



Review Article

EUDRAGIT-BASED NANOSTRUCTURES: A POTENTIAL APPROACH FOR OCULAR DRUG DELIVERY

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ABSTRACT

Drug delivery in ocular therapeutics is a challenging problem and is a subject of interest to scientists working in the multidisciplinary areas pertaining to the eye. Most ocular diseases are treated by topical drug application in the form of solutions, suspensions and ointment. These conventional dosage forms suffer from the problems of poor ocular bioavailability, because of various anatomical and pathophysiological barriers prevailing in the eye. Various efforts in ocular drug delivery have been made to improve the bioavailability and to prolong the residence time of drugs applied topically onto the eye. The potential use of polymeric nanoparticles as drug carriers has led to the development of many different colloidal delivery vehicles. Indeed, the association of an active molecule to a nanocarrier allows the molecule to intimately interact with specific ocular structures, to overcome ocular barriers and to prolong its residence in the target tissue. This review discusses the physicochemical characterization, fabrication techniques, therapeutic significances, patented technology of Eudragit based nanoparticles and future possibility in the field of ocular drug delivery.

Keywords: Eudragit, Ocular, Drug delivery, Nanoparticles.

INTRODUCTION

Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye. Moreover, the anatomy, physiology and barrier function of

the cornea compromise the rapid absorption of drugs¹. Frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action. But the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface².

Numerous strategies were developed to increase the bioavailability of ophthalmic drugs by prolonging the contact

time between the preparation, and therefore the drug, and the corneal/conjunctival epithelium. The use of a water-soluble polymer to enhance the contact time and possibly also the penetration of the drug was first proposed by Swan. Where very promising results and improved bioavailability were observed in animal studies, only a small increase in precorneal residence time was obtained in humans. There is no reliable correlation between the performance of ophthalmic vehicles in rabbits and in humans, mainly due to differences in blinking frequency³.

Prolonging pre-corneal residence time through viscosity enhancers and gels has only a limited value, because such liquid formulations are eliminated by the usual routes in the ocular domain. The highly sensitive corneal/conjunctival tissues towards penetration enhancers to maximize drug transport require great caution in the selection of the enhancer. An alternative approach is to develop a drug delivery system that would circumvent the problems associated with the conventional systems, and provide the advantages of targeted delivery of drugs for extended periods of time and be patient-friendly. The latter requisite becomes more crucial in cases where the patient has to use the drug preparation throughout his life, e.g. in glaucoma. These advantages have been reported in the literature through the use of nanoparticles⁴.

The potential of polymeric nanoparticles as an ocular drug delivery system has been explored by a colloidal system consisting of an aqueous suspension of nanoparticles. These nanoparticles can be rapidly fabricated under extremely mild conditions with their ability to incorporate bioactive compounds. The stability of colloidal particles in biological fluids containing proteins and enzymes is a crucial issue, because the size of the nanoparticles plays an important role in its ability to interact with mucosal surfaces and, in particular, with the ocular mucosa⁵.

In this context, eudragit has been investigated as a superior mucoadhesive cationic polymer due to its ability to develop molecular attraction forces by electrostatic interactions with the negative charges of mucin, which is determined by the formation of either hydrogen bonds, or ionic interactions between the positively charged amino groups of eudragit and negatively charged sialic acid residues of mucin, depending on environmental pH⁶.

In this review, we discuss the physicochemical characterization, fabrication techniques, therapeutic significances, patented technology of Eudragit based nanoparticles and future possibility in the field of ocular drug delivery.

CRITICAL BARRIERS IN OCULAR THERAPEUTICS

Topical instillation of an active compound is the first method choice of delivery in ocular therapy. However, due to the innate protective characteristics of the eye against the entry of foreign compounds, the bioavailability of an instilled compound is generally low. The various ocular barriers are:

Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1 μ l/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption. Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity. Anyway, most of small molecular weight drug dose is absorbed into systemic circulation rapidly in few minutes. This contrasts the low ocular bioavailability of less than 5%⁷.

Lacrimal fluid-eye barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal barrier is formed upon maturation of the epithelial cells. They migrate from the limbal region towards the center of the cornea and to the apical surface. The most apical corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. Despite the tightness of the corneal epithelial layer, transcorneal permeation is the main route of drug entrance from the lacrimal fluid to the aqueous humor⁸.

Blood-ocular barriers

The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uvea. This barrier prevents the access of plasma albumin into the aqueous humor, and limits also the access of hydrophilic drugs from plasma into the aqueous humor. Inflammation

may disrupt the integrity of this barrier causing the unlimited drug distribution to the anterior chamber. In fact, the permeability of this barrier is poorly characterised⁹.

The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelia. Despite its high blood flow the choroidal blood flow constitutes only a minor fraction of the entire blood flow in the body. Therefore, without specific targeting systems only a minute fraction of the intravenous or oral drug dose gains access to the retina and choroid¹⁰.

Unlike blood brain barrier, the blood-eye barriers have not been characterised in terms of drug transporter and metabolic enzyme expression. From the pharmacokinetic perspective plenty of basic research is needed before the nature of blood-eye barriers is understood.

EUDRAGIT SOLUTIONS

A major challenge in ocular therapeutics is the improvement of ocular drug bioavailability. As indicated before, conventional aqueous solutions topically applied to the eye have the inherent disadvantage that most of the instilled drug is lost within the first 15–30 s after instillation, due to reflex tearing and drainage via the nasolacrimal duct. Hence, many of the efforts at improving ocular drug delivery

the incorporation of viscosity building agents such as polyvinyl alcohol and methyl cellulose¹¹.

However, viscosity has been found to have a minor consequence in prolonging the ocular residence time of drugs. Thus, over the last years, the use of mucoadhesive polymers has attracted significant attention for the achievement of this objective. The capacity of some polymers to adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye by non-covalent bonds forms the basis of ocular mucoadhesion. Mucoadhesive polymers increase the drug residence time because the turnover of the mucus layer is very slow (approximately 15 to 20 h). Moreover, mucoadhesive polymers provide an intimate contact between the drug and the absorbing tissue, which normally results in a high drug concentration in the local area¹²⁻¹³.

Eudragit (EG) is copolymers of ethyl acrylate, methyl methacrylate and a low content of a ethacrylic acid ester with quaternary ammonium groups (trimethylammonioethyl methacrylate chloride) that has widely being used in ophthalmic preparations. The specific biadhesiveness of EG to the ocular surface was first observed in an ex-vivo study, in which the activity of radiolabelled EG was measured by scintillation counting after addition to a freshly excised cornea and exhaustive rinsing. Electrostatic attraction appears to be the major driving force for mucoadhesion. However, both hydrogen bonding and hydrophobic interactions are also supposed to have a role in this process.

Table 1: Eudragit nanoparticles in ocular drug delivery

Polymer	Loaded drug/ gene/ protein	Comments
Eudragit RS 100, RL 100	Ibuprofen Flurbiprofen Cloricromene Diclofenac diethyl ammonium Piroxicam Methylprednisolone	Drug level was improved in the aqueous humor after application of the drug- loaded nanosuspensions which did not show toxicity in ocular tissues. Improved the stability of cloricrome in ophthalmic formulations and its drug availability at the ocular level. Excellent encapsulation efficiency.

have been focused on increasing the duration of the drug contact time. The first step in this direction has been to enhance the precorneal retention of ophthalmic solutions by

Eudragit RL & RS are used to form water-insoluble film coats for sustained-release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying

permeability can be obtained by mixing the two types together. The neutral Eudragit NE/NM grades do not have functional ionic groups. They swell in aqueous media independently of pH without dissolving. Eudragit may additionally be used to form the matrix layers of transdermal delivery systems and have also been used to prepare novel gel formulations for rectal administration.

BIODISTRIBUTION: INTERACTION OF EUDRAGIT- BASED NANOPARTICLES WITH THE OCULAR EPITHELIA

Eudragit has been widely described as a highly mucoadhesive polysaccharide able to establish an intimate interaction with the mucus layer that covers the ocular mucosa. Infact, and as discussed earlier the spreading use of eudragit in ophthalmology has a basis on these properties, as it has been proven that eudragit can increase the residence time of the administered drug. The ability of eudragit to effectively interact with the ocular mucosa has been attributed not only to its cationic charge but also to its intrinsic properties. In addition, we have precisely shown that the presentation of eudragit in a nanoparticulated form significantly increases its retention at the ocular surface and, thus it's utility for ocular drug delivery.



Fig.1. SEM image of eudragit nanoparticle adherence on goat cornea

CONCLUSION

After more than one-decade of track-record reports on the potential of Eudragit for ocular drug delivery leads to some specific conclusions: (i) EG-based nanostructures have a more important ocular retention than EG solutions; (ii) different EG-based nanostructures can be tailored in order to accommodate different types of drugs, from lipophilic low

molecular weight compounds (i. e. indomethacin) to medium size peptides (Cyclosporin A) and large gene molecules; (iii) preliminary data have given indications of the good tolerance and acceptability of these nanocarriers from a toxicological perspective.

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