Gupta, SK Prajapati, M Balamurugan, M Singh, D Bhatia. Design and development of a proniosomal transdermal drug delivery system for captopril. *Trop J Pharm Res*. 6(2): 687-693(2007).

[33] AB Solanki, JR Parikh, RH Parikh. Formulation and optimization of Piroxicam proniosomes by 3-Factor, 3-Level Box-Behnken Design. *AAPS PharmSciTech*. 8(4): E1-E7(2007).

[34] JY Fang, SY Yu, PC Wu, YB Huang, YH Tsai. In vitro skin permeation of estradiol from various proniosome formulations. *Int J Pharm*. 215(1-2): 91-99(2001).

[35] A Alsarra, AA Bosela, SM Ahmed, GM Mahrous. Proniosomes as a drug carrier for transdermal delivery of ketorolac. *Eur J Pharm Biopharm*. 59: 485-490(2005).

[36] B Vora, AJ Khopade, NK Jain. Proniosome based transdermal delivery of levonorgestrel for effective contraception. *J Control Release*. 54: 149–165(1998).

[37] RH Muller, M Radtke, SA Wissing. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev*. 54: 131–155(2002).

[38] C Puglia, D Trombetta, V Venuti, A Saija, F Bonina. Evaluation of in vivo topical anti-inflammatory activity of indometacin from liposomal vesicles. *J Pharm Pharmacol*. 56: 1225-1232(2004).

[39] MS Roberts, PM Lai, SE Cross, NH Yoshida. Mechanism of transdermal drug delivery. *Mercel Dekker, New York*. 291-249(1997).

[40] VM Patel, BG Prajapati, MM Patel. Effect of hydrophilic polymers on buccoadhesive Eudragit patches of propranolol hydrochloride using factorial design. *AAPS PharmSciTech*. 8(2): 45(2007).

[41] SS Biju, S Talegaonkar, PR Misra, RK Khar. Vesicular systems: An overview. *Indian J Pharm Sci*. 68: 141-153(2006).

[42] PN Gupta, V Mishra, P Singh, A Rawat, P Dubey, S Mahor, SP Vyas. Tetanus toxoid loaded transfersomes for topical immunization. *J Pharm Pharmacol*. 57: 295-301(2005).

[43] HO Ammara, M Ghorabb, SA El-Nahhasc, IM Higazya. Proniosomes as a carrier system for transdermal delivery of tenoxicam. *Int J Pharm*. 405(1-2):142-52(2011).

[44] AB Solanki, JR Parikh, RH Parikh. Formulation and Optimization of Piroxicam Proniosomes by 3-Factor, 3-Level Box-Behnken Design. *AAPS PharmSciTech*. 8(4), 86(2007).

[45] M Mokhtar, OA Sammour, MA Hammad, NA Megrab. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. *Int J Pharm*. 361(1-2):104-11(2008).

[46] IA Alsarra, AA Bosela, SM Ahmed, GM Mahrous. Proniosomes as a drug carrier for transdermal delivery of ketorolac. *Eur J Pharm Biopharm*. 59(3):485-90(2005).

[47] A Azeem, N Jain, Z Iqbal, FJ Ahmad, M Aqil, S Talegaonkar. Feasibility of proniosomes- based transdermal delivery of frusemide: formulation, optimization and pharmacotechnical evaluation. *Pharm Dev Technol.* 13(2):155-163(2008).

[48] R Thakur, MK Anwer, MS Shams, A Ali, RK Khar, F Shakeel, EI Taha. Proniosomal transdermal therapeutic system of losartan potassium: development and pharmacokinetic evaluation. *J Drug Target*. 17(6):442-9(2009).

[49] A Gupta, SK Prajapati, M Balamurugan, M Singh, D Bhatia. Design and Development of a Proniosomal Transdermal Drug Delivery System for Captopril. *Tropical J. Pharm Res*. 6(2): 687-693(2007).

[50] J Varshosaz, A Pardakhty, SM Baharanchi. Sorbitan monopalmitate-based proniosomes for transdermal delivery of chlorpheniramine maleate. *Drug Deliv.* 12(2):75-82(2005).

[51] Jia-You Fang, Song-Yih Yu, Pao-Chu Wu, Yaw- Bin Huang, Yi-Hung Tsai. In vitro skin permeation of estradiol from various proniosome formulations. *Int J Pharm*. 215:91–99(2001).

[52] B Vora, AJ Khopade, NK Jain. Proniosome based transdermal delivery of levonorgesterel for effective contraception. *J. Control. Rel*. 54: 149-165(1998).

[53] HM El-Laithy, O Shoukr, LG Mahran. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: Preclinical and clinical studies. *Eur J Pharm Biopharm*. 77(1):43-55(2011).

[54] S Faiyaz, S Baboota, A Ahuja, J Ali, M Aquil, S Shafiq. Nanoemulsions as vehicles for transdermal delivery of aceclofenac. *AAPS PharmSciTech*. 8: Article 104(2007).