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Investigation of colon-specific dosage forms of ondansetron prepared with natural polymers

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The aim of this study was to develop colon-specific delivery systems of ondansetron using natural polymers such as guar gum and sodium alginate. For this purpose colon specific matrix tablets were prepared by a direct compression method. The physical properties of the tablets were tested and *in vitro* release studies were performed by a flow-through cell apparatus. The amount of polymers affected the *in vitro* drug release from the matrix tablets. A high amount of polymers provided slow drug release whereas the release of ondansetron from the tablets prepared with low amount of polymers was found to be fast. Ondansetron-alginate and/or guar gum matrix tablet formulations can deliver the drug to the small and large intestine thus these matrix may be a promising system for the reduction of visceral sensitivity and inhibition of motor activity in irritable bowel syndrome (IBS).

1. Introduction

Colon-specific drug delivery holds promise for direct, more effective delivery of therapeutic agents to the colon for patients being treated for illnesses, such as irritable bowel syndrome (IBS), colonic cancer, ulcerative colitis, Crohn's disease, etc. (Sinha et al. 2005). Over the last few years, different approaches have been reported in order to achieve specific colonic drug delivery, such as pro-drugs (Yokoe et al. 2003), matrix tablets (Krishnaiah et al. 2001) and film or compression coating with pH-sensitive or bacterial degradable polymers (Turkoglu and Ugurlu 2002; Vandamme et al. 2002).

Polysaccharides are hydrophilic, hydrosoluble and can form gels (Vandamme et al. 2002). Alginate, a polyanionic copolymer of mannuronic and guluronic sugar residues has received much attention in pharmaceutical dosage forms, particularly as a vehicle for controlled drug delivery (Takka et al. 1998; Lin et al. 2005; Bajpai and Sharma 2004). Solid preparations such as oral tablets, microcapsules, implants, topical delivery systems and liquid delivery systems based on alginate are available (Holte et al. 2003). Tablets with alginate have been prepared by direct compression, dry or wet granulation, and various coating techniques (Holte et al. 2003).

Guar gum is a natural non-ionic polysaccharide derived from seeds of *Cyamopsis tetragonolobus* (Leguminaciae). In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant, and in liquid oral and topical products as a suspending, thickening and stabilizing agent. Guar gum has also been investigated as a matrix tablet for delivery of water insoluble drugs to the colon (Krishnaiah et al 2001; Tuğcu-Demiröz et al. 2004).

Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by a diverse consortium of abdominal symptoms including abdominal pain, altered bowel function (bowel frequency and/or constipation), bloating, abdominal distension, the sensation of incomplete evacuation and the increased passage of mucus (Farthing 2004).

At present, there is no medication for the treatment of patients suffering from IBS. Available treatments are only able to reduce specific symptoms.

Ongoing research studies using a novel group of pharmacologic agents that bind to seratonin receptors are proving promising in the treatment of IBS, particularly those that bind to 5-hydroxytryptamine (5-HT)$_3$ and 5-HT$_4$ receptors sites (Rothstein 2000). 5-HT$_3$ receptors have a significant role in regulating the colonic motility. Clinical studies suggest that these agents may have a role in painful, diarrhoea-predominant IBS (Farthing 1999; Goldberg et al. 1996). Ondansetron, a 5-hydroxytryptamine-3 (5-HT$_3$) receptor antagonist appears to reduce visceral sensitivity and have inhibitory effects on motor activity in the distal intestine and may have a wider application in the prophylaxis and treatment of nausea and vomiting (Lamers 1991).

It has been demonstrated that ondansetron is well absorbed in the intestinal segments including the upper small intestine, the colon and the rectum (Hysu et al. 1994). Targeting of ondansetron to the colon may provide and adequate treatment for IBS and allow a reduction in dosage and possible systemic side effects.

Talley et al. (1990) assessed the effect of oral ondansetron on colonic transit in normal volunteers. To determine if ondansetron influences colonic transit, a randomized, double-blind, placebo-controlled crossover study was performed. Using a radiopaque marker technique, colonic transit was quantified in 39 healthy volunteers. On a standard 25 g fiber diet, 16 mg of ondansetron was given orally thrice daily. Mean total colonic transit time on placebo was 27.8 h, while on ondansetron it was 39.1 h. It was

reported that ondansetron has no effect on gastric emptying or small bowel transit although it can modify colonic transit (Talley et al. 1990).

Rodriguez et al. (1998) prepared a new multiparticulate system of ondansetron for colonic drug delivery based on a drug containing hydrophobic core microencapsulated with a pH-dependent polymer. In this work, a new dosage form intended for specific and controlled ondansetron delivery along the colonic region is described. The system consists of a hydrophobic core (CAB microspheres) encapsulated into pH-sensitive (Eudragit® S) microcapsules.

To our knowledge, there is no investigation of the colonic delivery of ondansetron with polysaccharides such as guar gum and alginate in the form of matrix tablets. Therefore, in this study we aimed to develop and investigate colon-specific matrix tablets of ondansetron with sodium alginate and guar gum. Guar gum is a bacterial degradable polymer whereas sodium alginate is a pH sensitive polymer.

2. Investigations, results and discussion

The drug content in each tablet were found to be between 8.03 ± 0.05 and 8.08 ± 0.01 mg. The hardness of the tablets was different from each other and the crushing force was in the range of 69.4 ± 0.7–123.6 ± 1.9 N.

Disintegration times of the tablets were determined and were found to be between 0.48 and 4.54 h. The greater the amount of polymer, the greater the disintegration time. C1 formulation disintegrated within 0.48 h in 0.1N HCl, thus not conformed the enteric coated disintegration procedure requirement of the USP 27 (Table 1).

It was observed that the disintegration time increased with the addition of large amounts of guar gum. The disintegration time of D2 tablets prepared with 150 mg guar gum was about 4.54 ± 0.23 h and it was longer than that of D1 tablets. This result shows that D2 formulation containing a high amount guar gum can be used for colon specific drug delivery.

A successful colon-specific drug delivery system is one which remains intact in the physiological environment of the stomach and small intestine but releases the drug in the colon. Different *in vitro* methods are used to evaluate different carrier systems for their ability to deliver drugs specifically to the colon. The ideal *in vitro* system should mimic the *in vivo* conditions. Drug release studies of colon-specific tablets have been performed in 0.1 M HCl for 2 h and in pH 7.4 buffer for 3 h, using the USP dissolution rate test apparatus (Apparatus 1, 100 rpm, 37 °C) in previous studies (Krishnaiah et al. 2001; Prasad et al. 1998). Ofori-Kwakye and Fell (2003) carried out drug release studies of the uncoated and film-coated paracetamol tablets by a paddle method. The dissolution media used were 0.1 M HCl (pH 1.5), pH 7.4 Sorensen's phosphate buffer and pH 6.0 Sorensen's phosphate buffer (with and without Pectinex® Ultra SP-L enzymes) to mimic the conditions pertaining in the stomach, small intestine and the colon, respectively. USP Dissolution Apparatus III (reciprocating cylinder) for the screening of guar gum-based colonic delivery formulations was used in another study (Wong et al. 1997).

In our study it was thought that, *in vivo* gastrointestinal transit conditions could best be imitated by an *in vitro* flow-through cell apparatus with different pH media. Therefore, the in vitro release studies from the matrix tablets were carried out this way. Four different media, namely, pH 1.2, pH 4.5, pH 6.8 and pH 7.4 for 2 h of each, were used for the release studies. Ashford et al. (1993) performed dissolution studies of salicylic acid tablets coated with Eudragit S® using a flow through dissolution apparatus. This study gives important information to the design of an optimum colonic delivery system.

The ability of guar gum to retain the integrity of tablets in the physiological environment of stomach and small intestine was assessed by conducting drug release studies at different pH values. D1 and D2 formulations prepared with guar gum released 19.8–25.9% of drug throughout the dissolution study, respectively (Fig. 1). It was observed that 10–15% of drug was released over 2 h. This shows that guar gum is partly capable of protecting the drug from being released in the physiological environment of stomach and small intestine.

Krishnaiah et al. (2001) also reported that colon specific matrix tablets of mebendazol with the combination of guar gum released 8–15% of the mebendazole over 24 h in the physiological environment of stomach and small intestine depending on the proportion of the guar gum used in the formulation. Bajaj et al. (2001) reported that the matrix tablet with combination of guar gum and HPMC released 45% of drug within 6 h in simulated gastric and small intestine fluids.

Guar gum can deliver drugs to the colon, due to its susceptibility to microbial degradation in the large intestine. Different methods, such as addition of galactomannanase

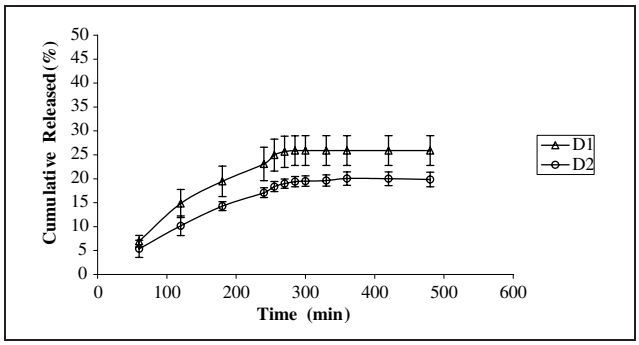

Fig. 1: Release of ondansetron from guar gum matrix tablets

Table 1: Physicochemical parameters of the tablets

FormNo	Weight Average (g) ± SD* (n = 20)	Diameter Average (mm) ± SD (n = 20)	Thickness Average (mm) ± SD (n = 20)	Hardness Average (N) ± SD (n = 20)	Friability %	Drug content Average (mg) ± SD (n = 10)	Disintegration Average (h) ± SD (n = 6)
C_1	100 ± 0	5.45 ± 0.00	2.88 ± 0.00	80.2 ± 0.8	0.33	8.04 ± 0.12	0.48 ± 0.95
C_2	100 ± 0	5.52 ± 0.00	2.75 ± 0.00	75.8 ± 0.9	0.43	8.06 ± 0.09	1.23 ± 0.92
C_3	131.1 ± 0.5	5.87 ± 0.00	2.78 ± 0.00	92.3 ± 1.3	0.41	8.04 ± 0.06	1.86 ± 0.68
C_4	213 ± 1.00	7.53 ± 0.00	3.11 ± 0.00	123.6 ± 2.7	0.37	8.08 ± 0.01	2.33 ± 0.32
D_1	131.2 ± 0.8	5.69 ± 0.00	2.85 ± 0.00	95.4 ± 1.3	0.48	8.03 ± 0.05	3.01 ± 0.72
D_2	213.3 ± 0.6	8.03 ± 0.00	3.21 ± 0.00	69.4 ± 1.0	0.37	8.05 ± 0.02	4.54 ± 0.23

* SD: Standard deviation

enzyme or rat caecal content to the dissolution medium has been used to mimic the colonic conditions (Prasad et al. 1998; Wong et al. 1997)

In our experiments, it was observed that the D2 matrix tablet with 150 mg guar gum released 19.8 ± 1.5% of ondansetron over 8 h. Upon introduction of enzyme content (galactomannanase enzyme at 19.6 U/L level) into the dissolution medium, the release of ondansetron from the matrix tablet increased. The total amount of ondansetron released after 10 h in the presence of galactomannanase enzyme was found to be 84.9 ± 5.9% (Fig. 2), Galactomannanase enzyme accelerated the release of ondansetron from the guar gum matrix tablet containing guar gum (formulation D2). This result showed the potential of the guar gum matrix tablets to undergo degradation in the presence of galactomannanase enzyme, and thus their ability to release the drug containing matrix into the colon.

In vitro release profiles of the ondansetron-alginate matrix tablets are shown in Fig. 3. It was observed that the type and the amount of alginate affected drug release. Sodium alginate is a pH-dependent polymer. The drug release increased in basic media. When we compared the C1 and C4 formulation, it was seen that the release of drug from the tablets was found to be statistically different from each other over 4 h at pH 1.2 and 4.5. The matrix tablet containing the highest amount of sodium alginate (C4) exhibited a drug release of 18.9 ± 6.2% whereas the C1 tablet containing the lowest amount of sodium alginate exhibited a drug release of 82.3 ± 4.8% over 4 h at pH 1.2 and 4.5. It was observed that the drug release from C1 and C4 tablets increased and reached 86.4 ± 5.5% and 91.6 ± 6.2 over 10 h at pH 6.8 and pH 7.4 respectively (Fig. 3).

In the literature several pH-dependent polymers were used to achieve colon specific delivery. Rodriquez et al. (1998) used the pH-dependent polymer Eudragit S to coat the cellulose acetate butyrate core of ondansetron for colonic drug delivery. The *in vitro* drug release studies with this system showed that no drug was released below pH 7, but it did not maintain its controlled release properties once the enteric polymer dissolved.

Xing et al. (2003) prepared a oral colon-specific drug delivery formulation using coated calcium alginate gel beads-entrapped liposome and bee venom peptide as a model drug and reported that the initial release of bee venom from the coated gel beads was low. Little bee venom could be measured in the pH 1.2 medium for 2 h. Only 5.55 ± 0.22% was released after 3 h and 15.98 ± 0.19% after 4 h. After 8 h about 90% had been released.

Iruin et al. (2005) also investigated the *in vitro* performance of alginate beads containing 5-ASA in order to achieve an oral system that protects the drug until it reaches the colon. They also used several polymers (Eudragit FS 30D, Eudragit S100 and chitosan) in the formulations. They reported that no release was observed at pH 6.0. Release was very slow at pH 6.8; averages about 20% an hour at pH 7.2 and was complete within 4 h at pH 7.4, and they concluded that Eudragit FS beads exhibited interesting dissolution profiles for the therapy of colon pathologies.

Ondansetron is a freely water soluble drug. In our case, although sodium alginate controlled the drug release over 10 h, no colon specific drug delivery system was obtained by only using sodium alginate in the form of matrix tablet. The amount of sodium alginate and guar gum affected the *in vitro* drug release. As the content of polymers in the tablet increased, the drug release decreased. It was concluded that sodium alginate itself was not able to prepare a colon-specific tablet of ondansetron but guar gum may be used to prepare colon-specific delivery of ondansetron, but more formulation work was necessary to develop an optimum formulation.

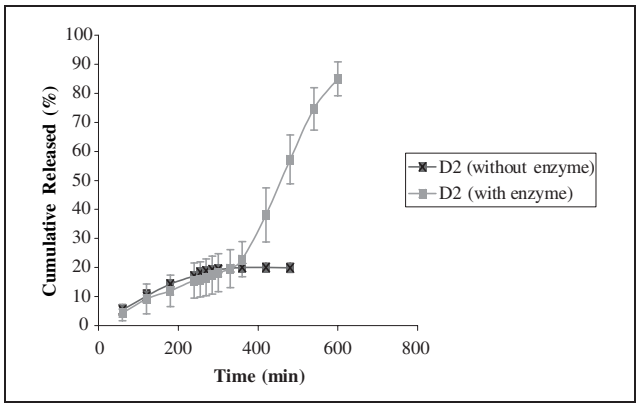

Fig. 2: Dissolution profiles of ondansetron from guar gum matrix tablets in the presence of galactomannase enzyme

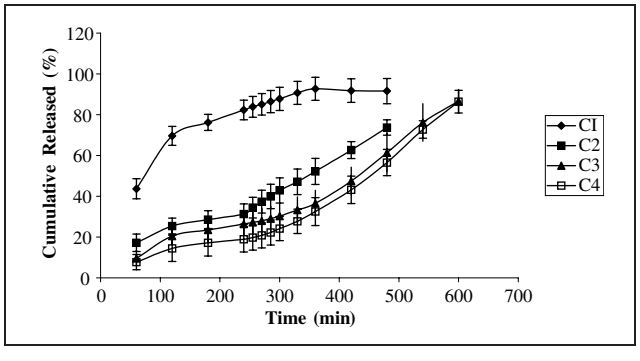

Fig. 3: Release of ondansetron from sodium alginate matrix tablets

3. Experimental

3.1. Materials

Ondansetron HCl, $2H_2O$ (Adeka, Turkey), sodium alginate Protanal LF 120M (FMC Biopolymer, Switzerland) (1600 cps, mannuronic/guluronic acid: 70/30), guar gum Supercol® U-NF (Viscosity of 1% w/v aqueous dispersion, 5133 cps at 25 °C Hercules, USA). Other materials, namely, microcrystalline cellulose (Avicel PH 102) (FMC Biopolymer, Switzerland), magnesium stearate (Riedel Mannouen, Germany), silicon dioxide (Aerosil 200) (Werksboschemigung, Germany) were of pharmacopoeial quality (US/NF).

3.2. Preparation of ondansetron matrix tablets

The compositions of the matrix tablets which were prepared by a direct-compression method are given in Tables 2 and 3.

Powder were passed through a #45 (0.350 mm) mesh screen separately and blended for 20 min, and then thoroughly mixed with 1% magnesium stearate. The mixture was compacted in the Erweka tablet machine (Korsh-Erweka GmbH, Germany), using a 6 or 8 mm flat-faced punch. Each tablet (average weight 100–213 mg) contained 8 mg of ondansetron.

Table 2: Formulation of the tablets with sodium alginate

Form. No	Sodium alginate LF 120M	Avicel PH102	Aerosil 200	Magnesium stearate
	mg	mg	mg	mg
C_1	20	70	1	1
C_2	60	30	1	1
C_3	90	30	1.5	1.5
C_4	150	50	2.5	2.5

Table 3: Formulation of the tablets with guar gum

Form. No	Guar-gum (Supercol® U-NF) (Hercules)	Avicel PH102	Aerosil 200	Magnesium stearate
	mg	mg	mg	mg
D_1	90	30	1.5	1.5
D_2	150	50	2.5	2.5

3.3. Physical characteristics of the tablets

Determination of uniformity of the single tablet mass was performed according to USP 27. Uniformity of ondansetron content was determined in randomly selected tablets of one series. Ten tablets were individually weighed and then each of them was dissolved at pH 7.4, 150 mL of phosphate buffer solution. The drug content of the tablets was assayed spectrophotometrically at 309 nm. The spectrophotometric assay method was fully validated according to USP 27.

Determination of tablet resistance to crushing was tested by an automatic hardness tester type HDT 1V-3 (CGS, Hardness tester, Germany). Resistance to crushing was determined for 10 randomly selected tablets.

Twenty tablets were tested for weight (AB 104, Mettler Toledo, Switzerland), thickness (Vernier Caliper, portable dial hand micrometer, Russia) and friability (Roche friability tester). Friability of uncoated tablets was performed according to USP 27. The mean values were calculated with standard deviation.

Six tablets were randomly selected to perform the enteric coated (USP 27) disintegration procedure, using a disintegration tester (Aymes, Turkey). The disintegration times were reported in hours. The results are shown in Table 1.

3.4. Drug release studies

The ability of the matrix tablets to remain intact in the physiological environment of the stomach and small intestine was assessed by conducting drug release studies under conditions mimicking mouth to colon transit.

The release of ondansetron from matrix tablets was investigated using a flow-through cell apparatus (USP Aparatus IV, Sotax A.G., Switzerland) at a flow rate of 8 mL/min, fitted with 22 mm dissolution cells. The tablets were tested for drug release for 2 h in 0.1 M HCl. The following dissolution conditions were established: 2 h in pH 4.5, 2 h in pH 6.8 phosphate buffer and lastly, 2 h at pH 7.4 at 37 °C. The dissolution tests of C1−C4 tablets were performed for 10 h.

To assess the susceptibility of guar gum being acted upon by the colonic bacteria, drug release studies were carried out in the presence of galactomannanase enzyme. This enzyme is capable of degrading guar gum (Friend 2005). Galactomannanase enzyme (from *Aspergillus niger*- 2.95 U/mL) (19.65 U/L) was added to pH 7.4 medium after 6 h to investigate the effect of the enzyme on the dissolution of the final formulation (Tablet D_2). The flow rate of the pH 7.4 dissolution medium containing enzyme was adjusted to 4 mL/min to extend the contact time of the tablet with galactomannanase enzyme. The spectrophotometric method was used to measure the concentration. There were no extra peaks observed with the galactomannanase enzyme at 200–400 nm. The effect of flow rate on the release was also investigated, but no significant differences were found.

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