Coating of Oral Beclomethasone Dipropionate Capsules With Cellulose Acetate Phthalate Enhances Delivery of Topically Active Antiinflammatory Drug to the Terminal Ileum

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Selective delivery of orally administered topically active antiinflammatory drugs to the terminal ileum and ascending colon could be potentially useful for patients with inflammatory bowel disease involving these sites. Because topical beclomethasone dipropionate (BDP) enemas have been used successfully in the treatment of distal idiopathic colitis, oral formulations of this drug were studied. Enteric-coated or uncoated capsules containing BDP were administered in a single-dose protocol on separate days to 6 healthy volunteers with postcolectomy ileostomies. Ileostomy effluent was collected for a minimum of 8 h and analyzed by high-performance liquid chromatography for BDP, its pharmacologically active derivative beclomethasone monopropionate (BMP), and inactive beclomethasone alcohol. Cellulose acetate phthalate coating of oral BDP capsules significantly increased the mean percentage recovery of BDP + BMP in ileal effluent (43.0% ± 24.1%) compared to uncoated BDP capsules (13.5% ± 8.5%, $p < 0.05$, Student's paired t-test). We conclude that oral cellulose acetate phthalate-coated BDP capsules may merit clinical trial in Crohn's ileitis and ileocolitis or in conjunction with BDP enemas for topical treatment of ulcerative colitis involving the whole colon.

Beclomethasone 17,21-dipropionate (BDP) is a topical corticosteroid that effectively treats asthma, allergic rhinitis, nasal polyposis, middle ear effusion, and rheumatoid larynx (1–5). When used in low doses, BDP has been shown to be free of many of the deleterious side effects associated with systemically absorbed adrenocorticosteroids. This is undoubtedly related to the surface-active antiinflammatory properties of BDP, which has been reported to be 5000 and 500 times more potent topically than hydrocortisone and dexamethasone, respectively, as measured by vasoconstriction assay (6,7). Topical administration of BDP as an inhalant to prednisone-dependent asthmatics has permitted many of these patients to slowly decrease and even completely discontinue their oral prednisone. Fortunately, these patients remain in remission and lose symptoms and signs of hyperadrenocorticism (1–3).

Many patients with idiopathic inflammatory bowel disease who require long-term or intermittent therapy with oral or rectal formulations of systemically absorbed adrenocorticosteroids suffer from side effects of these medications. Obviously, it would be

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Abbreviations used in this paper: BDP, beclomethasone 17,21-dipropionate; BMP, beclomethasone monopropionate; BOH, beclomethasone alcohol; CAP, cellulose acetate phthalate; HPLC, high-performance liquid chromatography.

preferable to treat these patients with a locally acting drug that could be effective in such low doses that insufficient drug would be absorbed to produce systemic toxicity. Beclomethasone 17,21-dipropionate may fulfill these requirements. Topically acting retention enemas of BDP in doses of 0.5–2.0 mg have been used successfully to treat patients with distal idiopathic ulcerative colitis and idiopathic proctitis without producing clinical evidence of Cushing's syndrome or measurable suppression of the hypothalamic-pituitary-adrenal axis (8–11). Retention enemas of BDP and other topical steroids may be helpful for rectal Crohn's disease as well (9,12).

Selective delivery of orally administered BDP to the distal small intestine and proximal colon would be potentially therapeutic for patients with Crohn's disease and extensive ulcerative colitis, as these sites of bowel inflammation are either inaccessible or are not reliably reached by rectal drug administration (13–18). Contradictory reports on the treatment of idiopathic inflammatory bowel disease with orally administered, topically acting corticosteroids have been published (19–21) but these medications were not specifically formulated to limit acid-peptic degradation or proximal small intestinal absorption.

Oral controlled-release products are usually designed to deliver bioavailable drug to the more proximal portions of the small intestine to enhance systemic absorption by limiting gastric acid destruction and modulating drug release from the preparation (22–31). Other strategies could be employed to enhance more distal drug delivery. For example, drug ingestion with meals could be avoided because food slows gastric emptying (32,33) and changes the gastric luminal environment. Motility-modifying drugs (34–36) could improve distal gastrointestinal tract drug delivery (e.g., metoclopramide) or prolong the drug-mucosa contact time (e.g., narcotics). Unfortunately, these strategies are complicated by the interindividual and intraindividual variability in motility (35,37) and the paucity of information on gut motility in disease (35,38), including idiopathic inflammatory bowel disease.

In this study, our goal was to develop an oral controlled-release formulation of BDP that would enhance delivery of pharmacologically active drug to the terminal ileum and right colon. Our approach was to modify the drug vehicle (gelatin capsule) with enteric coatings (bioerodable polymers) (23, 24,30,39), such as shellac and cellulose acetate phthalate (40,41), and to test these formulations in normal ileostomates. Recovery of adequate amounts of pharmacologically active drug in ileostomy effluents after ingestion of the various formulations of BDP would suggest that there would be selective delivery of antiinflammatory drug to the terminal ileum and right colon in patients with intact gastrointestinal tracts.

Materials and Methods

In Vitro Analysis of Enteric Coatings

The enteric coatings to be tested in ileostomate volunteers were required to be insoluble in acid buffer and soluble in more neutral buffers. Standard 5 × 10-mm size gelatin capsules (Eli Lilly, Indianapolis, Ind.) were dipped by hand five times into solutions of cellulose acetate phthalate (CAP) or pharmaceutical shellacs. Cellulose acetate phthalate was formulated by dissolving 75 g of cellulose acid hydrogen phthalate (Eastman Kodak, Rochester, N.Y.) in 50 ml of absolute ethanol (U.S. Industrial Chemicals, Tuscola, Ill.) and then adding 19 ml of dimethyl phthalate (Eastman Kodak) and acetone (Baker Chemicals, Phillipsburg, N.J.) q.s. to 1000 ml. The pharmaceutical shellac Opaglos (Colorcon Inc., West Point, Pa.) was diluted 1:1 by volume with acetone or absolute ethanol to reduce viscosity and to facilitate even coating. Capsule disintegration times of these coated capsules, plain uncoated gelatin capsules, and two commercial enteric microsphere preparations with established disintegration characteristics (Johnson & Johnson Products Inc., New Brunswick, N.J.; McNeil Pharmaceutical, Fort Washington, Pa.) were individually assessed by placing them in 200 ml of 0.1 M sodium phosphate buffers at pH 2, 6, and 7.5 and stirring constantly with a magnetic bar at ambient room temperature (22°–29°C). Capsule disintegration time was defined as the elapsed time before the two capsule halves broke apart or the microspheres had completely dissolved.

Assay for Beclomethasone 17,21-Dipropionate and Derivatives

A modified high-performance liquid chromatography (HPLC) technique for quantification of BDP, pharmacologically active beclomethasone 17-monopropionate (BMP), and pharmacologically inactive beclomethasone alcohol (BOH) from ileostomy effluent was developed by modifying previously published procedures (42–44). The HPLC assay was perfected by testing pure solutions of BDP, BMP, and BOH and ileostomy effluent samples spiked with known quantities of these drug standards (Schering Corp., Bloomfield, N.J.). Ileostomy effluent samples were diluted 1:2 by weight with deionized water and mixed with 100 μl of internal standard, 11 μg/ml of 17-hydroxyprogesterone (Steraloids Inc., Wilton, N.H.). Three-gram aliquots were extracted three times with 10 ml of nanograde dichloromethane (Mallinckrodt Inc., Parris, Ky.) by shaking for 1 min and centrifuging for 2 min at 2000 rpm. The combined extracts were washed successively with 2 ml of 0.1 N NaOH and 4 ml of deionized water (by shaking for 30 s and centrifuging for 1 min) and then dried under air in a 40°C water bath. The dried extract was taken up in 1 ml of methanol (Burdich & Jackson Laboratories, Muskegon, Mich.), added to 1.1 ml of deionized water, mixed, and applied to a C18 Bond-Elute column (Analytichem International, Harbor City, Calif.).

This was washed with 10 ml of deionized water and 5 ml of 45% methanol and then eluted with 2 ml of methanol. Fifty microliters of 20 μg/ml progesterone (Steraloids Inc.) was added to the eluate as a second internal standard, dried in a 40°C water bath, and taken up in 100 μl of methanol. Ten-microliter aliquots were injected into a Waters model 204 HPLC apparatus equipped with a 3.9-mm × 30-cm μ-Bondapak C18 column and a guard column filled with Bondapak C18/Corasil (Waters Associates Inc., Milford, Mass.) maintained at room temperature and operating at 4500 psi using a mobile phase consisting of 55% methanol and 45% 50-mmol/L sodium phosphate buffer, pH 3.0, at a flow rate of 3 ml/min. The eluate was monitored by a model 440 ultraviolet absorbance detector (254 nm) connected in series to a model 481 variable wavelength detector (238 nm) and a model 730 dual channel data processing module (Waters Associates). Under these conditions BOH, 17-hydroxyprogesterone, BMP, progesterone, and BDP eluted at 3.1, 6.0, 7.8, 11.6, and 21.3 min, respectively. Beclomethasone alcohol, BMP, and BDP concentrations were calculated using the internal standard (17-hydroxyprogesterone) peak-height ratio method (44).

Study Protocol

All 6 volunteers had undergone total proctocolectomy and ileostomy for ulcerative colitis at least 1 yr before this study. Ileostomate volunteers were selected for this study because their small intestinal transit is the same as normals with intact gastrointestinal tracts (45–49). At the time of their surgeries, they had no evidence of small intestinal disease and were not suspected of having Crohn's disease. All were asymptomatic at the time of the study and did not have excessive ileostomy output. All were female, aged 31–68 yr (mean 48.6 yr). No male volunteers were available for the study. The number of volunteers studied was limited to six by available resources.

The volunteers were admitted to the University of Washington Clinical Research Center where various BDP formulations and radiopaque markers were administered in separate capsules during different study sessions at least 1 wk apart (Figure 1). After an overnight fast, a single 5-mg dose of BDP with 100 mg of lactose filler (MCB, Gibbstown, N.J.) was administered in one of three vehicles with 100 ml of water: (a) in an uncoated gelatin capsule (control) (n = 6); (b) in a capsule with five coats of CAP (n = 6); or (c) in a capsule with five coats of pharmaceutical shellac diluted 1:1 with acetone (n = 3) or ethanol (n = 3). The volunteers were not informed of which BDP formulations they ingested. The BDP dose was given with 14 3-mm size radiopaque markers in two capsules with the corresponding enteric coating and with 20 1-mm size markers in two uncoated capsules to assess intestinal transit time (50,51) and the effects of enteric coating on marker recovery (Figure 1). Meals were withheld for an additional 1.5 h before a regular diet was resumed. Ileostomy effluent was collected and frozen at ~1–2-h intervals for at least 8 h. To be certain that an 8-h collection interval was adequate, ileostomy effluent was collected in a pilot study for 22.5 h after administration of uncoated or CAP-coated BDP capsules. To determine if BDP was absorbed, hourly blood samples were obtained in another pilot study from 1 volunteer for at least 9 h after administration of CAP or shellac-coated BDP or uncoated control BDP capsules.

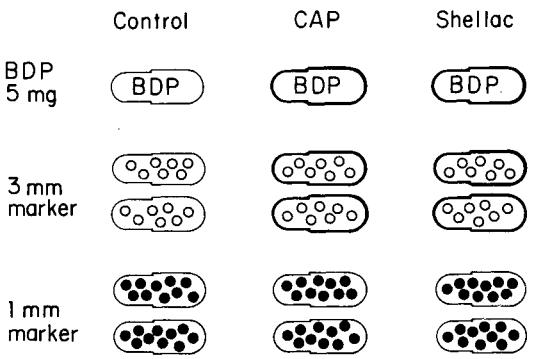

Figure 1. Capsules administered for each study session.

Each interval ileostomy effluent collection was weighed and the pH was measured (Nitrazine paper, Squibb & Sons Inc., Princeton, N.J.). Aliquots from each effluent collection were frozen together with the remaining effluent at −20°C for subsequent analysis. The aliquots were coded and blindly analyzed for BDP, BMP, and BOH by HPLC within 2 wk of collection. Total recovery of BDP and pharmacologically active BMP (6,7) for each study session was calculated and expressed as BDP, BMP, or BDP + BMP recovery as a percentage of the administered 5-mg dose of BDP. The ileostomy effluent collections were x-rayed and marker recoveries were determined for each study session. Sera from 1 volunteer were analyzed by HPLC for detectable BDP, BMP, and BOH. Drug and marker recoveries in ileostomy effluent were averaged and statistically compared using the Student's *t*-test (52).

A Notice of Claimed Investigational Exemption for a New Drug for the use of BDP in volunteers was filed with the U.S. Food and Drug Administration in 1982. The study protocol was approved by the University of Washington Human Subjects Review Committee and all volunteers provided written, informed consent prior to participation.

Results

In vitro analysis of the CAP and shellac test coatings and the two commercial enteric preparations generally showed reduced capsule disintegration times with increased buffer pH (Table 1). Uncoated gelatin capsules readily disintegrated in all three test buffers (<1 h). All but one of the enteric-coated preparations resisted disintegration at pH 2. The relatively short disintegration time of the undiluted shellac-coated capsule at pH 2 was attributed to uneven coating secondary to the high viscosity of this preparation. The diluted shellac-coated capsules had 4- to 12-fold greater disintegration times than CAP at pH 6 and comparable times at pH 7.5. The two commercial enteric microsphere prepara-

Table 1. Comparison of Capsule Disintegration Times of Individual Enteric-Coated Gelatin Capsules and Commercial Products in 0.1 M Sodium Phosphate Buffers of Varying pH

Capsule	Capsule disintegration time (h)		
	pH 2	pH 6	pH 7.5
Control (uncoated)	0.4	0.9	0.8
Cellulose acetate phthalate	>24	2.3	1.9
Shellac (undiluted)	3.9	16	2.7
Shellac:acetone	>24	24	1.9
Shellac:ethanol	24	8	2.1
Enteric microspheres[a]	>24	1.5	1.3
Enteric microspheres[b]	>24	1.2	1.0

[a] Johnson & Johnson Products, Inc., New Brunswick, N.J. [b] McNeil Pharmaceutical, Fort Washington, Pa.

tions resisted disintegration at pH 2 and readily disintegrated at pH 6 and pH 7.5.

High-performance liquid chromatography analyses of extracts of fresh ileostomy samples spiked with BDP standard revealed a 40%–100% conversion of BDP to BMP. This was eliminated by autoclaving the samples before spiking with the drug standards. Analyses of extracts of autoclaved ileostomy samples spiked to 1 μg/ml with BDP, BMP, and BOH yielded a mean percent relative recovery of 90% calculated from 20 assays. Analyses of frozen samples yielded steady recoveries of drug standards up to 2 wk after spiking. A control ileostomy sample was spiked with BDP to 1.145 μg/ml, frozen and run with each experimental sample assay. The precision of the method assessed as the percent coefficient of variation from 23 assays of this control was found to be 5.1%. The method shows a linear detector response to at least 100 μg/ml and the sensitivity was <50 ng/g for each steroid. As an additional check of the purity of the eluted steroids, the ratios of the sample peak heights at 254 and 238 nm were compared to the corresponding ratios in the standard and control (44).

Table 2. Mean Drug Recoveries in Ileostomy Effluent Following Single-Dose Administration of Beclomethasone 17,21-Dipropionate Formulations[a]

Drug	Control (n = 6)	CAP (n = 6)	Shellac (n = 6)
BDP	6.7 ± 3.8	24.8 ± 25.1	8.9 ± 7.0
BMP	6.8 ± 5.7	18.2 ± 13.7[b]	9.8 ± 9.2
BDP + BMP	13.5 ± 8.5	43.0 ± 24.1[b]	18.8 ± 13.5

BDP, beclomethasone 17,21-dipropionate; BMP, beclomethasone monopropionate; CAP, cellulose acetate phthalate. [a] Percentage of 5-mg dose ± SD. [b] $p < 0.05$ compared to control, Student's paired *t*-test.

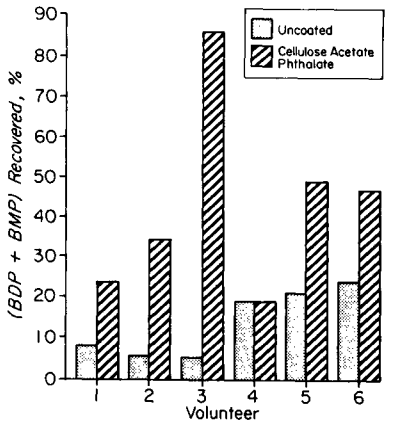

Figure 2. BDP + BMP recovery from ileostomy effluent as percentage of 5-mg dose in individual volunteers. Cellulose acetate phthalate coating enhanced recovery of BDP + BMP over uncoated control in 5 of 6 volunteers.

The mean percentage recovery of BDP and pharmacologically active BMP in ileostomy effluent from the 6 volunteers after oral administration of CAP-coated oral BDP (43.0% ± 24.1%) was superior to that of the shellac-coated preparation (data for shellac-acetone and shellac-ethanol combined, 18.8% ± 13.5%) and of the uncoated BDP control formulation (13.5% ± 8.5%) (Table 2, Figure 2). The mean percentage recovery of BOH was not significantly different after administration of the CAP-coated, shellac-coated, or uncoated BDP preparations (<3.0%). Analysis of ileostomy effluent collected for 12.5 additional hours after predetermined 10-h study periods following administration of either uncoated control BDP or CAP-coated BDP to one of the volunteers, did not yield any additional BDP, BMP, or BOH.

Typical drug recoveries in ileostomy effluent as a function of time are illusted in Figure 3. Beclomethasone 17,21-dipropionate and BMP generally appeared in the ileostomy effluent at the same time, 2–6 h (mean 4 h) after oral administration. This did not vary significantly with the different enteric coatings tested in this study.

The total recovery of all administered radiopaque markers was 63% (384 of 612). The overall recoveries of the 1- and 3-mm size markers administered in uncoated capsules and the 3-mm size markers in coated capsules were 52% and 92%, respectively ($p < 0.01$). However, paired analyses comparing recoveries of 3-mm size markers in uncoated capsules with 3-mm size markers in CAP-coated or shellac-coated capsules did not reveal statistically significant differences (Table 3). Recoveries of 1-mm size markers compared with 3-mm size markers were not significantly different on paired analysis, with the exception of markers in shellac-coated capsules

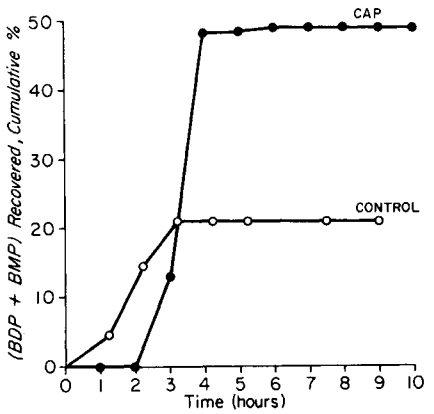

Figure 3. Cumulative BDP + BMP recovery as a function of time in a representative volunteer after administration of uncoated BDP (control) and CAP-coated BDP.

Table 3. Mean Marker Recovery in Ileostomy Effluent Following Administration of Beclomethasone 17,21-Dipropionate and Marker Capsules[a]

Marker	Control[b] (n = 6)	CAP[b,c] (n = 6)	Shellac[c] (n = 6)
3-mm size (same enteric coating as BDP test capsule), percentage of 14 administered	64 ± 43 (uncoated)	93 ± 21	93 ± 7[d]
1-mm size, percentage of 20 administered	45 ± 35 (uncoated)	65 ± 15 (uncoated)	40 ± 35 (uncoated)

BDP, beclomethasone 17,21-dipropionate; CAP, cellulose acetate. [a] Values expressed as mean ± SD. [b] p = not significant for 3-mm marker recovery compared to 1-mm marker recovery, Student's paired *t*-test. [c] p = not significant for 3-mm and 1-mm marker recovery from enteric-coated marker capsules compared to control, Student's paired *t*-test. [d] Some marker capsules with shellac:acetone coating were recovered intact in ileostomy effluent.

which were recovered in undissolved capsules in ileostomy effluent in 2 of the 6 volunteers. The 3- and 1-mm size markers generally appeared in the ileostomy effluent at the same time as BDP and BMP.

Ileostomy effluent mass collected, collection period duration, flow rate, and pH range were comparable for the control, CAP, and shellac coating study sessions (Table 4). Serum concentrations of BDP, BMP, and BOH did not exceed a 10-ng/ml detection limit in 1 volunteer for up to 9 h after administration of CAP- or shellac-coated BDP or uncoated control BDP capsules.

Discussion

Cellulose acetate phthalate has long been known to be an excellent enteric coating since its description by Hiatt in 1940 (53). It resists acid dissolution in the stomach, but where and how CAP breaks down in the gastrointestinal tract has been debated. Our in vitro assay results are consistent with prior studies (54) and show that raising the pH of a phosphate buffer to 6 or 7.5 results in disintegration of CAP-coated capsules. However, dissolution within the intestine may result from hydrolysis by luminal esterases (55). Past investigations have suggested that CAP coatings dissolve in the proximal small intestine (54,55). This led to the commercial production of various CAP-coated drugs, which bypass the stomach and can be more readily absorbed in the proximal jejunum. However, it has been appreciated recently that CAP coating of drugs may enhance their delivery to more distal sites in the small bowel and proximal colon (56) and our study with CAP-coated BDP confirms this.

The mechanisms by which pharmacologically active BMP and BDP were delivered to the terminal ileum were not directly determined by this study. The relative contributions of the resistance of CAP to dissolution and of the resistance of BDP to degradation and absorption are unknown. Presumably, acidic degradation of BDP was prevented by CAP coating, and intact BDP within its capsule entered the small intestine. The in vitro assay demonstrated the resistance of the shellac coating to acidic degradation, but its greater resistance (prolonged disintegration time) to degradation in pH 6 buffer compared with CAP coating did not confer any advantage when administered to the ileostomate volunteers. In fact, dissolution of the shellac coating was quite inconsistent in the volunteers because BDP + BMP recoveries in ileostomy effluent were not improved and shellac-coated marker capsules were occasionally passed intact.

Little is known about the luminal metabolism of

Table 4. Ileostomy Effluent Parameters Following Administration of Beclomethasone 17,21-Dipropionate and Marker Formulations[a]

Parameter	Control (n = 6)	CAP[b] (n = 6)	Shellac[b] (n = 6)
Total effluent collected (g)	261 ± 115	224 ± 60	226 ± 64
Collection period (*h*)	10 ± 1.9[c]	9.2 ± 0.5[c]	10.2 ± 1.8
Effluent flow rate (g/*h*)	25.8 ± 10.3	24.5 ± 7.4	22.5 ± 6.8
Effluent pH, range	6.5–7.5	6.5–7.5	6.0–7.5

CAP, cellulose acetate phthalate. [a] Values expressed as mean ± SD. [b] p = not significant for each parameter compared to control, Student's paired *t*-test. [c] One volunteer remained under study for 12.5 h beyond a predetermined 10-h collection period to assess late BDP and BMP recovery (see text). The additional 12.5 h is not included in the mean collection period for all 6 volunteers.

and possible destructive action of gut flora on orally administered BDP. It is perhaps surprising that any BDP or BMP was recovered in the ileostomy effluent when BDP was administered in uncoated capsules, which presumably dissolved and released BDP in the acidic environment of the stomach. However, other investigators have reported recovery of significant amounts of BDP and BMP in the feces up to 4 days after normal volunteers with intact gastrointestinal tracts were given oral BDP in a microfine suspension or within a gel capsule (42). These observations may be explained by fortuitous, rapid gastric emptying of the BDP capsule before it dissolves, hypochlorhydria, incomplete degradation by gastric acid, poor absorption, resistance to luminal chemical and enzymatic breakdown, resistance to bacterial degradation, and enhancement of all of these factors by rapid intestinal transit. Additionally, we have identified BDP in a morning bowel movement from a patient with distal ulcerative colitis more than 8 h after administration of a nighttime BDP retention enema (unpublished observations).

Our observation in the present study that the conversion of BDP to BMP was prevented by autoclaving ileostomy samples before spiking with the BDP standard suggests that bacterial or enzymatic destruction was inhibited by this procedure. This suggests further that our reported recoveries of BDP and BMP may be underestimates because of possible bacterial or enzymatic degradation during the 1–2 h between ileostomy effluent collections for freezing.

The recoveries of BDP and BMP in ileostomy effluent were quite variable among the volunteers, but paired analyses revealed statistically significant differences when CAP-coated BDP was compared with uncoated BDP (Table 2, Figure 2). The lower recoveries of BDP and BMP after administration of the uncoated control BDP capsules are not likely due to incomplete collection of ileostomy effluent during control sessions because (a) additional BDP, BMP, and BOH were not detected in ileostomy effluent for 12.5 h beyond the usual collection period in 1 volunteer; (b) marker recoveries were not significantly different in all three study sessions (Table 3); and (c) the ileostomy effluent collection period, amount collected, flow rate, and pH range did not differ in all three study sessions (Table 4). The variability in recoveries of drugs and markers may be explained by interindividual and intraindividual differences in gut motility, as well as variations in luminal absorptive and degradative processes for BDP. These processes probably account for the $<100\%$ recovery of administered BDP as well (42).

The recoveries of radiopaque markers among the volunteers for each study session were variable and exceeded 90% when they were administered in enteric-coated capsules (Table 3), but shellac-coated marker capsules were passed undissolved in 2 of 6 volunteers. Differences in 3-mm size marker recoveries were not statistically significant during the enteric-coated and uncoated control study sessions. There was a statistically significant difference in overall recovery of 3-mm size markers in coated capsules versus 1- and 3-mm size markers in uncoated capsules. This may have been due to gastric retention of these latter markers after dissolution of their plain gelatin capsule with subsequent delayed delivery into the small intestine. The difference was not likely caused by the different sizes of the markers (46–48,50). Although the paired analyses did not show significant differences in marker recoveries for each study session, administration of a larger number of marker capsules may have shown otherwise.

Other controlled release systems have been described for delivering oral 5-aminosalicylic acid to the small intestine and colon for treatment of Crohn's disease and ulcerative colitis (57–61). Oral CAP-coated BDP may offer certain advantages over these preparations because (a) BDP and BMP may be inherently resistant to intraluminal degradation and systemic absorption from the lumen as compared to 5-aminosalicylic acid (60–63) and (b) BDP and BMP could be better tolerated or be more effective than 5-aminosalicylic acid in selected patients.

In summary, oral administration of CAP-coated BDP capsules to healthy ileostomates produces a variable but significantly increased delivery of pharmacologically active BMP and BDP to the terminal ileum compared with uncoated capsules of BDP. A reliable extraction procedure and HPLC analytical technique for measuring BDP and BMP in ileostomy effluent has been developed. This can serve to evaluate other oral controlled release formulations of BDP that may further improve selective terminal ileal delivery of pharmacologically active medication. Repetitive dose experiments will be necessary to determine appropriate dosing intervals, to assess possible direct food interactions or indirect disruption of terminal ileal drug delivery by food-associated alterations in gut motility, and to determine dose-related hypothalamic-pituitary-adrenal axis suppression. Cellulose acetate phthalate-coated BDP or other controlled release formulations of BDP merit clinical trial in patients with Crohn's ileitis and ileocolitis or in patients with ulcerative pancolitis as an adjunct to BDP enema therapy.

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