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PRONIOSOME AN ADVANCED DRUG DELIVERY SYSTEM

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ABSTRACT

A method is presented for creating a dry product that may be hydrated right before use to make aqueous niosome dispersions that are comparable to those made by more laborious traditional procedures. These "proniosomes" increase ease in transportation, distribution, storage, and dosage while reducing issues with niosome physical stability such as aggregation, fusion, and leakage. This paper outlines the planning for niosomes generated from proniosomes are dispersed, compared to standard niosomes, and proniosome formulations are improved. Additionally, the differences between traditional and proniosome-derived niosomes are assessed in synthetic gastric or intestinal fluids, of their shape, molecular weight, particle size distribution, and drug release efficacy digestive fluid Proniosome-derived niosomes are on par with or superior than traditional niosomes in all comparisons**.**

KEYWORDS: Niosomes, Proniosomes, Drug release, Lipophilic, Hydrophilic Nanoparticles, Lipid -polymer hybrid nanoparticles.

INTRODUCTION

In the modern day, no single delivery technique can satisfy all the criterion, however a fresh approach has been taken approaches. Numerous fresh methods for covering numerous administrative methods to reach their targeted or controlled drug delivery. The main goal of Novel medication delivery methods help to keep dosages stable andlowering the effective medicatio amount in the system and adverse consequences. focuses the drug's impact locally by addressing drug carriers are used for drug delivery. Vesicular systems have attracted a lot of attention. as a vehicle for cutting-edge medication delivery. Encapsulation medication increases the time of effect and decreases toxicity. Niosomes and colloidal liposomes have benefits over traditional dosing forms. That is particles serve as drug storage and transport both in the system.[1]

In medication delivery systems, colloidal particle carriers like liposomes or niosomes are frequently used. Proniosomes today are made from niosomes and have significant benefits over them. By changing the composition of these carriers, the rate of medication release may be regulated. These carriers can also serve as drug reservoirs. Both hydrophilic and hydrophobic medications are encapsulated in the lipid vesicles (in lipid domain).[2]

These lipid vesicles are widely employed in several drug delivery systems such drug targeting, controlled release, and permeation enhancing of pharmaceuticals due to their capacity to transport a range of medications. However, if they are processed in dry form, several disadvantages can be addressed and avoided.

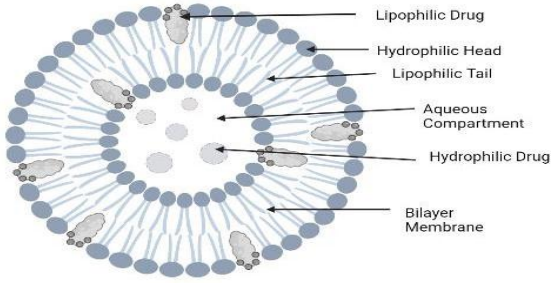

Fig : Structure of Proniosome

Figure 1: Structure of proniosome.

Proniosomes as drug carriers

Proniosomes are attractive drug delivery systems because they are more chemically stable and lack many of the drawbacks of liposomes. Proniosomes are surfactant-coated carrier vesicles that are prepared as dry formulations that may be rehydrated as needed. The resultant niosomes are remarkably comparable to traditional niosomes andare identical in size.

Proniosomes decrease stability issues during storage and sterilising since they are a dry, freely flowing substance. Proniosomes are a flexible delivery strategy since they also have the advantages of being simple to transport, distribute, measure, and store.[3]

Advantages of proniosomes

- Keeping the issue of physical instability, such as aggregation, fusion, and leakage.
- Limiting medication hydration prevents the dispersion from having a long shelf life.
- Proniosomes are surfactant-coated water-soluble carrier particles that may be hydrated right before usage to createniosomal dispersion by short agitation with hot aqueous solution. It has made distribution, storage, and transportation more convenient. Designing would be a suitable industrial product for dry niosomes.
- Proniosomal compositions should also avoid undesirable solvents. The systems don't need to be dispersed into the polymeric matrix; instead, they may be directly formed into transdermal patches.
- Proniosomes are a flexible delivery technology with the ability to work with a variety of active substances thanksto the storage.

Disadvantages of proniosomes

Proniosome disadvantages include their physical instability

- Aggregation.
- Fusion.
- Leaking of the entrapped drug.
- Sedimentation.[4]

Types of proniosomes

Dry granular proniosomes

- **Sorbitol based proniosomes**

They are a dry formulation made of sorbitol as a carriers and a non-ionic surfactant that is applied using waterand simple agitation.

- **Maltodextrin based proniosomes**

The rapid slurry approach was used to create maltodextrin-based proniosomes.

Liquid crystalline proniosomes

This form of proniosome serves as a reservoir for medication administration via transdermal distribution. A backing layer and a plastic sheet are included in the transdermal patch. The gel is equally distributed on the sheet.

Components of proniosomes

1) Surfactants

The surfactants were chosen based on their HLB. value. Because hydrophilic lipophilic balance (HLB) is an excellent indicator HLB is an indication of a surfactant's capacity to generate vesicles. A number about 4 and 8 was discovered to be consistent with creation of vesicles It has also been stated that hydrophilic Because of their high water solubility upon hydration, surfactants not achieve a condition of concentrated systems to allow aggregated and consolidated to create free hydrated units The structure is lamellar. Polysorbate, a water-soluble detergent In the presence of cholesterol, 20 produces niosomes. This is irrespective of the fact that the HLB number of this chemical is 16.7, and the HLB of a surfactant influences the degree of entrapment. The temperature of surfactants influences drug entrapment in vesicles. Spans with the highest phase transition temperature have the greatest drug entrapment, and vice versa. Span 40 and Span 60 generate bigger vesicles with more drug entrapment. Because of the high phase transition temperature and limited permeability, medication leakage fromthe vesicles is decreased. Higher HLB values of Span 40 and Span 60 result in a reduction in surface free energy, allowing the formation of bigger vesicles and hence a wider area exposed to the dissolving liquid and skin.

2) Stabilizers

Incorporation improves vesicle stability and permeability. The concentration of cholesterol has an essential effectin drug trapping in vesicles. There are allegations that As cholesterol levels rise, so does trapping efficiency. content as well as the use of Span 60, which has a greater Temperature of transition It has been shown that extremely high The presence of cholesterol has a negative influence on drug entrapment. with relation to the vesicles This might be because to cholesterol. Above a certain level, the normal bi-layered structure begins to be disrupted. structure, resulting in drug entrapment failure.

3) Carriers maltodextrin

The application of maltodextrin as a carrier in the manufacture of proniosomes allowed for increased flexibility in the proportion of surfactants and other components that might be added. Sorbitol coating resulting in a cake- like bulk. [5]

Methods of preparation of proniosomes

1. Slurry method[6,7]

Proniosomes were made by adding the carrier and the whole surfactant solution to a round-bottomed flask attached to a rotating flash evaporator while under vacuum used to create a dry, free-flowing powder. Lastly, the formulation should be kept in a firmly sealed container in light refrigeration. The need for the generation of proniosomes is independent of the

surfactant solution to carrier material ratio It seems to be in good condition. The generated proniosomal powder is collected and containers sealed and kept at 4°C Proniosomes produced utilising the established slurry procedure as a carrier, maltodextrin is used. Per gramme of maltodextrin and medication, the needed volume of surfactants and lipid stock solution must be dissolve in the in a 100 mL spherical bottom flask holding the solvent carrier (maltodextrin). More chloroform can be added. In the case of alesser surfactant, added to generate a slurry loading. The flask must be connected to a rotating flash 50- 60 rpm evaporator to evaporator solvent at a 45-2°C temperature and a decreased pressure of 600 mm Hg till the quantity in the flask reached container in light refrigeration.

Advantages of slurry method
Maltodextrin is highly water soluble and was employed as a carrier system in the composition; they were easily encapsulated by simply putting surfactant to dried Maltodextrin in an organic solvent.

It prevents the active component and surfactant from oxidation and hydrolysis due to the homogeneous coating.

The greater surface area leads in a thinner surfactant layer, which speeds up the rehydration process.

Disadvantages of slurry method
The procedure is time-consuming and requires specialist vacuum and nitrogen gas apparatus.

The thin-film method only allows for preset batch sizes. As a result, material is frequently squandered, and tiny batch sizes and doses can be time-consuming.

2. Coacervation phase separation method
This approach may be used to create pheniosomal gels by combining a surfactant, lipid, and medication in a widemouthed glass vial with a tiny quantity of alcohol. The mixture is placed in a heated up water bath at 60-70°C for 5 minutes, or until the surfactants mixture is entirely dissolved. The small aqueous phase is then added to the aforesaid vial and warmed until a clear solution forms, which is subsequently turned into proniosomal gel upon cooling. Proniosomes were transformed to equally sized niosomes after being hydrated.

Advantages of coacervation phase separation method
The procedure is simple and time-consuming, therefore no specialist equipment is required. On a lab scale, small dosage formulations can be generated.

Specifically designed for gel preparation

3. spray coating method[8,11]
The surfactant is mixed with a solvent system and spray onto the carrier in this approach. The solvent is then evaporated. Because of carriers is soluble in the organic liquid, this process is repeated until the necessary surfactant loading is reached. Hydration of this coating permits the creation of a micellar vesicle when the carrier dissolves. These niosomes have a consistent size distribution and are comparable to those manufactured using traditional procedures. A rotating flash evaporator may be connected to a 100 ml round bottom flask carrying thenecessary amount of carrier. A surfactant and cholesterol combination should be created and sequentially sprayed over the carrier's surface in a round bottom flask on a rotary evaporator. The evaporator must be purged before the rotating flask may be spun in a water bath under vacuum for 15-20 minutes at 65-70 o C. This procedure must be carried out until all the surfactant solutions have been administered. The evaporation process should be repeated until the powder is totally dry.

Advantage of the slow spray coating method:
It is a straightforward approach ideal for hydrophobic drugs with no worries about the stability or hydrolysis susceptibility of the active medicinal component.

Disadvantages of slow spray coating method:
The procedure is time-consuming and requires specialist vacuum and nitrogen gas apparatus.

The thin-film method only allows for preset batch sizes. As a result, material is frequently squandered in minute quantities; a modest dosage batch might be time-consuming.

Mechanism of action[12,14]
The precise method of drug penetration into vesicle through the skin has not yet been discovered; penetration will be influenced by the nature and kind of drug employed, the formation of vesicles, and the temperature at which proniosomes are converted to niosomes. The lipids that are employed to make proniosomes serve as a carrier thatwill establish a deposit at the site of action and so maintain the action. The lipid (ceramides) portion of the stratumcorneum, which is packed densely as a bilayer by hydrogen bonding, is the rate-limiting stage in the penetration of the drug through transdermal drug delivery. The lipid bilayer will be strengthened and stabilized by the hydrogen bonding, which will subsequently impart the stratum corneum's barrier property. When applied to the skin, proniosomes will hydrate into niosomes. This raises the gradient of concentration, which raises the pressurerequired for drug diffusion through the stratum corneum.

Factors affecting the formulation proniosomes[15]
The proniosomes' properties are influenced by a number of processing and formulation factors. They include the length of the surfactant chain, the amount of cholesterol, the amount of total lipids, the charge of lipids, the pH of the dispersion medium, and the type of alcohol employed in the preparation.

1) Surfactant chain length

Proniosomes are frequently prepared using spans. Spans have a distinct alkyl chain but the same head group. A longer alkyl chain length results in greater entrapment effectiveness. The efficiency of entrapment moves in the following order: Span 60 (C18)>Span 40 (C16)>Span 20 (C12)>Span 80. (C18). The head groups in Span 60 and Span 80 are the identical, however Span 80 has an unsaturated alkyl chain. The increased permeability of liposomes is caused by the inclusion of double bonds into the paraffin chains, which may help to explain why the Span 80 formulation has a reduced entrapment efficiency.

2) Cholesterol content

Cholesterol either boosts or reduces the percentage entrapment efficiency depending on the surfactant type or concentration in the recipe.

3) pH of the hydration medium

The pH of the hydrating medium was shown to have a significant impact on the percentages entrapment efficiency of niosomes generated by hydrating of proniosomal gels of Span 60/cholesterol (9:1). For example, when the pH declined from 8 to 5.5, the proportion of flurbiprofen encapsulated rose by nearly 1.5 times.

The inclusion of an ignitable carboxylic group in flurbiprofen's chemical structure may account for the rise in percentage encapsulation efficiency caused by reducing the pH. Lowering the pH may increase the quantities of unionised flurbiprofen, which has a greater partitioning to the bilayer lipid phase than ionised flurbiprofen.

4) Total lipid concentration

Flurbiprofen's % encapsulation efficiency improved when the lipid content climbed between 25 to 200 mol/ml, respectively.

Flurbiprofen's % encapsulation efficiency increased linearly as total lipid content increased. On the other hand, raising the lipid content from 25 to 200mol/ml reduced the quantity of flurbiprofen entrapped. As a result, the proportion of lipid involved in encapsulation reduces as lipid concentration increases.

5) Drug concentration

Flurbiprofen concentrations in proniosomes made from Span 60/cholesterol (9:1) increased both % entrapment efficiency and the amounts of medication enclosed per mol total lipids after hydration and production of niosomes.

6) Charge of the lipids

The incorporation of either diacetyl phosphate (DCP) or stearylamine (SA), which causes negative charge, reduced the percentage encapsulation efficiency of flurbiprofen into niosomal vesicles.

Characterization of proniosomes

1. Vesicle morphology

Vesicle morphology is the study of the size and form of proniosomal vesicles. The size of proniosomal vesicles may be determined using the dynamic light scattering technique in two ways: without and with agitation. The greatest vesicle size arises from hydration without agitation. Scanning electron microscopy (SEM) may also be used to determine the size and form of vesicles. The size of vesicles must be determined before they may be applied topically. The size of captopril vesicles was determined after dispersion agitation since the energy used in agitated result in the breaking of larger vesicles to tiny vesicles. Captopril vesicles were determined to be 11.38-25.06 mm (without agitation) and 4.14-8.36 mm (with agitation) (with agitation). As a result, increasing the lipophilicity of the surfactant monomer results in a smaller vesicles, since surface energy reduces as hydrophobic nature increases.[16]

Lower HLB haloperidol proniosomes seemed to be predominantly spherical and distinct, with crisp borders andsmooth and solid surfaces. The fluidity of the bilayers of the deformable vesicles was discovered to be the primary distinction between deformable and rigid vesicles.

2) Shape and surface morphology:

Surface morphology refers to the roundness, smoothness, and aggregation development of a surface. SEM, optical microscopy, and transmission electron microscopy were used to investigate it (TEM).[17]

3) Scanning electron microscopy[18]

Proniosome surface shape and size distribution were dispersed onto double-sided tape that was adhered to aluminium stubs. The aluminium stub was put in the vacuum chamber of a scanning electron microscopy (PhilipsXL 30 ESEM with EDAX). A gaseous secondary electron detector (working pressure: 0.8 tor, accelerating voltage: 30.00 KV) XL 30 was used to view the samples for morphological evaluation (Philips, Netherlands)

4) Optical microscopy[19]

After appropriate dilution, the Niosomes were placed on glass slides and observed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) at a magnification of 1200X for morphology inspection. The photomicrograph of the preparations was also taken with a digital SLR camera from the microscope.

5) Angle of repose[15,19,21]

A funnel technique was used to determine the angle of repose of dried proniosomes powder. The Proniosomes powder was put into a funnel that was set up such that the funnel's 13mm exit orifice was 5cm above a flat black surface. The powder falls from the funnels to form a cones on the surface, and the angle of repose is computed by measuring the cone's height and the diameter of its base.

6) Encapsulation efficiency

The encapsulation efficiency of proniosomes is measured when the unentrapped medication is separated.

Separation of unentrapped drug is done by the following techniques[22]

Dialysis:

At room temperature, the aqueous niosomal dispersion is dialyzed against a suitable dissolving media, after which samples are taken out of the medium at appropriate intervals, centrifuged, and their drug concentration is examined using UV spectroscopy.

Gel filtration:

By gel permeation chromatography of niosomal dispersion over a sephadex G50 column, the free drug is extracted. It is then separated with the appropriate mobile phase and examined using analytical methods.

Centrifugation:

The surfactant is separated after centrifuging the niosomal solution. To create a niosomal suspension devoid of unentrapped medication, the pellet is first cleaned and then re-suspended.

Determination of entrapment efficiency of proniosomes:

The unentrapped medication was separated from the niosomal solution using a thorough dialysis procedure and centrifugation process. The niosomal solution was placed in a dialysis tube and secured with an osmotic cellulose membrane on one side. The dialysis tube was then put in 100 ml of saline buffer with a specific pH and swirled on a magnetic stirrer. Through the use of an osmotic cellulose membrane, the unentrapped medication and niosomal solution were separated and added to the medium. After 6 hours of laborious dialysis, optical density measurements were recorded, and a UV spectrophotometric approach was used to estimate the amount of medication entrapped. [23]

Methods for the characterization of proniosomes[24]

Parameter used for characterization of proniosomes mentioned in Table

Parameter	Instrument / Method Used
Optical microscopy	Haemocytometer
Vesicle morphology	Dynamic light scattering method
Penetration and permeation studies	CLSM [confocal laser scanning microscopy]
Morphology	TEM [transmission electron microscopy]
Drug Release	Franz diffusion cell
Angle of repose	Funnel Method

Application of proniosomes

1) Proniosome in gene delivery[25,28]

As a substitute to viral gene delivery techniques, certain non-viral vectors have been discovered. Proniosomes are non-viral vectors that have showed promise as gene delivery methods because they are inexpensive, simple to make, stable, cheap to produce, and less time-consuming than other non-viral vectors. harmful owing to non- ionic surfactant presence.

2) Applications in cardiology

Captopril is delivered transdermally to treat hypertension using prososomes as the carrier. The research demonstrates that the proniosomal mechanism results in prolonged release in the body of the medicine. To encapsulate the medication, sorbitan esters, cholesterol, and lecithin are used.[29]

3) Application in diabetes

Span, soy, lecithin, diacetyl phosphate, and cholesterol were employed in the skin permeation process of furesamide proniosomes. Overall results point to proniosomes as a non-invasive method of furesamide administration. [30]

4) Cosmetic formulation

Medicinal substances that can be included into proniosomal carrier systems (such as cleansers, moisturisers, and sunscreens) nutritive, anti-wrinkle, and anti-aging components, among others.[31]

5) Delivery of peptide drugs

The difficulty of avoiding the enzymes that would break down oral peptide medication delivery has long existed the polypeptide. Using niosomes to effectively a defence against gastrointestinal peptides for the peptides investigation into breakdown.[13]

CONCLUSION

Proniosomes are a cutting-edge and fantastic medication delivery mechanism. For a topical, anti-infective, and anti-cancer method of administration, typically. Extensively The usage of proniosomal formulation dermatology is used to treat skin conditions including psoriasis, melanoma, and bacterial and fungal infections. Proniosomes are osmotically active and have the ability to improved medication stability and less adverse effects to other vesicular systems in comparison. PNIOSOMATIC GEL formulation is more comfortable and is mostly used in medication aiming for medication release that is steady and under control (hydrophilic as well as hydrophobic). as a result of the most efficient skin trapping and optimum skin penetration. They possess favourable physicochemical characteristics, however industrial handling, production, and storage Overall, A highly efficient vesicular drug delivery system is the proniosome system for a variety of medicines with therapeutic effects. Then they therapy that is adequate

than conventional drug delivery systems.

REFERENCES

1. Rao R, Kakar R, Anju G, Sanju N. Proniosomes: An Emerging Vesicular System in DrugDelivery and Cosmetics. Der Pharmacia Lettre, 2010; 2 (4): 227-239.
2. Almira I, Welesh AB, baill DG. Maltodextrin based proniosomes. AAPS PharmSciTech, 2001; 3: 1.
3. Alsarra IA, Bosela AA, Ahmed SM, Maheous GM. Proniosomes as a drug carrier for transdermal delivery of ketoralac. Eur J Pharm Biopharm, 2005; 59: 485-490.
4. Pandey N, Proniosomes and ethosomes: New prospect in transdermal and dermal drugdelivery system, IJPSR,2011; 2(8): 1988-1996.
5. Arunotharyanun P, Bernard MS, Craig DQH, Uchegbu TF, Florenace AT. The effect of processing ariables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. Int J Pharm, 2000; 201: 7.
6. Walve JR, Rane BR, Gujrathi NA, Bakaliwal SR, Pawar SP. Proniosomes: A SurrogatedCarrier for Improved Transdermal Drug Delivery System, IJRAP, 2011; 2 (3): 743 - 750.
7. Akhilesh D, Faishal G, Kamath JV. Comparative Study of Carriers used in Proniosomes, International Journal of Pharm Chem Science, 2012; 1(1): 164-173.
8. Bangham AD, Standish MM and Watkins JC, J. Mol. Biol, 1965; 13: 238-252.
9. T. Yoshioka, B. Sternberg and AT. Florence, Int. J. Pharm, 1994; 105: 1-6.
10. Jain NK, Controlled and novel drug delivery system, CBS publishers anddistributors, NewDelhi, 2003; 1: 270.
11. Khandare JN, Madhavi G, Tamhankar BM, Niosomal novel drug delivery system.
12. Chandraprakash K.S., Udupa N., Umadevi P. and Pillai G.K. Pharmacokinetic evaluationof surfactant vesicles containing methotrexate in tumor bearing mice. Int. J. Pharma, 1990; R1- R3: 61.
13. Muller RH, Radtke M, Wissing SA, Solid lipid nanoparticles (SLN) and nanostructuredlipid carriers (NLC) in cosmetic and dermatological preparations, Adv. Drug Deliv. Rev, 2002; 54: 131–155.
14. Vyas S.P., Khar R,K., Niosomes Targeted and Controlled Drug delivery, 249 – 279
15. Hu C. and Rhodes D.G. Proniosomes: a novel drug carrier preparation. Int. J. Pharm, 1999; 185: 23-35.
16. Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A. The preparation and properties of niosomes non-ionic surfactant vesicles. J Pharm Pharmacol, 1985; 37: 863- 868.
17. Biju SS, Talegaonkar S, Misra PR, Khar RK. Vesicular systems: An overview. Indian J Pharm Sci, 2006; 68: 141- 153.
18. Mahdi, Jufri, Effionora, Anwar, Joshita, Djajadisastra, Preparation of Maltodextrin DE 5- 10 based Ibuprofen Proniosomes, MajalahIlmukefarmasian, 2004; 1: 10-20.
19. Solanki A, Parkihk J and Parikh R, Preparation, characterization, optimization and stability studies of Aceclofen acproniosomes, Iranian. J. Pharm Research, 2008; 7(4): 237-246.
20. Welesh AB, Rhodes DG, SEM imaging predicts quality of niosomes from maltodextrin based proniosomes,Pharm.Res, 2001; 18: 656.
21. Chauhan S, Luorence MJ, The preparation of polyxyethylene containing non-ionic surfactant vesicles,J.Pharm. Pharmacol, 1989; 41: 6.
22. Gayatri DS, Venkatesh P, Udupa N, Niosomalsumatriptan succinate for nasal administration, Int. J. Pharm. Sci, 2000; 62(6): 479-481.
23. Kapil S, Rao R, Saini V. Preparation and evaluation of lornoxicamniosomal gel. Int Res J Pharm, 2012; 3: 378-83.
24. Upadhye S, Rafik IN. Proniosomes: A novel vesicular drug delivery system. Am. j. PharmTech res, 2020; 10(2): 260-73.
25. Attia IA, El-Gizawy SA, Fouda MA, et al. AAPS Pharm Sci Tech, 2007; 8(4): 106-109.
26. Parikh DK, Ghosh TK. AAPS Pharm Sci Tec, 2005; 6(2): 144-149.
27. Sudhamani T, Priyadarisini N, Radhakrishna. Int Pharm Tech Res, 2010; 2(2): 144-154.
28. Shamsheer SA, Sabareesh M, Khan PR, et al. Applied Pharma Sci, 2011; 01(08): 185.
29. Gupta A, Prajapathi S, BalaMurugan K. Design and development of a proniosomal trandermal drug delivery system of captopril. Trop J Pharm Res, 2007; 6: 687-93.
30. Azeem A, Ahmad FJ, Talegaonkar S. Exploration of skin permeation mechanism of frusemide with proniosomes. Pharmazie, 2009; 64: 735-40.
31. Alli MS. Srilakshmi. Ch, Ganesan G. Proniosome Gel: An Effective Novel Therapeutic Topical Delivery System. Int J of PharmTech Res, 2013; 5: 1754-1764.