International Journal of Pharmaceutics, 8 (1981) 153–156

Short Communication

A new in vitro dissolution test for controlled-release theophylline tablets

J.H.G. JONKMAN *,**, R. SCHOENMAKER *, N. GRIMBERG * and R.A. DE ZEEUW **

* *Laboratory for Drug Analysis, Kerkstraat 14, 9401 GW Assen and* ** *Laboratory for Pharmaceutical and Analytical Chemistry, Department of Toxicology, State University, Ant. Deusinglaan 2, 9713 AW Groningen (The Netherlands)*

(Received February 6th, 1981)
(Accepted February 11th, 1981)

The use of controlled-release drug products can be advantageous because such dosage forms may reduce unwanted toxic effects due to high peak concentrations. It is also likely, that patient compliance will increase when the patient has to take fewer doses per day (Bogentoft and Sjögren, 1980) and when unwanted side-effects occur less frequently. Controlled-release drug preparations are especially recommended when the drug has a relatively short half-life and a narrow therapeutic range.

Theophylline meets both of these specifications: its half-life is approximately 4–9 h and the therapeutic range is 10–20 mg/l. Conventional theophylline dosage forms require drug intake every 6 h (Weinberger et al., 1978; Jonkman et al., 1980; Mellstrand et al., 1980). Such a schedule may result in low trough levels in the morning resulting in a breaking through of the symptoms in most asthma patients. The use of properly designed controlled-release preparations may eliminate this 'morning dip'. On this rationale, several drug manufacturers have introduced controlled-release theophylline preparations in recent years.

The release pattern of a drug from various controlled-release dosage forms may differ substantially, depending on the particular design of such a dosage form (e.g. barrier coating either of beads or of the whole tablet; insoluble matrix, eroding matrix, hydrophilic gel matrix; osmotic pump, etc.; Marshall, 1979; Bogentoft and Sjögren, 1980; Cabana, 1980). For this reason it is important to determine the in vivo release characteristics; however, this is difficult in practice. An in vitro dissolution method that correlates well with in vivo rate and extent of absorption may simplify product development, testing and quality control. However, such a test for controlled-release preparations has not yet been described in any official pharmacopoeia or compendium.

The aim of this study was to develop a method that is simple, easy to operate with an existing apparatus and able providing good correlation with in vivo data.

As controlled-release tablets pass the entire upper gastrointestinal tract, we decided that the method should at least involve a pH-change. Because some controlled-release preparations are prepared in such a way that disintegration occurs before drug release can happen, we felt that we should check the disintegration test as described in the Ph. Eur. with an additional pH-change of the medium (N.B. This test is identical to the disintegra-

tion test described in U.S.P. XX/NF XV). The test is an oscillating tube method and the apparatus involved in this test is a standard piece of equipment in most laboratories. The main part of the apparatus is a rigid basket-rack assembly supporting 6 cylindrical glass tubes, the lower end of which is covered by a stainless steel wire mesh. Provision is made for the tubes to be raised and lowered through a distance of 5–6 cm some 28–32 times per minute in a test fluid maintained between 35 and 39°C. Continuous agitation of the tablets is ensured in this way and by the presence of a specially designed plastic disc, that can move up and down freely in the tubes.

A modification of this disintegration apparatus is described in U.S.P. XX/NF XV as Apparatus 3 for the Dissolution Test.

The modifications involve the following: (a) the discs are not used; (b) the apparatus is adjusted so that the bottom of the basket-rack assembly descends to 1.0 ± 0.1 cm from the inside bottom surface of the vessel on the downward stroke (instead of 2.5 cm); (c) the 10-mesh stainless-steel cloth in the basket-rack assembly is replaced with 40-mesh stainless-steel cloth; and (d) 40-mesh stainless-steel cloth is fitted to the top of the basket-rack assembly.

In our investigations an Erweka ZT 3 was used (Erweka Apparatenbau, 6056 Heusenstam, F.R.G.), after applying the described modifications.

The volume of the dissolution medium was 900 ml. Samples (about 2 ml) were taken every 15 min by means of a syringe and filtered through a Millex-G.S. 0.22-μm filter (Millipore S.A., 67 Molsheim, France). Each sample was replaced by an equal volume of the medium.

The pH of the medium was kept at 1.0 (1 N hydrochloric acid) for 2 h. The beaker with the medium was then removed and replaced with one containing a solution of pH = 6.8 (phosphate buffer as described in Ph. Eur. under 'Disintegration Test', Enteric Coated Tablets). Each test was performed on one tablet and the mean and standard deviation of 6 replicate determinations were calculated. The concentration of theophylline in the samples was determined by measuring the UV absorption at 270 nm.

The applicability of this new dissolution test for controlled-release tablets was examined by comparing the obtained in vitro data with in vivo data as described in our reports on the disposition and clinical pharmacokinetics with two commercially available tablets (Jonkman et al., 1981a, b). The results on Theolair Retard (= Theolair S.R. = Nuelin S.R.) 250 mg tablets (Riker Laboratories, Loughborough, England; batch number 790109 US) are given in Fig. 1 and those on Theo-Dur (=Theolin) 300 mg tablets (Draco, A.B., Laboratories, Lund, Sweden; batch number 940480) are represented in Fig. 2.

The release of theophylline from Theolair Retard 250 mg tablets was found to be highly pH-dependent. In the acid medium only 30.5 ± 0.5% (mean ± S.D.) of the dose was released from the dosage form. When the hydrochloric acid was replaced by the buffer, it took only an additional 1.25 h to release the remaining theophylline completely. The release rate constant in the acid medium was about 0.2 h^{-1} and in the buffer about 1.7 h^{-1}, thus being about 8 times faster. This biphasic dissolution process would seem to correlate with a biphasic absorption phenomenon as found in various patients (Jonkman et al., 1981b), an example being depicted in Fig. 1 (patient 3). It may be assumed that the inflection point in the absorption curve represents gastric emptying. The absorption rate constant found in these patients was 2–8 times faster in the intestines

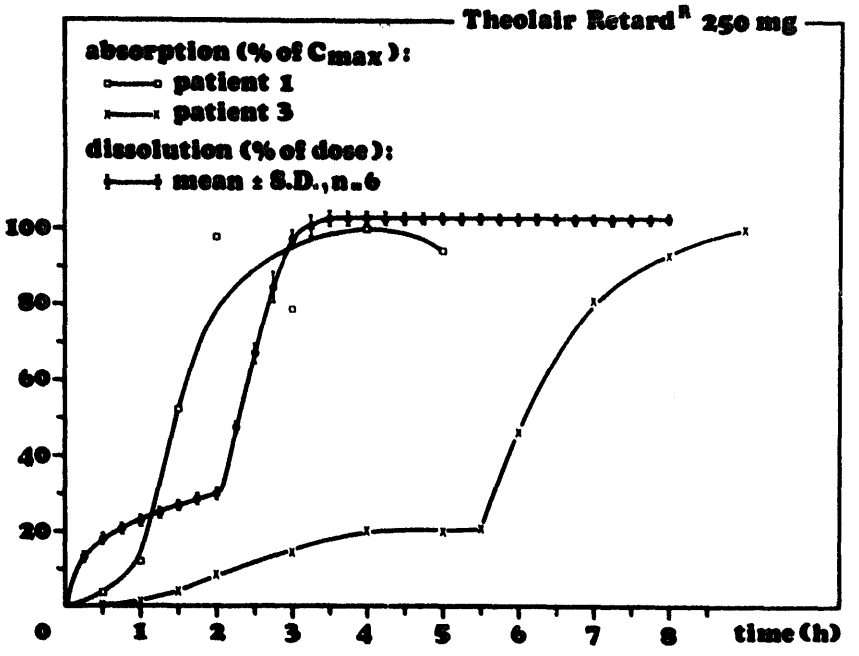

Fig. 1. The in vitro release of theophylline from Theolair Retard 250 mg tablets compared to the in vivo absorption in two typical patients. The in vitro dissolution is expressed as percentage of the dose. The pH of the medium was (arbitrarily) changed after 2 h from 1.0 to 6.8. The in vivo absorption is given by expressing the theophylline serum concentrations at different time points as percentage of the maximum concentration. Patient 1 is typical for a monophasic (intestinal) absorption process. (Note the correlation of the slope of the absorption curve with that of the dissolution curve obtained in a medium of pH = 6.8). Patient 3 is representative for biphasic (gastric and intestinal) absorption phenomenon. (Note the correlation of the two phases of the absorption curve with the slopes of the dissolution curves obtained at pH = 1.0 and pH = 6.8).

than in the stomach (probably effected by individual differences in intestinal/gastric motility). This compares well with the dissolution data, especially when realizing that the pH-change was performed arbitrarily after 2 h, whereas gastric emptying may vary from 0.5 to 7 h (Blythe et al., 1959). In the remaining patients only a monophasic absorption was seen (e.g. patient 1 in Fig. 1) The slope of the curve is about the same as observed in the second phase observed in patient 3; this might be an indication that we are now dealing with a short stay of the tablet in the stomach, followed by intestinal absorption.

With the Theo-Dur 300 mg tablets, 29.6 ± 2.0% (mean ± S.D.) of the dose was released within 2 h in the acid medium. The rate of release in the buffer solution was almost the same and it took about 5 h more to obtain complete dissolution of theophylline. One halved tablet together with a whole tablet released theophylline about 10–15% faster than whole tablets alone did. After 2 h, 32.4 ± 2.2% (mean ± S.D.) of a dose of 450 mg (the dose used in our clinical study) was released. The variation in release rate between the 6 Theo-Dur 300 mg tablets was found to be somewhat higher than between the 6 Theolair Retard 250 mg tablets. The profile of the dissolution curve was found to correlate well with the shape of the absorption curve. Both processes seem to be pH-independent and monophasic (see Fig. 2).

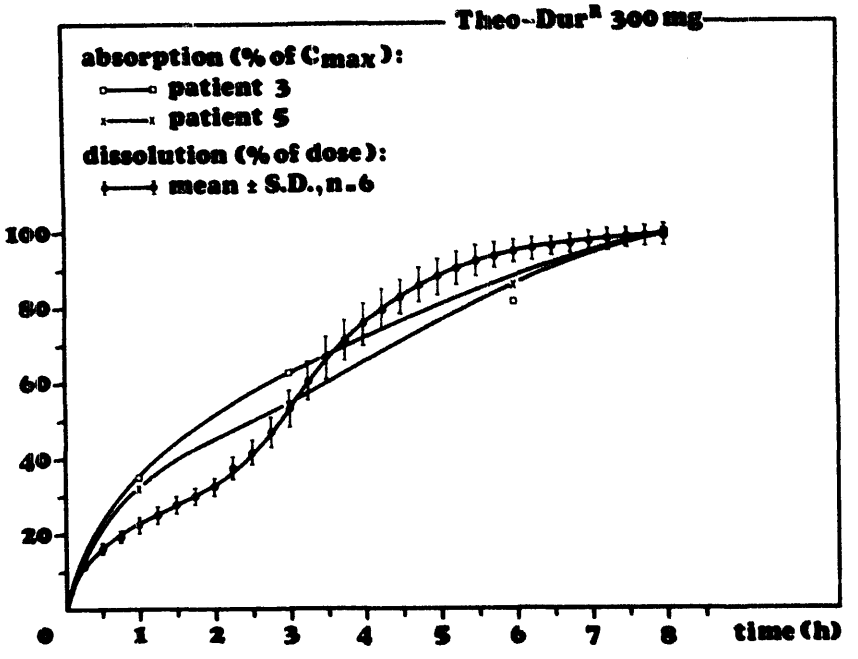

Fig. 2. The in vitro release of theophylline from Theo-Dur 300 mg tablets compared to the in vivo absorption in two typical patients. See also legend of Fig. 1.

Therefore, this modified dissolution test would seem to be a useful tool in designing new controlled-release dosage forms as well as for the quality control of such dosage forms.

REFERENCES

Bogentoft, C. and Sjögren, J., In Breimer, D.D. (Ed.), Towards Better Safety of Drugs and Pharmaceutical Products, Elsevier/North-Holland Biomedical Press, Amsterdam, 1980, pp. 229–246.

Blythe, R.H., Grass, G.M. and Mac Donnell, D.R., The formulation and evaluation of enteric coated aspirin tablets. Am. J. Pharm., 131 (1959) 206–216.

Cabana, B.E., In Breimer, D.D. (Ed.), Towards Better Safety of Drugs and Pharmaceutical Products, Elsevier/North-Holland Biomedical Press, Amsterdam, 1980, pp. 301–322.

Jonkman, J.H.G., Berg, W.Chr., Schoenmaker, R., De Zeeuw, R.A., Greving, J.E. and Orie, N.G.M., Disposition and clinical pharmacokinetics of microcrystalline theophylline. Eur. J. Clin. Pharmacol., 17 (1980) 379–384.

Jonkman, J.H.G., Koëter, G.H., Schoenmaker, R., De Vries, K., Greving, J.E. and De Zeeuw, R.A., Serum and saliva theophylline correlation after administration of a sustained release preparation. Eur. J. Clin. Pharmacol., (1981a) in press.

Jonkman, J.H.G., Berg, W.Chr., De Vries, K., De Zeeuw, R.A., Schoenmaker, R. and Grimberg, N., Disposition and clinical pharmacokinetics of theophylline after administration of a new sustained release tablet. (submitted for publication).

Marshall, K., In Banker, G.S. and Rhodes, C.T. (Ed.), Modern Pharmaceutics, Marcel Dekker, New York, 1979, pp. 359–428.

Mellstrand, T., Svedmyr, N. and Fagerström, P.-O., Absorption of theophylline from conventional and sustained-release tablets, Eur. J. Respir. Dis., Suppl. 109, 61 (1980) 54–61.

Weinberger, M., Hendeles, L. and Bighley, L., The relation of product formulation to absorption of oral theophylline. New Engl. J. Med., 299 (1978) 852–857.