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# Bioavailability of meclofenamate from experimental sustained-release microcapsules in beagle dogs

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**Abstract**

This investigation was carried out to evaluate the absorption characteristics of experimental meclofenamate sustained-release microcapsules, prepared by an emulsion-solvent evaporation method using high molecular weight cellulose propionate polymer and polyethylene glycol (PEG) 2000 in a ratio of 1:2:1 drug:polymer:PEG, using eight male beagle dogs. Meclofenamate was administered intravenously at a dose of 40 mg and orally as a single dose (50 mg) of conventional capsules (Meclomen®), oral solution and microcapsules on four separate occasions. Statistically significant differences were observed between the microcapsules and the other two oral treatments in both the peak plasma concentration ($C_{max}$) and the time of peak concentration ($T_{max}$). No significant difference was found between the three oral treatments in the area under the plasma concentration–time curve (AUC), indicating a comparable extent of absorption. The absorption rate ($C_{max}$/AUC) was significantly slower following the administration of microcapsules. Both the mean residence time (MRT) and the mean absorption time (MAT) were dramatically increased following oral administration of the microcapsules compared to the conventional capsules and the oral solution. The mean (in-vivo) dissolution time (MDT) for the prepared microcapsules was 2.14 h and for the conventional capsules 0.3 h, which were found to be consistent with the in-vitro availability of the drug. Duncan's multiple range test indicated no significant difference between the oral solution and the conventional capsules in any of the calculated pharmacokinetic parameters. The absolute bioavailability from the oral solution, the conventional capsules and the experimental microcapsules was 74.6, 67.9 and 72.5%, respectively.

*Keywords:* Meclofenamate; Sustained-release; Cellulose propionate; Microcapsules; Oral solution; Conventional capsules; Bioavailability; Mean time parameters; Beagle dogs

## 1. Introduction

Meclofenamate is a nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of acute and chronic rheumatoid arthritis and osteoarthritis. The recommended adult dose is 200 to 400 mg/day in three to four divided doses (Eberl, 1978; Ward et al., 1978; Willkens, 1978; Zuckner et al., 1978; Willkens and Vreed, 1981). The drug is also used for menorrhagia in doses of 100 mg three times daily (Vargyas et al., 1987). Following oral administration, peak plasma levels are reached in 0.5 to 2 h. The drug is extensively metabolized in man and it is primarily excreted in the urine (Koup et al., 1990). The mean biological half-life of meclofenamate sodium was reported to


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be 3 h following multiple doses (Glazko et al., 1978) and the drug is over 99% bound to plasma proteins. Meclofenamate has adverse effects in common with those for most NSAIDs. These include diarrhea, nausea, vomiting, ulcers, abdominal pain, and skin rash. This drug is not recommended as the initial drug because of the gastrointestinal side effects. A sustained-release oral formulation of meclofenamate can offer the advantage of maintaining relatively constant blood levels for a long time and minimizing fluctuations in the maximum and minimum plasma concentrations resulting from multiple dosing. Thus, less incidence of undesirable side effects is expected. Such a dosage form will also improve patient compliance.

The objective of this study was to evaluate the in-vivo absorption characteristics of meclofenamate sustained-release microcapsules prepared with high molecular weight cellulose propionate polymer and polyethylene glycol (PEG) 2000 at a ratio of 1:2:1 drug:polymer:PEG using the emulsion-solvent evaporation method (Deasy, 1984). Comparisons with commercially available conventional capsules and oral solution were also performed. The absolute bioavailability of meclofenamate from the developed sustained-release microcapsules, the prepared oral solution and the commercially available conventional capsules was also determined.

## 2. Materials and methods

Meclofenamate sodium (Sigma Chem. Co., St. Louis, MO, USA), high molecular weight cellulose propionate polymer (Aldrich Chem. Co., Milwaukee, WI, USA), polyethylene glycol and hydrochloric acid (BDH Chemicals Ltd., Poole, UK), liquid paraffin (E. Merck, Darmstadt, Germany), Span 80 and Tween 80 (Koch-light Lab. Ltd., England) were used as received from the suppliers. Acetone and n-hexane (E. Merck, Darmstadt, Germany) were of spectral grade. Heparinized blood collection tubes (5 ml) were obtained from Greiner Labortechnik (Austria). Polypropylene tubes (4 ml) were obtained from Sterlin Ltd. (Hounslow, England). Meclofenamate conventional capsules (Meclomen®), 50 mg (Parke-Davis, USA), were purchased from the USA. Meclofenamate sodium solution (20 mg/ml) for intravenous administration was prepared at the King Khalid University Hospital, King Saud University.

### *2.1. Preparation of meclofenamic acid*

Forty grams of meclofenamate sodium was dissolved in 100 ml of acetone and then 18 ml conc. (10 N) HCl was added. After stirring for 5 min, the slurry was filtered through Wattman filter paper and the precipitated meclofenamic acid was dried at 50°C for 12 h, then grinned and passed through sieve mesh No. 120. Identification and purity was confirmed by infra-red spectroscopy (IR) and checking the m.p. (257–259°C).

### *2.2. Preparation of microcapsules*

Microcapsules were prepared by an emulsion-solvent evaporation technique using meclofenamic acid as the starting active ingredient due to the solubility of meclofenamate sodium in the solvent used, which resulted in unsuccessful production of suitable microcapsules. The drug was dispersed in a polymeric solution of cellulose propionate containing PEG 2000 at 1:2:1 drug:polymer:PEG ratio forming the internal phase. The dispersion was added dropwise to liquid paraffin containing 1.0% Span 80 and was emulsified by stirring at 800 rpm using a paddle stirrer. Following solvent evaporation at room temperature the stirring was continued for 30 min at 40°C to ensure complete removal of the solvent. The microcapsules produced were filtered, washed with n-hexane and dried overnight under reduced pressure.

### *2.3. In-vitro release studies of the developed microcapsules*

The release characteristics of the microcapsules were studied using the USP XXII basket method. An accurately weighed amount of microcapsules equivalent to 50 mg meclofenamic acid filled in hard gelatin capsules was added to 900 ml phosphate buffer solution, pH 8.0 with 0.02% Tween

80, at 37 ± 0.5°C and stirred at 50 rpm. The meclofenamate concentration at given time intervals was automatically monitored at 279 nm using a Philips PU 8620 (UK) spectrophotometer connected to 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 properties of meclofenamate conventional 50 mg capsules (Meclomen®) were also investigated using the same dissolution system.

### 2.4. Animal study

Eight male beagle dogs, weighing between 12 and 15.8 kg (13.1 ± 1.5 kg, mean ± SD) were used in the present study. Meclofenamate was administered on four occasions separated by at least 3 weeks between each treatment. The animals remained in good health throughout 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 allowed free access to water. During the experimental period each dog was placed in the upright position in the restainer stand. The legs were shaven and a cephalic vein was cannulated using an 18-gauge cannula. The cannula was used for intravenous administration and blood sampling.

### 2.5. Study design and blood sampling

The four treatment periods were as follows:

(1) Meclofenamate sodium solution administered intravenously at a dose equivalent to 40 mg meclofenamic acid (20 mg/ml).
(2) Meclofenamate sodium solution administered orally by gastric intubation at a dose equivalent to 50 mg meclofenamic acid.
(3) Meclofenamate conventional capsules, Meclomen®, containing 50 mg meclofenamic acid as the sodium salt, administered orally by gastric intubation.
(4) Meclofenamate microcapsules prepared in our laboratory filled in hard gelatin capsules, containing 50 mg meclofenamic acid, administered orally by gastric intubation.

In the case of treatments 3 and 4 the capsules were washed down the tube using 50 ml water.

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 8.0 h post intravenous administration and before and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0 and 8.0 h post oral administration of the meclofenamate solution and before and at 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, and 8.0 h post oral administration of the conventional capsules and before and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0 and 12.0 h post oral administration of meclofenamate microcapsules.

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

### 2.6. Analysis of plasma samples

Meclofenamate plasma concentrations were measured using a validated high-performance liquid chromatographic assay method previously developed in our laboratory (Niazy et al., 1994).

### 2.7. Pharmacokinetic analysis

Pharmacokinetic parameters of meclofenamate following oral administration were determined from 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 the 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 elimination half-life ($t_{1/2}$) was calculated from the equation:

$$t_{1/2} = 0.693/K_{el}$$

The percentage of the concentration at the eighth hour following oral administration of the solution, conventional capsules and the prepared microcapsules, estimated as a percentage of the

maximum concentration, was also computed. The rate of absorption was also evaluated by means of the ratio $C_{max}/AUC_{o\rightarrow oo}$.

The data of plasma meclofenamate 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), the mean (in-vivo) dissolution time and the absolute bioavailability ($F$) were calculated using the following equations:

$$MRT = AUMC/AUC$$

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

$$MDT = MAT_{solid} - MAT_{solution}$$

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

where, $MRT_{extravascular}$ is the mean residence time after oral administration and $MRT_{iv}$ denotes the mean residence time after intravenous administration. $MAT_{solid}$ is the mean absorption time after oral administration of the conventional capsules and the prepared microcapsules and $MAT_{solution}$ is the mean absorption time after oral administration of the solution formulation.

### 2.8. Statistical analysis

The pharmacokinetic characteristics of meclofenamate following oral administration of the solution, conventional capsules and the prepared microcapsules were evaluated statistically using one-way analysis of variance (ANOVA) for repeated measurements. Duncan's multiple range test was applied (if ANOVA indicated significant difference) to find the source of possible differences between the various treatment phases of the study. Differences between two related parameters were considered statistically significant for $p \leq 0.05$. All analyses of the data were performed with a statistical software package (Statistical Analysis System, SAS Institute, Inc., Cary, NC, USA).

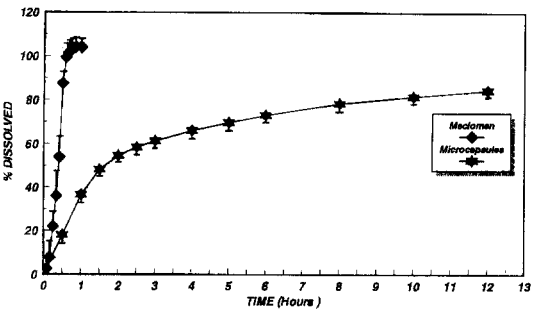


Fig. 1. Release (%, mean ± SD) of meclofenamate from conventional capsules (Meclomen®) and the experimental microcapsules formulation.

## 3. Results and discussion

The in-vitro dissolution profiles of the developed meclofenamate sustained-release microcapsules and the commercially available conventional capsules 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. About 100% of meclofenamate in the conventional capsules was dissolved within 30 min, using the USP XXII dissolution method for meclofenamate capsules. On the other hand, the prepared meclofenamate microcapsules released 36% of the drug in 1.0 h and 84% after 12 h.

The mean plasma concentration–time curves following the oral administration of a 50 mg single dose of meclofenamate from the conven-

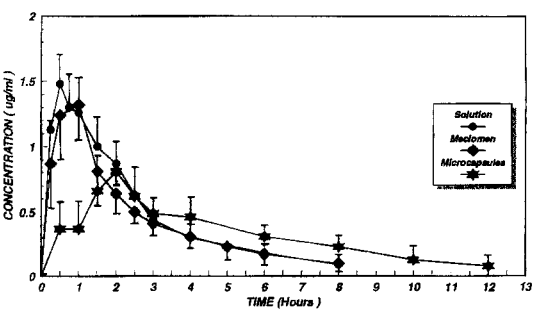


Fig. 2. Mean (± SD) plasma concentrations of meclofenamate after oral administration (50 mg) of the prepared solution, the conventional capsules (Meclomen®) and the experimental microcapsules formulation to eight beagle dogs.

Table 1
Mean pharmacokinetic parameters of meclofenamate after oral administration (50 mg) of the solution, the conventional capsules (Meclomen®) and the microcapsules to eight beagle dogs[a]

| Parameter | Solution | Meclomen® | Microcapsules | $p$-value[b] |
|---|---|---|---|---|
| $AUC_{o\rightarrow\infty}$ ($\mu$g h/ml) | 4.27 ± 1.17 | 3.89 ± 0.083 | 4.15 ± 1.01 | 0.7611 NS |
| $C_{max}$ ($\mu$g/ml) | 1.61 ± 0.43 | 1.46 ± 0.37 | 0.98 ± 0.39 | 0.0035 S |
| $T_{max}$ (h) | 0.69 ± 0.22 | 0.75 ± 0.27 | 2.31 ± 0.75 | 0.0001 S |
| $K_{el}$ ($h^{-1}$) | 0.290 ± 0.035 | 0.279 ± 0.033 | 0.278 ± 0.025 | 0.7103 NS |
| $t_{1/2}$ (h) | 2.42 ± 0.29 | 2.51 ± 0.28 | 2.51 ± 0.23 | 0.7692 NS |
| $C_{max}$/AUC ($h^{-1}$) | 0.382 ± 0.084 | 0.375 ± 0.050 | 0.234 ± 0.062 | 0.0010 NS |
| MRT (h) | 3.02 ± 0.34 | 3.32 ± 0.25 | 5.16 ± 0.91 | 0.0001 S |
| % concentration at 8 h[c] | 6.09 ± 1.68 | 7.12 ± 1.49 | 26.65 ± 15.78 | 0.0008 S |

[a]Values presented as mean ± SD of eight dogs.
[b]$p$-value of the analysis of variance between treatments.
[c]Percentage of the concentration at the eighth hour estimated as percentage of the maximum concentration.
S = significant; NS = not significant.
Duncan's multiple range test indicated no significant difference between the oral solution and the concentional capsules in any of the calculated pharmacokinetic parameters.

tional capsules, the solution and the experimental microcapsules are shown in Fig. 2. Examination of the plasma profiles presented in Fig. 2 and the individual dog data demonstrate similar profiles for the solution and the conventional capsules, whereas marked variation was observed following the microcapsules administration.

The mean plasma concentrations obtained with the microcapsules were lower until 2.5 h following administration; thereafter, the concentrations were higher. Meclofenamate was measurable at the last sampling time (12 h) in all dogs following microcapsules administration and the drug was only measurable up to the eighth hour after dosing with the conventional capsules. Further, the percentages of the concentration at the eighth hour time, estimated as percentage of the maximum concentration following the administration of the solution, conventional capsules and the microcapsules, were 6.1, 7.12 and 26.65%, respectively. The mean pharmacokinetic parameters of meclofenamate after oral administration of the three dosage forms are listed in Table 1.

The absorption of meclofenamate, following oral administration of the solution and the conventional capsules, was rapid reaching a peak plasma concentration in 0.69 and 0.75 h, respectively. No statistical difference was found between the two treatment groups in either the time or the magnitude of the peak generated (Duncan's multiple range test). Following the microcapsules administration the mean $T_{max}$ was 2.31 h (range 1.5 to 4.0 h) post dosing. The peak plasma concentration ($C_{max}$) was lower following the administration of the microcapsules (0.98 $\mu$g/ml) compared to the conventional capsules (1.46 $\mu$g/ml) and the solution (1.61 $\mu$g/ml). Statistically significant differences were found between the microcapsules, conventional capsules and the oral solution in both the time and the magnitude of the peak generated ($p < 0.05$). Nevertheless, no statistical difference was found between the three treatments in the area under the plasma concentration–time curve ($AUC_{o\rightarrow\infty}$), indicating 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 capsules.

The absorption rate of meclofenamate from the prepared microcapsules, the oral solution and the conventional capsules 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). No statistically significant difference was found between the oral solution and the conventional capsules, whereas a

statistically significant difference was found between the former two and the microcapsules which provided slower rate of absorption (Table 1).

The sustained-release characteristics of the microcapsules were also reflected in the mean time parameters. The mean residence time (MRT) and the mean absorption time (MAT), introduced by Yamaoka et al. (1978) and Cutler (1978), were shown to be useful parameters for predicting the behavior of the drug in the body after oral administration. Both parameters were dramatically increased following oral administration of the microcapsules compared to the conventional capsules. The MRT value for the microcapsules is 155% greater than that for the conventional capsules (Table 1). The delayed absorption of meclofenamate (longer $T_{max}$) following the microcapsules administration might explain the increase of MRT compared with the conventional capsules. This hypothesis is supported by the fact that the elimination rate constant and elimination half-life remain unaltered in the microcapsules-treated dogs. Indeed, the MRT is a composite variable, which describes all kinetic processes of a drug in the body, including absorption and disposition (Yamaoka et al., 1978). Assuming that neither the distribution nor the systemic clearance of meclofenamate are changed as a consequence of microcapsules administration, the increase in MRT is mainly due to delayed absorption of meclofenamate. This is further reflected in the MAT parameters. The MAT of the microcapsules is about 2.8 times greater than that of the conventional capsules, which clearly demonstrates a longer time period for absorption of meclofenamate with the microcapsules. These results (MRT and MAT) in the moment analysis indicated that the residence time in the gastrointestinal tract of the microcapsules was longer than that of the conventional capsules. The relatively higher AUC (yet not significant) of the microcapsules might be brought about by the continued drug release from the microcapsules retained in the gastrointestinal tract.

The mean (in-vivo) dissolution time (MDT) for the conventional capsules is 0.3 h and for the microcapsules 2.14 h; this is consistent with the in-vitro availability of the drug.

The absolute bioavailability of meclofenamate from the oral solution, conventional capsules and the microcapsules was 74.6, 67.9 and 72.5%, respectively.

The results of the analysis of variance of the pharmacokinetic parameters $AUC_{0\rightarrow\infty}$, $C_{max}$, $T_{max}$, $K_{el}$, $t_{1/2}$, MRT and $C_{max}/AUC$ indicated that none of these variables showed any significant difference with regards to dogs between the three oral treatment periods.

In conclusion, meclofenamate sustained-release microcapsules were successfully prepared by the emulsion-solvent evaporation method. The microcapsules showed a slow dissolution in vitro and a typical 12 h sustained release. In-vivo results demonstrated prolonged absorption of meclofenamate with the developed microcapsules. Therefore, the experimental formulation studied has the potential for consideration of manufacturing of sustained-release meclofenamate dosage form.

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## References

Cutler, D.J., Theory of the mean absorption time, an adjunct to conventional bioavailability studies. *J. Pharm. Pharmacol.*, 30 (1978) 476–478.

Deasy, P.B., Microencapsulation and Related Drug Processes, Dekker, New York, 1984.

Eberl, R., European studies of sodium meclofenamate (Meclomen®) in long-term treatment. *Curr. Ther. Res.*, 23 (Suppl.) (1978) 131–137.

Gibaldi, M. and Perrier, D., Pharmacokinetics, Dekker, New York, 1982.

Glazko, A.J., Chang, T., Borondy, P.E., Dill, W.A., Young, R. and Croskey, L., Metabolic disposition of meclofenamic acid (Meclomin®) in laboratory animals and in man. *Curr. Ther. Res.*, 23 (Suppl.) (1978) S22–S41.

Koup, J.R., Tucker, E., Thomas, D.J., Kinkel, A.W., Sedman, A.J., Dyer, R. and Sharoky, M., A single and multiple dose pharmacokinetic and metabolism study of meclofenamate sodium. Biopharm. Drug Dispos., 11 (1990) 1–15.

Lacey, L.F., Keene, O.N., Duquesnoy, C. and Bye, A., Evaluation of different indirect measures of rate of drug absorp-

tion in comparative pharmacokinetics. *J. Pharm. Sci.*, 83 (1994) 212–215.

Niazy, E.M., Khidr, S.H. and El-Sayed, Y.M., High-performance liquid chromatographic determination of meclofenamate sodium in plasma. *J. Liq. Chromatogr.*, 17 (1994) 2331–2341.

Schall, R. and Luus, H., Comparison of absorption rates in bioequivalence studies of immediate release drug formulations. *Int. J. Clin. Pharmacol. Ther.* Toxicol., 30 (1992) 153–159.

Vargyas, J.M., Campeau, J.D. and Mishell, D.R., Treatment of menorrhagia with meclofenamate sodium. *Am. J. Obstet. Gynecol.*, 157 (1987) 944–950.

Ward, J.R., Bolzan, J.A. and Brame, C.L., Sodium meclofenamate (Meclomen®). Dose determining studies. *Curr. Ther. Res.*, 23 (Suppl.) (1978) S60.

Willkens, R.F., Experiences in the treatment of osteoarthritis of the hip and knee with sodium meclofenamate (Meclomen®). *Curr. Ther. Res.*, 23 (Suppl.) (1978) 81–89.

Willkens, R.F. and Vreed, P., Sodium meclofenamate in the treatment of rheumatoid arthritis: a double-blind comparison with aspirin and placebo. *Pharmatherapeutica*, 2 (1981) 587–596.

Yamaoka, K., Nakagawa, T. and Uno, T., Statistical moments in pharmacokinetics. *J. Pharmacokinet. Biopharm.*, 6 (1978) 547–558.

Zuckner, J., Baldossare, A. and Harris, G.S., Sodium meclofenamate (vs placebo) in the treatment of rheumatic arthritis. *Curr. Ther. Res.*, 23 (Suppl.) (1978) S66–S71.