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A Review: Solid Lipid Nanoparticles For Ocular Drug Delivery System

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Abstract: Solid lipid nanoparticles (SLNs) have emerged as promising carriers for ocular drug delivery systems due to their unique characteristics. These nanoparticles are composed of biocompatible lipids, providing a stable matrix for drug encapsulation. The solid nature of SLNs offers improved physical stability, preventing drug leakage and degradation during storage. The small particle size of SLNs facilitates efficient penetration through ocular barriers, enhancing drug bioavailability within the eye. Moreover, SLNs can be surface-modified to control drug release rates and improve targeting specificity. In the context of ocular drug delivery, SLNs offer advantages such as reduced systemic side effects and prolonged drug retention in the eye, leading to enhanced therapeutic outcomes. The biodegradable nature of lipid-based carriers further contributes to their safety profile. Overall, solid lipid nanoparticles represent a promising platform for the development of effective and safe ocular drug delivery systems, addressing the challenges associated with conventional formulations and improving patient compliance.

Key words: nanoparticles, eye, drug delivery, conventional formulations

I. INTRODUCTION

According to World Health Organization, the prevalence of eye conditions is expected to increase in the following years as a result of population aging, the associated rise of non-communicable diseases (diabetes, cardiovascular diseases), along with various lifestyle factors, such as an unhealthy diet, smoking, extensive usage of digital devices, etc. *[1,2,3,4]* Nanotechnology is a promising field that allows the improvement of the therapeutic efficiency, compliance, and safety of ocular drugs. Lipid-based nanocarriers are one of the most interesting colloidal drug delivery systems once they are biodegradable and biocompatible. Therefore, they have secured the title of nanoscale carrier[5]. More recently, biological agents, such as inhibitors of tumor necrosis factor alpha (TNF-α), have been tested [6]. solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are interesting carriers for ophthalmic applications[7] SLNs and NLCs can be designed to treat the most critical ocular disorders, such as joint ocular drug inflammation or infection, glaucoma, or diseases that affect posterior eye structures. These systems are an innovative approach that has been considered a promising strategy for treating some disorders in the retina [6]. Drug delivery systems based on nanocarriers are highly interesting due to their small particle size, low ocular irritation potential and suitable drug availability. Moreover, for topical drug delivery, the nanocarrier should overcome the mucous layer of the corneal surface. Therefore, nanocarriers made of polymers or lipids with mucoadhesive properties are of particular relevance [8]. The application of nanocarriers represents a promising means to selectively deliver and concentrate drugs in ocular lesions. Among all the nanocarriers, polymer-based nanocarriers PNCs) and lipid-based nanocarriers (LNCs) are particularly attractive. Specifically, both PNCs and LNCs have been shown to enhance penetration, retention and solubility, reduce toxicity, prolong release, and enable targeted delivery of the drug [8, 9]. In addition to these common characteristics, uniquely, the PNCs are provided with versatility by precise control

of particle characteristics and the ease of surface modification, while LNCs are offered with advantages such as formulation simplicity with a range of physicochemical properties, use of physiological lipids and GRAS excipients, and the industrial scale production facility at low cost [10, 11].

II. EYE ANTAMOY

Generally, human eye structures are distinguished according to their location in the eyeball, where the eye is divided into two segments (anterior and posterior) (Figure 1A), or according to their functionalities, where it is divided into three different layers—an outer (fibrous), middle (vascular) and inner (neuronal) coat [12]. The outer layer (fibrous tunic) consists of the cornea (at its front) and sclera, occupying five-sixths of the coat [13]. Its main functions are related to maintaining the shape of the eyeball, and providing protection to the inner ocular tissues [14]. The middle layer, also referred to as uvea, is composed of the iris and the ciliary body (in the anterior), and the choroid, forming the posterior uvea [15]. The retina represents the innermost layer, which is involved in the visual perception process by converting light energy into neuronal signals, which are transmitted to the visual cortex of the brain by the optic nerve [16, 17].

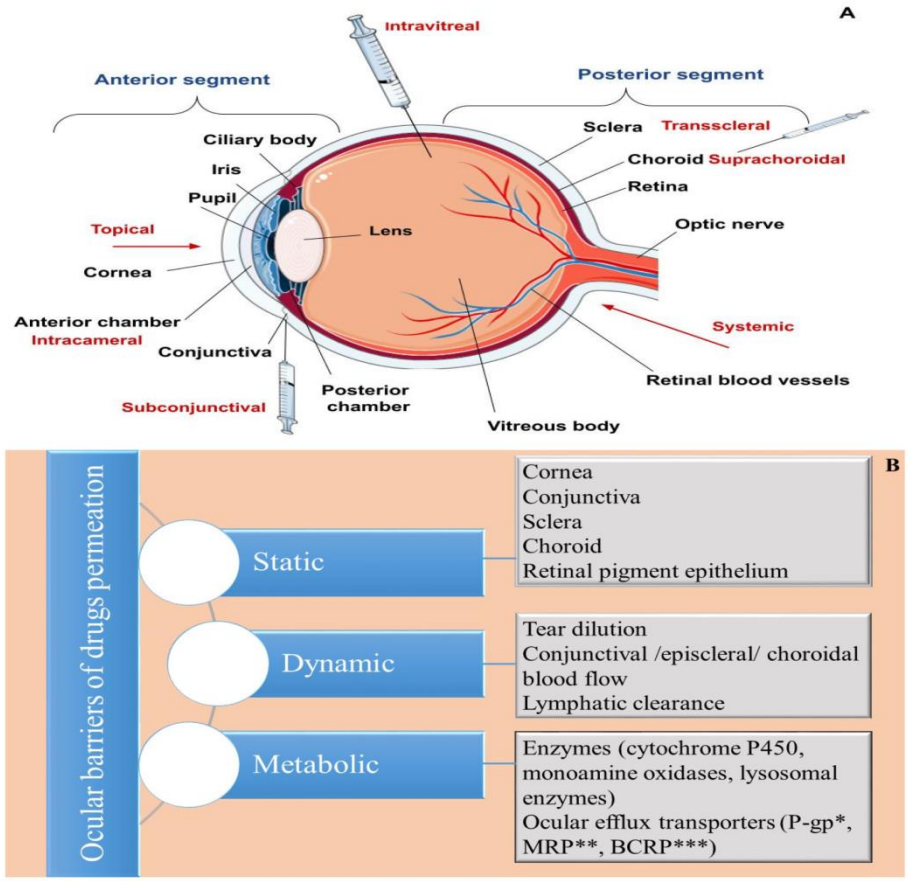


Figure No. 1: An overview of (A) ocular anatomy and routes for administration. (B) Ocular drug delivery barriers. * P-glycoprotein; ** Multidrug-resistant protein; * Breast cancer resistance protein.**

The cornea

The cornea is the most anterior part of the eye, in front of the iris and pupil. It is the most densely innervated tissue of the body, and most corneal nerves are sensory nerves, derived from the ophthalmic branch of the trigeminal nerve [18]. The cornea of an adult human eye has an average horizontal diameter of about 11.5 mm and a vertical diameter of 10.5 mm, and a curvature that remains rather constant throughout life [19]. The cornea is the main route for drug absorption after topical instillation, often referred to as a static (anatomical) barrier. It is a transparent, highly specialized, avascular structure comprising six layers: the corneal epithelium, Bowman's layer, stroma, Dua's layer, Descemet's membrane, and endothelium [20].

The Retina

The retina is the tissue that lines the inner surface of the eye, surrounding the vitreous cavity. During embryogenesis, the vertebral retina develops from the optic cup. The latter is formed by invagination of the optic vesicle, which is an outgrowth of the embryonic forebrain. The inner wall of the optic cup (surrounding the vitreous cavity) ultimately becomes the neural retina; the outer wall (surrounded by the choroid and sclera) becomes the retinal pigment epithelium (RPE)[21].

Conjunctivitis

Conjunctivitis (pink eye) is an inflammation or swelling of the conjunctiva. It is one of the most common eye problems, although it is rarely severe and unlikely to damage vision if treated early. Conjunctivitis can be caused by allergens, infections or chemicals. [22] Allergic conjunctivitis mainly affects people already suffering from seasonal allergies. Contact lens users are predisposed to allergic conjunctivitis, especially if the lenses are not replaced frequently. Infectious conjunctivitis is caused mostly by streptococcal, staphylococcal bacteria and contagious viruses thriving in common cold [23].

Iris

The iris is a circular, colored, contractile structure, which surrounds an aperture in its center (the pupil). It regulates the constriction or dilation of the pupil according to the light intensity, via parasympathetic/sympathetic activation, respectively [24]. The melanin-containing cells in the eye (localized to the iris/ciliary body at the front and in the choroid/retinal pigment epithelium in the posterior) can bind drug molecules via electrostatic and van der Waals forces, as well as by charge interactions. The formed complex may be considered a "reservoir", releasing drugs at a slow rate, therefore, it can also be used in a drug-targeting approach to achieve prolonged action in the corresponding (pigmented) ocular areas[20].

Lens

The lens is located behind the iris and the pupil, and is characterized by its transparent appearance, biconvex shape, great index of refraction, and high concentration of proteins in its structure (i.e., crystallins). Its main functions include light transmission and focusing it onto the retina to obtain a distinct image [**20**,**25**].

3. Advantages and Disadvantages of nanoparticle in ocular drug delivery system

3.1 Advantages:

1. Provide high stability to incorporated drug.
2. Feasibility of incorporating both hydrophilic and lipophilic drugs.
3. Improve bioavailability of poorly water soluble molecules.
4. Ease in sterilization and scale up.
5. Immobilizing drug molecules within solid lipids provides protection from photochemical, oxidative, and chemical degradation of sensitive drugs, with reduced chances of drug leakage. [26]
6. Drying by lyophilization is achievable.
7. Provide opportunities for targeted and controlled release of drug.
8. Biocompatible and biodegradable compositional ingredients [27].

3.2 Disadvantages:

1. SLNs are compactly packed lipid matrix networks (ideal crystalline structure) having low space for drug encapsulation, leading to poor drug loading capacity
2. Various factors affect the loading or encapsulation of drugs in SLNs, such as interaction of drug and lipid melt, nature or state of lipid matrix, drug miscibility with lipid matrix, and the drug being dispersed or dissolved in the lipid matrix
3. Chances of drug expulsion following polymeric transition during storage
4. The dispersions have a high (70–90%) water content [26].

4. Lipid Nanoparticles

The penetration through the ocular barriers can be possible by the employment of small particles, such as polymeric nanoparticles, liposomes, hydrogels, nano-micelles, dendrimers, and nanosuspensions [8]. On the other hand, liposomes are spherical vesicles consisting of one or more concentric phospholipid bilayers. Liposomes are able to enhance the active corneal permeability because of their ability to come in close contact with cornea and conjunctiva as well as increase the extent of corneal uptake by prolonging the corneal contact time [28, 29]. Liposomes as a drug delivery system have improved therapies for a range of biomedical applications by stabilizing therapeutic compounds, overcoming obstacles to cellular and tissue uptake, and improving bio-distribution of compounds to target sites *in vivo* [30].

4.1 Method for solid lipid nanoparticle

High-Pressure Homogenization

The high-pressure homogenization is a well-established and powerful technique. It consists of pushing a liquid with high pressure through a narrow gap. The fluid accelerates trough a very short distance at very high velocity, leading to shear stress and cavitation forces that shatter the particles down to the submicron range [31]. There are two different procedures to perform this technique: hot and cold homogenization.

• Hot homogenization: the procedure is carried out at temperatures higher than the melting point of the solid lipid. The drug is melted with the lipids and then dispersed in a hot aqueous phase with surfactants by a high-shear mixing device. Afterwards the system is cooled down and the lipid solidifies, forming the nanoparticles.

• Cold homogenization: the drug is solved in the lipid melted mixture and is quickly solidified by cooling down with dry ice or liquid [31, 32]

Solvent Emulsification-Evaporation

The lipid is dissolved in a water-immiscible organic solvent and is emulsified in an aqueous phase by high speed homogenization. Afterwards, the solvent is evaporated by mechanical stirring at room temperature and reduced pressure, forming the lipid nanoparticles.

Solvent Emulsification-Diffusion

In this method, a water-miscible solvent and water are saturated with each other. The lipid and the drug are dissolved in water saturated solvent, and this organic phase will be later emulsified with solvent saturated aqueous solution containing stabilizer using mechanical stirring. Then, water is added to the emulsion and the solvent is eliminated by vacuum distillation or lyophilization.

Ultrasonication or High Shear Homogenization

The procedure is carried out at temperatures higher than the melting point of the solid lipid. The lipid is melted, dispersed into the warm aqueous phase, which contains surfactant, and then is emulsified by probe sonication or by high-speed stirring. The preemulsion is placed into ice-water bath and ultrasonicated using probe sonicator.

Supercritical Fluid Extraction of Emulsions

The lipid material, the drug and the surfactant are dispersed into an aqueous solution, and then the mixture is introduced in a high-pressure homogenizer to form an emulsion. Afterwards, the mixture is introduced from one end of the extraction column at a constant flow rate, and the supercritical fluid is introduced at a constant flow rate in a counter-current manner. Finally, lipid nanoparticles are obtained by continuous extraction of solvent from the emulsion.

Microemulsion Based Method

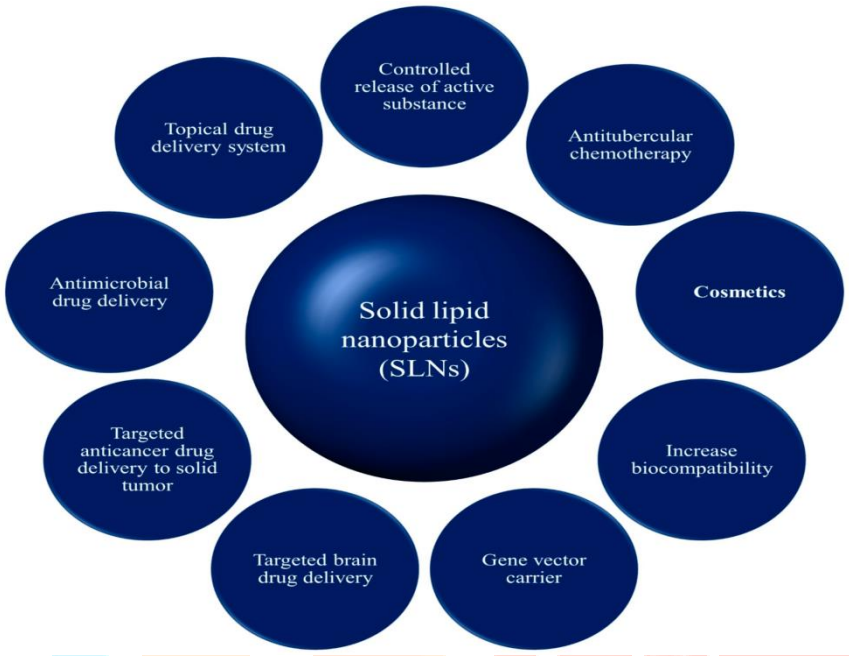
A mixture of a low melting fatty acid, an emulsifier and water are stirred at a temperature higher than the melting point of the lipid. The hot microemulsion is dispersed in cold water under stirring [8].

5. Application of nanoparticle in ocular drug delivery system:

1. Nanotechnology is changing the perception of drug administration using conventional dosages. It can revolutionize the way new therapies are developed and optimize the existing ones by combining science and technology and the ability to manipulate structures and properties at the nanoscale range.[5]
2. Particle size, particle size distribution, and stability are some of the most significant issues in formulating dispersed systems for ocular administration.
3. Other potential advantages of nanoscale drug delivery systems in ocular therapy are the possibility of self-administration by patients as eye drops, no impairment of sight because of small dimensions of the delivery systems, possible uptake into corneal cells, and targeting toward affected tissues, reducing potential side effects and required doses[33].
4. Nanotechnology is changing the perception of drug administration using conventional dosage forms.
5. Nanotechnology has the potential to revolutionize the way we develop new therapies, as well as optimize existing ones.
6. In the pharmaceutical sciences, the term nanoparticle refers to a particulate drug delivery system where particle size is in the nanometre range (1–1000 nm). Nanoparticles are being investigated extensively in order to develop drug delivery systems capable of allowing penetration through physiological barriers.

7. Nanoparticles are either in the form of matrix-dispersion (nanospheres) or a membrane-reservoir type (nanocapsules), where drugs can be dissolved, entrapped, encapsulated, and dispersed within the particles or adsorbed on the surface of these particles [34].
8. SLNs enhance the bioavailability of entrapped drugs via modification of the dissolution rate, and can be used to improve tissue distribution and targeting of drugs. Possible applications of SLNs are represented in below figure. [26]

Figure No.2: Applications of Nanoparticles



9. Oral drug administration is common and preferred route due to good patient compliance, non-invasiveness and therapeutic success, but poorly water-solubility of drugs is limiting step for the absorption of them. Thus an approach is needed to improve the bioavailability of drugs.
10. Lipid-based delivery systems in the recent decades have shown many advances for this purpose. These systems include a wide range of formulations such as self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), nanoemulsions, SLNs and NLCs. Since in these systems, drug is dissolved in the lipid thus makes the potential for improving the bioavailability of poorly soluble drugs in water, especially lipophilic drugs.
11. In fact, these systems can increase dissolution of drug, residence time and lymphatic uptake. A good thing is that toxicity has not been observed in most cases [35].
12. LNPs easily incorporated into carriers which inhaled to the lungs, therefore able to provide a deep lung deposition, good adhesion and elongated retention in the lung. Also due to improved and prolonged therapeutic effects, SLNs and NLCs have a longer dosing interval and better compliance for patients.
13. They are typically particulate systems for various drug delivery applications. Advantages of drug release of fat in the lungs including: control of the release profile, prolonged release, faster in vivo degradation and better tolerability compared to particles made from some polymeric materials such as PLA or PLGA.
14. Pulmonary delivery of SLNs is not widely accepted because of toxicity issues but when the physiologic lipids are used, is estimated to be safer than polymer-based systems.
15. Dry powder formulations or aqueous suspensions of SLNs can be used for pulmonary drug delivery. Many studies are available about SLNs as local delivery carriers or as systemic delivery carriers for small molecules and for macromolecules respectively by pulmonary administration [36, 37].
16. SLNs can improve the ability of the drug to penetrate through the blood-brain barrier (BBB). Abbas et al. targeted clonazepam to brain via intranasal olfactory mucosa utilizing nanolipid carriers that were co-loaded with superparamagnetic iron oxide nanoparticles (SPIONs), both for the guidance of nanocarrier and holding in external magnetic field.
17. The nanolipid carriers are incorporated in situ in thermosensitive mucoadhesive gels, resulting in the enhanced delivery of clonazepam.

18. This study raises the light on new intranasal management of epilepsy with reduction in clonazepam peripheral harmful effects [38].
19. Immunologic adjuvant are substances that are used to augment the degree, stimulation, or robustness of vaccines. In this sequence, Stelzner et al. developed squalene containing steam sterilized SLNs based adjuvant system for a yeast-based vaccine. Size of squalene loaded SLN measured by static and DLS technique was found to be in the range of 120–170 nm.
20. Evaluation of the developed vaccine adjuvant on a mouse model showed excellent efficacy against the harmful bursal virus disease. Squalene-based adjuvants represented high biocompatibility and also demonstrated immune stimulation properties, which is comparable with Freund's adjuvant [39].

6. Conclusion:

In conclusion, solid lipid nanoparticles (SLNs) have demonstrated significant potential as a versatile and efficient platform for ocular drug delivery systems. The unique properties of SLNs, including their biocompatibility, solid matrix, and small particle size, contribute to improved stability, enhanced bioavailability, and controlled release of drugs within the ocular tissues. The surface modification capabilities of SLNs allow for customization of drug release profiles and targeting strategies, further optimizing therapeutic outcomes. Additionally, the reduced risk of systemic side effects and prolonged drug retention in the eye make SLNs a promising candidate for improving patient compliance in ocular treatments. As research in this field progresses, the continued exploration of SLNs in ocular drug delivery holds great promise for addressing the challenges associated with traditional formulations and ultimately improving the efficacy and safety of ocular therapeutics.

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