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TOPICAL GEL OF LIPOSOMAL DRUG DELIVERY SYSTEM-A REVIEW

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ABSTRACT

Liposomes have been established as a promising novel drug delivery vehicle in several different basic sciences. Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shells consisting of lipids arranged in a bilayer configuration. Liposomes are acceptable superior carriers having ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. It also has affinity to keratin of horny layer of skin and can penetrate deeper into skin and hence give better absorption. Liposomes may act as a solublizing matrix for poorly soluble drugs and penetration enhancer when applied on the skin as well as local depot at the same time diminishing the side effects of these drugs. Topical liposome formulations could be more effective and less toxic than conventional formulations. The liposome gel formulations could perform therapeutically better effects than the conventional formulations, as prolonged and controlled release topical dosage forms, may lead to improved efficiency and better patient compliance.

KEYWORDS: Liposomes, Topical drug delivery, Elastic liposome.

INTRODUCTION

Liposomes

Liposomes, which are biocompatible phospholipid vesicles that are capable of incorporating both hydrophilic and lipophilic drugs, have been widely investigated in dermatology as topical agents as well as transdermal carrier systems. conventional liposomes do not deeply penetrate the skin, but rather they remain confined to the upper layer of the stratum corneum serving as a drug reservoir.

With the advent of drug design, lipid based drug delivery system has gained immense impetus due to their ability to serve as efficient carriers for poorly water soluble drugs. They are competent in encapsulating the drug and providing important advantages of targeted delivery, long circulation, low toxicity, sustained-release, non-immunogenicity and protecting the encapsulated drugs from the destructive action of the external environment. Liposomes are simply vesicles in which an aqueous volume is entirely enclosed by membrane composed of lipid molecules usually phospholipid. Liposomes were first discovered in 1960's by Bangham and Colleagues and were initially used as model for studying the biological membrane. Liposomes are highly versatile structures for research, therapeutic, and analytical applications. They are basically composed of a lipid bilayer with the hydrophobic chains of the lipids forming the bilayer and the polar head groups of the lipids oriented towards the extravesicular solution and inner cavity. Their structure is similar to that of cells, and thus can be used conveniently as a vessel for studying interactions between membrane lipids and biomolecules such as DNA and proteins, permeability of ions an drugs and elucidating the mechanism of action of antibiotics on target organisms.

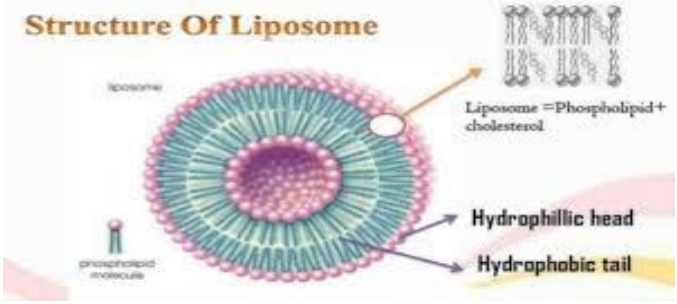

Fig 1: Structure of liposome.

Topical liposomes

Topical drug delivery is an attractive route for local and systemic treatment. Liposomes are acceptable and superior carriers and have ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. It also has affinity to keratin of horny layer of skin and can penetrate deeper into skin and hence give better absorption. In the formulation of topical dosage forms, attempts are being made to utilize drug carriers that ensure adequate localization or penetration of drug within or through the skin in order to enhance the local and minimize the systemic effects or to ensure adequate percutaneous absorption. When applied on the skin, liposomes act as a solublizing matrix for poorly soluble drugs, penetration enhancer and local depot at the same time reducing the side effects of these drugs. Thereby topical liposome formulations could be more effective and less toxic than conventional formulations.

MECHANISM OF LIPOSOME FORMATION

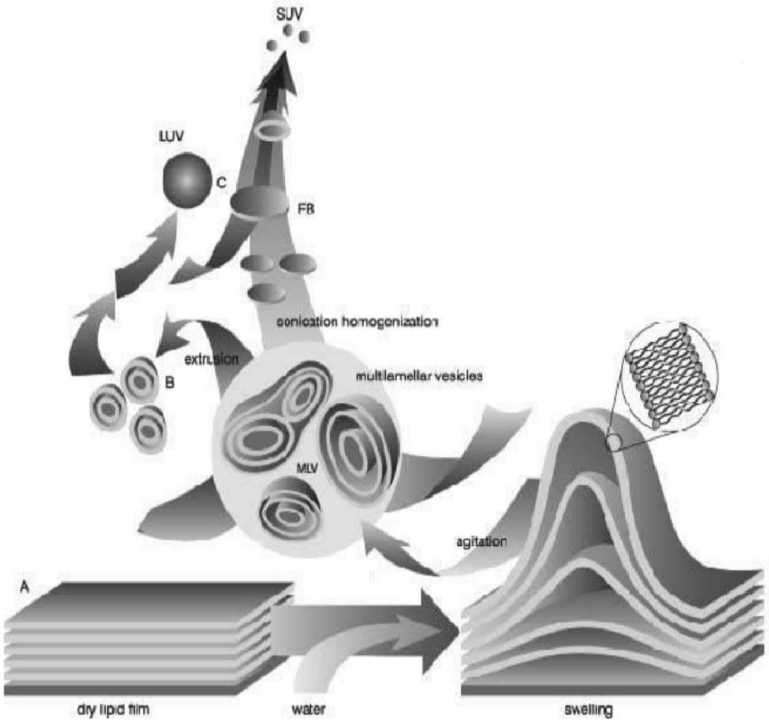

Fig 2: Mechanism of liposome formation.

Classification of liposomes

Multilamellar Large Vesicles (MLV): In MLV, vesicles have an onion structure. Classically, several unilamellar vesicles will form on the inside of the other with smaller size, making a multilamellar structure of concentric phospholipid spheres separated by layers of water.

Unilamellar vesicles (UV): In UV liposomes, the vesicle has a single phospholipid bilayer sphere enclosing the aqueous solution. UV vesicles can be prepared in various sizes.

Small unilamellar vesicles (SUV) - 20 to 40 nm.

Medium sized unilamellar vesicles (MUV) – 40 to 80 nm.

Large unilamellar vesicles (LUV) – 10 to 1000 nm.

Giant unilamellar vesicles (GUV) - > 1000 nm.

Oligolamellar vesicles (OLV): OLV have large central aqueous cores surrounded by 2 to 10 bilayers.

Multivesicular vesicles (MVV): MVV first described as large clusters of smaller compartments sharing common bilayers, have been redefined to cover all structures of nonconcentric vesicles inside a larger vesicle of 200nm to 3µm.

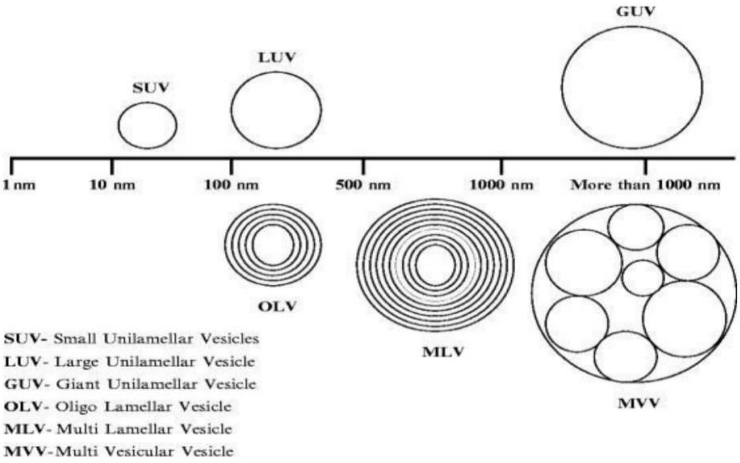

Fig 3: Classification of liposomes.

Advantages of Liposomes

- It can carry both water and lipid soluble drugs.
- Provides selective passive targeting to tumor tissues (liposomal doxorubicin).
- Liposomes increased efficacy and therapeutic index of drug (actinomycin-D).
- Liposome increased stability via encapsulation.
- Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations.
- Liposomes help reduce the exposure of sensitive tissues to toxic drugs.
- Flexibility to couple with site-specific ligands to achieve active targeting.
- Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
- It provides sustained release.
- It can be administered through various routes.
- It has direct interaction of the drug with cell.

Disadvantages of liposomes

- Liposomes are leaky thus causing premature release of drug.
- Poor encapsulation efficiency for hydrophilic molecules.
- Expensive.
- Short shelf life.
- High production cost

Elastic liposomes

Liposomes are not suitable for transdermal delivery, because they cannot reach the deeper layers of the skin, being trapped in the superior layers of stratum corneum. To overcome this problem, the researches introduced a novel generation of vesicular elastic systems. The main advantage of these ultradeformable vesicular systems is the elasticity of the bilayer, given by the surfactant molecules allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the vesicles.

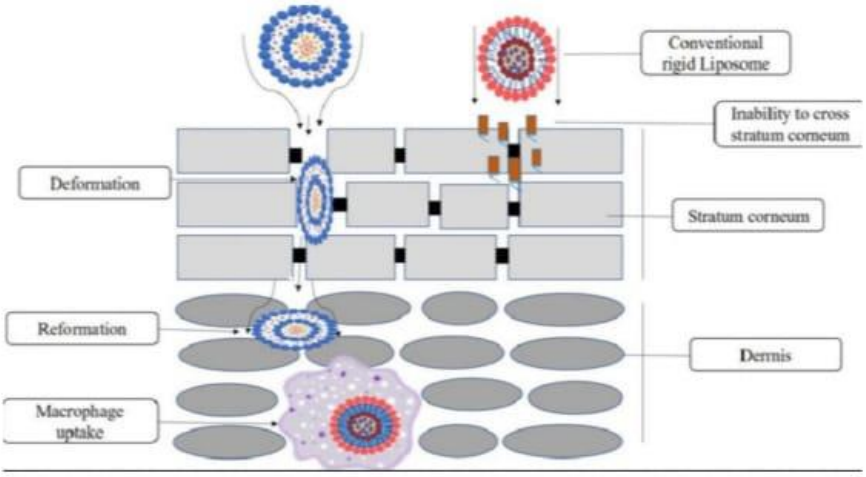

Fig 4: Permeation nature of liposomes.

Method of preparation of liposomes

• Passive loading techniques

In these passive loading technique the drug is encapsulated by incorporating an aqueous phase of a water-soluble (hydrophillic) drug or an organic phase of a lipid-soluble drug initially or at predetermined stage during the preparation of the liposomes. The huge drug encapsulation efficiency can be achieved with the help of these passive loading technique which is more suitable for lipid-soluble drugs with a high resemblance to the lipid membrane. Liposomal encapsulation technology (LET) is the latest delivery method used by medical researcher to transmit drugs that act as healing promoters to the definite body organs.

Mechanical Dispersion Method

In these method variety component are mainly combined by co-dissolving the lipids in an organic solvent and after that the organic solvent is then separated by film deposition under vaccum. When all the solvent is evaporated, the solid lipid mixture is hydrated using aqueous phase. The lipids spontaneously swell and hydrate to form liposomes.

The following are types of mechanical dispersion methods:

Lipid film hydration method

The lipid-film hydration procedure is the most common and simple method for preparation of MLV by dissolving phospholipids in the organic solvents: dichloromethane, chloroform, ethanol and chloroform-methanol mixture (2:1 v/v; 9:1 v/v; 3:1 v/v). A thin and homogeneous lipid film is formed when solvent is evaporated under vacuum at the temperature 45-60 ºC. Nitrogen gas is involved in order to completely remove the residual solvent. A solution of distilled water, phosphate buffer, phosphate saline buffer at pH 7.4 and normal saline buffer are used in hydration step. The time for the hydration process varied from 1 h to 2 h at the temperature 60- 70 ºC. In order to obtain full lipid hydration, the liposomal suspension is left overnight at 4 ºC. The lipid-film hydration method can be used for all different kinds of lipid mixtures.

Micro-emulsification method

An equipment called as microfluidizer is used to prepare small vesicle from concentrated lipid suspension. The lipids can be introduced into the fluidizer as a suspension of large MLVs. This equipment pumps the suspension at very high pressure through the 5mm screen. Then it is forced long microchannel, which direct two streams of fluid collide together at right angle and very high velocity. The fluid collected can be recycled through the pump and interaction chamber until vesicles of spherical dimension are obtain.

Sonication

Sonication is perhaps the most extensively used method for the preparation of SUV. Here, MLVs are sonicated either with a bath type sonicator or a probe sonicator under a passive atmosphere. The main disadvantages of this method are very low internal volume/encapsulation efficacy, possible degradation of phospholipids and compounds to be encapsulated, elimination of large molecules, metal pollution from probe tip, and presence of MLV along with SUV.

French pressure cell

French pressure cell involves the extrusion of MLV through a small orifice. An important feature of the French press vesicle method is that the proteins do not seem to be significantly pretentious during the procedure as they are in sonication. An interesting comment is that French press vesicle appears to recall entrapped solutes significantly longer than SUVs do, produced by sonication or detergent removal. The method involves gentle handling of unstable materials. The method has several advantages over sonication method. The resulting liposomes are rather larger than sonicated SUVs. The drawbacks of the method are that the high temperature is difficult to attain, and the working volumes are comparatively small (about 50mL as the maximum).

Membrane extrusion

In this method, MLVs is reduced by passing them through a membrane filter of defined bore size. There are two types of membrane filter. The tortuous bath type and the nucleation track type. The former is used for sterile filtration. In this random bath arises between the criss cross fibres in the matrix. Liposomes that are larger than the channel diameter get struck when one tries to pass them though such membrane. The nucleation track is composed of thin continuous sheet of polycarbonate. They will offer less resistance to passage of liposomes as these consist of straight sided pore holes off exact diameter bored from one side to another. This method can be used to process both LUVs and MLVs.

Dried reconstituted vesicles

In DRV method freeze drying of a dispersion of empty SUVs are to be done and then dispersion of it with the aqueous fluid containing the material to be entrapped. This leads to hydration of solid lipids in finely reduced size form. Though, the step of freeze-drying is introduced to freeze and lyophilize a performed SUVs dispersion rather than to dry the lipids from an organic solution. This leads to an ordered membrane structure as compared to random matrix structure, which on addition of water can rehydrate, fuse and reseal to form vesicles with a high encapsulation efficiency. The water soluble hydrophilic materials to be entrapped are added to the dispersion which are empty SUVs and they are dried together, so the material for inclusion is present in the dried precursor lipid before the final step of addition of aqueous medium.

Freeze-thawed liposome

SUVs are rapidly frozen and thawed slowly. The short-lived sonication disperses aggregated materials to LUV. The creation of UV is as a result of the fusion of SUV

throughout the processes of freezing and thawing. This type of synthesis is strongly inhibited by increasing the phospholipid concentration and by increasing the ionic strength of the medium. The encapsulation efficacies from 20% to 30% were obtained.

Solvent Dispersion Method

In these methods lipids are first dissolved in an organic solution and then brought into contact with aqueous phase containing materials to be entrapped within liposome. At the interface between the organic and the aqueous phases the phospholipids align themselves to form a monolayer, which is important step to form the bilayer of liposome.

Ether injection (solvent vaporization)

A solution of lipids dissolved in diethyl ether or ether-methanol mixture is gradually injected to an aqueous solution of the material to be encapsulated at 55°C to 65°C or under reduced pressure. The consequent removal of ether under vacuum leads to the creation of liposomes. The main disadvantages of the technique are that the population is heterogeneous (70 to 200 nm) and the exposure of compounds to be encapsulated to organic solvents at high temperature.

Ethanol injection

Lipid solution of ethanol is rapidly injected to a huge excess of buffer. The MLVs are at once formed. The advantages of the method are that the population is heterogeneous (30 to 110 nm), liposomes are very dilute, the removal all ethanol is difficult because it forms into azeotrope with water, and the probability of the various biologically active macromolecules to inactivate in the presence of ethanol.

Double emulsion method

In this process, an active ingredient is initially dissolved in an aqueous phase (w1) which is then emulsified in an organic solvent containing polymer to form a primary w1/o emulsion. This primary emulsion is then mixed in an emulsifier which also consist of aqueous solution (w2) to form a w1/o/w2 double emulsion. The extraction of the solvent leaves microspheres in the aqueous external phase, making it possible to separate them by filtering or centrifuging.

Reverse phase evaporation method

The lipid mixture is added to a round bottom flask and the solvent is removed under reduced pressure by a rotary evaporator. The system is purged with nitrogen and lipids are re-dissolved in the organic phase which is the phase in which the reverse phase vesicle will form. Diethyl ether and isopropyl ether are the usual solvents of choice. After the lipids are re-dissolved the emulsion are obtained and then the solvent is removed from an emulsion by evaporation to a semisolid gel under reduced pressure. Phosphate buffer saline or citric-Na2HPO4 buffer is added to aqueous phase with aim to improve the efficiency of liposome formulations. The formation of liposomes is allowed by continued rotary evaporation of the organic solvents under vacuum. Nonencapsulated material is then removed. The resulting liposomes are called reverse phase evaporation vesicles (REV). This method is used for the preparation of LUV and OLV formulation and it has the ability to encapsulate large macromolecules with high efficiency.

Stable pluri lamellar vesicles

This method of pluri lamellar vesicle preparation followed by formation of water-in-organic phase dispersion with an excess of lipid which further introduce to drying under continued bath sonication with an irregular stream of nitrogen. SPLVs require a large aqueous core, the common of the entrapped aqueous medium being located in the compartment in between adjacent lamellae. The percent entrapment normally ranges around 30%.

Detergent Removal Method

In this method the phospholipids are brought into close contact with the aqueous phase via detergents, which associate with phospholipids molecules. The structures formed as a result of this association are known as micelles. They are composed of several hundreds of component molecules. The concentration of detergent in water at which micelles start to form is called CMC. Below CMC the detergent molecule exist in free solution. As the detergent molecule is dissolved in water at concentration higher than the CMC, micelle form in large amounts. As the concentration of detergent added is increased more amount of detergent is incorporated into the bilayer, until a point is reached where conversion from lamellar form to spherical micellar form take place. As detergent concentration is further increased, the micelles are reduced in size.

Dialysis

Detergents are mainly soluble in both aqueous as well as organic media and there is an equilibrium within the detergent molecules in the water phase, and in the lipid environment of the micelle. The CMC can give an indication to the position of this equilibrium. Upon reducing the concentration of detergent in the whole aqueous phase, the molecules of detergent can be washed away from mixed micelle by dialysis. The action of egg PC with a 2:1 molar ratio of sodium cholate followed by dialysis which lead to theformation of vesicles (100nm). A commercial version of the dialysis system is available under the trade name LIPOPREPTM (Diachema AG, Switzerland).

Column Chromatography

Phospholipids in the form of either sonicated vesicles or as a dry film, at a molar ratio of 2:1 with deoxycholate form UV of 100nm. Deoxycholate remove using column chromatography. This could be done by the passing the dispersion over a Sephadex G-259 column presaturated by constitutive lipids and preequilibrated using hydrating buffer.

Dilution
Upon dilution of aqueous mixed micellar solution of detergent and phospholipids with buffer, the micellar size and the polydispersity increase fundamentally, and as the system is diluted beyond the mixed micellar phase boundary, a spontaneous transition from poly-dispersed micelles to vesicles occurs.

• **Active loading**: The exploitation of liposomes as drug delivery system is encouraged with the advancement of well-organized encapsulation procedures. The membrane from the lipid bilayer is in general impermeable to ions and larger hydrophilic molecules. Ions transport can be synchronized by the ionophores though permeation of neutral and weakly hydrophobic molecule can be inhibited by concentration gradients.

A few weak acids or bases yet, can be transported throughout the membrane because of various transmembrane gradient, such as electric, ionic (pH) or specific salt (chemical potential) gradient. Some method exists for improved incorporation of drugs, including remote (active) loading method which load drug molecules into preformed liposome using pH gradient and potential difference across liposomal membrane. A concentration variation in proton concentration across the membrane of liposomes can drive the loading of amphipathic molecule.

Active loading methods have the following benefit over passive encapsulation technique,
a) It will lead to high encapsulation efficiency and capacity.
b) Leakage of the encapsulated compounds can be reduced.
c) "Bed side" loading of drugs therefore limiting loss of retention of drugs by diffusion, or chemical degradation while storage.
d) Process is flexible for constitutive lipid, as drug is loaded after the formation of carrier unit.
e) It also reduces the safety hazard by avoiding biologically active compounds in the preparation step during dispersion.

EVALUATION OF LIPOSOMAL GEL

Appearance
Physical appearance and homogeneity were evaluated by visual inspection.

Entrapment efficiency
Entrapment efficiency of liposomes was determined by separating the unentrapped drug with the influence of centrifugation. The liposomes are centrifuged at 20000 rpm for 1 h at controlled temperature. Supernatant containing unentrapped drug was withdrawn and analyzed under UV–visible spectrophotometer against phosphate buffer pH 7.4 at 660 nm. Entrapment efficiency was calculated as follows,

Entrapment efficiency (%) = ((Total amount of drug – Amount of drug in the supernatant)/Total drug added)) X 100.

Drug content
The gel sample (100 mg) was withdrawn, dissolved in phosphate buffer pH 7.4 and drug content was determined using UV spectrophotometer at 660 nm.

pH
pH measurement is essential to guarantee the non-irritating nature of the liposomal gel. The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated.

Viscosity
The measurement of viscosity of the prepared gel was done with a Viscometer. The gels were rotated at 1.5 rotations per minute and viscosity was measured in Cps.

Extrudability
In this test, sample is extruded from the tube by usual procedure. A closed collapsible tube containing gel was passed firmly at crimped end. When the cap was removed, gel extrudes until pressure was dissipates. The weight in grams required to extrude 0.5cm ribbon of gel in 10 seconds was determined.

Spreadability
Spreadability of gel is carried out by using glass plates. 0.5 g of gel was applied within a circle of 2 cm diameter pre marked on a glass plate, over which a second glass plate was placed. A weight about 500 g was placed to rest on upper glass plate for 10 min. The increase in the diameter due to gel spreading was observed and recorded.
Spreadability (%) = (Increase in diameter /Initial diameter) × 100

Microscopic analysis
Liposomes or liposomal gel can be visualized by an optical light microscope and projection microscope. A drop of the prepared sample was placed on a glass slide and carefully covered with a cover slip. The excess amount was drained off by using filter paper and was then observed by optical light microscopy and projection microscope.

Scanning electron microscope (SEM)
The morphological characteristics of the liposomes are determined using a vega3 tescan scanning electron microscope (SEM).The samples were placed on the sample holder. After 5 min of instrument stabilization, surface imaging of the liposomes was carried out at 30 kV, and images were focused for analysis.

Particle size determination

Particle size determination is important for drug penetrability into the skin and helps for good formulation. The mean particle diameter and polydispersity index (PDI) of the liposomes are determined by using a Malvern Zetasizer Nano.

In vitro drug release study

In vitro drug release study was carried out using Franz diffusion cell. The cell consists of receptor and donor compartment. The F6 gel was placed in donor compartment and dialysis membrane was used for diffusion. Phosphate buffer pH 7.4 was used as dissolution medium and temperature was maintained at 37 ± 0.5 °C. Aliquots of 2 ml were collected at 15 min time interval for 2 h and fresh buffer solution was added to obtain sink condition. The concentration of drug was determined by UV–visible spectrophotometer at wavelength 660 nm. Percentage drug release was calculated and plotted against time.

Stability Study

As per ICH Guidelines, Stability study was performed. The gel formulation was kept in stability chamber at 40℃ ± 2℃, 75% RH ± 5% RH for a period of one month. The stored products were visually examined for any signs of instability, including discoloration and phase separation. In addition, the formulations were analyzed concerning drug content, pH and viscosity.

CONCLUSION

The topically applied liposomal formulations, particularly those prepared from lipid mixtures of composition similar to the stratum corneum, would be an effective delivery system for the treatment of skin diseases. Since these liposomal formulations provide sustained, enhanced levels in deeper strata of the skin, they have the capacity to meter a sufficient quantity of drug into deeper tissue to treat the skin symptomology. Such metering should also reduce the incidence of undesirable side effects arising from systemic administration, or enhanced systemic absorption of drug.

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