THE PHARMA RESEARCH

A Journal of Pharmacy Research

Original Article

ISSN- 0975-8216

Impact- 0.529 Refer website

PRONIOSOMES - DRUG CARRIER FOR TRANSDEMAL DRUG DELIVERY SYSTEM

Chirag madhu*, Kamal Saroha, Sachin kamboj, Meenakshi Goel

Affilfiation:

Department of Pharmaceutics, Kurukshetra University, Kurukshetra , Haryana, India

ABSTRACT

Nanotechnology is an advancing technology which brings revolutionary changes in the field of science including drug delivery, diagnosis, neutraceuticals and biomedical for implants and prosthesis. Provesicular system is one of the advancing nanotechnologies. Provesicular system resolve the stability issues pertaining to the conventional vesicular system i.e. liposomes and niosomes. Proniosomes are water soluble, solid colloidal particles that are coated with surfactant which can be hydrated to form niosomal dispersion immediately before use by brief agitation in hot aqueous media. Proniosomes minimizes the problem such as aggregation, fusion and leaking which are associated with niosomes. This article presents the methods of preparation of proniosomes, their characterization techniques and the name of drugs which is employed in this system.

Key Words: Nanoparticles, Nanotechnology, Niosomes, Proniosomes, Transdermal, Provesicular

INTRODUCTION

Niosomes act as a novel drug delivery system in which the drug is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agent. Niosomes are alternative to liposomes as they posses greater stability and overcome the problem associated with liposomes like chemical instability, various purity of phospholipids and high cost *[1]*. Niosomes are osmotically active and are stable on their own while also increasing stability of the entrapped drug*[2-3]*. Although niosomes as drug carriers have shown advantages such as being cheap and chemically but they are associated with some problem as written *[4]*:

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of dispersion.

So, to increase shelf life and stability of niosomes Proniosomes are developed. Proniosomes are dry formulations of surfactant coaled carriers which can be rehydrated by brief agitation in hot water. The resulting niosomes are very similar to conventional niosomes and more uniform in size.

Proniosomes are dry solid in form which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing so the proniosome can be provided in capsule form.

- A proniosomes formulation based on maltodextrin was also developed that has a potential applications in deliver of hydrophobic or amphiphillic drug. The better of these formulations used a hollow particle with exceptionally high surface area. The principle advantage with this formulation was the amount of carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared. Because of the ease of production of proniosomes using the maltodextrin by slurry method, hydration of surfactant from proniosomes of a wide range of compositions can be studied *[5-6]*.

Gels:

Gels have a variety of applications in the administration of medications orally, topically, intranasal, vaginally and rectally. Some gel systems are transparent and others are translucent, since the ingredients involved may not be completely dispersed or they may form aggregates which disperse light. Gels are semisolid systems consisting of suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid.

Table 1: General classification and description of gels

Class	Description	Examples
Inorganic	Usually two-phase systems	Aluminium hydroxide gel, bentonite magma
Organic	Usually single-phase systems	Carbopol, tragacanth
Hydrogels	Contains water	Silica, bentonite, pectin, sodium alginate, methylcellulose, alumina
Hydrogels	Contains water	Silica, bentonite, pectin, sodium alginate, methylcellulose, alumina
Organogels	Hydrocarbon type	Petrolatum, mineral oil/polyethylene gel, Plastibase
	Animal/vegetable fats	Lard, cocoa butter
	Soap-base greases	Aluminium stearate with heavy mineral-oil gel
	Hydrophilic organogels	Carbowax bases *[PEG ointment]*
Hydrogels	Organic hydrogels	Pectin paste, tragacanth jelly
	Natural and synthetic gums	Methylcellulose, sodium carboxymethylcellulose, Pluronic F-127
	Inorganic hydrogels	Bentonite gel *[10% to 25%]*, Veegum

Most topical gels are prepared with organic polymers, such as carbomers, which impart an aesthetically pleasing, clear sparkling appearance to the product, and are easily washed of the skin with water[55]. There are a variety of semi-synthetic celluloses in use as thickeners in gel formulations. These include methylcellulose, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose. Branched-chain polysaccharide gums, such as tragacanth, pectin, carrageenan and agar, are of naturally occurring plant origin; therefore they can have widely varying physical properties, depending on their source. By far the most extensively employed gelling agents in the pharmaceutical and cosmetic industries are the carboxyvinyl polymers known as carbomers.

Formulation of Gel

a. Polymers and other compounds used in formulation of Gel :

1. Natural Polymers
   e.g. alginates, carrageenan, tragacanth, pectin, xanthum gum, gellan gum, guar gum, chitosan, agar, gelatin
2. Acrylic polymers e.g. carbomer934P, propylene glycol
3. Cellulose derivatives e.g. carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose
4. Polyethylene
5. Colloidally dispersed solid e.g. microcrystalline silica, clays, microcrystalline cellulose
6. Surfactants e.g. poloxamer, non-ionic surfactants
7. Other gellants e.g. beeswax, carnauba wax, cetyl ester wax, aluminium stearate

b. Solvent employed in Gel

e.g. Polyethylene glycol *[*PEG-400, PEG-600 etc.*]*, Propylene glycol, Ethanol etc.

c. Cosolvent

e.g Propylene glycol, Glycerine etc.

d. Disinfectant

e.g. Ethanol

e. Humectant

e.g. propylene glycol, glycerine

f. Antiseptic agent

e.g. Peppermint oil

g. Penetration Enhancer

1. Natural: eugenol, camphor, cineole, limonene
2. Synthetic:Ethanol, Azone, Oxazolidinones, N,N-Dimethylaminoacetate

Mechanism of Drug Transport through skin:

There is a direct contact of proniosomes formulation with skin after applies so it is better to discuss the potential interactions between skin and vesicle formed in proniosome/ noisome formulation. It is still not clear which factors influence the vesicle skin interactions. But it is clear that Proniosomes should be hydrated to form niosomal vesicles before the drug is release and permeates across skin.

Two types of vesicle skin interactions observed during in vitro studies using human skin.

1.] When vesicles came in contact with stratum corneum aggregate, fuse and adhere to the surface of cell. It is believed that this type of interaction leads to high thermodynamic activity gradient of the drug at the interface of vesicle and stratum corneum which is driving force for penetration of lipophillic drug across the stratum coerneum.

2.] This type of interaction involves the ultrastructural changes in the intercellular lipid regions of the skin and its deeper layer at maximum depth of about 10 nm as revealed by Freeze Fracture Electron Microscopy and Small Angle X-Xay Scattering. The other factor which could also explain the ability of vesicles to modulate drug transfer across the skin is [7-8]:

1] Nature of drug

2] The lipid bilayer of niosomes acts as a rate limiting membrane barrier for drugs.

3] Dehydration of vesicles

4] The vesicles act as penetration enhancer to reduce the barrier properties of the skin.

5] Skin and composition of vesicles.

6] Biophysical factor

Preparation of proniosomal Gel:

There are basically 3 methods for preparation of proniosomes which are

1] Slurry Method

2] Coacervation Phase Separation Method

3] Slow Spray coating method.

1] Slurry Method: This method involves formation of slurry by addition of the carrier and the entire surfactant solution in a round bottom flask. This is fitted to a rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Then the flask was removed and kept under vacuum overnight. The obtain powder was collected in a sealed container and kept at 4^0C. The time required for proniosome production is independent of the ratio of surfactant solution to carrier materials and appears to be sealable [5, 9, 10, and 11].

2] Coacervation Phase Separation Method: This method is widely used for preparing proniosomal gel. In this surfactant, lipid and drug are taken in a dry wide mouth glass vial of 5.0 ml capacity and small amount of alcohol added to it. All the ingredients are mixed well and warmed over water bath at 60-70^0 for 5 min. 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 *[2, 12]*.

3] Spraying Method: In this method the surfactant is added to an organic solvent and sprayed onto carrier. Then the solvent is evaporated. This process is repeated until the desired surfactant loading is achieved, because the carrier is soluble in the organic solvent. As the carrier dissolved, hydration of this coating allows the formation of multilamellar vesicles *[13-14]*.

Table 2: Composition or Formulation of Proniosomes:

Ingredients	Examples	Uses
Non-ionic surfactants	Span-20,40,60,80 Tween-20,60,80	To increase rate of permeation
Cholesterol		Membrane stabilizer and to improve stability
Lecithin		Penetration enhancer
Coating materials	Glucose monohydrate, Maltodextrin,sorbitol	For coating

Table 3: Characterization of Proniosomes:
Methods for characterization of Proniosomes

	PARAMETER	METHOD
1.	Vesicle size	SEM, TEM, LASER DIIFFERACTION METHOD *[9,15]*
2.	Angle Of Repose	Funnel Method *[16]*
3.	Entrapment Efficiency	Diode array spectrophotometer, centrifugation method, dialysis method*[1,17]*
4.	Zeta potential determination	Z.P Probe model
5.	In Vitro permeation study	Franz Diffusion Cell*[18]*, Kesharv Chien Diffusion Cell*[1]*, Flow Through Diffusion Cell

Vesicle size Analysis: This analysis involves the measurement of size and shapes of vesicles. Size of vesicles can be measured by dynamic light scattering method in two conditions without agitation and with agitation. Hydration without agitation results in largest vesicle size. SEM and TEM both can be used for measurement of size and shape. *[19]*

- The size distribution of niosomes with teens was significantly lower than that with span surfactant.
- Hydrophobicity of surfactant monomer leads to a small size vesicles since surface

energy decreased with increasing the Hydrophobicity.*[12]*

2. Angle of Repose: The angle of repose of dry proniosomes powder was measured by funnel method. The proniosomes powder was poured in to a funnel which was fixed at a position so that the 13 mm outlet orifice of funnel is 5 cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of cone and diameter of its base. *[9, 20]*

3. Entrapment efficiency: Entrapment efficiency of the niosomal dispersion can be evaluated by separating the entrapped drug by dialysis *[9,21,22]*, centrifugation method*[9,20,22]*. By this amount of entrapped drug can be calculated from total drug incorporated.

Entrapment efficiency = Amount of drug entrapped/Total drug x 10

- The entrapped efficiency of proniosomes composed of tween was relatively low as compared to span.
- The cholesterol content also effect the entrapped efficiency as the cholesterol content decrease the entrapment efficiency.*[18]*
- Higher entrapment efficiency of vesicles of span 60 rather than span 40 is predictable because of its higher alkyl chain length.*[23]*

4. Zeta Potential Determination: - Zeta potential is analyzed to measure the stability of noisome by studying its colloidal properties. It is measured by Zeta Potential Probe which based on electrophoretic light scattering and laser Doppler velocimetry method. The temperature was set at 25^0C and charge on vesicle and their mean zeta potential values with standard deviation of 5 measurements were obtained directly from the measurement *[24]*. The higher charge on the surface of vesicle produce repulsive force between vesicle which made them stable devoid of agglomeration and faster setting provide an evenly distributed suspension *[25]*.

5. In Vitro permeation study: The rate of permeation of drugs from proniosomal formulations can be determined by using Dialysis tubing method *[26]*, Franz diffusion cell *[27, 28]*, Chien diffusion cell method and reverse dialysis method *[26]*. Proniosomes interact with skin and contribute to improvement of Transversal drug delivery and one of the possible mechanism for niosomal permeability enhancement is structural modification of upper membrane of skin i.e. stratum corneum. Both phospholipids and non-ionic surfactants used in proniosomes act as penetration enhancers, leading to increase the permeation of many drugs *[29]*.

Table 4: List of Drugs which were used to deliver by Proniosomes

DRUG	CATEGORY	REFERENCE
1. VALSARTAN	ANTI-HYPERTENSIVE	2011
2. IBUPROFEN	NSAIDS	2010
3. CELECOXIB	COX INHIBITOR	2010
4. HYDROCORTISONE	CORICOID HORMONE	2009
5. LOSARTAN POTASSIUM	ANGIOTENSIN ANTAGONIST	2009
6. FUROSEMIDE	ANTI-HYPERTENSIVE	2009
7. INDOMETHACIN	NSAIDS	2009
8. PIROXICAM	NSAIDS	2008
9. FLURBIPROFEN	NSAIDS	2008
10. CAPTOPRIL	ANTI-HYPERTENSIVE	2007
11. CHLORPHENIRAMIN MALEATE	SKIN DISORDER	2005
12. KETOROLAC	NSAIDS	2004
13. ESTRADIOL	FOR T/T IN MENAUPAUSE	2001
14. LEVONORGESTEROL	CONTRACEPTIVE AGENT	1998

Conclusion:-

Proniosomes are dry form of niosomes which are surfactant coated and rehydrated to form noisome by adding hot water with agitation. This system has found to be more stable and does not show the problem associated with niosomes. It delivers active agent in high concentration through skin. For further enhancement in delivery of drug through skin by proniosomes is a new challenge to us and we have opportunities for development of Novel Drug Delivery System.

References:

1. Vora B; Khopade AJ; Jain NK. J. Control. Release, 1998, *[*54*]*, 149-165
2. Baille AJ, Florence AT, Hume LR, Muirhead GT and Rogerson A. The preparation and properties of niosomes non-ionic surfactant vesicles J. Pharm. Pharmacol., 1985, 37: 863-868.
3. Rogerson A, Cummings j, willmott n and Florence AT. The distribution of doxorubicin in mice following administration in niosomes. J. Pharm. Pharmacol., 1988, 40: 337-342.
4. jeama,F., Uchegbv, Suresh P. Vyas. Non-ionic surfactant based vesicles *[*niosomes*]* in drug delivery. Int. J. Pharm., 1998, 172, 33-70.
5. Almira, J., Blazek-Welsh, Rhodes, D.G. pool Maltodextrin- Based Proniosames. AAPS Pharm Sci Tech, 2001, Article 1.
6. Mahdi, Jufri, Effionora, Anwar, Joshita, Djajadisastra, 2004. Preparation of Maltodextrin DE 5-10 based ibuprofen Proniosomes. 2001; 18: 656-661.
7. Tovitov E., Junginger HE; Weiner ND., Nagai T; Mezei M.J. Pharm. Sci., 1994, *[*83*]*, 1189-1203.

8. Junginger HE ; Hofland HEJ; Bouwstra JA. Cosmet. Toil, 1991, *[*106*]*, 45-50
9. AB Solanki, PR Parikh and RH Parikh. AAPS Pharm. Sci. Tech., 2007 8*[4]*, E1-E7.
10. AI Blazek-Welsh and DG Rhodes, Pharm. Res., 2001, 18, 656-661.
11. S. Perrett, M. Golding and WP Williams, Pharm. Pharmacol., 1991, 43: 154-161.
12. Ankur Gupta, Sunil Kumar Prajapati, M Balamurugan, Mamta Singh and Daksh Bhatia, Tropical J. Pharm Res., 2007, 6*[2]*: 687-693.
13. AD Bangham, MM Standish and JC Watkins, J.Mol. Biol., 1965, 13: 238-252.
14. T. Yoshioka, B. Sternberg and AT. Florence, Int.J.Pharm., 1994,105: 1-6.
15. Y.Hao, F. Zhao, N.Li, Y Yang and K.Li.Int.J.Pharm., 2002,244: 73-80.
16. H.Lieberman, L.Lachman, J.Schwartz, Pharmaceutical Dosage Forms: Tablets, Vol.2, 2nd ed., 1990, Marcel Deeber, New York, pp. 229,
17. A.Abd-Elbary, HM. El-Laithy and MI Tadrus, Int.J.Pharm., 2008,357 *[*1-2*]*: 189-198.
18. JY Fang, Yu Sy, Wu PC, YB Huang and YH Tsai, Int.J.Pharm., 2001, 215: 91-99.
19. C.J.Tank, C.H.Borkhataria, A.H.Baria, R.P.Patel., S.Tamizharasi, K.S.Dipen, D.P.Sandi,R.P.Ghanshaym, Int. J. Chem. Tech. Res. 2009, 1*[3]*, 567-573.
20. A.Alsarra, A.A.Bosla, S.M.Ahmed and G.M.Mahrous. Pronisomes as a drug carrier for transdermal delivery of Ketrolac. Eur. J.Pharm. and Biopharm., 2004, Xx: 1-6
21. Chauhan S. and Luorence M.J. The preparation of polyoxyethylene containing non-ionic surfactant. Vesicles. J. Pharm. Pharmacol. 1989; 41: 6p.
22. Ajay Solanki, Jolly Parikh and Rajesh Parikh. Preparation, Characterization, Optimization and stability studies of Aceclofenac Proniosomes Iranian J.Pharm Research, 2008;7*[4]*: 237-246.
23. C.HU, D.G. Rhodes, Int.J.Pharm., 1999, 185,23-35.
24. Effect of charged and Non-ionic Membrane Additives on Physicochemical Properties and Stability of Niosomes Varaporm Buraphacheep Junyaprasert, Veerawat Teeranachadeekul, and Tasaneeya Supaperml AAPS Pharm Sci Tech, 2008, 9, 3.
25. S.Tamizharasi, S.Biradar, V.Rathi, J.C.Rathi,Int.J.Chem.Tech.Res., 2009, 1 *[3]*, S17-S23.
26. R.H.Muller, M.Radtke, S.A. Wissing, Solid Lipid nanoparticles *[*SLN*]* and nanostructured lipid carriers *[*NLC*]* in cosmetic and dermatological preparations, Adv- Drug Deliv. Rev. 2002, 54 131-155
27. Puglia C, Trombetta D, Venuti V, Saija A, Bonina F, Evaluation of in vivo topical anti- inflammatory activity of indomethacin from leposomal vesicles

.J,Pharm,Pharmacol. 2004, 56: 1225-1232.

28. Vyas S.P., Khar R,K.,M Niosomes Targeted and Controlled Drug delivery, 249-279.