**References**

1 A. A. Alousi, A. E. Farah, G. Y. Lesher and C. J. Opalka, Jr., Fed. Proc. Fed. Am. Soc. Exp. Biol. *37*, 3692 (1978).
2 G. Y. Lesher and C. J. Opalka, US-Pat. 4,107,315; C.A. *90*, 103844r (1979).
3 F. W. Gubitz, J. Labelled Compd. *18*, 755 (1981).
4 Z. Arnold, Collect. Czech. Chem. Commun. *28*, 863 (1963).
5 M. C. Gómez, V. Gómez-Parra and F. Sánchez, private communication.

[KPh 284]

Arch. Pharm. (Weinheim) *317*, 185–188 (1984)

# Availability of Metoclopramide in vitro and in vivo

**In-vitro- und in-vivo-Verfügbarkeit von Metoclopramid**

Hartmut Vergin*, Konrad Strobel und Jochen Grätzel v. Grätz

Bereich Forschung und Entwicklung der Ludwig Heumann & Co. GmbH, Heideloffstr. 18–28, D-8500 Nürnberg, F.R.G.
Eingegangen am 5. Oktober 1983

Metoclopramide (4-amino-5-chloro-2-methoxy-*N*-2-diethyl-aminoethyl-benzamide) is recommended for use in gastrointestinal diagnostics and in treating various types of vomiting and a variety of functional gastrointestinal disorders. The drug increases the motility of the stomach and gastric emptying rates. It may provide symptomatic relief in dyspepsia and possibly in vertigo and reflux oesophagitis[1-2].

When given orally, metoclopramide is readily absorbed but shows a wide range in bioavailability which might be partially due to interindividual first-pass metabolism[3]. On the other hand, the available formulations could be responsible for these variations. In order to compensate for the latter, new metoclopramide formulations are required; sustained release preparations are of particular interest here. Evaluation of the dissolution model adopted and choice of formulations can be simplified if the relationship between *in-vitro* dissolution and *in-vivo* availability is known. In this respect, the mean dissolution time *in-vitro* $T_{diss\text{-}vitro}$ and the mean transit time in the organism $T_{sys}$ were used for the correlation of two different tablet and two different sustained release formulations of metoclopramide.

## Experimental Part

The dissolution rates of the tablets (n = 6) and the sustained release formulations (n = 6) were determined by the half-change method[4] using rotating bottles. The assembly consists of a motor-driven six bladed wheel (30 rpm), with a capacity for a maximum of six 100 ml vessels. Each vessel is filled with 100 ml simulated gastric fluid (USP XX) without pepsin and the test-dose is added. Once an hour starting 60 min from the beginning of the investigation half of the vol. of the dissolution medium is removed and substituted by simulated intestinal fluid (USP XX) without pancreatin. The temp. was maintained at 37 °C throughout the whole investigation period using a water bath with

0365-6233/84/0202-0185 $ 02.50/0

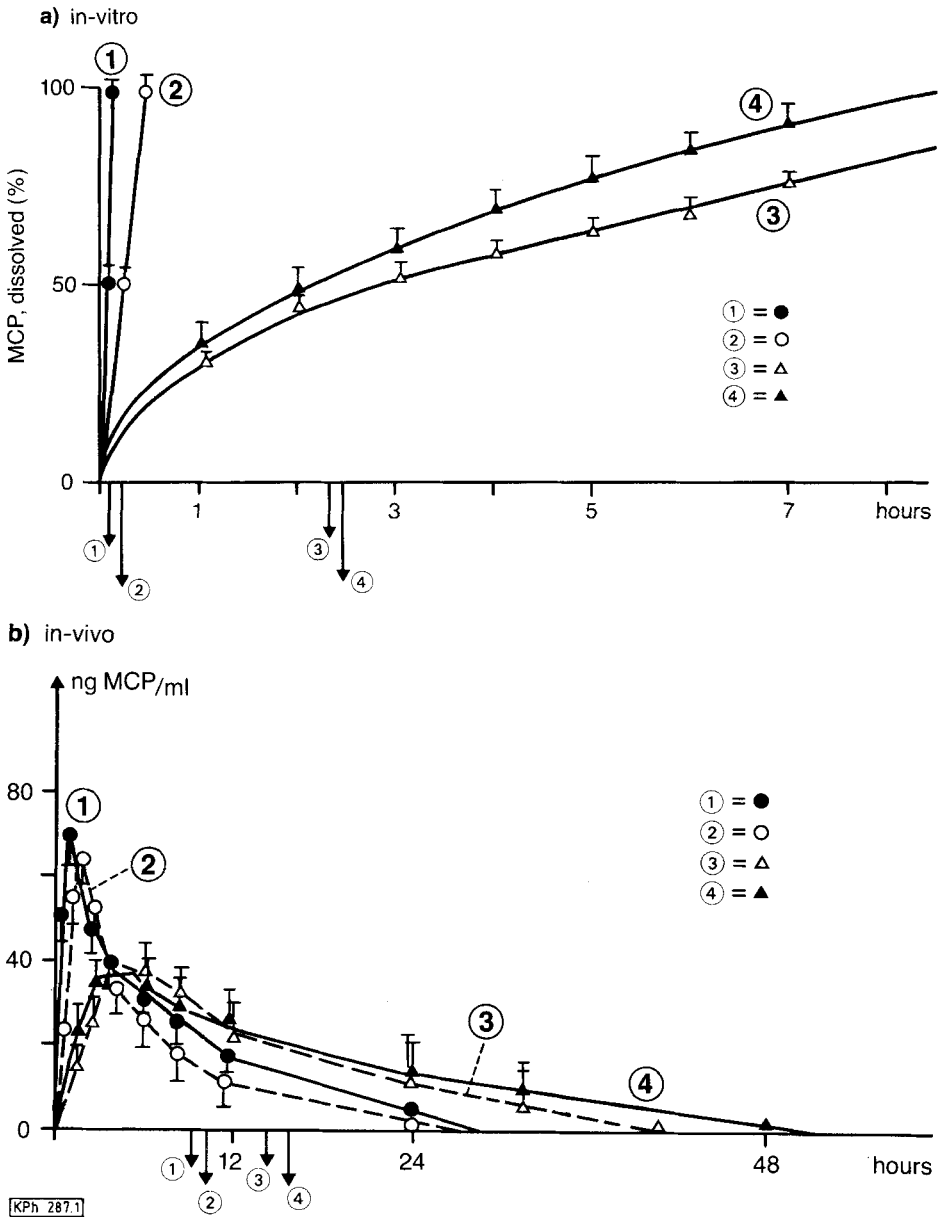


**Fig. 1:** a) Dissolution of 4 metoclopramide (MCP) formulations. 1, 2 = tablet forms; 3, 4 = sustained release formulations. ⌔ = $T_{diss\text{-}vitro}$
b) Plasma levels following single doses of tablets 1 and 2 and sustained release formulations 3 and 4 in healthy volunteers. ⌔ = $T_{sys}$
(In both figures mean values and standard deviations are given; the latter being in one direction only for graphical clarity)

thermostat. The area between the dissolution curve and the total amount $A_t$ of drug finally dissolved (ABC) divided by $A_t$ is used to express the mean dissolution time *in-vitro*, $T_{diss\text{-}vitro} = ABC/A_t$[5].

The mean transit time $T_{sys}$ in vivo comprises all time dependencies attributable to all conceivable processes which are sequences of the drug pathway form the administered drug formulation to its final elimination from the body. $T_{sys}$ can be considered as being the time-coordinate of the centroid of the area under the plasma level curve. $T_{sys}$ can simply be obtained by dividing the area between the transit curve and its threshold value ($ABC_{trans}$) by the area under the plasma level curve (AUC[6]), $T_{sys} = ABC_{trans}/AUC$[6].

An intraindividual comparative single-dose study (cross-over) was carried out under carefully controlled conditions on 10 healthy volunteers in order to establish the bioavailability of two metoclopramide tablet formulations[7]. In additional open single-dose studies the pharmacokinetics of metoclopramide were investigated after administration of newly developed sustained-release dosage forms of the drug on 12 healthy volunteers[7]. For both studies metoclopramide was administered following an overnight fast. A standard diet was given to all volunteers starting 1.5 h after drug application.

The analysis of unchanged metoclopramide in plasma was carried out using HPLC[8]. The drug dissolved *in-vitro* was determined by spectrophotometry at 308 nm. A two compartment open model was taken as a basis for the calculation of the plasma concentration curves (AUC-values).

Fig. 1a shows the dissolution curves of the tablet forms 1 and 2 and the sustained release formulations 3 and 4. The arrows below the time-axis represent the mean dissolution times ($T_{diss\text{-}vitro}$) being 3, 12, 138 and 147 min for the tablet forms 1 and 2 and the sustained release formulations 3 and 4.

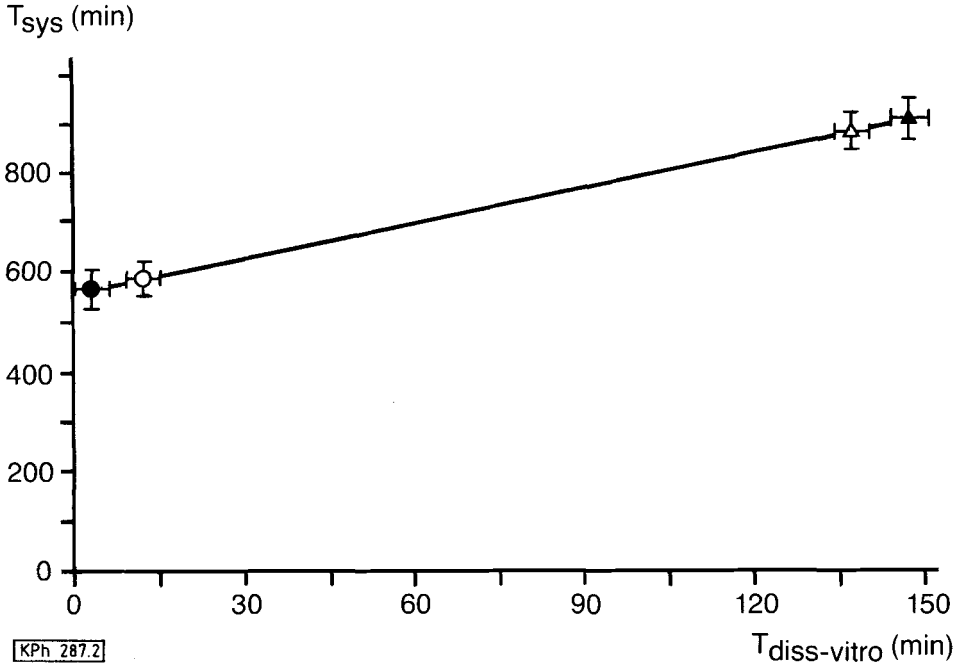


**Fig. 2:** *In-vitro/in-vivo* correlation of 4 metoclopramide solid dosage forms (● = tablets 1, ○ = tablets 2, △ = sustained release formulation 3, ▲ = sustained release formulation 4) (Mean values and standard deviations).

Mean transit time values ($T_{sys}$) were calculated from the blood level curves given in Fig. 1b. $T_{sys}$-values for each formulation are represented by vertical arrows below the time-axis and are determined to be as follows: 520 and 590 min for tablet forms 1 and 2, and 847 and 905 min for sustained release formulations 3 and 4.

According to *von Hattingberg* and *Brockmeier*[5] the additivity of mean times within a sequence of biopharmaceutical subsystems is expressed by a linear relationship of $T_{diss\text{-}vitro}$ and $T_{sys}$ in the organism. Fig. 2 demonstrates the validity of this hypothesis. The intercept $T_{diss\text{-}vitro} = 0$ would therefore represent the mean transit time of a metoclopramide solution. From the flat slope of the linear regression curve it can be seen, that the dissolution of the metoclopramide formulations is slower *in-vivo* than *in-vitro*. The results indicate excellent *in-vitro/in-vivo* correlation of the metoclopramide availability in all solid dosage forms investigated.

**References**

1 M. Eisner, Digestion *16*, 409 (1974).
2 A. G. Johnson, Postgrad. Med. J. Suppl. 4 *49*, 29 (1973).
3 D. N. Bateman and D. S. Davies, Lancet *1979*, 166.
4 K. Münzel, Dtsch. Apoth. Ztg. *104*, 844 (1964).
5 D. Voegele, H. M. von Hattingberg and D. Brockmeier, Acta Pharm. Technol. *27*, 115 (1981).
6 H. M. von Hattingberg and D. Brockmeier in G. Bozler and J. M. van Rossum (Eds): Drug Development and Evaluation Techniques, Vol. 6, pp. 315 ff, Gustav Fischer Verlag, Stuttgart–New York 1982.
7 H. Vergin, G. B. Bishop-Freudling, K. Strobel and D. S. Reeves, Arzneim. Forsch. *33*, 458 (1983).
8 G. B. Bishop-Freudling and H. Vergin, J. Chromatogr. Biomed. Appl. *273*, 453 (1983).

[KPh 287]

---

Arch. Pharm. (Weinheim) *317*, 188–191 (1984)

# Zum Verhalten von 2-Indolcarbohydraziden in Natriumethanolat-Lösung

**Behaviour of 2-Indolecarbohydrazides in Sodium Ethoxide Solution**

Jochen Lehmann*, Khadiga M. Ghoneim[+)] und Adel A. El-Gendy[+)]

Pharmazeutisches Institut der Universität Bonn, Kreuzbergweg 26, 5300 Bonn 1. – [+)] Dept. of Org. Chemistry, Faculty of Pharmacy, Cairo Univ., Cairo, Egypt.
Eingegangen am 2. November 1983

Im Rahmen synthetischer Arbeiten mit 2-Indolcarbohydraziden beobachteten wir, daß sich **1a, b** bei Raumtemperatur in ethanolischer Ethanolat-Lösung zu den Acylhydrazonen **2a, b** umsetzen. Die Strukturen von **2a, b** sind durch IR-, $^1$H-NMR- und MS-Daten sowie durch unabhängige Synthese von **2b** aus **1b** und 5-Chlor-2-indolcarbohydrazid abgesichert.

0365-6233/84/0202-0188 $ 02.50/0