

PRNIOSOMAL GEL AS A CARRIER FOR IMPROVED TRANSDERMAL DRUG-DELIVERY

Astha Mishra *, Anupriya Kapoor, Shilpi Bhargava
Advance Institute of Biotech and Paramedical Sciences
Department of Pharmaceutics, Kanpur U P India

ABSTRACT:

Drug delivery system aims at delivering the therapeutic agent to the desired site of action. Proniosomes are promising drug carriers and are more advantageous than the conventional niosomes and liposomes. The advancements in the niosome lead to the evolution of proniosomal delivery systems. Proniosomes are non-ionic based surfactant vesicles which may be hydrated immediately before use to yield aqueous niosome dispersions. They can incorporate both lipophilic as well as hydrophilic drugs. Proniosomal gel is basically used for the topical/transdermal applications. The given article highlights all the salient features of a proniosomal gel, its advantages over niosomes and liposomes, its method of preparation and its methods of characterization.

Keywords: Drug delivery, Proniosomes, Proniosomal gel, Niosomes, liposomes, transdermal

*Correspondence Author: Astha Mishra Email: asthamishra13@gmail.com

Received: 20/10/2011

Accepted: 08/11/2011

INTRODUCTION:

Drug delivery systems are used to ensure that the drugs get into the body and reach the area where they are needed. These systems must take a number of needs into account, ranging from ease of delivery to the effectiveness of the drug. [1]

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, ointments, injectables as drug carriers. Therefore to achieve as well as to maintain the drug concentration within the therapeutic effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day.

Recently several technical advancements have been made. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the release of drug delivery, sustaining the duration of

therapeutic activity and targeting the delivery of drug to the site of action. [2]

To pursue optimal drug action, functional molecules could be transported by a carrier to the site of action and released to perform their task.

TRANSDERMAL ROUTE:

Transdermal is a route of administration wherein active ingredients are delivered across the skin for systemic distribution. Transdermal drug delivery is an alternative to the conventional oral and parental routes as a means of achieving constant therapeutic levels of the drug. Proniosomes offer a versatile vesicle drug delivery concept with potential for delivery of drugs via transdermal route. This would be possible if proniosomes form niosomes upon hydration with water from skin following topical application under occlusive conditions. [3]

PRNIOSOMES:

The advancements in the niosome lead to the evolution of proniosomal delivery systems.

Proniosomes are non-ionic based surfactant vesicles which may be hydrated immediately before use to yield aqueous niosome dispersions. Proniosomes are nowadays used to enhance drug delivery in addition to conventional niosomes. They are converted into niosomes respectively upon simple hydration or by the hydration of skin itself after application.

Proniosomes exist in two forms

- i) Semisolid liquid crystal gel.
- ii) Dry granular powder

Of these two forms the proniosomal gel is mainly used for topical / transdermal application.

Proniosomal gel:

Proniosomes are vesicular systems, in which the vesicles are made up of non-ionic based surfactants, cholesterol and other additives. Semisolid liquid crystal gel (proniosomes) prepared by dissolving the surfactant in a minimal amount of an acceptable solvent, namely ethanol and then hydration with least amount of water to form a gel. These structures are liquid crystalline compact niosomes hybrids that can be converted into niosomes immediately upon hydration or used as such in the topical/transdermal applications. Proniosomal gels are generally present in transparent, translucent or white semisolid gel texture, which makes them physically stable during storage and transport.

Advantages of Proniosomal gel: Liposomes and niosomes are well known drug/cosmetic delivery systems. But these delivery systems have been reported to have many disadvantages in terms of preparation, storage, sterilization, etc. The disadvantages of liposomes and niosomes are given below, which can be overcome by proniosomes.

- Liposomes and niosomes are dispersed aqueous systems and have a problem of degradation by hydrolysis or oxidation.

- Liposomes and niosomes require special storage and handling.
- Sedimentation, aggregation or fusion on storage is usually seen.
- In liposomes, purity of natural phospholipids is also variable.
- Difficulty in sterilization, transportation, distribution, storage uniformity of dose and scale up.
- Incomplete hydration of the lipid/surfactant film on the walls during hydration process.[4]

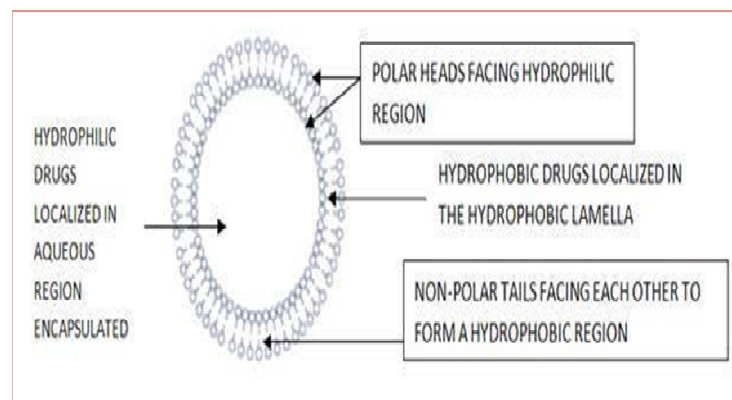
ACTION OF PRNOSOMES:

Proniosomes show their action after they are converted to niosomes on hydration.

Proniosomes hydration → Niosomes .

The hydration may occur either by the skin or by the addition of aqueous solvents.

Proniosomes can entrap both hydrophilic as well as lipophilic drugs.



The fig. 1 below shows the entrapment of drug in niosome.[5]

MATERIAL AND METHOD OF PREPARATION OF PRONIOSOMAL GEL:

TABLE I: Ingredients used for the preparation of proniosomal gel

Sr. no.	Ingredients used	Example	Use
1	Surfactants (Non-ionic)	Spans , Tweens	To increase rate of permeation
2	Cholesterol		To improve stability of vesicles
3	Lecithin		Penetration enhancer
4	Solvent	Ethanol, methanol	For solubilizing drug, surfactant.

METHOD OF PREPARATION OF PRONIOSOMAL GEL:

Proniosomal gel can be prepared by the use of coaservation phase separation method. In this method the accurately weighed amount of drug, surfactant and cholesterol are taken in a clean and dry wide mouthed glass vial and solvent should be added to it. All these ingredients have to be heated and after heating all the ingredients should be mixed with glass rod. To prevent the loss of solvent, the open end of the glass vial can be covered with a lid. It has to be warmed over water bath at 60-70°C for 5 minutes until the surfactant dissolved completely. The mixture should be allowed to cool down at room temperature till the dispersion gets converted to a proniosomal gel.

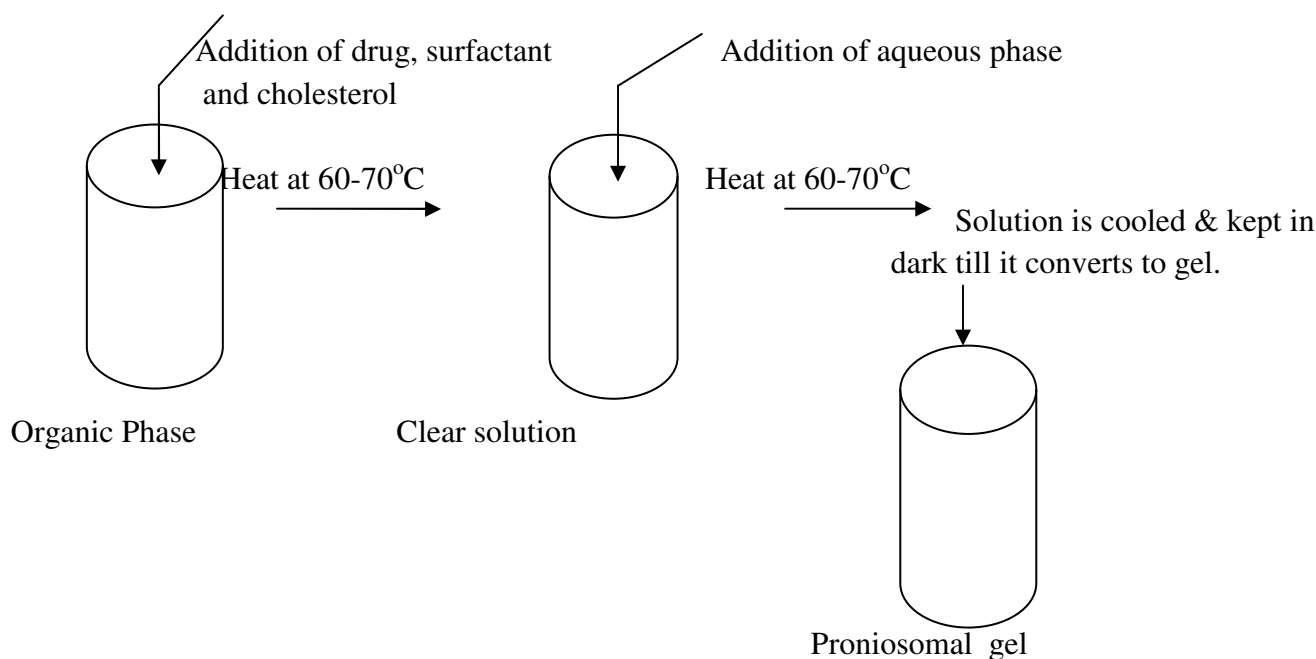


Fig 2 Represents the steps involved in the preparation of proniosomal gel.

CHARACTERIZATION OF PRONIOSOME GEL: [6]

Various methods of characterization are shown in Table II.

TABLE II

Sr. no.	Parameter	Method
1.	Vesicle size analysis	Optical microscopy
2.	Shape and Surface morphology Characterization	Scanning Electron microscope Transmission Electron Microscope
3.	Entrapment efficiency	Centrifugation method, Diode array spectrophotometer.
4.	Invitro release study	Franz diffusion cell, Keshary chien cell
5.	Stability studies	Stability chamber.

Vesicle Morphology:

Determination of vesicle size is important for the topical application of vesicles. The vesicle size can be measured using Optical Microscope.

Encapsulation efficiency:

The entrapment efficiency of proniosomes can be calculated by various methods such as dialysis method or centrifugation method.

Entrapment efficiency = Amount of drug entrapped/total amount of drug × 100

The various literature searches revealed that the encapsulation efficiency of spans is higher than tweens. Cholesterol content also affects the entrapment efficiency of drug. As the cholesterol content of the formulation decreased, the encapsulation of drug also decreased. Higher entrapment efficiency of vesicles of span 60 is predictable because of its higher alkyl chain length.

The entrapment efficiency also depends on characteristic of drug like lipophilic drug have higher encapsulation efficiency than hydrophilic drugs.

Release rate profiles of drug:

One of the most important characteristic of proniosomal formulation is their sustained release

characteristics. The release rate profile of drugs can be performed using Franz-diffusion cell, Keshary chien cell, or cellophane dialyzing membrane or U.S.P dissolution apparatus type I.

Stability Studies:

Stability studies can be carried out by storing the prepared proniosomes at various temperature conditions like refrigeration temperature (2°-8°C), room temperature (25°± 0.5°C) and elevated temperature (45° ± 0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter is periodically monitored. [7]

Ammar et al. (2011): Formulated different proniosomal gel bases. They were characterized by light microscopy, and assessed for their drug entrapment efficiency, stability, and their effect on *in vitro* drug release and *ex vivo* drug permeation. The lecithin-free proniosomes prepared from Tween 20: cholesterol (9:1) proved to be stable with high entrapment and release efficiencies. The *in vivo* behaviour of this formula was studied on male rats and compared to that of the oral market product. The result of the study showed that the investigated

tenoxicam loaded proniosomal formula proved to be non-irritant, with significantly higher anti-inflammatory and analgesic effects compared to that of the oral market tenoxicam tablets. [8]

Goyal et al. (2011): Prepared and evaluated the anti-inflammatory activity of guggulipid loaded proniosomal gel. The formulated proniosomal based gel formulation was characterized for particle size entrapment efficiency, *in vitro* drug release and *in vivo* anti-inflammatory activity using carrageenan induced rat hind-paw method. The result of the study showed that proniosomal formulation of guggulipids holds an immense potential for development of topical herbal anti-inflammatory formulation comparable to topical NSAIDs. [9]

Aboelwafa et al. (2010): The aim of this work was to investigate the effects of formulation variables on development of carvedilol (CAR) proniosomal gel formulations as potential transdermal delivery systems. Different non-ionic surfactants like polyoxyethylene alkyl ethers, namely Brij 78, Brij 92, and Brij 72; and sorbitan fatty acid esters (Span 60) were evaluated for their applicability in preparation of CAR proniosomal gels. In Span 60 proniosomes, on increasing percent of cholesterol, a decrease in release rate was observed, while in Brij 72 proniosomes, an enhancement in release rate was observed on increasing amount of CAR added. Permeation experiments showed that skin permeation was mainly affected by weight of proniosomes and that Span 60 proniosomal gels showed higher permeation enhancing effect than Brij 72. [10]

Kakkar et al. (2010): Non-ionic surfactant vesicles of valsartan, were prepared by coacervation phase separation method. The prepared systems were characterised for encapsulation efficiency, shape, size and *in vitro* drug release. Stability study was carried

out to investigate the leaching of drug from the proniosomal system during storage. The encapsulation efficiency of proniosomes prepared with Span 60 was superior to that prepared with Span 40. [11]

Alam et al. (2010): A low dose proniosomal gel containing celecoxib was developed for the treatment of osteoarthritis. All the prepared formulations were subjected to physicochemical evaluations and anti-inflammatory studies. The entrapment was greater than 90%. The vesicle shape was determined with the help of transmission electron microscopy. The vesicle size, size distribution, and polydispersity studies were performed using photon correlation spectroscopy. Anti-inflammatory studies were performed using the rat hind-paw oedema induced by carrageenan (1% w/v). The obtained results showed that the proniosomal formulation significantly improved the extent of celecoxib absorption than conventional capsule. [12]

Sankar et al. (2009): Proniosomes, a novel drug delivery approach for increasing permeation of hydrocortisone through the skin, were investigated. Proniosome hydrocortisone gel was prepared by a coacervation-phase separation method using different combinations of non-ionic surfactants with cholesterol and lecithin. Proniosome formulations were characterized for vesicle size, entrapment efficiency, and drug content uniformity. Span 20: Span 40, Span 20: Span 60 and Span 20: Span 80, combinations showed good entrapment compared with Span: Tween combinations. The results of the study indicated that topical application of hydrocortisone in the form of proniosomes leads to prolonged action. [13]

Gupta et al. (2009): The present investigation aimed at formulation, and performance evaluation of

vesicular drug carrier system, proniosomal gel for transdermal delivery of antifungal agent, griseofulvin. Proniosomal gel (PNG) formulations of griseofulvin were prepared, and characterized for vesicles shape, size, entrapment efficiency, and drug permeation across pig ear skin. The effects of different non-ionic surfactants on transdermal permeability profile were assessed. Results indicated that the optimized PNG formulation of griseofulvin had better skin permeation potential than plain drug solution in water. [14]

Thakur et al. (2009): The purpose of the current study was to investigate the feasibility of proniosomes as transdermal drug delivery system for losartan potassium. Different preparations of proniosomes were fabricated using different nonionic surfactants, such as Span 20, Span 40, Span 60, Span 80, Tween 20, Tween 40, and Tween 80. Proniosomal transdermal therapeutic system (PNP-H) was found to be the optimized one as it gave better release of drug and better permeation in a steady-state manner over a desired period of time, that is, 24 h through rat skin. The results showed an increase in bioavailability as compared to the oral dose. [15]

Chandra et al. (2008): In this study permeation of piroxicam from proniosome based reservoir type transdermal gel formulation across excised rat abdominal skin was investigated using Keshery Chein diffusion cell. It was observed that Span 60 based formulations produced vesicles of smallest size and higher entrapment efficiency while those of Span 80 produced vesicles of least entrapment efficiency. Incorporation of lecithin further enhanced entrapment efficiency. Anti inflammatory studies revealed that proniosome based transdermal drug delivery system of piroxicam were promising carriers for delivery of piroxicam. [16]

Mokhtar et al. (2008): Proniosomal gels or solutions of flurbiprofen were developed based on span 20 (Sp 20), span 40 (Sp 40), span 60 (Sp 60), and span 80 (Sp 80) without and with cholesterol. Nonionic surfactant vesicles (niosomes) formed immediately upon hydrating proniosomes. The influence of different processing and formulation variables was demonstrated. The release of the prepared niosomes in phosphate buffer (pH 7.4) was illustrated. Results indicated that the EE% followed the trend Sp 60 (C₁₈) > Sp 40 (C₁₆) > Sp 20 (C₁₂) > Sp 80 (C₁₈). [17].

Gupta et al. (2007): The aim of the study was to develop a proniosomal carrier system for captopril for the treatment of hypertension that is capable of efficiently delivering entrapped drug over an extended period of time. The potential of proniosomes as a transdermal drug delivery system for captopril was investigated by encapsulating the drug in various formulations of proniosomal gel composed of various ratios of sorbitan fatty acid esters, cholesterol, lecithin prepared by coacervation-phase separation method. The formulated systems were characterized in vitro for size, vesicle count, drug entrapment, drug release profiles and vesicular stability at different storage conditions. Stability studies for proniosomal gel were carried out for 4 weeks. The results of the study showed that proniosomes are a promising prolonged delivery system for captopril and have reasonably good stability characteristics. [18]

Alsarra et al. (2005): Investigated permeation of ketorolac across excised rabbit skin from various proniosomal gel formulations using franz diffusion cell. Proniosomes prepared with Span 60 provided a higher ketorolac flux across the skin than did those prepared with Tween 20 (7- and 4-fold the control, respectively). A change in the cholesterol content did not affect the efficiency of the proniosomes and the reduction in the lecithin content did not significantly

decrease the flux ($P>0.05$). The encapsulation efficiency and size of niosomal vesicles formed by proniosome hydration were also characterized by specific high performance liquid chromatography method and scanning electron microscopy. The results of the study indicated that Proniosome may be a promising carrier for ketorolac and other drugs, especially due to their simple production and facile. [19]

Varshousaz et al. (2002): Developed proniosomal gel for transdermal drug delivery of chlorpheniramine maleate (CPM) based on Span 40 and extensively characterized *in vitro*. The system was evaluated for the effect of composition of formulation, type of surfactants and alcohols on the drug loading, rate of hydration, vesicle size, polydispersity, entrapment efficiency, and drug release across cellulose nitrate dialysis membrane. The results of the study showed that proniosome that contained Span 40/lecithin/chol prepared by ethanol showed optimum stability, loading efficiency, and particle size and release kinetic suitable for transdermal delivery of CPM. [20]

You Fang et al. (2001): Investigated the skin permeation of estradiol from various proniosomal gel formulations across excised rat skin *in vitro*. Proniosomes with Span 40 and Span 60 increased the permeation of estradiol across skin. Presence or absence of cholesterol in the lipid bilayers of vesicles did not reveal difference in encapsulation and permeation of the associated estradiol. The types and contents of non-ionic surfactant in proniosome are important factors affecting the efficiency of transdermal estradiol delivery. The results of the study showed that the

types and contents of non-ionic surfactant in proniosomes are important factors affecting the efficiency of transdermal estradiol delivery. [21]

Vora et al. (1998): Developed a proniosome based transdermal drug delivery system of levonorgestrel (LN) and extensively characterized it both *in vitro* and *in vivo*. The system was evaluated *in vitro* for drug loading, rate of hydration (spontaneity), vesicle size, polydispersity, entrapment efficiency and drug diffusion across rat skin. The effect of composition of formulation, amount of drug, type of Spans, alcohols and sonication time on transdermal permeation profile was observed. The stability studies were performed at 4°C and at room temperature. The results of the study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrol for effective contraception. [22]

CONCLUSION:

Proniosomes are water soluble carrier particles that are coated with a surfactant and can be hydrated immediately before use to yield aqueous niosomal dispersion. They are more stable than the niosomes and liposomes. They can incorporate both lipophilic as well as hydrophilic drugs. They have emerged as a challenging carriers for drug delivery via transdermal/topical route. It has become a useful dosage form for transdermal drug delivery due to the simple and cost effective scale up production procedure. Proniosomes have enabled to overcome all the stability problems associated with the niosomes and liposomes such as fusion, aggregation on storage.

TABLE III Different studies related to the application of proniosome gel for transdermal delivery

Sr. No.	Drug	Category	Result	Reference
1.	Tenoxicam	N.S.A.I.Ds	The investigated proniosomal gel proved superior to the oral market tablets in anti-inflammatory properties.	8
2.	Guggul-Lipid	Herbal	Proved superior to the N.S.A.I.D.S existing in the market.	9
3.	Carvedilol	Anti-hypertensive	Proniosomal gel for improved transdermal delivery were investigated using various surfactants	10
4.	Valsartan	Anti-hypertensive	The encapsulation efficiency of span 60 was superior to span 40.	11
5.	Celecoxib	N.S.A.I.Ds	The proniosomal formulation improved the extent of absorption than conventional capsules.	12
6.	Hydrocortisone	N.S.A.I.Ds	The application of hydrocortisone in the form of proniosome leads to prolonged action.	13
7.	Griseofulvin	Antifungal	Results indicated that the optimized PNG formulation of griseofulvin had better skin permeation potential than plain drug solution in water.	14
8.	Losartan Potassium	Anti hypertensive	The result of the study showed an increase in bioavailability as compared to the oral dose.	15
9.	Piroxicam	N.S.A.I.Ds	The results showed that proniosome based transdermal drug delivery system of piroxicam were promising carriers for delivery of piroxicam.	16
10	Flurbiprofen	N.S.A.I.Ds	Results indicated that the EE% followed the trend Sp 60 (C ₁₈) > Sp 40 (C ₁₆) > Sp 20 (C ₁₂) > Sp 80 (C ₁₈).	17

REFERENCES:

1. Smith S.E. What are drug delivery systems? (www.wiseweek.com).
2. Chien Y. W. Novel Drug Delivery System. Second Edition. *Informa Health Care U.S.A*; 1.
3. Gupta A., Prajapati S. K., Balamurugan M., Singh Mamta, Bhatia Daksh. Design and development of a proniosomal transdermal drug delivery system for captopril. *Tropical Journal of Pharmaceutical Research*, June 2007; 6 (2): 687-693.
4. Saroha K., Dr. Nanda S., Yadav N. Proniosome Gel: potential carrier system in topical/transdermal delivery for drugs and cosmetics/cosmeceuticals-a review (www.pharmainfo.net).
5. Sudhamani T.,Priyadarisini N.,Radhakrishnan M. Proniosomes-a promising drug carriers.International Journal of Pharm Tech Research.June 2010;2(2):1446-1454.
6. Kakar R., Rao rekha, Goswami A., etal. Proniosomes: An Emerging Vesicular System in drug delivery and cosmetics-a review Scholars research library.
7. Sanker V.,Rukmani K.,etal. Proniosomes as drug carriers-A review.
8. Ammar H.O., Ghorab M., El- Nahhas S.A, I.M. Higazy. Proniosomes as a carrier system for transdermal delivery of tenoxicam. *International Journal of Pharmaceutics*, 2011; 405: 142-152.
9. Goyal Chetna, Ahuja Manish, Sharma K.Surendra. Preparation and evaluation of anti-inflammatory activity of guggul-lipid loaded proniosomal gel. *ActaPoloniaePharmaceutican Drug Research*, 2011; 68: 147-150.
10. Ahmed Aboelwafa, Doaa El-Setouhy, Aliaa Elmeshad. Comparative study on the effect of some polyoxyethylene alkyl ether and sorbitan fatty acid ester surfactants on the performance of transdermal carvedilol proniosomal gel using experimental design. *AAPS Pharm Sci Tech*, 2010; 44: 1591-1602.
11. Kakkar Rishu, Rao Rekha, Dahiya Navin Kumar and Nanda Sanju. Formulation and characterisation of valsartan proniosomes. *Maejointernational journal of Science and Technology*, 2010; 5: 146-158.
12. Mohamed Nasr. *In vitro* and *in vivo* evaluation of proniosomes containing celecoxib for oral administration. *AAPS Pharm Sci Tech*. 2010; 11(1): 85–89.
13. Sankar V, Praveen C, Prasanth K.G, et al. Formulation and evaluation of a proniosome hydrocortisone gel in comparison with a commercial cream. *Pharmazie*. 2009; 64: 731-4.
14. Sandeep Gupta, Dheeraj Ahirwar, Neeraj K Sharma, Deenanath jhade. Proniosomal Gel as a carrier for improved transdermal delivery of griseofulvin: Preparation and in vitro characterization. (www.pharma info.net).
15. Thakur R,Anwer, Shams M.K, M S ,et al. Proniosomal transdermal therapeutic system of losartan potassium: development and pharmacokinetic evaluation. *J. Drug target*. 2009; 6: 442-9.
16. Chandra A. and Sharma P. K. Proniosome based drug delivery system of piroxicam. *African Journal of Pharmacy and Pharmacology*. 2008; 2(9): 184-190.
17. Mokhtar Mahmoud, Ahmed Ibrahim, Omaima A. Sammour, . Hammad Mohamed A and Nagia A. Megrab. *In vitro* evaluation of proniosomes as a drug carrier for flurbiprofen. *AAPS PharmSciTech*. 2008 ; 9(3): 782–790.
18. Gupta Ankur, Prajapati Sunil Kumar, Balamurugan M, Singh Mamta, Bhatia Daksh. Design and development of a proniosomal transdermal drug delivery system for captopril. *Tropical Journal of Pharmaceutical Research*, 2007; 6 (2): 687-693.
19. Alsarra I A, Bosela AA, Ahmed S.M, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac.

European Journal of Pharmaceutics and Biopharmaceutics. 2005; 59(3): 485-490.

20. Jaleh Varshosaz, Abbas Pardakhty, Seied Mohsen, Hossaini Baharanchi. Sorbitan monopalmitate-based proniosomes for transdermal delivery of chlorpheniramine maleate. *Informa Health Care*. 2005; 12(2): 75-82.

21. Fang JY, Yu SY, Wu PC, Huang YB, Tsai YH. In vitro skin permeation of Estradiol from various

proniosomal formulations. *International Journal of Pharmaceutics*. 2001; 215(1-2): 91-9.

22. Vora B., Khopade K.A., and Jain N.K. Proniosome based transdermal delivery of levonorgestrel for effective contraception. *Journal of controlled release*. 1998; 54(2): 149-165.