



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203




Human Journals

Review Article


November 2019 Vol.:16, Issue:4

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A Review on Novel Delivery System: Solid Lipid Nanoparticles



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals



ISSN 2349-7203

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Submission: 21 October 2019
Accepted: 27 October 2019
Published: 30 November 2019



HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: Solid lipid nanoparticles, Characterization, Nanotechnology, applications

ABSTRACT

Solid lipid nanoparticles (SLN) are the most alternative method for particulate carriers especially developing formulations of nanotechnology with several applications in different fields like drug delivery, clinical medicine, etc. The different substances have been entrapped into both lipophilic and hydrophilic molecules, lipid Nano-particles, and labile compounds such as proteins and peptides. Solid lipid nanoparticles are a beneficial method for the successful incorporation of the poorly water-soluble drugs and they increase the bioavailability of the drugs. Solid lipid nanoparticles having a nanometer size range hence they can protect the drug in contradiction of *in-vitro* and *in-vivo* degradation and it releases the drug in a controlled manner at specific drug targeting sites. The different production methods which are suitable for large scale production and applications of solid lipid nanoparticles are defined. The present review emphasized the utility of SLN in terms of its advantages over other formulation, production methodology, characterization, and applications.

INTRODUCTION

Solid lipid nanoparticles presented in 1991 speak to another bearer framework to convention colloidal dosage forms, for example, - emulsions, liposomes and polymeric miniaturized nanoparticles [1]. Nanoparticles created using strong lipids are plotting real focus as a novel colloidal carrier for intravenous applications. The solid lipid nanoparticles comprise of round strong lipid particles in the nanometer ranges, which are scattered in water or watery surfactant arrangement. Typically, they are made of strong hydrophobic centers taking a monolayer of phospholipids covering. The hydrophobic chains of phospholipids are encompassed in the fat framework. They can convey lipophilic or hydrophilic medications [2]. SLN are sub-micron colloidal transporters extending from 50 to 1000 nm, which are placid of physiological lipid, scattered in water or fluid surfactant solution [3]. SLN consolidates the upsides of polymeric nanoparticles, fat emulsion and liposomes however simultaneously maintains a strategic distance from a portion of their hindrances. They have various focal points, for example, great biocompatibility, nontoxic, stable against blend, hydrolysis, biodegradable, physically steady and great bearer for lipophilic drugs [4]. They are a significant distinction between lipid emulsion and liposomes. The essential structure of a lipid emulsion is an unbiased lipophilic oil-primarily encompassed by a monolayer of amphiphilic lipid. Conversely, liposomes contain an external bilayer of the amphiphilic particle, for example, a phospholipid with a watery segment inside [5].

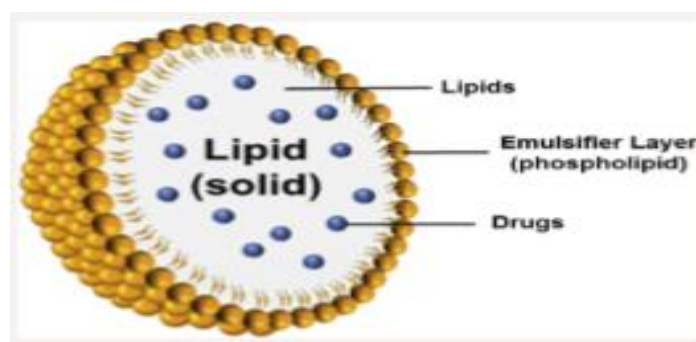


Figure No. 1: Proposed structure of SLN

Nanotechnology:

Nanotechnology is a novel technology expected to bring revolutionary changes in the field of life sciences like drug delivery, nutraceuticals, production of medicine and diagnostics. Nanotechnology is the arrangement of nanosized structures containing active pharmaceutical

ingredients. These are small colloidal particles usually made up of biodegradable and non-biodegradable polymers and diameter is around 200nm. Nanotechnology, as characterized by the National Nanotechnology Initiative (NNI), is the examination and utilization of structures generally in the size scope of 1 to 100nm. The objective of nanotechnology is the same as that of medication: to analyze as precisely and ahead of schedule as would be prudent and to treat as successfully as conceivable with no reactions utilizing controlled and focused on medication conveyance approach [6].

Aims of solid lipid nanoparticles [7]

- Possibility of controlled drug release.
- Increased drug stability.
- High drug payload.
- No bio-toxicity of the carrier.
- Avoidance of organic solvents.
- Incorporation of lipophilic and hydrophilic drugs.

Drug delivery system developed using Nanotechnology principles are [8]

1. Nanoparticles
2. Solid Lipid Nanoparticles
3. Nanosuspension
4. Nano-emulsion
5. Nanocrystals

Advantages of Solid lipid nanoparticles [9]

- Increased skin penetration and skin permeability.
- Biocompatible and biodegradable nature.
- Accumulation and film formation which promote skin hydration.

- Raw materials used in the SLN is similar to that of emulsion.
- Increased drug solubility and longer skin deposition.[10]
- Avoid system absorption and side effects in topical drug delivery systems.
- Increases the possibility of specific follicular drug targeting.
- Good long-term stability during the storage period.
- Easier to manufacture than biopolymeric nanoparticles.
- The high concentration of functional groups can be achieved.

Large scale production is possible.

Disadvantages of Solid lipid nanoparticles [11]

- Restricted transdermal drug delivery.
- Poor drug loading capacity.
- Difficult to load hydrophilic drugs due to partitioning effects during the production process.
- Loss of high amounts of the drug.
- Lack of robust controlled drug release.
- Unpredictable gelation tendency and particle growth.

Table No. 1: Comparison between liposomes, lipid emulsions, solid lipid nanoparticles [12]

PROPERTY	SLN	POLYMER NANOPARTICLES	LIPOSOMES	LIPID EMULSION
Systemic Toxicity	Low	> to SLN	Low	Low
Large scale production	Yes	No	Yes	Yes
Cytotoxicity	Low	> to SLN	Low	Low
Residues from organic solvents	No	Yes	may or may not	No
Sterilized by autoclaving	No	No	No	Yes
Sustained release	Yes	No	< to SLN	No
Avoidance of RES	No	No	Yes	Yes

Principle of Drug Release from SLN[13]

The medication discharge from lipid nanoparticles are as per the following:

There is an indirect relationship between medication discharge and the parcel coefficient of the medication. The greater surface area of smaller molecule measure in nanometer range produce higher medication discharge. Slow medication discharge can be achieved when the medication is equally scattered in the lipid framework. It mainly depends on the sort and medication tangle model of SLN. Crystallization of the lipid carrier and high portability of the medication leads to quick medication discharge [14]. This SLN medication fuse model is vital to the medication discharge design. The original drug released rapidly in the first 5 min in the drug –enriched shell model as a result of the external layer of a particle due to the larger surface area of the drug on the particle surface. The outbreak release is reduced by increasing particle size and prolonged release, for example, lipid macromolecules. These type of surfactant and its concentration will interact with the outer shell and affect its structure, low surfactant concentration leads to a slight burst and extended drug release and the particle size effect on drug release rate it directly depends on various parameters such as the composition of SLN preparation, production method and its conditions.

Types of NPS as a carrier for drug and diagnostic agents[15]

- Nanosuspensions and nanocrystals
- Magnetic nanoparticles
- Liposomes

- Ceramic NPS
- Liposomes
- Polymeric NPS
- Fullerenes and dendrimers
- SLNP (Solid lipid nanoparticles)
- Nano-shells coated with gold
- Nanometers and carbon nanotubes
- Polymeric micelle
- Nano-shells coated with gold

Preparation of solid lipid nanoparticles.[16]

There are two basic preparation techniques for solid lipid nanoparticles.

1. Hot homogenization

2. Cold homogenization

A) Ultra-sonification or high-speed homogenization

B) Solvent emulsification-evaporation technique

C) Solvent emulsification-diffusion technique

1. **Hot homogenization [17]:** Lipid is melted to generally 5⁰C above its melting point, the drug is dissolved in the melted lipid, then lipid melted drug is dispersed in an aqueous surfactant solution of the same temperature. It gives the pre-emulsion formulation then it passed through a high-pressure homogenizer. The preparation of this process is hot o/w type emulsion, cooling of this emulsion gives to the crystallization of the lipid and obtained the formation of solid lipid nanoparticle.

2. Cold homogenization [18]: Drug is dissolved in the melted lipid and cooled up to solidification. The solid material is ground by a mortar mill. The obtained lipid microparticle is dispersed in a cold surfactant solution at room temperature or below its room temperature. The solid-state of the matrix act as portioning of the drug to the water phase hence, it leads to entrapment efficiency remains unchanged even during storage of the aqueous solid dispersion.

Hot and cold homogenization technique in the production of solid lipid nanoparticles

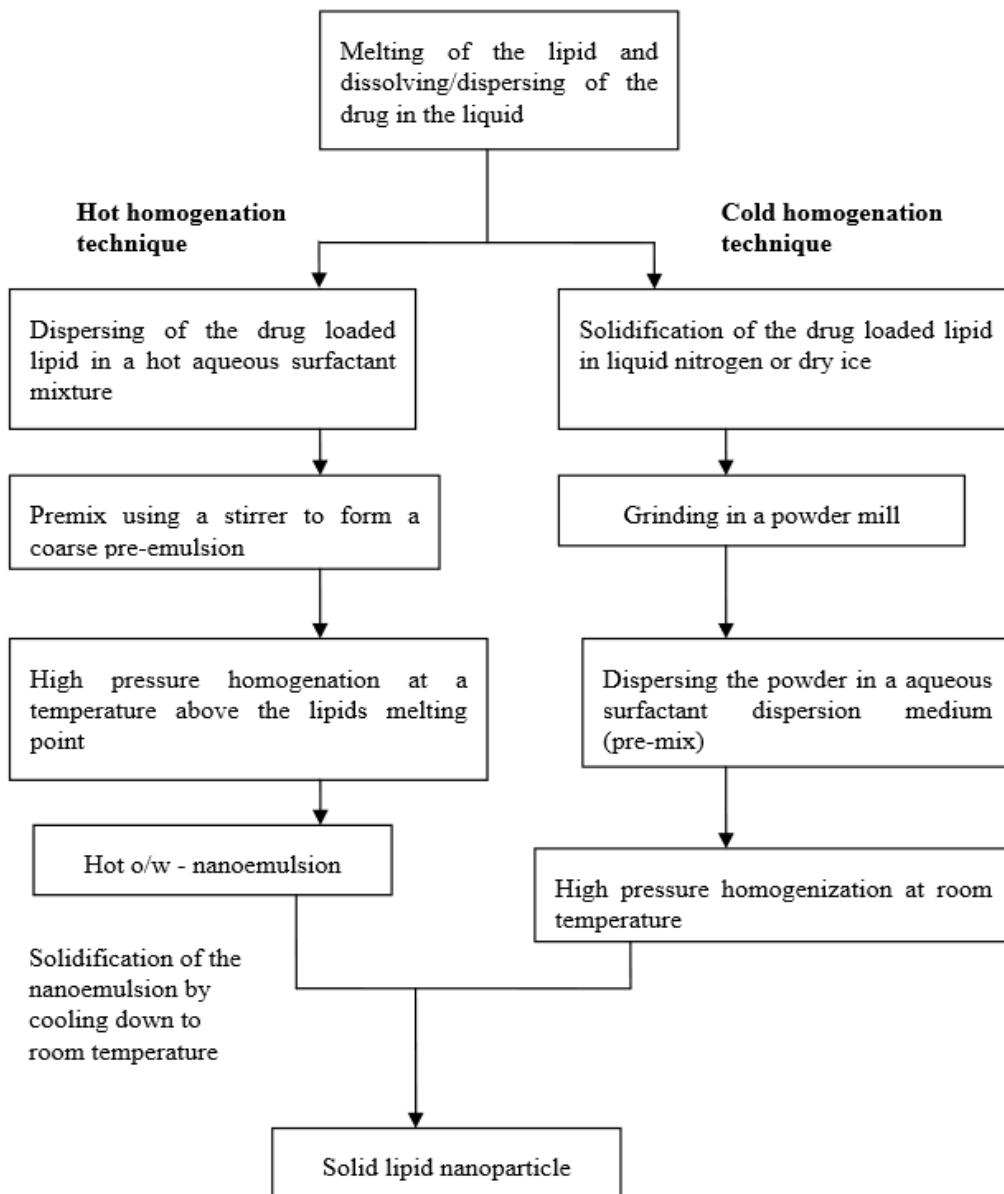


Figure No. 2: Hot and cold homogenization technique

Other various methods of preparation of SLNs

1. Spray drying method[19]

It is an alternate technique that is a cheaper method than the lyophilization process. This recommends the use of lipids with a melting point of more than 70°C. The best results by the spray drying technique are found with an SLN concentration of 1% in a solution of trehalas in water or 20% trehalas in the ethanol-water mixture. This method causes drug particle aggregation due to high temperature.

2. Double Emulsion Method[20]

The double emulsion (w/o/w) method is a novel method based on the solvent emulsification–evaporation and it is widely used for the preparation of lipid nanoparticles loaded with hydrophilic drugs. Hence, the drug and emulsifiers are encapsulated in the inner aqueous phase of w/o/w double emulsion.

3. Precipitation technique[21]

These solid lipid nanoparticles can also be prepared by a precipitation technique which is characterized by the need for solvents. The glycerides will be dissolved in an organic solvent (e.g. chloroform) and the drug solution will be combined in an aqueous phase. After the evaporation of an organic solvent, the lipid will be precipitated and producing nanoparticles.

4. Film ultrasound dispersion [22]

The drug and lipid were dissolved in suitable organic solutions, after evaporation, decompression, and alternation of the organic solutions, a lipid film is obtained, then the aqueous solution of the emulsions was added. Using the ultrasound with the investigation to the diffuser at later, the SLN with the minute and uniform sized particle is formed.

Types of solid nanoparticles [23]

There are three drug incorporation models which describe drug release from SLN.

1. Type 1 or Homogenous matrix model:

Type I is derived from a solid mixture solution of lipid and active ingredients. The SLN type 1 formation can be prepared by the cold homogenization technique. A lipid blend can be made without using solubilizing surfactant then drug dispersed in the lipid matrix. After solidification of this blend, it gives strong interaction between lipids and drugs.

2. Type 2 or Drug enriched shell with the lipid core model

The formation of type 2 model by the hot technique, and the active ingredient concentration in the melted lipid is low during the cooling process of the hot o/w emulsion the lipid will react first, leading to a gradually increasing concentration of active ingredients in the remaining melt, an outer shell get solidify containing both active ingredient and lipid. The outer surface of the particles leads to burst release. The release of active ingredients from the outer shell can be controlled by the incorporation of coenzymes.

3. Type 3 or Drug enriched core with the lipid shell model

The core model can take place when the active ingredient concentration cooling leading to the supersaturation of the lipid drug. Precipitation of drugs in melted lipids reduces the solubility of the active in the melt. These active molecules precipitate leading to the formation of a drug enriched core.

Factors affecting the filling capacity of a drug in lipid are[24]

- the solubility of the drug in lipid melt.
- miscibility of drug melt and lipid melt.
- chemical structure of solid matrix lipids.
- The physical structure of solid matrix lipid.
- polymorphic state of lipid material

Different materials used for the preparation of SLNs[25]

Table No. 2: Materials used for SLN preparation

Sl. No.	LIPIDS	SURFACTANT AND CO-SURFACTANTS
1.	Triacylglycerol's- Tricaprin Trilaurin Trimyristin Tripalmitin.	Phospholipids: Soya lecithin, Egg lecithin Phosphatidylcholine
2.	Acylglycerols: Glycerol monostearate, Glycerol palmitostearate	Ethylene oxide/propylene oxide copolymers: Poloxamer 188, Poloxamer 407, Poloxamine 908
3.	Fatty acids: Stearic acid, Palmitic acid, Decanoic acid Behenic acid	Sorbitan ethylene oxide/propylene oxide copolymers: Polysorbate 20, Polysorbate 60, Polysorbate 80
4.	Waxes: Cetyl palmitate	Alkyl aryl polyether alcohol polymers: Tyloxapol
5.	Cyclic complexes: Cyclodextrin	Bile salts: Sodium cholate, Sodium glycocholate, Sodium taurocholate, Sodium taurodeoxycholate, sodium salt
6.	Hard fat types: Witepsol W 35 Witepsol H 35	Alcohols: Ethanol, Butanol (11)

Characterization of SLN quality and structure [26]:

Characterization of the SLNs is necessary for its quality control. Though, it is a serious challenge due to the nanosize of the particles and the complexity and dynamic nature of the drug delivery system. The important parameters evaluated for the SLNs include particle size, size distribution kinetics (zeta potential), degree of crystallinity and lipid modification (polymorphism), the coexistence of additional colloidal structures, the time scale of distribution processes, the content of drug, *in-vitro* drug release and surface morphology study.

Physicochemical characterization

- Particle size and Zeta potential
- Differential scanning calorimetry (DSC)
- Atomic force microscopy (AFM)
- Electron microscopy

- Dynamic light scattering (DLS)
- Nuclear magnetic resonance (NMR)

Particle size and Zeta potential [27]

SLNs are submicron-sized, the physical stability of SLNs depends on their particle size and shape. The most powerful technique for determination of particle size is photon correlation spectroscopy detects size range of 3nm to 3 μ m and laser diffraction (LD) detects in size range of 100 nm to 180 μ m. However, PCS is a good tool to characterize nanoparticles. The LD method is based on the requirement of the diffraction angle on the particle size and smaller particles lead to more intense scattering at high angles compared to the higher ones.

Zeta potential [28] majorly measured to predict the storage stability of the colloidal dispersions. It can be carried out using a zeta potential analyzer or zettameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size and zeta potential measurement [29]. A higher value of zeta potential may cause to de-aggregation of particles.

The zeta potential should be between -100 to + 100 mV for dispersion to remain physically stable.

4°C - Most favorable storage temperature.

20°C - Long term storage did not result in drug-loaded SLN combination or loss of drug

50°C - A rapid growth of particle size is observed.

Differential scanning calorimetry (DSC) [30]:

DSC and powder X-ray diffractometry is performed to measure the degree of crystallinity of the particle dispersion and to measure several individual properties of a preparation. The rate of crystallinity of the sample can be determined by the evaluation of the melting enthalpy of the bulk material along with the melting enthalpy of the dispersion. Using this technique, it is possible to observe fusion and crystallization and DSC can also be used to detect oxidation, as well as other chemical reactions in the preparations.

Atomic force microscopy (AFM) [31]:

In this method, a probe tip with atomic-scale sharpness is restored across a preparation to

produce a topological map depending on the forces at play between the tip and the surface. The probe can be pulled across the sample (contact mode), or (non-contact mode), with the exact nature of the particular force performed to distinguish among the sub techniques. That ultra-high resolution is obtainable with this method, along with the ability to map a sample according to properties in addition to size.

Electron microscopy [32]

Morphological examination of the sample can be measured by using both Scanning electron microscopy (SEM) and transmission electron microscopy (TEM). They provide a way to directly observe nanoparticles. However, TEM has a small size limit of detection.

Dynamic light scattering (DLS) [33]

These DLS also is known as photon correlation spectroscopy records the variation in the intensity of the scattered light on the microsecond time scale. DLS is majorly used to analyze nanoparticles and Examples include determining the nanogold size, latex size, protein size, and colloid size. Usually, this technique is used for the determination of submicron particles and sizes less than a nanometer.

Nuclear magnetic resonance (NMR)[34]

This NMR can be used to determine both the qualitative nature and size of Nanoparticles. NMR is widely used in medicine in the form of magnetic resonance imaging. NMR is used industrially mainly for repetitive analysis of chemicals. The technique is also used to measure the ratio between water and fat in foods, detect the flow of corrosive fluids in pipes and to study molecular structures of crystals.

Determination of Incorporated Drug [35]

The determination of drug incorporated in SLNs is very important to measure the amount of incorporated drug to measure the release characteristics. The amount of drug encapsulated per unit wt. of nanoparticles is measured after separation of the free drug in the medium and solid lipids from the aqueous medium and the separation of the free drug can be done by ultracentrifugation, gel permeation chromatography, or centrifugation filtration. The free drug can be assayed by a standard analytical technique such as HPLC, spectrophotometer method, etc.

EVALUATION PARAMETERS

a) *In-vitro* drug release [36]

Different methods used to study the *in-vitro* release of the drug are:

1. Dialysis tubing

In-vitro drug release can be achieved by using dialysis tubing. The solid lipid nanoparticle dispersion is placed in the pre-washed dialysis tubing which can be tightly sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature, at specific intervals the samples are withdrawn from the dissolution medium. After centrifugation analyzed for the drug content by using a suitable analytical method.

2. Reverse dialysis

This technique is similar to dialysis tubing but it contains several small dialysis sacs of 1 mL dissolution medium that are placed in SLN preparation. The SLN's are then displaced into the medium.

3. Franz Diffusion Cell:

The SLN's formulation is placed in the donor chamber of the Franz diffusion cell is fitted with a cellophane membrane. The sample preparation is then analyzed against a suitable dissolution medium, at suitable intervals the samples are withdrawn from the dissolution medium and measured for drug content using a suitable technique like spectroscopy and HPLC methods.

b) Rheology [37]

Rheological measurements of preparations can be performed by Brookfield Viscometer, using a suitable spindle number. The viscosity depends on the dispersed lipid drug content. If the lipid content is greater, the flow becomes non-Newtonian from Newtonian.

c) Acoustic methods [38]

It is another ensemble approach for determining the size using acoustic spectroscopy, it measures the attenuation of sound waves of particles through the fitting of physically relevant equations. Also, the oscillating electric field produced by the movement of charged particles

under the influence of acoustic energy and also can be detected to provide information on surface charge.

Storage stability of SLN [39]

The physical properties of SLN's during prolonged storage can be determined by measuring changes in zeta-potential, particle size, drug content determination, appearance and viscosity as the function of time. The other external parameters such as temperature and light appear to be of primary play important role in the long term stability.

Applications of solid lipid nanoparticles [40]

Solid lipid nanoparticles lead to better stability and ease of upgradability to produce a large scale as compared to other formulations. The various application of SLN as follows,

1. SLNs for topical use:

SLNs and have been used for topical applications for various drugs such as anti-cancer, antifungals, etc. because this method is useful for the improvement of penetration with controlled release.

2. Oral SLNs in anti-tubercular chemotherapy

Anti-tubercular drugs such as rifampicin, isoniazid loaded SLN systems, were capable to decrease the dosing frequency and improve patient compliance, anti-tubercular drug-loaded SLN are prepared by using the emulsion solvent diffusion technique.

3. SLNs as cosmeceuticals:

The SLNs have been applied in the formulation of sunscreens and as an active carrier agent for molecular sunscreens and UV blockers. The *in-vivo* studies of 4% SLN showed 31% of skin hydration after 4 weeks compared to another conventional cream. Better localization has been developed for vitamin A supplements.

4. SLNs for potential agriculture application:

When Essential oil is incorporated in SLN, were able to reduce the rapid evaporation compared to other emulsions and the systems have been used in the agriculture field as a suitable carrier for the preparation of ecologically safe pesticides.

5. Stealth nanoparticles:

These offer a novel and unique drug-delivery system that evade rapid clearance by the immune system. Theoretically, nanoparticles can target specific cells. As per Studies antibody labeled stealth lipobodies shown increased delivery to the target tissue in available sites. Stealth solid lipid nanoparticles have been successfully tested in animal models with marker molecules and drugs.

CONCLUSIONS

Now a day's novel drug delivery systems like nanotechnology which has been taken over by the pharmaceutical industry. Solid lipid nanoparticle is a successful method for enhancing the solubility of poorly water-soluble drugs such as anti-inflammatory, antifungal, antimicrobial, etc. The possibility of incorporating both the lipophilic and hydrophilic molecules and the possibility of the several administrations make the SLNs delivery system all the more promising SLNs will open a new channel for the effective delivery of a vast variety of drug molecules. SLN having size nanometer range particles increases the bioavailability of various classes of drugs. Clear advantages of SLN include the composition (physiological compounds), the rapid and effective production process including the possibility of large-scale production, the avoidance of organic solvents and the possibility to produce carriers with higher encapsulation efficiency. The present articles review different methods used for the controlled release of the drugs at specific sites and to be promising nanocarrier for the topical delivery of drugs.

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