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Solid Lipid Nanoparticles Loaded Transdermal Patch for Improving Skin Permeation

	
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Abstract

A transdermal patch is used for delivery of medications through the skin for treating systemic illnesses. Transdermal drug delivery systems, also known as “patches” offers a variety of benefits such as controlled release, reduced systemic side effects, painless, and patient compliance through multi-day dosing. Solid lipid nanoparticles (SLNs) have been in use as carriers for enhanced skin delivery of drugs. Permeation enhancement is primarily due to small size and swelling of stratum corneum by an increase in skin hydration caused by the occlusive film of SLN. Here review various aspects of SLNs loaded Transdermal Patches including their mechanism of penetration, preparation, evaluation parameters, prospective advantages and disadvantages. Solid nanoparticles (SLNs) have good biocompatibility, low toxicity and lipophilic drugs are better delivered by SLNs and the system is physically stable.



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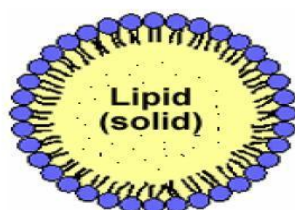
INTRODUCTION

Many of the recent formulation approaches utilize Nanotechnology i.e. the preparation of Nano-sized structures containing the Active Pharmaceutical Ingredient. Nanotechnology is the study and use of structures in the size range of 1 to 1000 nm¹. Some of the important Drug Delivery System developed using Nanotechnology principles are- Nanoparticles, Solid Lipid Nanoparticles, Nanosuspension, Nanoemulsion and Nano crystals². The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.

SOLID LIPID NANOPARTICLES

SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve the performance of pharmaceuticals.

SLNs are one of the novel colloidal carrier systems. They have good biocompatibility, low toxicity and lipophilic drugs are better released by solid lipid nanoparticles and it is physically stable.



Structure of Solid Lipid Nanoparticles (SLN)

Advantages of solid lipid nanoparticles

Controlled and target drug release.

Excellent biocompatibility.

Improves stability of pharmaceuticals.

High and enhanced drug content.

Chemical protection of thermolabile incorporated compounds.

Raw materials essential as same as in emulsions.

Long-term stability.

Incorporation of lipophilic and hydrophilic drugs.

Disadvantages of solid lipid nanoparticles

Particle growth.

Unpredictable gelation tendency.

Unexpected dynamics of polymeric transitions.

Preparation of solid lipid nanoparticles

Solid lipid nanoparticles prepared from lipid, emulsifier, and solvent by using different methods are given below³.

Methods of Preparation of solid lipid nanoparticles



High-pressure homogenization (HPH)

It is a reliable and powerful technique, which is used for the production of SLNs. High-pressure homogenizers push a liquid with high pressure (<2000 bar) through a narrow gap. The fluid accelerates on a very short distance to very high velocity (over 1000 Km/hr). Very high shear stress causes the particles down to the submicron ranges. Generally, 5-10% lipid content is used but up to 30% lipid content has also been investigated. It has two approaches like hot homogenization and cold homogenization; work on the same concept of mixing the drug in bulk of lipid melt.

Hot homogenization:

It is carried out at temperatures above the melting point of the lipid; so known as the hot homogenization of an emulsion. By high-shear mixing, a pre-emulsion of the Drug loaded lipid melt and the aqueous emulsifier phase is obtained. In general, higher temperatures result in the reduction in particle sizes due to the decreased viscosity of the aqueous phase. High

temperatures increase the degradation rate of the drug as well as the carrier. Increasing the homogenization pressure or the number of rotations results in a decrease of the particle size because of the high kinetic energy of the particles.

Cold homogenization

It has been generated to overcome various issues associated with hot homogenization such as temperature induced drug degradation, drug distribution patterns and production of supercooled melts. In this method, the drug loaded lipid melt is cooled to reduce solid lipid into lipid microparticles and these lipid microparticles are dispersed in a cold surfactant solution to produce a pre-suspension. This pre-suspension is homogenized at room temperature; the gravitation force is strong enough to break the lipid microparticles to solid lipid nanoparticles.

Solvent evaporation

In this lipophilic material is dissolved in a water-immiscible organic solvent (e.g. cyclohexane) that is emulsified in an aqueous phase. Upon evaporation of the solvent, nanoparticles dispersion is formed by precipitation of the lipid in the aqueous medium by producing nanoparticles of 25 nm in size ranges.

Microemulsion based method

This method is based on the dilution of microemulsions. Generally defined as microemulsions are two-phase systems; consists of an inner and outer phase. The hot microemulsion is dispersed in cold water by stirring. SLN dispersion can be used as granulation fluid for transferring into a solid product (tablets, pellets) by granulation process, but in the case of low particle content, too much of water needs to be removed. High-temperature gradients cause rapid lipid crystallization and prevent aggregation. Due to the dilution step; the predictable lipid contents are much lower compared with the HPH based formulations.

Spray drying method

Spray drying method is an alternative technique to the lyophilization process. This suggests the use of lipid with the melting point more than 70°C. SLN concentration of 1% in a

solution of trehalose in water or 20% trehalose in a methanol-water mixture; these are the two best results obtained the pattern.

Double emulsion method

Where the drug is encapsulated with a stabilizer to prevent the partitioning of a drug into external water phase during solvent evaporation in the w/o/w double emulsion.

Precipitation method

In the organic solvent like chloroform; triglycerides are dissolved and the solution will be emulsified in an aqueous phase. Nanoparticulates are formed after the evaporation of an organic solvent.

Film-ultrasound dispersion

The lipid and the drug were put into suitable organic solutions, after decompression, rotation, and evaporation of the organic solutions, a lipid film is formed, then the aqueous solution which includes the emulsions was added. The SLN with uniform particle size is obtained by using the ultrasound with the probe to diffusion.



Evaluation of the Solid lipid nanoparticles

Drug Content Uniformity:

Three films of each formulation were taken in a separate 100ml volumetric flask; 100ml of pH 7.4 phosphate buffer was added and stirred continuously for 24 h. Then the solutions were filtered, diluted and analyzed on a UV spectrophotometer.

Moisture content:

The prepared films are individually weighed and placed in a desiccator containing calcium chloride at room temperature for 24 h. After a specific time interval, the films are to be weighed again until they show an unvarying weight. The % moisture content was calculated by using the following formula.

$$\% \text{ moisture content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final weight}} \times 100$$

In-vitro release study

Dissolution studies are carried out in a USP dissolution apparatus using 900ml of dissolution medium at $37 \pm 0.5^{\circ}\text{C}$, and a rotation speed of 50 rpm was used. An aliquot of sample is periodically withdrawn and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed spectrophotometrically.

TRANSDERMAL PATCHES

Transdermal drug delivery system is topically administered medicaments⁴. Transdermal patches are the pharmaceutical preparation of varying sizes, containing one or more active ingredient intended to be applied to the unbroken skin in order to deliver the active ingredient to the systemic circulation after passing through the skin barriers. It avoids first pass effect. They deliver the drugs into the systemic circulation at a predetermined and controlled rate. By diffusion process, the drug enters the bloodstream directly through the skin. However, there is the high concentration of the patch and low concentration in the blood; the drug will keep diffusing into the blood for a long period of time to maintain the constant rate of the drug in the blood stream or systemic circulation.

Composition of Transdermal Patches



Polymer Matrix

The polymer controls the release of the drug from the device. The following factors should be considered for a polymer to be used in transdermal patches.

- The polymer should be stable.
- The polymer should be non-toxic.
- The polymer should be easily manufactured.
- The polymer should be inexpensive.

Types of polymer

(a) Natural polymers

Cellulose derivative, Gelatin, Waxes, Proteins, Shellac, Natural rubber, starch.

(b) Synthetic Elastomers

Hydrin rubber, silicone rubber, Nitrile, Acrylonitrile, Neoprene.

(c) Synthetic polymers

Polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyamide, polyurea.

Drug

Drug solution in direct contact with the release liner.

Physiochemical properties

- (a) The drug should have a molecular weight less than 1000 Daltons.
- (b) The drug should have the affinity for both lipophilic and hydrophilic phases.
- (c) The drug should have a low melting point.

Biological properties

- (a) The drug should be potent.
- (b) The half-life ($t^{1/2}$) of the drug should be short.
- (c) The drug must not produce the allergic response.
- (d) Tolerance to the drug must not develop under zero-order release profile of transdermal patches.

Permeation Enhancer

The flux J. of drug across the skin can be written as

$$J = D \frac{dc}{dx}$$

$$J = \text{Flux}$$

$$D = \text{Diffusion coefficient}$$

$$C = \text{Concentration of the diffusing spectres}$$

$$X = \text{Spatial coordinate}$$

(a) Solvents

These compounds increase penetration possibly by swelling the polar pathway.

e.g.: Alcohols–Methanol & ethanol, / Dimethyl acetamide Propylene Glycol and Glycerol.

(b) Surfactants

The surfactant has the ability to alter the penetration due to the polar head group and the hydrocarbon chain length

i) Anionic surfactant: - Sodium lauryl sulfate, Diacetyl sulphosuccinate

ii) Nonionic Surfactant: - Pluronic F127, Pluronic F68

iii) Bile Salt: - Sodium taurocholate, Sodium deoxycholate.

(c) Miscellaneous Chemicals

Enhance the permeation Eg. Urea, calcium thioglycolate.

Other excipients



(a) Adhesives

The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device.

i) It should not be irritant

ii) It should be easily removed

iii) It should not leave a residue on the skin

Types of Transdermal Patches

There are four types of transdermal patches⁵:

- Single-layer drug-in-adhesive
- Multi-layer drug in adhesive
- Drug reservoir-in-adhesive:

- Drug matrix-in-adhesive

Transdermal Permeation

Skin is the most intensive and really accessible organ of the body as only a fraction of the millimeter of tissue separates its surface from the underlying capillary network⁶.

The various steps involved in the transport of drug from patch to systemic circulation are as follows.

1. Diffusion of drug from drug reservoir to the rate controlling membrane.
2. Diffusion of drug from rate limiting membrane to stratum corneum.
3. Sorption by stratum corneum and penetration through the viable epidermis.
4. Uptake of a drug by a capillary network in the dermal papillary layer.
5. Effect on the target organ.

Formulation of Solid Lipid Nanoparticles loaded Transdermal Patches⁷

Membrane permeation – controlled system

These systems be a multilaminate process e.g. Transdermal Nitro. These are consisting of three parts held together by two layers of drug- SLN containing adhesive. Firstly the drug-SLN is processed into the physical/chemical form required for incorporation of the product. These are dissolved in a solvent to form the uniform solution. These adhesive compositions are deposited as a thin film by the removal of the solvent.

Adhesive dispersion type system

The manufacturing process can be divided into following parts.

(I) Preparation of individual matrix solution

Raw material [Polymer, softening agent] is dissolved in an organic solvent to obtain a standard or stock solution. Then the matrix solution is prepared from the stock solution. The active SLN and other non-soluble additives are added.

(II) Coating the individual matrix layers

The individual layers are made by coating the solution (above) and removing the solvent by drying using coating machine. This machine consists of two units

(A) The coating unit

(B) Drying unit.

(A) Coating unit

The solvent based formulations are coated; based on the viscosity, solid contents, flowability and surface tension of the matrix solution.

(B) Drying Unit

The solvent is evaporated from the adhesive mass by running the coated web through a drying channel using a transport system like the cranked shaft, conveyor belt.

Matrix diffusion controlled system



With the plastic materials the drug-SLN is generally kneaded with the solution of Polyvinyl chloride in an organic solvent and granulated waxy matrix is prepared by dispersing the drug-SLN in molten fat followed by congealing. The granules are then compressed into tablets. The gum swells and the drug-SLN diffuse out of it.

Micro sealed dissolution–Controlled system or Encapsulation

The drug-SLN particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes. The dissolution rate of coat depends upon the solubility and thickness of the coating which may range from 1 to 200 microns.

Evaluation of the SLN-Transdermal Patches

Drug Content Uniformity

Three patches of each formulation are taken in the separate 100ml volumetric flask; 100ml of pH 7.4 phosphate buffer is added and stirred continuously for 24 h. The solutions were

filtered, diluted suitably and analyzed on a UV spectrophotometer. The average of drug contents of three films was taken as the final reading.

Folding Endurance


Folding endurance is measured by manual repeated folding of the film at same place till it broke. The number of time the film is folded without breaking is the folding endurance value.

Patch weight and thickness

The weight of each film was measured with the help of a digital balance and the average weight was calculated. Similarly, the thickness of each film was measured using screw gauge at different positions of the film and the average was calculated.

Moisture content

The prepared films are individually weighed and placed in a desiccator containing calcium chloride at room temperature for 24 h. After a specific time interval, the films are to be weighed again until they show an unvarying weight. The % moisture content was calculated by using the following formula.


$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{Final weight}} \times 100$$

In-vitro release study

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Ex-vivo permeation study

Diffusion studies are carried out in a Franz diffusion cell. The required size of rat skin is mounted carefully on diffusion cells, donor solutions consisting SLN containing drug⁹. The receiver compartment was filled with phosphate buffer of pH 7.4 at $37 \pm 0.5^{\circ}\text{C}$ and a rotation of 600 rpm was used. For each experiment, 1 ml of the receiver medium was withdrawn at the predetermined time and all samples were filtered and analyzed spectrophotometrically.

CONCLUSION

It can be easily concluded that the preparation and evaluation of SLNs, transdermal patches, and SLN loaded transdermal patches can be of different types; varies upon some factors like change in polymers, availability of instruments as well as solvents and also with the application mode. SLN as the carrier in transdermal patches may provide new opportunities for the development of novel improved therapies.

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