International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 3, Issue 3, 2011

Research Article

RELEASE OF METFORMIN HYDROCHLORIDE FROM ISPAGHULA - SODIUM ALGINATE BEADS ADHERED COCK INTESTINAL MUCOSA

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Received: 25 May 2011, Revised and Accepted: 19 June 2011

ABSTRACT

Ispaghula husk-sodium alginate beads were prepared by ionic gelation method using calcium chloride in different concentration as crosslinking agent. Fresh cock intestinal mucosa was used to assess the sustained release effect of Ispaghula husk on metformin hydrochloride from beads adhered on cock intestinal mucosa. The beads were spherical, free flowing and brown in colour. The beads obtained were evaluated for drug entrapment efficiency, particle size, swelling behaviour, mucoadhesivity, and release behaviour after adhering to mucosa. The drug entrapment efficiency varied from 38-60% in different formulations. The beads were more swellable in phosphate buffer (pH 7.4). It was observed that up to 98% loaded drug was released within 10 hours in phosphate buffer. The mucoadhesivity of beads was significantly different in both acidic and alkaline medium.

Key words: Metformin HCl, Sodium alginate beads, Mucoadhesive Controlled release device

INTRODUCTION

A mucoadhesive controlled release device can improve the effectiveness of a treatment by helping to maintained the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site. The combination effect of the direct drug absorption and the decrease in the excretion rate by mucoadhesion allow for an increased bioavailability of the drug with a smaller dosage and less frequent administration[1].

Ispaghula from *Plantago Ovata* Frosk., belonging to the Plantaginaceae family, contain 10-30% mucilage. The husk mucilage is a white, fibrous material that is hydrophilic in nature and forms a clear, colourless mucilaginous gel by absorbing water. Two hydrophilic fractions from the husk have been separated from the mucilage. One fraction (eq.wt. 700; uronic acid 20%) is soluble in cold water while another fraction (eq.wt. 4000; uronic acid 3%) is soluble in hot water. Thermally and acid treated husk has been reported for matrix tablet formulation. Alginates (polysaccharides) obtained from brown algae are known to be hemocompatible and do not accumulate in any organ of the body. Alginates can be considered as block polymers which mainly consist of mannuronic acid (M), guluronic acid (G), and mannuronic acid-guluronic acid (MG) block. Alginate has been used as matrix material in medicine to achieve a controlled release drug delivery due to its hydrogel forming properties[2].

Metformin hydrochloride is a biguanide glucose lowering agent used in type II diabetes (Non-insulin dependent diabetes mellitus NIDDM). Its glucose lowering effect is due to the metabolic activities at several sites (biophase), including liver, intestinal muscle cells and adipocytes. It has a short half-life (1.5- 4.5 hours), so repeated administration (250mg twice or thrice daily) is required to maintain effective plasma concentrations. It is absorbed from upper intestine within 6 hours. Administrations of a sustained- release, once a day Metformin hydrochloride dosage form could reduce the dosing frequency and improve the patient compliance[3].

In the present investigation, the mucoadhesion and sustaining effect of ispaghula husk on metformin hydrochloride release from the alginate beads adhered on the fresh cock intestinal mucosa was studied.

MATERIALS AND METHODS

Ispaghula husk was purchased from the local market (Unjha, Gujarat). Metformin HCl was procured from Alkem laboratories Ltd. Mumbai. Calcium chloride was obtained from Rankem, New Delhi. All other chemicals and reagents used were of analytical grade from commercial source and used and used without further modification.

Methods

Preparation of Ispaghula- sodium alginate beads loaded with Metformin HCl

The beads were prepared by ionic gelation method by using calcium chloride as counter ion. Briefly, sodium alginate and ispaghula dispersion were prepared separately in distilled water and metformin hydrochloride was added in ispaghula dispersion. Each dispersion was stirred mechanically for 10 minutes at 1500 rpm. Afterwards, both the dispersion were mixed and homogenized at 1000 rpm for 10 minutes. The final dispersion containing drug thus obtained was ultrasonicated for 5 minutes for debubbling. The ratio of drug to polymer was maintained 1:4 in all formulations. The drug-polymer dispersion was added via a 23-gauze needle in to gently agitated calcium chloride solution. The $CaCl_2$ concentrations used were 2, 5, 8, 13% w/v. The droplets were gelled in to discrete, spherical beads upon contact with calcium chloride. Each batch of beads was left for 20 minutes to cure in calcium chloride solution. The $CaCl_2$ solutions were decanted and each was washed three times with 250 ml of water, dried in hot air oven at 40° for 48 hours, and stored in airtight container in vacuum desiccators until used[4, 5].

Drug entrapment efficiency

The drug loading efficiency of beads was determined by using following formula-

$$\text{Dose loading efficiency} = \frac{\text{Actual drug content in beads}}{\text{Theoretical drug content in beads}} \times 100$$

Accurately weighted, 150 mg beads were taken in 250 ml of phosphate buffer (pH 7.4) and kept for 50 hours with occasionally shaking. The polymer debris formed after disintegration of beads was removed by filtering through Whatman filter paper (No.40). The drug content in the filtrate after suitable dilution was determined spectrophotometrically (Hitchi-U-2001, Japan) at 233nm[6].

Particle size determination

The particle size was determined by using binocular microscope (Olympus). The mean particle size was counted by observing the number of divisions of ocular micrometer covering the beads. The ocular micrometer was previously calibrated by stage micrometer[7].

Swelling behaviour

The beads were soaked in distilled water, phosphate buffer (pH 7.4) and 0.1 HCL for swelling behaviour. The swelled beads were removed at preset time interval and weighed after drying the surface water by tissue paper. Swelling index was determined by following formula -

$$\text{Swelling Index} = \frac{\text{Weight of beads after swelling} - \text{dry weight of beads}}{\text{Dry weight of beads}} \times 100$$

Mucoadhesivity testing

The mucoadhesivity testing of drug loaded beads was assessed by wash off method. Freshly excised pieces of cock intestinal mucosa were mounted on glass slide with cyanocrylate glue. About 50 beads were spread out on each piece of mucosa and then hung to arm of a tablet disintegration machine. The tissue specimen was given a regular up and down movement in 1 litre vessel containing mucoadhesivity medium maintained at 37±0.5° C. At preset time interval, the beads still remaining adhered to underline mucosa were counted up to 10 hours. The media used were 0.1N HCL and phosphate buffer (pH 7.4) [8].

Drug release from beads adhered on cock intestinal mucosa

The drug loaded Ispaghula husk-Sodium alginate beads were weighted accurately (100mg) and spread out on the intestinal tissue specimen that was attached to a glass support. The beads were wetted by spraying the release medium as 0.1 N HCL and phosphate buffer (pH 7.4) used in the study. After hydration of beads, the support was inserted in 1000ml beaker and inclined at angle 60° with the help of beaker wall. The mucosa containing beads was washed with aerated release medium maintained at 37±0.5°C . The flow rate of the medium was 0.5 ml/min. The concentration of metformine hydrochloride in the washings was determined spectrophotometrically (Hitachi, U-2001, Japan) at 233nm[9-10].

Table 1: Formulations containing Ispaghula husk: Sodium alginate

S.No.	Formulation code	Ispaghula husk: sodium alginate	$CaCl_2$ conc. (w/v)	Particle size (mean value±SD)	Drug entrapment efficiency (mean value±SD)	Swelling index in distilled water (mean value±SD)
1	A_1	4:3	1	1321.66±1.432	38.53±1.23	233.52±1.1
2	A_2	4:3	4	1193.33±2.041	44.77±2.42	274.28±1.0
3	A_3	4:3	7	902.33±0.553	47.00±2.05	327.37±0.6
4	A_4	4:3	12	902.66±0.429	54.59±0.65	375.58±0.6
5	A_5	2:3	1	1165.33±0.742	43.4±2.66	181.61±1.2
6	A_6	2:3	4	942.66±2.987	50.36±2.16	199.20±1.8
7	A_7	2:3	7	864.33±0.987	55.34±1.09	218.72±0.5
8	A_8	2:3	12	815.33±1.234	60.35±1.67	249.19±2.1

*SD=standard deviation of three successive values; Mean of three readings (n=3)

Table 2: Mucoadhesivity of different formulation in 0.1 N HCl and phosphate buffer (pH 7.4)

S.No.	Formulation code	Percentage of beads adhered to the mucus in 0.1 N HCL at different times (hour)								
		0.5	1	1.5	2	3	4	6	8	10
1	A1	100	96 (2.9*)	84 (3.1)	77 (1.9)	74 (2.8)	73 (1.9)	71 (1.3)	69 (1.3)	65 (1.2)
2	A2	92 (1.8)	88 (0.5)	82 (1)	78 (1.3)	77 (2.8)	76 (1.6)	76 (1.8)	72 (0.5)	70 (1)
3	A3	95 (2.1)	95 (0.9)	94 (2.0)	92 (1.3)	92 (2.6)	89 (0.6)	89 (0.6)	87 (0.8)	80 (2.1)
4	A4	100	100	100	100	96 (1.2)	96 (0.5)	95 (1.6)	92 (2.1)	86 (0.6)
5	A5	97 (1.6)	97 (1.8)	95 (0.6)	93 (1.3)	81 (1.8)	81 (1.5)	75 (2.3)	67 (1.2)	67 (1.8)
6	A6	100	100	98 (2.8)	92 (1.9)	79 (1.0)	78 (2.1)	71 (1.6)	67 (1.0)	63 (1.4)
7	A7	98 (1.3)	98 (1.6)	96 (2.1)	93 (2.5)	85 (o)	85 (2.1)	83 (1)	83 (1.8)	74 (2.7)
8	A8	100	98 (1.8)	91 (0.6)	91 (0.5)	82 (2.6)	78 (1.3)	78 (0.5)	73 (2)	73 (0.6)
S.No	**Formulation Code**	**Percentage of beads adhered to the mucus in phosphate buffer (pH 7.4) at different times (hour)**								
		0.5	1	1.5	2	3	4	6	8	10
1	A1	100	84 (2.5)	80 (2.5)	77 (1.1)	77 (1.1)	71 (1.2)	60 (1.2)	42 (2.8)	36 (1.2)
2	A2	96 (1.6)	84 (2.8)	91 (1.5)	91 (1.0)	85 (1.8)	80 (1.9)	63 (1.8)	55 (1.3)	42 (1.3)
3	A3	100	100	83 (1.2)	82 (1.8)	80 (2.4)	76 (1.2)	51 (1.5)	45 (1.2)	32 (1.5)
4	A4	88 (1.2)	80 (2.5)	80 (1.9)	73 (1.4)	69 (2.4)	65 (1.9)	43 (3.2)	37 (2.3)	30 (2.3)
5	A5	100	82 (2.3)	81 (2.5)	77 (1.9)	77 (2.4)	61 (1.2)	61 (2.8)	54 (2.8)	46 (1.3)
6	A6	96 (1.6)	94 (2.8)	92 (1.5)	90 (2.0)	86 (1.8)	81 (1.9)	60 (1.8)	54 (2.0)	42 (1.3)
7	A7	100	100	83 (1.6)	82 (1.8)	80 (2.2)	78 (2.1)	55 (2.4)	44 (1.6)	41 (1.6)
8	A8	88 (1.2)	80 (2.5)	79 (1.5)	73 (1.4)	70 (2.1)	66 (1.9)	59 (3.2)	43 (2.3)	40 (2.4)

* Values shown in parenthesis are the standard deviation (SD) of three readings.

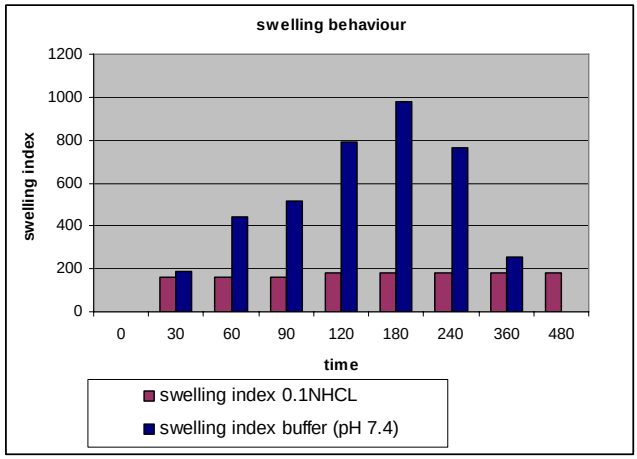

Fig. 1: Swelling behaviour of Ispaghula-Sodium alginate beads in phosphate buffer (pH 7.4) and 0.1 N HCL

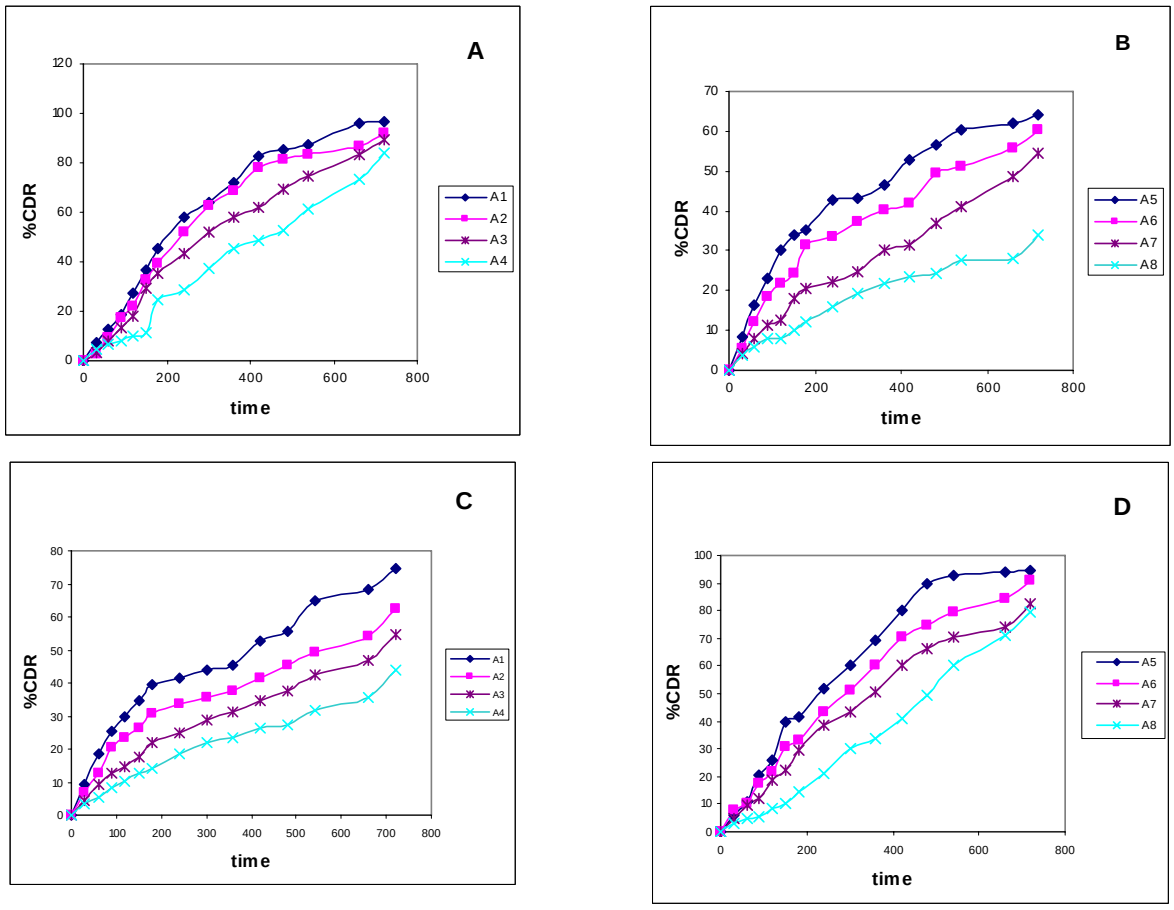

Fig. 2: Release of different formulation adhered on fresh cock intestinal mucosa in 0.1 N HCL (A&B) and phosphate buffer (pH 7.4) (C & D)

RESULTS AND DISCUSSION

The different formulations used have been summarised in the table 1. The calcium chloride concentration was varied in the range of 1 - 12 % w/v to analyze effect on size distribution, swelling behaviour, mucoadhesivity, drug release entrapment efficiency etc. Increasing the calcium chloride concentration as shown in table decreased the average size of beads. This is because of the higher crosslinking density and shrinkage of polymeric gel in the case of higher amount of crosslinking (i.e., $CaCl_2$). The higher ratio of sodium alginate to Ispaghula husk, the particle size also decreased that may be attributable due to higher

guluronic/mannuronic acid to be cross linked. The negatively charged drop of alginate forms a bead matrix by interaction with the positive calcium ion in the coagulation fluid by crosslinking between the carboxylate anion of alginate gulucuronate and the calcium ion. Spherical, stable Ispaghula husk -sodium alginate beads were obtained when the mixture of alginate and metformine hydrochloride was dropped in solution containing Ca^{++} in various amounts.

Beads remained after drug release on the underline cock intestinal mucosa, small holes were observed that indicated the diffusion of drug during release study. The lowest entrapment efficiency of metformin hydrochloride was observed in sodium alginate – Ispaghula husk beads at low Ca^{++} ion concentrations. At lower concentration of the divalent ions, the beads might have larger pores due to Insufficient crosslonking that results in lower entrapment. The higher entrapment efficiency was obtained in 2:3 ratio formulations. It may be due to higher degree of crosslinking as the quantity of sodium alginate increased. The apparent gelation of calcium alginate matrices seemed to occur rapidly but the further rearrangement of the gel structure continued for along period. In Ispaghula husk, the xylan backbone with (1⍰3) and (1⍰4) β –D linkages is highly substituted with arabinose or aldobiouronic acid residues, which are fully extended, and inflexible. It seems that aldobiouronic acid may participate in crosslinking with $CaCl_2$ and consequently further improving the entrapment efficiency.

In 0.1 N HCL the ratio of water uptake by beads was low to that obtained at pH 7.4. Maximum water uptake was obtained at 2 - 3 hours in phosphate buffer after which the erosion and breakdown occurred. These results suggest that the dried gel particles will swell slightly in stomach and as they are subsequently transferred to upper intestine, where the metformine is to be absorbed, the particle begin to swell more and behave as matrices for controlled release of loaded drug.

In mucoadhesivity testing, it was observed that in 0.1 N HCL, the beads remained attached up to 65% after 10 hours as shown In table 2. In phosphate buffer (pH 7.4) the rate decreased up to 30%. The husk consists of hydrophilic residue (e.g. L-arabinofuranose) or ionic residue (e.g. uronic acid) which bind water at the surface or within the gel. The L-arabinofuranosyl groups may also bind non-specific water (i.e. osmotic in origin). The substitute flexible chains can diffuse in to the mucous layer and may remain adhered for a long time. The decreased mucoadhesion percentage of the erosion of calcium ion crosslinking in phosphate buffer (pH 7.4)

In the experimental model used in the study to follow the drug release from the beads adhered on intestinal mucosa, 0.1N HCL and phosphate buffer (pH 7.4) obtained results that could represent the basis for the prediction of beads behaviour in *vivo*. Afterwards, the beads were placed on mucosa, hydrated and swelled. The release of metformin from beads was 34 - 96% in 12 hours in 0.1 N HCL. The slowest release was found in 3:2 (sodium alginate : Ispaghula husk) prepared in 12%w/v $CaCl_2$ where up to 81.90% of the loaded drug was released in 12 hours in phosphate buffer (pH 7.4). The drug released data from different formulations has been depicted in fig.2. Since a certain amount of the drug could also be released from beads in the washings before and during washing process.

Metformin release may result of two processes i.e. drug release from adhered beads and from beads washed off. The beads were swelled less in 0.1 N HCL than phosphate buffer and these remained adhered for a long time in acidic medium consequently resulting in slow and prolonged release in 0.1 N HCL. Also, the flexible, non - crosslinkled polymeric ionized arabinoxylan chains of Ispaghula may penetrate in underline mucosa resulting in prolonged release which could otherwise be washed off together with the dissolved drug. Furthermore, the release of cationic drug, metformin hydrochloride could be retarded due to the electrostatic interaction between the negative charge of ionized carboxyl group present in alginate and Ispaghula (in the form of uronic acid) and positive charge of metformine.

CONCLUSION

In this study it can be concluded that Ispaghula husk, a natural polymer can be microencapsulated with sodium alginate and prolong the release of hydrophilic drug, a metformin hydrochloride after adhering to mucosa. As the husk is composed of polysaccharide.

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