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The gastrointestinal passage and release of beclomethasone dipropionate from oral delivery systems in ileostomy volunteers

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Aims To study the delivery of 15 mg beclomethasone 17,21-dipropionate (BDP) to the distal part of the small bowel for three oral sustained-release formulations (I-III) and a reference capsule in volunteer ileostomists, and to compare these findings with the *in vitro* dissolution profiles.

Methods Two groups of nine ileostomy volunteers (aged 20–61 years), who were otherwise healthy, were enrolled in the study. The recovery of BDP and its metabolite beclomethasone 17-monopropionate (B17P) in ileostomy effluent was investigated in a cross-over study after administration of formulations I or II or a reference capsule containing micronised BDP, and in a second open study after administration of formulation III. Radio-opaque granules were coadministered for evaluation of gastrointestinal passage. Ileostomy effluents were collected hourly for 10–12 h following drug intake. After marker beads had been counted on X-rays, ileostomy collections were analysed for BDP and its metabolites. Cumulative recovery, lag-time and mean transit time were determined for drug and marker beads.

Results Gastrointestinal passage characteristics were similar for all treatments. Total drug recovery was approximately three times higher for the sustained-release formulations than for the reference capsule. Recovery of B17P from stoma fluid samples was significantly lower for formulation III than for formulations I and II.

Conclusions The novel oral formulations delivered substantial amounts of steroid drug at the distal small bowel/proximal colon, which may warrant further studies to evaluate clinical applicability.

Keywords: beclomethasone, ileostomy, inflammatory bowel disease, sustained-release

Introduction

The application of steroid therapy in inflammatory bowel disease (IBD) has been shown to be effective since 1955 [1]. However, the complications of steroid therapy are well-known and have been reviewed in relation to IBD [2]. Since beneficial effects can be achieved with topical application (enema) of steroid [3], poorly absorbed corticosteroids or corticosteroids exhibiting a substantial first pass effect are widely used in the treatment of IBD located distally in the gastrointestinal tract [4]. A therapeutic challenge in IBD is the treatment of severe exacerbations in the more proximal parts of the gastrointestinal tract. Oral administration of steroids in therapeutically effective doses using conventional dosage forms is not possible without serious side-effects. Current oral therapeutic strategies therefore also favour the use of steroid drugs that are poorly absorbed or substantially inactivated during first pass [5–8]. A further improvement in corticosteroid therapy would be an enhanced delivery of steroid drug at the distal part of the small intestine or proximal colon.

Beclomethasone 17,21-dipropionate (BDP) is a potent glucocorticosteroid, with major application in topical treatment of asthma. After i.v. administration BDP inhibits plasma cortisol levels with equal potency as dexamethasone. The therapeutic effect of BDP observed in asthma and IBD is likely to be related to the anti-inflammatory properties of BDP, which have been reported to be between 5000 and 500 times as strong as those for cortisol and dexamethasone, respectively, as measured by the vasoconstriction assay [9]. It is not entirely clear whether the actual beneficial effects are related to BDP and/or its metabolite beclomethasone 17-monopropionate (B17P), that possesses comparable anti-inflammatory properties to BDP. The hydrolysis from BDP to B17P occurs very rapidly in human liver and human lung homogenate, with subsequent deactivation of the compounds. Apart from the conversion in liver and lung tissue, B17P is also formed in human serum and intestinal juices, probably by pancreatin [10, 11].

Experimentation with topical application of BDP in IBD has revealed that low and intermediate doses are therapeutically effective without causing systemic steroid related side-effects and without interfering with the hypothalamic-pituitary-adrenal axis [12–15]. Similarly, BDP is effective without causing systemic effects during aerosol therapy in asthma. Despite the facts that 80–90% of the inhaled dose is deposited in the oropharynx and subsequently swallowed

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[9], and that the drug is well absorbed after oral administration [16], no systemic corticosteroid effects have been reported with aerosol therapy of BDP at doses of up to 1 mg day^{-1}. These findings indicate that the likelihood of systemic steroid effects is low with these low doses. Thus, if sustained-release preparations can achieve topical delivery of BDP to the distal ileum and proximal colon as well as relatively low absorption of BDP in the small intestine, such BDP formulations may be beneficial in the treatment of proximal IBD without causing significant side-effects.

In the present studies, experimental sustained-release BDP formulations for oral use were tested. These formulations were developed to accomplish increased delivery at the terminal ileum and colon. The objective of the first study was to examine the recovery of BDP and its metabolites from two oral preparations of BDP in comparison with a plain capsule for reference in ileostomy effluent. The aim of a second study was to compare another extended release formulation with the formulations investigated in the first study.

Methods

Subjects

Nine volunteer ileostomists were recruited for each study. Their characteristics are listed in Table 1. The protocols of the studies were approved by the medical ethics committee of Leiden University Hospital, and the protocol of the first study was also approved by the medical ethics committee of the Academic Medical Center of the University of Amsterdam. All subjects gave written informed consent.

The ileostomy was for ulcerative colitis or polyposis coli and had to be in place for at least 1 year. Ileostomy effluent had to be sufficiently fluid to allow frequent sampling. All subjects were judged to be in good health after a medical screening before the start of the study which included a medical history, physical examination, 12-lead ECG and routine blood and urine analysis. None of the subjects had required recent medical treatment, with the exception of regular vitamin B12 administration in 4 of the 18 subjects.

Trial medication

Four types of 15 mg BDP-containing formulations were investigated in the studies. Formulations I, II and III were sustained release tablets and the fourth formulation (reference) was a plain capsule containing micronised BDP and lactose.

The tablets were prepared from granules containing either Eudragit® RL/RS (formulations I and II) or Eudragit® RL30D/RS30D (formulation III), and microcrystalline cellulose. Granules were made using a wet granulation method. The granules were dried and the dried granules were blended with the extragranular ingredients microcrystalline cellulose, cross-linked polyvinylpyrrolidone and magnesium stearate, and subsequently compressed in tablets.

The *in vitro* release profiles of all formulations were obtained according to the USP XXI paddle method and are depicted in Figure 1. Assuming that the time required for the 1 mm granules to reach the ileostomy is $\approx$4 h, it can be estimated that, compared with the capsule, approximately three times more drug will remain in the experimental

Table 1 Patient characteristics.

Subject	*Gender*	*Age (years)*	*Duration stoma (years)*	*Previous disease#*	*Concomitant medication*
			Subjects participating in study 1		
I-1	M	51	7	UC	vit B12 (every 2 months)
I-2	F	47	5	UC	Cimetidine (irregular)
I-3	F	62	4	UC	Temazepam (irregular)
I-4	F	32	3	UC	
I-5	F	50	15	UC	
I-6	M	30	3	UC	vit B12
I-7	F	34	5	UC	paracetamol (3 × 500 mg) between occasions 1 and 2
I-8	F	44	15	UC	vit B12
I-9	M	20	4	UC	
			Subjects participating in study 2		
II-1	M	42	12	UC	Ibuprofen[$]
II-2	M	44	3	PC	Paracetamol/Codeine[$]
II-3	M	23	4	UC/MC	
II-4	F	32	8	UC	vit B
II-5	F	27	2	UC	
II-6	F	48	3	UC	
II-7	M	47	24	UC/MC	vit B12/folic acid
II-8	F	45	1	UC	
II-9	M	51	11	UC	

#UC: ulcerative colitis; PC: polyposis coli; UC/MC: diagnosis uncertain ulcerative colitis/Crohns' disease.
[$]Single occasion within 48 h before participation in the study.

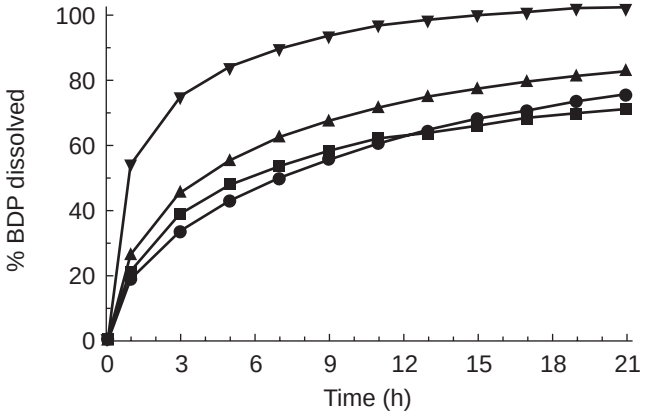

Figure 1 Dissolution profiles for the three sustained-release formulations (formulation I ●, formulation II ▲, formulation III ■) and the reference capsule (▼). The amount of BDP dissolved is expressed as the percentage of original amount BDP present in the various formulations. Testing conditions were: USP XXI paddle; 1000 ml containing 2% Cetomacrogol®1000; velocity: 75 r.p.m.; acidity: 0–30 min pH = 1.3, >30 min pH = 7.

formulations. Theoretically, this amount should be available for release at the distal small bowel.

Trial design and treatments

Study I was an open cross-over study with a wash-out period of at least 7 days with nine subjects. Treatments for this study were formulation I, II and the capsule. All nine subjects received these three treatments according to a 3×3 Latin square design. Study 2 was an open study in which nine subjects were studied on a single occasion in which BDP was administered as formulation III. For all treatments coadministration with a capsule containing 20 radio-opaque marker beads took place. These beads were 2–3 mm pieces (external diameter of 1.55 mm) prepared from a teflon radio-opaque central venous catheter.

Study days

For both studies the same time schedule was followed. Subjects were studied after an overnight fast from 24.00 h and abstaining from alcohol from 24 h before the start of each occasion. Study days always started at ≈08.00 h. After the subjects had changed their ileostomy bag and a urine pregnancy test was negative for the female subjects, drug administration took place at $t = 0$. Subjects swallowed the drug containing formulation and the capsule with the radio-opaque markers with 100–200 ml of mineral water. Ileostomy effluent was collected hourly for 10–12 h in preweighed bags and the volume was determined by weighing. Subsequently, effluent was frozen immediately and stored at below -35° C until analysis. Food intake during the day was standardized with breakfast served 1 h after drug intake, and lunch and dinner after 4.5 and 10 h. The subjects were asked to drink at least 100 ml of fluid hourly to ensure sufficient effluent. Until lunch only water was allowed and from 7 h after drug intake water, fruit juices and a cup of tea. Twelve hours after drug intake on the last occasion in study I and on the single occasion in study 2, routine blood and urine analysis took place.

Specific methods

Stoma fluid samples were analysed for BDP, B17P, beclomethasone 21-monopropionate (B21P) and beclomethasone.

Ileostomy effluent was thawed and the marker beads removed. For all treatments, stoma fluid was lyophilised in total. For formulation III, a potassium fluoride solution was added to the stoma fluid before lyophilization. The powder was then suspended in dichloromethane (DCM; formulations I, II and reference capsule) or in 80% acetone/20% 0.0175 M acetic acid to ensure dissolution of the release-modifying excipient, BDP and its metabolites. The suspension was then filtered through a glassfibre filter and the residue was washed with DCM (formulations I, II and reference) or with acetone/acetic acid (formulation III). From the acetone/acetic acid collection the acetone was evaporated and the aqueous residu was extracted with DCM during 5 min shaking. The DCM fraction (formulation III) and the DCM filtrate and washings (formulations I, II and reference), respectively, were evaporated to dryness. The remaining residue was redissolved in ethanol. This was followed by a solid phase extraction, using AASP C2 cartridges to separate BDP and its metabolites from unknown components extracted in the previous procedure. Subsequently quantification of drug and metabolites took place using h.p.l.c. The h.p.l.c. system consisted of a Perkin Elmer (series 4) quaternary pump equiped with a Waters Guard-PAK μbondapak C18 precolumn and a Chrompack (25 cm × 4.6 mm) analytical column (packed with Chrompack Chromospher C18, 5 μm) and a 254 nm u.v. absorbance detector (Waters Model 440). The mobile phase consisted of 50% water and 50% acetonitrile.

The limit of detection for BDP and its metabolites in stoma fluid is $\approx 20\ \text{ng ml}^{-1}$, but is difficult to estimate accurately because of large variability in stoma fluid composition. Using the methods described above, the *in vitro* recovery of BDP from either formulation added to stoma fluid was found to be 84–99%, independent of the formulation.

Marker bead detection

The frozen ileostomy bags were X-rayed at the department of Radiology of the Leiden University Hospital and the granules counted from the X-ray.

Data analysis and statistics

The cumulative amount of drug or number of markers recovered in ileostomy effluent was calculated for each subject-treatment combination. In addition, the transit time and the time until first appearance (lag time) were determined for both marker and drug. Mean values, s.d. and ranges are given. Mean transit time was calculated as the sum of the product of the amount of drug (respectively the number of markers) and midpoint time for each collection period, divided by the total amount of drug (respectively number of markers) recovered.

Comparisons were made for these parameters between the different formulations used in study 1 by paired *t*-tests

after overall ANOVA, and between formulation III (study 2) and the respective formulations used in study 1 by unpaired *t*-tests. Results are reported with 95% confidence intervals for the difference (95% CID).

Results

All subjects completed the study. The treatments were well tolerated, with mild headache (11 times) being the only reported adverse event. Laboratory testing of blood and urine revealed no clinically significant abnormalities.

For each study, the data of one subject were excluded from analysis, as the stoma effluent could not be processed adequately. In the first study, the stoma effluent of one subject yielded an oily substance after evaporation, which did not dissolve in methanol. In the second study, the sample of another subject was lost during processing. Beclomethasone could not be detected in any of the effluent collections. Beclomethasone-21-propionate (B21P) was found occasionally, but only in negligible amounts when compared with B17P. Hence, determinations of beclomethasone and B21P were disregarded.

The recovery of drug and marker beads occurred almost simultaneously. First appearance of drug occurred after on average 2 h, and drug recovery was complete after 8–9 h. The cumulative recoveries for BDP, B17P, total steroid (calculated as BDP + B17P) and the markers are summarized in Table 2, and a graphical presentation is shown in Figure 2. The gastrointestinal passage characteristics are tabulated in Table 3.

Because substantial intraindividual and interindividual variation in gastrointestinal passage exists, as judged by the total amount of markers excreted, the mean values for recovery of drug and marker beads were also calculated for each formulation using only the data from those volunteers from whom at least 75% of the markers were recovered (Table 2). These data give an indication of drug recovery under conditions of adequate gastrointestinal passage.

When combining the data for both studies, the overall recovery of the markers was 433/640 = 68%. In study 1, the mean cumulative marker recovery was 72% (range 5–100%) for formulation I, 76% (range 30–100%) for formulation II, and 58% (range 0–100%) for the reference capsule. These values did not differ significantly, which indicates that the gastrointestinal passage for each treatment in the first study was comparable. The mean cumulative marker recovery in the second study was 65% (range 20–100%), which is not significantly different from the recoveries found in the first study. Mean lag times for BDP (2.8 h) and markers (2.5 h) for all study treatments were not different (95%CID: −0.3/0.9). Mean transit times for BDP (4.3 h) and marker beads (4.3 h) were also identical (95%CID: −0.3/0.4). Analysis of the data from study 1 and 2, showed that gastrointestinal passage for both groups of volunteers were comparable. Correlation between cumulative marker and steroid recovery (Figure 3) showed that correlation

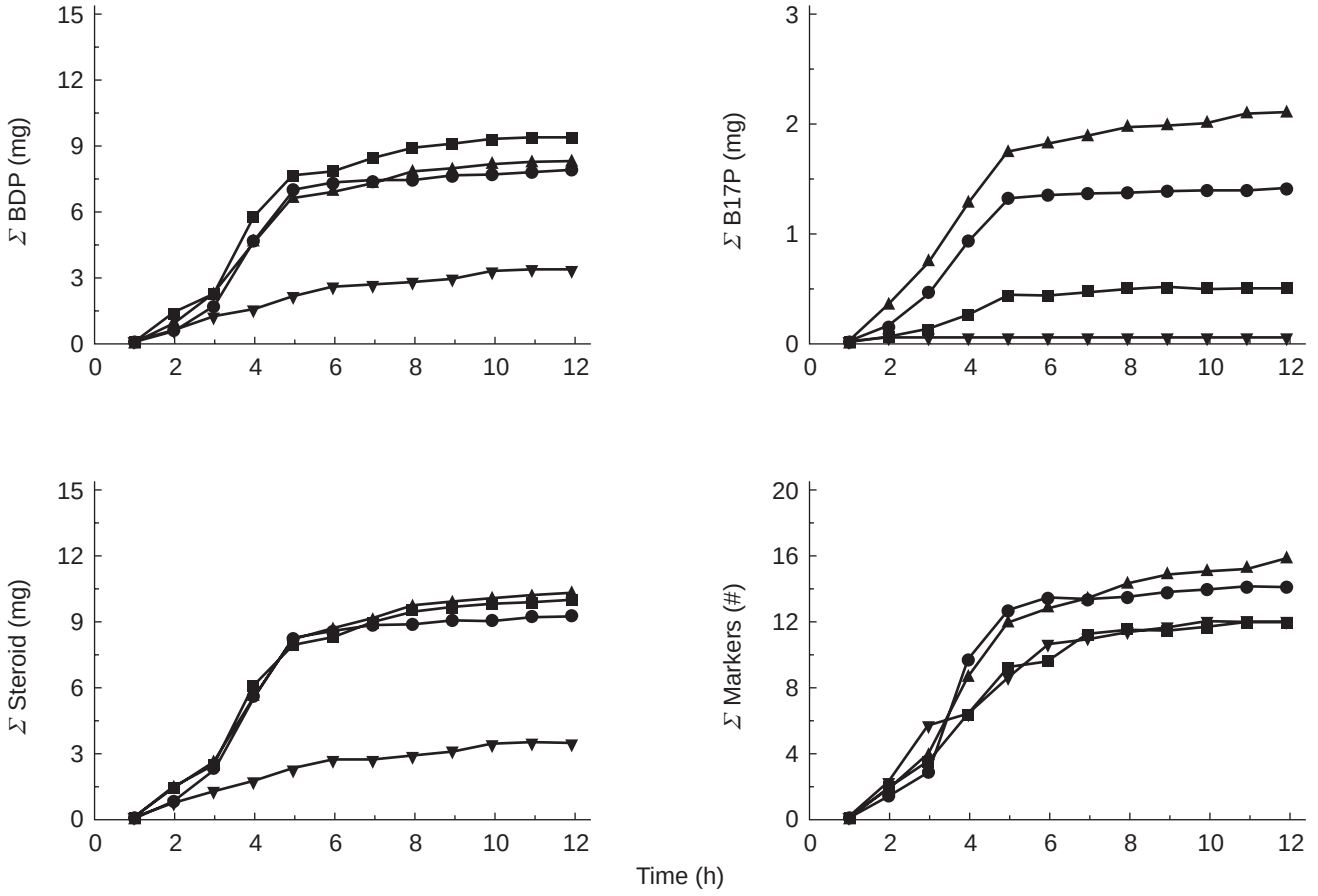

Figure 2 Average cumulative recoveries of beclomethasone dipropionate (Σ BDP), beclomethasone 17-monopropionate (Σ B17P), total steroid (Σ Steroid) and marker beads (Σ Markers) for the various treatments (formulation I ●, formulation II ▲, formulation III ■, reference capsules ▼).

Table 2 Cumulative drug and marker bead recovery in ileostomy effluent.

	Formulation I				*Formulation II*				*Reference capsule*					*Formulation III*			
	BDP	*B17P*	*MRK*	*STER*	*BDP*	*B17P*	*MRK*	*STER*	*BDP*	*B17P*	*MRK*	*STER*		*BDP*	*B17P*	*MRK*	*STER*
Subject	*(mg)*		*(#)*	*(mg)*	*(mg)*		*(#)*	*(mg)*	*(mg)*		*(#)*	*(mg)*	*Subject*	*(mg)*		*(#)*	*(mg)*
I-1	5.67	1.81	20	7.48	6.96	3.64	20	9.60	1.93	0.03	16	1.96	II-1	8.39	1.12	10	9.51
I-2	10.25	2.47	20	12.72	3.21	0.74	6	3.95	3.74	0.09	7	3.83	II-2	9.24	0.34	5	9.58
I-3	6.20	1.02	10	7.22	9.50	2.19	19	11.69	3.18	0	8	3.18	II-3	10.58	0.33	20	10.91
I-4	10.89	1.11	20	12.00	11.41	1.19	18	12.60	3.39	0.04	15	3.43	II-4	5.10	0.20	4	5.30
I-5	7.99	1.14	13	9.13	7.10	2.88	18	9.98	3.34	0.04	19	3.38	II-5	10.92	0.42	10	11.34
I-7	0.25	0.03	1	0.28	8.78	1.51	11	10.29	0.52	0.03	7	0.55	II-7	10.48	0.41	20	10.89
I-8	10.69	1.74	20	12.43	10.05	2.54	20	12.59	6.14	0.09	20	6.23	II-8	9.81	0.61	18	10.42
I-9	9.15	1.26	11	10.41	7.39	2.08	10	9.47	3.25	0.02	0	3.27	II-9	9.22	0.47	17	9.69
AVG$^{\$}$	7.64	1.32	14.4	8.96	8.05	2.10	15.3	10.02	3.19	0.04	11.5	3.23	AVG$^{\$}$	9.22	0.49	13.0	9.71
s.d.$^{\$}$	3.58	0.71	7.0	4.11	2.50	0.94	5.4	2.76	1.59	0.03	7.0	1.61	s.d.$^{\$}$	1.86	0.28	6.6	1.91
AVG#	9.38	1.78	20.0	11.16	9.00	2.48	19.0	11.29	3.70	0.05	17.5	3.75	AVG#	10.02	0.46	18.8	10.48
s.d.#	2.48	0.56	0	2.47	1.93	0.90	1.0	1.43	1.76	0.03	2.4	1.79	s.d.#	0.63	0.12	1.5	0.57
n	*n*=4				*n*=5				*n*=4					*n*=4			

Cumulative amounts of beclomethasone dipropionate (BDP), beclomethasone 17-monopropionate (B17P), totally recovered steroid (STER), radio-opaque markers (MRK). The average value for each parameter and each treatment was calculated for all subjects (AVG$^{\$}$) and the subjects in which more than 75% of the marker beads was recovered (AVG#).

Table 3 Gastro-intestinal passage characteristics.

	Formulation I				*Formulation II*				*Reference capsule*					*Formulation III*			
	Lag time (h)		*Transit time (h)*		*Lag time (h)*		*Transit time (h)*		*Lag time (h)*		*Transit time (h)*			*Lag time (h)*		*Transit time (h)*	
Subject	*BDP*	*MARK*	*BDP*	*MARK*	*BDP*	*MARK*	*BDP*	*MARK*	*BDP*	*MARK*	*BDP*	*Subject*	*MARK*	*BDP*	*MARK*	*BDP*	*MARK*
I-1	4	3	4.28	3.75	2	1	3.01	3.50	3	2	3.83	3.63	II-1	2	2	4.36	4.90
I-2	2	2	2.96	4.05	1	1	3.70	7.17	2	2	3.99	3.50	II-2	2	3	4.73	4.30
I-3	4	3	4.56	3.70	3	3	4.11	3.87	4	4	7.25	4.50	II-3	1	1	1.74	1.70
I-4	3	2	3.55	3.45	3	2	4.03	4.78	2	4	5.82	5.37	II-4	1	2	4.42	3.50
I-5	2	3	4.75	3.46	3	2	2.81	2.50	1	2	3.08	2.50	II-5	3	3	3.96	5.10
I-7	2	9	7.98	9.50	4	4	5.48	6.86	2	6	6.38	5.57	II-7	1	1	3.46	3.85
I-8	2	1	2.92	2.45	2	2	2.73	3.00	2	2	1.72	1.55	II-8	1	2	3.07	3.56
I-9	4	3	4.72	4.95	5	4	6.61	7.10	5	#	6.91	#	II-9	6	6	7.31	6.97
AVG	2.9	3.3	4.47	4.41	2.9	2.4	4.06	4.85	2.6	3.1	4.87	3.80	AVG	2.1	2.5	4.13	4.04
s.d.	1.0	2.4	1.61	2.17	1.2	1.2	1.37	1.94	1.3	1.6	2.00	1.47	s.d.	1.7	1.6	1.60	1.54

#No marker beads were detected for subject I-9. Hence, lag time and transit time could not be determined.

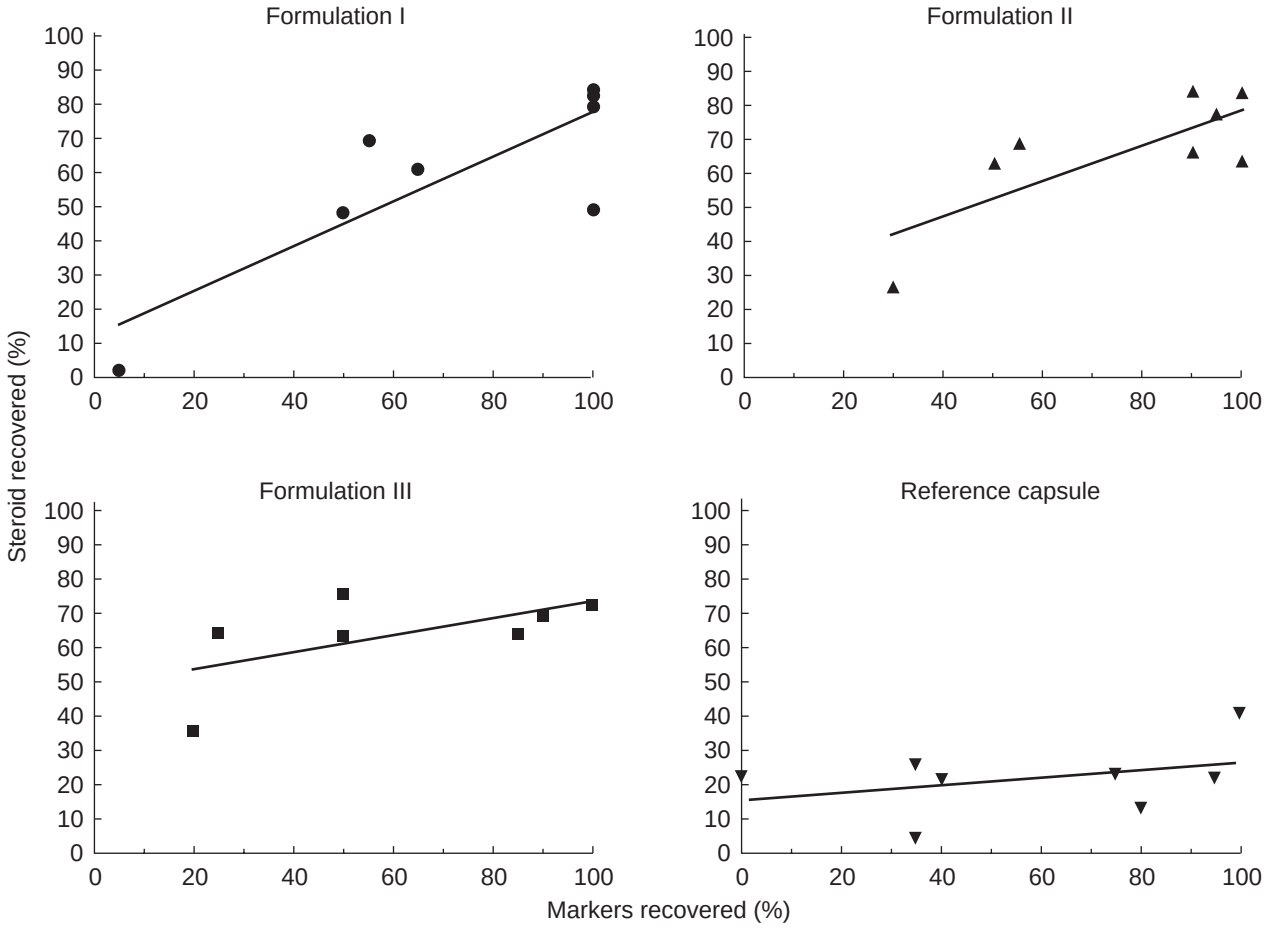

Figure 3 Scatter graphs showing the correlation between the percentage of excreted marker beads and the percentage of total drug that was recovered for the sustained-release formulations I-III and the capsules used for reference (reference capsules). Correlation coefficients were: 0.84, 0.78, 0.64 and 0.39 for formulation I, II, III and the reference capsules, respectively.

coefficients were 0.84 ($P<0.05$), 0.78 ($P<0.05$), 0.64 ($P>0.05$) and 0.39 ($P>0.05$) for formulation I, II, III and the capsule, respectively.

Over the total collection period, all experimental formulations released significantly less drug than the reference capsule during passage through the small intestine. From formulation I 60% (s.d. 27%; range 2–85%) of the dose was recovered in the stoma fluid. This value was 67% (s.d. 18%; range 26–84%) for formulation II and 22% (s.d. 11%; range 4–42%) for the capsule. Paired *t*-tests showed that for both formulations I and II the recovered dose differed significantly from the drug recovery for the capsule (95%CID: 22/54% and 29/62% for formulations I and II, respectively). Total steroid recovery from formulation III (study 2) was 65% (s.d. 13%; range 35–76%) of the administered dose. This was significantly higher than the recovery from the capsule (95%CID: 31/56%), but did not differ from the drug recoveries for formulations I and II (95%CID: −28/18% and −15/19%).

The cumulative recoveries of parent drug (7.6 and 8.1 mg) and metabolite (1.3 and 2.0 mg) were almost identical for formulations I and II in study 1 (95%CID for BDP: −4.1/3.3 mg; 95%CID for B17P: −1.6/0.3 mg). The cumulative total steroid excretion from formulation III did not differ significantly from the experimental tablets used in the first study. However, the amount of drug recovered as B17P after formulation III (0.5 mg) was clearly different from the values for experimental formulations I (1.3 mg) and II (2.0 mg) (95%CID: 0.3/1.4 mg and 0.9/2.1 mg) (see Figure 3).

Discussion

In the present study, the amount of BDP reaching the distal part of the small intestine was determined after oral administration of specially designed sustained-release formulations. All formulations were found to release significantly less drug during small intestinal passage than the control formulation, while having similar passage characteristics.

The studies were carried out in patients with an ileostomy, in whom the recovery of the steroid in the ileostomy effluent can be assumed to be representative of the amount delivered to this part of the gut in patients with an intact gastrointestinal tract. The experimental setup using two groups of volunteers was chosen because preparation III was developed after termination of study 1.

Together with the drug containing formulations, radio-opaque marker beads of 2–3 mm were administered to monitor differences in gastrointestinal passage. In fact, relatively slow gastrointestinal passage might reduce steroid recovery from stoma fluid, especially for sustained-release formulations. Therefore, a parallel evaluation of drug recovery was performed for data where at least 75% of marker beads were recovered.

The gastrointestinal passage, indeed, exhibited large inter and intraindividual variation. The overall recovery of the markers over both studies was 68%. This is in good agreement with earlier reported data [17]. On the basis of the *in vitro* dissolution profiles, it could be expected that the experimental formulations would release about half the amount of steroid in comparison with the capsule during small intestinal passage, thus delivering 3–4 times as much active drug to the distal part of the ileum when compared with the capsule. This idea is indeed reflected by the *in vivo* excretion data, which show a higher steroid recovery for the sustained-release formulations. Although the absolute amounts were slightly higher, the total amounts of steroid recovery from ileostomy effluent corresponded well with *in vitro* dissolution profiles.

The recoveries of total drug and marker were found to correlate significantly for the formulations I and II, which is in line with previous findings by Levine *et al.* [17]. For formulation III and for the reference capsule, however, this correlation was rather poor. For the reference capsule, the poor correlation between drug and marker recovery may be the result of systemic absorption of BDP or metabolite, but for formulation III this cannot be explained easily. It may however, be an indication for different *in vivo* dissolution and absorption characteristics for this formulation, as compared with formulations I and II. It was found that 60–70% of the drug content of the experimental formulations arrived at the desired site of action, which exceeds the recovery values reported by Levine *et al.* [17] who used cellulose acetate phtalate coated capsules containing plain BDP.

The cumulative steroid recovery indicates that for the formulations $\approx$11 mg of steroid (out of 15 mg BDP administered) will reach the distal part of the ileum, which is considerably more than the 4 mg of steroid recovery for the reference capsule. However, the amount of drug available for topical action will also depend on the actual release of BDP from the dosage form. If BDP is converted to B17P within several minutes of release, as has been shown to occur in artificial intestinal fluid [11], the amount of B17P in the effluent would be indicative for the therapeutic potency of a formulation. Although unpublished data from our group suggest that conversion of BDP to B17P in stoma fluid at 37° C may be highly variable, the recovery of B17P for the sustained release formulations by far exceeds that for the reference capsules. Because of the apparent instability of BDP in stoma fluid, BDP recovered from ileostomy effluent is believed to stem mainly from the undissolved remainder of the administered formulation. Thus, based on BDP/B17P recovery, formulations I and II appear to be the most favourable dosage forms for delivering BDP to the distal part of the ileum. However, whether this will be sufficient for topical anti-inflammatory action in IBD patients, remains to be determined. Especially when BDP action at the site of the colon is considered, a possible drawback is that changes in faecal viscosity may affect the release of BDP from the applied formulation.

The data on the cumulative drug recovery indicate that after administration of the dose of BDP with the sustained-release tablets a substantial amount of drug was not recovered over the 10–12 h sampling period. Individual and mean data indicate that it is reasonable to assume that no substantial amounts of drug would be recovered after 8–9 h of sampling, even if fluid sampling were extended over a longer period. The present findings therefore suggest that after administration of 15 mg BDP in the formulations tested, a substantial part of the dose of BDP may be available for absorption in the small intestine. This was also true with data from only those subjects in which marker bead recovery was almost complete; in these cases over 25% of the administered dose is possibly absorbed. Hence, it is conceivable that side-effects might occur with either formulation, especially after chronic administration [9, 18]. However, administration of an Eudragit® S-coated formulation of the poorly absorbed prednisolone metasulphabenzoate for 12 weeks to patients with ulcerative colitis has previously been shown to cause no systemic side-effects at therapeutically effective doses (30–60 mg daily) [19].

In the context of the treatment of inflammatory bowel disease, the ideal characteristics of a dosage form may be the simultaneous occurrence of low absorption of steroid during small intestinal passage and delivery of active substance at the distal ileum, as indicated, in the case of BDP, by a high recovery of steroid with a high fraction of B17P in the stoma effluent. From the formulations in the present study therefore formulation II appears to be the most favourable.

In conclusion, the sustained-release BDP preparations used in this study show advantageous gastrointestinal passage characteristics in comparison to a plain capsule for treatment of inflammatory bowel disease. However, therapeutic effectiveness and the occurrence of systemic effects remain to be determined.

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