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# In vivo evaluation of sustained-release microspheres of metoclopramide hydrochloride in beagle dogs

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**Abstract**

The in vivo absorption characteristics of metoclopramide hydrochloride microspheres prepared from cellulose propionate polymer by an emulsion-solvent evaporation method were evaluated using six male beagle dogs. Metoclopramide was administered intravenously at a dose of 4 mg and orally as a single dose (10 mg) of microspheres and conventional tablets (Plasil®) on three separate occasions. Statistically significant differences were found between the two oral treatments in both the time and magnitude of the peak generated ($p < 0.05$). The absorption rate ($C_{max}$/AUC) was significantly slower following the administration of microspheres. No significant difference was found between the two treatments in the area under the plasma concentration-time curve (AUC), indicating a comparable extent of absorption. The mean residence time (MRT) and mean absorption time (MAT) were dramatically increased following microsphere administration compared to the conventional tablets. The absolute bioavailability of metoclopramide from the microspheres and the conventional tablets was 72 and 65%, respectively. The in vivo results were found to be consistent with the in vitro availability of the drug.

*Keywords:* Metoclopramide hydrochloride; Sustained release; Microsphere; Conventional tablet; Bioavailability; Beagle dog

## 1. Introduction

Metoclopramide hydrochloride is a commonly prescribed drug used for the management of gastrointestinal disorders such as gastric stasis, gastroesophageal reflux and for the prevention of cancer chemotherapy-induced emesis (McEvoy, 1991). It is readily absorbed from the gastrointestinal tract (Bateman, 1983). The maximum plasma concentration after an oral dose of a conventional tablet formulation is reached in about 1 h (Graffiner et al., 1979; Bateman et al., 1980; Ross-Lee et al., 1981). The drug has a short biological half-life (3–4 h) and is usually administered in a dose of 10–15 mg given up to four times daily in order to maintain effective concentration throughout the day. In long-term therapy, fluctuation in the plasma concentrations, with high concentration peaks, are common for drugs with rapid absorption and elimination (Ritschel, 1989). To avoid this, a sustained-release formulation that involves twice daily administration is an appropriate form of medication. The adverse ef-

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fect of metoclopramide on the central nervous system caused by high plasma peaks (Bateman, 1983) can be avoided through the use of such formulation.

Spherical pelletization with polymers is one method used to modify the dosage form and to retard the drug release rate. Since the micropellets can be widely distributed throughout the gastrointestinal tract, microspheres provide several advantages over other sustained-release systems, especially matrix-type tablets. They improve drug absorption and minimize side effects due to the localized build up of irritating drugs against the gastrointestinal mucosa (Li et al., 1988).

The objective of this study was to evaluate the in vivo absorption characteristics of metoclopramide sustained-release microspheres prepared with cellulose propionate polymer at 1:2 drug/polymer ratio using the emulsion-solvent evaporation method (Deasy, 1984). Comparison with commercially available conventional tablets was also performed. The method of preparation of the microspheres as well as the effect of various formulation variables on the preparation, the release properties and the surface topography of the metoclopramide microsphere are described in detail elsewhere (Khidr et al., 1995).

## 2. Materials and methods

Metoclopramide hydrochloride was kindly supplied by the Saudi Pharmaceutical Industries and Medical Appliances Corp. (SPIMACO, Saudi Arabia). Heparinized blood collection tubes (5 ml) were obtained from Greiner labortechnik (Austria). Polypropylene tubes (4 ml) were purchased from Sterlin Ltd (Hounslow, UK). Metoclopramide conventional tablets (Plasil®), 10 mg batch no. 193 (Lepetit, Milan, Italy) were purchased from a local market.

### 2.1. Preparation of the microspheres

Microspheres were prepared by an emulsion-solvent evaporation technique. The drug was dispersed in a polymeric solution of cellulose propionate in acetone at 1:2 drug/polymer ratio forming the internal phase. The dispersion was added dropwise to liquid paraffin containing 1.0% Span 80 and was emulsified by stirring at 900 rpm using a paddle stirrer. Following solvent evaporation at room temperature, stirring was continued for 30 min at 40° C to ensure complete removal of solvent. The microspheres produced were filtered, washed with *n*-hexane and dried overnight under reduced pressure.

### 2.2. In vitro release studies

The release properties of the microspheres were studied using the USP XXII basket method. An accurately weighed amount of microspheres equivalent to 20 mg metoclopramide filled in hard gelatin capsules was added to 750 ml 0.1 N HCl (pH 1.2) at 37 ± 0.5° C and stirred at 50 rpm for 2 h followed by another 4 h in sodium phosphate buffer solution (pH 6.8). The metoclopramide concentration at given time intervals was automatically monitored at 309 nm using a Philips PU 8620 (UK) spectrophotometer connected with an IBM computer Model PS 30 using the TDS Software program from Philips and the results were taken as the average of six readings.

The release characteristics of metoclopramide conventional 10 mg tablets (Plasil®) were also investigated using the same dissolution system.

### 2.3. Animals

Six male beagle dogs, weighing between 10 and 16 kg (12.2 ± 2.1 kg, mean ± S.D.), were used in the present study. Metoclopramide was administered on three occasions separated by at least 3 weeks between each treatment. The animals remained in good health through the entire period of the study. The dogs were starved for about 18 h prior to drug administration and continued fasting until 4 h post-dose, but were allowed water ad libitum. During the experimental period each dog was placed in the upright position in the restrainer stand. The cephalic vein of the forelimb was cannulated using an 18 gauge cannula. The cannula was used for intravenous administration and blood sampling. The same six dogs were

used throughout the intravenous and oral dosing experiments.

### 2.4. Study design and blood sampling

The three treatment periods were as follows:

(1) Metoclopramide administered intravenously at a dose of 4 mg, Plasil® (10 mg/2 ml).
(2) Metoclopramide conventional tablets administered orally by gastric intubation at a dose of 10 mg, Plasil® (10 mg/tablet).
(3) Metoclopramide microspheres prepared in our laboratory filled in hard gelatin capsules (equivalent to 10 mg metoclopramide) administered orally by gastric intubation.

Multiple blood samples (5 ml) were collected in evacuated glass tubes before and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 and 8 h post-intravenous administration and before and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h post-oral administration of the conventional tablets and before and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 h post-oral administration of metoclopramide microspheres.

The plasma was then separated after centrifugation and stored frozen at −20° C pending analysis.

### 2.5. Analysis of plasma samples

Metoclopramide plasma concentrations were measured using a sensitive and validated high-performance liquid chromatographic assay (El-Sayed et al., 1994).

### 2.6. Pharmacokinetic analysis

Pharmacokinetic parameters for metoclopramide following oral administration were determined from the plasma concentration-time data. The maximum plasma concentration ($C_{max}$) and the corresponding time ($T_{max}$) were obtained directly from the individual plasma concentration-time data. The area under the plasma concentration-time curve (AUC) and the area under the first moment curve (AUMC) were estimated by linear trapezoidal rule and extrapolated to infinity using standard techniques (Gibaldi and Perrier, 1982). The apparent elimination rate constant ($K_{el}$) was calculated by the technique of least-squares regression analysis.

The percentage of the concentration at 6 h following oral administration of the conventional tablets and the prepared microspheres, estimated as a percentage of the maximum concentration was also computed. The rate of absorption was also evaluated by means of the ratio $C_{max}/AUC_{0-\infty}$.

The data of plasma metoclopramide concentrations following intravenous administration were analyzed by a linear two-compartment pharmacokinetic model with elimination from the central compartment.

The mean residence time of the drug in the body (MRT), the mean absorption time (MAT) and the absolute bioavailability (F) of the microspheres and the conventional tablets were calculated using the following equations:

$$MRT = \frac{AUMC}{AUC}$$

$$MAT = MRT_{po} - MRT_{iv}$$

$$F = \frac{AUC_{po}}{AUC_{iv}} \times \frac{dose_{iv}}{dose_{po}}$$

where, $MRT_{po}$ is the mean residence time after oral administration and $MRT_{iv}$ denotes the mean residence time after i.v. administration.

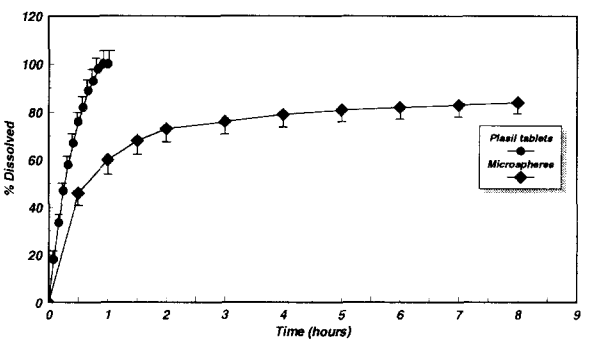


Fig. 1. Release (%, mean ±SD) of metoclopramide from conventional tablets (Plasil®) and the experimental microsphere formulation.

### 2.7. Statistical analysis

The pharmacokinetic characteristics of metoclopramide following oral administration of the conventional tablets and the microspheres were evaluated statistically using analysis of variance (ANOVA). Differences between two related parameters were considered statistically significant for $p$ values equal to or less than 0.05. All analysis of the data was performed with a statistical software package (Statistical Analysis System, SAS Institute, Inc., Cary, NC, USA).

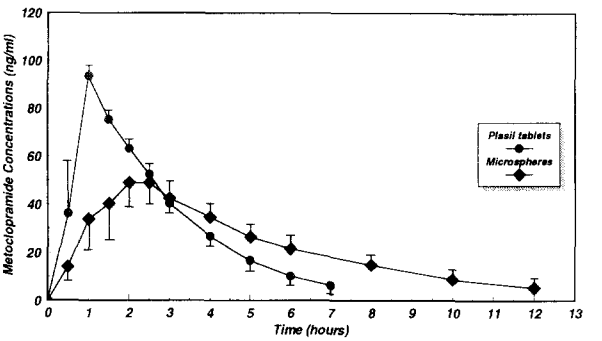


Fig. 2. Mean (±SD) plasma concentrations of metoclopramide after oral administration (10 mg) of the conventional tablets (Plasil®) and the experimental microsphere formulation to six beagle dogs.

## 3. Results and discussion

The in vitro dissolution profiles of the two formulations are shown in Fig. 1. It is clear that the two profiles are significantly different from each other with respect to the percent drug dissolved at any time interval. More than 75% of metoclopramide in the conventional tablets was dissolved within 30 min, and 100% in 50 min, using the USP XXII dissolution method for metoclopramide tablets. On the other hand, the experimental microsphere formulation was designed to release the drug over 8–10 h. 46% was dissolved in 30 min and 84% at 8 h.

The mean plasma levels as a function of time after the oral administration of a 10 mg single dose of metoclopramide in both the conventional tablet and the experimental formulation are shown in Fig. 2. Examination of the two profiles exhibited in Fig. 2 and of individual dog data demonstrate the presence of marked variation with the two products. The mean plasma concentrations obtained with the microspheres were lower until 2.5 h following administration, thereafter, the concentrations were higher. Metoclopramide was measurable at the last sampling time (12 h) in four dogs following microsphere administration and the drug was only measurable up to the 7th hour after dosing with the conventional tablets. Further, the percentage of the concentration at 6 h (common sampling time for both treatments) estimated as a percentage of the maximum concentration following the administration of the conventional tablets and the microspheres was 11 and 38.4%, respectively.

The mean pharmacokinetic characteristics of metoclopramide following oral administration of

Table 1
Mean pharmacokinetic parameters of metoclopramide following oral administration of the microspheres and the conventional tablets to six beagle dogs [a]

| Parameter | Microspheres | Conventional tablets | $P$ value [b] |
|---|---|---|---|
| $AUC_{0-\infty}$ (ng h ml$^{-1}$) | 289.58 ± 23.0 | 260.32 ± 13.16 | > 0.05 |
| $C_{max}$ (ng ml$^{-1}$) | 56.35 ± 5.57 | 93.58 ± 2.96 | < 0.05 |
| $T_{max}$ (h) | 2.17 ± 0.61 | 1.00 ± 0.0 | < 0.05 |
| MRT (h) | 5.17 ± 0.31 | 2.78 ± 0.13 | < 0.05 |
| MAT (h) | 2.84 ± 0.34 | 0.45 ± 0.21 | < 0.05 |
| $C_{max}/AUC_{0-\infty}$ (h$^{-1}$) | 0.195 ± 0.02 | 0.360 ± 0.01 | < 0.05 |
| % concentration at 6 h [c] | 38.43 ± 7.14 | 10.95 ± 0.69 | < 0.05 |

[a] Data presented as mean ± S.D.
[b] $P$ value of the analysis of variance between treatment.
[c] Percentage of the concentration at the 6th hour estimated as percentage of the maximum concentration.

the two products are listed in Table 1. The absorption of metoclopramide from the conventional tablets was rapid, reaching peak plasma concentration in 1 h in all dogs whereas, following experimental microsphere administration, the mean $T_{max}$ was 2.17 h (range 1.5–3.0 h) post-dosing. The peak plasma concentration ($C_{max}$) was lower following the administration of the microspheres (56.4 ng/ml) compared to the conventional tablets (93.6 ng/ml). Statistically significant differences were found between the two treatments in both the time and the magnitude of the peak generated ($p < 0.05$). Nevertheless, no statistical difference was found between the two treatments in the area under the plasma concentration-time curve ($AUC_{0-\infty}$), indicating a comparable extent of absorption. The delayed absorption with lower peak concentrations and higher concentrations during the elimination phase can be regarded as a major advantage of the new formulation over the conventional tablet.

The rate of absorption of metoclopramide from the prepared microspheres and the conventional tablets was also evaluated using the ratio $C_{max}/AUC$. This ratio is held to be a good parameter for evaluation of the absorption rate of prolonged-release formulations (Schall and Luus, 1992; Lacey et al., 1994). A statistically significant difference was found between the two treatments with the microspheres providing a slower rate of absorption.

The sustained-release characteristics of the microspheres were also reflected in the mean residence time (MRT) and the mean absorption time (MAT) of metoclopramide in the body. MRT is also a useful parameter, especially in cases where the drug (such as metoclopramide) is eliminated rapidly (Stienijans et al., 1992). Both parameters were dramatically increased following oral administration of the microspheres compared to the conventional tablets. The MRT values for the microspheres and conventional tablets were 5.17 and 2.78 h, respectively, whereas the MAT values were 2.84 and 0.45 h, for the microspheres and conventional tablets, respectively.

The absolute bioavailability of metoclopramide from the microspheres and the conventional tablets was 72 and 65%, respectively.

The results of the analysis of variance of the pharmacokinetic parameters, AUC, $C_{max}$, $T_{max}$, MRT and MAT indicated that none of these variables showed any significant difference with regards to dogs between the two treatments.

In conclusion, prolonged absorption of metoclopramide was reached with the system prepared. The test preparation studied can therefore be regarded as worthy of consideration for the manufacture of sustained-release metoclopramide product.

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