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Monitor: molecules and profiles

Monitor provides an insight into the latest developments in drug discovery through brief synopses of recent presentations and publications together with expert commentaries on the latest technologies. There are two sections: *Molecules* summarizes the chemistry and the pharmacological significance and biological relevance of new molecules reported in the literature and on the conference scene; *Profiles* offers commentary on promising lines of research, emerging molecular targets, novel technology, advances in synthetic and separation techniques and legislative issues.

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Drug delivery

Mucoadhesive ocular inserts as an improved delivery vehicle for ophthalmic indications

Drugs for ophthalmic indications are traditionally administered as aqueous eye drops. These formulations, however, offer poor bioavailability of the drug because of rapid elimination from the tear compartment. To maintain therapeutic levels, frequent instillations are often required, an inconvenience that leads to low patient compliance.

Ophthalmic drug delivery systems

Numerous ophthalmic drug delivery systems have been developed to achieve higher bioavailability of the drugs, including microspheres, nanoparticles, liposomes and ocular inserts. The advantages of ocular inserts, solid devices that are placed directly in the cul-de-sac of the eye, are many. These advantages include prolonged contact with the eye, controlled release, reduction in systemic side effects, and increased shelf life. Despite these advantages, ocular inserts have not been used extensively in ocular therapy.

There are several reasons for this underuse; primary among them is that the foreign body sensation caused by ocular inserts leads to low patient compliance. Furthermore, if an insert lacks appropriate mucoadhesive properties it can move around on the eyeball, causing more irritation, and can even be lost entirely. Finally, if the insert erodes and breaks into smaller pieces, it can cause blurring of vision. Yet contact lenses can be worn for extended periods of time with relatively few patient complaints. If an appropriate ocular insert could be developed for administration of ocular therapies, some of the advantages of the delivery system could be realized.

Ocular inserts

Recently, Hornof and coworkers have reported their efforts to design an insoluble, mucoadhesive ocular insert to address these concerns [1]. The study also indicated that the resulting insert would be well tolerated by patients, based on acceptability studies conducted with healthy volunteers. The inserts were made from poly(acrylic acid) modified with cysteine, which has been shown to have excellent mucoadhesive properties. *In vitro* release studies were performed with two diclofenac salts and fluorescein as model drugs. The *in vivo* human studies were conducted with fluorescein, which is used regularly as a diagnostic agent in ophthalmology. Fluorescein has a safe toxicological profile and can be detected readily by noninvasive fluorophotometric methods.

The preparation of the inserts was relatively straightforward, and the complete details will not be presented here. The poly(acrylic acid)-cysteine conjugate polymer (PAA-cys) was prepared by standard peptide-coupling methods. Appropriate drug-loaded and blank inserts were prepared. For the blank inserts, PAA-cys was gamma-sterilized, dissolved in distilled water and adjusted to pH 5 or 6. The solution was lyophilized and tabletted by compression to produce inserts of 1 mg and 2 mm in diameter. Drug-loaded inserts were prepared in a similar fashion by adding an appropriate amount of drug (fluorescein or diclofenac salt) to the PAA-cys solution and lyophilized and tabletted in the same manner. Appropriate control inserts made from unmodified PAA were also similarly prepared.

Behavior of mucoadhesive polymers

The swelling behavior of mucoadhesive polymers has a great impact on their adhesive properties, drug release and stability. Rapid uptake of water by the polymer can result in mucus dehydration; this favors interdiffusion between the polymer and mucus layer. Control inserts made from unmodified PAA were completely dissolved in water in 15 min. By contrast, no dissolution of PAA-cys inserts was observed, and they showed good cohesive properties for over 24 h. The water-uptake and swelling behavior of the PAA-cys inserts was dependent upon the pH of the polymer. The total amount of simulated lacrimal fluid

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absorbed by PAA-cys inserts (pH 6), was 1.8-fold higher than that of PAA-cys inserts (pH 5) and 1.4 fold higher than that of PAA-cys inserts (pH 5.5). Complete hydration of the inserts occurred in less than 60 min, and resulted in a 40-fold (pH 6) and 22-fold (pH 5) increase in weight, as well as an increase in diameter from 2 mm to 4 mm.

PAA-cys inserts exhibited a controlled drug release, which was highly dependent upon the pH of the matrix and the solubility of the incorporated drug. For example, sodium fluorescein is highly soluble and was completely released from PAA-cys inserts (pH 7) in 30 min. By contrast, fluorescein-free-acid incorporated in a PAA-cys insert (pH 5.5) was released at a controlled rate over ~4 h.

Two salts of the anti-inflammatory drug diclofenac were also investigated *in vitro*. Despite being more soluble than fluorescein, diclofenac sodium exhibited a controlled release from PAA-cys inserts (pH 6) over a period of 8 h. The authors believe the most likely reason for this observation is ionic interactions between the amino group of diclofenac and the carboxylic acid groups of the PAA-cys matrix. To decrease the release rate of diclofenac, the less soluble diclofenac tris(hyroxymethyl)aminomethane salt was also synthesized and incorporated into PAA-cys inserts. The lower solubility of this diclofenac salt led to a release rate that approached zero order after 1 h and, after 8 h, <40% of the diclofenac had been released from the insert.

Test formulations

Fourteen healthy volunteers were asked to test three different formulations of the PAA-cys inserts. A group of four volunteers evaluated 1 mg PAA-cys inserts (pH 6). A second group of four volunteers evaluated 1 mg PAA-cys inserts (pH 5). A third group of six volunteers evaluated 1.5 mg PAA-cys inserts (pH 5.5) containing 15% fluorescein.

The volunteers were asked to evaluate the acceptability of the inserts on a simple questionnaire, which included questions on the ease of application, irritation immediately after application, irritation after prolonged use, lacrimation, blurring of vision, and foreign body sensation. All questions were scored on a yes/no or 1–5 scoring system, as appropriate. Each volunteer was also asked how long they kept the insert in the eye. In general, irritation scores were low. Application of the inserts was well tolerated because of the small dimensions of the inserts. Moderate irritation was observed only immediately after application. Once sufficiently hydrated in the cul-de-sac of the eye, irritation decreased significantly. Lacrimation did not increase substantially and, because the inserts remained in place and did not disintegrate, no blurring of vision was reported. Most volunteers could tolerate the insert for over 8 h.

In vivo *drug release studies*

The first *in vivo* drug release studies with PAA-cys inserts in humans were performed with fluorescein as a model drug. The pharmacokinetic parameters of fluorescein concentration in the cornea/ tearfilm compartment after administration of 225 μg of fluorescein in three different dosage forms – a 1.5 mg PAA-cys insert, a 1.5 mg PAA insert or aqueous eye drops containing 0.5% sodium fluorescein – were compared. The fluorescein level after applying a single PAA-cys insert exhibited an increase during the first hour followed by almost a plateau during the next 7 h. The observed release rate was much slower than that observed from this insert *in vitro* because of the difference in physiological conditions.

In the *in vitro* case, the insert was immersed in 10 ml of buffer, whereas on the surface of the eye a tear volume of 7–10 μl is present with a turnover of approximately 0.6 μl min^{-1}. When applied as aqueous eye drops, the highest fluorescein concentration was observed within 2 min of application and in less than 2 h the fluorescein level was undetectable. When applied as an unmodified PAA insert, the pharmacokinetic profile of fluorescein release was similar to that of aqueous eye drops, due to rapid dissolution of the insert.

This study indicates that an ocular insert based on thiolated PAA, PAA-cys, could be a promising new solid device for use as an ocular insert dosage form. *In vivo* studies in human volunteers demonstrated a sustained release of a model drug, and the inserts were well accepted by the volunteers. This new device could be highly beneficial for the treatment of ocular inflammation and infections, because current treatment regimens require frequent instillations of aqueous eye drops to maintain therapeutic levels of drug. The added convenience of a sustained release dosage form could be particularly useful for overnight dosing.

Reference

1 Hornof, M. *et al.* (2003) Mucoadhesive ocular insert based on thiolated poly (acrylic acid): development and *in vivo* evaluation in humans *J. Control. Release 89*, 419–428

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