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RESEARCH ARTICLE

SOLID LIPID NANOPARTICLES- A RECENT APPROACH TO THERAPEUTICS

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ABSTRACT

Solid lipid nanoparticles (SLN) are at the emerging stage of the fastest developing field of nanotechnology with many useful applications in drug delivery and research. Because of their unique nano size properties, solid lipid nanoparticles give the possibility to develop new therapeutics. The talent to incorporate drugs into nanocarriers gives a new thought in drug delivery that could be used for drug targeting. Therefore solid lipid nanoparticles hold great promise for achieving the goal of site specific drug delivery. This review presents a broad introduction of solid lipid nanoparticles discussing their aims, procedures for preparation, advantages, limitations, applications, patents related to the field and marketed products for skin developed as solid lipid nanoparticles.

Key words: Nanotechnology, Solid lipid nanoparticles, nano size, patents, marketed products for skin.

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INTRODUCTION

Nanotechnological products are unique and possess new characteristics entirely different from original base products from which they are derived. It is also defined as nanomaterials i.e. the materials which have one or more external dimensions or an internal structure in the nano range. The term nanotechnology originally originated from the Greek word meaning dwarf (Patel and Parixit, 2011). About 4000 years ago, nanotechnology was applied in the hair dye preparation because of its better benefits than the normal materials unknowingly by prehistoric Egyptians and Romans (Bangale *et al*., 2012).

Mechanism of skin penetration of nanoparticles

Skin is the largest organ of the human body and is made up of three layers such as epidermis, dermis and hypodermis. The epidermis is divided into several layers and the outermost layer is called stratum corneum, which is responsible for the various functions of the skin due to its lipophilicity and cohesion between the cells. The possible passive routes are intercellular, transcellular and the appendageal route by which a molecule can cross the stratum corneum. A variety of cosmaceutical products containing nanoparticles already exist in the market, but the safety concerns of the same with respect to its skin penetration and dangers related to it raises the question whether to use or not the nanoparticles in cosmaceuticals. The question can be answered when the manufacturer of the same studied the safety profile of the nanocosmaceuticals in the public domain. The skin penetration of the nanoparticles and the transport through the skin is determined by the physicochemical properties of nanoparticles and by the vehicles, ingredients used and skin conditions. The dermal absorption of nanoparticles does not occur immediately, but it may occur in certain conditions. Previously nanocosma ceuticals were used only in the healthy skin, but in recent days the usage also extends to unhealthy skin too. In such conditions skin may be having the impaired barrier properties which may lead to further complications. Many research reports states that the topical nanomaterials are penetrating through hair follicle openings and skin pores and they also reported that minimal amount of active ingredient was found below stratum corneum and it is not a serious issue, but in future the most reliable reports extensive study opinion may strengthen this preliminary report (Raj *et al*., 2012; Lohani *et al*., 2014).

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Solid lipid nanoparticles

Particulate drug carriers are under intensive study for many years based on the formulation such as oil-in-water (o/w) emulsions, liposomes, microparticles and nanoparticles. These systems are developed based on the two polymer system such as synthetic and natural macromolecules. The vesicles of phospholipids were rediscovered as `liposomes' in 1965 by Bangham and made their entry in cosmetic industry in 1986 (Müeller *et al*., 2000).

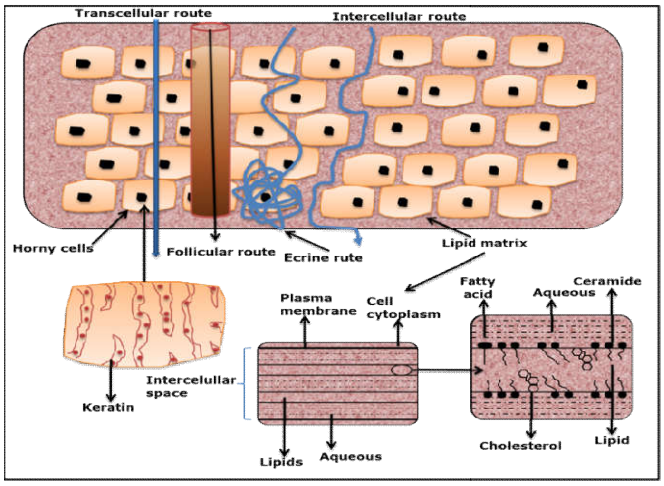

Figure No.1 Schematic representation of penetration routes of drugs throughout the skin (Chavez *et al.*, 2012)

In the early nineties there was a focus on the development of newer nanocarriers to replace the liposomes due to its disadvantages. The newer nanoparticles were developed based on polymers which were called polymeric nanoparticles (Mehnert and 2001). In 1998 the new range of nanoparticles called Solid lipid nanoparticles (SLN) found to be efficient than older versions of nanoparticles. Current number of researches is updated on Solid lipid nanoparticles for various purposes as it has several advantages (Garud *et al*., 2012). The production of lipid nanoparticles and microparticles can be done by spray congealing method which was first discovered by Speiser *et al.* Nanopallets were prepared in early eighties for per oral administration. The lipids can be used in Solid lipid nanoparticles, which are well tolerated by the body. For example the glycerides are composed of fatty acids, which are present in emulsion for parenteral nutrition.

The large scale production of SLNs is as easy as it can be prepared by using simple techniques like high pressure homogenization techniques or SLN can be prepared via Microemulsion as an alternative method (Mehnert and Mäder, 2001). Solid lipid nanoparticles are successful carrier systems for poorly water soluble drugs and cosmetically active drugs. The colloidal particles ranging from 10-1000 nm are synthesized from synthetic and natural polymers are proved to be superior in optimizing drug delivery and reducing toxicity. The polymeric nanoparticles have emerged as a suitable alternate to liposomes as drug carriers. The success rate of nanoparticles for the drug delivery depends on the capacity to circumvent the anatomical barrier sustained release profile and the stability of the nanopreparation in determined size range. SLN are next generation submicron sized particles of emulsion in which liquid lipid have been replaced by solid lipid. SLNs can be simply defined as a colloidal carrier composed of physiological lipid, dispersed in water with surfactants (Jain *et al*., 2011).

Advantages of SLN

- Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods.
- Improved bioavailability of poorly water soluble molecules.
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application
- Possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment
- SLNs have better stability compared to liposomes
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- High concentration of functional compound achieved.
- Lyophilization possible (Ekambaram *et al*., 2012), (Garud *et al*., 2012).

Disadvantages of SLN

- Poor drug loading capacity.
- Drug expulsion after polymeric transition during storage.
- Relatively high water content of the dispersions (70-99.9%). (Kamble and Jagdale, 2010)

Methods of preparation

High shear homogenization (HSH): Firstly this method was used for the production of Solid lipid nanoemulsions. It involves high pressure homogenization which pushes the liquid with high pressure (100-2000 bar) through a narrow gap ranging a few microns. Very high shear stress and cavitation forces break the particles down to submicron range. Two general approaches to achieve HSH are hot homogenization and cold homogenization processes (Ghada and Rania, 2009).

Hot homogenization: Is carried out at temperatures above the melting point of the lipid. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase (same temperature) is obtained by high shear mixing device. The resultant product is a hot o/w emulsion and the cooling of this emulsion leads to crystallization of the lipid and the formation of SLNs. Smaller particle sizes are obtained at higher processing temperatures because of the lowered viscosity of the lipid phase. However, high temperature leads to the degradation rate of the drug and the carrier. Increasing the homogenization temperature or the number of cycles often results in an increase of the particle size due to the high kinetic energy of the particles. Generally, 3-5 homogenization cycles at a pressure of 500-1500 bar are used (Ghada and Rania, 2009).

Cold homogenization: Is a method which is developed to over-come the temperature related degradation problems, loss of drug into the aqueous phase and partitioning associated with hot homogenization method. Here, drug is incorporated into melted lipid and the lipid melt is cooled rapidly using dry ice or liquid nitrogen. The solid material is ground by a mortar mill. The prepared lipid microparticles are then dispersed in a cold emulsifier solution at or below room temperature. However, compared to hot homogenization, larger particle sizes and a broader size distribution are typical of cold homogenization samples (Ghada and Rania, 2009).

Double Emulsion: In this method, the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase during solvent evaporation in the external water phase of w/o/w double emulsion. Li *et al.* (2010) prepared Solid lipid nanoparticles loaded with bovine serum albumin (BSA) using double emulsion method (Garud *et al*., 2012).

Table No. 1. Recent patent review on nanoparticles based skin preparation

Title	Publication no.	Publication date	Applicant	Ref no
Thermal treatment of acne with nanoparticles	US 8834933B2	Sept 16, 2014	Sienna Labs. Inc	[16]
Novel nanoparticles formulation for skin delivery	US20120195957A1	August 2, 2012	Mandip Singh Sachdeva , Ram Patolla	[17]
Nanoparticles dispersion for detection of skin health conditions and diagnostic kit thereof	W02014108758A1	July 17, 2014	ITC Limited	[18]
Polymeric nanoparticles for photosensitizers	WO2013/020204	February14, 2013	Quest Pharmatech Inc.	[19]
Mitadichol® liquid and gel nanoparticles formulation	US20140275285A1	September 18, 2014	NanoRx, nc	[20]
Virucidal materials	W02007093808A2	August 23, 2007	Queen Mary and Westfield College	[21]
Compositions containing lipid micro or nanoparticles for the enhancement of the dermal action of solid particles	W02010051918A2	May 14, 2010	Pharmasol GmBh	[22]
Virion derived protein nanoparticles for delivering diagnostic or therapeutic agents for treatment of skin related diseases	W02013009717A1	January 17, 2013	Los Pinos Elisabet De	[23]
Protein nanocarriers for topical delivery	US20120195947A1	August 2, 2012	Omatanu P. Perumel	[24]
Triggered cargo release from nanoparticles stabilized liposomes	EP2545533A1	January 16, 2013	The Reagent of the University of California	[25]
SLN of Roxithromycin for hair loss and acne	W02014077712A1	May 22, 2014	Gdanski Universytet	[26]

Table No. 2. Marketed nanoskin care products

Marketed Product	Manufacturer	Type of nanoproduct	Use
MAX SPF 29	Dermazone Solutions	Nanospheres	Moisturizer
Leorex hypoallergenic wrinkle nano remover	Global Med Technologies	Nano Silicon dioxide	Anti Wrinkle
Revlon colorstay natural powder	Revlon	Nano Aluminium	Foundation effect
Rivatalift intense	L'Oreal	Nanosomes	Anti wrinkle
Neutrogena line	Johnson and johnson	Novasomes	Antiacne
Hydra flash bronzer	Lancome	Nanocapsules	Moisturizer
Pureology COLOURMAX	Pureology	Nonoemulsion	Hair Colour
Calming alcohol free nanoemulsion	Chanel precision	Nanoemulsion	Skin softner
Olay complete UV protective moisture lotion	Proctor and gamble	Zinc oxide and titanium dioxide nanomaterial	Moisturizer
Sultan facial sun defense cream	Boots	Zinc oxide and titanium dioxide nanomaterial	Sunscreen
Eye tender	Kara vita	Nanospheres	Anti wrinkle
Nano gold firming treatment	Chantecaille	Nanogold particles	Antiageing
Nano cyclic cleanser silver	Nano cyclic	Nanoparticles	Cleanser
Dior Snow Pure UV Base SPF 50	Dior	Nanoparticles	Sunscreen

Characterization of SLNs: Characterization of SLN is a serious challenge due to the colloidal size of the particles and the complexity and dynamic nature of the delivery system. The important parameters evaluated for the SLNs include particle size, size distribution kinetics (Zeta potential), degree of crystallanity and lipid modification (polymorphism), time scale of distribution processes, drug content, *in-vitro* drug release and surface morphology (Garud *et al*., 2012).

Measurement of the particle size and Zeta potential: The physical stability of SLNs is attributed to their particle size. Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most powerful techniques for determination of particle size. PCS (also known as dynamic light scattering) measures the fluctuation in the intensity of the scattered light. The particle size determination by photon correlation spectroscopy (PCS) detects size range of 3nm to 3µm and by laser diffraction in size range of 100 nm to 180 µm. The LD method is based on the dependence of the diffraction angle on the particle size. Smaller particles cause more intense scattering at high angles compared to the larger ones. Zeta potential measurement can be carried out using zeta potential analyzer or zetameter. Before measurement, SLN dispersions are diluted 50-fold with the original dispersion preparation medium for size determination and Zeta potential measurement. Zeta potential measurements allow predictions about the storage stability of colloidal dispersions (Ekambaram *et al*., 2012).

Electron microscopy: Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) provide way to directly observe nanoparticles. It permits the determination of from the surface of the sample while TEM uses electrons transmitted through the sample (Kamble and Jagdale, 2010).

Atomic force microscopy (AFM): It is an advanced microscopic technique which is used to view the original unchanged shape and surface properties of the particles. AFM measures the force which is acting between surface of the sample and the tip of the probe, when the probe is kept in close proximity to the sample (Ghada and Rania, 2009).

X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC): The geometric scattering of radiation from crystal planes within a solid allow the presence or absence of the crystal nature thus permitting the degree of crystallinity to be assessed. DSC can be used to determine the nature and speciation of crystallinity within nanoparticles through the measurement of glass and melting point temperatures and their associated enthalpies (Ekambaram *et al*., 2012).

Estimation of incorporated drug

Entrapment efficiency: This is the prime importance in SLN, since it influences the release characteristics of drug molecule. The amount of drug encapsulated per unit weight of nanoparticles is determined after separation of the entrapped drug from the SLN formulation. This separation can be carried out using the techniques such as ultracentrifugation, centrifugation filtration and gel permeation chromatography (Ekambaram *et al*., 2012).

In vitro drug release

Dialysis tubing: In vitro drug release could be achieved using dialysis tubing. The Solid lipid nanoparticles dispersion is placed in pre-washed dialysis tubing which can be hermetically sealed. The dialysis sac then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the dissolution medium at suitable intervals, centrifuged and analyzed for the drug content using a suitable analytical method (Tsai and Hantash, 2008).

Reverse dialysis: In this technique a number of small dialysis sacs containing 1 ml of dissolution medium are placed in SLN dispersion. The SLN's are then displaced into the medium (Tsai and Hantash, 2008).

Applications of SLNs

SLN for Parenteral application: Wissing *et al.* (2004) reviewed that parenteral use of SLN is quite safe and well tolerated as they consist of physiologically well-tolerated ingredients and they have good storage capabilities after lyophilization or sterilization. When injected intravenously, SLN are very small to circulate in the microvascular system. Therefore, SLN have been suggested for viral and non-viral gene delivery. Cationic SLN have potential benefits in targeted gene therapy in treatment of cancer. Treatment of central nervous system diseases such as brain tumors, AIDS, neurological and psychiatric disorders is possible via SLNs as hydrophilic coating of colloids improves the transport of these through BBB and tissue distribution

SLN for Nasal Application: Nasal administration was a promising alternative route of drug administration due to fast absorption and rapid onset of drug action and avoiding degradation of labile drugs in the GI. SLN were proposed as alternative transmucosal delivery systems by various research groups. The role of PEG coating of polylactic acid nanoparticles in improving the transmucosal transport of the encapsulated bioactive molecule reported to be successful by Tobio *et al*, 1998.

SLN for Respiratory Application: The lungs offer a high surface area for drug absorption by avoiding first-pass effects. SLN can be proposed as carriers of anti-cancer drugs in lung cancer treatment or peptide drugs to improve their bioavailability. In a recent study, antitubercular drugs (rifampicin, isoniazid and pyrazinamide) were incorporated into various formulations of solid lipid particles ranged from 1.1–2.1 μm and formulations were nebulized to guinea pigs by mouth for direct pulmonary delivery. Nebulization of solid lipid particles carrying antitubercular drugs was observed to be successful in improving drug bioavailability and reducing the dosing frequency for better management of pulmonary tuberculosis.

SLN for Ocular Application: Bio-compatibility and mucoadhesive properties of SLN improve their interaction with ocular mucosa and prolong corneal residence time of the drug, with the aim of ocular drug targeting. Cavalli *et al.*, (2002) evaluated SLN as carriers for ocular delivery of tobramycin in rabbit eyes. As a result SLN significantly enhanced the drug bioavailability in the aqueous humor. Cavalli *et al.*, (1995) also studied pilocarpine delivery via SLN, which is commonly used in glaucoma treatment, earlier. They reported very similar results in order to enhance the ocular bioavailability of drug.

SLN for Topical application: SLN and NLC are very attractive colloidal carrier systems for skin applications due to their various desirable effects on skin besides the characteristics of a colloidal carrier system. They are well suited for use on damaged or inflamed skin because they are based on non-irritant and non-toxic lipids. Researchers have reported intensively on the topical application of SLN. During the last few years, SLN and NLC have been studied with active compounds such as Vitamin E, tocopherol acetate, retinol, ascorbyl palmitate, clotrimazole, triptolide and phodphyllotoxin for topical application. A completely new, recently discovered area of application is the use of SLN in sun-protective creams.

SLN in Cancer chemotherapy: From the last two decades several chemotherapeutic agents have been encapsulated in SLN and their *in-vitro* and *in-vivo* efficacy have been evaluated. Tamoxifen, an anticancer drug has been incorporated in SLN to prolong the release of drug following i.v. administration in breast cancer (Kamble and Jagdale, 2010).

Market potential: The projected market research on skin care products signals strong growth perspective in future. The market growth is expected to rise rapidly at an annual growth rate of 7.7%. The projected market potential is expected to reach $31.84 billion by 2016. The Asian countries such as Japan, China and India expected to offer a huge impact on this global skin care market (Venkateswarlu and Manjunath, 2004).

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