



Journal of Medical Sciences

ISSN 1682-4474

science
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JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

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Review Article

J. Med. Sci., 15 (3): 130-134
1st April, 2015
DOI: 10.3923/jms.2015.130.134

Proniosomal Gel: A Promising Drug Carrier for Boswellic Acids

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Dermal delivery of drugs through proniosome gel is a recent candidate receiving considerable attention. Boswellic Acids (BAs) are pentacyclic triterpenoids; the major constituents of the gum resin derived from the plant *Boswellia serrata* (family Burseraceae). The BAs have low oral bioavailability due to its lipophilic nature and high first pass metabolism. Proniosomes offer an acceptable vesicle delivery concept with the potential for transdermal drug delivery. This review covers various aspects of proniosomes including mechanism, methods of preparation emphasizing on scope and potential of proniosomal gel as a potential delivery system for boswellic acids.

Key words: Topical delivery, anti-inflammatory, *Boswellia serrata*, bioavailability

INTRODUCTION

Proniosome gel preparations are semisolid liquid crystal products of non-ionic surfactants prepared by dissolving the surfactant in a minimum amount of an solvent (organic solvent such as ethanol) and aqueous phase (water). These structures are liquid crystalline compact niosomes hybrids that can be converted into niosomes immediately upon hydration (Fang *et al.*, 2001b). Proniosome gel in topical/dermal delivery doesn't require hydration prior to application instead these can be applied, as such or loaded on a base material of emulsion, gel, ointment, etc. prior to application. The base material helps in the application of the formulation on to the skin and dilution of active material (Gupta *et al.*, 2007; Vora *et al.*, 1998). Proniosome gel offers a great potential to reduce the side effects of drugs and increased therapeutic effectiveness. Proniosomes can entrap both hydrophilic and hydrophobic drugs. These are generally present in transparent, translucent or white semisolid gel texture, which makes them physically stable during storage and transport. Due to presence of minimal solvent system, the proniosomes thus formed are the mixtures of many phases of liquid crystal as lamellar, hexagonal and cubic phase liquid crystals (Tiddy, 1980).

These liquid crystals present an attractive appearance because of their, transparency and high viscosity, compositions. Addition of water leads to interaction between water and polar groups of the surfactant results in swelling of bilayers (Sagar *et al.*, 2007; Comelles *et al.*, 2007). These days proniosomes are used to enhance drug delivery in addition to conventional niosomes. These preparations are becoming well-liked ones in recent time due to their semisolid/liquid crystalline compact nature when compared to niosome dispersion (Walve *et al.*, 2011).

Boswellic acids are pentacyclic triterpenes from gum resin isolated from *Boswellia serrata* tree belonging to the family Burseraceae (Singh and Atal, 1986). Utilisation of Boswellic Acids (BAs) into various herbal formulations has experienced increasing demand worldwide. Animal studies and pilot clinical trials support the potential of BAs for the treatment of a variety of inflammatory diseases like inflammatory bowel disease, rheumatoid arthritis, osteoarthritis and asthma. Compared to NSAIDs, it is expected that the administration of BAs formulations is associated with better tolerability (Upaganlawar and Ghule, 2009). Despite its versatile approach, BAs have low oral bioavailability especially 11-keto- β -boswellic acid (KBA) and 3-acetyl-11-keto- β -boswellic acid (AKBA), because of their lipophilic nature and not solubilising into the intestinal fluid thus limiting its systemic availability. High first pass metabolism also plays a crucial role in limiting the systemic availability of Bas (Karlina *et al.*, 2007; Kruger *et al.*, 2008; Sharma *et al.*, 2004). Topical application of BAs at the site of inflammation can overcome their systemic side effects and improve their therapeutic activity (Singh *et al.*, 2008). It is an established

fact that topical formulations like proniosomal gel enhances the topical delivery of lipophilic drugs (Kumar and Rai, 2011). Till date many studies have focused on loading boswellic acids in several dosage forms such as liposomes, solid lipid nanoparticles etc. but none of these proved to be ideal delivery system devoid of any limitation or side effects. Therefore, present review summarizes, the scope and potential of proniosomal gel, as metabolically stable formulation for BAs.

Structure: Proniosomes generally have a microscopic lamellar structures. These combine non-ionic surfactant and cholesterol followed by hydration in the aqueous media. The surfactant molecule direct themselves so that the hydrophilic ends of the non-ionic surfactant orient outward and hydrophobic ends are oriented towards the opposite direction to form the bilayer (Walve *et al.*, 2011).

Drug characteristics to be developed as proniosome gel: The drug selection criteria could be based on the following assumptions:

- Low aqueous solubility of drugs
- High dosage frequency of drugs
- Short half life
- Controlled drug delivery suitable drugs
- Higher adverse drug reaction drugs (Thejaswi *et al.*, 2011)

Types of proniosomes: Proniosomes can be categorized in two major divisions such as:

- Dry granular type of proniosomes
- Liquid crystalline proniosomes

Dry granular type of proniosomes: Dry granular type of proniosomes involves the coating of water-soluble carrier, such as; sorbitol and maltodextrin with surfactant. The result of coating process is a dry formulation in which each water-soluble particle is covered with thin film of surfactant. It is essential to prepare vesicles at a temperature above the transition temperature of the non-ionic surfactant being used in the formulation (Hu and Rhodes, 1999; Arunothayanun *et al.*, 2000; Blazek-Welsh and Rhodes, 2001a, b).

Liquid crystalline proniosomes: When the surfactant molecules are kept in contact with water, there are three ways through which lipophilic chains of surfactants can be transformed into a disordered, liquid state called lyotropic liquid crystalline state (neat phase). These three ways are increasing temperature at kraft point, addition of solvent, which dissolves lipids and use of both temperature and solvent. Neat phase or lamellar phase contains bilayer arranged in sheets over one another within dominant aqueous layer. The

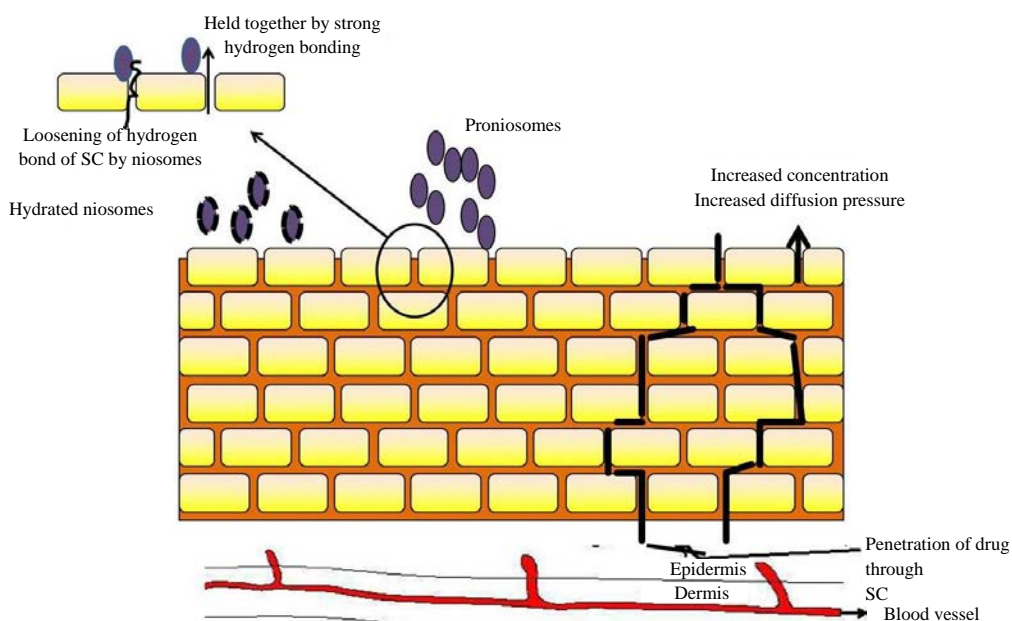


Fig. 1: Mechanism of action of proniosomes

liquid crystalline proniosomes or proniosomal gel acts as a reservoir for transdermal delivery of drug. The transdermal patch involves aluminum foil as the backing material along with plastic sheet (of suitable thickness stuck to the foil by means of adhesive). Proniosomal gel is spread evenly on the circular plastic sheet followed by covering of nylon mesh (Fang *et al.*, 2001a; Friberg *et al.*, 1976; Perrett *et al.*, 1991).

Mechanism of action of proniosome gel: Skin has a very tough diffusion barrier that is lipid bilayer in the stratum corneum inhibiting penetration of the drug moiety, which is the rate limiting barrier for penetration of drugs. Vesicular systems (Liposomes and niosomes) are promising system to cross this permeation barrier but their major drawback is their instability which can be overcome by using provesicular approaches that is proniosomes. The delivery system not only enhances the delivery of active agent through skin but also controls the rate of release (Touitou *et al.*, 1994).

Mechanism of drug transport through skin: As studies performed on the transdermal/topical application of vesicles have rendered conflicting results. It is still not clear which factors influence the vesicle–skin interactions and play an important role in determining the efficiency of drug transport through the skin. But it is clear that when proniosomes applied to the skin they get hydrated and form niosome vesicles. When vesicles come in contact with stratum corneum aggregate, fuse and adhere to the surface of cell. It is believed that this type of interaction leads to a high thermodynamic activity gradient of the drug at the interface of vesicle and stratum corneum, which is the driving

force for penetration of the lipophilic drugs across the stratum corneum (Yadav *et al.*, 2010) as shown in Fig. 1.

PREPARATION OF PRONIOSOMAL GEL

Coacervation phase separation method: Preparation of proniosomal gel is mainly accomplished by coacervation phase separation method. Proniosomal gel preparation is based on the fact that, when surfactant and other components are dissolved using an organic solvent with the aid of heat and limited concentration of hydrating medium is added. Limited hydration medium enables formation of gel instead of dispersion. Accurately weighed or required amount of surfactant, carrier (lecithin), cholesterol and drug can be taken in a clean and dry wide mouthed glass vial (5 mL) 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 min 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 (Gupta *et al.*, 2007).

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 disadvantage of liposomes and niosomes as their special storage and handling conditions, sedimentation,

aggregation, use of unacceptable solvents in the preparation etc. can be overcome by proniosomes. Liposomes and niosomes are dispersed aqueous systems and have a problem of degradation by hydrolysis or oxidation but there is no such condition with use of proniosomal gel (Mokhtar *et al.*, 2008). Further proniosomal gel formulations avoids hydrolysis of encapsulated drugs, thus limiting the shelf life of dispersion (Shukla and Tiwari, 2011). Entrapment of both hydrophilic and hydrophobic drugs can be done with use of proniosomal gel (Kumar and Rajeshwarrao, 2011). These formulations shows controlled and sustained release of drugs due to depot formation. These formulations are biodegradable, biocompatible and non-immunogenic to the body (Kumar *et al.*, 2011).

Topical delivery of boswellic acids: Application of topical formulation through the skin requires a non toxic, dermatologically acceptable carrier, which not only control the release of the agent for prolong action but also enhances the penetration to the skin layer. Previous studies indicated that boswellic acids possess low oral bioavailability due to their lipophilic nature and do not solubilises into the intestinal fluid thus limiting its systemic availability. High first pass metabolism also plays a crucial role in limiting the systemic availability of BAs. As it is well known that topical formulations enhances the delivery of lipophilic drugs and also bypass the first pass metabolism which increase the systemic availability of these drugs. Proniosomal gel carrier system can entraps both hydrophilic as well as hydrophobic agents. There is great scope for boswellic acids to be incorporate in the proniosomal gel delivery system. By combining the emulsifying action of phospholipids with BAs, the drug and lipid complex provides enhanced bioavailability and improved pharmacokinetics (Brinon *et al.*, 1999; Mehta *et al.*, 2014; Cioca *et al.*, 1991).

PRNIO SOMAL GEL AS FUTURE POTENTIAL DELIVERY SYSTEM

Proniosome gel system is superior form of niosomes, which can be employed for various applications in delivery of therapeutic agents at desired site. If proniosomal gel is used topically these are easily hydrated using aqueous phase or by skin itself. Their incorporation into base gel/cream/ointment along with other ingredients leads to a stable dosage form. These formulations can be used for topical/transdermal applications for various medicinal purposes. Proniosome gel has an affinity towards biological membranes which helps in enhancing the permeation of drugs through skin. Reported studies indicate that it has become a useful dosage form for drug permeation into the skin, especially due to their simple, scaling-up production procedure and ability to modulate drug delivery across the biological membranes. There is a strong need for exploring the proniosomal delivery systems for cosmetics, herbal actives and nutraceuticals (Mokhtar *et al.*, 2008; Yoshioka *et al.*, 1994).

CONCLUSION

Use of proniosomal gel in the boswellic acid formulation will lead to better targeting of drug at tissue destination provide prompt onset and prolonged duration of action due to maintenance of effective concentrations in the skin thereby bioavailability problems with boswellic acids can be overcome.

REFERENCES

- Arunothayanun, P., M.S. Bernard, D.Q.M. Craig, I.F. Uchegbu and A.T. Florence, 2000. 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: 7-14.
- Blazek-Welsh, A.I. and D.G. Rhodes, 2001a. Maltodextrin-based proniosomes. *AAPS PharmSci.*, 3: 1-8.
- Blazek-Welsh, A.I. and D.G. Rhodes, 2001b. SEM imaging predicts quality of niosomes from maltodextrin-based proniosomes. *Pharm. Res.*, 18: 656-661.
- Brinon, L., S. Geiger, V. Alard, J. Doucet, J.F. Tranchant and G. Couarraze, 1999. Percutaneous absorption of sunscreens from liquid crystalline phases. *J. Controlled Release*, 60: 67-76.
- Cioca, G., J.A. Hayward, M.L. Tan, M. Herstein and W.P. Smith, 1991. Liquid crystal containing cosmetic and pharmaceutical compositions and methods for utilizing such compositions. US Patent 4999348A, Washington, DC., USA. <https://www.google.com/patents/US4999348>.
- Comelles, F., J. Sanchez-Leal and J.J. Gonzalez, 2007. Influence of ionic surfactants on the formation of liquid crystals in oleic acid/glycol/water systems. *J. Surfactants Detergents*, 10: 137-144.
- Fang, J.Y., C.T. Hong, W.T. Chiu and Y.Y. Wang, 2001a. Effect of liposomes and niosomes on skin permeation of enoxacin. *Int. J. Pharm.*, 219: 61-72.
- Fang, J.Y., S.Y. Yu, P.C. Wu, Y.B. Huang and Y.H. Tsai, 2001b. *In vitro* skin permeation of estradiol from various proniosome formulations. *Int. J. Pharma.*, 215: 91-99.
- Friberg, S., K. Larsson and G.H. Brown, 1976. Liquid Crystals Side Chain Polymers. In: *Advances in Liquid Crystals*, Brown, G.H. (Ed.). 2nd Edn., Academic Press, USA., ISBN: 9780120250028, pp: 173.
- Gupta, A., S.K. Prajapati, M. Balamurugan, M. Singh and D. Bhatia, 2007. Design and development of a proniosomal transdermal drug delivery system for captopril. *Trop. J. Pharm. Res.*, 6: 687-693.
- Hu, C. and D.G. Rhodes, 1999. Proniosomes: A novel drug carrier preparation. *Int. J. Pharm.*, 185: 23-35.
- Karlina, M.V., O.N. Pozharitskaya, V.M. Kosman and S.A. Ivanova, 2007. Bioavailability of boswellic acids: *In vitro/in vivo* correlation. *Pharma. Chem. J.*, 41: 569-572.
- Kruger, P., R. Daneshfar, G.P. Eckert, J. Klein and D.A. Volmer *et al.*, 2008. Metabolism of boswellic acids *in vitro* and *in vivo*. *Drug. Metab. Dispos.*, 36: 1135-1142.

- Kumar, G.P. and P. Rajeshwarrao, 2011. Nonionic surfactant vesicular systems for effective drug delivery-an overview. *Acta Pharm. Sin. B*, 1: 208-219.
- Kumar, K. and A.K. Rai, 2011. Development and evaluation of proniosome-encapsulated curcumin for transdermal administration. *Trop. J. Pharm. Res.*, 10: 697-703.
- Kumar, R., S. Kumar, S.S. Jha and A.K. Jha, 2011. Vesicular system-carrier for drug delivery. *Der Pharmacia Sinica*, 2: 192-202.
- Mehta, M., S. Satija, A. Nanda and M. Garg, 2014. Nanotechnologies for boswellic acids. *Am. J. Drug Discov. Dev.*, 4: 1-11.
- Mokhtar, M., O.A. Sammour, M.A. Hammad and N.A. Megrab, 2008. Effect of formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. *Int. J. Pharm.*, 361: 104-111.
- Perrett, S., M. Golding and W.P. Williams, 1991. A simple method for the preparation of liposomes for pharmaceutical applications: Characterization of the liposomes. *J. Pharm. Pharmacol.*, 43: 154-161.
- Sagar, G.H., M.A. Arunagirinathan and J.R. Bellare, 2007. Self-assembled surfactant nano-structures important in drug delivery: A review. *Indian J. Exp. Biol.*, 45: 133-159.
- Sharma, S., V. Thawani, L. Hingorani, M. Shrivastava, V.R. Bhate and R. Khyani, 2004. Pharmacokinetic study of 11-Keto beta-Boswellic acid. *Phytomedicine*, 11: 255-260.
- Shukla, N.D. and M. Tiwari, 2011. Proniosomal drug delivery system-clinical applications. *Int. J. Res. Pharm. Biomed. Sci.*, 2: 880-887.
- Singh, G.B. and C.K. Atal, 1986. Pharmacology of an extract of salai guggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent. *Agents Actions.*, 18: 407-412.
- Singh, S., A. Khajuria, S.C. Taneja, R.K. Johri, J. Singh and G.N. Qazi, 2008. Boswellic acids: A leukotriene inhibitor also effective through topical application in inflammatory disorders. *Phytomedicine*, 15: 400-407.
- Thejaswi, C., K.M. Rao, M. Gobinath, J. Radharani, V. Hemafaith and P. Venugopalaiah, 2011. A review on design and characterization of proniosomes as a drug carrier. *Int. J. Adv. Pharm. Nanotechnol.*, 1: 16-19.
- Tiddy, G.J.T., 1980. Surfactant-water liquid crystal phases. *Phys. Rep.*, 57: 1-46.
- Touitou, E., H.E. Junginger, N.D. Weiner, T. Nagai and M. Mezei, 1994. Liposomes as carriers for topical and transdermal delivery. *J. Pharm. Sci.*, 83: 1189-1203.
- Upananlawar, A. and B. Ghule, 2009. Pharmacological activities of *Boswellia serrata* Roxb: Mini review. *Ethnobotanical Leaflet*, 13: 766-774.
- Vora, B., A.J. Khopade and N.K. Jain, 1998. Proniosome based transdermal delivery of levonorgestrel for effective contraception. *J. Controlled Release*, 54: 149-165.
- Walve, J.R., B.R. Rane, N.A. Gujrathi, S.R. Bakaliwal and S.P. Pawar, 2011. Proniosomes: A surrogated carrier for improved transdermal drug delivery system. *Int. J. Res. Ayurveda Pharm.*, 2: 743-750.
- Yadav, K., D. Yadav, K. Saroha, S. Nanda, P. Mathur and N. Syan, 2010. Proniosomal gel: A provesicular approach for transdermal drug delivery. *Der. Pharmacia. Lett.*, 2: 189-198.
- Yoshioka, T., B. Sternberg and A.T. Florence, 1994. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan triester (Span 85). *Int. J. Pharm.*, 105: 1-6.