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Research Article

Developmental Studies on Alginate Films for Ophthalmic Use

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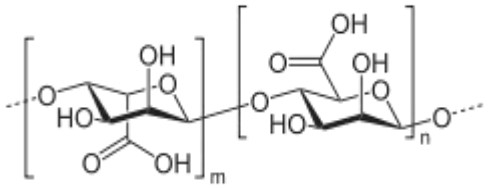
Abstract: Sodium Alginate is a natural amylose carbohydrate distilled from alga. In the area of topical ocular administration, important efforts concern the design and the conception of new ophthalmic drug delivery systems which are able to prolong the residence time. The use of inserts, which are solid devices to be placed in the cul-the-sac or on the cornea, represents one of the possibilities to reach increased residence time and thus improve bioavailability. Naturally occurring water-soluble anionic polysaccharides which are hydrophilic, but can be made insoluble by cross-linking with polyvalent cations are preferred. These are compatible with the tissues of the eye and are bioerodible. They include the seaweed gums such as algin, alginic acid, etc. In the present work, Sodium alginate as a bioerodible material was studied and evaluated for its possible utilization as an ocular insert. The alginate films were hardened using three different polymetallic salts like Calcium Chloride($CaCl_2$), Barium Chloride ($BaCl_2$) and Zinc Chloride ($ZnCl_2$). Commonly used ophthalmic drug-Timolol maleate was tried. Later the effects of hydrophobic coating on the release rates were studied by coating the film with 4% Ethyl cellulose in Chloroform. It was seen that Sodium alginate films insolubilized using $CaCl_2$, $BaCl_2$ and $ZnCl_2$ could be used as bio-erodible material for ophthalmic use. The films showed promising drug release through diffusion controlled release process. Coating with hydrophobic material was found to decrease the initial fast release though the pattern remained unchanged. Thus Sodium alginate films hardened with Ethyl cellulose shows promising effect as a bio-erodible material for ocular inserts.
Keywords: Alginic acid, Timolol maleate, ophthalmic formulations, ocular bioerodible inserts

INTRODUCTION

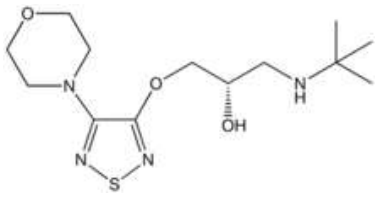
Alginic acid, also called algin or alginate, is a viscous gum that is abundant in the cell walls of brown algae. It colorranges from white to yellowish-brown, and takes filamentous, granular and powdered forms. It is a linear copolymer with homopolymeric blocks of (1-4)-linked β-D-mannuronate (M) and its C-5 epimer α-L-guluronate (G) residues, respectively, covalently linked together in different sequences or blocks [1].



Commercial varieties of alginate are extracted from seaweed, including the giant kelpMacrocystispyrifera, Ascophyllumnodosum, and various types of Laminaria. It is also produced by two bacterialgeneraPseudomonas and Azotobacter.

Alginates are water soluble anionic polysaccharides, which are hydrophilic but can be made insoluble by cross linking with polyvalent cations. They are compatible with the tissues of the eyes and are bioerodible. A preferred group of polyvalent metal cations which are non toxic to the mammalian patients being treated used for cross linking are Calcium, Barium, Zinc and Aluminum. The chemical compoundSodium alginate is the sodiumsalt of alginic acid. Its empirical formula is $NaC_6H_7O_6$[2,3].

Timolol Maleate is widely used in the treatment of glaucoma. The structural formula is as shown below:



Chemically it is (*S*)-1-(*tert*-butylamino)-3-(4-morpholino-1, 2, 5-thiadiazol-3-yloxy) propan-2-ol. It is water soluble, moderately lipophilic, non selective β-blocking drug, with an Octanol – water partition coefficient of 1.16 at pH 7.4 at 37 ^oC. It has half life of 2 to 5 hours [4,5].

Timolol maleate eye drops (0.25%, 0.5%) are effective in lowering the Intraocular pressure (IOP) in patients with glaucoma by about 26 to 38% [6]. Simple aqueous solutions remain in cul-de-sac for 60 seconds and a decrease in IOP is achieved within 3 hours [7].

Hence if the formulation remains in contact with the cornea for more than 60 seconds than the IOP lowering effect of the drug may be increased.

Traditional topical ophthalmic formulations have poor bioavailability due to rapid precorneal elimination, conjunctival absorption, and solution drainage by gravity, induced lacrimation and normal tear turnover. This leads to frequent instillations of concentrated medication to achieve the desired therapeutic effect. Systemic absorption of the drug and additives drained through the nasolacrimal duct may result in some undesirable side effects [8-10].

These observations suggest that increased contact time between drug and corneal tissue could both be beneficial for patient compliance and improve the therapeutic effect. One way of achieving above objective is by using solid ophthalmic inserts. These are more effective in increasing the contact time, provide prolonged drug release, need less frequent administration schedule and avoid pulsed release of the drug.

Of these bioerodible inserts are those which innocuously disintegrate as a unit structure over a prolonged period of time in response to the environment in the eye and which material is absorbed by the eye and surrounding tissues or otherwise is dissipated.

The objective of the present work was to prepare and evaluate alginate films for their possible utilization as ocular bioerodible inserts.

MATERIALS AND METHODS

All chemicals were of AR grade and purchased from LOBA Chemie Pvt. Ltd. Timolol maleate was a gift sample from Centaur Pharmaceuticals Pvt. Ltd. Tivim, Goa.

In all the experiments, a batch was prepared from 100 gms of the film mixture solution containing 7.5% Sodium alginate as the film forming material. The drug and plasticizer (glycerol) both at 40% w/w were added based on the dry weight of the polymer.

The basic formula employed was:

Sodium alginate	7.5 g
Glycerol	3.0 g
Drug	3.0 g
Water	86.5g
Total	100 g

Weighed amount of Sodium alginate was hydrated by dispersing it in weighed quantity of water. The drug was dissolved in glycerin and the mixture was uniformly dispersed in the alginate solution.

From the above mixture a weighed quantity (3g) was taken and cast on a glass plate with a glass bangle serving to limit the area. The plates were kept undisturbed for 16 hours. The dried films were then cut to size using a cork borer (internal diameter – 1.06cm). These films were then insolubilized in a bath of 3 different divalent metallic salt solutions i.e. 10% solutions of Zinc chloride, Barium chloride and Calcium chloride for 5 hours.

After insolubilization period, the films were washed in a glycerin bath (50%) and allowed to dry at room temperature.Invitro drug release was carried out on the films. As the films hardened by $ZnCl_2$ did not yield consistent results for drug release, further batches were prepared by using $BaCl_2$ and $CaCl_2$ as hardening agents

From results obtained it was found that the films released the drug very fast and hence it was thought of coating the films with 4% ethyl cellulose in chloroform. The coated films were also analyzed for their drug release profiles and results obtained were tabulated and graphed as follows:

- % Cumulative drug released per 3.35 sq.cm. v/s time in hours
- % Cumulative drug released per sq.cm. v/s sq.root of time
- Log cumulative % drug retained per 3.35sq.cm. v/s Time in hours
- Log cumulative % drug released per sq.cm. v/s log time

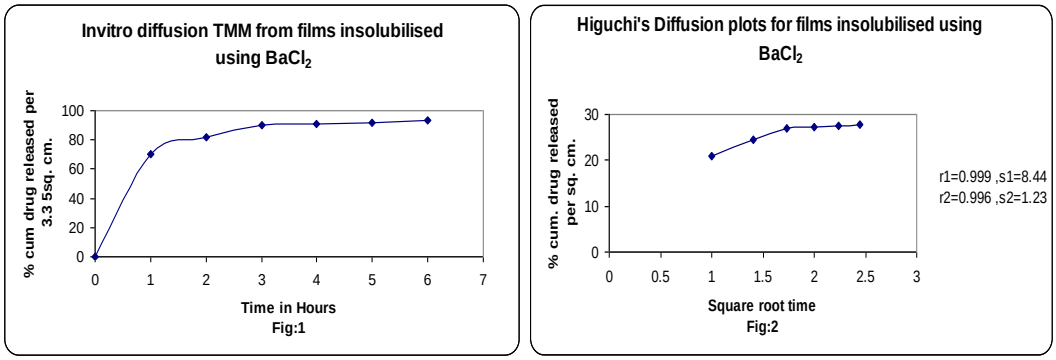
RESULTS AND DICUSSION

The results of drug release in case of films insolubilized using $BaCl_2$ show two linear segments in the graphical representation of data as per Higuchi's equation (Fig. 2). The data also obeys first order rate kinetics as shown by two linear segments in Fig 3. It indicates that initially there is quick release of the drug followed by slower release. The double log plots (Fig. 4) also gave two linear segments. Here slope values indicate that the drug release was by Fickian diffusion without any swelling.

The results of drug release in case of films insolubilized using $BaCl_2$ and coated with 4%EC are shown in Fig. 5-8.

The results of drug release in case of films insolubilized using $CaCl_2$ are shown in Fig 9-12.

The results of drug release in case of films insolubilized using $CaCl_2$ and coated with 4%EC are shown in Fig. 13-16.



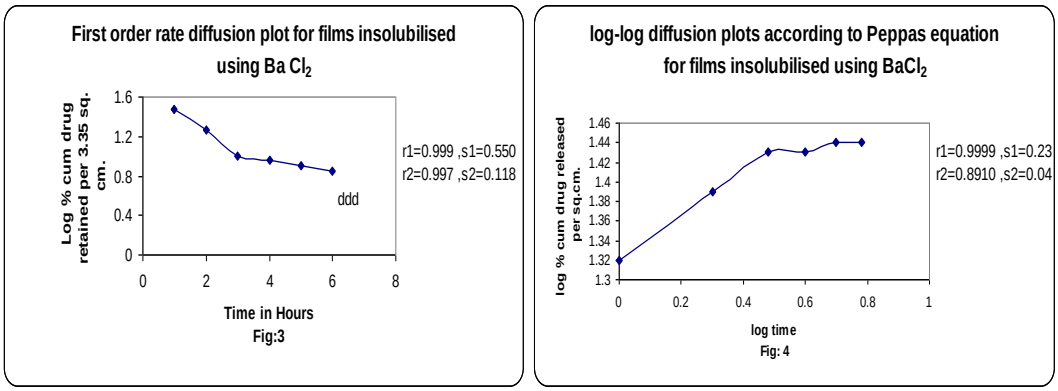
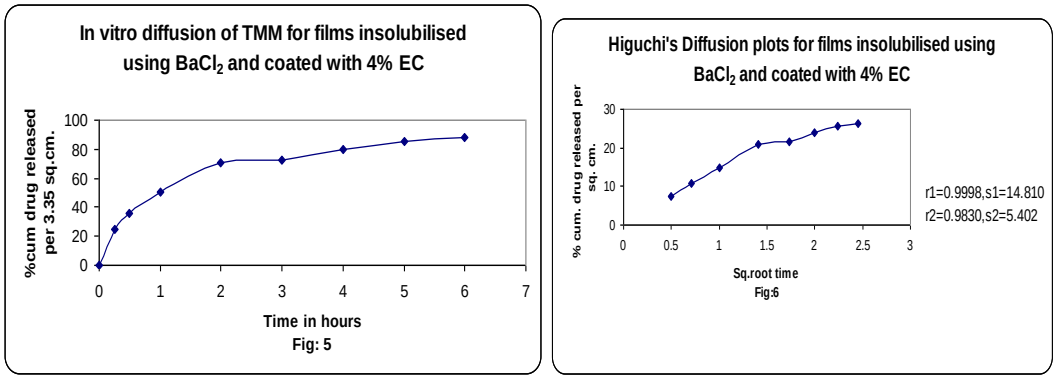


Fig. 1-4: Effect of $BaCl_2$Insolubilised Films



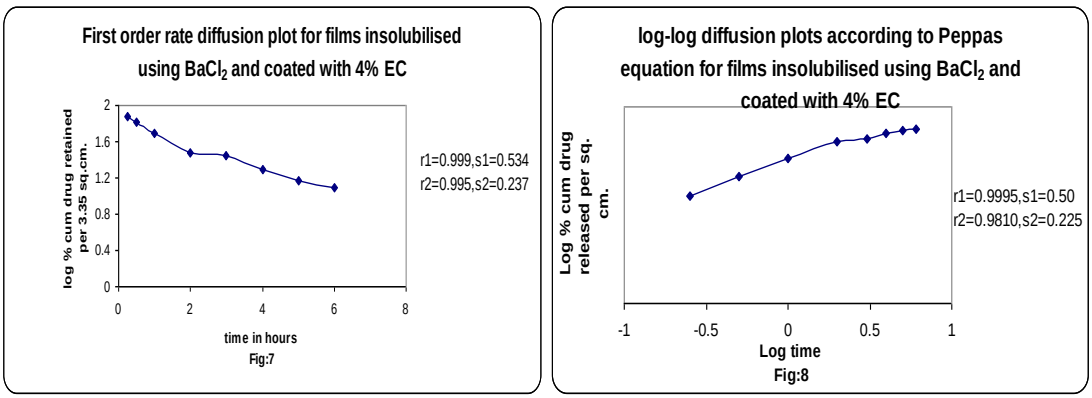


Fig. 5-8: Effect of $BaCl_2$Insolubilized Films Coated with 4% EC

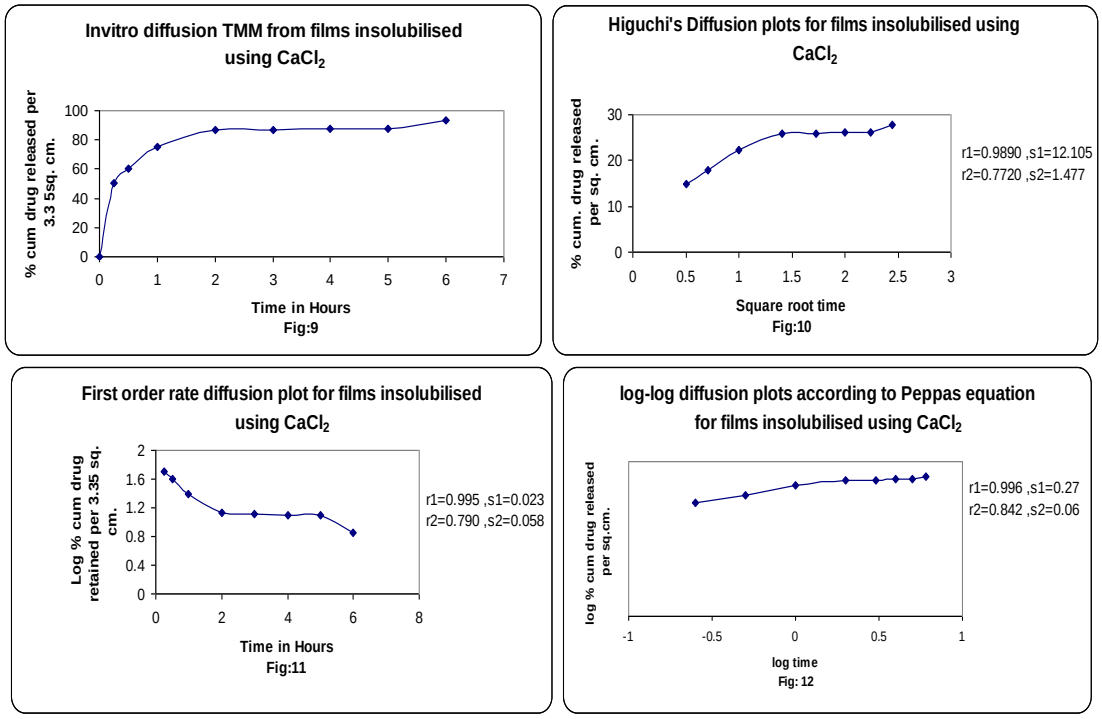


Fig. 9-12: Effect of $CaCl_2$ insolubilized films

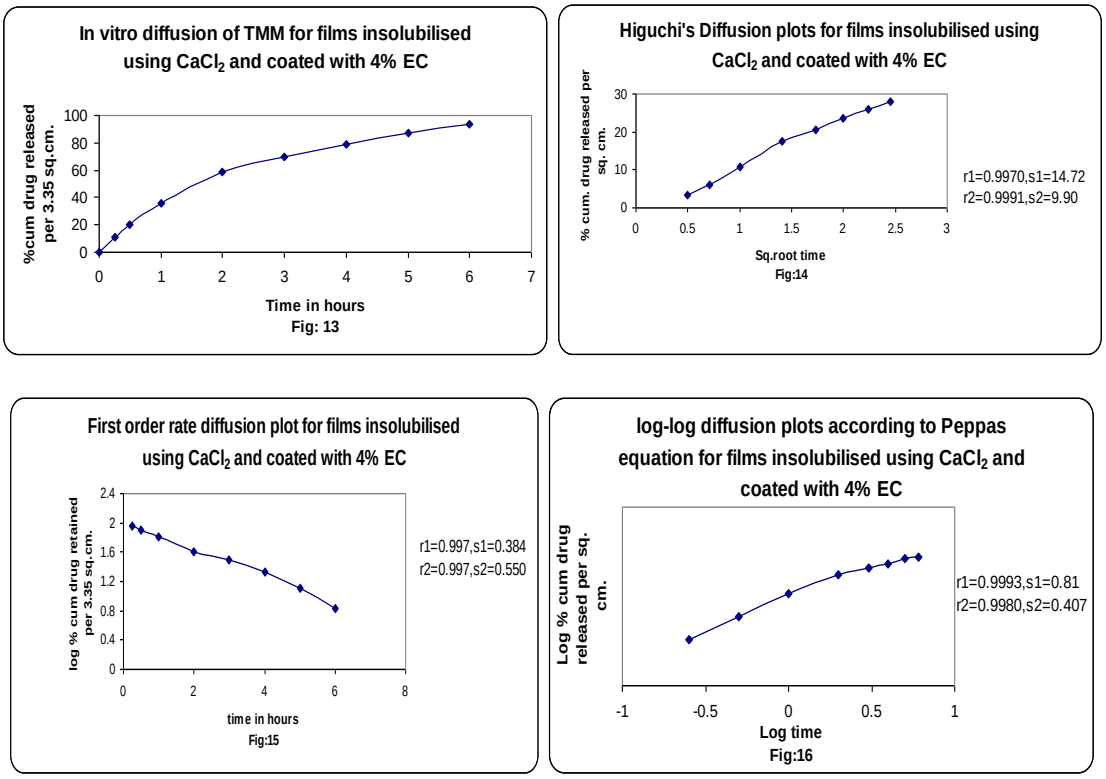


Fig. 13-16: effect of $CaCl_2$Insolubilized Films Coated with 4% EC

Thus it seems that Sodium alginate films insolubilized with $BaCl_2$ and $CaCl_2$ and further coated with 4% ethyl cellulose may be used as material for bioerodible ocuserts. Normally ocuserts are supposed to release the drug over long period of time. The embedded drug should be lipophilic as the study proved that hydrophilic salts are not ideal candidates. The aim of present work was to investigate the possible utilization of Sodium alginate films as bioerodible ocuserts and the results are encouraging.

CONCLUSION

The films showed promise in that the drug release was diffusion controlled and for $BaCl_2$ and

$CaCl_2$ insolubilized films, drug was released in two steps – first quick release followed by slower release. Coating with hydrophobic material was found to decrease the initial fast release, though pattern remained the same. Thus in conclusion Sodium alginate films hardened with $BaCl_2$ and $CaCl_2$ and coated with Ethyl Cellulose show promise as a biodegradable material for ocular insert, provided hurdle of inability to incorporate hydrophilic drugs is overcome so as to guarantee the success of these films.

ACKNOWLEDGEMNTS

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