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Research paper

Evaluation of alginate based mesalazine tablets for intestinal drug delivery

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Abstract

The aim of this study was to develop the alginate based mesalazine tablets for intestinal delivery. Sodium alginate is a biocompatible, natural polymer with pH-sensitive gel-forming ability.

Matrix tablets were prepared with two types of sodium alginate of different amounts. The in vitro release characteristics of mesalazine from alginate tablets were compared with those of the commercial product (Salofalk®). X-ray imaging was used to monitor the tablets throughout the gastrointestinal system.

Although alginate tablets gave a faster release in an acidic medium compared with the commercial product (Salofalk®), the cumulative amount of released drug of the optimum formulation was found to be almost the same as that of the commercial product at the end of 4 h. The alginate type and amount in the matrices played an important role in basic media. The release of the optimum formulation containing low viscosity alginate was found to be almost identical to that of the commercial product in acidic and basic media.

Tablets were visualized to determine whether they were located in the terminal ileum or cecum for 3–6 h. Mesalazine-alginate matrix tablet formulations can deliver the drug to the small and large intestine. Thus, the alginate matrix system may be a promising system for the treatment of Crohn's disease involving both the ileum and large intestine.

Keywords: Mesalazine; Alginate; Intestinal drug delivery; X-ray imaging

1. Introduction

Oral administration is the most convenient and preferred means of drug delivery into systemic circulation [1]. For a number of drugs this approach is generally adequate. In some situations it would be highly beneficial to target a drug to a particular site within the gastrointestinal tract, either to maximize therapeutic response or to reduce side effects caused by drug delivery to an inopportune region of the gut. In recent years there has been a significant increase in available strategies for providing site-specific delivery in the gastrointestinal tract [2].

The natural pH environment of the gastrointestinal tract varies from acidic to slightly alkaline. pH-sensitive hydrogels may be an alternative for site specific drug delivery. In the design of oral delivery of peptide or protein drugs, pH-sensitive hydrogels have attracted increasing attention [3]. Swelling of such hydrogels in the stomach is minimal, and thus the drug release is also minimal. The extent of swelling increases as hydrogels pass down the intestinal tract due to the increase in pH. A variety of synthetic or natural polymers with acidic or basic pendent groups have been employed to fabricate pH-sensitive hydrogels. Among them, alginate is one of the more commonly used [4].

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Alginates, which are naturally occurring substances found in brown seaweed and algae, have received much attention for use in pharmaceutical dosage forms, particularly as a vehicle for controlled drug delivery. The formation of a matrix upon hydration causes a gelatinous layer which can act as a drug diffusion barrier [5,6]. Alginate is a family of polysaccharides composed of α-L-guluronic acid and β-D-mannuronic acid residues, arranged in homopolymeric blocks of each type and in heteropolymeric blocks. The alginate monomer composition is reported to have a major impact on the drug release properties of the different formulation systems [7].

Liew et al. [8] used 17 grades of sodium alginate with different properties to screen the factors influencing drug release. It was reported that alginate particle size, viscosity and concentration affect not only the rate of drug release, but also the release mechanism [8].

Mesalazine, or 5-aminosalicylic acid (5-ASA), has been used for several years in the treatment of inflammatory bowel disease. When pure mesalazine is administered directly in the proximal part of the small bowel or orally as a conventional tablet, it is rapidly and almost completely absorbed, with little drug reaching the distal small intestine and colon [9]. Therefore the premature absorption of mesalazine can be prevented by the preparation of enteric coated tablets or colon-specific dosage forms. Orally administered delayed-release mesalazine acts locally from within the lumen of the inflamed bowel and is partly absorbed into systemic circulation. To prevent proximal small-intestinal absorption, and allow mesalazine to reach the inflamed small bowel and/or colon, a variety of mesalazine delivery systems have been developed [9,10].

5-ASA can be effective in treating Crohn's disease and ulcerative colitis if the drug can be delivered topically onto the inflamed intestinal lining. Most patients with Crohn's disease involving both the ileum (distal small intestine) and large intestine must take 5-ASA orally [11,12]. There are several formulations of mesalazine. One of them is the Salofalk® tablet which has an outer coating with a semi-permeable membrane of ethylcellulose and an inner coating of acrylic resin (Eudragit L). This pH-sensitive polymer is resistant to gastric conditions but soluble above pH 6.0 in the intestine. In this formulation mesalazine is designed to be released in highly dispersed form in the distal small bowel and the colon [13].

The aims of the present study were to develop a site specific matrix tablet of mesalazine with sodium alginate and to investigate the in vitro release characteristics of the tablets and to compare them with those of the commercial product (Salofalk®). The developed dosage form was also monitored in vivo in healthy volunteers. The transit of drug delivery systems throughout the gastrointestinal tract was monitored in vivo either in animals using various techniques [14,15] or in humans using γ-scintigraphy [16,17] or X-ray studies [18–20]. X-ray imaging was used in the present study. To our knowledge no in vivo X-ray study has been performed with alginate tablets.

2. Materials and methods

2.1. Materials

The mesalazine was a kind gift of the Ali Raif Drug Co., Turkey. Two different grades of sodium alginate, namely Protanal LF 240 D and Protanal LF 120 M, were kindly supplied by FMC Biopolymer (Switzerland). Viscosity measurements of 1% w/v aqueous dispersion of the polymers were carried out using a Brookfield viscometer (Brookfield Model LVTD, USA) at 25 °C. The viscosities of the alginates were 1600 cPs and 720 cPs for protonal LF 240 D and LF 120 M, respectively. Other materials, namely microcrystalline cellulose (Avicel PH 102) (FMC Biopolymer, Switzerland), magnesium stearate (Riedel Mannouen, Germany), silicon dioxide (Aerosil 200) (Werksboschemigung, Germany) and barium sulphate (Opti-Up, Lafayette Pharmaceuticals, USA), were of pharmacopeial quality (US/NF). The commercially available mesalazine product, Salofalk® (S®) (Batch No. 99F 10E), was kindly supplied by the Ali Raif Drug Co. (Turkey).

2.2. Preparation of mesalazine matrix tablets

Due to the poor flowability of the drug powder, matrix tablets of mesalazine were prepared using the slugging method.

Mesalazine, alginate and Avicel PH 102 were passed through a #45 (0.350 mm) mesh screen separately and blended for 20 min. The mixture was compacted in the Erweka tablet machine (Korsh-Erweka GmbH, Germany), using a 20 mm flat-faced punch. Slugged tablets were broken and passed through a #18 (1 mm) mesh screen. Then Aerosil 200 and magnesium stearate were added and mixed for an additional 5 min. Tablets were compressed, using the Erweka tablet machine with a 12 mm flat-faced punch. Each tablet (average weight of 660 mg) contained 250 mg of mesalazine. The compositions of the matrix tablets are given in Table 1. Barium sulphate was added to the final formulation (Tablet C) for in vivo studies.

2.3. Physical characteristics of the tablets

The tablets were characterized immediately after preparation. Twenty tablets were tested for weight (AB 104, Mettler Toledo, Switzerland), thickness (Vernier Caliper, portable dial hand micrometer, Russia), diametrical crushing force (CGS, Hardness tester HDT 1V-3, Germany) and friability (USP 27/Roche friability tester). The mean values were calculated with confidence intervals (CI).

The disintegration time of the tablets was determined using the compendial USP method with the disintegration apparatus (Aymes, Turkey). Six tablets were evaluated from each formulation. The apparatus was operated using simulated gastric fluid for 1 h. Then the dissolution medium was replaced with simulated intestinal fluid.

Table 1
Formulation of the tablets

Code	Mesalazine (mg)	Alginate (LF 240 D) (mg)	Alginate (LF 120 M) (mg)	Avicel PH102 (mg)	Aerosil 200 (mg)	Magnesium stearate (mg)	Barium sulphate (mg)
A1	250	350	–	48	5	6.5	–
A2	250	150	–	248	5	6.5	–
A3	250	75	–	323	5	6.5	–
B1	250	–	350	48	5	6.5	–
B2	250	–	250	148	5	6.5	–
B3	250	–	150	248	5	6.5	–
C	250	–	150	148	5	6.5	100

The drug content of the tablets was measured spectrophotometrically. For this purpose 10 tablets were individually weighed, and then each of them was dissolved at pH 7.4 in 150 mL buffer solution. Samples were assayed spectrophotometrically (Beckman DU-600, ABD) at wavelengths of 298 nm (pH = 1.2, 4.5) or 330 nm (pH = 6.8, 7.4). The spectrophotometric assay method was fully validated according to USP 27. The same experiments were carried out with the commercial product Salofalk®.

The results are shown in Table 2.

2.4. Drug release studies

Drug release from the tablet formulations was assessed using the flow-through dissolution apparatus at a flow rate of 8 ml/min, fitted with 22 mm dissolution cells (USP Aparatus IV, Sotax AG, Switzerland). Six tablets from each formulation were tested. The tablets were tested for drug release for 2 h in 0.1 M HCl, based on the assumption that the average gastric emptying time is about 2 h [21,22]. The following dissolution media were used: 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 considering the pH of the GI tract [23–25].

The flow rate of 8 mL/min was chosen to keep the sink conditions during the dissolution test in all dissolution media. Mean data values are presented with their deviation (means ± SD). Following the drug release test for release comparison, analysis of variance (ANOVA) was used for all data analysis.

2.5. In vivo studies

X-ray imaging was used to monitor the tablets throughout the gastrointestinal system. Eight healthy volunteers, six female and two male, with a mean age of 29 years (range 22–40) and 50–80 kg body weight, participated in in vivo studies. They were non-alcoholics, non-smokers and had not taken any drugs. The purpose of the study had been fully explained, and all volunteers gave their written consent. Each subject orally ingested barium sulphate containing alginate matrix tablets with 200 ml of water, after an overnight fast. Abdominal radiographs were taken at fixed time intervals, and the tablets were visualized using X-ray imaging to establish whether they had reached the large intestine or not over 6 h. Volunteers were served with food after 2 h (breakfast) and 4 h (lunch) after the administration of the tablet.

In the present study, X-ray imaging was used on the tablets, in order to monitor the alginate matrix tablets throughout the gastrointestinal system and to test them in vivo. Meanwhile the fluoroscopy technique was also applied to subjects to ascertain where the tablets localized through the GI system. The position of the tablets in the body was monitored at different points in time.

The Ethics Committee of the Faculty of Medicine, Gazi University, in accordance with internationally accepted principles, had approved the experimental protocol (2001/5). Each volunteer received about 0.1 rem of radiation during the taking of the gastrointestinal X-ray radiograph. Normally, in a routine abdominal investigation

Table 2
The physical characteristics of the tablets

Code	Weight average (g) ± SD ($n = 20$)	Diameter average (mm) ± SD ($n = 20$)	Thickness average (mm) ± SD ($n = 20$)	Strength average (N) ± SD ($n = 20$)	Friability (%) ($n = 10$)	Disintegration time average (h) ± SD ($n = 6$)	Mesalazine content average ± SD ($n = 10$)
A1	0.648 ± 0.016	12.1 ± 0.0	4.40 ± 0.06	128.1 ± 0.8	0.38	3.30 ± 0.18	253 ± 5
A2	0.643 ± 0.058	12.1 ± 0.2	4.48 ± 0.09	132.9 ± 1.1	0.33	2.50 ± 0.33	248 ± 6
A3	0.661 ± 0.038	12.2 ± 0.2	4.53 ± 0.04	135.6 ± 0.7	0.36	2.15 ± 0.72	249 ± 3
B1	0.668 ± 0.047	12.1 ± 0.0	4.38 ± 0.03	123.5 ± 1.1	0.39	3.10 ± 0.81	245 ± 1
B2	0.670 ± 0.018	12.1 ± 0.1	4.43 ± 0.08	128.9 ± 1.5	0.32	2.35 ± 0.93	251 ± 0
B3	0.661 ± 0.003	12.0 ± 0.0	4.41 ± 0.03	130.6 ± 0.8	0.31	2.15 ± 0.14	250 ± 3
C	0.664 ± 0.081	12.0 ± 0.4	4.39 ± 0.06	133.9 ± 0.9	0.41	2.20 ± 0.22	250 ± 1
S®	0.515 ± 0.005	11.4 ± 0.0	5.64 ± 0.03	–	–	6.17 ± 0.27	256 ± 8

with barium sulphate, a patient receives 0.7 rem of radiation [26]. Therefore, the total radiation dose (about 0.5 rem) received by each volunteer was found not to be higher than that of standard abdominal radiography.

3. Results and discussion

All the tablet formulations were evaluated from the point of the view of the physical properties of the tablets (Table 2) and their in vitro releases. The tablet strengths were almost identical for all of the formulations, and the crushing forces were found to be in the range of 123.5–135.6 N (Table 2). The effect of alginate type and amount on the disintegration process was important as it starts to swell immediately on contact with water. The disintegration times of the tablets varied between 2.15 ± 0.72 to 3.30 ± 0.18 and 2.15 ± 0.14 to 3.10 ± 0.81 min for the formulations prepared with high and low viscosity alginate, respectively. As expected the increase in the amount of alginate delayed the disintegration time for both types of alginate (Table 2).

The mean drug content of all the mesalazine tablets was found to be in the range of 245–253 mg. This indicates that the tablets passed the content uniformity test, as they contained 98.1–102% of mesalazine.

The release profiles of the commercial product (Salofalk®) were investigated using the paddle or flow through dissolution methods [27,28]. Rudolf et al. [27] carried out the in vitro release of several mesalazine preparations and compared their multi-unit dosage forms. In that study the paddle method was used and dissolution studies were performed in different media such as pH 1.2, 4.5, 6.8 and 7.4. In our experiments flow-through cell apparatus was used since it was thought that in vivo GI transit conditions may be best imitated by in vitro flow-through cell apparatus using different but sequential pH media.

The in vitro release profiles of the tablets are shown in Figs. 1 and 2. As can be seen from Figs. 1 and 2 the amount of alginate was found to affect the drug release significantly between 4 and 8 h at pH 6.8 and 7.4 ($P < 0.05$), whereas there was no statistically significant effect for the first 4 h for the two different types of alginate ($P > 0.05$). Mesalazine has good solubility at both acidic and neutral pHs (10.2, 8.12, and 9.37 mg/mL at pH 1.2, 6.8 and 7.4, respectively) [29]; this would ensure that drug release is primarily dependent on the properties of the matrix and not on drug solubility.

When we compared the alginate types from the perspective of in vitro release profiles, no significant difference was found between the release of drug from the tablets prepared with two different types of alginate for the first 4 h at pH 1.2 and 4.5. The comparison of in vitro release profiles of the formulation with those of the commercial product (Salofalk®) showed that the matrix tablets released 8.4–11.9% of the drug during the first 2 h at pH 1.2, whereas no mesalazine release was found from Salofalk® tablets at pH 1.2 (Fig. 1). However drug release increased

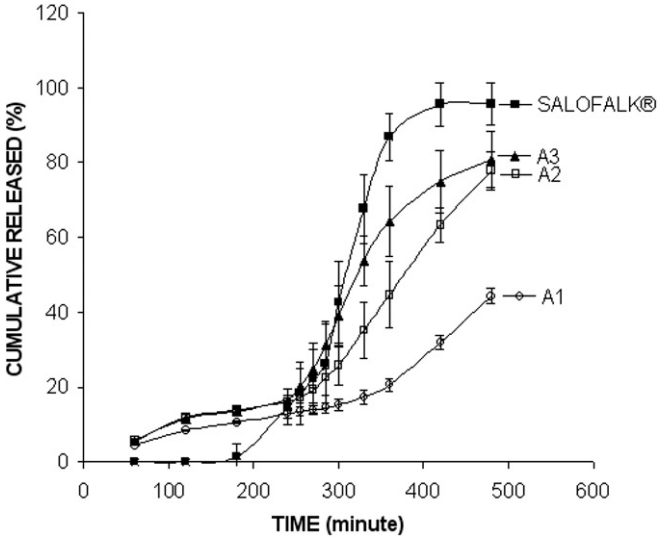

Fig. 1. Dissolution profiles of mesalazine from the Alginate-LF 240 D matrix tablets and commercial tablet Salofalk®. {A1 (350 mg Alginate-LF 240 D), A2 (150 mg Alginate-LF 240 D), A3 (75 mg Alginate-LF 240 D).}

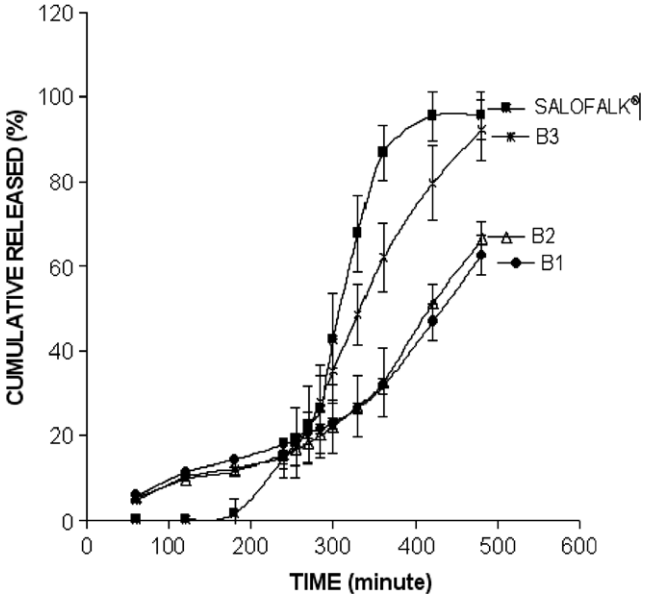

Fig. 2. Dissolution profiles of mesalazine from Alginate-LF 120 M tablets and commercial SALOFALK® tablet. {B1 (350 mg Alginate-LF 120 M), B2 (250 mg Alginate-LF 120 M), B3 (150 mg Alginate-LF 120 M).}

at pH 4.5, and it was found that 12.8–16.7% and 14.7% of the drug were released from the A1–A3 tablets and Salofalk® tablets, respectively, over 4 h (Fig. 1).

It was observed that the alginate type and amount in the matrices played an important role in basic media. The drug release decreased when the amount of high viscosity alginate increased in the matrices of A1, A2 and A3 formulation in basic media (Fig. 1). A1 and A3 formulations released 20% of drug within 6 and 4 h, respectively. Cumulative release of drug from A3 formulation was approximately 80%, whereas, 44% drug had been released from A1 formulation at 8 h. The increasing amount of alginate

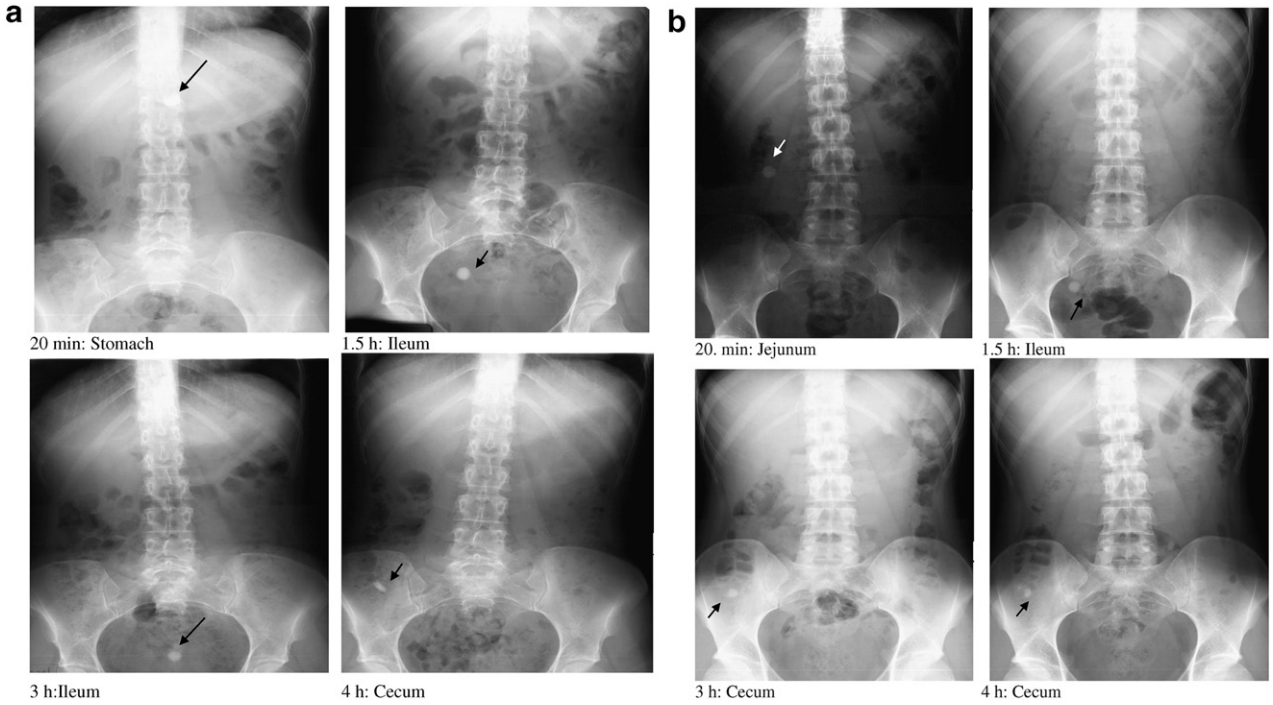

Fig. 3. The localization of the tablet in the gastrointestinal tract in subject 1 (a). The localization of the tablet in the gastrointestinal tract in subject 2 (b).

results in the increase in the viscosity of the gel layer, which retards the drug diffusion from the tablet [8].

The release profiles of B1 and B2 formulations were found to be almost identical in basic media. It was observed that the release rates of B1 and B2 formulations were found to be slow compared with B3 formulation (Fig. 2).

Formulation B3 released 20% and 40% of drug approximately at 4.5 and 5 h similar to Salofalk® tablets. The 47% and 80% release were obtained in 7 h for B1 and B3 formulations, respectively. On the other hand, 80% of drug had been released at 7 h from B3 formulation and at 6 h from Salofalk® tablets (Fig. 2). Salofalk® tablets released mesalazine more rapidly due to the increase in pH because of enteric coating. Efentakis and Koutlis [30] also reported that the viscosity of sodium alginate affected the release rate of furosemide from hard gelatin capsules. Low viscosity formulations exhibited greater erosion, while high viscosity formulations exhibited less erosion and drug release was completed in 8 h.

Although Salofalk® tablets are acid resistant enteric coated tablets, almost the same amount of drug was released with B3 and Salofalk® tablets (Fig. 2). Therefore, tablet B3 was chosen for further in vivo studies, and formulation C was prepared with the addition of barium sulphate as a marker for monitoring the tablets through the GI system.

From the abdominal radiographs, taken at different points of time, it was seen that after 20 min the tablets remained in the stomach in five subjects, whereas the tablets had reached the upper intestinal region in the other three subjects. The X-ray image of tablets throughout the gastrointestinal systems is shown in Fig. 3 for two subjects (subjects 1 and 2).

The position of the tablets at different time intervals is shown in Table 3. The tablet formulation reached the ileum after approximately 1.5 h in four subjects (subjects 1–4).

Table 3
The position of the tablets throughout the gastrointestinal tract in the subjects at certain points in time

Subjects	20 min	1.5 h	3 h	4 h	5 h	6 h
1	Stomach	Ileum	Ileum	Cecum	ND[a]	ND
2	Jejunum	Ileum	Cecum	Cecum	ND	ND
3	Stomach	Ileum	Cecum	ND	ND	ND
4	Jejunum	Terminal ileum	Transverse colon	ND	ND	ND
5	Stomach	Jejunum	Ileum	Ileum	Disentegrated	ND
6	Stomach	Stomach	Ileum	Ileum	Terminal ileum	Cecum
7	Duodenum	Jejunum	Jejunum	Disentegrated	ND	ND
8	Stomach	Jejunum	Terminal ileum	Disentegrated	ND	ND

[a] ND, not detected.

However, the tablets were monitored in the jejunum in the other three subjects (subjects 5, 7 and 8) at 1.5 h. Krishnaiah et al. [16] reported that the mean gastric emptying time was found to be 1.08 ± 0.11 h and the mean small intestinal transit time was 1.75 ± 0.25 h, while evaluating guar gum as a matrix tablet for colonic drug delivery using gamma scintigraphy.

The tablets were seen in the cecum, transverse colon and terminal ileum at 3 h in subjects 2, 3, 4 and 8. However, the tablet was monitored in the cecum at 4 h in subject 1. For four subjects (3, 4, 7 and 8) the intensity of the tablet image decreased at 4 h, due to possible disintegration of the tablet, and finally the tablet was not detected at 5 and 6 h, except in the case of subject 6, because of complete disintegration.

It was reported that the average small intestinal transit time and cecal arrival time were 3.11 and 4.6 h, respectively [31].

In our previous study, X-ray imaging showed that the colonic arrival time of the guar gum-mesalazine matrix tablets was 3–8 h for six volunteers, whereas it took 24 h for two volunteers [29]. It was reported that the tablets were visualized in the ileum for seven subjects, and the tablets reached the colon in five of them.

Our in vivo experiments showed that the tablets reached the small intestine in 3 h in the majority of healthy volunteers and this finding agrees with that observed by the above studies. The in vitro release test experiments of the tablets showed that $10.1 \pm 0.3\%$ of the active compound was released in the first 2 h. These results indicate that alginate matrix tablets reached the upper part of the large intestine after releasing a small amount of mesalazine.

It was observed that the transit time of the tablets throughout the gastrointestinal tract was variable. Billa et al. [31] also reported wide intersubject variations in the gastric emptying values.

It was concluded that mesalazine-alginate matrix tablet formulations can deliver the drug to the small and large intestine. Thus, the alginate matrix tablets may be a promising site specific delivery system for the treatment of Crohn's disease involving both the ileum and large intestine.

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