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Enteric-coated cholylsarcosine microgranules for the treatment of short bowel syndrome

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Abstract

Cholylsarcosine (CS) is a semisynthetic bile salt that may be useful in bile salt replacement therapy of short bowel syndrome (SBS). In SBS the bile salt pool becomes depleted, disturbing the uptake of dietary lipids and resulting in weight loss. Previous studies showed that CS in a simple capsule formulation of 1.5–12 g day^{-1} can increase the uptake of lipids but often results in gastric irritation. In this work a microgranule dosage form was developed to protect the gastric mucosa while facilitating rapid generation of CS levels in the duodenum. CS microgranules were produced by wet granulation and coated with Eudragit L30D-55 in a fluidized-bed coater. The in-vitro dissolution rate of CS from the microgranules was investigated with USP apparatus under fasted- and fed-state conditions. CS release was delayed under simulated gastric conditions (pH 1.2 and 4.5) but was very fast at higher pH values (5.5, 5.8 and 6.5) more typical of the duodenum. In a pilot clinical trial, four patients received 4 g CS with meals (1.5 g with lunch, 2.5 g with dinner) for 1 week. The parameters investigated were fat absorption coefficient (FAC%), serum β-carotene level and faecal weight. Although study numbers were too small to achieve statistical significance, the serum β-carotene level and FAC% increased in the three patients who completed the trial. As expected, the fecal weight did not change. The results indicate that the CS microgranules are promising for the treatment of the intraluminal bile salt deficiency in patients with SBS.

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Introduction

Short bowel syndrome (SBS) occurs when a patient is left with < 200 cm of functional small intestine. SBS may be congenital (infants with intestinal atresia) or it can be an acquired condition. In the latter case SBS usually results from surgical resection of bowel due to recurrent Crohn's disease, tumour, volvulus, trauma or vascular failure. After the resection of small intestine severe nutrient and fluid malabsorption often occurs (Buchman 1997). In other cases, severe malabsorption may occur even though the bowel length is intact; this is termed functional SBS. Functional SBS can result from refractory sprue, congenital villus atrophy or radiation enteritis. The extent of malabsorption depends on the age of the patient, the length of remaining bowel, the presence of colon and ileocaecal valve and the extent of adaptation of the remaining bowel. Resection of the jejunum typically causes less severe nutritional problems than does loss of ileum (Longmire-Cook et al 1992). Despite the fact that most nutrients are normally absorbed in the proximal jejunum, when the jejunum is resected the residual ileum is able to adapt and assume the role of macronutrient absorption. By contrast, when the ileum is resected the jejunum is not able to take on important functional roles of the ileum, such as bile acid reuptake (Buchman et al 2003).

The clinical features of bile acid malabsorption are summarized in Figure 1 (Riecken & Schulzke 1992; Eusufzai 1995). The active reuptake of the bile salts is important for the conservation of the circulating bile acid pool, which is secreted during digestion. Bile salts are necessary for the digestion of the dietary lipids as they form mixed micelles with lipids such as fatty acids and monoglycerides, thereby promoting lipid digestion and absorption (Lillienau et al 1992). If the bile salts are depleted, for example in patients with SBS, the uptake of the lipids will be disturbed, resulting in diarrhoea and steatorrhoea (Lillienau et al 1993). Diarrhoea occurs because

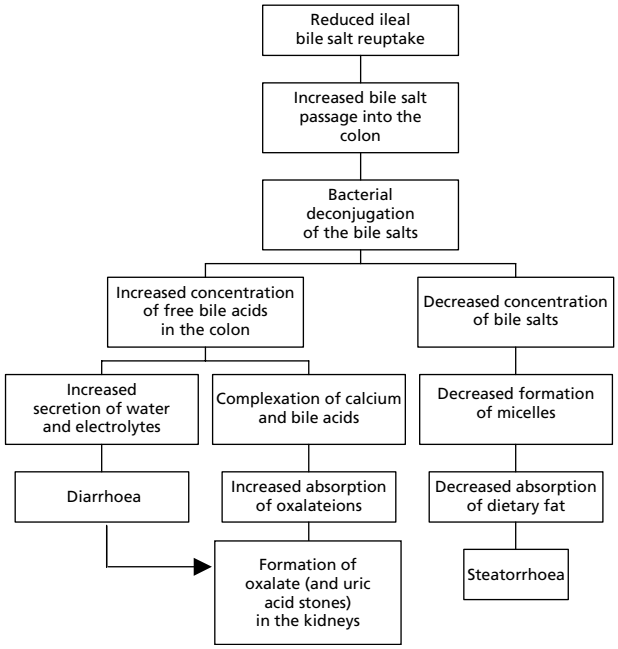

Figure 1 Schematic diagram of the clinical features of bile acid malabsorption (Riecken & Schulzke 1992; Eusufzai 1995).

of insufficient conservation of electrolytes and water due to the loss of ileal surface (Arrambide et al 1989). Additionally, the severe bile salt malabsorption results in an increased passage of bile salts into the colon, which in turn inhibits water and electrolyte conservation by the colon mucosa (Mekhjian et al 1971). The decreased bile salt concentration also leads to impaired micellar solubilization of fatty acids and monoglycerides in the proximal intestine, which in turn reduces their absorption and results in steatorrhoea (Poley & Hofmann 1976).

Replacement with naturally occurring bile salts is problematic because of bacterial deconjugation in the colon, which also leads to diarrhoea (Popovic et al 1999). In contrast, cholylsarcosine (CS), a semisynthetic bile salt that does not undergo bacterial deconjugation, has no secretory effects and lacks toxicity (Schmassmann et al 1993); thus it has been proposed as an alternative for bile salt replacement therapy for SBS (Schmassmann et al 1993). Previous animal and human studies showed that a dose of 1.5–12 g day^{-1} CS can increase fat absorption but in this amount the gastric mucosa can be damaged, since conjugated bile acids are known to damage the gastric mucosal barrier in a concentration-dependent manner (Kapral et al 2004).

A new formulation of CS with the following properties was subsequently proposed: the formulation should be tasteless, avoid injury to the oesophageal or gastric mucosa, empty from the stomach together with the meal and dissolve rapidly in the small intestine. To protect the gastric mucosa, CS was packaged in microcapsules coated with a pH-sensitive coating that would dissolve above pH 6.8. To ensure that the particles empty from the stomach with the meal, the microgranules had to be less than 2 mm in diameter. The gastric-juice-resistant pellets developed were tested by Popovic et al in patients (Popovic et al 1999). The results were discouraging in that the CS pellets caused increased abdominal pain and diarrhoea. All unwanted effects appeared within a few days of initiating the CS pellet treatment. The same patients showed none of these side-effects when they were later administered CS in an uncoated formulation. However, an uncoated formulation is unacceptable owing to the extremely bitter taste of CS and gastric irritation. Popovic concluded that the lack of efficacy and the undesirable side-effects were not as a result of the CS but rather a failure of the dosage form. It was suggested that the coating did not dissolve early enough and either caused a transient intestinal obstruction or dissolved in the large bowel rather than in the small intestine, resulting in irritation at the large CS dose used (Popovic et al 1999).

An earlier and faster release of the CS would be expected to decrease the observed side-effects and increase fat uptake. Coated CS granules with a more suitable release profile were therefore developed and investigated both in-vitro and in-vivo.

Materials and Methods

Materials

CS (lot #98010027) was purchased from Prodotti Chimici e Alimentari S.p.A., Italy. Kollidon VA 64 (lot #53-3271) was acquired from BASF AG, Germany. Eudragit L30 D-55 (lot #1200814181) was bought from Röhm Degussa-Hüls Group, Germany and Saccharose pulvris (lot #05013041) was ordered from Südzucker AG, Germany. All other chemicals used for the manufacture of the granules, and the in-vitro and in-vivo tests were analytical grade or equivalent, and purchased commercially.

Methods

Preparation of the coated CS granules

The CS granules were manufactured using the wet granulation technique. The composition of the granules was Saccharose pulvris (10%), CS (90%) and Kollidon VA 64 (2%). The first step was to blend the Saccharose pulvris with the CS. The Kollidon VA 64 was separately dissolved in aqua purificata and the solution added stepwise in small amounts to the powder blend until a homogeneous mass was achieved. A Primax mixer (Primax DR 600 W, Küpper-Primax GmbH, Germany) was used for these steps in the manufacture. Afterwards the wet bulk was granulated by forcing it first through a sieve of mesh size 2 mm and then through a sieve of mesh size 1 mm. The resulting granules were dried in a hot air oven (40°C for 24 h) and classified using a sieve tower. Only particles exceeding 0.4 mm in diameter were subsequently used for the coating procedure.

To coat the CS granules a suspension of Eudragit L30-D55 was prepared as follows. An aqueous dispersion

(657 mL) containing Eudragit L30-D55 polymer (267 g) and triethyl citrate (TEC; 16 g) as the plasticizer was stirred overnight. In a separate step, glycerol monostearate (GMS; 2 g) as a glidant and polysorbate 80 (1 g) as an emulsifier were added to water (370 g) prewarmed to 60°C and stirred until a fine, homogeneously dispersed emulsion was obtained. The emulsion was then added in small amounts to the Eudragit L30-D55 polymer dispersion under constant mixing. The proportion of solids in the final dispersion was 24.6% (w/w). The percentage of GMS was 3% based on the dry weight of the polymer.

For the coating trials a Mini-Glatt (Glatt GmbH, Germany) equipped with a Wurster coating device was used. The spray nozzle was used in the bottom spray mode, the diameter of the nozzle was 0.5 mm and the spraying pressure was 1.3 bar. The inlet air temperature was 38–42°C and the product temperature 28–34°C. The pressure of the drying air was 0.2 bar. The total spraying time was 435 min using a spraying rate of $0.95\,g\,min^{-1}$. After coating, the granules were dried (15 min in the fluid bed and 24 h at 40°C in a hot air oven) and classified with a sieve tower.

Sieve analysis of the CS granules

The granules and the coated granules were sized using analytical sieves (Analysette, Fritsch, Germany). To determine the particle size distribution of the granules, sieves with mesh sizes from 0.09 to 1 mm were used.

Scanning electron microscopy

The morphology of the surface and the film thickness were examined by scanning electron microscopy (SEM) (S–4500 Hitachi field emission electron microscope, Germany). Samples were coated with gold using a sputter coater. To evaluate the film thickness, the granules were sliced radially before applying the gold sputter coating.

Dissolution tests

An Erweka Type DT 6R dissolution tester (Erweka, Germany), USP Apparatus 2 (paddle) was used for initial dissolution studies. The volume of media was 500 mL, the temperature was held at 37 ± 0.5°C and the stirring rate was $100\,rev\,min^{-1}$. To simulate pH conditions in the gastrointestinal (GI) tract, four compendial media were used. The dissolution rate of the granules was first investigated over 2 h at either pH 1.2 (simulated gastric juice fluid SGF, without pepsin USP 24) or pH 4.5 (phosphate buffer, Ph. Eur. 2000) to simulate fasted- and fed-state gastric pH conditions, respectively. To verify fast release of the CS in the duodenum, the dissolution rate of the granules was further tested over a period of 40 min at pH 5.5 and 5.8 (phosphate buffer, Ph. Eur. 2000).

To attain a better simulation of the physiological conditions and to compare the two different in-vitro dissolution methods, the tests were also conducted with a USP Apparatus 3, Caleva BioDis release rate tester (RRT8, Caleva Ltd, UK). The residence times used to simulate the passage through the different regions of the GI tract and the corresponding media are shown in Table 1. A relatively short gastric residence time was selected because of the very small particle size of the granules, which facilitates emptying with the liquid phase of the meal. Biorelevant pH gradients for the simulation of fasted and fed conditions were used (Klein 2002). The volume of media was 220 mL per vessel, the temperature was held at 37 ± 0.5°C and the dip rate was $10\,dp\,min^{-1}$. An intermediate mesh size of 420 μm was chosen for the top and bottom mesh in the sample holders. All studies were performed at least in triplicate.

Detection of released CS

An HPLC method (Rossi et al 1987) was used to determine the amount of CS released. The system consisted of a RP 18 column, Hibar (5 μm, ODS, 250×4.6, Merck, Germany), an HPLC pump (L6620 Intelligent Pump, Merck Hitachi, Germany), an autosampler (L7200, Merck Hitachi, Germany), a UV/VIS detector (Lambda Max Model 481, Waters, UK) and an integration software system (PC Integration Pack 3.90, Kontron Instruments S.p.A., Italy). The mobile phase was a solution of methanol (75%) and potassium dihydrogen phosphate 0.001 M (25%). The pH value (5.35) was adjusted with sodium hydroxide (5 M) and phosphoric acid (85%). The flow rate was $0.8\,mL\,min^{-1}$, the injection volume was 20 μL and the detection wavelength was 210 nm. Under these conditions CS typically eluted at 6.15 ± 0.15 min.

Pilot clinical trial

Four patients with SBS were entered in a small pilot study. An overview of their pertinent data is given in Table 2. The clinical parameters investigated were fat absorption coefficient (FAC%), serum β-carotene level and faecal weight.

Table 1 Dissolution media and residence times for the simulated fasted- and fed-state dissolution tests with USP Apparatus 3 (BioDis)

GI region	Conditions	Dissolution media	pH	Dwell time (min)	Reference
Stomach	Fasted	SGFsp	1.2	60	USP XXIII
	Fed	Phosphate buffer	4.5	20	Ph.Eur.2000NT
Proximal duodenum	Fasted	Phosphate buffer	5.5	10	Ph.Eur.2000NT
	Fed	Phosphate buffer	5.8	10	Ph.Eur.2000NT
Distal duodenum	Fasted	Simulated fasted state intestinal	6.5	45	
	Fed	fluid without bile	6.5	45	

Table 2 Characteristics of SBS patients treated with CS microgranules

No.	Age	Sex	Basic disease (body weight; height)	Extent of ileostomy
1	42	F	Operated on because of Crohn's disease 1977 (69 kg; 165 cm)	100 cm remaining
2	58	F	Operated on because of Crohn's disease 1971 (52 kg; 163 cm)	50–60 cm remaining
3	50	F	Operated on because of Crohn's disease 1986 (62 kg; 162 cm); ileostomy	100–150 cm remaining
4	62	F	Operated on because of ovarian cancer (55 kg; 168 cm); enteritis because of radiation hazards	No resection (Functional SBS)

Table 3 Design of the pilot clinical trial of patients suffering from SBS

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Administration of CS microgranules (CS)								CS	CS	CS	CS	CS	CS	CS	
Monitoring (M)	M							M							M
Nutrition protocol (NP)				NP	NP	NP	NP				NP	NP	NP	NP	
Stool collection (SC)					SC	SC	SC					SC	SC	SC	

After a 1-week lead-in, 4 g day^{-1} CS microgranules were administered on day 8 through day 14 of the trial (CS). Monitoring of FAC%, β-carotene, stool weight, vital functions and blood values (M), nutrition records (NP) and collection of stools (SC) were conducted at various times during the trial as indicated in the table.

In the first week of the trial the patients kept nutrition records on days 4–7 and collected stool on days 5–7. In the second week 4 g day^{-1} of CS microgranules with meals (0 g at breakfast, 1.5 g at lunch and 2.5 g at dinner) was added to the protocol. The design of the pilot clinical trial is portrayed in Table 3. The study was initiated in July 2001 after the protocol had been approved by the ethical review board of the Johann Wolfgang Goethe University, Frankfurt (#E109/01) and the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). All patients gave informed consent and were deemed to be compliant.

Stool analyses

The fat absorption coefficient FAC% reflects the degree of malabsorption. In healthy people the FAC is about 95% or higher. Stool was collected over 3 days (72 h). Faecal weight was measured and fat determined in a sample of homogenized stool by near-infrared reflectance analysis (Stein 1996). Fat intake was estimated from the dietary diary and calculated from dietary tables. The FAC% was then calculated according to the following formula:

$$\text{FAC\%} = ((\text{fat intake (g } 24\,\text{h}^{-1}) - \text{stool (g } 24\,\text{h}^{-1}))/(\text{fat intake (g } 24\,\text{h}^{-1})) \times 100$$

β-carotene analyses

The serum β-carotene level is an indirect parameter for the detection of steatorrhoea. If fat absorption is defective, the uptake of β-carotene and other lipophilic substances (e.g. vitamins A, D, E and K) will be reduced too. Because there is only a small depot for β-carotene in the human body, β-carotene serum levels reflect changes in absorption status quickly, within a period of 1 to 4 weeks. To measure serum β-carotene levels, a blood sample is extracted with ethanol in ether and then centrifuged. After this procedure the yellow coloration of the ether phase is investigated photometrically. Diagnostically, serum β-carotene levels $> 100\,\mu\text{g}\,\text{dL}^{-1}$ exclude steatorrhoea, whereas β-carotene values $< 47\,\mu\text{g}\,\text{dL}^{-1}$ exclude normal fat digestion (Lembcke et al 1994).

Results

Characteristics of CS microgranules

The microgranules had a CS content of 92.4%, an average particle size of 0.6 mm, a tap density of $0.517\,\text{g}\,\text{mL}^{-1}$ and a Hausner factor of 1.09. The friability was 0.15%. The granule morphology is depicted in Figure 2A. After coating, the average particle size of the CS microgranules was 0.75 mm. The microgranules themselves were non-spherical with some rough edges, but the polymer film was homogeneous and uniform. The film thickness was approximately 105 μm after applying 27% applied polymer, based on the weight of the granules. Typical surface and cross-sections of the microgranules are shown (SEM) in Figures 2B–D.

Dissolution tests of the CS microgranules

The coated CS microgranules developed show slow drug release under gastric conditions, as documented in

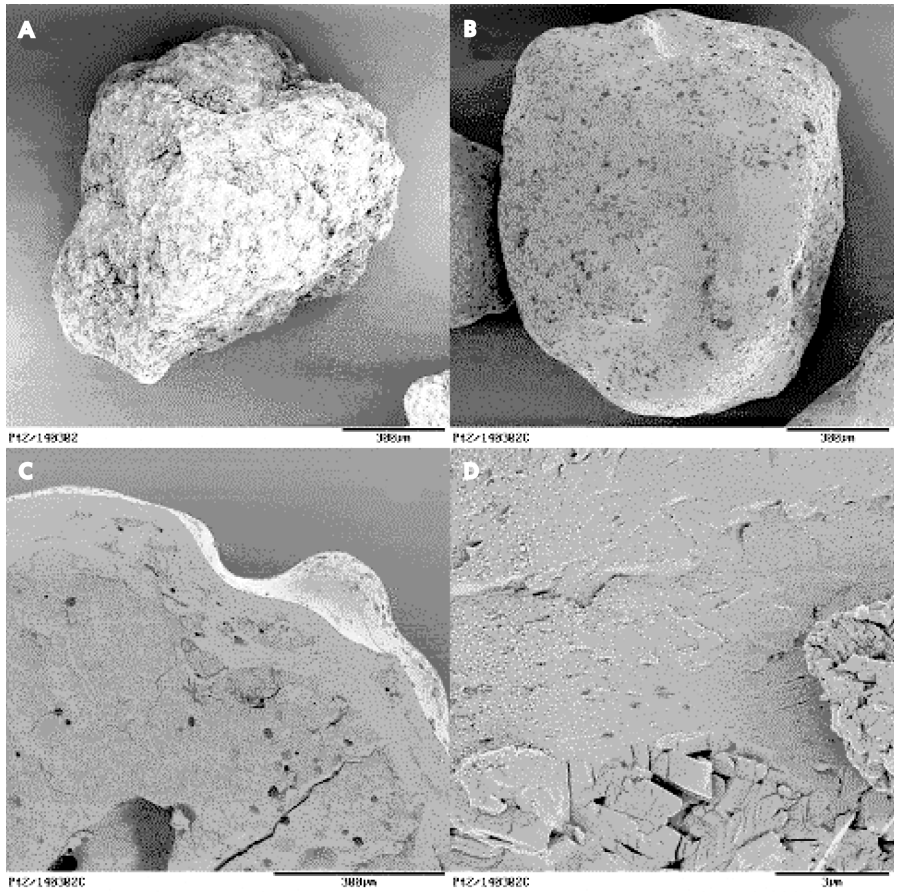

Figure 2 (A) SEM image of the CS microgranule surface before coating (magnification 30×). (B) SEM image of the CS microgranule surface after coating with Eudragit L30D-55 (magnification 30×). (C) SEM cross-section of CS microgranule coated with Eudragit L30D-55 (magnification 250×). (D) SEM cross-section of coated CS microgranule (magnification 1000×).

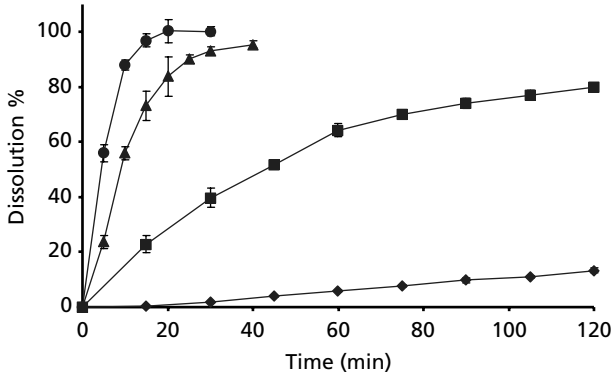

Figure 3 Dissolution profiles of CS microgranules under simulated gastric and duodenal conditions using USP Apparatus 2 (paddle) (mean ± s.e.m.). Gastric conditions: ◆, SGFsp pH 1.2; ■, phosphate buffer pH 4.5. Duodenal conditions: ▲, phosphate buffer pH 5.5; ●, phosphate buffer pH 5.8.

Figure 3. At pH values typical of the fasted stomach CS release is very slow, about 10% in 2 h at pH 1.2. The gastric mucosa of the patients should not be damaged by CS in the small amounts released. Since the patients need to take the microgranules with the meal for optimal therapeutic results, the dissolution of the microgranules under pH conditions more typical of the fed stomach was also investigated. About 25% was released in the first 20 min, climbing steadily to 80% after 2 h. Since gastric transit is shorter in SBS patients than in healthy subjects, gastric emptying occurs concurrently with the dissolution of the microgranules. With this release and emptying pattern a good mixing of the CS with the food components can be assumed and a rapid formation of micelles in the duodenum is expected.

At pH values corresponding to the duodenum the microgranules dissolved very quickly (Figure 3), facilitating CS availability for fat digestion, which is normally completed within the first 100 cm of the intestine (Brunner et al 1974). At pH values of 5.5 and 5.8 over 90% of the CS dissolved within 25 and 15 min, respectively. The fast disintegration and dissolution can be explained by the solubility behaviour of the polymer Eudragit L30-D55, which is soluble at pH values above 5.5. The good water solubility of the granulation agents Saccharose pulvris and Kollidon VA 64, and of CS also contribute to the rapid dissolution profile.

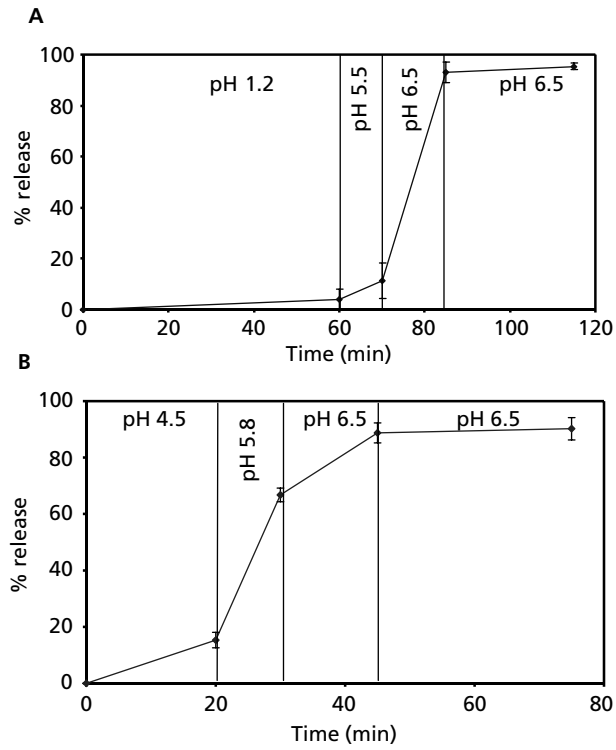

Figure 4 (A) Dissolution profile of CS microgranules under simulated fasted conditions using USP Apparatus 3 (BioDis) (mean ± s.e.m.). (B) Dissolution profile of CS microgranules under simulated fed conditions using USP Apparatus 3 (BioDis) (mean ± s.e.m.).

The results of the Bio-Dis investigations (Figures 4A and B) corroborate the data from the paddle dissolution tests. The release profiles obtained with the USP Apparatus 3 are easily explained on the basis of the granule design concept. Under simulated fasted conditions (Figure 4A) there is only a very slight release of CS in the stomach (4% in 60 min); the polymer and the granules do not dissolve. In the course of the rapid transit through the proximal duodenum (~10 min) the amount of free CS rises just to 11% but as soon as the granules reached regions with a higher pH level (6.5), e.g. proximal jejunum, the release of CS is very fast (92% in 15 min). The rapid dissolution of the CS proximal in the small intestine is particularly crucial to improving lipid digestion in SBS patients.

Under simulated fed conditions (Figure 4B) dissolution commences in the stomach. At pH 4.5 small amounts of CS (15% in 20 min) are released. Following gastric emptying, granules should release up to two-thirds of their contents in the duodenum (pH 5.8) and release should be complete within a half an hour (pH 5.8/6.5). Additionally, any dissolved CS would empty either with the liquid or solid fraction of the meal. The benefits to the patients of this dosage form are expected to include the taste neutrality of the granules, combined with protection of the stomach mucosa (small amounts released before gastric emptying) and an increased efficiency of digestion and uptake of dietary lipids.

Treatment of patients with SBS

Four patients with SBS were enrolled in a pilot study to receive 4 g day^{-1} (0, 1.5 and 2.5 g) of CS granules over a period of 1 week and the effect of treatment on the FAC%, β-carotene serum levels and the stool weight was investigated. No medication was given with breakfast because the bile salt pool in humans is able to, at least partially, regenerate overnight. During the day the loss of bile salts becomes worse and must be supplemented (Weinand & Stein 1999). The patients preferred to mix the microgranules with yoghurt and eat the blend with meals. It was possible to mix the microgranules with the meal without the coating dissolving, resulting in excellent masking of the very bitter taste of the CS. This contributed substantially to the compliance of the patients.

Two of the patients who entered the study had a short small bowel combined with a functioning colon, one had a short small bowel but no colon and the fourth had both a small bowel and a colon but suffered from functional SBS due to radiation exposure. The patient with functional SBS had to exit the study early due to abdominal pain and worsening diarrhoea, so results from this patient could not be included in the analysis. After treatment with CS granules over a period of 1 week, the remaining three SBS patients showed an increase in FAC% (ranging from 17 to 29%) and β-carotene levels (ranging from 25 to 1000%) without any effect on stool weight (Table 4), despite the large variation in the extent of bowel resection and the degree of intraluminal bile salt deficit in the patients (Table 2).

Discussion

In light of the disappointing experience of Popovic et al (1999) with coated CS pellets, the results of the investigations with the new developed microgranules were very encouraging for the treatment of patients with SBS.

Table 4 Effect of CS microgranules on clinical parameters in patients with SBS who completed the pilot trial (n = 3)

	Patient 1		Patient 2		Patient 3		Effect of treatment (mean ± s.e.m.)
	Before CS	With CS	Before CS	With CS	Before CS	With CS	
Fat absorption coefficient (%)	71.62	84.24	61.02	78.9	25.6	32.38	13 ± 4
β-carotene levels ($\mu g\,dL^{-1}$)	40	50	4	44	25	67	31 ± 14
Stool quantity (g $72\,h^{-1}$)	1945	2281	2748	2160	1564	1710	−35 ± 398

The gastric-juice-resistant pellets developed by Popovic et al were pH sensitive and dissolved at pH values above 6.8. All patients treated showed side-effects and had to stop the medication after a few days because of worsening diarrhoea and abdominal pain. The same patients showed none of these unwanted effects with an uncoated CS formulation. It was concluded that the side-effects must have been caused by the dosage form of the coated pellets. In particular, the dissolution pH of 6.8 seems to have been problematic. Because of the fast GI transit times in patients with SBS, little or none of the CS would be released in the proximal duodenum, resulting in little or no assistance in the digestion of the dietary lipids. Popovic et al hypothesized that the undissolved pellets reached the large bowel and released high amounts of CS and polymer there, resulting in transient intestinal obstruction and its unwanted consequences (Popovic et al 1999). The microgranule formulation introduced here appears to ameliorate all of these problems.

The improved concept, with a pH sensitive coating that dissolves above pH 5.5, is superior to the former formulation in that CS release is already initiated, albeit slowly, in the stomach. Taking into account the simultaneous dissolution and gastric emptying of the microgranules, no damage of the gastric mucosa should occur. This is largely supported by the in-vivo results; three of four patients in the pilot study had no unwanted gastric effects such as nausea or vomiting. Only the patient with the functional SBS was forced to stop taking the CS granules because of abdominal pain and worsening diarrhoea. This negative result might be explained by the very sensitive mucosa arising from the exposure of this patient to radiation. Nevertheless, some improvements in the administration schedule of the CS granules can still be made. All patients complained of some abdominal irritation on the first day. Even though these complaints soon diminished, it is hypothesized that starting with a smaller dose, which is then gradually increased over several days, may be more appropriate.

The main advantage gained with the new dosage form is the high amount of CS released before and in the proximal duodenum. In-vitro tests showed that an appropriately early release rate is achieved under simulated fed conditions. At pH values of 6.5 the new granules dissolve completely in a very short time, whereas the Popovic formulation was just starting to dissolve at this pH value. In-vivo results confirmed that enough CS would be released in the duodenum to enhance fat digestion. Indeed, all three patients who finished the pilot trial showed an increased fat absorption coefficient and β-carotene level (Table 4).

Lack of problems with diarrhoea further indicates that the granules did not dissolve too late, since this effect is a result of CS release in the large bowel. Although fragments of the coating were often detected in the stool, the increased fat absorption observed and the good solubility of CS suggest that only undissolved polymer was excreted. A reason for this observation could be the relatively high quantities used for the coating combined with the short total GI transit time in these patients. As expected, and in accordance with previous studies, CS had no significant influence on stool weight (Heydorn et al 1999) in patients with or without colon. Generally it could be said that patients with lower stool outputs showed a slight increase in stool weight whereas patients with very high and frequent outputs showed a slight decrease. This trend, while not statistically significant, is also in line with previous studies.

In summary, results with the new CS granule prototype demonstrate that an earlier and faster release of CS enhances the treatment of SBS; nevertheless the dosage form could be further optimized. The granules should have a more spherical form and a slightly larger particle size to reduce their surface area:mass ratio. This would lead to a lower polymer and excipient requirement while still achieving equivalent dissolution profiles. A modern, affordable and well-tolerated therapy of SBS is expected to be the outcome of these studies.

Conclusions

A new, enteric, coated microgranule dosage form of CS for the therapy of SBS was shown to achieve the objectives of tastemasking, protection of the gastric mucosa and a fast release of the CS in the proximal duodenum under simulated fasted- and fed-state conditions. The in-vitro and in-vivo results indicate that the CS granules developed are promising for the treatment of intraluminal bile salt deficiency in patients with SBS. The period of the treatment and the number of patients in the pilot clinical trial is currently being extended, and further optimization of the administration schedule and dosage form is underway.

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