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# Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation

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**Aims**
The aims of the study were to: (1) evaluate the gastrointestinal transit, release and absorption of budesonide from tablets with a new multimatrix formulation (MMX®) designed to release the drug throughout the whole colon, and (2) assess the influence of food on budesonide bioavailability.

**Methods**
Two phase I studies, each comprising 12 healthy males, were performed. Gastrointestinal transit of $^{153}$Sm-labelled tablets containing 9 mg budesonide was evaluated by means of pharmaco-scintigraphy. The effect of food was tested by comparing plasma pharmacokinetics after intake of a high fat and high calorie breakfast with fasting controls.

**Results**
$^{153}$Sm-labelled tablets reached the ascending colon after a mean ± SD 9.8 ± 6.9 h. Initial tablet disintegration was observed in the ileum in 42% and the ascending and transverse colon in 33% of subjects. Ninety-six per cent of the dose was absorbed into the systemic circulation during passage through the whole colon including the sigmoid. Food significantly decreased $C_{max}$ values from 1429 ± 1014 to 1040 ± 601 pg mL$^{-1}$ ($P = 0.028$) and AUC values from 14 814 ± 11 254 to 13 486 ± 9369 pg h$^{-1}$ mL$^{-1}$ ($P = 0.008$). Mean residence time and $t_{max}$ increased by 12–29%. There was no drug accumulation after 1 week of once daily oral administration of budesomide.

**Conclusions**
MMX®-budesonide tablets appear suitable for targeted colonic drug delivery. Transit parameters and low systemic bioavailability warrant further studies with the new formulation.

## Introduction

The pharmacological treatment of inflammatory bowel diseases (IBD) is determined by the location, extent and severity of the disease within the gastrointestinal tract. The drugs include aminosalicylate formulations, corticlonal antibodies [1, 2]. Although corticosteroids are an effective option for disease management, dose- and duration-dependent side-effects might limit their long-term use. Budesonide, a nonhalogenated glucocorticosteroid (16α, 17-butylidendioxy-11β, 21-dihydroxy-1,4-

corticosteroids, characterized by potent local anti-inflammatory activity, and was initially introduced for the treatment of asthma and rhinitis. Due to an extensive first-pass elimination its systemic bioavailability is only 10–15% compared with other corticosteroid formulations, thus, improved safety and tolerability might be anticipated [2].

For the treatment of IBD, budesonide has been evaluated either as oral controlled-ileal-release formulation targeting the distal ileal and right-sided colonic region in Crohn's disease [3], or as enema for the treatment of left-sided ulcerative colitis or sigmoiditis [4]. However, there are no budesonide formulations available for the oral treatment of distally located IBD. To allow the homogenous release of budesonide along the whole colon at a controlled rate, new gastro-resistant, extended release tablets characterized by a multimatrix structure (i.e. MMX®-tablets containing 9 mg budesonide), have been developed.

To evaluate the *in vivo* performance of such novel delivery systems, the noninvasive technique of gamma-scintigraphy is routinely employed [5]. This technique allows monitoring of the gastrointestinal-transit of orally ingested dosage forms, to identify the exact time and region of disintegration and to follow the release of the active ingredient. Consequently, it is possible to relate the plasma and urine pharmacokinetics of the drug to the scintigraphic pattern within the gastrointestinal-tract and to determine the rate and extent of absorption in a defined region of interest (a process termed 'pharmaco-scintigraphy'). In the present study, budesonide tablets were labelled by the addition of a non-radioactive tracer, which is not absorbed from the gastrointestinal-tract, namely samarium-152-oxide, which was converted to samarium-153 ($^{153}$Sm) by neutron activation before tablet administration [6].

The present paper describes the results of two independent studies with MMX®-tablets in healthy subjects designed to (1) evaluate the gastrointestinal-transit, release and absorption of budesonide from MMX®-tablets using pharmaco-scintigraphy; (2) assess the influence of food on the bioavailability of budesonide; (3) characterize the steady-state pharmacokinetics of budesonide, and (4) evaluate safety and tolerability of the new MMX®-budesonide formulation after a 1-week, once daily treatment regimen.

## Subjects and methods

### *Study design*

Two independent, phase I studies were performed in two different study populations. One was a single dose pharmacokinetic study, the other was a single-blind, randomized, balanced, single and multiple dose pharmacokinetic study. Both were approved by the local Ethics Committees and were performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline of the European Commission (EC-GCP guideline). All subjects received a detailed description of the study and written informed consent was obtained.

### *Study populations*

Twelve male healthy Caucasian subjects took part in each study. In the first, the mean age of the subjects was 32 ± 5 years, mean height 178 ± 6 cm, mean weight 81.1 ± 12.5 kg, and mean BMI 25.5 ± 3.1 kg m$^{-2}$. In the second study the mean age was 22 ± 4 years, mean height 177 ± 8 cm, mean weight 74.1 ± 9.2 kg, and BMI 23.5 ± 2.6 kg m$^{-2}$.

Before start of each study, subjects were evaluated by medical history, physical examination, 12-lead electrocardiogram, measurements of blood pressure and heart rate, complete haematology with differential white blood cell count, blood chemistry, hepatitis B surface antigen, hepatitis C antibody and HIV antibody tests, urinalysis and urine drug screening. Subjects were excluded if they had taken any prescribed medication or over-the-counter drugs within a period of 2 weeks before the study. Subjects were excluded from the pharmaco-scintography if they had undergone any diagnostic analysis with radioactive tracers or X-rays during the 6 months preceding the study.

### *Study medication*

The study medication for both studies was provided by Cosmo S.p.A., Lainate (MI), Italy, and consisted of round, film-coated, gastro-resistant, extended-release tablets, with multimatrix structure (MMX®) [7], a diameter of 10 mm, a weight of 330 mg, and each containing 9 mg budesonide. Tablets were designed for slow and graded budesonide release in the colon, and consisted of an inner lipophilic matrix in which the active ingredient was dispersed, an outer hydrophilic matrix generated by *in situ* hydration of selected polymer chains and a third amphiphilic matrix promoting the inert matrix wettability. Tablets were film-coated with polymethacrylate to provide gastro-resistance.

For scintigraphy, 5 mg of $^{152}Sm_2O_3$ (1.67% w/w per tablet) was added to each tablet. Stable $^{152}$Sm-oxide was subsequently transformed into the radioactive, γ-ray-emitting $^{153}$Sm isotope by neutron activation. Before the start of the study, preliminary tests were performed on $^{152}Sm_2O_3$ tablets to determine the most optimal conditions for activation. Tablets were irradiated for different

($10^{11}$–$10^{13}$ neutrons $cm^{-2}$ $s^{-1}$) to obtain the intended radioactivity level of 0.8 MBq/tablet (i.e. 0.16 MBq/mg $Sm_2O_3$) at the time of drug administration. *In vitro* dissolution tests were performed to verify that the release profiles of the tablets were not significantly altered by the irradiation procedure. After irradiation, the budesonide content of the tablet was determined to verify that no degradation of the drug had occurred. Neutron activation was found not to alter the pharmaceutical properties and the analytical purity of the formulation. The mean (±SD) amount of radioactivity administered was 1.1 ± 0.4 MBq/dose, which is in compliance with the Council Directive 96/29 EURATOM, and with the general guidelines of the World Health Organization.

*Experimental design*

Subjects attended the Clinical Trial Center in the evening before drug administration and remained under observation for 24 h postdose. During their stay, subjects received standardized meals according to normal caloric needs for adult healthy males of normal weight with slight physical activity. After an overnight fast, the study medication was administered orally between 07.00 and 08.00 h with a defined amount of water. Thereafter, subjects underwent scintigraphic scans, blood and urine sampling at predetermined intervals up to 24 h postdose. To improve scan interpretation, each subject had four radioactive point sources taped to their skin in the following anatomical sites: the lower end of the sternum, the umbilicus, and the left and right iliac spine. The transit of budesonide tablets along the gastrointestinal-tract was recorded with the subjects sitting under a large field of view, double-head γ-camera (Axis, Picker®) equipped with a low-energy, all-purpose, parallel-hole collimator. Scanning was performed at 3 min postdose, and at approximately 20-min intervals up to 3 h, and then at 30-min intervals up to 10 h. Additional scans were taken at 12 and 24 h postdose. In each subject, the following regions of interest (ROIs) were identified: stomach, small intestine, terminal ileum-caecum, ascending colon, transverse colon, descending colon, sigmoid colon. Data were stored electronically. The location of the labelled formulation in the gastrointestinal-tract was established by viewing the image on a monitor. Quantitative data were obtained by measuring the count rates recorded from the ROIs. The geometric mean values of the corresponding anterior and posterior count rates were calculated and corrected for radioactive decay. The appearance or disappearance of the labelled formulation to or from the ROIs was evaluated by recording the time of the first and last appearance of

Venous blood samples (10 mL) were taken from an arm vein at the following times: 0 (predose), 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, and 24 h. Plasma samples, obtained by centrifugation were stored at ≤ –20 °C until analysis.

*Single-dose pharmacokinetic and effect of food study*

Subjects attended the Clinical Trial Centre in the evening before drug administration and received a standardized dinner between 20.00 and 21.00 h Subjects were randomized into two groups of six. In the morning, one group received a high fat, high caloric breakfast, i.e. 1000 kcal with fat accounting for 50% of the total caloric content. One MMX®-budesonide tablet was administered within 30 min after the start of breakfast with a defined amount of water. The other group received one MMX®-budesonide tablet after an overnight fast of at least 10 h. All subjects were discharged on the third day and returned to the Clinical Trial Centre after a 7-day wash-out period for the second phase of the cross-over study.

*Multiple–dose pharmacokinetic study*

After a 7-day wash-out period the 12 subjects who took part in the single dose study attended the trial centre and remained confined for 8 consecutive nights. One MMX®-budesonide tablet was administered once daily in the morning after an overnight fast of 12 h for 7 consecutive days. Subjects were discharged on day 8.

Venous blood samples (10 mL) were collected from an arm vein at predose on days 2, 4, 6 and 7, and at the following time points after the last dose on the 7th treatment day: 0 (predose), 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36 and 48 h. Plasma samples, obtained by centrifugation were stored at ≤ –20 °C until analysis.

*Clinical assessment*

The nature, severity and frequency of adverse events, laboratory values outside the normal range and abnormal ECG measurements were documented.

*Budesonide analysis*

All plasma samples were analysed for their budesonide content at Pharmakin GmbH, Ulm, Germany using a validated GC-MS/NCI method with SIM-detection. Fifty microlitres of triamcinolone acetonide and 50 µL of 2 M NaOH were added to previously thawed and homogenized 1 mL plasma samples. Budesonide was extracted into n-pentane: dichloromethane (70 : 30 v/v). After centrifugation the organic layer was evaporated to dryness under a stream of nitrogen at 40 °C. For derivatization

ethylamine in acetonitrile was added to the dry residue. After a reaction time of 15 min at room temperature, the mixture was dried under nitrogen stream and the residue reconstituted in 30 µL of ethyl acetate. Two microlitres of the derivatized extract were subjected to GC-MS analysis. The gas chromatograph was equipped with fused silica capillary column for the separation of budesonide and internal standard triamcinolone acetonide and coupled to a mass spectrometer. The carrier gas was helium 5.0 at a flow rate of 2.6 mL $min^{-1}$. The GC–MS interface was at a pressure of 10.1 psi and a temperature of 285 °C. The negative chemical ionization mode was used with methane 3.5 as ionization gas. The lower limit of quantification (LLQ) of the assay was 50.0 pg $mL^{-1}$. Precision at the LLQ expressed as a coefficient of variation was 6% for the samples from both studies.

### *Data analysis*

In the pharmaco-scintigraphic study the relative percentage of drug absorption in the time during which the radioactivity was detectable in the target region (i.e. between the ascending and the descending colon), was taken as primary outcome parameter and was calculated by means of the following equation: Relative percentage absorption = $100 \times (AUC_{target}/AUC_{24})$, where $AUC_{target}$ is the area under the plasma *vs.* time curve in the target region and $AUC_{24}$ the area under the plasma concentration *vs.* time curve for drug up to 24 h postdosing. The following variables were described: (1) gastric emptying time; (2) small intestinal transit; (3) ileal transit; (4) colonic transit; (5) time of initial tablet disintegration. Measurement of the distribution of radioactivity was achieved by determining the count rates recorded from the ROIs. Geometric means of corresponding anterior and posterior count rates were calculated and corrected for radioactive decay. Whenever plasma samples were missing at the start and end times of transit in the relevant regions, plasma concentrations were obtained by linear interpolation of the concentrations available at the times immediately preceding and following the time of interest.

For both studies the pharmacokinetic parameters for budesonide were calculated using Kinetica Software, Version 2000 (Innaphase Corporation, Philadelphia, PA, USA).

### *Statistical analysis*

Mean ±SD data were calculated using SAS® software version 8.2 for Windows® (SAS Institute Inc., USA). Statistical comparisons of pharmacokinetic data were performed using Kinetica Software. A *P*-value <0.05 $C_{max}$ values were compared using the analysis of variance (ANOVA) at the level of significance of $P < 0.05$ with study treatment (single dose *vs.* multiple dose) as covariate and the 90% CI for log-transformed data. The coefficient of accumulation after repeated administration was calculated as the repeated/single dose ratios for $C_{max}$ and AUC.

According to the latest version of an FDA guideline on Food-Effect Bioavailability and Fed Bioequivalence Studies [8], 'an absence of food effect on BA is not established if the 90% CI for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80–125% of either $AUC_{\infty}$ ($AUC_{48}$ when appropriate) or $C_{max}$'. Thus, AUC and $C_{max}$ calculated for the two diet regimens (fed and fasted) after administration were compared by analysis of variance (ANOVA) for a cross-over design (log-transformed data) at the level of significance $P < 0.05$. The 90% CI for the ratio of population geometric means between fed and fasted condition was calculated. $t_{max}$ after administration of drug under fed or fasted conditions was compared using the nonparametric Friedman test (nontransformed data).

## Results

MMX®-budesonide tablets were detected by scintographic imaging in the ascending colon between 4 and >24 h after dosing (Figure 1). The drug left the descending colon at 12 to >24 h postdosing. To estimate the relative percentage of budesonide absorbed from the target region (i.e. that between the ascending and the descending–sigmoid colon) the $AUC_{target}/AUC_{24}$ ratio was calculated from the plasma AUC over the time during which radioactivity was detectable in the target region (mean ± SD $AUC_{target}$: 15 114 ± 14 402 pg $h^{-1}$ $mL^{-1}$) and plasma AUC values during the 24 h observation period (mean $AUC_{24}$: 15 607 ± 14 549 pg $h^{-1}$ $mL^{-1}$). The mean relative absorption was 95.9 ± 4.2% indicating that during the study period absorption of budesonide occurred throughout the whole colon including the sigmoid.

Initial tablet disintegration/erosion (ITD) started at 9.48 ± 5.11 h after administration either in the small intestine ($n = 2$), the ileum ($n = 5$), the ascending ($n = 2$), transverse ($n = 2$) or sigmoid colon ($n = 1$). Individual times and location are given in Table 1. The times of tablet residence in different ROIs were 17–117 min (stomach), 37 min to 9.95 h (small intestine), 0.5–12 h (ileum), 1.5 to >15.5 h (ascending colon), 2 to >17 h (transverse colon), and 12 to >17 h (descending colon).

**Table 1**
Individual times and locations of initial tablet disintegration (ITD) within the gastrointestinal tract of $^{153}$Sm-labelled MMX®-budesonide tablets

| Subject | ITD (h) | Location in the gastrointestinal tract |
|---|---|---|
| 01 | >24 | Sigmoid colon |
| 02 | 8.5–9 | Ascending colon |
| 03 | 12–24 | Ileum/ascending colon |
| 04 | 10–12 | Small intestine/ileum |
| 05 | 4–4.5 | Ileum/ascending colon |
| 06 | 10–12 | Ileum |
| 07 | 5.5–6 | Transverse colon |
| 08 | 7–7.5 | Small intestine/ileum |
| 09 | 6–6.5 | Ileum |
| 10 | 8–8.5 | Ileum/ascending colon |
| 11 | 9.5–10 | Transverse/descending colon |
| 12 | 6.5–7 | Ascending/transverse colon |

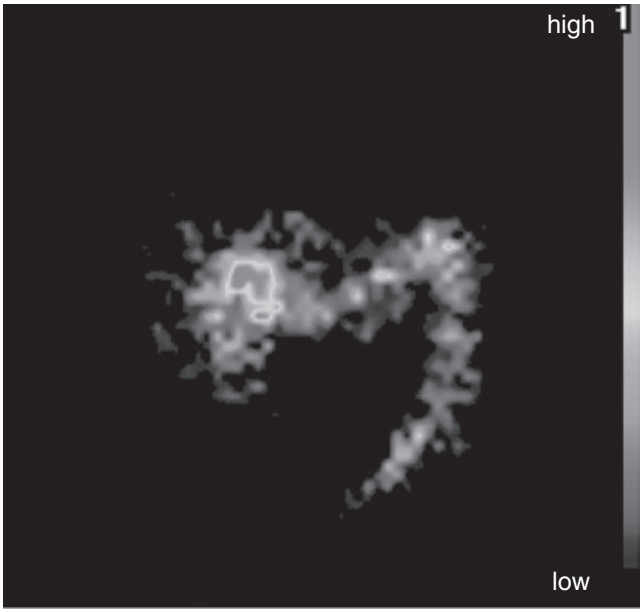
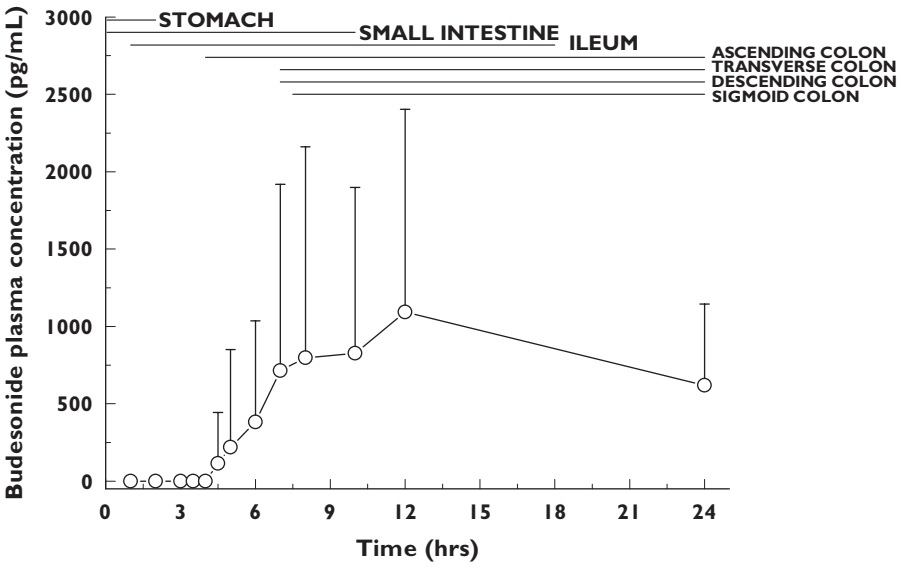



**Figure 1**
A representative scintigraphic image, depicting the dispersion of $^{153}$Sm-labelled MMX®-budesonide tablets in the colon. The image shown was acquired approximately 7 h after drug administration

**Figure 2**
The mean ±SD plasma concentration *vs.* time profile of budesonide after single-dose administration of $^{153}$Sm-labelled MMX®-tablets to 12 healthy males. Lines depict periods between minimal time to arrive and maximal time to leave different gastrointestinal regions




drug administration, transit times in the transverse, descending and sigmoid colon and the percentage of drug absorption in the target ROI were approximated or not available.

Budesonide was first detected in plasma 6.8 ± 3.2 h post administration ($t_{lag}$) (Figure 2). The mean time to reach $C_{max}$ ($t_{max}$) was 14.0 ± 7.7 h and the mean $C_{max}$ of 1768.7 ± 1499.8 pg mL$^{-1}$. The difference between $t_{max}$ the time during which most of the drug is released and absorption dominates over elimination.

Following oral single dose administration, budesonide was detectable in plasma between 3 and 16 h under fasting conditions and between 5 and 16 h after a meal. The corresponding peak concentrations occurred between 12 and 24 h and between 10 and 36 h. Mean budesonide plasma concentration *vs.* time profiles after

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