A REVIEW ON SOLID LIPID NANOPARTICLES BASED TOPICAL GEL

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Abstract: This review on solid lipid nanoparticles for topical gel formulation explores the potential of using the solid lipid nanoparticles (SLNs) for formulating them in a topical gel. Researchers have prepared SLNs by incorporating piroxicam into polymer matrix using various methods of preparation but mainly focusing on a highly recommended and used method, that is; by solvent extraction method and high-pressure homogenization. They have also highlighted the advantages of using SLNs as a delivery system in topical gel formulation. Nowadays topical gels are extensively used in the treatment of various diseases and skin conditions and the new emerging novel drug delivery system - SLNs, just blend with each other well with respect to their properties and the ability to increase the therapeutic efficacy of the drugs having poor solubility and bioavailability and including drugs that show systemic side effects. The formulation studies of SLNs based topical gels also showed satisfactory results like that of the reported standards for all characterization such as the organoleptic properties, particle size, polydispersity index, zeta potential, calibration curve, differential scanning calorimeters and partition coefficient. Overall, this review is about the SLNs which are formulated in a topical gel can be used for a variety of applications. This review also provides an overview on the method of preparations used by the researchers and some other key points which are highlighted by the authors in their topic.

Keywords: Solid lipid nanoparticles, topical drug delivery, solvent extraction, high pressure homogenization.

1. INTRODUCTION

This review focuses on the areas of study on the newly emerging research on nanoparticles in the field of pharmaceutics. The researchers have used various methods for the preparation of nanoparticles, specifically the solid lipid nanoparticles (SLNs) which are a type of nanoparticles having a diameter range between 50nm to 1000nm. The methods used are mainly common, but the drugs used for this type of formulation by the researchers are chosen from a wide classification. SLNs are the type of nanoparticles which are considered a promising drug delivery system due to their ability to deliver a wide range of drugs like anti-inflammatory drugs, antimicrobials, anticancer, peptides, proteins, etc. and encapsulate them irrespective of their nature as hydrophobic or hydrophilic drugs. However, their low drug loading capacity has centered their use as a topical gel formulation primarily, but are also used in oral delivery, ophthalmic delivery and parenteral delivery. SLNs show their prominent features in the means of their biocompatibility and biodegradability. They provide controlled and sustained drug release, provide protection of drugs from degradation, enhance the drug absorption and can target specific sites in the body. The preparation of SLNs, their characterization, types and applications have been well reviewed in the past with particular emphasis by other researchers. Therefore, the focus of this review is to provide a comprehensive discussion on the physiology of the skin, topical drug delivery system and nanoparticles which are some major points in the field of research done by researchers on this topic.

2. LITERATURE SURVEY

2.1 The Skin

The skin is the largest multifaceted organ covering our body, acts as a protective barrier from external environment and maintains homeostasis by preventing water loss, governing body temperature and protecting against pathogenic microorganisms and toxic substances. It is made up of many layers which are essential to be studied to understand the topical drug delivery. Three major layers of the skin include the epidermis, dermis and hypodermis.[1] The epidermis is the outer most layer of the skin. It doesn’t have any blood vessels. It is subdivided into stratum corneum, stratum lucideum, stratum granulosum, stratum spinosum and stratum basale. Stratum corneum consists of tightly packed dead cells filled with keratin and thus it becomes a challenge for penetration of drugs in the topical delivery systems. The dermis is the middle layer of the skin. It has a rich network of blood vessels and hair follicles. It
is made up of connective tissue, collagen and elastin which gives strength and elasticity to the skin. The deepest layer
of skin is the hypodermis. It is made up of adipose tissues which store fat and provide insulation to the body.[1]

![Layers of the Skin](image)

**Figure 1: layers of skin**

The skin is also associated with the pH gradient, with the surface being acidic and the inner layers at physiological pH. This helps in making a protective barrier to prevent microorganisms from invading deeper skin layers. It has a metabolic barrier with enzymes such as esterase and protease present in the skin tissue.[1]

In recent decades, macromolecules like proteins, lipids, nucleic acids, etc. research has stated about them not being able to diffuse through skin layers. Thus, carrier medicated drug delivery systems like nanoparticles can penetrate the skin but there is a strong physical, metabolic and physicochemical barrier embedded in the skin that limits the number of drugs that can be delivered topically in effective amounts.[2]

### 2.2 TOPICAL DRUG DELIVERY SYSTEM

A topical drug delivery system refers to a method of administration of a medication on the skin or the mucous membrane where it gets absorbed into the systemic circulation or shows local effects. This type of drug delivery system is primarily intended to show local effects and thus:

- Potentially eliminate the need for systemically administered drug therapies
- Minimize the total dose required to reach the target site
- Reduce side effects

Topical delivery of drug provides targeted delivery to the site of action from the site of administration, shows greater patient compliance than the oral dosage forms and avoids first pass metabolism.[2]

Topical products are generally available as liquid, ointments, gels, creams and foams. They can be homogeneous viscous solution, semisolid solution or a suspension of an active pharmaceutical ingredient. The gel bases are made up of hydrogel polymers such as carbomers, cellulose and Pluronic.[3] The researchers have chosen the topical gel as their main formulation for SLNs as they provide several advantages over other topical products like creams and ointments. Their main area of research focus on the formulation of SLNs in topical gel as:

- Gels are non-greasy and do not clog pores.
- They provide rapid absorption of the drug molecule because of the amount of hydration they provide to the skin as compared to other topical products.
- Their viscosity and spreadability assured its ease of application.
- It showed less skin irritation.[4]
- Fourier transform infrared (FTIR) spectroscopy was used to check the compatibility of the drug with formulation excipients. It showed no distinct interaction of the drug.[4]
- FTIR also ensured proper entrapment of drug in the gel formulation.[4]
- They provide cooling effects for irritated skin.

Nanoparticles have emerged as a promising delivery system for topical drug delivery applications. Their small size allows deeper penetration into the skin. They are used as a drug delivery system for topical applications, allowing increased drug concentration in the carrier to enhance drug flux into and through the skin. They offer a wide range of advantages like improved drug stability, enhanced permeation, enhanced permeability and targeted delivery to specific skin layers. They therefore help increase a drug’s bioavailability and increase the residence time of the drug. This route of administration is best suited for the drugs which shows systemic side effects and are instable in gastric environment.

Overall, the topical drug delivery systems offer a valuable approach to medication administration, providing targeted and effective delivery while potentially minimizing systemic side effects and the use for nanoparticles in formulating as topical gels shows promising results in the drug delivery. However, it is very important to consider individual patient
needs and consult with a healthcare professional to determine the most appropriate delivery method for a specific medication and condition.

2.2.1 Topical Delivery and Skin
Topical drug delivery system based on nanoparticles offer controlled release of hydrophobic and hydrophilic drugs showing prolonged drug action and for that the study of physiology of skin is necessary as nanoparticles can be targeted into the deeper layers of skin and can bypass skin’s barrier function and enhance the penetration of drugs into the underlying layers. Topical delivery of drugs through skin is somewhat challenging and to overcome them one must keep in mind the physicochemical properties of skin and how they affect the topical drug delivery.[1]

The most important factor is permeability which determines how quickly the drug molecule will penetrate the skin layers which depend upon the lipophilic or hydrophilic nature of the drug. Hydration of the skin is also an important feature as dry skin is less permeable than hydrated skin. The pH of the skin plays a crucial role which is slightly acidic of 4.5-5.5 and provides barrier function and antimicrobial activity. The pH of this formulation depends upon the physicochemical property of the drug and should be maintained to that of the pH of the skin to avoid instability of the drug.

Various substances and chemical agents are used during formulation of these SLNs based gel. They include:
- pH adjusters: The pH adjusters help to maintain the pH of the gel within 4.5-5.5 to prevent skin irritation.
- Gelling agents: These agents increase the viscosity of the formulation such that they can be easily spread over the skin surface.
- Permeation enhancers: They are the most important part of a topical formulation as they enhance the penetration of drug molecules across the skin barriers.
- Preservatives: They prevent the grow of microorganisms in the formulation and ensure its stability and increase their shelf life.
- Emulsifiers
- Perfumes and colorants
- Thickening agents
- Antioxidants

2.2.2 Mechanism of Skin Permeation
The mechanisms of skin permeation ability of a drug molecule have been studied by many researchers globally. They have provided many theories of penetration. These drug molecules can traverse across the skin by various mechanism but mostly through:
1) Transcellular route
2) Paracellular route
3) Trans appendageal route
4) Passive diffusion
5) Endocytosis
6) Phagocytosis

Major transport system for skin permeation of drug molecule include:
- Transcellular pathway
- Paracellular pathway
- Transappendageal pathway
- Passive diffusion
The transcellular pathway is one of the two main pathways by which drug penetrates the skin and enter systemic circulation and drug traverse from one cell to another. Whereas in paracellular pathway, the drugs diffuse through the intercellular lipid domains. The trans appendageal involves hair follicles and sebaceous glands. The most common pathway is the passive diffusion involving diffusion of drug molecules along with the concentration gradient. Drugs can also be transported via endocytosis and phagocytosis in which drug molecules enters the cells and or gets engulfed.

2.3 NANOPARTICLES
Nanoparticles are tiny, controlled release depot systems like matrices, reservoirs or hydrogels. Their size ranges from 1nm to 100nm which are measured by coulter counter method. They are made up of a variety of materials like metals, polymers, lipids, etc.[2] They have unique physical and chemical properties due to their small size because of which they are used in a wide range of applications like the drug delivery system and shows promising results. Nanoparticles help in reducing the non-specific delivery to non-target tissues and can be used for targeted delivery to the cells and tissues. They are injectable and are convenient for large hydrophilic molecules to enter the cells. Moreover, they improve the stability of the drug and increase the shelf life by 10-100%.

Microparticles are analogous to nanoparticle but differ in size range, that is; 1-100μm. Small molecules, proteins, peptides, nucleic acids, etc. Encapsulated in a particle can be adsorbed or covalently linked to the target site and show its action. These particles can either be capsules or solids. Nanoparticles with hydrodynamic diameter greater than 100nm cannot traverse through endothelium. Particles in the range of 6-100nm cannot pass through the glomerular basement membrane, whereas those in the range of 1-6nm cross faster.[2] Nanoparticles with hydrodynamic diameter less than 1nm interact with endothelial glycocalyx resulting in inverse size dependent filtration and the smaller particles cleared slowly. Other applications of nanoparticles include imaging like MRI, CT scans, etc. They are also used to remove pollutants from water and soil and in energy fuels. The image you sent shows a handwritten note on particle synthesis, with different synthesis methods listed for polymers and metals.

2.3.1 Type of Nanoparticles
1) Lipid based nanoparticles
   a. Nano emulsion
   b. Solid lipid nanoparticles
2) Inorganic nanoparticles
   a. Iron oxide nanoparticle
   b. Gold nanoparticle
   c. Graphene nanoparticle
   d. Single layer graphene
3) Polymeric nanoparticles
   a. PLGA
   b. Dendrimer
   c. Hydrogel
   d. Nano micelles

Figure 3: types of nanoparticles
2.3.2 Synthesis of Nanoparticles
Nanoparticles can be synthesized by various methods and are designed according to their use. The main materials used in their synthesis are polymers. These polymers are carefully chosen based on their compatibility with the active pharmaceutical ingredient as well as the other excipients and are of good analytical grade. The method of nanoparticle preparation can be classified as follows:

A. Chemical methods

a. For formulating drugs in polymer form
Polymerization: In this process, nanoparticles are formulated by linking molecules to each other to make a nanoparticle which is of size less than 100nm. Various methods used for this process is:
1. Emulsion polymerization
2. Precipitation polymerization
3. Ionic gelation
4. Interfacial polymerization

b. For formulating drugs in metal form
In this formulation process, various methods can be employed like:
- Reduction-oxidation (redox)
- Crystallization
- Salt formation

B. Physical methods
Nanoparticles made by physical method of preparation are eco-friendly and scalable and thus these methods are extensively used in the preparation of nanoparticles. They involve the use of physical processes to create nanoparticles from bulk substances. They do not involve any chemical reactions and thus offer many advantages over the chemical methods. They thus are free from the use of hazardous chemicals which are frequently used in the chemical methods and are also free from toxins that are generated in the byproducts of the chemical methods. Some of the major physical methods used on a regular basis include:
1. Solvent evaporation
2. Double emulsion
3. High pressure homogenization
4. Spray drying
5. Hot melt extrusion
6. Gelation
7. Solvent removal
8. Phase separation or coacervation

2.4 SOLID LIPID NANOPARTICLES
Solid lipid nanoparticles nanoscale colloidal drug carriers made up of solid lipid matrix with an average diameter of 50nm to 1000nm.[3] They provide additional benefits as they have uniform particle size, increased surface area, improved dissolution and improved drug loading. They also provide a controlled and targeted drug delivery system along with better saturation solubility of poor water-soluble drugs. These unique features make SLNs potential vehicles to target dermal/transdermal delivery. For topical drug delivery of SLNs, they should be formulated in an appropriate semisolid dosage form.[2]
The solid lipid nanoparticles are composed of physiological and biodegradable lipids exhibiting low systemic toxicity and low cytotoxicity. The lipid particles having small size ensures close contact with the stratum corneum and thus increases the amount of drug penetrating into the mucosa or the skin.[3] SLNs thus are suitable for the use in the topical delivery on the wounds as well as on the inflamed skin as they are made up of particles which are non-irritant and non-toxic.[2]

2.4.1 Types of SLNs
Based on their structure and location of the drug in the lipid matrix, the SLNs can be classified into three main types:
- Homogenous matrix-based (solid solution model): These types of SLNs consist of drug candidates either molecularly dispersed in lipid matrix or dispersed in the form of amorphous clusters. They are obtained by high-pressure homogenization method in case of highly lipophilic drugs.[3]
- Drug enriched shell based SLNs: They are formed during phase separation method of preparation of nanoparticles. They are best suited for the drugs that have low solubility in lipids.[3]
- Drug enriched core based SLNs: They are formed when drug precipitates before the recrystallization of lipids. They are best suited for the drugs that have low solubility in solid lipids but high solubility in liquid lipids.[3]
2.4.2 Commonly used Drugs

<table>
<thead>
<tr>
<th>APPLICATION</th>
<th>DRUG</th>
<th>TYPE OF NANOPARTICLE</th>
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<tbody>
<tr>
<td>Antifungal</td>
<td>Amphotericin B</td>
<td>Liposomes</td>
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<td>Griseofulvin</td>
<td>SLNs</td>
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<td></td>
<td>Terbinafine HCl</td>
<td>Lipid carriers (LCs)</td>
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<td>NSAIDs</td>
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<td></td>
<td>Ibuprofen</td>
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<td></td>
<td>Flurbiprofen</td>
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<td>Naproxen</td>
<td>Polymeric micelles</td>
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<td>Etoricoxib</td>
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<td></td>
<td>Etofenamate</td>
<td>Liposome</td>
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<td>Anti-cancer</td>
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<td>5-Fluorouracil</td>
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<td>Acne</td>
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<td>Tretinoin</td>
<td>Nanogels</td>
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2.5 METHOD OF PREPARATION OF SLNs

2.5.1 Solvent Evaporation

Solvent evaporation is a simple and versatile method used for the synthesis of nanoparticles from a variety of materials, including polymers, metals, and ceramics. In this method two phases, aqueous and organic are used in which a surfactant is used in aqueous phase along with distilled water while in organic phase polymer along with hydrophobic drug with chlorinated solvent. Both the aqueous and organic phase are subjected to the process of emulsification to obtain an oil in water emulsion. The volatile solvent of this emulsion is evaporated and hence this process is named solvent evaporation as it involves evaporation of solvent to obtain small particles.[10] Thus, to summarize:

- Dissolve the material (polymer) and the drug of interest in a volatile solvent.
- Form an emulsion of the solution in a continuous phase (usually water).
- Evaporate the solvent from the emulsion.
- Collect the particles and wash them to remove any residual solvent or surfactants.

Organic solvents used are mainly methylene chloride, chloroform, ethyl acetate, etc.[10]
Advantages of the solvent evaporation method
The solvent evaporation method has several advantages over other particle synthesis methods, including:
- This method is relatively easy to learn and implement.
- This method can be used to synthesize a wide variety of particles from different materials.
- This method can be scaled up to produce large quantities of particles.
- The method is relatively inexpensive to implement.[10]

Challenges of the solvent evaporation method
- The volatile solvents used can be flammable and toxic, so it is important to take appropriate safety precautions when using them.
- There is a need to control the evaporation rate carefully because if the solvent evaporates too quickly, the particles may not have enough time to grow to the desired size and if the solvent evaporates too slowly, the particles may aggregate or form large crystals.[10]

2.5.2 High Pressure Homogenization Method
HPHM is a mechanical method for the preparation of nanoparticles which involves forcing a liquid suspension through a narrow orifice or valve at very high pressure which measures typically in between 100 and 1000 bar. This high pressure forces the particles in the suspension to collide with each other and with the walls of the orifice breaking them into smaller particles.[10] Steps involved in this method include:
1. Preparation of suspension: The drug and the polymers and other materials are suspended in appropriate solvents which would not interact with the materials, to make a suspension of a high concentration.
2. Homogenization: This suspension is then forced through a narrow orifice or valve at a very high speed and at high pressure so as the particles to collide with each other and break down into smaller particles.
3. Collection of nanoparticles.

Advantages of HPHM
- It can be used to prepare nanoparticles of a wide range of materials.
- HPHM can be easily scaled up to produce nanoparticles on a large scale.
- It typically produces nanoparticles with a narrow size distribution.
- HPHM can be used to produce nanoparticles with a desired size and shape.

Disadvantages of HPHM
- HPHM requires a high amount of energy to operate.
- It can generate a lot of heat, which can damage the nanoparticles.
- HPHM equipment is typically more expensive than other homogenization methods.

2.5.3 Double Emulsion Method
The double emulsion method is a mechanical technique for synthesizing particles with a variety of core-shell and hollow structures. In this method of preparation, primary emulsion of the core material in a continuous phase and another secondary emulsion of the primary emulsion in a second continuous phase is prepared. After this, the shell material or the core material are then solidified. Particles are then collected and washed to remove any residual emulsifiers or other chemicals. The double emulsion method is particularly well-suited for synthesizing particles with complex core-shell and hollow structures.[10] This is because the double emulsion template provides a controlled environment for the nucleation and growth of the particles.
2.5.4 Spray Drying
Spray drying is a method of producing a dry powder from a liquid or slurry by rapidly drying it with a hot gas.[10] Steps involved in the spray drying process include:

- Atomization: The liquid or slurry is atomized, or broken down into small droplets, using a nozzle.
- Drying: The droplets are sprayed into a hot gas chamber, where they dry rapidly. The hot gas is usually air, but other gases, such as nitrogen, can also be used.
- Separation: The dried powder particles are separated from the hot gas and collected.

The polymer dispersion is atomized into small droplets using a five-nozzle atomizer. The droplets are then sprayed into a heated chamber (65-100°C). The solvent evaporates from the droplets, leaving behind dried polymer particles.[10]

2.5.5 Gelation
Gelation is the process by which a hydrogel microparticle dispersion is transformed into a solid polyanhydride microparticle dispersion. In this process the hot melt polymer is added to the cool oil phase containing hydrogel particles. This addition causes the hydrogel to gel and form a 3D network of polymer chains and this network traps the oil phase.[10] Stepwise procedure of gelation includes:

- Hydrogel microparticle dispersion by crosslinking a polymer solution with a crosslinker.
- Hydrogel microparticle dispersion in an oil phase.
- Hot melt polymer addition to the cool oil phase.
- The hot melt polymer melts and forms a solution in the oil phase.
- The hot melt polymer solution diffuses into the hydrogel microparticles, causing them to gel.
- The gelation process results in the formation of a three-dimensional network of polymer chains that traps the oil phase.
- Particle dispersion collected by filtration or centrifugation.[10]

3. CONCLUSION
Over the past few decades, a series of research has contributed to our understanding on the use of SLNs for topical/transdermal delivery. SLNs have demonstrated significant improvement in drug penetration through the skin by forming an occlusive layer. In conclusion, the collaborative efforts of dedicated researchers have significantly advanced our understanding of "Solid Lipid Nanoparticles (SLNs) Based Topical Gel" and its potential applications in pharmaceutical and cosmetic formulations. Through a multidisciplinary approach, these researchers have demonstrated expertise in pharmaceutical sciences, nanotechnology, and dermatology, shedding light on the promising features of SLNs in topical drug delivery systems. The reviewed studies underscore the versatility of SLNs in encapsulating a wide range of drugs, from hydrophilic to hydrophobic compounds, offering a versatile platform for formulating effective topical medications. The lipid matrix of SLNs contributes to their biocompatibility and biodegradability, addressing key considerations for dermatological applications.

In essence, the review on "Solid Lipid Nanoparticles Based Topical Gel" showcases the researchers' commitment to advancing scientific knowledge in a rapidly evolving field. Their collective efforts have illuminated the potential of SLNs, while also laying the groundwork for future investigations and innovations in pharmaceutical and cosmetic research.

4. REFERENCES