Preparation and Characterization of a Novel Once-Daily Formulation of Diltiazem Using Arabinogalactan as a Channeling Agent

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Received 22 March 2011; accepted 4 January 2012
DOI 10.1002/app.36755
Published online in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: The aim of the present study was to develop a once-daily, delayed controlled release formulation for diltiazem. Developed formulation consists of two coated tablets inserted into a capsule; the first tablet is intended to produce a fast release profile, while the second tablet with a unique controlling membrane containing arabinogalactan as a channeling agent was designed to achieve a delayed controlled release profile for diltiazem. The *in vitro* characteristic of formulation was determined in terms of the surface morphology of the coated tablet, and the impact of the different polysaccharide in coating on the dissolution and *in vitro* drug release. Arabinogalactan was found to be most appropriate channeling agent to control *in vitro* drug release. When tested in buffer (pH 6.8) the formulation produced a desired delayed controlled release dissolution profile for over 24 h. Surface morphology of the coating film clearly demonstrated channeling formation on contact with the media. © 2012 Wiley Periodicals, Inc. J Appl Polym Sci 000: 000–000, 2012

Key words: Diltiazem; modified release; polysaccharide; channeling agent; arabinogalactan

INTRODUCTION

Traditionally, drug delivery is meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. A second generation drug-delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents,[1] these systems turned to be one of the most successful systems in delivering the drug molecule.[2] But still for many drugs, use of such systems is not suitable. The main obstacles for continuous prolonged release formulation with drug like diltiazem are the fact that the drug has a relatively short half-life,[3] and is highly water soluble. Thus, any matrix formulation with a single unit releasing the drug may face difficulties in achieving a release profile which will allow a once-daily administration. There are various solutions to such a problem and one of them is designing a modified-release formulation by creating a drug reservoir in the formulation which will act at a later stage, and will not terminate the full dose at an early stage post-administration. However, developing oral modified-release tablets of water soluble drugs with prolonged release characteristics has proved especially challenging. Unless the tablets are properly formulated, the drug may be released at a faster rate than intended, resulting in undesirably high concentrations upon oral administration.[4]

Diltiazem is a potent vasodilator, increasing blood flow and variably decreasing the heart rate via strong depression of atrioventricular node (AV) node conduction. Its pharmacological activity includes potent vasodilator of coronary and of peripheral vessels.[5] This reduces peripheral resistance and afterload. A thorough search of the literature revealed several publications describing modified-release formulations for the oral administration of diltiazem. For example, several researchers investigated guar gum-based matrix formulations, alone or in combination with hydroxypropyl methyl cellulose (HPMC), to provide a sustained release profile.[6–9] Al-Suwayeh et al. evaluated the release profile of compressed casein-chitosan microspheres in which HPMC, carbopol, and/or egg albumin were included in the dry mix prior to compression.[10] Pursuing a different line, El-Kamel et al. investigated the use of several types of alginate beads to control the release of diltiazem.[11] Most of these studies describe sustained release profiles that were completed *in vitro* within about 8 h.

The literature also mentions the incorporation of channeling agents in the core or in the coating, usually in an attempt to obtain zero order release in connection with colonic delivery or time-controlled delivery. Formulations based on this concept generally use a hydrophilic/hydrophobic polymer

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mixture to produce the required channels, for example, a controlled porosity osmotic pump-based drug-delivery system.[12] Unlike the elementary osmotic pump, which consists of an osmotic core with the drug surrounded by a semi-permeable membrane drilled with a delivery orifice, the controlled porosity of the membrane was accomplished by the use of different channeling agents in the coating, with cellulose acetate as the semi-permeable membrane. The channeling agents tested by the authors were diethyl phthalate, dibutyl phthalate, and polyethylene glycol 400.[12] In addition, polysaccharides such as galactomannan, inulin, amylase, and others have been proposed for colonic deliveries.[13]

There are several modified-release formulations of diltiazem in the market. All control the release rate using HPMC, and most rely on encapsulated spheroid technology.[14] However, the literature on modified-release oral solid-dosage formulations of diltiazem HCl does not appear to mention the incorporation of arabinogalactan or of any other highly soluble drug in a complex modified-release formulation containing galactans and comprising two tablets, each with a controlled core and coating. Furthermore, no published study compares arabinogalactan with other polysaccharides as channeling agents or examines their influence *in vitro* as was carried out in the present manuscript.

Arabinogalactan is a highly branched polysaccharide consisting of a galactan backbone with side chains of galactose and arabinose with unusual water solubility (70% in water). It is extracted from the Larix tree and is available in a 99.9% pure form with reproducible molecular weight (MW) and physicochemical properties. It has been found to be stable in powders and aqueous solutions and has been tested in pharmaceuticals as a binder and for delivery to the colon, where its enzymatic degradation produces the porosity needed for the planned release. The high water solubility, biocompatibility, and biodegradability make arabinogalactan as a potential drug carrier.[15,16]

The aim of the present study was to design a novel oral modified-release system consisting of two tablets in a capsule suitable for once-daily administration of diltiazem and to investigate the *in vitro* characteristics of this new system. Arabinogalactan was used as channeling agent to achieve a delayed controlled release profile for diltiazem. By optimizing the thickness of the outer coat and arabinogalactan concentration, time-dependent release of the active ingredient can be obtained.

MATERIALS AND METHODS

Materials

The following materials were used: diltiazem hydrochloride (Fermion, Espoo, Finland); sodium carboxymethylcellulose (Acdisol: DMV International, NCB-Iaan, Vegel, The Netherlands); fumaric acid (Gadiv Petrochem. Inc., Israel); lactose monohydrate (DMV International NCB-Iaan, Vegel, The Netherlands); polyvinylpyrrolidone (povidone k-30: BASF, Ludwigshafen, Germany); magnesium stearate (Merck, Germany); ethylcellulose 100 cps (Hercules Inc., VA); triethyl citrate (Morflex Inc, Greensboro, North Carolina); talc (Luzenac, Malanaggio, Italy); poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.2 (Eudragit® RL 30D: Degussa, Rohm Pharma, Darmstadt, Germany); arabinogalactan (Larex Inc., MN); hard gelatin capsules (Capsugel, Cedex, France); alcohol (Gadot, Haifa, Israel). Phenol was purchased from Sigma (Rehovot, Israel). Sulfuric acid, ethanol high-performance liquid chromatography (HPLC) grade, acetonitrile HPLC grade, phosphoric acid analytical grade, *N*,*N*-dimethyl octylamine, and potassium dihydrogenphosphate were received from Sigma (Israel) and were used for the HPLC analyses. All solvents were of analytical grade.

Formulation preparation

The formulations (as detailed in Table I) were prepared according to the following manufacturing process: First granules for tablet core formation were prepared, for preparation of granules diltiazem, sodium carboxymethylcellulose (Na CMC) and fumaric acid (when present in the composition) were sieved through 600-μm sieves and mixed thoroughly. Thereafter, granulating solution was prepared, for preparation of granulating solution Povidone k-30 and ethylcellulose 100 (when both were used or ethylcellulose alone) were completely dissolved in alcohol. Then, the sieved materials were placed in a fluid bed (Glatt, Germany) and the granulating solution was applied using the top spray. The wet granulates obtained were then dried till a loss on drying for granules is less than 1.5%. The dried granulate was mixed with lactose in a blender for 15 min. Magnesium stearate was sieved through a 600-μm sieve, and added to the blender. The resulting blend was mixed for 3 min, and then compressed in a rotary tableting machine (Korsch, Germany) using 7 mm diameter punches.

After tablet preparation, coating of these tablets were carried out in a perforated pan coater (Thai Coater, Thailand). The coating materials were suspended in purified water and tablets were coated with this coating solution. Thereafter, both cores and coated tablets were tested for physical parameters like weight, thickness, and diameter of tablets obtained. Finally, one tablet containing 100 mg and other containing 140 mg diltiazem, in accordance with the formulations listed in Table I, were inserted in a hard gelatin capsule to form final formulation.

TABLE I
Composition and Physical Parameters of Three Formulations, Containing Tablets with Different Quantities of Arabinogalactan and Different Arabinogalactan/Polymer Ratios in their Coatings

Composition	Batch no.					
	Tablet A	Tablet B	Tablet A	Tablet D	Tablet A	Tablet F
Formulation	Capsule 1 [Batch Nos. A & B]		Capsule 2 [Batch Nos. A & D]		Capsule 3 [Batch Nos. A & F]	
Core						
Diltiazem HCl	100	140	100	140	100	140
Na CMC	4	8	4	8	4	8
Fumaric acid	30	–	30	–	30	–
Lactose DC	35	60	35	60	35	60
Povidone K-30	4	–	4	–	4	–
Magnesium stearate	2	4	2	4	2	4
Ethyl cellulose 100	–	3	–	3	–	3
Average core weight (mg)	175	215	175	215	175	215
Core tablet size:						
Diameter (mm)	7.0–7.2	7.0–7.2	7.0–7.2	7.0–7.2	7.0–7.2	7.0–7.2
Thickness (mm)	4.5–4.8	5.4–5.8	4.5–4.8	5.4–5.8	4.5–4.8	5.4–5.8
Coating						
Citroflex 2	2.5	3	2.5	3	2.5	3
Talc	4	6	4	6	4	6
Eudragit RL30D	0.6	0.9	0.6	0.9	0.6	0.9
Eudragit RS30D	2.5	12	2.5	12	2.5	12
Arabinogalactan	–	–		1.3	–	2.5
Average tablet weight (mg)	184.6	236.9	184.6	238.2	184.6	239.4
Polymer/total coating weight ratio	0.32	0.59	0.32	0.56	0.32	0.53
Arabinogalactan/polymer ratio				0.1		0.2
Tablet size:						
Diameter (mm)	7.1–7.3	7.1–7.3	7.1–7.3	7.1–7.3	7.1–7.3	7.1–7.3
Thickness (mm)	4.6–4.9	5.1–5.5	4.6–4.9	5.6–6.0	4.6–4.9	5.6–6.0
Capsule size	#0	#0	#0			

In vitro drug release from tablet

Three different capsules, each comprising the two types of tablets (specified in Table I) were tested for their *in vitro* drug release characteristics. The comparative dissolution of the capsules was assessed by USP 24 method using paddles type Apparatus II. Two different dissolution medium were used including water (pH $\sim$ 5.5) and phosphate buffer (pH 6.8). Other variables include a total volume of 900 mL dissolution medium and a stirring speed of 50 rpm at 37°C throughout the test. A low speed of rotation (50 rpm) was used to assure optimum discrimination. Diltiazem HCl concentrations in release samples were determined over a period of 24 h by HPLC analytical method with UV detection at 240 nm.

Diltiazem assay

The amount of diltiazem was quantified by HPLC using a Varian Star system with Lichrospher RP-18, 5 μm (125 $\times$ 4 mm) columns and a wavelength of 240 nm.[17] The mobile phase consisted of ethanol : acetonitrile : buffer pH 4.5 in a ratio of 5 : 25 : 70, respectively. The buffer was prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 1 L water, adding 0.1 mL of *N*,*N*-dimethyloctylamine and finally adjusting pH to 4.5 using 0.1*M* phosphoric acid. The solvent flow rate was adjusted to 1.5 mL/min with an injection volume of 20 μL.

Surface morphology of coated tablets

Surface morphology of coated tablets was evaluated before and after treatment with artificial gastric juice. Artificial gastric juice was prepared by dissolving 2 g of sodium chloride and adding 80 mL of 1*M* hydrochloric acid in double distilled water (DDW) and volume was adjusted upto 1000 mL with DDW. Prepared tablets were inserted into 500 mL of artificial gastric juice to determine the morphology of the coated tablets in artificial gastric juice. The tablets with solution were then placed in an incubator held at 37°C for 24 h, after which the tablet was carefully removed from the solution and dried for 24 h. After drying these treated and untreated tablets were sliced using sharp blade sputtered with gold (Polarone E5100, England) and observed under scanning electron microscopy (Qanta 2000 microscope).

Film studies

Diltiazem diffusion across polymeric films containing different polysaccharides

The rate of release of diltiazem across polymeric coating films containing three different polysaccharides

was evaluated and compared. The films were prepared as detailed for the coating formulation in Table I, but contained: dextran, MW = 188,000 Da; or glucose, MW = 180 Da; or arabinogalactan, MW = 17,000 Da, as channeling agent. The release profile was evaluated by measuring the diffusion of the drug from one cell containing buffer (pH 7.4) to a second cell containing the same buffer and separated from the first by films containing one of the channeling agent at two concentrations. The film lacking any polysaccharide was used as control. A 200 μL sample was taken at each sampling time point. Each sample was analyzed for diltiazem content by HPLC analytical method.

Arabinogalactan release from the film

Release behavior of arabinogalactan from the prepared films was also determined, for this, first films were prepared by mixing the ingredients detailed in the formulation on a small glass plate and allowed to dry in 40°C until drying and film formation. The three coating films similar to the coating formulation listed in Table I were suspended in up to 10 mL DDW. For each composition, 300 μL of the suspension was poured into a 20-mL bottle and left to dry at room temperature overnight. Thereafter, 20 mL of 0.1*M* HCl solution was poured into each bottle. The solution was replaced and sampled at constant intervals. The bottles were maintained at 37°C throughout the tests. The polysaccharide content in the medium was determined by phenol sulfuric acid assay.[18]

RESULTS AND DISCUSSION

The aim of this formulation development was to achieve a desired delayed controlled-release profile, to provide drug reservoir for over 24 h. To achieve this "two tablets in a capsule" concept was utilized (Fig. 1). First tablet was tailored to have a drug core matrix with a coating designed to give a short lag time and then a fast release profile, while second tablet was tailored to have a drug core matrix and a coating with a rate controlling membrane designed to produce a delayed controlled-release profile. The rate controlling membrane coating composed of a water insoluble polymer and a hydrophilic channeling agent (arabinogalactan) that is leached out when exposed to releasing media.

Formulation preparation

All the tablets were prepared by the process already described in section Formulation Preparation. Various different compositions with different excipients were investigated (Table I) to obtain final formulation. The function of each component of the tablet

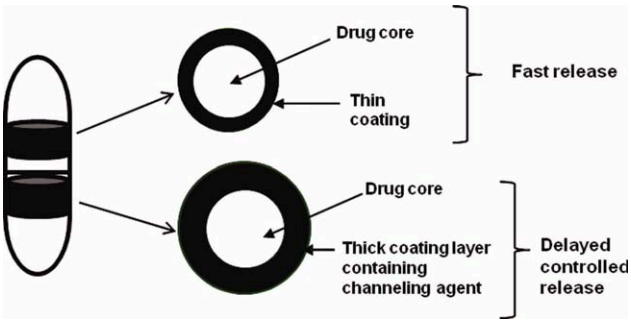

Figure 1 Schematic diagram of the developed delivery systems with two tablets in gelatin capsule shell. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

core was as follows: Na CMC, tablet disintegrating agent; lactose, tablet filler; fumaric acid, acidulate agent which was found to stabilize the formulation; polyvinylpyrrolidone, tablet binder; ethyl cellulose, tablet binder; magnesium stearate, tablet lubricant. In the coatings, triethyl citrate served as plasticizer, talc as anti-sticking agent, Eudragit® as controlled release coating agent (film) and arabinogalactan as channeling agent. In the developed formulation, Capsule 1 contained no channeling agent, while Capsules 2 and 3 both contained arabinogalactan as channeling agent; Capsule 3 contained a double quantity of the arabinogalactan (Table I). Once these different tablet formulations were obtained they were then physically characterized for average tablet weight, tablet size etc., results obtained are detailed in Table I.

In vitro drug release from tablet

Developed formulations were evaluated for *in vitro* drug release characteristics by comparing the dissolution profile of each formulation. The *in vitro* dissolution results in water are given in Figure 2; each curve represents the mean for six capsules tested in parallel. Considering nature of these three capsules formulations and presence of two different tablets in capsule, modified-release profile was obtained in dissolution test (Fig. 2) for these formulations. The profile for Capsules 1 and 2 are nearly similar. For both Capsules 1 and 2; the first release was obtained upto 5–6 h from the start and the second release phase occurred from the capsule after about 12–14 h and extended upto 24 h. Capsule 3 also produced a modified-release profile, with release occurring in approximately 8-10 h. However, this profile is having a single continuous release phase and differed from the previous two, which exhibited two distinct release phases. The elimination of the two phase characteristics occurred most probably due to the double content of arabinogalactan. This double content of arabinogalactan resulted in a higher dissolution rate in the

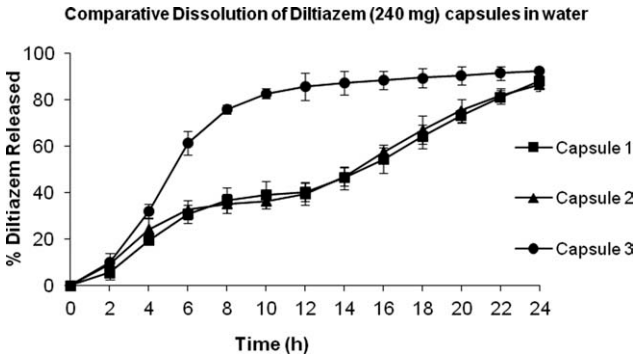

Figure 2 Mean dissolution profiles ($n = 6$) of capsule formulation 1, 2, and 3. Percent diltiazem released was determined using Apparatus II, 50 rpm, at 37°C in 900 mL of water.

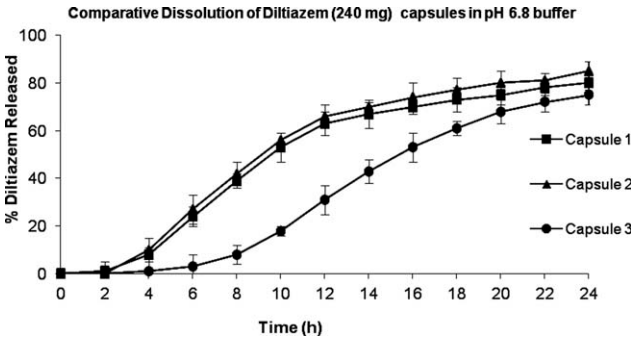

Figure 3 Mean dissolution profiles ($n = 6$) of capsule formulations 1, 2, and 3. Percent diltiazem released over time was determined using Apparatus II, 50 rpm, at 37°C in 900 mL of pH 6.8 buffer.

water media was most probably due to faster dissolution of the polysaccharide which was present in the highest amount in this formulation.

The release profiles of these formulations were reexamined in buffer of pH 6.8, commonly used as a dissolution medium for testing modified-release products. Same rotation speed of 50 rpm was again adopted to assure the best discrimination capabilities of this test. Taking into consideration the intestinal pH it may be a more relevant test for anticipating its pharmacokinetic profile *in vivo*. Interestingly, in buffer 6.8 the results were reversed (Fig. 3); it was found that Capsule 3 exhibits more prolonged release profile as compared to Capsules 1 and 2. Capsule 3 resulted in decreased dissolution rate in the buffer media most probably due to slow dissolution of the polysaccharide (which was present in the highest amount in this formulation) in this buffer media. In addition, diltiazem release is also influenced by the ionic strength and the pH of release medium and these parameters also supports the profile obtained in buffer for formulation of Capsule 3.

This prolonged release profile obtained from Capsule 3 has an advantage for a drug such as diltiazem that has a relatively short half-life and high solubility. Such formulation actually provides a kind of drug reservoir and initiates its release later after administration. Such mechanism may ensure a prolonged release throughout the gastrointestinal tract and also avoid dose dumping as compared to a regular matrix core modified-release tablets. Therefore, it may be considered that Capsule 3 formulation would provide the best 24 h coverage as compared to those containing lesser amount of arabinogalactan. Furthermore, the lag time until release starts may enable an evening administration and thus, allowing proper chronotherapy, resulting in higher drug concentration in the morning, which is the time considered with the highest risk in cardiovascular patients.

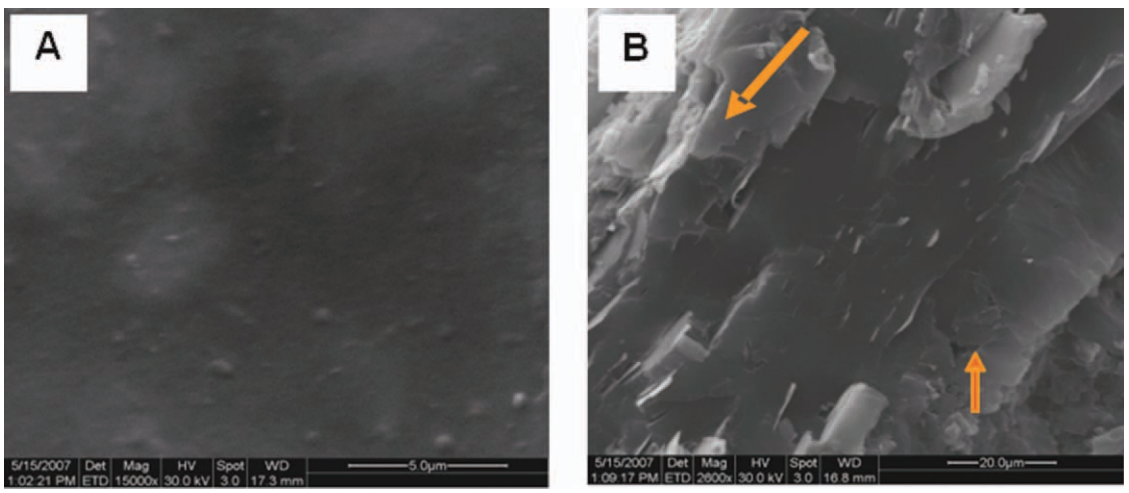

Figure 4 SEM images showing (A) surface of untreated coated Tablet F and (B) cross-section of untreated coated Tablet F. Surface of coated tablet is intact and is free of cracks or breaks. Big arrow represent coating and small arrow represents core of the tablet. Images were obtained using a Qanta 2000 microscope (30 kV). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

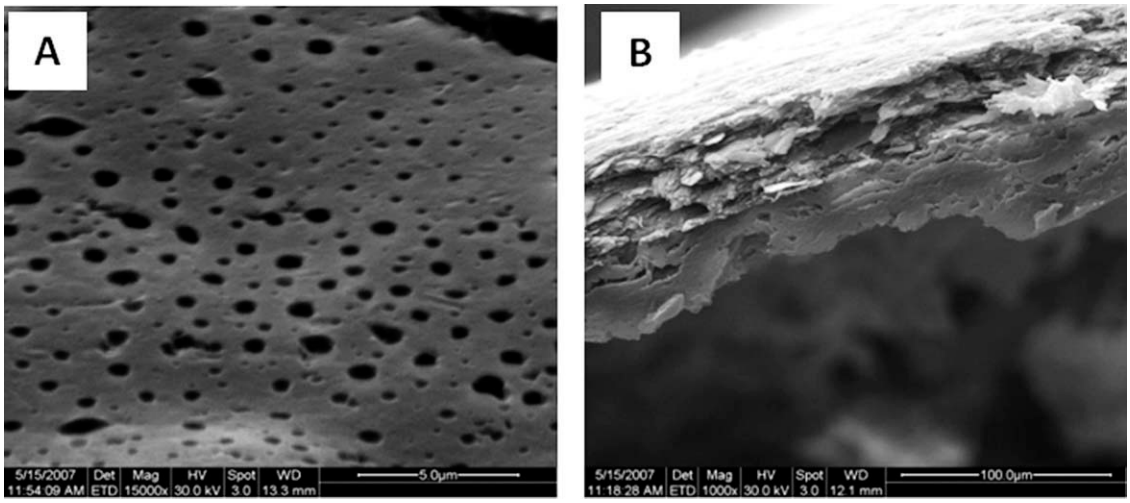

Figure 5 SEM images showing (A) surface of coated Tablet F and (B) cross-section of coated Tablet F after treatment with artificial gastric juice (1*M* hydrochloric acid). Exposure of the tablet to artificial gastric juice causes extensive pitting of the coating. Holes with diameters range from about 0.3 to about 1.5 μm were observed in coating layer. Images were obtained using Qanta 2000 microscope (30 kV).

Surface morphology of tablet coating

SEM evaluation was carried to determine surface morphology of coated tablets containing arabinogalactan. These tablets are prepared according to the formulation of Tablet F in Table I. The evaluation was carried out before and after treatment with artificial gastric juice. Both the tablet surface and slices across the tablet were assessed. The plane surface of an untreated coated tablet can be seen in Figure 4(A): the film surface is intact and is free of cracks or breaks. The cross-sectional slice [Fig. 4(B)] exhibits a similar picture: the untreated film coating looks whole. Exposure of the tablet to artificial gastric juice caused extensive pitting of the coating, as seen in Figure 5(A) (coating surface) and Figure 5(B) (coating cross-section). Holes observed on coating were present throughout the coating layer. Inside of core looks flaky and has become permeable as observed from SEM [Fig. 5(B)].

Arabinogalactan release from tablet coating

Release of arabinogalactan was responsible for the porosity of the films on exposure to gastric juice. In order to evaluate the rate of release of the polysaccharide from the film, films with arabinogalactan/polymer ratios of 0, 0.1, and 0.2 were prepared similar to the coating formulation detailed in Table I for Tablets B, D, and F, respectively, and suspended in DDW. Arabinogalactan content in the medium was determined over a period of 150 min. From the resulting release profile it is clear that the fastest and largest release was from the film containing the more quantity of arabinogalactan (Fig. 6).

Diltiazem diffusion across polymeric coating membranes containing different polysaccharides

In order to study the impact of molecular size on drug release from our formulation, the character of the diltiazem release profile was examined for coating membranes containing different types of polysaccharide. Films were prepared using arabinogalactan, dextran, or glucose (MW of 17,000, 188,000 and 180 Da, respectively) in accordance with coating formulations specified for Tablets D and F in Table I. Diltiazem transition across the films was evaluated as percentage of drug compound remaining in the cell into which it was originally introduced (Fig. 7). Each line in the graph in Figure 7 represents a different type of film. For each film, the drug concentration was 100% at time zero, and the experiment was continued until it could be extrapolated to zero.

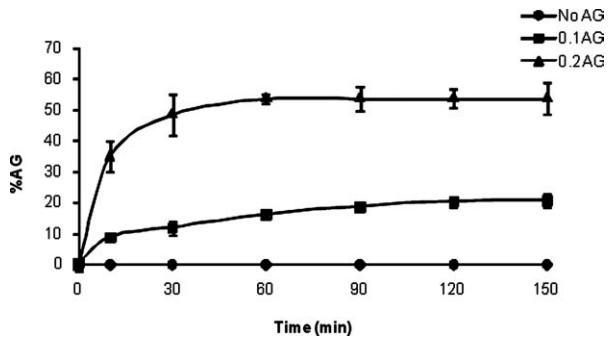

Figure 6 Percent arabinogalactan (%AG) release profiles ($n = 3$) over time for films containing arabinogalactan/polymer in ratio of 0.1 and 0.2, and as a control films containing no arabinogalactan. Films were prepared in accordance with coating formulations for Tablets D, F, and B, respectively.

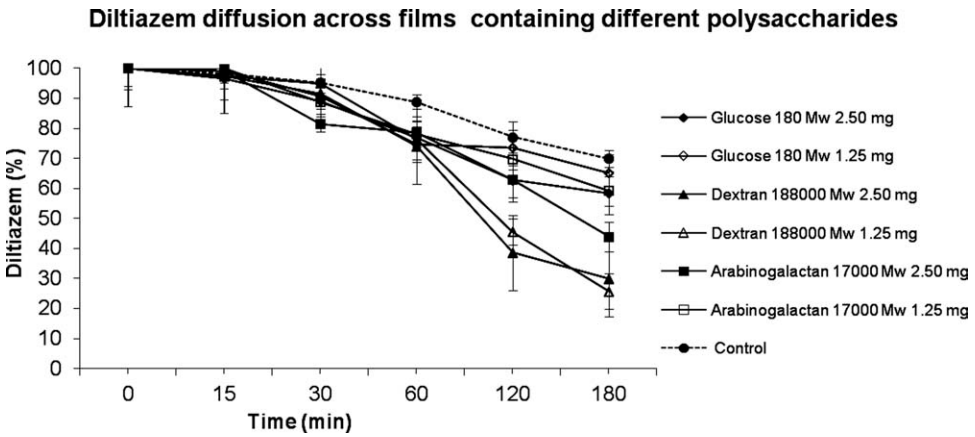

Figure 7 Transition of diltiazem across films containing polysaccharides of different molecular weight at two concentrations. Graph shows changes in mean diltiazem concentration over time. Control was run with film prepared with specified polymer but excluding polysaccharide ($n = 3$).

As a control, the test was run under the same conditions using membrane prepared without polysaccharide. Of the different polysaccharides tested, arabinogalactan was found to be the most adequate channeling agent from the standpoint of achieving the desired diltiazem release profile; dextran, a semi-synthetic, has a comparatively high molecular weight and allows excessively fast permeation of the drug across the coating film by creating larger channels throughout the polymeric film; the higher the molecular weight of the polysaccharide is, the larger the channels are and therefore the diffusion through the films obtained is faster and more significant. In contrast, glucose has a low molecular weight and could leach out from the film with time reducing storage stability, might dissolve within the coating providing too small channels due to its molecular weight, and is not preferred in drugs formulations also due to limitations in certain type of patients. Thus, arabinogalactan, a natural compound, is stable, easy to use through the coating process, has adequate particle size and molecular size for the channels formation and seems to provide the desired modified-release profile and so far never used in such tablets formulation. Overall, films containing polysaccharide provided faster transition of diltiazem than the control film.

CONCLUSIONS

Formulation was prepared successfully achieving a modified-release profile *in vitro*, suitable for once-daily administration. Arabinogalactan was found to provide the suitable channeling agent to control *in vitro* drug release from this formulation. In buffer, the formulation produced a delayed controlled release profile for diltiazem for over 24 h. Such formulations ensure a prolonged release throughout the gastrointestinal tract with a lag time until release starts and avoiding, dose dumping as compared to a regular matrix core modified-release tablets. Hence, the formulation achieved a modified-release profile *in vitro* suitable for once-daily administration.

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