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A Review on Solid Lipid Nanoparticles for Ocular Drug Delivery System

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A B S T R A C T

Solid Lipid Nanoparticles consist of a solid lipid matrix which is ability to stabilize in a surfactants having particle size of 50-1000 nm. The Solid lipid nanoparticles are the effective lipid based colloidal carriers which were introduced as an alternative to the conventional carriers such as SLNs based on synthetic polymers or natural macromolecules. It enhances the oral bioavailability of the low aqueous soluble drugs due to their potential to enhance gastrointestinal solubilization. To improve the therapeutic efficacy of the drugs having low bioavailability, as well as to reduce their effective dose requirement. The various proportions of gels are incorporated in SL Nanoparticles, Gel formation of nanoparticles applied on the eye based on the classification of drug it may various in action. Appropriate analytical techniques for the characterization of SLN like photon correlation spectroscopy, scanning electron microscopy, differential scanning calorimetry are highlighted. Aspects of SLN route of administration and the *in vivo* fate of the carriers Applications with respect of routes of administration such as oral, parenteral, topical, pulmonary etc. These polysaccharides are renewable resources which are currently being explored intensively for their applications in pharmaceutical, cosmetics, biomedical, biotechnological, agricultural, food, and non-food industries.

Keywords: Solid lipid Nano particles, Ocular Drug delivery system, Insitu gels

A R T I C L E I N F O

CONTENTS

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1. Introduction

SLN are widely used to improve bioavailability and to achieve sustained release. To overcome hepatic first-pass metabolism and to enhance bioavailability, intestinal lymphatic transport of drugs can be exploited. Transport of drugs through the intestinal lymphatic via the thoracic lymph duct to the systemic circulation at the junction of the jugular and left sub clavian vein, avoids pre systemic hepatic metabolism and therefore enhances circulation via the lymphatics. Lipid-based drug delivery systems leishmanial infections, shows poor bioavailability enhance the bioavailability of lipophilic drugs by lymphatic transport of biosynthesized chylomicrons associated with the drugs. Solid Lipid Nanoparticles consist of a solid lipid matrix (at room and body temperatures) which are stabilized by surfactants and have a mean size of 50- 1000 nm and stabilized by surfactants.

Methods of preparation: Various methods of preparations of solid lipid nanoparticles have been proposed to meet different objectives[1]. The following are methods used for preparing solid lipid nanoparticles.

High pressure homogenization technique:

This technique was first developed by Muller and Lucks. High pressure homogenization technique can be employed for both hot and cold homogenization processes where the initial common step involves dispersing or dissolving the drug in a melted lipid phase[2].

Hot High Pressure Homogenization:

Initially the lipid is melted approximately above 5°C it's melting point followed by dispersing or dissolving the drug in the melted lipid to produce an oil phase. The simultaneously, a suitable surfactant is dissolved in water to produce an aqueous phase which is also heated to maintain at a temperature similar to the oil phase. Then the melted lipid phase is dispersed in the aqueous phase using a high speed stirrer to form a pre emulsion. This pre emulsion is passed through a high pressure homogenizer with optimized conditions of pressure and cycles to obtain an aqueous suspension of nanoparticles.

Cold High Pressure Homogenization:

Similar to the hot homogenization method, initially the lipid is melted approximately above 5°C its melting point and dispersing or dissolving the drug in the hot melted lipid to produce a clear and homogeneous oil phase followed by cooling the melt using dry ice or liquid nitrogen to form a solid drug dispersed lipid matrix. A high cooling rate will provide dispersion where the drug is uniformly distributed in the matrix. Then the solidified lipid matrix is reduced to microparticles by ball or mortar milling. This dispersion of lipid microparticles is then dispersed in a cold surfactant and is allowed to pass through a high pressure homogenizer to form a suspension containing nanoparticles of the drug[3].

For substances which are thermo labile, cold high speed homogenization is the preferred method as the time of exposure to the heat is less when compared to the hot high speed homogenization method. The cold high pressure homogenizer technique can also be used when the lipid matrix consists of lipids with high melting points. This technique is less effective in dispersing the lipids and during the production the solid lipid matrix remains in the solid state despite high temperatures observed in the high speed homogenizer.

Solvent emulsification- evaporation technique:

This technique was initially developed by Sjostrom and Bergenstahl (1992). Initially, the lipid material is dissolved in water-immiscible organic solvents like cyclohexane or dichloromethane or chloroform or methylene chloride, followed by the addition of drug to it. An aqueous phase containing surfactant is prepared and the organic phase is emulsified into it by stirring at high speeds. Then the organic phase is allowed to evaporate under mechanical stirring or reduced pressure to obtain an o/w emulsion consisting of a dispersion of nanoparticles which is formed by precipitation of the lipid in the aqueous medium [2]. The solvent evaporation step must be quick for the formation of smaller particles as it prevents the aggregation of particles. This technique can be best applied for the incorporation of hydrophilic molecules such as proteins and peptides. A brief schematic representation of the process is given in figure. 1

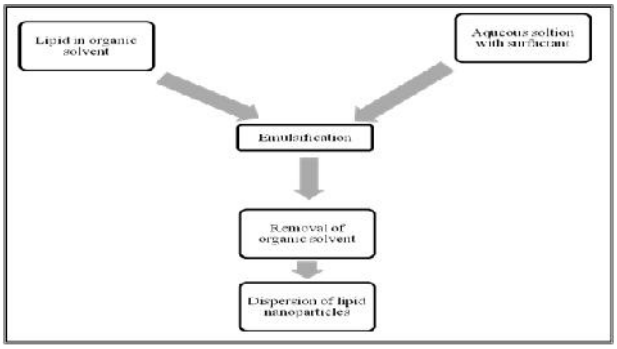

Figure 1: Schematic representation of solvent emulsification technique

2. Barriers of the Eye Surface Removal

Lachrymal secretions wash away topically applied drugs continuously and the excess of the lachrymal fluid flows down the naso lachrymal duct. Due to the presence of an extensive network of capillaries in the conjunctival sac and the nasal cavity, most of the drugs applied topically are absorbed into the systemic circulation, thereby reducing the ocular bioavailability to 5–10% only. Systemic absorption from the ocular surface can cause side-effects, especially if the patient has various medication needs [3]. The human cul-de-sac can usually accommodate ~ 30 µL of fluids,

whereas the instilled volume from eye drops is ~ 50 µL. Therefore, large volumes of the medicament are lost through spillage from the cul-de-sac. Nasolachrymal drainage further limits the ocular absorption. These limiting factor under pre therapeutic efficiency and reduce the pre-corneal half-life of drugs to ~ 1–3 min.

Epithelial Barrier:

This is the main route through which topically administered drugs reach the aqueous humor. The cornea is a multilayered tissue consisting of the epithelium, the endothelium, and the stroma. The epithelial layer is lipophilic and consists of tight junctions that limit the entry of hydrophilic drugs and macromolecules into the cornea and the aqueous humor. This barrier can be breached by an epithelial defect by sub conjunctiva injection. In some eye conditions such as glaucoma and conjunctivitis, the corneal absorption increases significantly due to the morphological changes. This, along with the use of permeation enhancers and muco-adhesives, can be explored further to achieve better corneal penetrations [4]. Hence, the epithelium is the main barrier for hydrophilic drugs while the stroma and endothelium limit the entry of lipophilic drugs.

Blood–aqueous barrier:

This barrier is situated in the anterior segment of the eye and is composed of endothelial cells in the uvea. It limits the entry of hydrophilic drugs from the systemic circulation into the aqueous humor. This barrier gets disrupted sometimes due to inflammation and results in enhanced temporary drug permeation. Together with the blood–retinal barrier they make up the blood–ocular barrier [4]. The epithelium of the iris and the ciliary bodies pump anionic drugs out from the aqueous humor to the systemic circulation.

Blood–retinal barrier:

Situated in the posterior chamber, this barrier limits the entry of drugs from the systemic circulation to the retina. It is composed of retinal pigment epithelium (RPE) and the tight walls of the retinal capillaries. Although drugs can reach the choroid extra vascular space easily through the leaky and extensive vasculature of the choroid, their retinal access is denied by RPE and retinal endothelia [5]. The blood–retinal barrier, along with the blood–aqueous barrier, protects the eyes from the entry of xenobiotics and harmful substances. This physiological defense mechanism limits drug delivery to the retina and vitreous humor via the choroid through the systemic circulation.

Ocular Drug Delivery System:

The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration. Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time [6]. Consequently it is imperative to optimize ophthalmic drug delivery; one of the ways to do so is by addition of polymers of various grades, development of in situ gel or colloidal suspension or using erodible or non erodible insert to prolong the pre corneal drug retention.

3. Routes of Ocular Drug Delivery

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue [7].

- **Topical route**
- **Sub conjunctival administration**
- **Intravitreal administration**

Topical route:

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, jellifying formulations, ointments, and inserts).

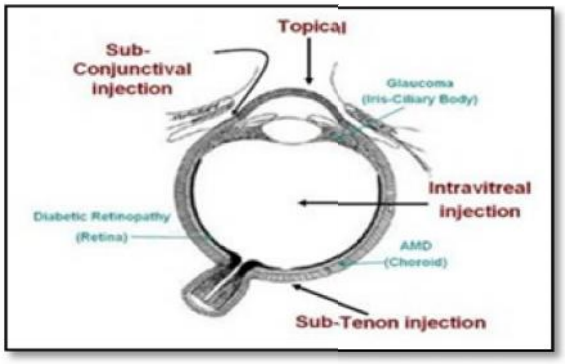

Figure 2: Different Routes for Ocular Drug Delivery

Subconjunctival administration:

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

Intravitreal administration:

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that rapidly in the vitreous but the mobility of large molecules, particularly positively charged is restricted.

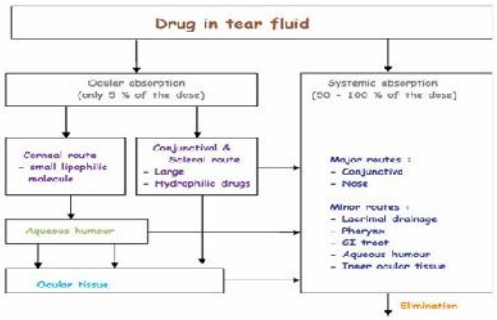

Figure 3: Ocular Drug Absorption

Mechanism of ocular drug absorption:

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea 8.

Table 5: Barriers for the Ocular delivery

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16-17
Thickness	- - - - - -	0.57 mm	0.4 – 0.5mm
Structural Composition	Mucus membrane Epithelium Vasculature	5 layers Epithelium Bowman's membrane Stomata Descemet's membrane Endothelium	Collagen fibers Water Proteoglycans Monopolysaccharides Elastic fibers Fibroblast

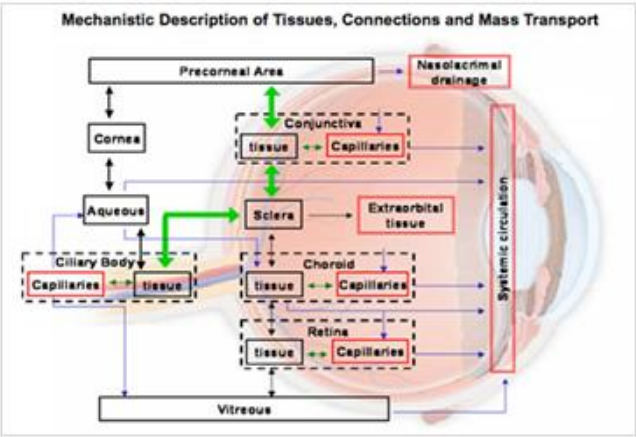

Figure 4: Mechanism Description of Tissues, Connections and Mass Transport

Nasolacrymal drainage system:

The Nasolachrymal drainage system consists of three parts: the secretary system, the distributive System and the excretory system. The secretary system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation [9]. The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the nasolachrymal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculated; the lachrymal sac; and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla.

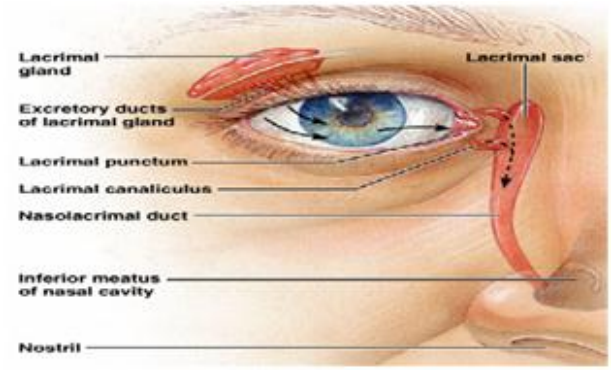

Figure 5: Nasaolachrymal Drainage Apparatus

Interests of novel ophthalmic drug delivery:

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fueling the demand for novel drug delivery [10]. The emergence of new and innovative means for improving therapeutic efficacy suggests that a greater choice of dosage forms will be provided to physicians and patients in the next decade. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss.

Preparation of SLN Loaded Gels

Then selected drugs of SLNs were incorporated in the Selected gels at the various concentration prepared installed into the eye [11].

Method of Evaluation of gel:

Preliminary evaluation of gel (gelation temperature): The different formulations of selected combinations were evaluated for gelation temperature. The gelation temperature was determined by heating the solution (1-20c)/min in a test tube with gentle stirring until gel was formed. The gel was said to have formed when there was no flow after container was over turned [12].

Determination of pH: The pH of the SLN Gel was determined using a calibrated pH meter [12].

Measurement of Gel Strength:

A sample of 50 gm of gel was placed in a 100 ml graduated cylinder and gelled in a thermostat at 370c. The apparatus for measuring gel strength was allowed to penetrate in selected gel [13]. The gels strength, which means the viscosity of the gels at physiological temperature, was determined by the time (seconds), the apparatus took to sink 5cm down through the prepared gel.

Viscosity Studies:

The rheological studies were carried out using Brookfield programmable. The gel under study was placed in a small sample holder with a facility of water circulation. Water was circulated in the jacket with the help of water immersion pump. Initially ice-cold water was circulated and then hot water to raise the temperature gradually. The

temperature sensing probe was lowered in the gel was recorded [14]. Spindle number SS64 was lowered vertically in it. The spindle was rotated at varying speed.

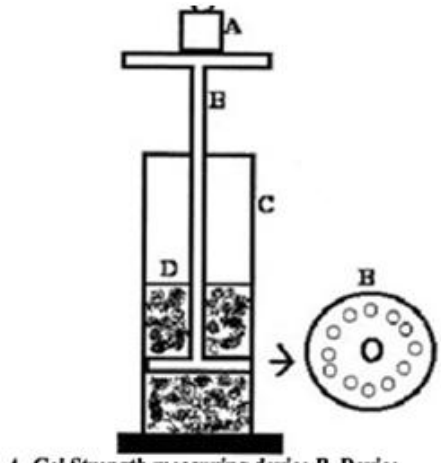

Figure 6: Measurement of Gel Strength

Determination of mucoadhesive Force:

The mucoadhesive force of all the optimized batches was determined as follows, a section of mucosa was cut from the chicken cheek portion and instantly fixed with mucosal side out onto each glass vial using rubber band. The vial with chicken cheek mucosa was connected to the balance in inverted position while first vial was placed on a height adjustable pan [15]. Oral gel was added onto the nasal mucosa of first vial. . Before applying the gel, 150µL of simulated saliva solution was evenly spread on the surface of the test memberane. Then the height of second vial was so adjusted that the mucosal surfaces of both vials come in intimate contact. Two minutes time of contact was given. Then weight was kept rising in the pan until vials get detached. Mucoadhesive force was the minimum weight required to detach two vials. The cheek mucosa was changed for each measurement.

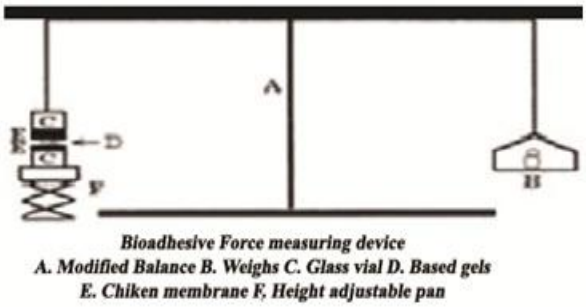

Figure 7: Bioadhesive force measuring device

Content Uniformity:

Buccal cavity of Isolation of chicken cheek mucosa from the anterior healthy chicken was obtained from the local slaughter house. It was cleaned and the mucosa was re-moved from the anterior buccal cavity. The mucosa was stored in normal saline with few drops of gentamycin sulphate injection, to avoid bacterial growth[16]. After the removals of blood from the mucosal surface it become ready for use

Diffusion Medium:

The diffusion medium used was phosphate buffer 7.4 pH, Assembly of diffusion cell for in–vitro diffusion studies the oral diffusion cell was designed as per the dimension given. The diffusion cells were placed on the magnetic stirrers. The outlet of the reservoir maintained at 37±0.5. C and was connected to water jacket of diffusion cell using rubber latex tubes. The receptor co presentment was filled with fluid. Then the prepared chicken cheek mucosa was mounted on the cell carefully so as to avoid the entrapment of air bubble under the mucosa. Intimate contact of mucosa was ensured with receptor fluid by placing it tightly with clamp [17]. The speed of the sitting was kept content throughout the experiment.With the help of micropipette 1ml of sample was withdrawn at a time intervals of fifteen min. from sampling port of receptor compartment and same volume was the replaced with receptor fluid solution in order to maintain sink condition. The samples were appropropriately diluted and the absorbance was measured at 260 nm using UV-VIS spectrophotometer.

4. Conclusion

The Sample dilution or water removal might significantly change the equilibrium between the different colloidal species and the physical state of the lipid. The different polymers are prepared in various concentrations are incorporated on the eye contain lachrymal fluids washing topically applied the drugs continuously and the excess of the fluid flows down the naso lachrymal duct. The appropriate characterization of the complex surfactant/lipid dispersions requires several analytical methods in addition to the determination of the particle size. The SLN are very complex systems with clear advantages and disadvantages to other colloidal carriers. Further work needs to be done to understand the structure and dynamics of SLN on molecular level

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6. References

[1] Attama AA, Schicke BC, Müller-Goymann CC. Further characterization of theobroma oil-beeswax admixtures as lipid matrices for improved drug delivery systems. Eur J Pharm Biopharm, 64: 294–306, 2006.

[2] Cavalli R, Caputo O, Carlotti ME, Trotta M, Scarnecchia C, Gasco MR. Sterilization and freeze-drying of drug-free and drug-loaded solid lipid nanoparticles. Int J Pharm, 148: 47–54, 1997.

[3] Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MF. Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int J Pharm, 238: 241–245, 2002.
[4] Liu J, Gong T, Wang C, Zhong Z, Zhang Z. Solid lipid nanoparticles loaded with insulin by sodium cholate-phosphatidylcholine- based mixed micelles: preparation and characterization. Int J Pharm, 340: 153–162, 2007.
[5] Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. Eur J Pharm Biopharm, 50: 161–177, 2000.
[6] Almeida, A.J., Runge, S., Müller, R.H. Peptide-loaded solid lipid nanoparticles (SLN): influence of production parameters. Int J Pharm. 149:255–65, 1997.
[7] Bocca, C., Caputo, O., Cavalli, R., Gabriel L., Miglietta A., and Gasco M. R. Phagocytic uptake of fluorescent stealth and non- stealth solid lipid nanoparticles. *Int. J. Pharm.* 175:185–193, 1998.
[8] S. Collaud, Q.A. Peng, R. Gurny, N. Lange, Thermosetting gel for the delivery of 5-amino levulinic acid esters to the cervix, J. Pharm. Sci. 97, 2680–2690.
[9] J. Hartikka, A. Geall, V. Bozoukova, D. Kurniadi, D. Rusalov, J. Enas, J.H. Yi, A. Nanci, A. Rolland, Physical characterization and in vivo evaluation of poloxamer-based DNA vaccine formulations, J. Gene Med. 10, 770–782, 2008.
[10] L. Mayo, F. Quaglia, A. Borzacchiello, L. Ambrosio, M.I. La Rotonda, A novel poloxamers/ hyaluronic acid in situ forming hydrogel for drug delivery: rheological, mucoadhesive and in vitro release properties, Eur. J. Pharm. Biopharm. 70, 199–206, 2008.
[11] Y.X. Wang, Y.B. Tan, X.L. Huang, Y.J. Che, X. Du, Synthesis of biodegradable amphiphilic thermo-responsive multiblock polycarbonate and its selfaggregation behavior in aqueous solution, J. Appl. Polym. Sci. 112, 1425–1435, 2009.
[12] P. Alexandridis, J.F. Holzwarth, T.A. Hatton, Micellization of poly(ethylene oxide) poly(propylene oxide)–poly(ethylene oxide) triblock copolymers in aqueous-solutions – thermodynamics of copolymer association, Macromolecules 27: 2414–2425, 1994.
[13] G. Dumortier, J.L. Grossiord, F. Agnely, J.C. Chaumeil, A review of poloxamer 407 pharmaceutical and pharmacological characteristics, Pharm. Res. 23:2709 - 2728, 2006.
[14] J. Juhasz, V. Lenaerts, P. Raymond, H. Ong, Diffusion of rat atrial natriuretic factor in thermoreversible poloxamer gels, Biomaterials 10, 265–268, 1989.
[15] S.C. Miller, B.R. Drabik, Rheological properties of poloxamer vehicles, Int. J. Pharm. 18, 269–276, 1984.
[16] J.C. Gilbert, C. Washington, M.C. Davies, J. Hadgraft, The behavior of pluronic- F127 in aqueous-solution studied using fluorescent-probes, Int. J. Pharm. 40 93–99, 1987.
[17] A.H. El Kamel, In vitro and in vivo evaluation of pluronic F127-based ocular delivery system for timolol maleate, Int. J. Pharm. 241, 47–55, 2002.