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## Review on Proniosomes



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### ABSTRACT

The present article gives an elaborative study of proniosomes as a specialized drug delivery system. Proniosomes are thirsty preparation of water-soluble transporter particles that are covered with surfactant and can be slow out as desired and dry to form liposomal diffusion directly earlier use on brief worry in boiling aqueous media within minutes. Novel vesicular systems, such as proniosomes which is one of the advanced nanotechnologies which minimizes problems of vesicular systems such as aggregation, fusion, and leakage of drug and also minimizes additional transportation, distribution, storage, and dosing problem. Conventional vesicular systems such as niosomes and liposomes are faced in nature and stability related problems. The analysis object offers the vision about these methods lengthwise with a new vesicular method known as proniosomes. The concept proniosomes has demonstrated the potential in enhancing the oral bioavailability, targeting drugs to the specific site and also permeation of drugs across the stratum corneum. It prolongs the existence of the drug in systemic circulation and finally reduces the toxicity. The objective of this study is to introduce and develop proniosomes as a carrier system for various pharmaceutical applications.

## INTRODUCTION

The development of novel drug delivery systems has received promising control of drug release in the body, which is either of temporal or spatial nature or both. The control drug action at a predetermined rate, or maintains a relatively constant, with minimization of undesirable side effects. It also localizes drug action by the spatial placement of control release systems adjacent to, or in the diseased tissue or organ; or target drug action by using carriers to deliver the drug to particular target cell type<sup>1</sup>. Several novel drug delivery systems are now available for various routes of administration, to achieve controlled and targeted drug delivery. Incorporation of the drug in vesicular structures is one such system, which can be assumed to prolong the release of the drug in the systemic circulation, and reduce the toxicity. Several vesicular drug delivery systems such as liposomes<sup>2</sup>, niosomes<sup>3</sup>, transfersomes, and pro vesicular systems like proliposomes and proniosomes have been developed<sup>4</sup>. Niosomes are unilamellar or multilamellar vesicles that are made up of non-ionic surfactants and can entrap amphiphilic and hydrophobic solutes<sup>5</sup>. Niosomes have shown advantages as drug carriers, such as being a cheap and chemically stable alternative to liposomes, but they are associated with problems related to physical stability, such as fusion, aggregation, sedimentation, and leakage on storage<sup>6</sup>. Proniosomes are the advanced niosomal formulation containing carrier and surfactant these are hydrated before using in the preparation. The hydration results in the formation of aqueous niosome dispersion. Proniosomes decreases the aggregation, leaking and fusion problem associated with niosomal formulation<sup>7</sup>.

## PRONIOSONES

Non-ionic surfactant vesicles known as niosomes are microscopic lamellar structures formed on the admixture of a non-ionic surfactant, cholesterol and diacetyl phosphate with subsequent hydration in aqueous media. Proniosomes provide a versatile novel vesicular drug delivery concept with the potential for the delivery of drugs through the transdermal route. Because proniosomes form niosomes upon hydration with water from the skin under suitable conditions. Proniosomes minimizes problems of niosomes like aggregation, fusion and leaking, and transportation, storage, dosing problems. The transdermal therapeutic system provides a considerable advantage over the non-invasive parenteral route for drug therapy, it avoids first-pass gut and hepatic metabolism decreases side effects. Provesicular systems had attracted researchers as an alternate strategy for the transdermal delivery of drugs because of

the non-toxicity and penetration effect of lecithin/surfactants. Provesicular systems have been exploited in oral drug delivery in the form of tablets, beads or capsules and have shown improved dissolution and absorption characteristics<sup>8</sup>.

### **ADVANTAGES OF PRO-NIOSOMES**

The advantages of pro-niosomes are as follows:

1. Proniosomes avoids the problems of physical stability such as fusion, aggregation, sedimentation, and leakage on storage<sup>9</sup>.
2. Avoiding the problem of chemical stability like hydrolysis of encapsulated drugs which limits the shelf life of the dispersion<sup>9</sup>.
3. Ease of storage and handling<sup>10</sup>.
4. No difficulty in sterilization, transportation, distribution, storage uniformity of dose, and scale-up<sup>11</sup>.
5. Drug delivery improves bioavailability and minimum side effects<sup>11</sup>.
6. It shows controlled targeted and sustained release of drugs due to depot formation<sup>11</sup>.
7. It can entrap both hydrophilic and hydrophobic drugs<sup>11</sup>.
8. It is biodegradable, biocompatible, and non-immunogenic to the body<sup>11</sup>.
9. The shape, size, composition, and fluidity of niosomes drug can be controlled when required<sup>11</sup>.

### **COMPONENTS OF PRONIOSOMES**

The essential components for the delivery system are as follows:

#### **1 Surfactants:**

Surfactants are the surface-active agent usually organic compounds that are having both hydrophobic and hydrophilic groups in nature. Therefore, surfactants contain both a water insoluble (hydrophobic) and a water soluble (hydrophilic) component. They can act as

wetting agents, emulsifiers, solubilizers and permeability enhancers<sup>12</sup>. The most common non-ionic amphiphiles used for vesicle formation are as follows (Table)<sup>13</sup>.

**Table No. 1: Common non-ionic amphiphiles used for vesicle formation**

Sl. No	Non-ionic Amphiphiles	Examples
1	Alkyl ethers and alkyl glyceryl ethers	Polyoxyethylene 4 lauryl ether Polyoxyethylene cetyl ethers Polyoxyethylene stearyl ethers
2	Sorbitan fatty acid esters	Span 20, 40, 60, 80
3	Polyoxyethylene fatty acid esters	Tween 20, 40, 60, 80

## 2 Carrier material:

The carrier when used in the proniosomes preparation. It permits the flexibility of the preparation in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration<sup>14-15</sup>. Commonly used carriers are listed below Table.

**Table No. 2: Commonly used carriers**

Sr. No.	Carrier materials investigated
1	Maltodextrin
2	Sorbitol
3	Spray dried lactose
4	Glucose monohydrate
5	Lactose monohydrate
6	Sucrose stearate

## 3 Membrane stabilizer

Cholesterol and lecithin are mainly used as membrane preservatives. Steroids are important components of the cell membrane and their presence in membrane brings about significant changes in bilayer stability, fluidity, and permeability. Cholesterol is a naturally occurring steroid used as membrane additive. Cholesterol prevents aggregation of the formulation by repulsive steric or electrostatic effects. It leads to a transformation from the gel state to the

liquid phase in the vesicular systems. Phosphatidylcholine is a major component of lecithin. It has low solubility in water and can form liposomes, bilayer sheets or lamellar structures depending on hydration and temperature. Depending upon the source from which they are obtained they are as named as egg lecithin and soya lecithin. It acts as stabilizing as well as a penetration enhancer. It is found those vesicles composed of soya lecithin are larger than vesicles composed of egg lecithin probably due to the difference in the intrinsic composition<sup>16-17</sup>.

#### 4 Solvent and Aqueous phase

In the proniosomes formulation, alcohol is used because it has a great effect on vesicle size and drug penetration rate. Vesicles formed from different alcohols in that Ethanol have greater solubility in water hence leads to the formation of the highest size of vesicles instead of isopropanol which forms the smallest size of vesicle due to branched-chain present. Phosphate buffer pH 7.4, 0.1% glycerol, hot water is used as the aqueous phase in the preparation of proniosomes<sup>17</sup>.

#### ACTION OF PRO-NIOSOME

Proniosome is a middle state of niosome formation as shown in Figure 1. The conversion of proniosome formulation into niosomes can be achieved by two-ways<sup>18-19</sup>.

1. Hydration by the skin: The hydration is achieved by the skin itself, i.e., the water in the skin is used to hydrate the proniosome formulation and conversion to niosomes.
2. Hydration by solvents: Aqueous systems, i.e., purified water, saline solution, and buffers are used to convert proniosomes into niosomes with or without agitation and sonication<sup>20-21</sup>.

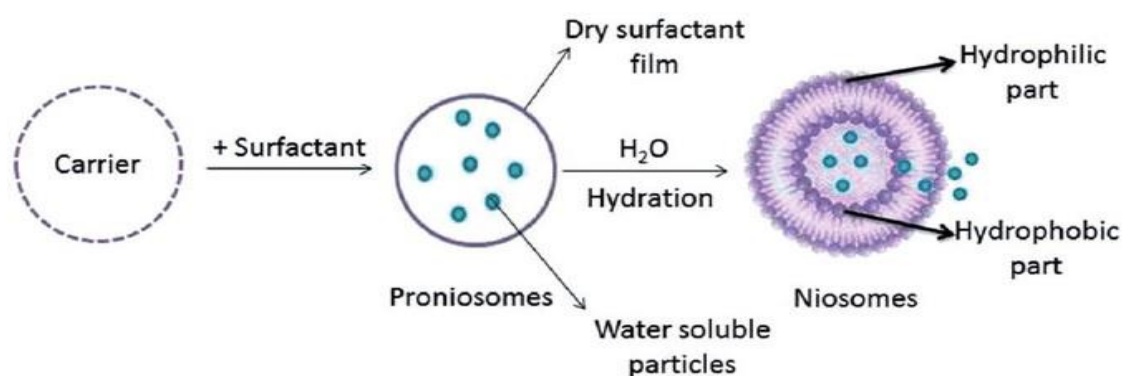


Figure No. 1: Action of niosome from proniosome

## FORMATION OF NIOSOMES FROM PRONIOSOMES

The niosomes can be prepared from the pro-niosomes by adding different types of the aqueous phase with the drug to the proniosomes with brief agitation. and the formation of niosome from the proniosome.

$$T > T_m$$

Where, T = Temperature,

$T_m$  = Mean phase transition temperature.

The formulation of niosomes from maltodextrin based proniosomes. This provides a rapid reconstitution of niosomes with the minimal residual carrier. In that slurry of maltodextrin, the surfactant was dried to form a free-flowing powder, which could be rehydrated by adding warm water<sup>22-25</sup>.

## STRUCTURE OF PRONIOSOMES

Proniosomes are microscopic lamellar structures. These are a combination of non-ionic surfactant and cholesterol along with hydration by in aqueous media. The surfactant molecule directs themselves such that the hydrophilic ends of the non-ionic surfactant orient outward, while the hydrophobic ends are in the opposite direction to form the bilayer. Both the liposomes and proniosomes are made from the bilayer, but the liposome's bilayer is made up of phospholipids whereas the proniosomes bilayer is made up of non-ionic surface-active agents. The formation of unilamellar or multilamellar proniosome also depends on the method of preparation<sup>26</sup>.

The pro-niosome is made up of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicles while the hydrophobic chains (both) face each other within the bilayer. Hence the proniosomes can hold both hydrophilic as well as hydrophobic drugs. Hydrophilic drugs hold within the space enclosed in the vesicle and the hydrophobic drugs are embedded within the bilayer<sup>27</sup>.

Proniosomal gel is present in transparent, translucent or semisolid gel structure. The formed proniosomes are a mixture of phases of liquid crystal such as lamellar, hexagonal, and cubic because of limited solvent presence. Here, the lamellar phase showed sheets of surfactant

arranged in a bilayer, hexagonal phase which showed the cylindrical compact structure arranged in a hexagonal fashion whereas cubic phase consists of curved continuous lipid bilayer extending to three dimensions<sup>28</sup>.

## METHOD OF PREPARATION

Proniosome preparation mainly comprised of non-ionic surfactants, coating carriers, and membrane stabilizers. The formulation may be prepared by the following methods.

### 1 Slurry method

Proniosomes can be prepared by the addition of carrier and the entire surfactant solvent in a round-bottomed flask which is attached to the rotary flash evaporator and then a vacuum is applied to form a dry and free-flowing powder. Finally, the obtained formulation should be stored in a tightly closed container. The time required for proniosome production is not dependent on the ratio of the surfactant solution and appears to be stable. The advantage of this method is a uniform coating on the carrier and protects the active ingredients, surfactants from hydrolysis.<sup>29-34</sup>

### 2 Slow spray coating method

The Preparation of proniosomes by slow spray coating method involves the spraying of surfactant in an organic solvent onto the carrier and then evaporating the solvent. This process is necessary to repeat until the desired surfactant loading has been achieved, due to the carrier is soluble in the organic solvent. The coating of surfactant on the carrier is very thin and hydration of this coating allows carrier dissolves. The obtained niosomes have uniform size distribution similar to those prepared by other conventional methods. The major advantage of this method is to provide a formulation of hydrophobic drugs in a lipid suspension with or without a problem. It is also found to interfere with the encapsulation of certain drugs<sup>29-34</sup>.

### 3 Co-acervation phase separation method

It is extensively used for the formulation of proniosomal gel. In this method, cholesterol, surfactant, and drug are dissolved in a suitable solvent in a wide-mouthed glass vial. After Mixing the glass vial is covered with a lid to prevent the loss of solvent because the solvent is heating in a water bath <sup>35</sup>. This process is repeated until the surfactants are dissolved

completely. Then, add a little amount of aqueous phase to get gel formation and not the dispersion, for example, diluted glycerol solution, and phosphate buffer. The above solution on the water bath is warmed until a clear solution is obtained, then which on cooling it converts into a Proniosomal gel as shown in Figure 2. The obtained gel is stored in the same glass tube in a dark place for characterization. After hydration of proniosomes gets converted into uniformly-sized niosomes<sup>36-37</sup>.

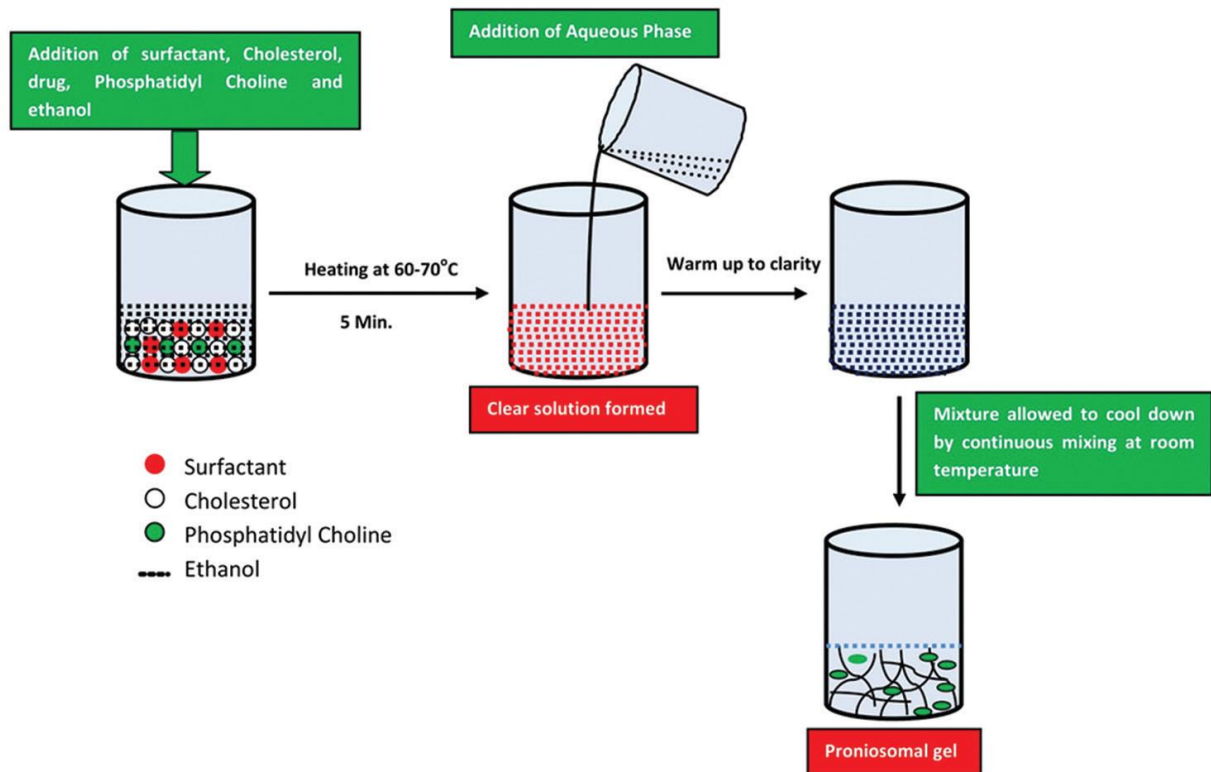


Figure No. 2: Co-acervation phase separation method

## EVALUATION PARAMETERS

Various techniques used for the optimization of the proniosomes are shown in Table.



**Table No. 3: Evaluation parameters of proniosomes**

Sl.No	Parameters	Techniques and instrument
1	Angle of repose	Funnel method <sup>38</sup> Cylinder method <sup>39</sup>
2	Aerodynamic behavior	Twin-stage impinge <sup>40</sup>
3	Particle/vesicle size and size distribution	Malvern mastersizer <sup>41</sup> Optical microscopy Laser diffraction particle size analyzer Coulter submicron size analyzer Photon correlation <sup>42</sup> Spectroscopy <sup>42</sup>
4	Determination of entrapment efficiency	Vesicle lysis using alcohol and propylene glycol <sup>41</sup> Dialysis method
5	Shape and surface morphology	Scanning electron microscopy (SEM) <sup>41</sup> Transmission electron microscopy (TEM) <sup>41</sup> Optical microscopy <sup>41</sup>
6	Sieve fractionation	Fritsch analysts sieve shaker <sup>43</sup>
7	Spontaneity (rate of hydration)	Neubauer chamber <sup>44</sup>
8	Separation of unentrapped drug	Exhaustive dialysis <sup>45</sup> Centrifugation (below 7000×g) Ultracentrifugation (150,000×g) Gel filtration
9	In vitro drug release studies	Franz diffusion cells <sup>46</sup> Keshary-chein diffusion cell <sup>45</sup> Cellophane dialyzing membrane Spectarpor molecular porous membrane tubing <i>In vitro</i> skin permeation studies USP dissolution apparatus <sup>46-4</sup>

### **PATENTS RELATED TO PRNIOSOME AND NIOSOME**

The following are the few patents related to proniosome and niosome (Table)

**Table No. 4: Patents related to proniosome and niosome**

Patent publication number	Inventors	Title
US 4830857A	R. Handjani, A. Ribier, G. Vanlerberghe, A. Zabotto, J. Griat	Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions <sup>48</sup>
US 6051250	Ribier, A.Simonnet, Jean-thierry	Process for the stabilization of vesicles of amphiphilic lipid (s) and composition for topical application containing the said stabilized vesicle <sup>49</sup>
US 06576625B2	A. Singh, R. Jain	Targeted vesicular constructs for cytoprotection and treatment of H. pylori infections <sup>50</sup>
US 06951655B2	Y. Cho, K. H. Lee	Pro-micelle pharmaceutical compositions <sup>51</sup>
WO/2010/12346	Madhavan, Eva-Kathrin	Madanagopal. Vesicular Systems and Uses <sup>52</sup>

## CONCLUSION

Proniosomes contain both nonionic surfactant and phospholipids, both can act as penetration enhancers and useful in increasing permeation of many drugs. These carrier systems have more scope in the future, particularly within the area of transdermal drug delivery. The provesicular systems have been gaining a lot of interest from various researchers and scholars, because of their advantages of prolonged and sustained release action, versatility and stability as a drug carrier. But future experiments should explore the quality and suitability of proniosomes with more drugs designed and improves effectiveness for intended therapy. So, that proniosomes are described as promising drug carriers and promising drug delivery modules.

## REFERENCES

- 1] Gandhi A, Sen SO, Paul A. Current trends in niosome as vesicular drug delivery system. Asian Journal of Pharmacy and Life Science ISSN. 2012 Sep;2231:4423.

- 2] Tamizharasi S, Dubey A, Rathi V, Rathi JC. Development and characterization of niosomal drug delivery of gliclazide. *Journal of Young pharmacists*. 2009 Oct 1;1(3).
- 3] Abdelbary G, El-gendy N. Niosome-encapsulated gentamicin for ophthalmic controlled delivery. *Aaps PharmSciTech*. 2008 Sep 1;9(3):740-7.
- 4] El-Ridy MS, Abdelbary A, Essam T, Abd EL-Salam RM, Aly Kassem AA. Niosomes as a potential drug delivery system for increasing the efficacy and safety of nystatin. *Drug development and industrial pharmacy*. 2011 Dec 1;37(12):1491-508.
- 5] Sankhyan A, Pawar P. Recent trends in niosome as vesicular drug delivery system. *Journal of Applied Pharmaceutical Science*. 2012;2(6):20-32.
- 6] Khandare JN, Madhavi G, Tamhankar BM. NIOSOMES-Novel Drug Delivery System. *Eastern Pharmacist*. 1994;37:61-.
- 7] Akhilesh D, Faishal G, Kamath JV. Comparative study of carriers used in proniosomes. *Int J Pharm Chem Sci*. 2012;3:6-12.
- 8] Kumar S. Proniosomal gel of flurbiprofen: formulation and evaluation. *Journal of drug delivery and therapeutics*. 2012 Jan 19;2(1).
- 9] Bachhav AA. Proniosome: A novel non-ionic provesicules as a potential drug carrier. *Asian Journal of Pharmaceutics (AJP): Free full-text articles from Asian J Pharm*. 2016 Sep 10;10(03).
- 10] Akhilesh D, Hazel G, Kamath JV. Proniosomes – A propitious provesicular drug carrier. *Int J Pharm Pharm Sci Res* 2011;1:98-103.
- 11] Kumar K, Rai AK. Development and evaluation of proniosomes as a promising drug carrier to improve transdermal drug delivery. *IRJP* 2011;2:71-4.
- 12] R Rao, R Kakar, G Anju, N Sanju. Proniosomes: An Emerging Vesicular System in Drug Delivery and Cosmetics. *Der Pharmacia Lettre* 2010; 2(4): 227-239.
- 13] Sulthana AA, George BJ, Samuel J, Thomas N, Daisy PA, Carla B. PRONIOSOMES: A FUTURE REVOLUTIONARY DRUG DELIVERY SYSTEM. *International Journal of Pharmaceutical, Chemical & Biological Sciences*. 2015 Oct 1;5(4).
- 14] Akhilesh D, Faishal G, Kamath JV. Comparative study of carriers used in proniosomes. *Int J Pharm Chem Sci*. 2012;3:6-12.
- 15] N Pandey. Proniosomes and Ethosomes: New Prospect in Transdermal and Dermal Drug Delivery System. *IJPSR* 2011; 2(8): 1988-1996.
- 16] K Kumar, AK Rai. Development and Evaluation of Proniosomes as a promising drug carrier to improve transdermal drug delivery. *IRJP* 2011; 2 (11): 71-74.
- 17] K Yadav, D Yadav, K Saroha, S Nanda, P Mathur. Proniosomal Gel: A provesicular approach for transdermal drug delivery. *Der Pharmacia Lettre* 2010, 2(4): 189-198.
- 18] Cserháti T. Alkyl ethoxylated and alkylphenol ethoxylated nonionic surfactants: Interaction with bioactive compounds and biological effects. *Environ Health Perspect* 1995;103:358-64.
- 19] Hofland HE, van der Geest R, Bodde HE, Junginger HE, Bouwstra JA. Estradiol permeation from nonionic surfactant vesicles through human stratum corneum *in vitro*. *Pharm Res* 1994;11:659-64.
- 20] Fang JY, Yu SY, Wu PC, Huang YB, Tsai YH. *In vitro* skin permeation of estradiol from various proniosome formulations. *Int J Pharm* 2001;215:91-9.
- 21] Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D. Design and development of a proniosomal transdermal drug delivery systems for captopril. *Trop J Pharm Res* 2007;6:687-93.
- 22] Blazek-Welsh AI, Rhodes DG. Maltodextrin - Based proniosomes. *AAPS PharmSciTech* 2001;3:1-9.
- 23] Blazek-Welsh AI, Rhodes DG. SEM imaging predicts the quality of niosomes from maltodextrin-based proniosomes. *Pharm Res* 2001;18:656-61.
- 24] Jufri M, Effionora A, Joshita D. Preparation of maltodextrin DE 5-10 based ibuprofen proniosomes. *Majalah Ilmu Kefarmasian I* 2004;1:10-2036.
- 25] Solanki AB, Parikh JR, Parikh RH. Formulation and optimization of piroxicam proniosomes by 3-factor, 3-level Box-Behnken design. *AAPS PharmSciTech* 2007;8:E86.
- 26] Giddi HS, Arunagirinathan MA, Bellare JR. Self-assembled surfactant nano-structures are important in drug delivery: A review. *Indian J Exp Biol* 2007;45:133-59.

- 27] Comelles F, Sanchez-leal J, Gonzalez JJ. Influence of ionic surfactants on the formation of liquid crystals in oleic acid/glycol/water systems. *J Surfactants Detergents* 2007;10:137-44.
- 28] Murdan S, Gregoriadis G, Florence AT. Interaction of a nonionic surfactant-based organogel with aqueous media. *Int J Pharm* 1999;180:211-4.
- 29] JR Walve, BR Rane, NA Gujrathi, SR Bakaliwal, SP Pawar. Proniosomes: A Surrogated Carrier for Improved Transdermal Drug Delivery System, *IJRAP* 2011; 2 (3): 743 -750.
- 30] IF Uchegbu, SP Vyas. Non-ionic surfactant based vesicles (niosomes) in drug delivery. *International Journal of Pharmaceutics* 1998; 172: 33-70.
- 31] R Jukanti, D Annakula, MR Errabelli, S Bandari. Provesicular drug delivery systems: An overview and appraisal. *Arch. Appl.Sci.Res.* 2010; 2(4): 135-146.
- 32] ND Shukla, M Tiwari. Proniosomal Drug Delivery System– Clinical Applications. *Intenational Journal of Research in Pharmaceutical and Biomedical Sciences* 2011; 2 (3): 880-887.
- 34] D Akhilesh, G Hazel, JV Kamath. Proniosomes – A Propitious Provesicular Drug Carrier, *Int. J. Pharm PharmSciRes* 2011; 1 (3): 98-103.
- 35] Varshosaz J, Pardakhty A, Baharanchi SM. Sorbitan monopalmitate-based proniosomes for transdermal delivery of chlorpheniramine maleate. *Drug Deliv* 2005;12:75-82.
- 36] Iwai H, Fukasawa J, Suzuki T. A liquid crystal application in skin care cosmetics. *Int J Cosmet Sci* 1998;20:87-102.
- 37] Ram A, Thakur A, Mittal VK. Proniosomal provesicular system for transdermal delivery of hydralazine for hypertension. *Asian J Pharm Clin Res* 2012;5:1-7.
- 38] Raymond CR, Paul JS, Sian CO. *Handbook of Pharmaceutical Excipients*. 5th ed. Great Britain: Pharmaceutical Press; 2006. p. 713-7, 580-4.
- 39] Radha GV, Rani TS, Sarvani B. A review on proniosomal drug delivery system for targeted drug action. *J Basic Clin Pharm* 2013;4:42-8.
- 40] Abd-Elbary A, El-laithy HM, Tadros MI. Sucrose stearate-based proniosome-derived niosomes for the nebulisable delivery of cromolyn sodium. *Int J Pharm* 2008;357:189-98.
- 41] Sankar V, Ruckmani K, Durga S, Jailani S. Proniosomes as drug carriers. *Pak J Pharm Sci* 2010;23:103-7.
- 42] Nasr M. *In vitro* and *in vivo* evaluation of proniosomes containing celecoxib for oral administration. *AAPS PharmSciTech* 2010;11:85-9.
- 43] Waghmode M, Ashar S. Proniosomal drug delivery systems: An overview. *Int J Pharm Chem Sci* 2012;1:1044-56.
- 44] Parthibarajan R, Rubinareichal C, Loganathan S. Formulation and evaluation of methotrexate proniosomal powder. *Int J Pharm Pharm Sci* 2012;4:175-8.
- 45] Yadav K, Yadav D, Saroha K, Nanda S, Mathur P. Proniosomal gel: A provesicular approach for transdermal drug delivery. *Sch Res Libr* 2010;2:189-98.
- 46] Prakash SG, Joshi VG. An engineered specificity of irinotecan loaded proniosomes: Design and characterization. *Int J Drug Deliv* 2011;3:472-80.
- 47] Aburahma MH, Abdelbary GA. Novel diphenyl dimethyl bicarboxylate provesicular powder with enhanced hepatoprotective activity: Preparation, optimization, *in vitro/in vivo* evaluation. *Int J Pharm* 2012;422:139-50.
- 48] Handjani R, Ribier A, Vanlerberghe G, Zabotto A, Griat J. Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions, U.S. Patent US 4830857A; 1989.
- 49] Ribier A, Simonnet JT. Process for the stabilization of vesicles of amphiphilic lipid(s) and composition for topical application containing the said stabilized vesicles, U.S. Patent US 6051250; 2000.
- 50] Singh A, Jain R. Targeted vesicular constructs for cytoprotection and treatment of *H. pylori* infections, U.S. Patent US 06576625B2; 2003.
- 51] Cho Y, Lee KH. Pro-micelle pharmaceutical compositions, U.S Patent US 06951655B2; 2005.
- 52] Madhavan N, Eva-Kathrin S, Madanagopal K. Vesicular Systems and Uses There of WO/2010/12346; 2010