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Recent Patents on Drug Delivery & Formulation **2014,** *8,* **000-000**

New Mucoadhesive Polymeric Film for Ophthalmic Administration of Acetazolamide

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Received: July 10, 2014; Revised: August 29, 2014; Accepted: September 1, 2014

Abstract: This article reports the results concerning the design and manufacture of a novel polymeric film for ocular administration of acetazolamide (AZM), and a patent document presented to INPI- National Institute of Industrial/Intelectual Property. The system was designed using mucoadhesive polymers, such as carbomer (CB974P) and sodium carboxymethylcellulose (NaCMC), combined with the poloxamer (POL407) which behaves as a swelling modulator, surfactant and slightly plasticizer. The maximum amount of AZM to be incorporated without loss of homogeneity or precipitation of the drug, was 0.04 mg AZM/mg of the film. The addition of a polymeric coating based on Eudragit RSPO (cationic permeable polymethacrylate polymer) allowed optimizing drug release. The coating in a proportion of 10% (determined as percentage of total weight of the film) seemed to be the most adequate, since 80% of controlled drug release was achieved along 240 minutes. This coating membrane did not affect the mucoadhesive properties of the swellable polymers. Thus, the system obtained, showed good efficiency and the intra ocular pressure (IOP) decreased according to the results derived from *in vivo* studies performed on normotensive rabbits. Finally, irritation scored studies demonstrated that these systems were not irritant for rabbit´s ocular mucosa.

Keywords: Acetazolamide, bioadhesive films, glaucoma, ophthalmic delivery.

1. INTRODUCTION

Eye is a unique and very valuable organ with singular structural and functional properties, with a particular behavior. Normally, it is an extremely robust organ, although it sometimes appears as a very sensitive tissue. There are a variety of diseases affecting the eye and occasionally, systemic diseases may affect the vision [1].

The design of a drug delivery system aiming to target a particular tissue of the eye has become a major challenge for scientists in this field [2]. Topical application of drugs to the eye is the most common and well-accepted route of administration for the treatment of different eye disorders and consequently, many ophthalmic drug delivery systems are available. Most common ophthalmic preparations are solutions (drops) and ointments, which conform about 70% of the eye dosage formulations in the market. However, when these preparations are instilled into the cul-de-sac, they are rapidly drained away from the ocular cavity (about six minutes after administration) due to tear flow and lachrymal nasal drainage. Only a small amount is available for its therapeutic effect (1-3%) resulting in very frequent dosing [3]. So, in order to overcome these problems, new pharmaceutical ophthalmic formulations such as in-situ gels, nanoparticles, liposomes, nanosuspensions, and microemulsions have been proposed and developed aiming to increase drug bioavailability after eye instillation [4].

For treatment of some chronic ophthalmic pathologies (i.e. glaucoma), patient adherence is recognized as being a key factor for the success of the treatment. However, treatment adherence in chronic diseases is estimated to be only 75% [5] at best.

Glaucoma involves progressive optic nerve damage, associated with loss of visual function and frequently related to elevated intraocular pressure (IOP). The different performances of selected drugs lead to a wide range of possibilities for glaucoma treatment. However, the major challenge for the ophthalmologist is the appropriate dosage for each patient [6].

Acetazolamide (AZM), a carbonic anhydrase inhibitor (CAI), is nowadays used orally for the reduction of intraocular pressure (IOP) in patients suffering from glaucoma, in the pre-operative management of closed angle glaucoma or as adjuvant therapy in the treatment of open angle glaucoma [7]. In order to obtain the desired IOP, large oral doses of AZM have to be administered. However, numerous side effects usually appear due to the wide distribution of carbonic anhydrase in body organs, among which the most frequent are diuresis and systemic acidosis, and in some cases severe dyscrasias.

Although the deleterious systemic side effects of AZM can be avoided if AZM is topically administered to the eyes, the poor aqueous solubility (0.7mg/ml) and low corneal

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1872-2113/14 $100.00+.00

permeability (4.1x10-6 cm/s), plus an insufficient time of drug retention in the administration area, may negatively affect the bioavailability of AZM. Regarding this, in an earlier work, we were able to increase AZM bioavailability in rabbits by the development of an ophthalmic aqueous formulation containing a ternary complex, compounded by AZM, hydroxypropyl-ß-cyclodextrin (HP-ß-CD) and triethanolamine (TEA) [8]. Similar results were also observed when AZM was carried by nanostructures of ascorbyl laurate, leading to a noticeable increase in the ocular bioavailability of the drug [9]. However, in both cases the effect was relatively transient, and further studies were necessary in order to provide a longer residence time of the formulation on the eye surface.

The aim of the present study is to develop and evaluate a novel formulation consisting in a coated polymeric film, which is able to modulate drug release from the system. Properties such as mucoadhesiveness, drug release, pharmacological effectiveness (IOP decrease in normotensive rabbits) and potential irritant effects were evaluated.

2. MATERIALS AND METHODS

2.1. Chemicals

Acetazolamide (AZM) (Parafarm, Buenos Aires, Argentina), polyethylene glycol 400 (PEG400) (Parafarm, Buenos Aires, Argentina); Sodium Carboxymethylcellulose (NaCMC) ultra high viscosity grade 1500-4500 mPa.s (Fluka AG, Buchs SG, Switzerland); Eudragit RSPO (Evonik Röhm GMBH, Pharma Polymers, Germany) (Eu RSPO) and Polyethylene glycol 600 (PEG 600) (Parafarm, Buenos Aires, Argentina). Carbomer 974P (CB974P) was kindly provided by BF-Goodrich (Cleveland, OH, USA) and Poloxamer 407 (POL 407) was kindly given by BASF (Ludwigshafen, Germany).

2.2. Formulation and Film Preparation

Polymeric films were prepared by the casting method using water as a solvent, according to a methodology previously used in our laboratory with slight modifications [10]. Briefly, a mixture of CB974P and NaCMC (1:1) was dispersed in water at 20-25°C and stirred under vacuum. Then, AZM, PEG 400 and POL 407 were also dispersed in water at 20-25°C and added to the CB974P/NaCMC aqueous dispersion under gentle stirring. The film-forming gel was poured into molds specially designed for thin films (0.2 mm thickness) and then dried into an oven (45-50°C) for 24 hrs. until constant weight was reached. The film thus obtained was denoted "uncoated film" (Film A), and its composition is detailed in Table **1**.

All prepared films showed appropriate mechanical strength for application on the eye surface [10, 11, 14].

2.3. Preparation of "Coated Film"

Coating solution was prepared as follows: 0.6 g of Eu-RSPO and 0.14 g of PEG600 were dissolved in isopropylalcohol: acetone (1:1) to produce a 6% (W/W) organic solution of the polymer (Eu RSPO). "Uncoated film" was submerged into this solution, aiming to achieve the homogeneous wetting of the film. Subsequently, it was placed in a fan-assisted oven at 40°C for 3 hrs. This procedure was repeated until 3 films were obtained coated with a weight gain of 5%, 10% and 15%. The respective compositions of films B1 (5%), B2 (10%) and B3 (15%), are detailed in Table **1**.

2.4. Content Uniformity

Small discs of 4 mm from 6 different films (n=45) were cut and weighed before being placed in test tubes containing 10 ml of Ringer solution and stirred for 72 hrs. Previously, we had corroborated that this period of time was long enough to guarantee the total release of AZM incorporated to each disc.

The AZM concentrations in Ringer solution were measured using an UV-Vis spectrophotometer (Shimadzu UV 160-A, Shimadzu Corporation, Kyoto, Japan) at 267 nm. The homogeneity index (HI) was calculated from the ratio between the amount of AZM and the weight of each disc (Eq. 1).

$$HI = C_{AZM} / W_f \quad \text{Eq. 1}$$

where C_{AZM} is the amount of AZM and W_f is the weight of the disc.

2.5. Swelling Ratio and Disintegration Rate Measurement

The determination of the swelling ratios of the films (series A and B) was carried out utilizing a method described by Llabot *et al.* [11]. At predetermined time intervals (from 5 to 120 min); hydrated samples were removed and weighed after blotting the surface water with filter paper. The swelling ratio (SR) was calculated using W_S/W_P (Eq. 2), where W_S and W_P are the wet and dry weights of the films, respectively.

$$SR = W_S / W_P \quad \text{Eq. 2}$$

Table 1. Composition of assayed films.

Film	AZM	CB974P	NaCMC	POL407	PEG400	Eu RSPO(*)
	mg				mL	% weight gain
A	30	250	250	250	30	-
B1	30	250	250	250	30	5
B2	30	250	250	250	30	10
B3	30	250	250	250	30	15

(*) The amount of Eu-RSPO is expressed in terms of weight gained in the coating process.

A similar procedure was used for swelling ratio determination of coated films. In addition, a visual inspection of the integrity of the film coating (Carl Zeiss magnifying glass, Germany) was also performed in order to detect possible spalling, cracking or discontinuity of the Eu-RSPO membrane.

2.6. *In vitro* Drug Release Measurement

Drug release assay was carried out as follows: discs of 8 mm diameter (approximately 0.15 mg of AZM / disc) were placed in test tubes with 5 ml of Ringer solution (sink conditions). These tubes were set in a continuous moving shaker bath at 35.5°C, and at predetermined time intervals each tube was removed. The amount of AZM was determined (n=3) at 267 nm using an UV-Vis spectrophotometer (Shimadzu UV 160-A, Shimadzu Corporation, Kyoto, Japan).

2.7. *In vivo* studies

2.7.1. Determination of Intraocular Pressure (IOP) in Animals

Animals

New Zealand white rabbits, (basal IOP average = 11.39±0.92 mmHg), weighing 2-2.5 kg were used. The rabbits were provided with food and water ad libitum in a temperature-controlled room (21°±5°C) and exposed to 12 hrs. light: 12 h dark cycles. A week of adaptation in the facilities, animals were admitted to the experimental sessions.

All experimental procedures were carried out conformed to the ARVO (Association for Research in Vision and Ophthalmology) guides, the European Communities Council Directive (86/609/EEC) about the use of animals in research and the Institutional Care and Use Committee of the School of Chemistry of Córdoba University, Córdoba, Argentina, who reviewed and approved the protocols.

After a week of adaptation in the facilities, the animals were admitted to the experimental session.

Assay

IOP (mm Hg) was measured using a Perkins MK2 tonometer (HS Clement Clarke, England) calibrated according to the manufacturer's instructions. Before tonometry, infant blepharostate was used to maintain the eyelids open during the measurements. A mixture of topical anesthesia (0.5% solution of proparacaine HCl) and fluoresceine salt (0.25% solution of Grant®, Alcon® Montevideo- Uruguay) was applied (50 µl) on the cornea in order to improve animal welfare during the test and to achieve the necessary contrast (fluoresceine salt) before each measurement of intraocular pressure. The fluoresceine salt was used to outline and make clearly visible the area of cornea flattened by the split prism tonometer head. All determinations were performed three times at each interval, and the means were calculated. In all cases, the IOP was measured at -30, 0, 30, 60, 120, 180, 240, 300, 360, and 420 min.

The rest of IOP was measured two or three times a day, during the two days before drug administration. In this way, the normal baseline for each animal was established before the next treatment. The experiments were always carried out at the same time of day.

A piece of film of 4 mm in diameter was placed in the conjunctival sac of the rabbit right eye, loaded with AZM (0.7 mg AZM). In the contralateral eye, film without AZM was placed in the same way. The assays were performed using twelve animals and the differences in IOP between each group were expressed as the means (mmHg) ± standard error of the mean (S.E.).

2.7.2. Ocular Irritation Test

The potential ocular irritancy and/or damaging effects of the formulations under test were evaluated using a slightly modified version of the Draize test [8]. This test was performed in twelve eyes of six male New Zealand white rabbits weighing 2-2.5 kg. A piece of film of 4 mm in diameter was placed in the conjunctival sac of the right eye, and the left eye was used as control. Pre- and post-exposure evaluations of the eyelids, conjunctiva, cornea and iris were performed by external observation under adequate illumination, and additional information was provided by a binocular indirect ophthalmoscope (Neitz IO-α small pupils, Japan) and 20-diopter lens (Nikon, Japan).

For each observation, one drop of fluoresceine salt (0.25%) was instilled to contrast the potential corneal injury. A rating of ocular irritation or damage was scored Table **2**. for each observation (0, 60, 120, 180, 240, 300, 360 and 420 min) according to Table **2**.

2.8. *In vivo* Bioadhesion

Twelve rabbits were selected and divided into 2 groups. In the first group, 4 mm disc diameter uncoated film (film A) was placed in the conjunctival fornix of each eye. Similarly, in the second group, discs of the same diameter of coated film (Film B) were inserted. The changes in size and adhesion intensity were observed by means of a binocular indirect ophthalmoscope (Neitz IO-α small pupils, Tokyo, Japan) and 20-diopter lens (Nikon, Tokyo, Japan). The magnitude of these changes was quantified according to the score detailed in Tables **3** and **4**.

2.8. Statistical Analysis

In order to study the different variables related to drug distribution, AZM release, IOP curves, bioadhesion and irritation test, a descriptive statistical analysis and specific tests were performed as well. Non-parametric Kolmogorov-Smirnov test was applied to verify the correct distribution of the drug. For release assays, a ***t*** test for independent samples was used in order to compare the means of drug release in each time point. In order to infer the mean differences in IOP between treatments, different linear models were fitted: i) a model for independent errors and ii) two residual covariance models for longitudinal data. Penalized likelihood criteria (AIC and BIC) and various diagnostic tools showed that the mixed model (considering the rabbit as a random effect) were the most appropriate.

Table 2. Ocular irritation scores.

Score value	Formulation effects
0-8	No irritation
9-20	Mild irritation
21-40	Mild to moderate irritation
41-60	Moderate irritation
61-80	Serious injury
81-110	Very serious injury

Table 3. The degree of adhesion of the film *in vivo*.

Adhesión	Film
0	Moved spontaneously out of the eye
1	Was maintained in the fornix, but did not adhere to the palpebral or bulbar conjunctiva permanently
2	Remained in the fornix and attached to a particular conjunctive even when carrying out maneuvers of the eyelid
3	As above but in this case the film remained attached even when rubbing maneuvers took place of the palpebral
4	Remained attached even when trying to move it with a spatula

Table 4. Reference resizingn and film thickness *in vivo*.

Score value	Size and thickness
0	No variation
1	Increased by 1/4 of its original size
2	Increased by 1/2 of its original size
3	Doubled in size

3. RESULTS

3.1. Content Uniformity

Table **5** showed the ***p*** value for tested samples. As can be appreciated, AZM was homogeneously distributed in the film.

3.2. Swelling Ratio and Disintegration Rate Measurement

The results obtained from film A (uncoated film) were similar to those reported by Llabot *et al.* [11], with a reported swelling ratio of 5. No film disintegration occurred during the time tested. The films of series B were also analyzed visually. In the case of films B1 and B2, no changes were observed. However, in film B3, it was noted that the capping layer was broken, thus leaving the film exposed to the dissolution medium.

3.3. *In vitro* Drug Release Measurement

Results concerning AZM release from films A and B are shown in Fig. (**1**). For the former, a relatively fast drug delivery was observed since during the first 5 min 80% of the AZM was released. After this time, the delivery was practically constant, reaching a plateau throughout the studied period.

For film B ("coated films"), a delay in drug delivery was observed that was not proportional to the weight gained (WG) of the coating. 80% of the AZM was released at 30 min in the case of film B1 (%5 WG), at 60 min for film B3 (%15 WG) and at about 240 min for film B2 (%10 WG). Therefore, the last one was selected for further studies regarding IOP diminution and potential irritant effects. On the other hand, the release rate from film B was significantly lower than from film A (***t*** test).

3.4. Measurement of Intraocular Pressure (IOP) in Animals

In this assay, we evaluated the comparative effect of "uncoated" and "coated films" as IOP decreasing. In Fig. (**2**). IOP versus time can be shown.

As expected, film A was the least efficient. Its behavior was concordant with the faster drug release observed during

Table 5. ***p*** **value determination using non-parametric Kolmogorov-Smirnov test.**

FILM	SIGNIFICANCE (*p*=)
FILM A 1	0.664
FILM A 2	0.101
FILM A 3	0.164
FILM A 4	0.123
FILM A 5	0.678
FILM A 6	0.712

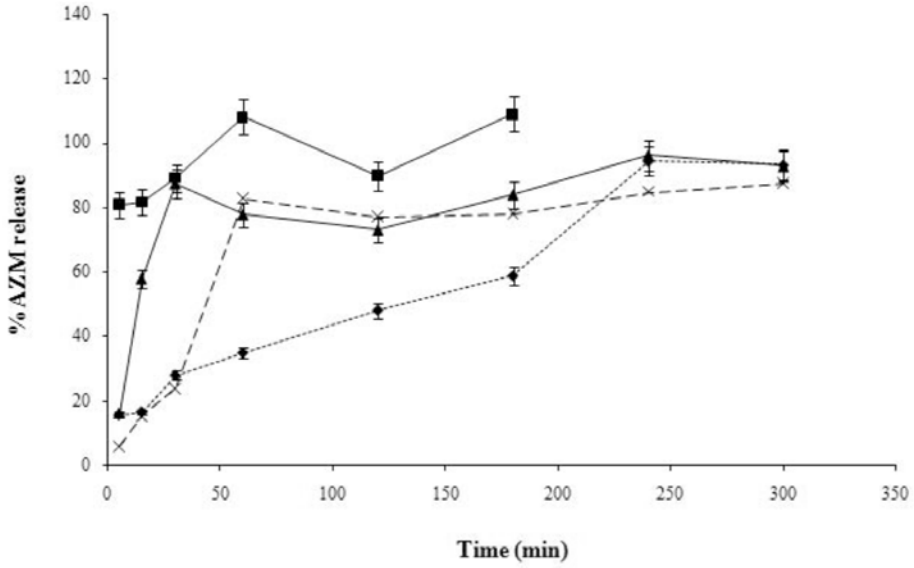

Fig. (1). ***In vitro*** release profile of acetazolamide (AZM).
■ Film A; ♦ Film B2; x Film B3; ▲Film B1.

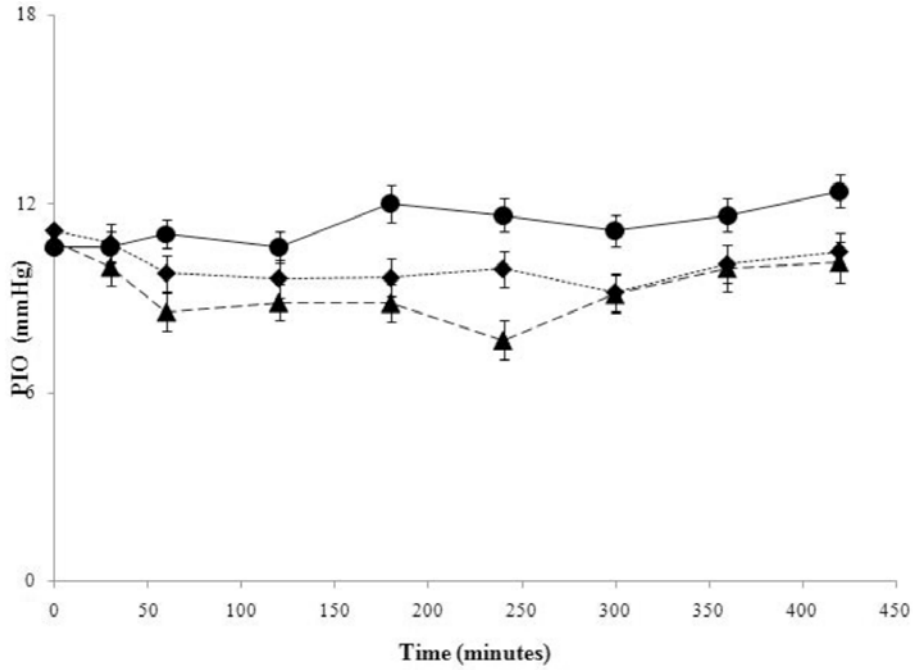

Fig. (2). Effect of the different films on the IOP of normotensive rabbits.
• Control Film; ■ Film A; ▲ Film B2.

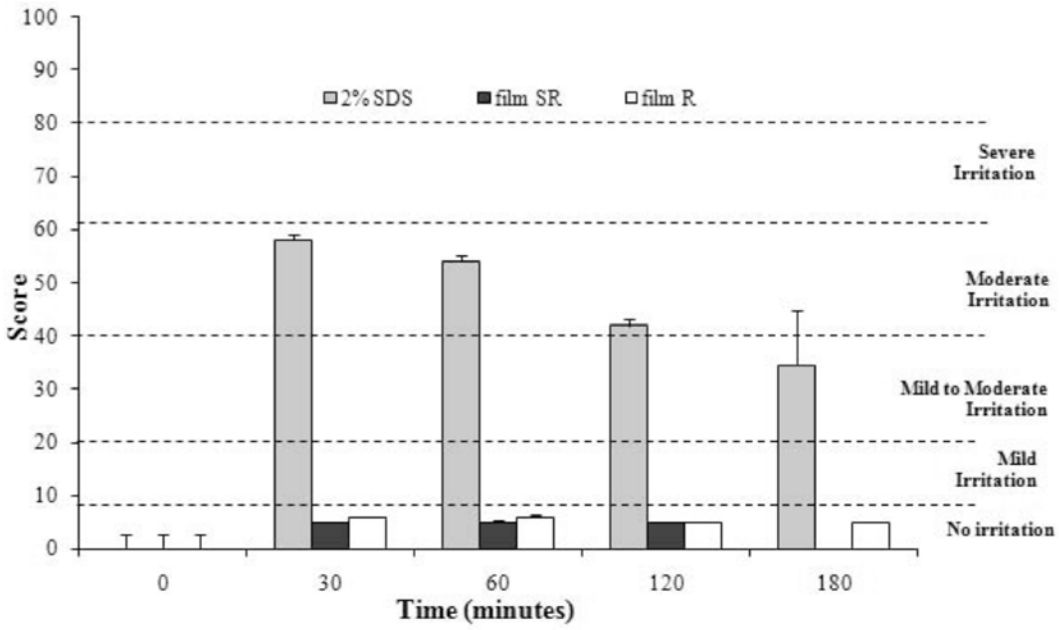

Fig. (3). ***In vivo*** ocular irritation test in rabbit eyes. Scored values for the different formulations.
■ Film A; ■ SDS control; □ Film B2.

in vitro experiments, which facilitated the rapid elimination of AZM from eye surface.

In contrast, film B2 (coated) showed a maximum decrease at 240 minutes (37%), after which, the IOP began to rise steeply up to 7 hrs, but without reaching the value of the baseline IOP.

From the linear mixed model adjusted significant differences between the adjusted means of the treatments were detected.

Significant differences between the means of each treatment were observed using a statistical method based on a linear mixed model

3.5. Ocular Irritation Test

For this study, the classical irritant compound sodium lauryl sulfate (SDS) was selected for comparison (positive control). In this case, according to the results from the score, films A and B2 seemed to be innocuous since no irritation was observed Fig. (**3**). However, the lesions produced by the SDS were classified as moderate to severe.

3.6. *In vivo* Bioadhesion

Uncoated film bioadhesion (A) was moderately greater than the coated film (B2). The variations in film size and thickness were also modified due to the coating. In this case, film B2 showed less variation in size than film A. Table **6** shows that the maximum time of mucoadhesion for film A and film B2 were around 3 and 2 days, respectively.

Taking these results into account, we conclude that the coating process did not markedly affect the film bioadhesiveness.

4. DISCUSSION

According to reports from literature, film casting method is undoubtedly the most widely used manufacturing process for making polymeric films, mainly due to the ease of the process and the low cost [12]. The process consists of at least six steps: casting solution preparation; degasification; transferring appropriate volume of solution into a mold; drying of casting solution; cutting the final dosage form to obtain the desired amount of drug; and packing. During the films manufacture, particular importance is given to the rheological properties of the solution or suspension, air bubbles entrapment, content uniformity and residual solvents in the final dosage form [13].

4.1. Design Rationality of Films

In previous works, we designed films by combining two well known mucoadhesive polymers, such as Carbopol 974P and NaCMC. The proportion of each polymer was fixed by taking into account key parameters related to gel forming film as well as final films (gel viscosity, mucoadhesion intensity, modulation of release and convenient physical-mechanical properties of the film) [10, 11, 14]. In order to obtain a better drug release modulation, we used a film coating compounded by Eu-RSPO®, which is a copolymer of ethyl acrylate and methyl methacrylate with low content of methacrylic acid ester containing quaternary ammonium groups. This polymer, although it is water permeable, is insoluble and possesses independent swelling pH. These properties allow the Eu-RSPO coating to modulate the income of the solvent, with the consequent sustained drug release.

Even though Eu-RSPO does not usually possesses mucoadhesive properties, in this study we observed good bioadhesion to the eye surface.

Table 6. Degree of adhesion of film A and film B2.

	Score at 30 min	Score at 24 hrs	Score at 48 hrs	Score at 72 hrs	Variation size
Film A	3	2	2	2	2
Film B2	3	2	1	0	1

4.2. Content Uniformity

One of the main challenges in the film formation by casting process is to assure the content uniformity in the formulation [15]. Only few reports dealing with this key point can be found in literature. In this case, the uniformity of AZM in the film was determined by performing a random sampling according to the methodology described in section 2.4. The obtaining of a homogeneous dispersion was only possible when drug concentration was lower than 30 mg (related to the polymeric proportion detailed in Table **1**). Based on the interpretation of the statistic results of this study. At higher concentration, we observed agglomeration of solid particles leading to no homogeneity problems.

4.3. Swelling Ratio and Disintegration Rate Measurement

In the case of mucoadhesive films, two key properties have to be balanced in order to get the best biopharmaceutical performance.

On one hand, the amount and kinetic of water intake must be aiming enough to favor the dissolution and diffusion of the drug. On the other hand, the increase of film volume (size) after hydration and swelling, which generates bioadhesion, has to be high enough to guarantee a minimal residence time but sufficiently low to limit excessive swelling that could be detrimental for patient acceptability (i.e. discomfort and/or blurred vision).

In this case, aiming to prevent the excessive swelling we incorporated POL407, which works as film plasticizer. Besides, POL407 has a noticeable influence in swelling behavior as the result of hydrophobic and hydrophilic interactions with CB974P after water intake, leading to formation of table complexes. The hydrophobic interaction may take place between polypropylene oxide groups (PPO) of POL407 and the aliphatic side chains of polyacrylic acids of Carbomer. Also, interactions may occur between hydrophilic groups of POL407 (ethylene oxide, PEO) and [-COOH] groups of Carbomer, through hydrogen bonds; and the intensity of these interactions will depend on the poloxamer/polyacrylic acid ratio.

However, in the case of the coated films (B series), the results (section 3.2) evidenced the importance of the swelling process regarding system integrity and performance.

The polymeric coating has to have certain elastic properties in order to follow the volume increase of the system, due to the elongation process derived from swelling. The thickness of such coating showed to be a key factor regarding this point. In the case of films B1 and B2, the system was able to retain its integrity after the swelling whereas the film B3, where the coating layer was thicker, the rupture of the film was observed. As expected, this behavior affected the pattern of drug release from the films (see next section).

4.4. *In vitro* Drug Release

As discussed in previous sections, Eu-RSPO® coating has pronounced influence on the kinetic of swelling, and consequently on drug release. In this context, we observed the uncoated film A was not able to release AZM in a modulated way, since 80% was released in just 5 min. As previously mentioned, this rate is not convenient for ophthalmic drug delivery as the drug is quickly eliminated through the natural mechanisms of the eyes [16-19].

In the case of film B1, we observed a fast release, mainly, due to the polymeric coating was not thick enough to sustained drug delivery. On the contrary, for film B3 the coating was able to sustain drug release, but only until 30 min after administration; after that such release became very fast. This might have been a consequence of the coating layer rupture, which was not strong enough to support the mechanical stress provoked by swelling. Finally, in film B2 the coating was effective enough to modulate drug release without lack of coating layer integrity. According to these results, this formulation seems to be the most appropriate for AZM ocular administration.

4.5. *In vivo* IOP Measurements

Film A and film B2 as well, were able to produce a decreasing in IOP, in comparison to the IOP values from untreated animals (control). However, in the case of film B2 (coated) such effect was observed before (4 hrs.), and in higher intensity compared to film A (uncoated). This observation was in agreement with the *in vitro* release patterns for each formulation.

In this way, as expected, the uncoated films rapidly released a large amount of drug, which is inevitably eliminated from the eye's surface. Contrary, film B2 was able to modulate the drug release, thus enhancing the absorption of AZM. The maximal hypotensive effect (37%) is achieved at 4 hrs. After that, the IOP began to rise and approximately at 7 hrs. reached a value near normality. The values of the measured IOPs were significantly different compared to those from control group.

CONCLUSIONS

The results arising from this work demonstrated that mucoadhesive polymeric film may be a very useful tool for ocular drug administration, especially those with low aqueous

solubility and limited permeability. The addition of a surfactant seems to be a critical point in the optimization of the process of system manufacture. The addition of a polymeric coating (Eu-RSPO) improved the rate of drug delivery, achieving in the case of film B2 (film with 10% WG of coating) a useful release pattern of about 80% in 240 min. In addition, this film was able to remain attached to the ocular mucosa for at least 2 days without producing irritation. A good performance of the films was corroborated *in vivo* studies where a 40% of IOP reduction was observed in normotensive rabbits, in 4 hours (film B2).

PATENT REVIEW COVERAGE BASED ON TOPICAL GELS/FILMS OCULAR ADMINISTRATION

Several techniques for formulating gels intended for ophthalmic applications are described in a large number of pharmaceutical technology patents. For instance, GB-A-2013084 discloses aqueous gels for application of pharmaceutically active ingredients on the conjunctiva, comprising an ophthalmic drug and a polymer having carboxylic or anhydride functional groups.

In GBA1571832 and EPA0126684, two liquid drug delivery systems based on *in situ* forming gels used in the treatment of a variety of ocular diseases, can be seen.

WO9730704A2 describes a topical formulation based on carbonic anhydrase inhibitor for the treatment of macular edema and age-related macular degeneration. In the specification of this document, the possibility of administrate carbonic anhydrase inhibitor (acetazolamide or other) as a solid insert is revealed. The polymers to be used can be cellulose derivatives, such as sodium CMC or polyacrylic acid salts, ethyl acrylates. Also, synthetic materials such as an ethylene oxide polymer having a higher molecular weight can be used.

CN102166203 patent "Alleviating Eye pad for eye fatigue and preparation method thereof", discloses a patch to relieve an active ingredient used for eye´s fatigue. The excipients described are carbomer, Na CMC, polyacrylic resin adhesive, propylene glycol among others.

Similarly, the patent document CN102166203A shows an eye patch comprising an ophthalmic drug as an active ingredient, carbomer, Na CMC and polyacrylic resin adhesive.

In this context and taking into account the *state of the art,* to get new ophthalmic dosage form where the drug can be retained on the ocular surface still remains a challenge. This can be even more problematic if the drug to be incorporated is slightly soluble.

Considering all these aspects, the invention described in this article [20, 21] provides a novel controlled release system for the topical administration of acetazolamide ophthalmic having the advantages mentioned above and others.

CURRENT & FUTURE DEVELOPMENTS

In our opinion the future challenges related to ocular therapy based on polymeric developments will be based on novel more secure, reliable and efficient systems designed to prolong the therapeutic action by increasing the contact time of the formulation with the ocular surface.

This can be achieved by using films, inserts, mini Tablets or other systems enabling physical attachment of the dosage form on the conjunctiva.

Such systems will contribute to the improvement of ophthalmologic therapy.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Financial support from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), FONCyT Préstamo BID 2437/OC-AR PICT 2010-0380, and SECyT-UNC, is greatly acknowledged. We would like to thank Dr. Paul Hobson (native speaker) for revision of the manuscript.

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