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Predictive modelling of the behaviour of a controlled release buflomedil HCl formulation using scintigraphic and pharmacokinetic data

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Summary

A combined scintigraphic and pharmacokinetic study was carried out in seven healthy subjects to evaluate the effect of meal size on the behaviour of an oral controlled release preparation of buflomedil HCl (600 mg). Micronised resin radiolabelled with ^{111}In was incorporated into the tablets which were administered to subjects after either a light (646 kJ) or a heavy (3327 kJ) breakfast in a randomised cross-over study. The gastrointestinal transit of the formulation, and the buflomedil serum concentrations were monitored for 25 h following administration of the tablets. The mean gastric residence times ($\pm$SD) of the formulation after the heavy and light breakfasts were 6.2 ± 2.3 and 2.2 ± 0.2 h, respectively ($p < 0.01$; Wilcoxon Signed Rank test), however, transit through the small intestine was unaffected by the meal size. Complete disintegration of the tablet occurred in the large intestine in all cases, apart from in one subject where disintegration occurred in the small intestine after administration with a heavy breakfast. The peak serum drug concentration occurred at 4 h following a light meal (1.87 ± 0.53 μg ml^{-1}) and at 6 h following the heavy meal (2.16 ± 1.0 μg ml^{-1}). The area under the serum-concentration time curve was 21.7 ± 8.1 μg ml^{-1} h for the light meal and 24.8 ± 10.5 μg ml^{-1} h for the heavy meal. The transit data and the in vivo release rates of the radioactive marker from the tablet were used in a computer simulation to demonstrate that the observed serum concentrations could result from predominantly small intestinal absorption of the drug with a smaller contribution from colonic absorption.

Introduction

Buflomedil hydrochloride (Loftyl®, Lofton® and Bufedil®, Abbott Laboratories) is a vasoactive drug which improves perfusion in the impaired microcirculation of the peripheral and central vascular beds. The mode of action is not fully understood but the drug is known to exert a non-specific antagonism on α-adrenoceptors and is a weak calcium-channel antagonist.

The normal oral dosage regimen is 450–600 mg per day, usually administered in two to four di-

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vided doses. It is also available as a once-per-day controlled release formulation based on an alginate matrix consisting of two alginate salts in which drug release may be controlled by varying the ratio of alginate salts in the formulation (U.S. Patent 4,842,866). Nicholson et al., (1990) have proposed that zero-order release from this type of mixed alginate system is governed by the movement of solvent into the dry tablet core, based on in vitro experiments. However, in vivo, this may be further complicated by the more dynamic environment in which erosion of the hydrated gel layer could predominate over diffusional processes occurring after hydration.

The intake of food may influence this process in a number of ways. Firstly, the meal will alter gastric pH (Wilson and Washington, 1988) which may in turn alter the rate of formation of the matrix and the drug solubility. Secondly, the calcium content of the meal may affect the gelation of the alginate matrix and finally, the diffusion/erosion properties of the alginate matrix, once formed, may display some sort of pH dependency. All these factors may alter the rate of release of the drug. Drug release from a system may be affected by conditions of varied food intake which may alter the pharmacokinetic profile of the formulation (Wilson et al., 1989).

In the present study, gamma scintigraphy has been used to investigate the behaviour of a controlled release formulation of an ^{111}In-labelled buflomedil HCl tablet in man following administration with either a light or a heavy breakfast. The mean transit data and release characteristics of the formulation were used to construct a prediction of the serum concentration-time profile after light and heavy breakfasts. These data were compared with the data obtained by blood sampling using a commercial computer modelling package adapted for pharmacokinetic analysis (Washington et al., 1990).

Materials and Methods

Buflomedil HCl controlled release tablets containing 600 mg buflomedil HCl and 10 mg of micronised Amberlite resin (IRP-69, Rohm and Haas, Croydon, Surrey) radiolabelled with approx. 1 MBq ^{111}In were manufactured in the Department of Pharmaceutical Sciences, University of Nottingham, under the direction of Abbott Laboratories Ltd. In vitro dissolution of the ^{111}In-labelled buflomedil formulation was measured in water (USP XXI apparatus II) at 60 rpm (Fig. 1).

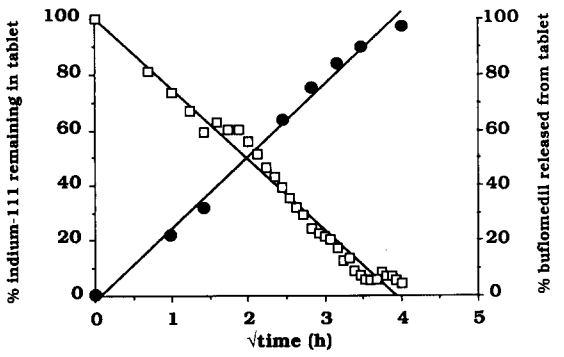

Fig. 1. Higuchi plots (% released vs $\sqrt{\text{time}}$) for dissolution of the tablet in vivo measured by amount of indium-111 associated with the tablet (□) after high fat meal compared with release of drug in vitro (●).

Seven healthy male volunteers, age range 19–29 years, mean weight 73 kg, participated in the study. The subjects were screened prior to entry to the trial and were excluded if they failed to satisfy the physician of their fitness to participate according to specific exclusions detailed in the protocol. The subjects gave written, informed consent prior to entry into the trial and were advised that they were free to withdraw from the trial at any time. Ethical approval for the study was obtained from the University of Nottingham Ethical Committee and permission to administer the isotopes from the Department of Health.

Each volunteer participated in the trial on two occasions; once after a light breakfast (toast, marmalade and orange juice, calorific value 646 kJ) and on another occasion after a heavy breakfast (cooked English breakfast, calorific value 3327 kJ) (Wilson et al., 1989). Allocation of the subjects to the groups was randomized and the cross-over study was performed one week later.

The subjects stood in front of the gamma camera and swallowed the ^{111}In-labelled buflomedil HCl tablet, with 100 ml of water containing 3 MBq ^{99m}Tc-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) to outline the gastrointestinal tract. Radioactive anterior and posterior markers were placed on the thorax opposite the stomach to allow accurate alignment of the images. Anterior and posterior images were taken every 15 min whilst the tablet was in the stomach, and then every 30 min until the tablet reached the colon. Thereafter images were taken hourly until the 16 h post-dose blood sample and then with the 24 h and 25 h post-dose samples. Meals were provided to the volunteers as follows:

8.00 am:	breakfast
11.30 am:	coffee
1.00 pm:	standard lunch (two filled rolls, one packet of crisps, orange juice, apple)
4.00 pm:	tea or coffee
8.00 pm:	evening meal (prawn cocktail; steak, chips and peas; dessert).

Each image was evaluated to determine the residence time of the tablet in the stomach, small intestine or colon. Images were examined for evidence of retention and also the time of tablet disintegration was noted. The percentage of radiolabel remaining with the intact unit was measured by counting the activity in regions of interest constructed around the tablet in each anterior and posterior view. The geometric mean of the anterior and posterior values was then calculated to compensate for changes in distance of the tablet from the detector as it passed through the gastrointestinal tract (Hardy and Perkins, 1985).

Blood samples (10 ml) were collected at 0 h (pre-dose) and then at 1, 2, 4, 6, 8, 10, 14, 16, 24 and 25 h post-dose. Samples were collected either from a cannula in the antecubital vein or by serial venepuncture. The blood samples were stored at room temperature to allow clotting and then centrifuged for 15 min at 1800 rpm. The serum from the blood samples was divided into two tubes and stored at -20°C prior to analysis of drug content.

Results

The activity of the tablets measured on the morning of each trial day and immediately prior to dosing was 1.1 ± 0.1 MBq which was within target specifications. Dissolution of the ^{111}In-labelled buflomedil formulation was found to be unaffected by the addition of labelled resin. Dissolution of the tablet in vivo, measured by the release of ^{111}In from the tablet, and the in vitro release of drug were compared using the Higuchi model (Higuchi, 1963) (Fig. 1). Release of buflomedil against $\sqrt{\text{time}}$, and of ^{111}In remaining in the tablet against $\sqrt{\text{time}}$ were linear and showed close agreement.

The heavy breakfast significantly delayed the gastric emptying of the unit compared to the light breakfast with mean gastric residence times of 6.2 ± 2.3 h and 2.2 ± 0.2 h, respectively ($p < 0.01$; Wilcoxon Signed Rank test), but transit of the formulation through the small intestine was unaffected by the meal size (3.5 ± 2.2 h light breakfast, 2.5 ± 1.3 h heavy breakfast). These findings are in accordance with our previously reported observations for single unit sustained release dosage forms (Wilson and Washington, 1988; Wilson et al., 1989). Disintegration of the tablet occurred in the large intestine in all cases apart from in one subject (SJ) where disintegration occurred in the small intestine after administration of the tablet with a heavy breakfast. There was no evidence of adhesion of the unit to the mucosa within the gastrointestinal tract.

The mean rate of disintegration of the tablet in vivo were similar after a light or heavy meal (Fig. 2). The mean data obtained from the two experiments were fitted to single exponential functions using a least-squares fitting program (MINIM) running on an Apple Macintosh computer. The disintegration rate constants were 0.19 h^{-1} for the tablet taken with the heavy breakfast and 0.16 h^{-1} when taken with the light breakfast. Complete disintegration of the tablet occurred at 10.8 ± 3.8 h after the light breakfast and 10.6 ± 2.3 h after the heavy breakfast.

The peak serum drug concentration occurred at 4 h following a light meal (1.87 ± 0.53 μg ml^{-1}) and at 6 h following the heavy meal (2.16 ± 1.0 μg

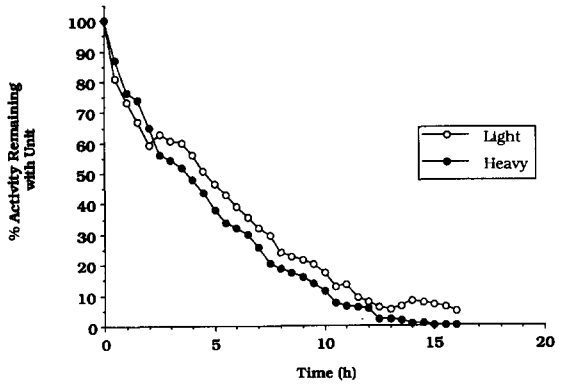

Fig. 2. In vivo measurement of percentage ^{111}In remaining with the unit after a light or heavy breakfast ($n = 7$).

ml^{-1}). The area under the serum-concentration time curve was 21.7 ± 8.1 μg ml^{-1} h for the light meal and 24.8 ± 10.5 μg ml^{-1} h for the heavy meal. This difference was small but statistically significant ($p < 0.05$, paired t-test).

The volume of distribution for buflomedil of 120000 ml was calculated from the terminal β-phase by the method of least-squares residuals using the 'NON-LIN' pharmacokinetic program running on an Apple Macintosh microcomputer. The mean half-life of elimination was 5.5 h after the light breakfast and 5.1 h after the heavy breakfast, which is in agreement with published data ($t_{1/2}$, 5–7 h; volume of distribution 1.6–2 l kg^{-1} (Clissold et al., 1987)).

Numerical modelling

Pharmacokinetic models were constructed using the numerical simulation package STELLA on the Apple Macintosh (Washington, et al., 1990). Fig. 3 illustrates the model used for the simulation, with the parameters and equations given in Fig. 4. The dose form is administered to the stomach, and passes through the small intestine to the colon. The transit of the dose form between these three gastrointestinal compartments is controlled by the

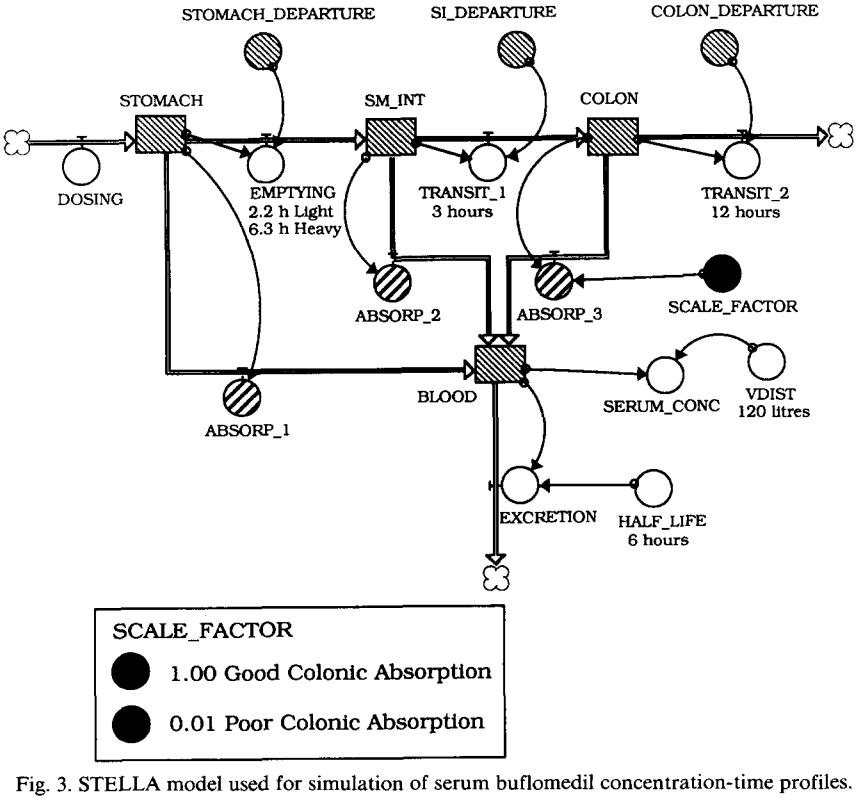

Fig. 3. STELLA model used for simulation of serum buflomedil concentration-time profiles.

STELLA Parameters for Simulating Behaviour of Buflomedil HCl CR Tablet

COLON = COLON + dt * (TRANSIT_1 - TRANSIT_2 - ABSORP_3)
INIT(COLON) = 0

BLOOD = BLOOD + dt * (ABSORP_1 + ABSORP_2 + ABSORP_3 - EXCRETION)
INIT(BLOOD) = 0

SM_INT = SM_INT + dt * (EMPTYING - TRANSIT_1 - ABSORP_2)
INIT(SM_INT) = 0

STOMACH = STOMACH + dt * (DOSING - EMPTYING - ABSORP_1)
INIT(STOMACH) = 0

1 **ABSORP_1 = 0.16*STOMACH**
2 **ABSORP_2 = 0.16*SM_INT**
3 **ABSORP_3 = SCALE_FACTOR*0.16*COLON**

COLON_DEPARTURE = 24
DOSING = PULSE (600000,0,48)
EMPTYING = IF (STOMACH>0) AND (TIME >STOMACH_DEPARTURE) THEN STOMACH/DT ELSE 0
EXCRETION = PLASMA*.693/HALF_LIFE
HALF_LIFE = 5.5
SERUM_CONC = BLOOD/VDIST
SCALE_FACTOR = 1

4 **SI_DEPARTURE = 5.7**
5 **STOMACH_DEPARTURE = 2.2**

TRANSIT_1 = IF(SM_INT>0) AND (TIME>SI_DEPARTURE) THEN SM_INT/DT ELSE 0
TRANSIT_2 = IF (COLON>0) AND (TIME>CAECUM_DEPARTURE) THEN COLON/DT ELSE 0
VDIST = 120000

Modifications for Heavy Meal

1. **ABSORP_1= 0.19*STOMACH**
2. **ABSORP_2 = 0.19*SM_INT**
3. **ABSORP_3 = SCALE_FACTOR*0.19*COLON**
4. **SI_DEPARTURE = 8.7**
5. **STOMACH_DEPARTURE = 6.2**

Fig. 4. The parameters and equations used in the STELLA model.

processes STOMACH_DEPARTURE, SI_DEPARTURE, and COLON_DEPARTURE, which are in turn obtained directly from the scintigraphic data. The processes ABSORP_1, ABSORP_2 and ABSORP_3 represent absorption from the stomach (considered negligible and included for completeness), small intestine and colon respectively. These absorption processes are actually a series combination of drug release and absorption, and so the flow indicated will model whichever process is rate limiting. For example, ABSORP_2 will reflect the device release rate, but ABSORP_1 will reflect the stomach's absorption rate since this is rate-limiting in this compartment. It is possible to construct a more complex model in which the release and absorption processes are separate, but this is not justified by the precision of the present experimental data.

Absorbed drug passes directly into the BLOOD compartment, whose volume is determined by the terminal phase of the drug elimination, as described above. The excretion rate is determined from the literature half-life of an i.v. bolus (Clissold et al., 1987). Since we are neglecting significant gastric absorption, there are only two variable parameters required to complete the model. These are ABSORP_2, which is obtained by fitting to the absorption phase of the plasma curve, and ABSORP_3, which is varied to assess the relative importance of colonic absorption. The model was run under two sets of circumstances. These were:

(a) Light and heavy meal. This simulation was performed by varying STOMACH_DEPARTURE, SI_DEPARTURE, and COLON_DEPARTURE as determined from the scintigraphic transit data with the appropriate meal.

(b) Significant and poor colonic absorption. This was performed by varying ABSORP_3 from ABSORP_2 (the same as the small intestine absorption rate, i.e. good absorption) to $0.1 \times$ ABSORP_2 (poor absorption).

Figs. 5a and b illustrates actual and predicted serum concentration-time profiles after the light and heavy meals respectively, in both the cases of good and poor colonic absorption. In both cases, the inclusion of significant colonic absorption causes a significant overestimate of the plasma concentrations at times greater than 10 h. If the possibility of colonic absorption is discounted, good agreement is found between the observed and predicted plasma concentrations.

Discussion

A close agreement was found between the release of drug and the percentage of indium remaining in the tablet and both plots were approximately linear with respect to $t_{1/2}$. The Higuchi equation predicts that the release from a tablet composed of a polymeric matrix with a dispersed active will maintain this relationship over a major portion of the release curve (Higuchi, 1963) and only deviates from this dependence when the concentration of drug in the tablet drops

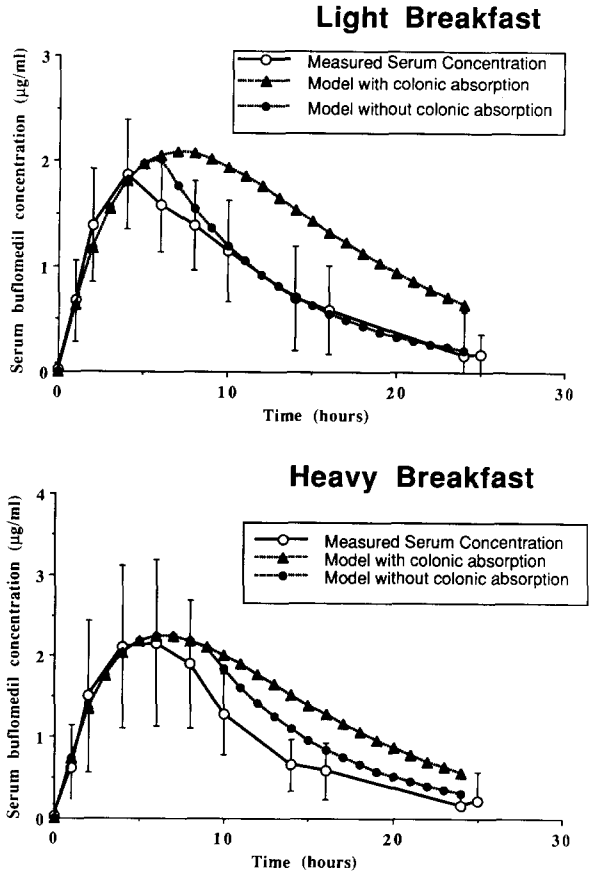

Fig. 5. (a) Plasma concentration time profile for buflomedil HCl after a light meal. (b) Plasma concentration time profile for buflomedil HCl after a heavy meal. (STELLA predicted profiles with efficient colonic absorption shown as filled squares; with poor colonic absorption shown as filled circles.)

below the saturation value (Heller, 1987). The ^{111}In-labelled resin is trapped within the formulation as an insoluble micro-particulate, and since the drug release mirrors the loss of the label, these data indicate that the controlled release mechanism for buflomedil CR is controlled by both diffusion and erosion of the matrix.

Previous work has shown that buflomedil is well absorbed from the gastrointestinal tract, with a linear relationship between the dose administered and the peak plasma concentration or the area under the plasma concentration-time profile (AUC) (Clissold et al., 1987). Comparison of the AUCs following oral and intravenous administration indicates that between 50 and 80% of an oral dose is available to the systemic circulation. This variability in part is due to first pass metabolism, which accounts for about 20% of an absorbed dose. The bioavailability of the 600 mg controlled release preparation has previously been shown not to be significantly affected by food (Clissold et al., 1987), although the present data show that there was a small but statistically significant increase in AUC_{0-24h} after the heavy compared with light breakfast. The retention of food in the stomach did, however, increase the time to peak concentration, although the trend was not significant. Tablets larger than about 5 mm are retained by the pyloric sphincter by the fed mode of gastric emptying (see Wilson and Washington, 1989) and this behaviour was entirely expected. Once the tablet is emptied from the stomach, food does not appear to have a large effect on small intestinal motility and this seems to be consistent in man with transit times between 2 and 4 h. From these remarks it is clear that the extent of colonic absorption is an important determinant of the performance of a sustained release formulation, since the formulation will spend an appreciable amount of time in the ascending colon. One of the most dramatic demonstrations of the importance of residence in the ascending colon is seen for the drug oxprenolol in which the AUC was significantly reduced in individuals with short colonic residence times (Davis et al., 1984).

We have found the numerical simulation programme STELLA extremely useful in the modelling of the interaction of pharmaceutical formulations with the gastrointestinal environment. The program, which runs on the Apple Macintosh has been used by ourselves and by other authors to investigate the behaviour of controlled release formulations (Grass and Morehead, 1989; Washington, et al., 1990). In particular, the length of time for which the tablet resides in the different regions of the gastrointestinal tract can be of paramount importance since the conditions in the gastrointestinal tract change as transit proceeds from the oral to the distal ends. Dressman (1989) has described the use of mean process time analysis, which has largely replaced the older intestinal reserve length theory, as a method of predicting

the importance of gastrointestinal transit in a variety of dosing situations. Her hypothesis is that once the colonic absorption time is longer than the release time, control of uptake no longer resides with the dosage form, but is partly governed by colonic membrane permeability. In this situation, the variability in absorption is less severe in the fed than the fasted state, reflecting upper gastrointestinal retention of the dosage form and hence longer contact time of the dissolved drug with more efficient sites of absorption in the upper intestine. In such a situation, there would be an increase in AUC_{0-24h} in the fed relative to the fasted state together with an increased T_{Cmax} as observed in the present study.

Due to the reduced surface area of the absorbing mucosa in the large intestine, it is perhaps not surprising that intrinsic absorption of drugs in this region of the gastrointestinal tract can be poor. There are, however, relatively few examples in the literature since this region of the gut is poorly understood. The regional variation in permeability appears to be due both to the smaller surface area and also to the relative importance of the paracellular and transcellular routes. Taylor and co-workers (1989) have described the absorptive pathways for a wide variety of compounds and has shown that paracellular absorption is virtually zero in the colon producing a marked decrease in absorption of hydrochlorothiazide as it enters the large intestine. Brockmeier and co-workers (1986) have shown similar poor absorption for solutions of piretanide (Arelix®) introduced into the human colon at colonoscopy.

In healthy, young, adult males capsules and tablets pass through the colon on average in 20–30 h (Hardy, 1989). Transit times are variable and influenced by the intake of food, by diet or disease and can range from 1 to more than 60 h (Hardy, et al., 1985, 1987). Colonic transit rates are not affected by capsule size and density over the range normally encountered for pharmaceutical preparations (Parker et al., 1988). In the present experiment, the formulation remained in the ascending colon for 4–8 h until it completely disintegrated and dispersed. Thus, if there is a lower intrinsic absorptive capacity for this drug, this factor is balanced by the long residence time in the colon. It is interesting that, in the simulation, a decrease in AUC_{0-24h} of the order of only 20% is anticipated if colonic absorption was reduced to one tenth the rate of intestinal absorption. One limitation of the simulations described is that they do not take into account the effect that meal size would have on first pass extraction of buflomedil. Since hepatic clearance has a major influence on the drug, these data would be useful to include to construct a better model.

In conclusion, it is predicted that colonic absorption of buflomedil hydrochloride is lower relative to the small intestine although successful once-a-day therapy can be achieved with the sustained release preparation described. Further studies are required to characterise the absorption of buflomedil of this region, although due to the relative inaccessibility of the proximal colon in man for direct measurements of absorptive capacity, such measurements will be difficult. Intubation of the ascending colon from the oral end severely disturbs the normal physiological function of the gut and appears to produce hypermotility (Krevsky et al., 1986). The use of sophisticated devices such as the high frequency capsule described by Bieck (1989) allows selective delivery under fluoroscopy in the gut of drug solution, but such techniques are extremely expensive and are not routinely available. Until the invention of suitable methodology indirect assessment by numerical simulation, assisted by scintigraphic and pharmacokinetic measurements, may remain the best tool In the design of sustained release formulations.

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