Department of Pharmaceutical Sciences[1], Department of Pharmacology[2] Faculty of Pharmacy, University of Padua, Italy

Effect of drug solubility on *in vitro* availability rate from suppositories with polyethylene glycol excipients

N. Realdon[1], Eug. Ragazzi[2] and Enr. Ragazzi[1]

Factors involved in the availability mechanism of different drugs from suppositories with polyethylene glycol (PEG) excipients were studied using an *in vitro* model of the rectal compartment with a porous membrane simulating the rectal barrier. Different from lipophilic excipients, the drug is released as a consequence of the progressive dissolution of PEG into the intrarectal aqueous phase. Drug concentration in this small intrarectal phase produces the gradient against the large volume of the plasmatic phase, which regulates the diffusion rate through the barrier. As with lipophilic excipients, drug solubility in water was found to be an important factor influencing suppository release rate. Nevertheless, PEG influenced *in vitro* drug availability considerably, by increasing both drug solubility and dissolution rate. The osmotic effect of PEG in the intrarectal compartment influenced the increase in volume of the aqueous phase. The results, compared with those obtained from suppositories with a lipophilic excipient, show a higher dissolution rate from PEG excipient, but a higher diffusion rate across the barrier did not always correspond. Drugs less soluble in water showed a greater availability from PEG suppositories. On the contrary the more soluble drugs were less available.

1. Introduction

Hydrosoluble excipients consisting of polyethylene glycol (PEG) mixtures are currently used in suppositories as an alternative to lipophilic excipients. The mechanism by which the drug is made available for absorption is different from that in suppositories with lipophilic excipients. With lipophilic excipients, drug particles immobilised in the solidified suppository mass can migrate and transfer into the small volume of aqueous phase in the intrarectal compartment. Here the drug can go into solution, following the melting of the excipient at rectal temperature [1]. PEG often has a melting temperature higher than the rectal temperature and when used as excipient, the drug is released gradually as a result of the progressive dissolution of the excipient in the intrarectal phase [2–6]. The volume of this phase is increased by the diffusion of water from the plasmatic phase by osmotic effect [7]. The drug concentration in the small volume of intrarectal phase regulates diffusion across the rectal barrier in relation to the concentration gradient between the intrarectal and plasmatic phases.

We wished to verify the influence of solubility in water of different drugs on the above-mentioned mechanism of drug availability from suppositories prepared with PEG. The same rectal compartment model as in the previous study on the effect of drug solubility on availability from suppositories with lipophilic excipients was used [8]. We wished to verify the influence of solubility in water of different drugs on the above-mentioned mechanism of drug availability from suppositories prepared with PEG. To compare results with those obtained with lipophilic excipients, we studied the same six drugs with different solubilities in water at rectal temperature, and pH conditions. The drugs used were: propyphenazone, naproxen, paracetamol, aminophenazone, aminophylline, guaifenesine.

2. Investigations and results

2.1. Suppository dissolution rate

The results of drug release rates from suppositories in contact with an aqueous phase at pH 7.4, expressed as the area under the dissolution curves (% drug dissolved $\times$ time), are shown in Fig. 1A in order of drug solubility in pH 7.4 buffer solution [8].

The presence of PEG led to an increase in dissolution rate in rectal conditions for some of the drugs studied. With the exception of propyphenazone, for two of the drugs with low solubility in water at pH 7.4 (naproxen, paracetamol) dissolution increased considerably. These drugs, in a 1 : 6 w/w ratio between drug and excipient, dissolved into the melted excipient to a great extent. After solidification of the suppositories the drug remained in "solid solution" and this condition allowed fast dissolution. The presence of PEG also contributed to increased solubility in the aqueous medium. Aminophenazone also showed an increase in solubility. No particular influence was observed for the two drugs easily soluble at 37 °C (aminophylline and guaifenesine).

2.2. In vitro drug availability

The suppositories with the six different drugs in PEG excipient were tested for drug availability using the same model of rectal compartment with porous membrane as used in a previous study with lipophilic excipients [8]. The results obtained, expressed as values of the area under release curves (%drug dissolved $\times$ time), are compared in Fig. 1B in order of solubility at 37 °C, as in the dissolution test above.

In the presence of a lipophilic excipient, drug availability can be correlated with drug solubility in water under rectal conditions. However, the presence of PEG influenced *in vitro* availability, considerably which could no longer be correlated with drug solubility. In fact, the mechanism of drug availability from suppositories is different. Drug release is not the result of the migration of drug particles from the melted excipient, and their transfer into the intrarectal aqueous phase. Instead, it is due to drug release as a result of dissolution of the excipient, which contributes to an increase in drug solubility. Moreover, the osmotic effect of PEG draws water into the rectal compartment followed by an increase in volume of the intrarectal phase [7]. This can influence the diffusion mechanism of

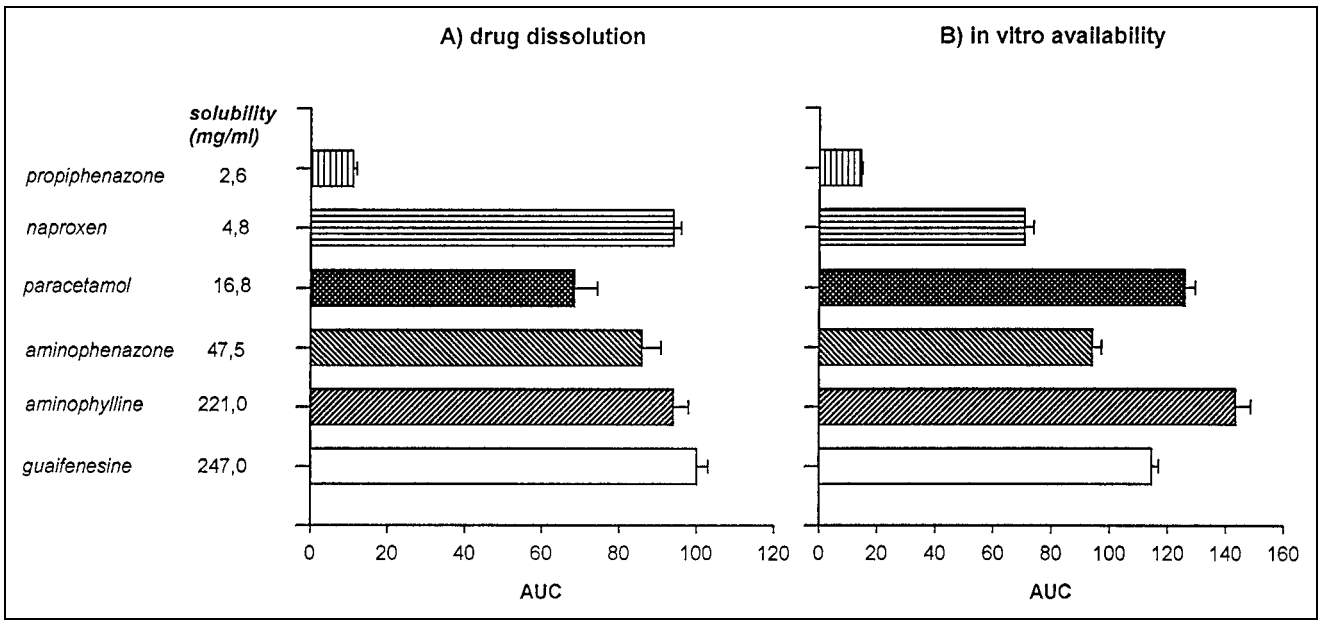

Fig. 1: Values of AUC (± SD) calculated for A) after 1 h dissolution curves (% drug dissolved × time), and B) after 3 h release curves (% drug released × time), from suppositories with PEG of the six different drugs used in order of their solubility (pH 7.4; 37 °C)

the drug through the barrier. In fact it appears that the results can neither be correlated with drug solubility nor with the dissolution test results.

2.3. In vitro release test

In the rectal compartment model used to test *in vitro* release of drugs from suppositories [8], the drug concentration in the small volume of the intrarectal phase appears to be the fundamental parameter for drug diffusion across the membrane simulating the rectal barrier. The drug dissolution rate from suppositories and drug solubility in the presence of PEG appear to be the principal parameters for explaining the behaviour in the release test.

Following the procedure adopted in our previous study [8], it was necessary to determine drug concentration in

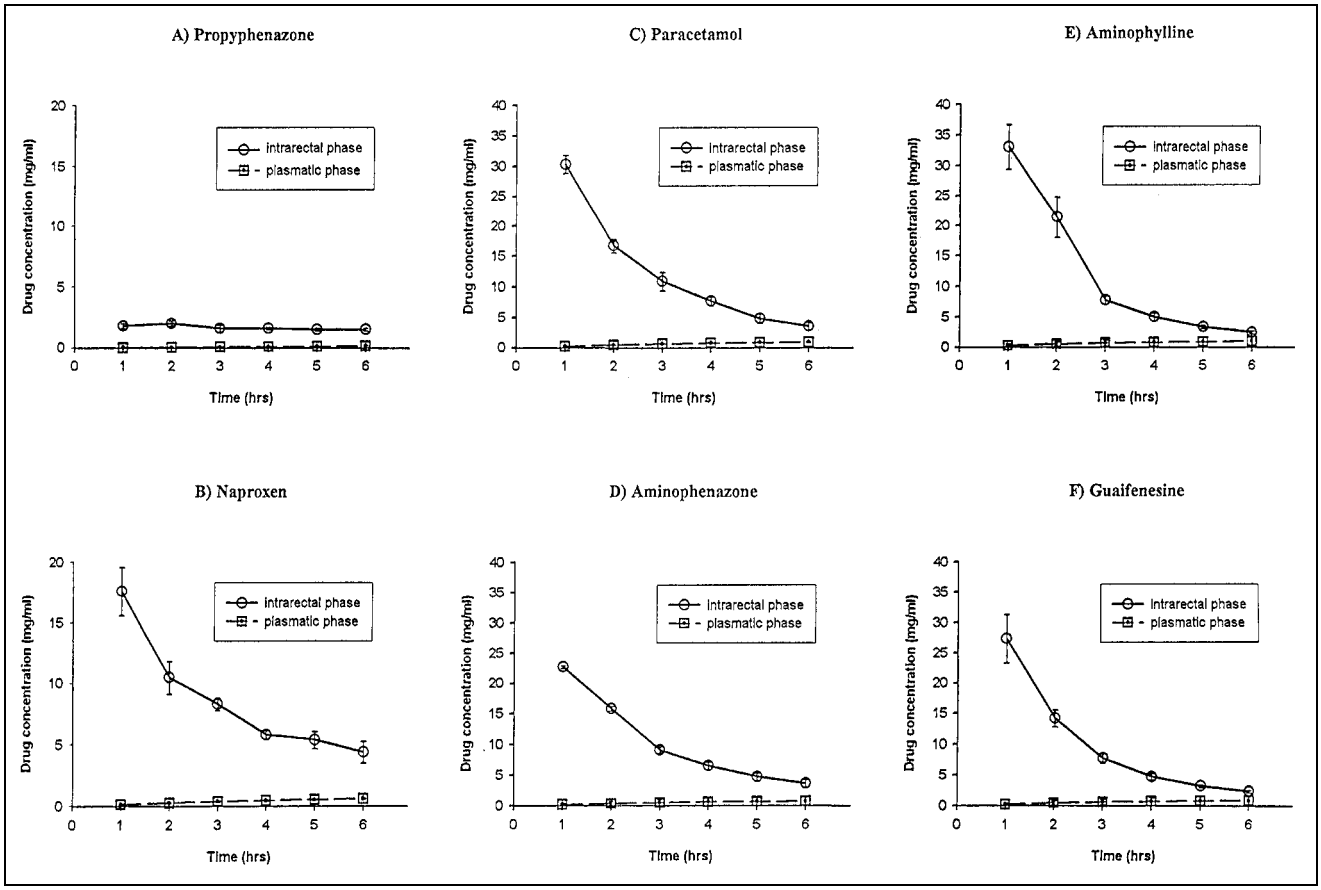

Fig. 2: Time course of concentrations of the different drugs studied in both the rectal ⊖ and plasmatic phase —□—

both the intrarectal and plasmatic phases and the volume of intrarectal phase at different time intervals during the release test *in vitro.*

In Fig. 2, concentrations of propyphenazone (A) and naproxen (B) in the intrarectal and plasmatic phases are compared. The two drugs, both with a low solubility in water, showed different dissolution rates in the presence of PEG. The low solubility of propyphenazone, more or less unchanged in the presence of PEG, produced a rapid saturation of the intrarectal phase, which was no longer receptive to further quantities of drug released as a result of dissolution of the excipient. Although values were low, the concentration remained constant. Thus a concentration gradient was ensured which allowed constant drug diffusion into the plasmatic phase, whose concentration remained low in any case. Total drug availability after 6 h never exceeded 10%.

The behaviour of naproxen was different. An hour after beginning the test, drug concentration in the intrarectal phase appeared high as a consequence of the solubilising effect of PEG. This produced a high concentration gradient which allowed fast diffusion in the plasmatic phase, resulting in high availability (see Fig. 1). This is also shown by the rapid and continuous decrease in intrarectal concentration while the drug transfers into the plasmatic phase.

High initial concentrations in the intrarectal phase were also observed for paracetamol and aminophenazone (Fig. 2, C and D). The solubilising effect of PEG was also evident for paracetamol which had higher intrarectal concentrations than aminophenazone, in spite of its lower solubility. In both cases the concentration gradient remained high enough to allow a good availability rate.

The higher solubility in water of aminophylline and guaifenesine produced a high initial drug concentration in the intrarectal phase (Fig. 2, E and F). The solubilising effect of PEG produced a higher concentration of aminophylline, although solubilities of both drugs were almost the same. The different courses of the intrarectal concentration curves show a greater availability of aminophylline, as can also be seen from the AUC values (see Fig. 1). This can be ascribed to an osmotic influence on drug diffusion across the membrane.

Fig. 3 shows the course of the osmotic effect of PEG on volumes of intrarectal compartment by diffusion of water from the plasmatic phase. The effect was limited with propyphenazone, with the lowest solubility, while for the other drugs it was considerable and almost equivalent, and cannot be correlated with either solubility or *in vitro* availability.

Drug availability kinetics from suppositories with PEG are compared in Fig. 4. With the exception of propyphenazone (whose low solubility led to a considerable quantity of drug remaining undissolved in the rectal compartment after dissolution of the excipient), the drugs demonstrated adequate availability with initial high peaks followed by successive amounts which could foresee a suitable support for therapeutic response.

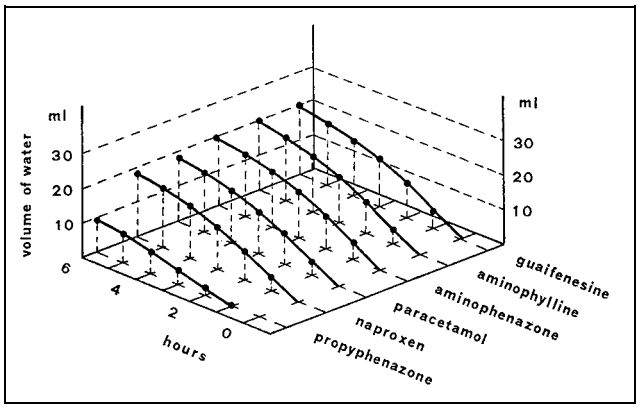

Fig. 3: Volume of water diffused into the intrarectal phase by osmotic effect during the release test of the different drugs from PEG suppositories

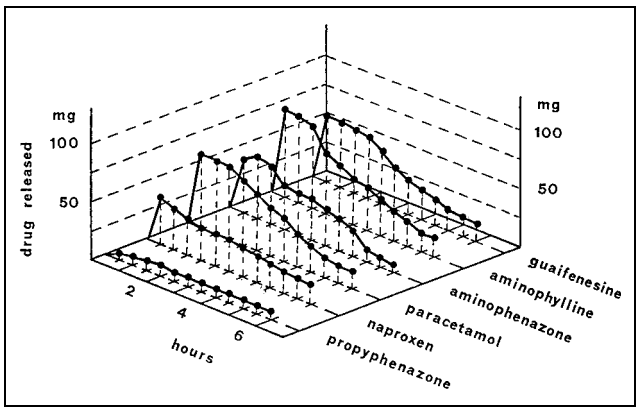

Fig. 4: Amounts (mg) of drug (having different solubilities in water) available in time from PEG suppositories

3. Discussion

In the *in vitro* model of the rectal compartment used, drug availability from suppositories is estimated by the amount of drug diffused across the porous barrier into the plasmatic phase. The diffusion rate is conditioned by drug concentration in the small volume of the intrarectal phase, which must be high enough to support a concentration gradient in the plasmatic phase necessary to ensure a diffusion flow. Drug concentration in the intrarectal phase is the parameter which the course of availability depends on. This is, in turn, conditioned by the solubility and dissolution rate of the drug released from the suppository. A correlation between drug solubility and drug rectal availability was shown in our previous study on suppositories with lipophilic excipients [8].

When using PEG as excipient, drug dissolution rates from suppositories are modified by the interaction with PEG, so that low solubility drugs, such as naproxen and paracetamol, have an increased dissolution rate (see Fig. 1). This allows intrarectal concentrations to be reached quickly, producing an intense and rapid diffusion into the plasmatic phase and thus a high overall availability. The results obtained may therefore explain different authors' observations regarding a greater availability of various drugs from suppositories with PEG compared with lipophilic excipients, either *in vitro* [9–16] or *in vivo* in animals [13, 16, 17–20], and in man [3–6, 10, 11, 21, 22].

Fig. 5 shows the results obtained with suppositories prepared with PEG compared with those of suppositories prepared with a lipophilic excipient (Witepsol H15), of the same volume (3 ml) and containing the same drugs in the same unitary dose (500 ml). In any case the use of PEG led to a higher dissolution rate (Fig. 5A). This can be ascribed above all to the different drug release mechanisms; in suppositories with lipophilic excipient by means of migration of drug particles from the melted suppository into the intrarectal aqueous phase, and in suppositories

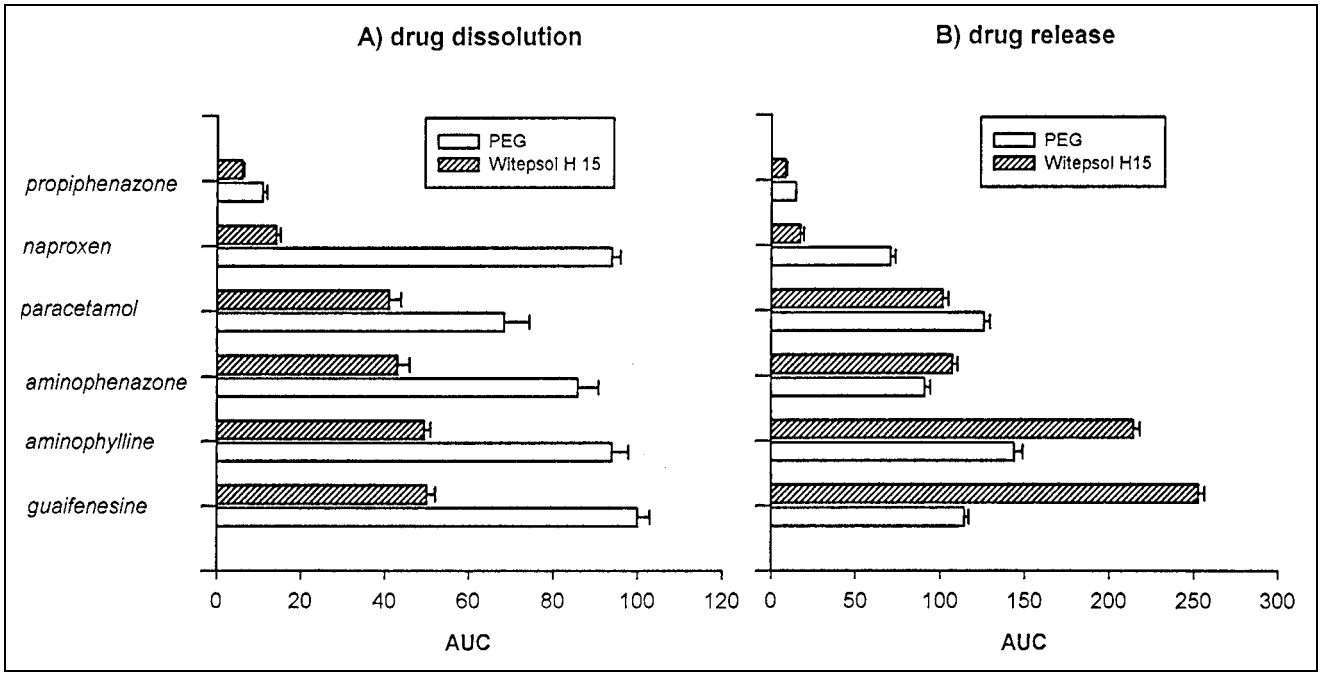

Fig. 5: Values of AUC (± SD) calculated for A) after 1 h dissolution curves (% drug dissolved × time), and B) after 3 h release curves (% drug released × time), of the six different drugs studied, from suppositories with lipophilic excipient (Witepsol H15) in comparison with those obtained from PEG suppositories

with PEG as a consequence of the progressive dissolution of excipient in the intrarectal phase. In some cases there is a solubilising effect, as seen for naproxen.

A higher drug diffusion rate across the porous barrier of the rectal compartment model did not always correspond to a greater dissolution rate with PEG (Fig. 5B). While the less soluble drugs (propyphenazone, naproxen, paracetamol) demonstrated greater availability from suppositories with PEG, the more soluble drugs had greater availability from suppositories with lipophilic excipient. This can be ascribed to the different osmotic conditions produced by PEG in solution in the intrarectal phase.

4. Experimental

4.1. Materials

Propyphenazone, paracetamol, aminophenazone, aminophylline and guaifenesine were purchased from A.C.E.F. (Fiorenzuola d'Arda, Piacenza, Italy) and naproxen from Alfa Wassermann S.p.A. (Milano, Italy). Polyethylene glycols (PEG) 400 and 4000 were also purchased from A.C.E.F.

4.2. Methods

4.2.1. Preparation of suppositories

Suppositories of 3 ml were prepared with each of the six drugs at the same dose of 500 mg. The excipient (PEG 400 and 4000 in a 40 : 60 ratio) was melted at 50 °C and the drug in a fine powder was uniformly dispersed by a Silverson turbomixer (Waterside, Chesham, U.K.). The melted mass was then poured into disposable PVC moulds and cooled to solidification at room temperature (18–20 °C). After 24 h the suppositories were refrigerated (5–10 °C) until use in the different tests.

4.2.2. Drug dissolution rate from suppositories

The conditions described in our previous paper [8] were followed using phosphate buffer pH 7.4, at 37 °C.

4.2.3. Contemporary determination of drug availability, and intrarectal phase volume and drug concentration

Each suppository was placed in a piece of dialysis tube (Visking Tubing, London, U.K.) 10 cm long and 25 mm diameter, closed at one end, which had previously been soaked in water overnight at room temperature. After the addition of 5 ml of phosphate buffer solution 1/15 M, pH 7.4, the tube was closed at the other end. The two ends of each tube were held by Perspex 1.5 × 3 cm clamps. Six suppositories were placed horizontally and radially 3 cm from the bottom of a cylindrical basin (25 cm in diameter and 10 cm deep) containing 3 l of buffer solution pH 7.4 thermostated to 37 °C and stirred constantly at 100 r.p.m. by a 10 cm blade stirrer. Every 15 min 2 ml samples of diffusion fluid were collected from each basin and replaced with the same amount of buffer solution. The concentration of drug released from suppositories was determined spectrophotometrically after suitable dilution with buffer solution at wavelengths of 267 nm for propyphenazone, 262 nm for naproxen, 242 nm for paracetamol, 260 nm for aminophenazone, 271 nm for aminophylline and 222 nm for guaifenesine. The test was carried out contemporaneously using six basins.

After 1 h the test was stopped for the first basin. The intrarectal phase was drawn up with a graduate syringe and measured. The volume of water diffused osmotically into the intrarectal compartment was calculated by subtracting the 5 ml of buffer solution initially introduced in each tube. Drug concentration was determined spectrophotometrically for the solution obtained from each tube. This operation was repeated hourly for the other five basins.

References

1 Moes, A. J.: Boll. Chim. Farm. **128**, 5 (1989)
2 Puech, A.; Lasserre, Y.; Jakob, N.; Duru, C.: J. Pharm. Belg. **36**, 332 (1981)
3 Marvola, M.; Jokila, P.; Komulainen, M.: Acta Pharm. Fenn. **90**, 211 (1981)
4 Abd El-Bary, A.; Ibrahim, S. A.; Elsorady, H.; Abd Elmonen, H: Pharm. Ind. **45**, 307 (1983)
5 Möller, H.: Parm. Ind., 46, 285 (1984)
6 Vromans, H.; Moolenaar, F.; Visse, J.; Meijer, D. K. F.: Pharm. Weekbl. sc. ed. **6**, 18 (1984)
7 Ragazzi, E.; Dalla Fini, G.; Dal Zotto, M.: Boll. Chim. Farm. **125**, 234 (1986)
8 Realdon, N.; Ragazzi Eug.; Ragazzi Enr.: Pharmazie **55**, 372 (2000).
9 Becirevic, M.; Petricic, V.: Pharmazie **41**, 338 (1986)
10 Stavchansky, G.; Wallace, J. E.; Geary, R.; Hecht, G.; Robb, C. A.; Wu, P.: J. Pharm. Sci. **76**, 441 (1987)
11 Kahela, P.; Laine, E.; Anttila, M.: Drug Dev. Ind. Pharm. **13**, 213 (1987)
12 Akala, E. O.; Adedoyin, A.; Ogunbona, F. A.: Drug Dev. Ind. Pharm. **17**, 303 (1991)
13 Lootvoet, G.; Beyssac, E.; Shiu, G.K.; Aiache, J. M.; Ritschel W. A.: Int. J. Pharm. **85**, 113 (1992)
14 Yamazaki, M.; Itoh, S.; Sasaki, N.; Tanabe, K.; Uchiyama, M.: Pharm. Res. **10**, 927 (1993)
15 Hammouda, Y. E.; Kasim, N. A.; Nada, A. H.: Int. J. Pharm. **89**, 111 (1993)

16 Shinoda, M.; Akita, M.; Hasegawa, M.; Nadai, M.; Hasegawa, T.; Nareshima, T.: Biol. Pharm. Bull. **18**, 1289 (1995)
17 Zein El-Din, E.; Sakr, F. M.; Hasheim, F.: Drug Dev. Ind. Pharm. **13**, 1973 (1987)
18 Yamazaki, M.; Itoh, S.; Sawanoi, M.; Kobayashi, M.; Suzuki, S.; Komatsu, T.; Tanabe, K.: J. Pharm. Pharmacol. **42**, 441 (1990)
19 Regdon, G.; Gebri, G.; Regdon, E.; Selmeczi, B.: Pharm. Ind. **53**, 296 (1991)
20 Ogiso, T.; Iwaki, M.; Tanino, T.; Fujii, J.; Paku, T.: Biol. Pharm. Bull. **16**, 315 (1993)
21 Moolenaar, F.; Kaufmann, B. G.; Visser, J.; Meijer, D. K. F.: Int. J. Pharm. **33**, 249 (1986)
22 Babar, A.; Fares, H. M.; Plakogiannis, F. M.: J. Pharm. Sci. **83**, 389 (1993)

Received May 29, 2000
Accepted June 15, 2000

Prof. Dr. Enrico Ragazzi
Dipartimento di Scienze Farmaceutiche
Via F. Marzolo, 5
35131 Padua
Italy
realdon@dsfarm.unipd.it