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Proniosome: A Novel Approach To Vesicular Drug Delivery System

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The present article depicts an elaborative study of proniosomes as specialized drug delivery system. Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. Provesicular systems, such as proniosomes which is one of the advancement in nanotechnology minimize problems of vesicular systems such as aggregation, fusion and leakage of drug and provide additional convenience in transportation, distribution, storage and dosing. Conventional vesicular systems such as liposomes and niosomes are particulate in nature and face stability related difficulty. The review article provides an insight about these approaches along with a novel vesicular approach known as proniosomes. This new emerging concept has demonstrated the potential in improving 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 goal of this study is to introduce and explore proniosomes as a carrier system for various pharmaceutical and cosmeceutical applications.

Keyword: Niosomes, Proniosomes, Surfactant, Stability, Colloidal particulate carriers.

1. Introduction

Vesicular systems have been receiving a lot of interest as a carrier for advanced drug delivery. Encapsulation of the drug in vesicular structures is one such system, which can be expected to prolong the duration of the drug in systemic circulation, and to reduce the toxicity by selective up taking. In the ensuing years, great strides were made toward understanding the way in which vesicular systems interact with the biological milieu at the molecular and cellular level[1]. No doubt that drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have proved to possess distinct advantages over conventional dosage forms because the particles can act as drug reservoirs, can carry both hydrophilic drugs by encapsulation or hydrophobic drugs by partitioning of these drugs into hydrophobic domains and modification of the particle composition or surface can adjust the drug release rate and/or the affinity for the target site. The vesicles in a dispersed aqueous system may suffer from some chemical problems associated with degradation by hydrolysis or oxidation as well as physical problems as sedimentation, aggregation, or fusion of liposomes during storage[2].

Two novel approaches were adopted in dealing with these problems to develop the proliposomes and to develop Niosomes" using non-ionic surfactants alternatives to phospholipids in preparing vesicles. Even though proliposomal

formulations are an improvement over conventional liposome dispersions in terms of the physical stability of the preparation, chemical instability is still present and therefore a vacuum or nitrogen atmosphere is recommended during preparation and storage to prevent the oxidation of phospholipids. In the later approach niosomes exhibit good chemical stability during storage but aqueous suspension of niosomes may exhibit problems of physical stability such as aggregation, fusion, leaking of entrapped drugs, or hydrolysis of encapsulated drugs, thus limiting their shelf life[2]. The latest approach in the field of vesicular delivery is to combine the two previously mentioned techniques by extending the pro-vesicular approach to niosomes through the formation of "proniosomes" which are converted to niosomes upon hydration[2]. There are a number of formulation approaches to resolve the problems of low solubility and low bioavailability. Proniosome technology offers novel solution for poorly soluble drugs. Proniosome is a dry free flowing, granular product that could be hydrated immediately before use and would avoid many of the problems associated with aqueous noisome dispersions and problem of physical stability[3].

1.1 Components of Proniosomes

The essential components for the delivery system are as follows.

1.1.1 Surfactant

Surfactants are the surface active agent usually organic compounds that are amphiphilic in nature (having both hydrophobic and hydrophilic groups). Therefore, a surfactant molecule contains both a water insoluble (lipophilic) and a water soluble (hydrophilic) component. They have variety of functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers[4]. The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids (Table 1).

Table 1: List of common nonionic amphiphiles used in prinosome formulations

Non-ionic amphiphiles		**Examples**
Alkyl ethers and alkyl glyceryl ethers		Polyoxyethylene 4 lauryl ether (Brij30)
Polyoxyethylene cetyl ethers(Brij 52, 56, 58)		
Polyoxyethylene stearyl ethers (Brij 72, 76)		
Sorbitan fatty acid esters		Span 20, 40, 60, 80
Polyoxyethylene fatty acid esters		Tween 20, 40, 60, 80

1.1.2 Carrier Materials

The carrier when used in the proniosomes preparation permits the flexibility 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[5,6]. Commonly used carriers are listed, they are sorbitol, Mannitol, Glucose, Lactose, Sucrose stereate.

1.1.3 Membrane Stabilizers

Cholesterol and lecithin are mainly used as membrane stabilizer. Steroids are important components of cell membrane and their presence in membrane and their presence in membrane brings about significance changes with regard to bilayer stability, fluidity and permeability. Cholesterol is a naturally occurring steroid used as membrane additive. It prevents aggregation by the inclusion of molecules that stabilize the system against the formation of aggregate by repulsive steric or electrostatic effects. It leads transition from the gel state to liquid phase in niosome system. Phosphatidylcholine is a major

component of lecithin. It has low solubility in water and can form liposomes, bilayer sheets, micelles 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 penetration enhancer. It is found those vesicles composed of soya lecithin are of larger size than vesicle composed of egg lecithin probably due to the difference in the intrinsic composition[7,8].

1.2 Solvent and Aqueous Phase

Alcohol used in Proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Ethanol has greater solubility in water hence leads to formation of highest size of vesicles instead of isopropanol which forms smallest size of vesicle due to branched chain present. Phosphate buffer pH 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation of proniosomes[8].

1.3 Drug

The drug selection criteria could be based on the following assumptions[7].

1. Low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Short half life.
4. Controlled drug delivery suitable drugs.
5. Higher adverse drug reaction drugs.

1.4 Formulation Considerations

It is necessary to understand the role of basic formulation aspects of proniosomes before preparation which includes selection of surfactant, cholesterol concentration, the hydration medium, nature of encapsulated drug.

1.5 Selection of Surfactant

Surfactants can improve the solubility of some poorly soluble drugs. Selection of surfactants should be done on the basis of HLB value which is a good indicator of the vesicle forming ability of any surfactant. The formation of bilayer vesicles instead of micelles not only depends upon the HLB values of the surfactant but also on the chemical structure of component and the critical packing parameter. The HLB value of a surfactant plays a key role in controlling drug entrapment of the vesicle it forms. Non-ionic surfactant are the most common type of surfactant used in preparing the vesicles due to the superiority over other counterparts having good stability, compatibility and toxicity aspects. It was found that the HLB value in between 4 and 8 was found to be compatible with vesicle formation. The entrapment efficiency of bilayered vesicle also depends upon the phase transition temperature (Tc) of the surfactant[4,9].

1.6 Cholesterol concentration

Cholesterol is an essential structural component of cell membrane and is required to establish proper membrane permeability and fluidity. It imparts rigidity to vesicles, which is very important under severe stress conditions. Cholesterol increases or decreases the percentage encapsulation efficiency depending on either the type of the surfactant or its concentration within the formulae. Cholesterol along with the addition of surfactant forms homogenous niosome dispersion rather than only a surfactant which forms a gel. Cholesterol is thus usually included in a 1:1 molar ratio in most formulations as it is known to abolish the gel to liquid phase transition of niosome systems resulting in niosomes that are less leaky. The amount of cholesterol to be added depends on the HLB value of the surfactants. As the HLB value increases above 10 it is necessary to increase the minimum amount of cholesterol to be added in order to compensate for the larger head groups. It was found that above a certain level of cholesterol, entrapment efficiency decreased possibly due to a decrease in volume diameter[8,10].

1.7 Hydration Medium

Phosphate buffer having various pH's are most widely used hydration medium for preparation of proniosome derived niosomes. The solubility of drug being encapsulated determines the actual pH of hydration medium. The temperature of hydration also plays an important role in

governing the self assembly of non-ionic surfactant into vesicles and affects their shape and size. In case of proniosomal gel preparation, the hydrating temperature used to make niosomes should usually be above the gel to liquid phase transition temperature of the system[4,10,11]. The proniosome derived niosomes are very similar to conventional niosomes and more uniform in size (Fig 1).

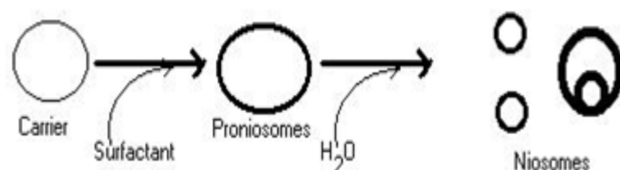

Fig 1: Formation of Niosome from Proniosome

1.8 Nature of Encapsulated Drug

The main factor in the consideration is the influence of an amphiphilic drug on vesicle formation. When drug was encapsulated in niosomes, aggregation occurred and was overcome by the addition of a steric stabilizer. When more drug is added the increase in its encapsulation could be the result of saturation of the medium. This suggests that the solubility of certain poorly soluble drugs can be increased by formulation in niosomes but only up to a certain limit above which drug precipitation will occur. Increase in drug concentration showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mole total lipids upon hydration and formation of niosomes[4,10].

1.9 Advantages of Proniosomes

1. Avoiding the problem of physical stability like fusion, aggregation, sedimentation and leakage on storage[12].
2. Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion[12].
3. Ease on storage and handling[13].
4. No difficulty in sterilization, transportation, distribution, storage uniformity of dose and scale up[7].
5. Drug delivery with improved bioavailability, reduced side effects[14].
6. Entrapment of both hydrophilic and hydrophobic drugs[4].
7. Shows controlled and sustained release of drugs due to depot formation[14].
8. Biodegradable, biocompatible and non immunogenic to the body[14].
9. Shape, size, composition, fluidity of niosomes drug can be controlled as and when required[14].

1.10 Method of Preparation

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

1.11 Slurry Method

Proniosomes can be prepared by addition of the carrier and the entire surfactant solution in a round bottomed flask which is fitted to rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Finally, the formulation should be stored in tightly closed container under refrigeration in light. The time required for proniosome production is independent of the ratio of surfactant solution to carrier material and appears to be stable. This method is advantageous because due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation. Along with that the higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient[9,13].

1.12 Co-Acervation Phase Separation Method

Proniosomal gels can be prepared by this method which comprises of surfactant, lipid and drug in a wide mouthed glass vial along with small amount of alcohol in it. The mixture is warmed over water bath at 60-700C for 5min until the surfactant mixture is dissolved completely. Then the aqueous phase is added to the above vial and warmed still a clear solution is formed which is then converted into proniosomal gel on cooling[9,11]. After hydration of proniosomes they

are converted to uniformly sized niosomes (Fig.1).

1.13 Types of Proniosomes

Depending on the method of preparation, the proniosomes exists in two forms

A) Dry granular proniosome: According to the type of carrier these are again divided as a) Sorbitol based proniosomes[15,16].

B) Maltodextrin based proniosomes Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier. These are made by spraying surfactants mixture prepared in organic solvent on to the sorbitol powder and then evaporating the solvent. It is useful in case where the active ingredient is susceptible to hydrolysis[17,18,19].

1.14 Characterization of Proniosomes

There are numerous methods for the characterization of proniosomes, depending on the aspect of the system under investigation. Such aspects include those that are related to the overall structure of proniosomes, for instance vesicle size, lamellarity, surface potential, morphology, and microscopy (Fig 2).

1. Vesicle shape

Proniosomes can be easily visualized by using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) and optical microscopy[20].

2. Optical Microscope Observation

The Proniosomal dispersion was spread on the glass slide using a glass rod. Formation of multilamellavesicles wasconfirmed by examining the ethosomal suspension under an optical microscope with the magnification power of 100 X. Photographs of vesicles were taken using Olympus camera[21,22].

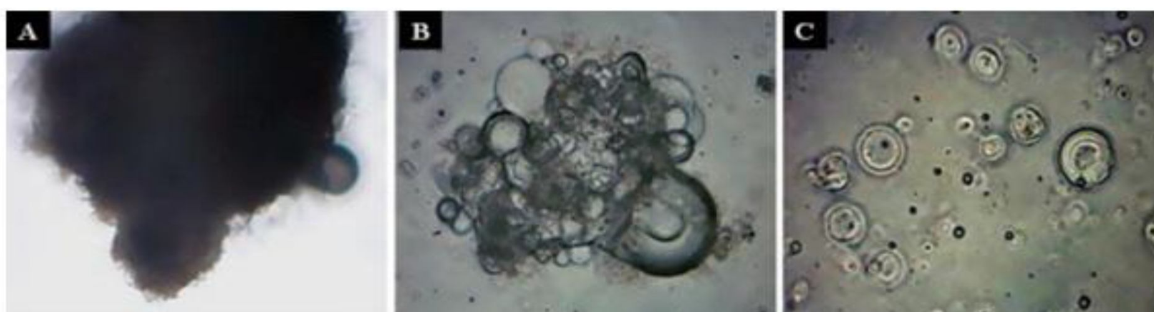

Fig 2: Optical microphotograoh showing (A) proniosome powder, (B) formation of vesicles on maltodextrin after hydration with phosphate buffer (pH 6.8), (C) noisome dispersion from proniosome powder upon gentle agitation.

3. Vesicle size and zeta potential

Particle size of the Proniosomes can be determined by dynamic light scattering (DLS) and photon correlation spectroscopy (PCS). Zeta potential of the formulation can be measured by Zeta meter [23, 24].

4. Transition temperature

The transition temperature of the vesicular lipid systems can be determined by using differential scanning calorimetry (DSC).

5. Drug entrapment

The entrapment efficiency of Proniosomes can be measured by the ultra centrifugation technique[25,26].

6. Drug Content

Drug content of the Proniosomes can be determined using UV spectrophotometer.

This can also be quantified by a modified high performance liquid chromatographic method[27,28].

7. Surface Tension Measurement

The surface tension activity of drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer[29,30].

1.15 Advantages of Proniosomal Drug Delivery

In comparison to other drug delivery systems[31,32].

1. The Proniosomal system is passive, non-invasive and is available for immediate commercialization.
2. Proniosomes are platform for the delivery of large and diverse group of drugs (peptides, protein molecules).
3. Proniosome composition is safe and the components are approved for pharmaceutical and cosmetic use .
4. Low risk profile- The technology has no large-scale drug development risk since the toxicological profiles of the Proniosomal components are well documented in the scientific literature.

1.16 Therapeutic Applications

Proniosomes, the high ethanol containing vesicles are able to penetrate the deeper layers of the skin and hence appear to be vesicles of choice for transdermal drug delivery of hydrophilic and impermeable drugs through the skin. Various drugs have been used with Proniosomal carrier. Because of their unique structure, Proniosomes are able to encapsulate and deliver through the skin highly lyphophilic molecules such as cannabinoids, testosterone, and minoxidil, as well as cationic drugs such as propranolol, trihexyphenidil, Cyclosporine A, insulin, Salbutamol etc. Proniosomes provides a number of important benefits including improving the drug's efficacy, enhancing patient compliance and comfort and reducing the total cost of treatment. Enhanced delivery of bioactive molecules through the skin and cellular membranes by means of an Proniosomal carrier opens numerous challenges and opportunities for the research and future development of novel improved therapies[33,34].

2. Conclusion

The development of proniosome represents a significant advance over the conventional vesicular systems. This concept of incorporating the drug into proniosomes for a better targeting at appropriate tissue destination and for controlled delivery is widely accepted by researchers. As a drug delivery device, proniosomes are osmotically active and stable. They do not require special conditions for handling, protection, storage or industrial manufacturing. The system had attracted researchers as an alternate strategy for transdermal delivery of drugs because it reduces the toxicity and enhances penetration effect of surfactants. A wide variety of active agents of different therapeutic actions can also be given by proniosomal drug delivery system in the form of tablets, beads or capsules. Based on the investigations proniosomal system appears to be an efficient drug carrier for the future with physical and chemical stability and potentially scalable for commercial viability.

3. References

1. T Sudhamani, N Priyadarisini, M Radhakrishan. Proniosomes– A Promising Drug Carrier. Int.J. Pharm Tech Res. 2010; 2(2): 1446-1454.
2. M Hanan, S Omar, Novel sugar esters proniosomes for transdermal delivery of Vinpocetine: Preclinial and clinical studies. European Journal of Pharmaceutics and Biopharmaceutics 2011; 77: 43-55.
3. 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.
4. PK Gannu, R Pogaku . Nonionic surfactant vesicular systems for effective drug delivery - an overview. Acta Pharmaceutica Sinica B 2011; 1(4): 208-219.
5. D Akhilesh, G Faishal, JV Kamath. Comparative Study of Carriers used in Proniosomes, Int.J Pharm Chem Sci 2012; 1(1): 164-173.
6. N Pandey. Proniosomes and Ethosomes: New Prospect in Transdermal and Dermal Drug Delivery System. IJPSR 2011; 2(8): 1988-1996.
7. 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.

8. 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.
9. 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.
10. IF Uchegbu, SP Vyas. Non-ionic surfactant based vesicles (niosomes) in drug delivery. International Journal of Pharmaceutics 1998; 172: 33-70.
11. 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.
12. ND Shukla, M Tiwari. Proniosomal Drug Delivery System– Clinical Applications. Intenational Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2 (3): 880-887.
13. D Akhilesh, G Hazel, JV Kamath. Proniosomes – A Propitious Provesicular Drug Carrier, Int. J. Pharm PharmSciRes 2011; 1 (3): 98-103.
14. AK Jha, R Kumar, S Kumar, SS Jha. Vesicular System -Carrier for Drug Delivery. Der Pharmacia Sinica 2011; 2(4): 192-202.
15. N Kishore. Proniosome Gel: Potential Carrier System in Topical/Transdermal Delivery for Drugs and Cosmetics/Cosmecueticals. 2010 [cited 2010 May 31]. Available from: URL: http://www.pharmainfo.net
16. K Ruckmani, V Sankar, S Durga, S Jailani. Proniosomes as Drug Carriers. Pak. J. Pharm. Sci. 2010; 23(1): 103-107.
17. SG Prakash, VG Joshi. An engineered specificity of Irinotecan loaded Proniosomes: Design and Characterization. International Journal of Drug Delivery 2011; 3:472-480.
18. A Gupta, SK Prajapati, M Balamurugan, M Singh. Design and Development of a Proniosomal Transdermal Drug Delivery system for Captopril. Tropical Journal of Pharmaceutical Sciences; 2007; 6 (2): 687-693.
19. D Akhilesh, G Faishal, P Prabhu. Development and Optimization of Proniosomes for Oral delivery of Glipizide. Int J Pharm Pharm Sci 2012; 4(3): 307-314.
20. D Akhilesh, VN Anoop, BP Rao. Formulation and Evaluation of Gliclazide loaded Maltodextrin based Proniosomes. International Journal of Research in Pharmaceutical and Biomedical Sciences 2011; 2(4): 1582-1589.
21. MH Aburahma, GA Abdelbary. Novel diphenyl dimethyl bicarboxylate provesicular powder with enhanced hepatoprotective activity: Preparation, optimization, in vitro/in vivo evaluation. International Journal of Pharmaceutics 2012; 422: 139-150.
22. R Jukanti, A Gurrapu, SR Bobbala, S Kanuganti. Improved oral delivery of Valsartan from maltodextrin based proniosome powders. Advanced Powder Technology 2011.06.005.
23. HA Marwa, AS Omaima. Optimizing Proniosomes for Controlled Release of Ketoprofen using Box-Behnken Experimental Design. IJPSR 2011; 2(8): 2195-2205.
24. M Nasr. In vitro and in vivo evaluation of proniosomes containing Celecoxib for oral administration. AAPS PharmSciTech 2010 Mar; 11 (1): 85-94.
25. T Sudhamani, V Ganesan, N Priyadarsini. Formulation and Evaluation of Ibuprofen Loaded Maltodextrin based Proniosome. International Journal of Biopharmaceutics; 2010; 1 (2): 75-81.
26. T Chintankumar. Formulation and Evaluation of Aceclofenac loaded Maltodextrin based Proniosome. Int.J. ChemTech Res. 2009; 1(3): 567-573.
27. T Sudhamani, V Ganesan, N Priyadarsini. Formulation and Evaluation of Ibuprofen Loaded Maltodextrin based Proniosome. International Journal of Biopharmaceutics; 2010; 1 (2): 75-81.
28. T Chintankumar. Formulation and Evaluation of Aceclofenac loaded Maltodextrin based Proniosome. Int.J. ChemTech Res. 2009; 1(3): 567-573.
29. AB Solanki, JR Parikh, RH Parikh. Formulation and Optimization of Piroxicam Proniosomes by 3-Factor, 3-Level Box-Behnken Design. AAPS PharmSciTech 2007; 8(4): E1-E7.
30. R Parthibarajan, C Rubinareichal, S Loganathan. Formulation and Evaluation of Methotrexate Proniosomal Powder. Int J Pharm Pharm Sci 2012; 4(1): 175-178.
31. BA Goud, R Jukanti, D Rambahu. Improved Oral Absorption of Carbamazepine from Sorbitan Monolaurate based Proniosome Systems containing Charged Surface Ligands. International Journal of Biological and Pharmaceutical Research 2012; 3(1): 37-42.
32. IA Alsarra , AA Bosela , SM Ahmed. Proniosomes as a drug carrier for transdermal delivery of Ketorolac. European Journal of Pharmaceutics and Biopharmaceutics 2005; 59:485-490.
33. 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, U.S. Patent US 4830857A, 1989.

34. Ribier, A. Simonnet, Jean-thierry. 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.