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Proniosomes: A Novel Nano Vesicular Transdermal Drug Delivery

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Abstract:
Drug delivery using nanotechnology is showing progressive changes by playing a vital role in developing new dosage forms. One of the technologies developed by using nano forms is vesicular drug delivery system. Such advancement in nano vesicular transdermal drug delivery is niosomes and proniosomes. Proniosomes are non-ionic surfactant coated dry forms, converted in to niosomes by hydration to yield an niosome dispersion having the capability of delivering drugs in a sustained manner for enhanced bioavailability and therapeutic effect. Proniosomes are superior to niosomes by displaying high physical and chemical stability, improved drug targeting with less production cost. This review gives relevant information regarding proniosomes and their preparation, characterization and their applications in transdermal route of drug delivery.

Keywords: Applications, Characterization, Drug delivery, Transdermal, Proniosomes, Vesicular delivery.

INTRODUCTION:

Delivery of drugs using colloidal particulate carriers and liquid crystalline compact niosomal hybrid such as niosomes[13, 30, 31] and proniosomes have distinctive advantages over conventional dosage forms[30, 31]. These vesicles are amphiphilic molecules having capability of entrapping both hydrophilic and hydrophobic drugs[4, 5, 12, 44]. Vesicular systems are lamellar structures comprised of amphiphilic molecules surrounded by an aqueous environment[1, 2, 3, 4]. Proniosmal drug delivery system[28, 29] is more advantageous by overcoming the drawbacks of liposomes[14] and liposomal drug delivery[22, 34, 35, 36, 37, 38] by using in various drug delivery systems[16, 19, 20] and having low formulation cost[25], long shelf life, better drug targeting at specified site in a sustained manner[17, 18, 21], permeation enhancement of drug[15] and minimizing physical stability problems such as fusion, leaking, aggregation and sedimentation on storage[4, 39] with additional advantages like its dry free flowing form, easy to transport, distribute, dosing, measuring and low toxic with more stability during storage and sterilization[23, 24, 26, 27]. All in turn favors in enhancing bioavailability and therapeutic efficacy[5,6,7,8,9,10,11]. The non-ionic surfactants are preferred in the proniosomes preparation than cationic, anionic and ampholytic surfactants because they have ability to enhance solubility which helps in increasing solubility and bioavailability of poorly water soluble drugs. For lab to large scale production no unacceptable solvents, precautions and conditions are required for formulation and preparation [32, 33].

Transdermal is a non-invasive mode of drug delivery route. It is an attractive route of drug administration to maintain drug levels in the blood for a sustained period of time locally and systemically. But, the effective barrier properties of the skin compared to other biological membranes making it a minor port for entry of drugs.

The versatile vesicular drug delivery through transdermal route[28, 47], proved to be beneficial due to the vesicles tendency to attach and adhere to the cell surface and leading to the increased permeation rate. However, the major pathways for drug permeation in the tissues is through sweat glands, stratum corneum layer[45, 46] and hair follicle associated with sebaceous glands.

Presently, very few studies are dealing with the proniosomes preparation and evaluation[40,41,42,43]. An attentive research is going on the utilization of proniosomes in the transdermal route of drug delivery. This article concisely reviews the trends and future perspective in the development of effective transdermal proniosomal drug delivery system.

TABLE 1: Different Materials Used For the Preparation Of Proniosomes.

S. No.	***Membrane stabilizers used***
1	Lecithin [29, 40, 43]
2	Cholesterol [39, 41]
	Coating materials investigated
1	Sucrose stearate [41]
2	Sorbitol [23, 29]
3	Lactose monohydrate [41]
4	Maltodextrin (Maltrin M500 and Maltrin M700) [27]
5	Glucose monohydrate [41]
	Non Ionic surfactants used
1	Polyoxyethelene 4 lauryl ether [1]
2	Polyoxyethylene cetyl ethers [1]
3	Span 20 [28, 43]
4	Span 40 [28, 40]
5	Span 60 [27, 28]
6	Span 80[28, 29]
7	Tween 20 [40, 43]
8	Tween 60 [40]
9	Tween 80 [40]

PREPARATION OF PRONIOSOMES:

1) SLURRY METHOD:

In a round-bottomed flask carrier powder and followed by surfactant solution is added to form slurry. If the surfactant solution added is less in volume, then to form slurry additional amount of organic solvent can be added. By using rotary vaccum evaporator the slurry in the flask made dry and free flowing. The flask was removed and kept overnight under vaccum. The proniosome powder formed is collected and sealed in containers and stored at 4°C[26, 27, 39, 48].

2) CO-ACERVATION PHASE SEPERATION METHOD:

In a glass vial of 5ml capacity, precisely weighed drug, surfactant and lipid are taken and followed by 0.5ml alcohol is added. The open end of the vial is closed with lid to prevent solvent loss and mixed well and warmed on water bath at 60-70°C, 5 minutes until all the ingredients are dissolved completely. Then the aqueous phase is added and warmed till a clear solution is formed and kept overnight to convert into proniosomal gel[28, 29].

3) SLOW-SPRAY COATING METHOD:

In this method surfactant in organic solvent is sprayed onto sorbitol powder and then solvent is evaporated. This process is repeated until the desired surfactant loading has been achieved. On hydration, the thin surfactant coating on the carrier dissolves and forms multilamellar vesicles[12, 49].

TABLE 2: The Components of Transdermal Systems

Components		Examples
Polymers	a) Natural polymer	Cellulose derivatives, gelatin, waxes, proteins, gums, starch, alginates, zein, shellac, natural rubber and chitosan etc.
	b) Synthetic elastomers	Polybutadiene, hydrene rubber, silicon rubber, polyisobutylene, nitrile, acrylonitrile, neoprene, butylrubber etc.
	c) Synthetic polymer	Poly vinyl alcohol, poly vinyl chloride, polyamides, polyuria, poly methyl methacrylate, polyethylene, polypropylene, polyacrylate, polyvinyl pyrrolidone etc.
	d) Others	Polyethylene glycol [50], eudragits[51], ethyl cellulose, poly vinyl pyrrolidone[52], hydroxyl propyl methyl cellulose[53], EVA[54], silicone rubber, polyurethane[55].
Plasticizers		Butyl benzyl phthalate, Trioctyl phosphate, Dioctyl phthlate (used in ALZA ocusert), Glycerol (Used in Nitro Dur), Polyethylene glycol, Poly propylene glycol etc.
Penetration enhancers	a) Solvents	E.g.: 1 water alcohols – Methanol, Ethanol. E.g.: 2 Alkyl methyl sulfoxides – Dimethyl sulfoxide E.g.: 3 pyrrolidones – 2 pyrrolidone, N methyl 2 pyrrolidone, N alkyl – 2 pyrrolidone.
	b) Miscellaneous Solvents	Propylene glycol, glycerol, silicone fluids, isopropyl palmitate etc.
	c) Surfactants	SLS, Dioctyl sulphosuccinate, tween (20, 40, 60, 80) polysorbates etc.
	d) Miscellaneous	Urea, terpenes, cineole etc.
	e) Essential oils	Cardamom oil, Caraway oil, Lemon oil, Menthol, d-limonene, Linoleic acid etc.
Adhesives		Polyacrylates, polyisobutylene and silicon based adhesives[39] etc.
Backing membrane		Metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate (alluminium foil) adhesive foam pad (flexible polyurethane) with occlusive base plate(alluminium foil disc) etc. vinyl, polyethylene and polyester films etc.
Peeling strip		Commonly the peel strips are made up of Alluminium foil, Polyester, Mylar etc.
Packaging.		Heat sealed foil pouches etc.

TABLE 3- Methods to Characterize Proniosomes

Parameters	Instruments / techniques
Size distribution and vesicle size determination	Malvern Mastersizer [41] Laser diffraction particle size analyzer [23, 39] Coulter submicron size analyzer [40]
Morphological characterization of surface and shape.	Scanning electron microscopy [43] Transmission electron microscopy [41]
Aerodynamic behavior	Twin-Stage Impinger [41]
Entrapment efficiency	Dialysis method [41] Vesicle lysis using alcohol and propylene glycol [4]
Permeation and penetration Studies	Franz diffusion cells [40] Cellophane dialyzing membrane [43] USP dissolution apparatus-I [29] *In-vitro* skin permeation studies [28, 40]

TRANSDERMAL CONTROLLED RELEASE DRUG ADMINISTRATION DEVICES:

The successfully launched commercially available transdermal drug delivery systems may be classified in to four types, depending on the technological approach.

1) Membrane permeation controlled transdermal therapeutic device :
The drug reservoir in this device is totally encapsulated in a compartment moulded from a metallic plastic laminate and a rate controlling polymeric membrane making a drug impermeable layer.

2) Adhesive dispersion type transdermal device :
In this device, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer, and spreading the medicated adhesive on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. Thin non-medicated rate controlling adhesive polymer of constant thickness was applied to produce an adhesive diffusion controlled drug delivery system.

3) Matrix diffusion controlled transdermal system :
Drug solid is homogeneously dispersed in a hydrophilic or lipophilic polymer matrix to form a drug reservoir and it is fabricated in to medicated disc with defined surface area and controlled thickness. The drug reservoir containing the polymer disc is attached to an occlusive base plate to form matrix diffusion transdermal device.

4) Micro reservoir dissolution controlled transdermal system :
This type of device can be considered as a combination of the both matrix and reservoir type drug delivery systems. By using high shear mechanical force, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of a water soluble polymer to form micro reservoir controlled device.

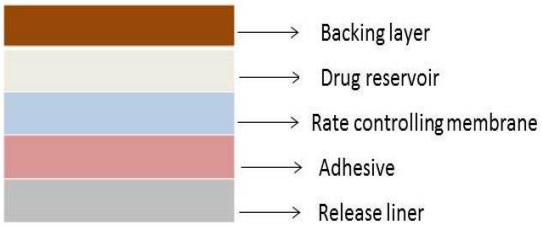

FIG. 1: Reservoir type transdermal patch

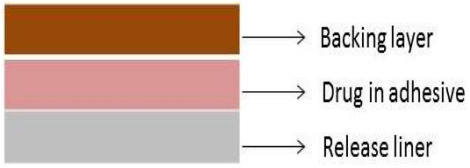

FIG. 2: Drug in adhesive type transdermal patch

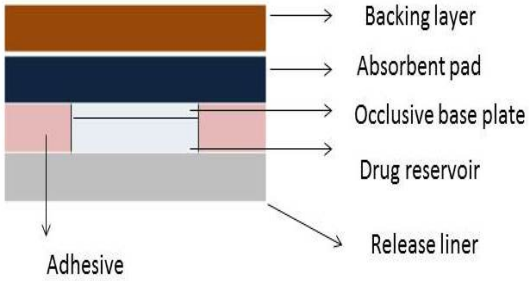

FIG.3: Matrix type transdermal patch

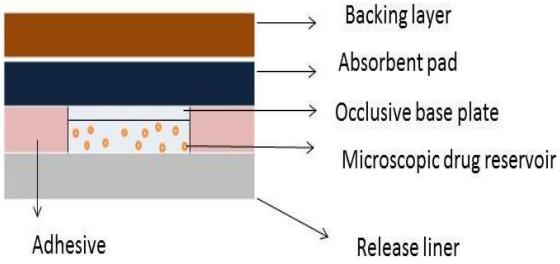

FIG. 4: Micro reservoir type transdermal patch

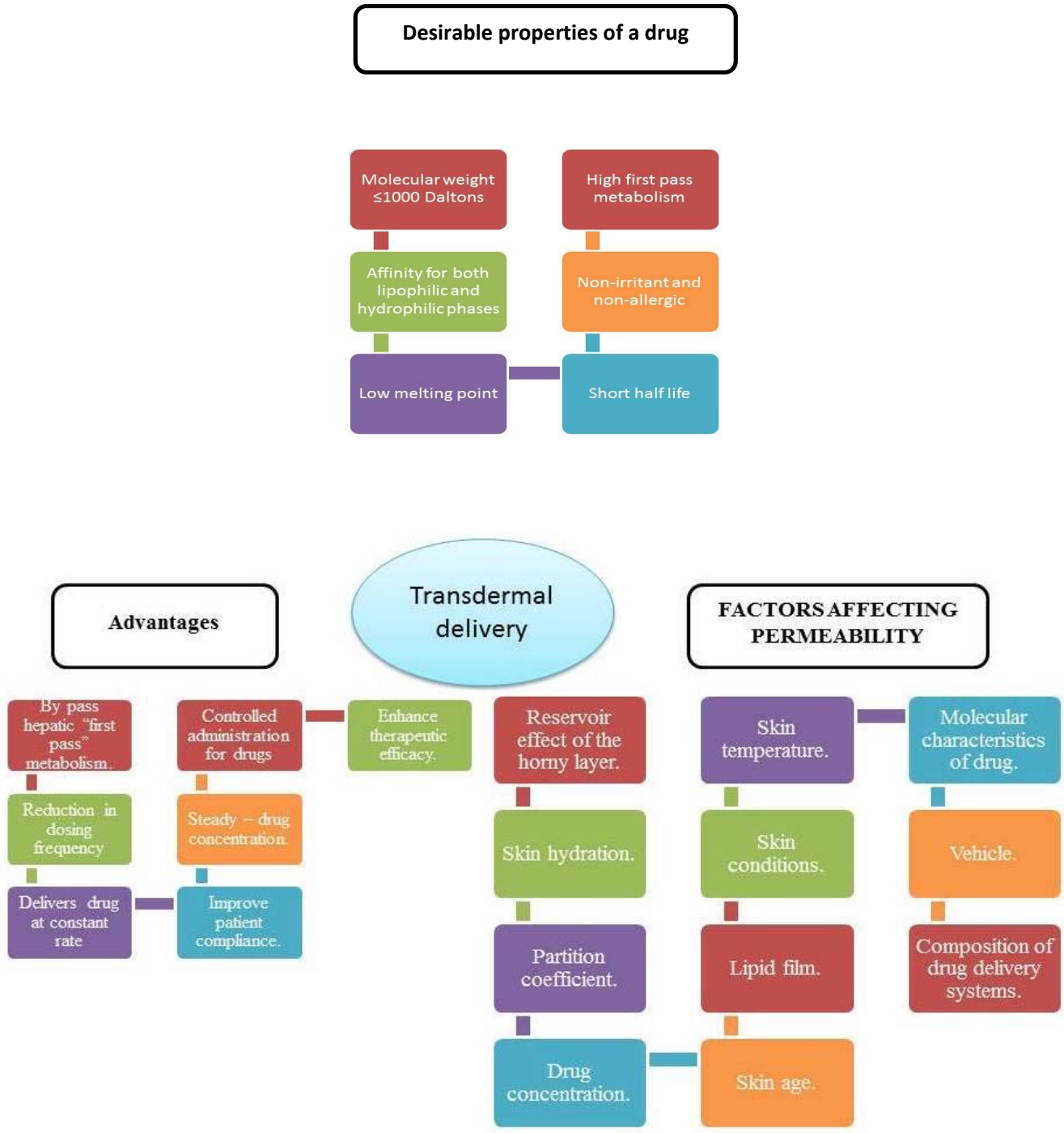

FIG. 5: Desirable properties, advantages and factors affecting the Transdermal drug delivery.

ROLE OF PRONIOSOMES IN DRUG TARGETING THROUGH TRANSDERMAL DELIVERY:

The major barrier to transdermal delivery of drugs is stratum corneum. Vesicular delivery via skin is beneficial in that drugs, which permeate via skin and reaches systemic circulation. For transdermal delivery, proniosomes are the best vesicular system because they act as a drug reservoir for a prolonged period of time and increases skin permeation. The formulation of drugs into proniosomes also helps in better physical and chemical stability of the drug and the vesicular nature of the delivery system helps the drug to permeate through skin with an ease and helps in reaching systemic circulation and the target site without losing any drug activity and providing better therapeutic efficacy.

TABLE 4: Applications

Drug	Pro-vesicular type/Application	Therapeutic category
Levonorgestrel [28]	Proniosomes (gel, patch)	Contraceptive agent
Flurbiprofen [57]	Proniosomes (gel, patch)	NSAID
Captopril [29]	Proniosomes (gel, patch)	Antihypertensive
Estradiol [40]	Proniosomes (gel, patch)	Female harmone
Ketorolac [43]	Proniosomes (gel, patch)	NSAID
Frusemide [42]	Proniosomes (gel, patch)	Diuretic
Losartan potassium [58]	Proniosomes (gel, patch)	Antihypertensive
Chlorpheniramine maleate [59]	Proniosomes (gel, patch)	Anti-histamine
Pseudo-ceramide [60]	Liquid crystal (topical)	Anti-wrinkle
Benzophenone4/octyl methoxycinnamate [61]	Liquid crystal (percutaneous)	Sunscreen agent
Vitamin A [62]	Liquid crystal (topical, patch)	Antioxidant
Cosmetic composition [45]	Liquid crystal (topical)	Skin cleansing agent
Tenoxicam [63]	Proniosomes (gel)	NSAID
Piroxicam [39]	Proniosomes (gel, patch)	NSAID
Vinpocetine [64]	Proniosomes (gel)	Cerebro-vascular and cerebral degenerative diseases
Timolol maleate [65]	Niosomes (topically)	Anti-glaucoma

CONCLUSIONS:

Non-ionic surfactant vesicular systems are a novel and efficient approach to drug delivery. Their membrane is mainly composed of non-ionic surfactants, cholesterol and the enclosed interior usually contains a buffer solution at appropriate pH. These formulations are becoming a useful dosage forms for various delivery systems. Niosomes are prepared by various methods and they depends on drug properties, cholesterol amount and surfactant type. They do not require respective special conditions for specific routes of administration. Overall, proniosomes are effective tool for drug targeting and have the potential to provide better treatment than conventional drug delivery system.

REFERENCES:

1) Gannu PK, Rajeshwarrao P., *Acta Pharmacol Sin*. 2011, 1(4), 208-219.
2) Negi LM, Garg AK, Chauhan M., *Pharm Times.* 2009, 41, 11-4.
3) Sankar V, Ruckmani K, Jailan S, Ganesan KS, Sharavanan S., *Pharmacol Online.* 2009, 2, 926-32.
4) Uchegbu IF, Vyas SP., *Int J Pharm*. 1998, 172, 33-70.
5) Uchegbu IF, Florence AT., *Adv Colloid Interface Sci*. 1995, 58, 1–55.
6) Bouwstra JA, Van HD, Hofland HE., *Colloids Surf A Physicochem Eng Asp*. 1997, 80, 123-4.
7) Rangasamy M, Ayyasamy B, Raju S, Develly SG, Shaik S., *J Pharm Res.* 2008, 1, 163-6.
8) Bhaskaran S, Lakshmi PK., *Acta Pharm Sci*. 2009, 51, 27-32.
9) Wadhe K, Kalsait R, Umekar M., *Arch Pharm Sci Res*. 2009, 1, 97–105.
10) Bajaj A, Desai M., *Pharm Times.* 2006, 38, 12-6.
11) Sankar V, Ruckmani K, Durga S, Jailani S., *Pak J Pharm Sci*. 2010, 23, 103-7.
12) Yoshioka, T., Sternberg, B., Florence, A.T., *Int. J. Pharm*. 1994, 105, 1–6.
13) Shahiwala A, Misra A., *J. Pharm. Pharm. Sci*. 2002, 5, 220-225.
14) Mishra D, Garg M, Dubey V, Jain S, Jain NK., *J. Pharm. Sci*. 2007, 96, 145-155.
15) Verma DD, Verma S, Blume G, Fahr A., *Eur. J. Pharm. Biopharm.* 2003, 55, 271-277.
16) Puglia C, Trombetta D, Venuti V, Saija A, Bonina F., *J. Pharm. Pharmacol*. 2004, 56, 1225-1232.
17) Gupta PN, Mishra V, Singh P, Rawat A, Dubey P, Mahor S, Vyas SP., *J. Pharm. Pharmacol*. 2005, 57, 295-301.
18) Barber R, Shek P., *In: Pharmaceutical Particulate Carriers* (Rolland, A., Ed.), Marcel Dekker, New York 1993, pp. 1–20.
19) B.W. Barry., *Eur. J. Pharm. Sci*. 2001, 14, 101–114.
20) S. Kim., *Drugs*. 1993, 46, 618–638.
21) D. Booser, G. Hortobagyi., *Drugs.*1994, 47, 223–258.
22) R.H. Muller, M. Radtke, S.A. Wissing., *Adv. Drug Deliv. Rev*. 2002, 54, 131–155.
23) Hu, C.J., Rhodes, D.G., *Int. J. Pharm.* 1999, 185, 23–35.
24) Verma S, Singh SK, Syan N, Mathur P, Valecha V., *J. Chem. Pharm. Res.* 2010, 2(2), 496-509.
25) Namdeo, A., Jain, N.K., *J. Microencapsul*. 1999, 16(6), 731 – 740.
26) Blazek-Welsh AI and Rhodes D., *AAPS Pharmacist*. 2001a, 3, 1-8.
27) Blazek-Welsh AI and Rhodes DG., *Pharm. Res.* 2001b, 8, 656-661.
28) Vora B, Khopade AJ and Jain NK., *J. Control. Rel*. 1998, 54, 149-165.
29) Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D., *Tropical J. Pharm Res.* 2007, 6(2), 687-693.
30) Schreier H and Bouwstra J., *J. Control Rel.* 1994, 30, 1-15.
31) Baillie AJ, Florence AT, Hume LR, Muirhead GT and Rogerson A., *J. Pharm. Pharmacol*. 1985, 37, 863-868.
32) Carafa M, Santucci E and Lucania G., *Int. J. Pharm*. 2002, 231, 21- 32.
33) Alsarra IA, Bosela AA, Ahmed SM and Mahrous GM., *Eur. J. Pharm. Biopharm*. 2005, 59, 485-490.
34) Hunt C and Tsang S., *Int. J. Pharm.* 1981. 8, 101-110.
35) Wong M and Thompson T., *Biochemistry*. 1982, 21, 4133-4139.
36) Niven RW, Carvajal MA and Schreier H., *Pharm. Res.* 1992, 9, 515-520.
37) Gregoriadis G., *Liposome Technology*, Vol.2. CRC Press Inc., Boca Raton, FL, 1984, pp.145.
38) Frfkjaer S, Hjorth E and Wfrtis O., Stability testing of liposomes during storage. In: Gregoriadis G editor. *Liposome Technology*, Vol.2. CRC Press Inc., Boca Raton, FL, 1984, pp.127.

39) Solanki, A.B., Parikh, JR., Parikh, R.H., *AAPS Pharm. Sci. Tech*. 2007,8(4), E1-E7.
40) Fang JY, Yu SY, Wu PC, Huang YB and Tsai YH., *Int. J. Pharm*. 2001, 215, 91-99.
41) Abd-Elbary A, El-laithy MI and Tadros HM., *Int. J. Pharm*. 2008, 357, 189-198.
42) Adnan Azeem, Nilu Jain, Zeenat Iqbal, Farhan Jalees Ahmad, Mohammad Aqil and Sushama Talegaonkar., *Pharm. Dev. Tech*. 2008, 13(2), 155-163.
43) Alsarra IA, Bosela AA, Ahmed SM and Mahrous GM., *Eur. J. Pharm. Biopharm*. 2005, 59, 485-490.
44) Niemiec, S.M., Ramachandran, C., Weiner, N., *Pharm. Res.* 1995, 12, 1184–1188.
45) Mitsuno, Y., Nomaguchi, K., Suzuki, T., US 4767625 issued Aug 1988.
46) Ciotti SN, Weiner N., *J. Liposomes Res.* 2002, 12, 143-148.
47) Huang, B.Y., Jung, B.H., Chung, S.J., Lee, M.H., Shim, C.K., *J. Contr. Release.* 1997, 49, 177–184.
48) Perrett, S., Golding, M., Williams, W.P., *J. Pharm. Pharmacol.* 1991, 43(3), 154-161.
49) Bangham, A.D., Standish, M.M., Watkins, J.C., *J. Mol. Biol.* 1965, 13, 238-252.
50) Bromberg L., *J Apply Poly Sci.* 1996, 59, 459-466.
51) Verma PRP, Iyer SS., *Drug Dev Ind Pharm.* 2000, 26, 471-476.
52. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK., *AAPS PharmSciTech*. 2007, 8(1), Article 2.
53. Gannu R, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y., *Current Drug Delivery*. 2007, 4, 69-76.
54. Gale R, Spitze LA., *Controlled Release Society*. 1981, 183.
55. Boretos JW, Detmer DE , Donachy JH., *J Biomed Mat Res.* 1971, 5, 373.
56. Franz TJ. *Transdermal Delivery*. In: Kydonieus A, ed. *Treatise on controlled drug delivery: Fundamentals, optimization, applications*. Marcel Dekker Inc. New York 1991, 341-421.
57. Mokhtar M, Sammour OA, Hammad MA, Megrab NA., *Int J Pharm*. 2008, 361(1-2), 104-11.
58. Thakur R, Anwer Mk, Shams MS, Ali A, Khar RK, Shakeel F, Taha EI., *J Drug Target*. 2009, 17, 442-449.
59. Varshosa J, Pardhakhty A, Mohsen S, Baharanchi H., *Int. J Pharm*. 2005, 12, 75-82.
60. Iwai H, Fukasava J, Suzuki T.A., *Int J Cosmet Sci*. 1998, 20(2), 87-102.
61. Brinon L, Geiger S, Alard V, Doucet J, Tranchant JF, Courazze G., *J Control release*. 1999, 60, 67-76.
62. Cioca G, James HA, Manuel LT, Herstein M, Walter P., US4999348 issued 1991-3-12.
63. Ammara HO, Ghorabb M, El-Nahhasc SA, Higazya IM., *Int J Pharm*. 2011, 405(1-2), 142-52.
64. El-Laithy HM, Shoukry O, Mahran LG., *Eur J Pharm Biopharm*., 2011, 77(1), 43-55.
65. Vladimir P Torchilin., *Nanoparticulates as Drug carriers; vesicles prepared by synthetic amphiphiles-polymeric vesicles and niosomes*, Imperial college press, London 2006, pp.95-117.