

Research Article

Preparation and *in vitro* Evaluation of Soluble Ophthalmic Films of Brimonidine Tartrate

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ABSTRACT

This study focuses on the treatment of Glaucoma with objectives overcomes certain disadvantages of Eye drops like the frequency of administration, drainage of medication by tear fluid, and greater therapeutic efficacy of drug (Brimonidine Tartrate) using ophthalmic films. The ophthalmic films of Brimonidine Tartrate were designed by solvent casting method containing PVA and PVP-k30 in different ratios as film formers, 20% v/v of PEG400 was added as plasticizer to 10 ml of distilled water. Films were evaluated for physicochemical characteristics such as folding endurance, drug content, thickness, pH of the surface, moisture absorption, moisture loss, and *in vitro* drug release. The drug release rates the prepared formulas didn't take more than 4 hrs, the prepared formulas had acceptable physical properties. Increasing the ratios of used polymers prolonged the time of drug release from the matrix. Formula C6 which had the biggest ratio of polymers showed a controlled release within 4 hrs, however, formula C1 showed the least time of drug release in 1 hour. The drug release from most of the formulations was according to zero order pattern with *n* value in the range (0.5-1) indicating that drug release from matrices was mainly happened by swelling and diffusion (non-Fickian pattern). Formula A6 by comparison with the rest of the prepared formulas showed slow release during 4 hrs

Keywords: brimonidine tartrate, ophthalmic films, PVA, PVP-k30, Solvent casting method, Franz cell.

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The ophthalmic films are classified according to their solubility behavior: Insoluble ophthalmic films, Soluble ophthalmic films, and Bio-erodible ophthalmic films.⁵

The main objective of the ophthalmic films is to increase the contact time between the preparation and the conjunctival tissue, to ensure a sustained release suited for topical or systemic treatment.

The advantages of ophthalmic films over the traditional ophthalmic preparation can be summarized as follows:

- Increased ocular residence, hence, prolonged drug activity and higher bioavailability with respect to standard vehicles.
- Release of drugs slowly.
- Accurate dosing (insert contains a precise dose, which is fully retained at the site of administration).
- Reduction of systemic absorption.
- Better patient compliance, due to reduced frequency of administration and less incidence of visual and systemic side-effects.
- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes.
- Increased shelf life with respect to aqueous solutions.
- Exclusion of preservatives, which reduce the risk of sensitivity reactions.

INTRODUCTION

Brimonidine tartrate (BRT) is an alpha-2 receptors agonists drug was used to treat glaucoma and ocular hypertension since it was approved by FDA in 1996, and it is available in ophthalmic solutions (Alphagan Z®). Activation of presynaptic alpha-2 receptors leads to decreased catecholamine release and decreased adenylate cyclase and cyclic adenosine monophosphate, which, in the ciliary body epithelium, leads to decreased aqueous production.¹

Various ocular barriers prevent permeation and precorneal retention of the drugs within the corneal region, where the cornea is the main route for topically applied drugs to gain access into the eye and the conjunctival/scleral route can also be efficient.²

regardless of the ease of access to the eye for traditional topical application of medication, efficient ocular drug delivery is hampered by a series of clearance mechanisms that protect the ocular structures from foreign matter. Upon administration of traditional eye drops they are immediately diluted in the tear film, followed by quick elimination by the action of blinking, wash out by tears and nasolacrimal drainage.^{3,4}



MATERIALS AND METHODS

Materials

BRT was from (Medichem SA, Spain), PVP-k30 was from (Shreeji Ltd, Mumbai, India). PVA was obtained from (Ranbaxy laboratories, India). PEG400 was from (Sigma-Aldrich, Germany)

Ophthalmic films

ophthalmic films were prepared by solvent casting technique. Formulas were obtained by adding the same hydrophilic polymers but in different ratios in 10 ml of distilled water as a solvent, PEG400 (20% w/w) of dry polymers weights. And 5 mg of the drug were added (Table 1). All ingredients were stirred for 3 hrs by a stirrer magnet then mixed with ultrasound for 30 minutes to obtain a homogenous solution. Finally, the prepared polymeric solution with the drug was poured on petri dishes then and covered with a glass funnel plugged with cotton to avoid fast of the evaporation solvent, for 48 hrs.

Drug excipient interactions

approximately 5 mg of a sample was scanned by differential scanning calorimetry (DSC), by using DSC131 (SETARAM, France) Temperature was varied between 25 to 400°C. DSC of pure drug, pure excipients, and their physical mixtures were analyzed.⁶

Evaluation of ophthalmic films

Thickness uniformity

The thickness of the prepared films was measured by screw gauge with digital reading in 3 different points, and the average was reported.⁷

Folding endurance

Folding endurance was measured by repeatedly folding the film at the same place until it get broken, The number of times the film could be folded at the same place without breaking represented the folding endurance value.⁸

Moisture uptake

Accurate weighted 3 films were kept in desiccators containing saturated solution of potassium chloride in the oven at 25°C. After three days, films were taken out and reweighed; and the percentage of moisture uptake was calculated using the formula below:⁹

$$\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss

Accurate weight of 3 films was kept in desiccators containing anhydrous calcium chloride in the oven at 25°C. After three days, films were taken out and reweighed; and the percentage of moisture loss was calculated from the formula below:¹⁰

$$\frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

pH of the surface

To measure the surface pH, the film was kept in the plate for 30 min in 0.1 ml of distilled water. The pH paper was placed on the surface and measured.¹¹

Drug content uniformity

Drugs-loaded ophthalmic films were placed in 10-mL volumetric flask and equilibrated with 10 ml of phosphate buffer (pH 7.4) for 5 hrs. The flasks were shaken during this period using ultrasound to extract the drug. Then it was filtered by 0.45 µm syringe filter. From the filtrate, it was assayed spectrophotometrically at 248 nm.¹²

In vitro drug release

In vitro release of BRT from the prepared ophthalmic films formulas, was studied by using franz cell which consists of the following parts:

- A receptor compartment contains 12 ml of phosphate buffer solution (pH 7.4).
- A donor compartment over which the ophthalmic film is fixed on a semi-permeable synthetic membrane of cellulose nitrate with a diameter of 0.45 µm.
- a Magnetic stirrer to stir the buffer solution in the receptor compartment at a speed of 50 rpm.
- The Franz cell was placed into a water bath with heater to maintain a temperature of 37° ±1 °C.
- Specific quantities of samples (2 ml) were withdrawn from the sampling port with a long needle syringe and replaced with an equal volume of phosphate buffer solution pH 7.4. The samples were analyzed using the spectrophotometrically at a wave length of 248 nm.¹³[13]

Kinetic of drug release

The kinetics models of releasing brimonidine tartrate from the studied formulas were analyzed according the following release models:

1. Zero order release
2. First order release
3. Hixson-Crowell model
4. Higuchi release model
5. Korsmeyer-Peppas model

The appropriate model was checked using Microsoft Excel 2019, and the correlation coefficient (R²) values were calculated. the model that produced the highest correlation coefficient among the prepared films was used for the assessment of drug release rates. For Korsmeyer-Peppas model, the results were illustrated depending on n values, when (0.5<n<1) means a non-Fickian diffusion and when n=0.5 indicates Fickian diffusion (Higuchi model).

Table 1: Formulations of ophthalmic films

Materials	C1	C2	C3	C4	C5	C6
*BRT (mg)	5	5	5	5	5	5
*PVP-k30 (mg)	75	75	150	300	500	800
*PVA (mg)	75	150	150	300	500	800
PEG400 (w/w)	20%	20%	20%	20%	20%	20%
Distilled water (ml)	10	10	10	10	10	10

*BRT: Brimonidine Tartrate, *PVP: Polyvinyl pyrrolidine, *PVA: Polyvinyl alcohol

RESULTS AND DISCUSSION

Drug excipient interaction studies (DSC)

Fig.1 shows the differential thermal scanning scheme of brimonidine tartrate, where it shows the presence of a sharp endothermic peak, at 215° C, and this indicates the presence of BRT in the crystalline state.^{14,15}

The apparent exothermic peak at 270°C indicates the thermal degradation of the drug. The same sharp peak was noticed when BRT was mixed with PVP-k30 as shown in (Fig. 2). While the melting peak shifted of about one degree by mixing the drug with PVA, (to 216°C) (Fig. 3), this could be due to a kind of interaction between BRT and PVA.

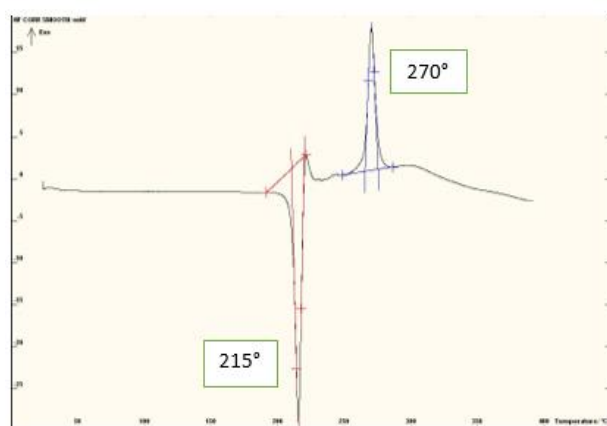


Figure 1: DSC thermogram of pure Brimonidine Tartrate

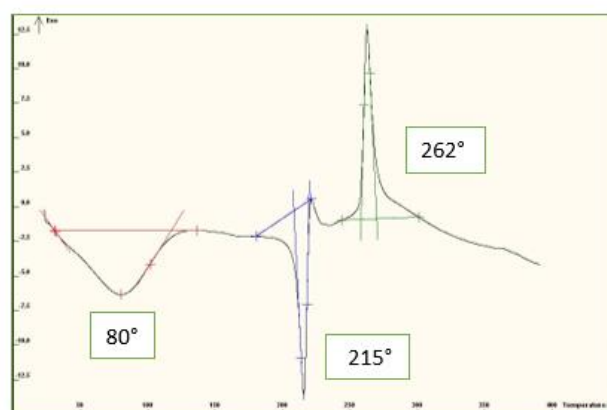


Figure 2: DSC thermogram of a physical mixture of Brimonidine Tartrate and PVP-k30

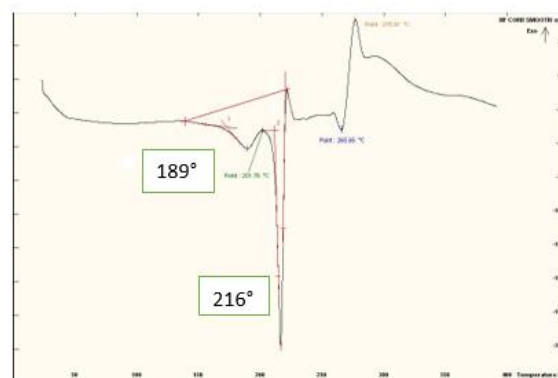


Figure 3: DSC thermogram of a physical mixture of Brimonidine Tartrate and PVA

Thickness uniformity

Results showed that the thickness of prepared films were in the range (0.1-0.35) mm as appears in (Table 2). It was noticed that more ratios of polymers the thicker the films were obtained.

Folding endurance

The results were within a range of (178-364) times (Table 2), it was observed that folding endurance increased when the polymers ratios of PVP-k30 and PVA were increased.

C7 was the best foldable formula, as it contains the highest ratio of film forming polymers (PVP-k30 and PVA) whereas C1 was the least foldable formula as it contains the lowest ratio of film former polymers.

Moisture uptake

C7 showed a maximum of moisture uptake (Table 2), because it contains a high ratio of hydrophilic polymers by comparison with the other formulations.

Moisture loss

C7 showed a maximum of moisture loss (Table 2), because it contains the highest ratio of hydrophilic polymers by comparison with the other formulations.

there is a proportional relationship between the concentration of hydrophilic polymers and the moisture uptake and loss of films.

Surface pH

Table 2 shows results of surface pH of the prepared formulas which were in the range (5.45-6.45), that indicates that the films don't have irritation potential, and the pH is within acceptable the range for eye.

Drug content uniformity

The results showed that the drug contents of all formulations were in the range 95% to 98% as (table 2).

Table 2: Physiochemical tests results

Formula code	Film thickness(mm) \pm SD*	Folding endurance \pm SD	Percentage of moisture uptake \pm SD	Percentage of moisture loss \pm SD	Surface pH \pm SD	%Drug content \pm SD
C1	0.1 \pm 0	178 \pm 1.75	1.26 \pm 1.58	0.72 \pm 0.2	5.5 \pm 0.04	97.24 \pm 1.22
C2	0.13 \pm 0.05	131 \pm 1.32	1.64 \pm 1.4	1.24 \pm 0.46	5.45 \pm 0.01	98.72 \pm 1.87
C3	0.16 \pm 0.11	228 \pm 1.8	1.7 \pm 1.21	1.7 \pm 0.51	6.45 \pm 0.02	95.22 \pm 1.12
C4	0.26 \pm 0.11	280 \pm 1.62	1.82 \pm 1.52	2.92 \pm 1.2	5.45 \pm 0.01	97.59 \pm 1.4
C5	0.3 \pm 0	322 \pm 1.59	2.63 \pm 1.67	3.43 \pm 0.6	5.5 \pm 0.05	95.37 \pm 1.89
C6	0.43 \pm 0.05	364 \pm 1.92	3.22 \pm 1.45	4.12 \pm 1.46	5.45 \pm 0.15	

*SD: Standard deviation

In vitro release study

The release profiles of BRT from the prepared ophthalmic films are shown in table 8. The percentage of drug release from formulation C1 was found to be 96.7% after 1 hr. The percentage of drug release from formulations C1, C2, C3, C4, C5 were found to be 95.2%, 98.6%, 98.1% and 97.8% after 2 hrs respectively. the release rate of the drug from

C6 containing the highest ratio of PVA and PVP-k30 was found to be 98.4% after hrs. C6 shows long release time by comparison with the other formulations. Results showed that increasing ratios of polymers may prolong release time of BRT through matrices system composed of PVA, PVP-k30 & PEG400.

Table 3: in-vitro drug release profile of films

T(h)	C1	C2	C3	C4	C5	C6
0.25	35.2 \pm 1.24	22.6 \pm 0.07	17.3 \pm 0.82	15.3 \pm 0.2	12.7 \pm 1.07	7.4 \pm 0.56
0.5	41.4 \pm 1.99	36.1 \pm 1.15	39.2 \pm 1.63	25.2 \pm 0.52	37.1 \pm 1.62	19.8 \pm 1.74
1	96.7 \pm 0.24	51.5 \pm 1.7	40.4 \pm 1.68	44.6 \pm 1.71	45.9 \pm 0.61	28.9 \pm 0.41
2		95.2 \pm 0.61	98.6 \pm 1.02	95.1 \pm 0.73	97.8 \pm 0.97	57.9 \pm 1.63
4						98.4 \pm 0.62

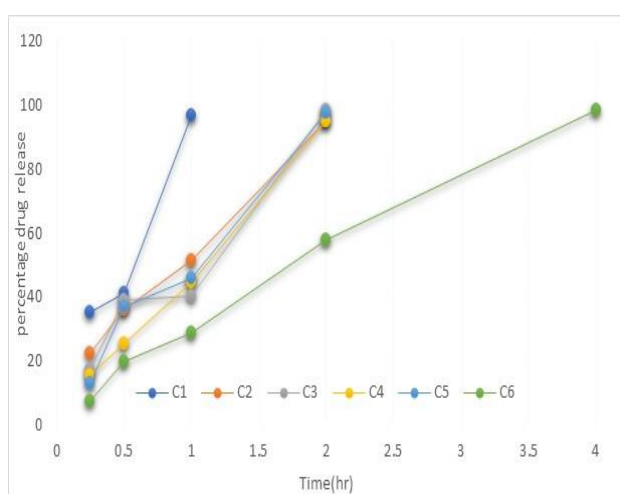


Figure 4: Release of Brimonidine Tartrate from prepared formulations

Drug Release Kinetics

Various kinetic models obtained upon fitting the curves of drug release from BRT loaded ophthalmic films are presented in Table 8. Comparison of the correlation coefficients (R^2) in Table 9 shows that the best fit with the highest R^2 was shown by zero order model for all films studied formulations. When fitted to the Krosmeier-Peppas model, of all formulations, the values of n were in the range (0.67-0.88), which showed evidence of coupling swelling and diffusion mechanism (non-Fickian) in these formulations.

Table 4: kinetic release from films

	Zero order	First order	Higuchi	Hixon-Crowell	Krosmeier-Peppas	
	R ²	R ²	R ²	R ²	R ²	n
C1	0.9426	0.9105	0.8929	0.9199	0.8665	0.72
C2	0.9955	0.9307	0.9741	0.9607	0.989	0.67
C3	0.9373	0.8882	0.8995	0.9102	0.9093	0.74
C4	0.9951	0.9215	0.9598	0.9516	0.9898	0.87
C5	0.9681	0.9067	0.9397	0.9542	0.9425	0.91
C6	0.9601	0.9795	0.9906	0.9838	0.9774	0.8

R²: correlation coefficient

CONCLUSION

In this study, ophthalmic films of Brimonidine Tartrate were formulated with different ratios of polymers PVA, PVP-k30, PEG400, six formulations were prepared.

The drug release lasted for 4 hours in formula C6 and not more than 2 hours in C2, C3, C4, C5. Kinetic release of BRT showed that all the formulations followed zero order model which is of preference as a model for ophthalmic drug release.

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