In situ gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations

Hugo Almeida, Maria Helena Amaral, Paulo Lobão and José Manuel Sousa Lobo

Laboratory of Pharmaceutical Technology, Drug Sciences Department, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira, N° 228, Porto 4050-313, Portugal

The low therapeutic efficacy exhibited by conventional ophthalmic solutions owing to precorneal elimination of the drug, drainage by gravity, nasolacrimal drainage, conjunctival absorption, and the absence of controlled release and of bioadhesive properties, can be overcome by the use of *in situ* gelling systems. The combination in the same formulation of different *in situ* gelling polymers with different stimuli-responsiveness mechanisms exploiting the unique physicochemical characteristics of the ocular tissues is one such strategy that has produced improved results compared with conventional systems. As we discuss here, the recent use of biodegradable and biocompatible polymers in colloidal carrier systems has proved to be the most effective strategy, resulting in the exponential increase of the bioavailability of the ophthalmic drugs.

The eye is unique in terms of its anatomical and physiological nature and defense mechanisms, which make the targeting of drugs to eye tissues one of the greatest challenges in drug delivery [1,2]. Topical instillation of drugs through eyedrops is the most important and well-accepted route of administration for the treatment of various eye disorders [1–3]. Conventional pharmaceutical formulations, such as solutions and suspensions, have many disadvantages, exemplified by rapid precorneal elimination, drainage by gravity, normal tear turnover, frequent instillation, enzymatic metabolism, nasolacrimal drainage, conjunctival absorption, and the absence of controlled release and of bioadhesive properties [3–7]. The residence time of most conventional ocular solutions is 5–25 min and only 1–10% of the topically applied drug is absorbed; in addition, a major part of the drug absorbed systemically results in systemic adverse effects [3,8,9].

The limited permeability of the ocular membranes contributes to the low absorption of ocular drugs, resulting in the short duration of the therapeutic effect and making a frequent dosing regimen necessary [3–5,10]. The instillation of highly concentrated eyedrops can cause adverse effects and cellular damage in ocular tissues [1].

One of the best strategies to increase or prolong the contact time of ophthalmic formulations with the ocular tissues is to increase the viscosity of the formulation using biodegradable and biocompatible polymeric hydrogels [1–4]. Hydrogels are 3D, hydrophilic, polymeric networks

Hugo Almeida received his degree in Pharmaceutical Sciences from the Faculty of Pharmacy, University of Coimbra (Portugal) in 2006, and a master's degree in Quality Control (branch: Drug Substances and Medicinal Plants) from Faculty of Pharmacy, University of Porto (Portugal) in 2009. In 2011, became PhD student in Pharmaceutical Sciences (branch: Pharmaceutical Technology) in the Laboratory of Pharmaceutical Technology, Drug Sciences Department, Faculty of Pharmacy, University of Porto (Portugal). He develops his research in the application of stimuli-responsive polymers in controlled and self-regulated drug delivery systems.

Maria Helena Amaral graduated in Pharmaceutical Sciences, Master in Quality Control of Medicines and PhD in Pharmaceutical Technology at the Faculty of Pharmacy, University of Porto. Assistant professor of Pharmaceutical Technology at the Faculty of Pharmacy, University of Porto since 2003. Her research areas are related to new drug delivery systems, ophthalmic formulations, stimuli-responsive polymers, dermopharmacy and cosmetology.

Paulo Alexandre Lourenço Lobão is an auxiliary professor at the Faculty of Pharmacy of the Porto University (FFUP). He teaches and researches at the Pharmaceutical Technology Department of the FFUP since 1992. The main theme of his research focuses on bioadhesion and sustained release dosage forms. He also works with medical devices.

Prof. Dr José Manuel Sousa Lobo, PhD in Pharmaceutical Technology in 1989. Full professor of Pharmaceutical Technology at the Faculty of Pharmacy, University of Porto. Director of the Department of Drug Sciences and President of the Scientific Council of the Faculty of Pharmacy, University of Porto. President of the Portuguese Pharmacopoeia and Expert in Industrial Pharmacy.

Corresponding author:. Almeida, H. (hperas5@hotmail.com)

1359-6446/06/$ - see front matter © 2013 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.drudis.2013.10.001

(homo- or copolymers) with physical properties that make them attractive for a variety of biomedical applications, particularly for the controlled local delivery of drugs [2]. The use of bioadhesive polymers result in an increase of ocular residence time, via their enhanced viscosity and mucoadhesive properties [2]. Given that the increase in the viscosity of ophthalmic formulations often causes blurred vision, it is essential to achieve the optimal range of viscosity as well as the most suitable rheological behavior that will ensure good efficacy and tolerance [3].

Other strategies to overcome the problems associated with the use of conventional eye drops is to use *in situ* gel-forming ophthalmic drug delivery systems prepared from polymers that exhibit reversible phase transitions (sol–gel) and pseudoplastic behavior to minimize interference with blinking [11]. The *in situ* gel-forming polymeric formulations offer several advantages, such as sustained and prolonged action compared with conventional drug-delivery systems [5]. From a manufacturing point of view, the production of such devices is less complex and, thus, lowers the investment and manufacturing costs [5]. The phase transition of the *in situ* gelling systems on the eye surface can have different causes, including: temperature and the pH in the precorneal region or the electrolyte composition of the tear film [12,13]. Thus, over the past few years, researchers have successfully developed different formulations using ophthalmic drugs with different kinds of *in situ* gelling polymers (e.g. thermo, pH and electrolyte-responsive polymers), viscosity-increasing agents and isotonic agents [3].

Recently, different ophthalmic drug delivery strategies have been used to develop colloidal carrier systems with biodegradable polymers [1,4,8,14–17]. These include hydrogels, polymeric micelles, nanosuspensions and lipid-based nanocarriers (excluding emulsions, liposomes, cubosomes and niosomes) [8,14–16]. Nanocarriers, such as nanoparticles (NPs), have the capacity to deliver ocular drugs to specific target sites and, thus, could revolutionize the therapy of many eye diseases because they increase the contact time of the administered drug with its target tissue [15]. The use of drug-loaded NPs (DNPs), with dimensions between 1 nm and 0.5 μm, prepared with biodegradable polymers [e.g. chitosan (CS), aminated gelatin, dextran, collagen, hyaluronic acid, poly-L-arginine, 2-hydroxypropyl-β-cyclodextrin, methylated-β-cyclodextrin, polyacrylates, poly(lactide-co-glycolide) (PLGA), poly(lactide) (PLA), poly ε-caprolactone and albumin] that operate via different techniques (e.g. solvent evaporation, spontaneous emulsification/solvent diffusion, salting out/emulsification–diffusion, ionotropic gelation and desolvation, constitutes a versatile drug delivery system, with an ability to overcome physiological barriers and guide the drug to specific cells or intracellular compartments either by passive or ligand-mediated targeting mechanisms [14,15,17].

An important advance will be the development of NPs suspended in an *in situ* gelling vehicle that forms a gel at the external ocular surface [17]. Liposomes are highly biocompatible and biodegradable drug carriers that offer advantages such as prolonged drug retention and improved drug absorption [8,17,18]. However, despite these advantages, liposomes present some limitations, such as their surface charge, low drug loading, manufacturing difficulties for sterile products and the instability of the lipid aggregated on the mucin surface [8,17,18].

Thus, such strategies offer several potential advantages as delivery systems for ocular administration, such as improving the bioavailability of poorly soluble drugs, targeted and controlled release and the reduction of adverse effects [4,17].

Anatomy of the eye

The eye is a complex optical system that collects light from the surrounding environment, regulates its intensity through a diaphragm, focuses it through an adjustable assembly of lenses to form an image, converts this image into a set of electrical signals, and then transmits these signals to the brain through complex neural pathways that connect the eye via the optic nerve to the visual cortex and other areas of the brain [19]. This organ, illustrated in Fig. 1, comprises several different structures with specific physiological functions.

The wall of the eyeball (globe) comprises three primary layers: the sclera, or outer layer (the fibrous protective layer with the transparent cornea anteriorly), the uvea, or middle layer (having a vascular and nutritive function, and contains pigmented tissue comprising the choroid, ciliary body and iris) and the retina, or inner layer (which is the neural, sensory stratum of the eye) [3,20,21].

Corneal permeability is the most important factor in determining the drug concentration in aqueous humor [3,7]. The cornea is the clear surface of the outer eye, which is approximately 0.5 mm thick and comprises five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and the endothelium layer [7,22]. This structure has two main functions: it acts as (i) a barrier preventing germs, dirt and other harmful material from entering the inner eye and (ii) the outermost lens of the eye [7]. Despite the cornea comprising five layers, only three (the epithelium, stroma and endothelium) are significant with respect to barrier resistance [7,22]. The epithelium is a rate-limiting barrier for the transcorneal diffusion of most hydrophilic drugs [3,7]. The tight junctions of the corneal epithelium serve as a selective barrier for small molecules and prevent the diffusion of macromolecules via the paracellular route [3,22]. The stroma acts as diffusion barrier to highly lipophilic drugs owing to the hydrophilic nature of the former

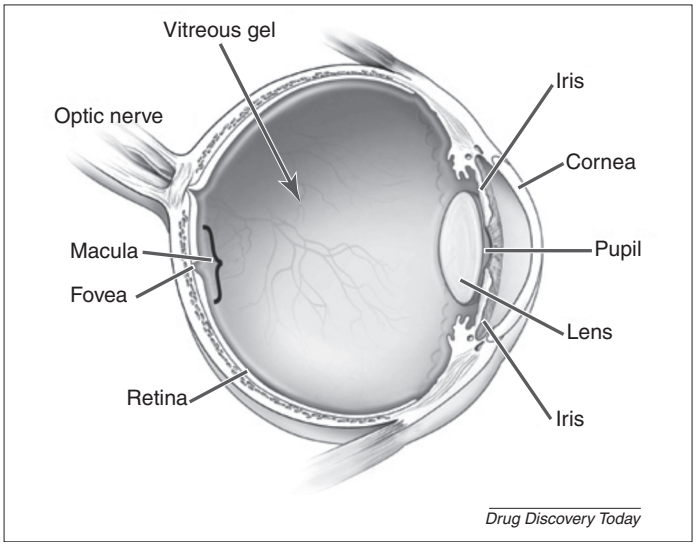

FIGURE 1

Anatomy of the eye globe. Courtesy: National Eye Institute, National Institutes of Health (NEI / NIH).

Download English Version:

https://daneshyari.com/en/article/2081285

Download Persian Version:

https://daneshyari.com/article/2081285

Daneshyari.com