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A REVIEW ON NOVEL APPROACH: PRONIOSOMAL GEL

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Abstract

Proniosomes, prepared in dry form and hydrated by agitation in hot water to form niosomes provide an alternative with prospective for drug delivery via the transdermal route. The transdermal route of drug delivery has many advantages for administration of drugs in local and systemic therapy. But skin is widely recognized for its effective barrier properties compared with other biological membranes. The low permeability of the skin makes it a dermal delivery is an alternative route, but dermal delivery is an alternative route. Newer drugs of lipophilic nature emerge poor bioavailability, irregular absorption, and pharmacokinetic changes. Therefore, this novel drug delivery system has been proved advantageous over other oral and topical delivery of drug candidates to bypass such disruption. This Proniosomal gel basically is a compact semi-solid liquid crystalline (gel) composed of non-ionic surfactants easily formed on dissolving the surfactant in a minimal amount of acceptable solvent and the least amount of aqueous phase and phosphate buffer. Topical application of gel under occlusive condition during which they are converted into nisomes due to hydration by water in the skin present itself. Proniosomal gels are typically present in transparent, translucent, or white semisolid gel texture, which makes them physically stable throughout storage and transport. This review provides an important overview of the preparation, formulation, evaluation, and application of Proniosomal gel as a drug delivery carrier.

KEYWORDS: Non-ionic surfactants, Coacervation phase separation, Topical drug delivery, Vesicular drug delivery, Proniosomal gel.

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Introduction

The drug delivery by transdermal route of drug delivery has many advantages for administration of drugs in local and systemic therapy. But, skin is widely recognized for its effective barrier properties compared with other biological membranes. The low permeability of the skin makes it a minor port of entry for drugs. The vesicular drug delivery thus potentially beneficial as vesicles tend to fuse and adhere to the cell surface; this is believed to increase the thermodynamic activity gradient of the drug at vesicle- stratum corneum interface thus leading to enhanced permeation rate. Understands the inherent tendency of nature, birds, and animals continued to struggles genesis of Mesopotamia, practicing the treatment by the pharmacist and share his knowledge for the benefit of suffered people. Tablets were used for illness, different routes of administration available for successive delivery of designed dosage forms.[1] Development of a formulation depends on the characterization of the active ingredient. Oral administration is a most preferred route with high patient compliance. However, bioavailability is poor progress observed reasons behind were poor solubility of drug candidate followed by less absorption.[2] Less aqueous solubility is the major drawback encountered with the formulation design of new chemical moiety.[3] Recent research focused on the development of hydrophobic active pharmaceutical ingredients[4] and reported that around 40% of new drugs showed poor aqueous solubility.[5] Different techniques have been used to improve solubility and better dissolution rates of poorly water-soluble drugs which include as particle size reduction, nano ionization, cosolvency, hydrotropic, pH adjustment, sono crystallization, supercritical fluid process, solid dispersion, inclusion complexation, self-emulsifying or self-micro emulsifying systems, and liquisolid methods.[6] A number of novel drug delivery systems have emerged in various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structures is one such system, and a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes, and pharmacosomes were developed.[7] Transdermal dosage forms, an alternative to conventional dosage formulations, are becoming popular due to their exclusive advantages. Improved bioavailability, controlled absorption, extra uniform plasma levels, painless and reduced side effects easy application.[8] However, benefits from the transdermal route, disadvantages of their formulations such as ointments, creams, and lotions with many disadvantages with sticky in nature, poor spread ability, and concerned about its stability issue. Oral solid dosage forms face problems such as gastric drug/enzyme instability and first-pass metabolism. Oral route has any further problems such as an unpleasant taste, odor, and color.

Delivery by Vesicular systems are novel means to increase the bioavailability of the enclosed drug with more advantages over than the conventional dosage forms. Liposomes were first in such type of delivery systems, but it was not so successful due to their several drawbacks.[10] Topical administration is the most preferred route for local delivery of therapeutic agents due to its convenience and easy access. The specific challenge of designing a therapeutic system is to achieve an optimal concentration of a certain drug at its site of action for an appropriate time span.[9] Niosomes or non-ionic surfactant vesicles are a microscopic lamellar structure of size range 10–1000 nm consisting of spherical, uni- or multi-lamellar and polyhedral vesicles in aqueous media.[11] But noisomes exhibits physicochemical stability problem on storage of dispersion, for example, aggregation, fusion, drug leakage or hydrolysis of the active compounds, thus raising concerns over their adoption.[12] Proniosomes were prepared as a dry powder for reconstitution before use by preserving the physical and chemical integrity of vesicles.[13] For transdermal delivery Proniosomal were prepared as gel-like concentrated niosomes suitable for topical application.[14] Proniosomes are semisolid, liquid crystal (gel) product of nonionic surfactant which on hydration converts into niosomes.[15,16] Proniosomes when applied onto the skin surface transform into niosomes due to the hydration by water from the skin which would provide an occlusive condition and offer a potential for drug delivery through the transdermal route.

Ingredients Formulation

Phospholipids and non-ionic surfactants in proniosomes can act as Penetration enhancers, since it was found that some phospholipids are able to fluidize the stratum corneum lipid bilayers and diffuse through them[17], whereas cholesterol gives stability and permeability to the vesicles.

Surfactants

It is acting as solubilizers, wetting agents, emulsifiers, and permeability enhancers.[18] Chiefly non-ionic surfactants were used in the formulation of proniosomal gel. Based on the

hydrophile-lipophile balance (HLB) values of the available surfactants, mainly categorized into w/o emulsifying agent (HLB 3–8) and o/w emulsifying agent (HLB 8–16)[19] usually the HLB value of 4–8 will give the vesicles with high compatibility. List of common nonionic amphiphiles used in proniosome formulations were mentioned in Table 1.[20]
a. Maltodextrin. b. Sorbitol. c. Spray dried lactose. d. Glucose monohydrate. e. Lactose monohydrate. f. Sucrose stearate.

Drug
The drug selection criteria could be based on the following assumptions.
1. The low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Short half-life.
4. Controlled drug delivery suitable drugs.
5. Drugs are having more adverse effects.[27]

Advantages
• Proniosomes were easily prepared and did not require special conditions of storage as like other vesicular systems.[28]
• Shows high EE.
• They can carry both hydrophilic and hydrophobic drugs.
• Extensively used in drug targeting for controlled release.

Easy to handle, storage, and transportation

Methods of preparation of proniosomal gel
❖ Coacervation phase separation.
❖ Slow spray coating method.
❖ Slurry method.

Coacervation phase separation
Proniosomal formulae were prepared by a method reported by Alsarra *et al*.[30] with slight modification, using different types of non-ionic surfactants, lecithin, and cholesterol. Appropriate amounts of proniosomal components mixed together with the drug were mixed..ith 2.5 ml of absolute ethanol in a clean and dry, wide-mouth glass tube. After mixing all the ingredients, the open end of the glass tube was covered with a lid to prevent loss of solvent from it and warmed in a water bath at 65 ± 3°C for ~5 min, until the surfactants were dissolved completely. Then, 1.6 ml of pH 7.4 phosphate buffer was added, and warming was continued on the water bath for ~2 min till a clear solution was observed. The mixture was allowed to cool down at room temperature until the dispersion was converted to a proniosomal gel.[31,32]

Slurry method
Carrier material to a 250-ml flask and the entire volume of surfactant solution was added the flask to form the slurry. If the surfactant solution volume is less, then additional organic solvent can get slurry. The flask was attached to a rotary evaporator was applied until the free-flowing. The flask was removed from the evaporator and kept under vacuum overnight. The proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to the carrier material and appears to be scalable.[33-35]

Slow spray - coating method
This method involves preparation of proniosomes by spraying surfactant in an organic solvent onto carrier material and then evaporating the solvent. Since the carrier is soluble in the organic solvent, it repeats the process until the desired has been achieved. The surfactant coating on the carrier is very thin, and hydration of this coating allows multilamellar when the carrier dissolves.[36,37] The resulting noisome is very similar to those produced by conventional methods, and the size distribution is more uniform. It is suggested that this formulation would provide hydrolysis for hydrophobic drugs formulation.[38]

EVALUATION OF PRONIOSOMES
%Entrapment efficiency
Proniosomal gel (0.2 g) was reconstituted with 10 ml of pH 7.4 phosphate buffer in a glass tube. The aqueous suspension was sonicated in a sonicator bath for 30 min. The naproxen containing niosomes were separated from the untrapped drug by centrifuging at 9000 rpm at 4°C for 45 min. The supernatant was taken, and the drug concentration in the resulting solution was assayed by ultraviolet (UV) spectrophotometer at a specific wavelength. The percentage of drug encapsulation was calculated by the following equation:
EE%=[(Ct–Cf)/Ct]×100..here Ct is the concentration of a total drug and Cf is the concentration of a free drug.[15,39]

Vesicle size and zeta potential analysis
The mean vesicle size, size distribution, and zeta potential were determined using a Dynamic Light Scattering technique by Malvern- Zetasizer (Nano ZS90). In a glass tube, 0.2 g proniosome gel was diluted with 10 ml of pH 7.4 phosphate buffer. The vesicle measurements were done at a temperature of 25±0.5°C. The polydispersity index (PI) was determined as a measure of homogeneity. PI is obtained as:

PI=(SD/vesicle size).
Small values of PI (<0.1) indicate a homogeneous population, while PI values >0.3 indicate high heterogeneity.[40]

MICROSCOPICAL EXAMINATION

Optical microscope

In a glass tube, 0.2 g proniosome gel was diluted with 10 ml of pH 7.4 phosphate buffer; a few drops of the formed niosomal dispersion were spread on a glass slide and examined for the presence of insoluble drug crystals using an ordinary light microscope with varied magnification powers (×10 and ×40). Photomicrographs were taken using a digital camera.[40]

Scanning electron microscopy (SEM)

The shape, surface characteristics, and size of the proniosomes were observed by SEM. In an attempt to illustrate the role of cholesterol in vesicle formation, the morphological differences in shape and surface characteristics of the prepared proniosome derived noisome of formulae having different cholesterol contents were examined using a scanning electron microscope. In a glass tube, 0.2 g proniosome gel was diluted with 10 ml of pH 7.4 phosphate buffer; the dispersion was sprinkled and fixed on an SEM holder with double-sided adhesive tape and coated with a layer of gold of 150 Å for 2 min using a Sputter Coater (Edwards, S-150A, England) working in a vacuum of (3×10−1 atm) of Argon gas.[41]

DSC

This method help to study the possible interactions between drug and vesicle ingredients by taking thermal properties. Thermal properties of the pure drug and the formulation were evaluated by differential scanning colorimetry (DSC) using a diamond (DSC) (Mettler star sw8.10). The analysis was performed at a rate 50c min-1 to 200oc temperature range under a flow of 25 ml/min. Highest EE% was chosen, and samples of 4 mg of each drug, surfactants, empty and drug-loaded proniosomes-derived niosomes were submitted to DSC analysis. The weighed amount of sample was then held from room temperature to 300°C at a rate of 10°C/min.[39]

Fourier transforms infrared spectroscopy (FTIR)

Drug powder was compressed into a pellet along with KBr using a hydraulic press. The IR spectrum of drug and final optimized formulations were recorded in the wavenumber region of 4000–400 cm-1 on FTIR.[39]

IN VITRO RELEASE

The release study employed the vertical glass Franz diffusion cells which have a diffusional surface area of 1.13 cm2 with the receptor compartment of 10 ml volume.[43] The cellulose dialysis membrane was soaked in distilled water overnight before cutting into suitable pieces. This soaking was conducted to ensure complete swelling of the membrane to provide a constant pore diameter throughout the experiment. The membrane was then mounted between the donor and receptor compartments before filling the receptor compartment with pH 7.4 phosphate buffer.
The diffusion cells were incubated into a thermostatically controlled circulator water bath. The temperature of the receptor compartment was maintained at 37±0.5°C, and the receiver medium was continuously stirred to prevent any boundary layer effects. Weight amount of proniosomal gels were loaded into the donor compartments; then it was covered with an aluminum foil to prevent evaporation. At predetermined time intervals, namely 1, 2, 3, 4, 6, 8, 12, 18, and 24 h, samples of 1 ml were taken from the receptor compartment and replaced immediately by fresh buffer solution; to maintain the “sink” conditions constantly and a constant volume as well. The samples were then assayed spectrophotometrically.
All release experiments were done in triplicates. The plot of cumulative percentage drug release was plotted against time. The obtained release data were subjected to kinetic treatment according to zero, first, Hixson Crowell, and Higuchi diffusion models. The correlation coefficient (r), the order of release pattern was determined in each case.

Rate of Spontaneity (Hydration)

The spontaneity of niosome formation is described as the number of niosomes formed after.ydration of proniosomes for 15 min.[44] Proniosomal gel (10 mg) was transferred to the bottom of a small-stoppered glass tube and spread uniformly. 1 ml of pH 7.4 phosphate buffer was added along the walls of the test tube and kept aside without agitation. After 15 min a drop of hydrated sample was withdrawn and placed on Neubauer’s chamber for counting number of niosomes eluted from a proniosomal gel.

PHYSICAL STABILITY

Aggregation or fusion of the vesicles as a function of temperature was determined as the change in

EE after storage.[35] The vesicles were stored in glass vials at room temperature (37°C) or kept in a refrigerator (4–8°C) for 3 months. The retention of entrapped drug and the mean particle size were measured after preparation and then after 1, 2, and 3 months of storage in an optimized formulation. Further, at the end of each month, the samples were also observed for any sign of drug crystallization under an optical microscope. Stability for formulation was defined in terms of retaining its initial EE for 3 months duration. A stable formulation was defined as those showing high EE (>60%) and high drug retention value (>90%), at each time interval.

Drug retained in proniosomes=(Entrapped drug after storage/ entrapped drug before storage) ×100. Concise evidence of published Proniosomal gel formulations and its influence on pharmacology . a study by Xu *et al*. revealed tacrolimus (FK506) for its ophthalmic delivery with a potential approach of proniosome derived niosomes with enhanced corneal permeation for effective anti-allograft rejection and ocular irritation. Researchers successfully formulated proniosomes loaded with FK506, incorporated lecithin as a surfactant and poloxamer 188, cholesterol acts as a stabilizer. With a small amount of ethanol and water in a trace amount, reconstituted to niosomes before to use. Prepared formulation was characterized for morphology, size, and zeta potential, and the surface tension was significantly lowered that enabled easy wettability of the hydrophobic surface of the corneal epithelium contributing for enhanced spread ability and enhanced permeation with high EE and also assessed for its stability. Furthermore, *in vitro* study on isolated rabbit corneal disclosed permeation of FK506 from niosomes significantly greater than that from control (Protonic®). Authors suggested that enhanced trans corneal permeation was due to poloxamer 188 and surfactant property of lecithin acted as penetration enhancers, surfactants improved solubility of FK506 significantly and low surface tension, enabled niosomes with desired wetting and spreading properties, and also drug retention studies in the cornea showed significantly high drug retention for the preparation than ointment. They postulated niosomes with the enhanced permeation of FK506 would achieve an effective therapeutic drug concentration for eye diseases through topical administration. Ocular irritation studies revealed no evidence of irritation when compared preparation and saline control group with no statistical difference. Histological investigations showed formulation influence on tissue integrity and corneal cell structure. The results demonstrated superior corneal biocompatibility of the prepared niosomes. *In vivo* studies were examined for immunosuppressive for topically administrated niosomes, in Wistar and Sprague-Dawley strains of rats. Results showed niosomes treated groups decreased corneal allograft rejection incident with significantly extended corneal allografts survival time when compared with control and blank groups. In conclusion, FK506 niosomes showed potential ophthalmic delivery.[40]

Gagandeep Benipal formulated a novel proniosomal system with ketoconazole (KTZ) where non-ionic surfactant (span 60) constituted proniosomes and assured enhanced delivery of KTZ transdermally under occlusive conditions. The author performed various *in vitro* tests which included encapsulation efficiency, size, and shape; a further formulation was optimized based on *in vitro* release and stability studies. The formulation showcased high EE, and exhibited vesicle size recommended for efficient transdermal delivery. They had also described the major role of cholesterol and lecithin concentrations for EE of a prepared formulation. From *in vitro* release studies, the developed proniosomal formulation guided significant protracted release profile compared to a conventional carbopol formulation. Stability studies proposed optimum 5±3°C for storage of the prepared formulation and observed no alteration in EE for the test period of 90 days. In conclusion, proniosomal gel loaded with KTZ exhibited potential delivery system.[41]

Another study by Badawi *et al*., developed dispersed permethrin proniosomesin powder and microemulsion based hydrogel for the treatment of scabies, the powdered proniosomes showed good flow, cyclohexane used as a solvent in preparation, it is less volatile than acetone also added cholesterol, Brij in formulation resulting highest entrapment. Topical proniosome prepared by modified slurry method without vacuum, Aerosil 200 used as insoluble carrier resulted into white color good flow granular powder. Tapped density found to be 0.498 g/ml, cars index 0.408 g/ml and assay of permethrin was 98.2%, and permeation. retention of proniosomes was 55.6%. However, unstable at accelerated stability storage conditions. Hence, a base adds to it for topical application for patient convenience and to overcome stability problems. Microemulsion-based hydrogel permethrin 5% was prepared it was a clear light yellow indicates no crystals present in it. Moreover, it is transparent yellow color shows homogeneity at 97.5%. Stable physically, after 6 months finally authors conclude that proniosomes of the permethrin microemulsion

based hydrogel is more effective than powder form and stable one and showed better spread ability, adhesion, viscosity, extrusion, and hydration finally comfort to apply to the patient for the treatment of scabies.[6]

Conclusion and Future Prospect

Gel of Proniosomal contains different kinds of constituents and selection of components need necessitate knowledge because properties of components changing from each other. Which includes surfactant, lecithin, cholesterol, and the role of method of manufacturing have specific advantages which induce quality of final formulation. Thus, the development of stable Proniosomal gel purely depending on the suitable ingredients and methodology involved the Proniosomal gel preparation is a better comfort, stable and extensively used in drug targeting for controlled release of both hydrophilic and hydrophobic drugs. The gel property of proniosomes maintaining better skin penetration and physicochemical properties. Whereas cholesterol gives stability and permeability to the vesicles by overcomes of, for example, aggregation, fusion, drug leakage, or hydrolysis of the active compounds; therefore, Proniosomal gel formulations novel transdermal dosage form is open for research to target specific dermatological as well as other systemic skin disorders. Topical administration of Proniosomal gel for the treatment of melanoma, psoriasis, bacterial, and fungal infections can be anticipated successfully by the development of Proniosomal gel formulation. More researches are carried out in this field to know the exact potential of this novel drug delivery system.

AUTHORS' CONTRIBUTION

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest..

REFERENCES

1. Bender GA. A history of pharmacy in pictures-great moments in pharmacy, Journal of the Amercian Pharmacists Association, 2002; 42: 170-182.
2. Yuksel N, Bayindir Z S, Aksakal E and Ozcelikay A T. In situ niosome forming maltodextrin proniosomes of candesartan cilexetil: In vitro and in vivo evaluations, *International Journal of Biological Macromolecules*, 2016; 453-463.
3. Kumar S and Singh P. Various techniques for solubility enhancement: An overview, *Pharma Innovation*, 2016; 5: 23-28.
4. Weissig V, Lizano C and Torchilin VP. Selective DNA release from DQAsome/DNA complexes at mitochondria-like membranes. *Drug Delivery*, 2000; 7: 1-5.
5. Abhishek VG, Salunhe Ks and Chaudhari SR. Review on self-micro- emulsifying drug delivery system. Amercian Journal of PharmTech Research, 2015; 5: 50-66.
6. Vemula VR, Lagishetty V and Lingala S. Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Review and Research, 2010; 5: 41-51.
7. Biju SS, Talegaonkar S, Mishra PR and Khar RK. A review onvesicular system. Indian Journal of Pharmceutical Science, 2006; 68: 141-153.
8. Ghulaxe C and Verma R. A review on transdermal drug delivery system. *Pharma Innovation*, 2015; 4: 37-43.
9. Singh Malik D, Mital N and Kaur G. Topical drug delivery systems: A patent review. Expert Opinion on Therapeutic Patents, 2016; 26: 213-228.
10. Khan R and Irchhaiya R. Noisome a potential tool for novel drug delivery. Journal of Pharmceutical Investigation, 2016; 46: 195-204.
11. Saini V, Bala NM, Jhawat V and Kamboj S. Vesicular drug delivery systems: A novel approach for drug targeting. International Journal of Drug Delivery, 2013; 5: 121-30.
12. Abdelkader H, Alani AW and Alany RG. Recent advances in non- ionic surfactant vesicles (niosomes): Self-assembly, fabrication, characterization, drug delivery applications and limitations. *Drug Delivery*, 2014; 21: 87-100.
13. Gupta A, Prajapati SK, Balamurugan M, Singh M and Bhatia D. Design and development of a proniosomal transdermal drug delivery system for captopril. *Tropical* Journal of Pharmceutical Research, 2007; 6: 687-693.
14. Kirjavainen M, Urtti A, Jääskeläinen I, Suhonen TM, Paronen P and Valjakka-Koskela R, Interaction of liposomes with human skin in vitro – the influence of lipid composition and structure. Biochimica Biophysica Acta, 1996; 1304: 179-189.
15. Jiao J. Polyoxyethylated nonionic surfactants and their applications in topical ocular drug
1. delivery. Advanced Drug Delivery Reviews, 2008; 60: 1663-1673.
16. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical

and Biopharmaceutical Principle in the Pharmaceutical Sciences. Philadelphia, PA: Lippincott Williams and Wilkins, 2011; 1-1231.
17. Sivaprasad S N, Kumar P L, Srinivas M, Brahmaiah B and Nama S. Proniosome: A novel approach to vesicular drug delivery system. International Journal of Drug Discovery, 2013; 3: 85-90.
18. Rawat AG (2011). Proniosome gel: Anovel topical delivery system. International Journal of Recent Advances in Pharmceutical research; 1: 1-10.
19. Dheeraj N, Deepshikha KP and Nidhi A. Development and characterization of liposomal drug delivery system for gossypin. International Journal of Pharmaceutical Sciences Review and Research, 2014; 27: 11-15.
20. Wilkhu JS, Ouyang D, Kirchmeier MJ, Anderson DE and Perrie Y. Investigating the role of cholesterol in the formation of non-ionic surfactant-based bilayer vesicles: Thermal analysis and molecular dynamics. International Journal of Pharmaceutics, 2014; 461: 331-341.
21. Li Q, Li Z, Zeng W, Ge S, Lu H and Wu C. Proniosome-derived niosomes for tacrolimus topical ocular delivery: In vitro cornea permeation, ocular irritation, and *in vivo* anti-allograft rejection. European Journal of Pharmceutical Sciences, 2014; 62: 115-23.
22. Benipal G. Design, development and evaluation of proniosomal gel of an antifungal drug ketoconazole. International Journal of Pharmceutical Sciences Review and Research, 2015; 31: 265-272.
23. Prasad V and Chaurasia S. Performance evaluation of non-ionic surfactant based tazarotene encapsulated proniosomal gel for the treatment of psoriasis. Material Science and Engineering C Material Biological Application, 2017; 79: 168-176.
24. Gupta A. Antidermatophytic activity of miconazole nanoformulation against Trichophyton rubrum. Asian Pacific Journal of Tropical Disease, 2015; 5: 707-710.
25. Abdelbary GA, Amin MM and Zakaria MY. Ocular ketoconazole-loaded proniosomal gels: Formulation, *ex vivo* corneal permeation and *in vivo* studies. *Drug Delivery*, 2017; 24: 309-319.
26. Sathyavathi A, Hasansathali A and Ilavarasan R. Formulation and evaluation of niosomal *in situ* gel ocular delivery system of brimonidine tartrate. *International* Journal of Pharmaceutical Sciences and Research, 2012; 2: 82-95.
27. Rita B and Lakshmi PK. Preparation and evaluation of modified proniosomal gel for
2. localized urticaria and optimization by a statistical method. Journal of Applied Pharmaceutical Science, 2012; 2: 85-91.
28. Farooqui N, Kar M and Singh RP. Formulation and evaluation of proniosomal gel for transdermal delivery of ketorolac tromethamine. Asian Journal of Pharmaceutics, 2016; 10: 394-400.
29. Thomas L and Viswanad V. Formulation and optimization of the clotrimazole-loaded proniosomal gel using 32 factorial designs. *Scientia Pharmaceutica,* 2012; 80: 731-748.
30. Radha CV and Chowdary CH. Formulation and evaluation of ornidazole proniosomal gel. Indo American Journal of Pharmaceutical Research, 2014; 4: 2657-2664.
31. Chandel A, Saroha K and Nanda S. Preparation and evaluation of pronisomal gel of neem seed oil. International Journal of Pharmaceutical Science and Nanotechnology, 2012; 5: 1780-4.
32. Das MK and Kumar R. Development of curcumin nano niosomes for skin cancer chemoprevention. International Journal of ChemTech Research, 2014-2015; 7: 747-54.
33. Pal P and Mishra SD. Formulation development and evaluation of antifungal proniosomal gel for topical application. World J Pharm Res., 2017; 6: 656-74.
34. Mehta M, Garg M. Proniosomal gel: A promising drug carrier for boswellic acids. J Med Sci., 2015; 15: 130-4.
35. Lathera V, Sharma D, Pandit D. Proniosomal gel-mediated transdermal delivery of bromocriptine: *In vitro* and *ex vivo* evaluation. J Exp Nanosci, 2016; 11: 1044-57.
36. Jain NK. Controlled and Novel Drug Delivery System. 1st ed. New Delhi: CBS Publishers and Distributors, 2003; 270.
37. Khandare JN, Madhavi G, Tamhankar BM. Niosomal novel drug delivery system. East Pharm., 1994; 37: 61-4.
38. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release, 1998; 54: 149-65.
39. 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.
40. El-Laithy HM, Shoukry O, Mahran LG. Novel sugar esters proniosomes for transdermal delivery of vinpocetine: Preclinical and clinical

studies. Eur J Pharm Biopharm, 2011; 77: 43-55.
41. Couvreur P, Fattal E, Andremont A. Liposomes and nanoparticles in the treatment of intracellular bacterial infections. Pharm Res., 1991; 8: 1079-86.