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Formulation and evaluation of sustained release ocular inserts of betaxolol hydrochloride using arabinoxylan from *Plantago ovata*

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Abstract: The purpose of the current studies was to develop ocular insert of betaxolol hydrochloride (BXH), using arabinoxylan (AX) as a film former. The inserts were prepared by sandwiching I mg of BXH between two films of AX. Six different formulations of ocular inserts were prepared in such a way that first three formulations contained varying concentrations of AX along with glycerol as plasticizer, whereas, rest of the formulations were added with 0.5mg of sodium alginate, sandwiched between two films of AX along with 1mg of BXH. Chemical compatibilities of the ingredients were assessed by using FTIR. Prepared ocular inserts were subjected to various physicochemical characterizations. The dissolution studies showed that ocular inserts containing sodium alginate with the AX showed sustained release effect better than the formulations with AX alone. Addition of sodium alginate resulted in inhibition of sudden release in initial phase and further sustained the release of drug from ocular inserts. Ocular inserts were pH compatible to the eyes as well as there was no interaction among the drug and excipients, suggesting that the selected excipients were suitable for the development of sustained release ocular inserts of BXH.

Keywords: Betaxolol hydrochloride, ocular inserts, sodium alginate, AX.

INTRODUCTION

Ophthalmic drops being the most widely used ocular dosage form, are not able to attain the required drug concentration at the site of application for the sufficient time duration. The instilled drug is washed out of the eye due to induced lacrimation and naso- lacrimal drainage. In addition to that, in case of some drugs such as topical corticosteroids, the dose repetition is required as frequently as 6 times a day (Gaballa *et al*., 2020). This results in a decreased drug efficacy and disease control, due to limited patient compliance. Different approaches were accomplished to increase the ocular bioavailability of traditionally used eye drops by the addition of viscosity enhancing polymers and gelling agents. These approaches improved the bioavailability to some extent, but on other hand reduced the patient compliance due to blurred vision and matted eyelids. By adopting "sustained release" approach in ocular inserts, the problem of limited pre-corneal drug residence time can be successfully addressed (Gote *et al*., 2019). By definition ocular inserts are sterile preparations with a solid or semisolid consistency having shape and size, suitable for ophthalmic use. Mostly, these are placed in lower formix and some times in the upper formix or on the cornea as well. The ocular inserts may increase the shelf life as compared to aqueous solutions. Moreover, the risk of hypersensitivity reactions is very small because preservatives are not included in these formulations. Although a large number of semi synthetic and synthetic polymers can be used to prepare the sustained release ocular inserts, the natural polymers can be preferred because of their non-toxicity, biocompatibility, easy availability and cost effectiveness. AX is important hemicelluloses in which arabinose side chains are linked to linear backbone of β-(1→4)-linked D-xylopyranosyl units. Psyllum husk is considered as one of the prime sources of AX. Its chemical structure and composition varies with the source, however, husk AX contains arabinose around 22%, xylose, galactose and glucose about 56.72%, 3.76% and 0.64% respectively along with mannose 0.40% and rhamnose 1.50%. It is a nonirritant and nontoxic pharmaceutical excipient, which can be used as suspending and flocculating agent in pharmaceutical suspensions at low concentrations (Bashir *et al*., 2014). However, comparatively high concentration can be used to formulate control released drug delivery systems (Iqbal *et al*., 2011).

BXH is a β1 adrenergic antagonist (cardio selective) and is effectively used to treat chronic (open angle) glaucoma and high intraocular pressure. It selectively blocks catecholamine stimulation of beta1-adrenergicreceptors present in the heart and vascular smooth muscles. This

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causes a decrease of systolic and diastolic blood pressure, cardiac rate, cardiac output and also reflex orthostatic hypotension. The drug also antagonizes beta 2-adrenergic receptors present in the vascular and bronchial smooth muscles competitively resulting in constriction of these muscles. Major therapeutic indications of BHX are high blood pressure (Fayyaz *et al*., 2019), arrhythmias, coronary heart disease and glaucoma (Hoyng and van Beek, 2000). In patients suffering from cardiac failure, the drug is also used to treat non-fatal cardiac problems. When beta1-receptors (found mainly in the heart) are stimulated by adrenaline, the heart rate and the blood pressure is increased, consequently oxygen consumption by heart is increased. BHX blocks these receptors, therefore have the opposite effect. It reduces the heart rate and blood pressure, and hence is valuable in conditions when the heart itself has inadequate supply of oxygen. It is usually used in patients with ischemic cardiac disease (Foody *et al*., 2002).

The current study was designed with the aim to develop sustained release ocular insert of BHX using a natural film former (AX) along with sodium alginate. The ocular inserts were prepared by using an easy and simple solvent evaporation method.

MATERIALS AND METHODS

Material

BXH was received as a gift sample from Atco Laboratories, Lahore, Pakistan. AX was extracted from Ispaghullah Husk (purchased from local market of Lahore), using alkali extraction method. Glacial acetic acid, Sodium hydroxide, Sodium alginate and Glycerol were obtained from Merck Germany.

Preparation of Ocular inserts

In a beaker of 100 ml capacity, 60mlof distilled water was taken. After passing through sieve no 120 accurately weighed AX was transferred to the beaker bit by bit with constant but slow stirring to avoid the entrapment of air. Then 0.1ml of glycerol was added and the stirring continued. After 60 minutes of stirring the mixture was poured into a clean and dry Petri dish of 88.5mm diameter and allowed to dry in oven at 40°C. After drying a thin film was obtained. The film was removed carefully from the surface of Petri dish before it gets dried completely. The film was further dried in oven. A micrometer was used to measure the thickness of the film at different places and average thickness of the film was determined. Three different types of films A, B and C were prepared using 600mg, 500mg and 400mg AX respectively. From these films circles of 5.3 mm diameter were cut by using a very sharp edge die.1mg of BXH was accurately weighted on a piece of butter paper using analytical weighing balance. A circular piece of the film 5.3mm in diameter was placed on a flat glass surface. The drug was transferred to the center of the film by using micro spatula. Another film was taken and thick polymer solution was applied on its margins with the help of very fine brush. The later piece of film was placed carefully on the first one using forceps and magnifying glass and the edges were pressed gently. The resulting ocular insert was placed in a Petri dish and dried in oven. After drying sealing paste was applied again on the margins to establish complete sealing. Then the ocular inserts were placed under UV light for 30 minutes for sterilization. The inserts were kept in tight glass container for further evaluation.

Composition of Ocular inserts

Six different formulations of ocular inserts were prepared. Formulations F_1, F_2 and F_3 contained AX 600mg, 500mg and 400 mg. Glycerol was used as plasticizer. Quantity of glycerol used in formulations F_1, F_2 and F_3 was 0.1ml, 0.083 ml and 0.066ml respectively. In formulations F_4, F_5 and F_6 amount of AX and glycerol was the same as in formulations F_1, F_2 and F_3 respectively but an additional polymer sodium alginate was used. In each of these three formulations, 0.5 mg of sodium alginate was sandwiched between two films of AX along with 1mg of betaxolol hydrochloride (table 1).

Physicochemical evaluation and characterization of ocular inserts

Physical appearance

To note the physical appearance of the prepared ocular inserts was the first step in their physicochemical evaluation. The color and shape of the ocular inserts was noted. The smoothness of the surface of the inserts was observed using a magnifying glass.

Surface pH

Three ocular inserts were selected from each formulation of the ocular insert and their surface pH was determined. In order to determine the surface pH of the inserts, the ocular inserts were put in a Petri dish with I ml of distilled water for half an hour at room temperature. The swollen inserts were removed and pH was determined with the help of pH meter.

Thickness

The thickness of the formulated ocular inserts was measured using digital micro meter having least count of 0.01mm (Mitutoyo, Japan). Average of 5 readings was taken and standard deviation values were calculated.

Weight uniformity

As weight variation among the formulated ocular inserts can lead to difference in drug content and in vitro behavior. The ocular inserts were weighed using an electronic balance (least count = 0.10mg). The average weight and standard deviation were then calculated and reported.

Swelling index (S.I)

For the determination of S.I, three inserts were taken, followed by their individual placement in test tubes with 4ml of distilled water. Inserts were weighed before adding them into test tubes and recorded as initial weight, and then after every half an hour, till the constant weight achieved and noted as final weight. After a period of 30 minutes, the ocular inserts were removed and the excess water on their surface was removed using a filter paper.

$$S.I\ (\%) = (\text{Increase in weight} \div \text{Initial weight}) \times 100$$

Chemical compatibility studies of the ingredients using FTIR spectroscopy

The compatibility of the ingredients is of great importance and that can be confirmed by FTIR spectroscopy. FTIR Spectrophotometer (Bruker Germany) was used to record the IR spectra of pure drug and formulations by KBr Disc method.

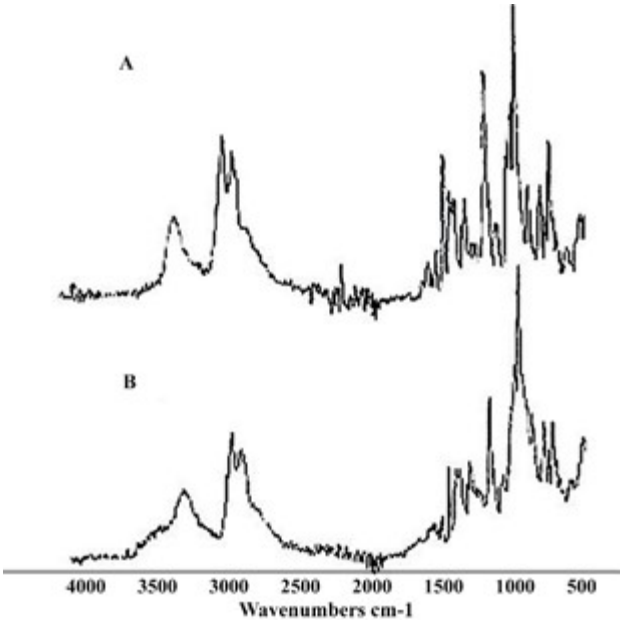

Fig. 1: (A) FTIR spectrum of BXH and (B) FTIR spectrum of the formulation (drug + excipients)

In-vitro drug release studies

To access the *in-vivo* behavior of the drug, *in vitro* drug release is an important predictor. The vial method with some modification and customization was employed to conduct the *in vitro* dissolution studies for 8 hrs. Individual insert form each formulation was taken and placed in 20 ml capacity test tube containing 10ml of phosphate buffer saline pH 7.4, previously warmed at 37±1 °C. These test tubes were placed on a reciprocating shaker and temperature was maintained at 37±1°C. The speed of the reciprocating shaker was adjusted to minimum in order to simulate the movement produced by blinking of the eye. From the test tubes 1ml samples were withdrawn carefully using pipette at specific interval and 1 ml of fresh dissolution medium was added to the tube at the time of each sampling to restore the volume of dissolution medium. The samples were appropriately diluted with the same medium and were analyzed at 233 nm using Shimadzu- Double beam 1601UV Spectrophotometer against blank.

Release kinetics models

Various kinetic models were employed to observe the mechanism and pattern of the drug release from the prepared ocular inserts. For this purpose, the release data has been subjected to Zero order, first order, Higuchi and Korsmeyer peppas model (Jafari *et al*., 2021).

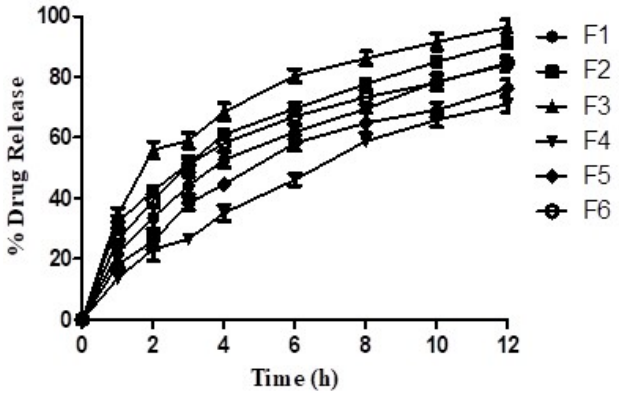

Fig. 2: Release profiles of BHX, released from the prepared ocular inserts

Similarity index

It is the statistical parameter, which is used to analyze the different formulation regarding the similarity of their drug release profile. The value of f_2 indicates that how similar the formulations are. Higher the value of f_2, more the similar are products. Difference factor (f_1) is the indicator of the difference between the release profiles of the two compared formulations. Similarity index of two formulations increases if f_1 lies closer to'0' and f_2 near to '100'(Zaman *et al*., 2014).

STATISTICAL ANALYSIS

Mean and standard deviations have been calculated by using GraphPad prism ver.7.01

RESULTS

Physicochemical characterization of prepared ocular inserts

Physicochemical characterization of prepared ocular inserts of BXH was carried out to find out their suitability for use. The findings were acceptable and confirming the success of the studies (table 2).

Drug- Excipients compatibility study by FTIR spectroscopy

Drug-excipients compatibility of the prepared ocular inserts was carried out by FTIR spectroscopy. FTIR

Table 1: Composition of different formulations of ocular inserts

Formulation	AX (mg)	BXH (mg)	Sodium Alginate (mg)	Glycerol (ml)
F1	600	1	_	0.1
F2	500	1	_	0.083
F3	400	1	_	0.066
F4	600	1	0.5	0.1
F5	500	1	0.5	0.083
F6	400	1	0.5	0.066

Physicochemical evaluation and characterization of ocular inserts

Table 2: Findings of different physicochemical parameters of prepared ocular inserts

Formulations	pH	Mean Thickness (mm)	Average Weight (mg)	Swelling index	Drug contents (%)
F1	6.74	0.303	8.6	33.81	96.5
F2	6.67	0.257	7.35	33.10	97.0
F3	6.71	0.246	6.2	32.35	100.3
F4	6.64	0.32	9.10	36.70	97.3
F5	6.78	0.263	7.75	38.79	99.4
F6	6.8	0.256	6.64	36.13	95.6

Table 3: Dissolution data modeling presenting release kinetics of BHX ocular inserts based on AX in phosphate buffer saline pH7.4

Kinetic models		F1	F2	F3	F4	F5	F6
Zero Order	R^2	0.944	0.951	0.894	0.977	0.937	0.906
	R_o	5.396	5.142	5.022	5.348	5.149	4.826
First Order	R^2	0.994	0.990	0.979	0.995	0.988	0.986
	K_1	0.140	0.176	0.245	0.101	0.110	0.133
Hixon Crowel Cube root	R^2	0.873	0.903	0.826	0.930	0.871	0.836
	KCH	0.177	0.110	0.101	0.155	0.136	0.111
Higuchi Model	R^2	0.991	0.993	0.963	0.992	0.985	0.973
	K_H	25.19	25.19	23.75	24.56	24.04	22.79
KorsmerPeppas Model	R^2	0.986	0.996	0.965	0.995	0.984	0.977
	kK_p	24.743	32.910	40.532	13.612	20.430	30.789
	n	0.501	0.413	0.359	0.677	0.541	0.415

spectrum of BXH was compared with the spectrum of the formulation. Both spectra showed comparable peaks for drug, which confirmed that the drug and the excipients were compatible having no significant interaction.

In vitro drug dissolution studies

Dissolution studies have reviled that AX alone as well as in the presence of sodium alginate possessed the potential to retard the release of drug (fig. 2). The drug has been sustained till the 12th hour of the studies. F1with comparatively highest quantity of the polymer (600mg) released 84.33±2.56% of the drug. F2 showed 91.16±2.67% of the drug release having 500mg of the polymer, while F3 with least quantity of the polymers which is 400mg, released 96.50±3.12% of the drug. Similar kind of behavior of the drug released was observed in F4, F5 &F6, which were formulated with the combination of AX and sodium alginate. But here it was seen more pronounced drug retarding effect by the polymer combination. F4 with highest concentration of AX with sodium alginate released least amount of the drug during 12 hrs studies and was found to be 71.06± 1.35%. F5 with moderate concentration showed moderate amount of the drug release which was 76.3±1.4% and F6 with minimum quantity of the polymers showed 84.00±1.60% of BHX (fig. 2).

Kinetic modeling

First order and Higuchi's model showed a good fit to the release profile data. This indicates that the release of the drug from the matrix slowed down with the passage of time. The zero order and Hixson models were relatively poor fit, indicating that the release of the drug would not remain constant over the described period of time (table 3) (Zaman *et al*., 2016b). However, the value of R^2 for Higuchi model have suggested the diffusion type of drug release mechanism, and it was further confirmed by the values of korsmeyer peppas kinetics. Furthermore, the F2, F3 and F6 were found to have fickian type of diffusion mechanism, as indicated by the value of 'n', conversely,

Table 4: Comparison of similarity index (f_2) and difference factor (f_1) of ocular inserts

Comparisons	Similarity index (f_2)	Difference factor (f_1)
F1 vs F2	47	12
F1 vs F3	32	28
F1 vs F4	36	24
F1 vs F5	52	11
F1 vs F6	59	7

the F1, F4 and F5 were seemed to be following non-fickian type of released pattern (table 3).

Similarity index

F1 was selected as reference formulation as this formulation showed suitable sustained effect with reasonable drug release. All other formulations were compared with it and their similarity (f_2) and difference (f_1) factors were calculated. Outcomes of the studies have disclosed that, the F6 was most similar (f_2=59) one from all the compared formulations (table 4). F5 showed reasonable similarity with 52 and 11, values of f_2 and f_1 respectively.

DISCUSSION

pH of all the formulations was found to be in the range of 6 to 7 showing neutral behavior and should be non-irritating to the eye surface (table 2). The pH of the formulations containing sodium alginate was also neutral as sodium alginate it-self has neutral pH as, describe by the various researchers in the previous studies (Rowe *et al*., 2009). The thickness of the ocular inserts was measured by a digital micrometer. Maximum thickness was observed for formulation F1, having highest polymeric contents and minimum for formulation F3 (with least polymer's concentration), indicating the polymeric concentration dependent trend in the thickness same was being observed in the literature (Zaman *et al*., 2016a). Similar trend was observed in weight variation test. An average weight of formulation F4 was highest due to maximum amount of AX and 0.5mg sodium alginate present in the formulation. Formulation F3 had the least weight due to absence of sodium alginate and minimum amount of AX present in the formulation. Swelling index, is an essential parameter to observe the ability of the polymer to retain the water. The good swelling properties may be attributed by the ability of the AX to absorb sufficient amount of water. This property has a major role in sustained release ability of the polymer as, greater the swelling of the polymer would result in more thick gel layer, through which a drug may be diffuse out to become the part of surrounding media (Rowe *et al*., 2009). It has been reported in the previous studies that in the presence of a swellable matrix, the penetration of water from the dissolution media into the matrix initiates the release of the drug. The hydration of polymer by water yields a gel like structure. The drug is dissolved in water and polymer chains are relaxed, consequently, the drug diffuses out of the matrix. The release of the drug mainly depends upon the solubility of the drug in the dissolution media. In such cases, where soluble drugs are included in matrix of swellable polymers, more media is penetrated into the matrix due to osmotic gradient which facilitate the drug release. More the media enters, more the polymer gets hydrated and more swelling occurs (Zaman *et al*., 2013). The current studies have exhibited the similar findings, where a hydrophilic drug was incorporated in swellable matrix. The AX, being a swellable polymer have retained the drug for suitable duration. Drug release was found to be between 71.06±1.349 to 96.56±3.12 from the formulations containing AX (F1-F3) and AX in combination with sodium alginate (F4-F6). Drug release was found to be in inverse relation with concentration of the polymer as, it was observed that release of the drug was decreased with increase in the polymer concentration. Additionally, when the released data was subjected to kinetic modeling, the diffusion type of release mechanism was justifying that the studies were in accordance to the previously reported studies, as a lot of studies have purposed that swellable matrix showed the diffusion type of drug release pattern (Cid *et al*., 2020).

CONCLUSION

The present study was carried out to investigate the ability of the AX as a sustained release polymer in ocular inserts to control the release of BHX. The studies might be considered as, AX alone as well as in the presence of sodium alginate has shown good drug retarding abilities. Furthermore, the selected set of ingredients was considered suitable for the preparation of sustained release ocular inserts of BHX.

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