DRUG DELIVERY SYSTEM FOR DELIVERY OF ACID SENSITIVITY DRUGS

This application is a US National Phase application of International Application PCT/EP2015/080503, filed 18 Dec. 2015, which designated the US and claims priority to European Patent Application No. EP14198912.9, filed 18 Dec. 2014, the entire contents of each of which are hereby incorporated by reference.

The present invention relates to a drug delivery system comprising a core and a shell. The present invention further relates to a fiber comprising a core and a shell. The present invention also relates to a process for the manufacturing of the drug delivery system.

The present invention in particular relates to the field of sustained drug delivery to the eye and more particularly to the treatment and/or prevention of raised intraocular pressure, such as that associated with glaucoma.

Glaucoma is one of the leading causes of blindness in the developed countries of the world. The chief pathophysiological feature of glaucoma is raised intraocular pressure. Surgery and/or drugs intended to lower intraocular pressure are the most common treatments for glaucoma. The principal pharmaceutical treatment in use today is the topical administration of drug solutions via eye drops. The drugs are for example miotics (e.g., pilocarpine, carbachol and echothiophate), which open the trabecular meshwork to increase the rate of fluid flow out of the eye.

Self-administration of eye drops often results in a substantial portion of the drop being lost due to overflow. A substantial portion of the drug solution that is delivered to the ocular surface is then immediately washed away by tears. Moreover, that portion of the drug which does penetrate the cornea results in an initial peak tissue concentration, followed by a gradual decrease, so that before the next administration of the eye drops the tissue concentration may be below the concentration needed to create the intended pharmacological effect. The variable and intermittent topical administration of eye drops, combined with the vagaries of patient compliance with the prescribed regimen, result in cycles of high and low concentrations of topical antiglaucoma agents in the eye, and the possible cycling of intraocular pressure. As a result of this the optic nerve might get irreversibly damaged over time. The ideal treatment would maintain a therapeutically effective amount of drug in the eye at all times.

Drug delivery systems comprising a core and a shell are known in the art. In EP2233112, a drug delivery device is disclosed shaped and sized for injection and comprising a core including one or more drugs; and a polymeric skin at least partially surrounding the core, whereby the skin comprises a polymer such as poly(vinyl acetate), poly(caprolactone), polyetliylene glycol, poly(dl-lactide-co-glycolide), ethylene vinyl acetate polymer, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), polyalkyl cyanoacralate, polyurethane or nylon.

A drug delivery system intended to provide sustained release of a drug should provide a controlled release, i.e., it should release the drug in a relatively linear manner over time, so as to maintain not only prolonged release but also a relatively constant and therapeutically effective concentration of the drug. The duration of release should be sufficiently long so that the insertion of the device is not inconveniently frequent. Depending on the condition to be treated, such devices may provide for controlled release over

a period of weeks, months or even years. This is of particular importance (benefit) for chronic patient conditions such as glaucoma.

In case that the drug is dispersed in the polymer matrix, the drug is released as it dissolves and diffuses out of the matrix. In devices based on the polymer matrix, the drug dispersed in the matrix may be present either in dissolved or dispersed form. Release follows Fickian kinetics from devices where the drug is dissolved. When the drug is dispersed in the polymer matrix, it is released according to $t^{1/2}$ kinetics until the concentration in the matrix falls below the saturation value, at which point the release rate slows down and Fickian release is observed. For these reasons, the maintenance of the drug concentration within the therapeutic window for a long period of time can be difficult to achieve with polymer matrix systems.

In some drug delivery systems, diffusion through the polymer matrix is extremely slow, and drugs are intended to be released only as the polymer matrix is degraded. It has proven to be difficult to use this approach to a linear release.

It is an object of the present invention to provide a drug delivery system that meets a linear release over time, that meets a prolonged release, and that meets a relatively constant and therapeutically effective concentration of drug.

In particular, it is an object of the present invention to provide an improved method for treating and/or preventing glaucoma and other indications associated with raised intraocular pressure by administering drugs to the eye in a manner that avoids the problems of variable drug concentration associated with topical administration without causing systemic side effects.

The object of the present invention is achieved in that a drug delivery system is provided comprising a core and a shell in which the core comprises a hydrolytically degradable polymer X which polymer backbone comprises pendant ester and acid functionalities and in which the shell comprises a hydrolytic degradable polymer Y.

Preferably the hydrolytic degradable polymers X and Y are different polymers.

Surprisingly it has been found that the drug delivery system according to the present invention not only provides a prolonged release but also a relatively constant release of a therapeutically effective concentration of the drug. Moreover it has been surprisingly found that the hydrolytically degradable polymer X does not built an acidic micro-climate in the polymer matrix during the polymer degradation despite that the hydrolysis of polymer X results in the generation of carboxyl groups.

The lack of acidic micro-climate is beneficial for maintaining the structure of acid-sensitive drugs which means for maintaining its stability. For example, ocular hyperemia and other side effects were observed in the early development of latanoprost and triggered the development of the prodrug (Latanoprost ester) structure in clinical use today. Latanoprost is a prostaglandin F2a analogue. Specifically, Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Latanoprost is an isopropyl ester and the ester was found to improve the ocular penetration and consequently ocular hypotensive potency. It is important that the ester form is stable enough not to be rapidly de-esterified, yet hydrolyzed by tissue esterases to have a full intraocular hypotensive effect. Thus, drug structure preservation is essential for high bioavailability (drug