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DEVELOPMENT AND EVALUATION OF DISSOLUTION TESTS USING CLINICAL DATA

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ABSTRACT

In the present investigation, the in vitro dissolution rates of five commercially available tablets and capsules containing nitrofurantoin were compared with the urinary excretion of the drug and with the calculated dissolution in man. The in vitro dissolution profiles were obtained using the Rotating Basket (USP), the Paddle Method and a Flow-through dissolution cell. No correlation could be found between in vitro and in vivo results using the Rotating Basket or Paddle Methods. With the Flow-through cell, a correlation (r = 0.97) could be shown for only four of the five dosage forms.

A new type of dissolution model has been developed, consisting of two, interconnecting Flow-through cells, in an attempt to enable in vitro/in vivo correlations to be made for all preparations

tested. In this novel model, the dosage form disintegrates in the "gastric" part of the model and some of the drug particles are continuously pumped into the "intestinal" part. This new model gave good correlations (r = 0.98) between in vitro and in vivo results for all the tablets and capsules of nitrofurantoin tested.

INTRODUCTION

In vitro tests are being increasingly used to determine the rates of dissolution of "problem" drugs from oral preparations. However questions have been raised concerning the ability of in vitro methods to accurately predict release in vivo.

In the present investigation, the question of how well in vitro release tests can be correlated with in vivo release studies has been examined with reference to the "problem" drug nitrofurantoin.

Nitrofurantoin is a sparingly soluble drug which is particularly suited to comparative in vitro/in vivo investigations, because its cumulative urinary excretion curve reflects, after a very short delay, the kinetics of release of the active ingredient from the dosage form. By using solutions of the drug, the active ingredient is in a readily available form from the very outset of the experiment. Studies in six subjects showed that within one hour, more than 75 %, and within 2 hours more than 90 % of the non-metabolised fraction of nitrofurantoin is excreted in the urine (1).

The particular suitability of nitrofurantoin for correlation studies of biopharmaceutical data has already led to several in vitro/in vivo comparative investigations with this drug (2,3,4,5,6). All of these studies have essentially attempted to show a correlation between the rate of dissolution of the drug in vitro and its renal excretion curve. Although not described as such by the authors, the in vitro tests used are really accelerated dissolution tests, i.e. the dissolution in vitro proceeds in all cases faster than the comparable release in vivo. Attempts are made to correlate very different rates of release by mathematical methods. Until now however, even this procedure, when applied to the testing of commercial preparations, has failed to show any correlation between in vitro and in vivo results.

Nitrofurantoin is used therapeutically in several different dosage forms. For oral administration, coated and uncoated tablets, as well as hard gelatine capsules are on the market. According to the manufacturers, the release of the drug in the majority of these preparations is controlled by the particle size of the active ingredient. A deviation from this formulation principle arises in a commercially available capsule where microcrystalline nitrofurantoin is contained in an acid-resistant coated and granulated form. With this preparation a different pattern of release is to be expected, since here, quantitative release can only occur after the drug has passed the stomach.

METHODOLOGY

In vitro studies

Paddle Method

900 ml of dissolution medium were poured into a triple-necked 1000 ml round bottomed flask and the dissolution test carried out at 37°C. The dimensions of the paddle corresponded to those given by Rothe (12). The speed of rotation of the paddle was 50/min.

Composition of the dissolution medium:

pH 3.0; physiological saline, adjusted to pH 3 with 0.1 N HCl.

pH 7.2; isotonic phosphate buffer USP with a pH of 7.2.

Rotating Basket Method

The procedure was carried out as specified in the USP XIX.

Flow Through Cell

According to Dibbern and Wirbitzki (13); details of the pH profile and flow rates are described by (9).

Two compartment dissolution model

The dimensions of the individuel flow through cells correspond to those described by Dibbern and Wirbitzki (13).

Fig. 1 shows the construction of the model used. The inner diameter of the connection between the dissolution compartments is 5 mm. The distance between the two cells is 20 mm. Cell A contains 12 glass beads around 8 mm diameter. There is a plastic sponge in

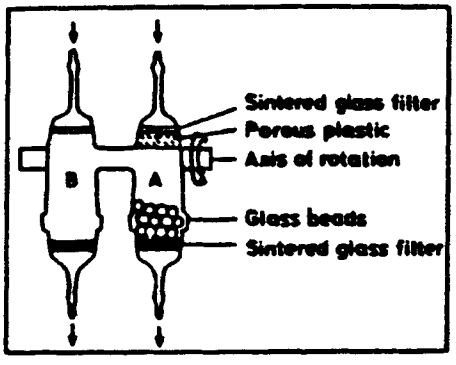

FIGURE 1
Diagram of the two compartment dissolution model used in these studies.

cell A up to the level of the connection with cell B. In this way accumulation of air bubbles in cell A during the experiment is avoided. The sponge is so arranged that any air is pumped into cell B.

During the experiment the cells are rotated by a slow running electric motor (3 revs/min) which turns three quarters of a revolution one way and then back. The two cells and a reservoir for dissolution medium are contained in a constant temperature water bath at 37°C. For an accelerated release test the following flow conditions were adjusted: cell A, inflow 200 ml/hr, outflow 100 ml/hr; cell B, inflow 100 ml/hr, outflow 200 ml/hr. For the release test providing time correlation the following flow conditions were adjusted: cell A, inflow 100 ml/hr, outflow 50 ml/hr; cell B, inflow 50 ml/hr, outflow 100 ml/hr; after 90 minutes: cell A, inflow 66 ml/hr, outflow 33 ml/hr; cell B, inflow 33 ml/hr, outflow

66 ml/hr. Physiological saline, adjusted to pH 3 by HCl is pumped into cell A. Isotonic phosphate buffer USP pH 7.2 is used in cell B.

The in vitro data presented in this study always represent the arithmetic means of at least 4 determinations.

In vivo investigations

Detailes of the in vivo studies, carried out in 4 or 6 subjects, are given in (7,8).

RESULTS

Cumulative urinary excretion

The cumulative urinary excretion of nitrofurantoin in man after administration of five commercially available preparations is shown in Fig. 2 a (7,8). Comparison of the results shows that the urinary excretion of nitrofurantoin after administration of tablets and hard gelatin capsules with macrocrystalline drug (Preparations B, C and D) follows a broadly similar pattern. The total amount of the drug eliminated in the urine with these preparations is about one third less than with the non retarded tablet preparation A. With the capsule preparation E containing acid-resistant, coated and granulated nitrofurantoin crystals, the urinary excretion proceeds significantly slower. The amount of drug eliminated with preparation E is over 50 % less than with the tablet preparation A.

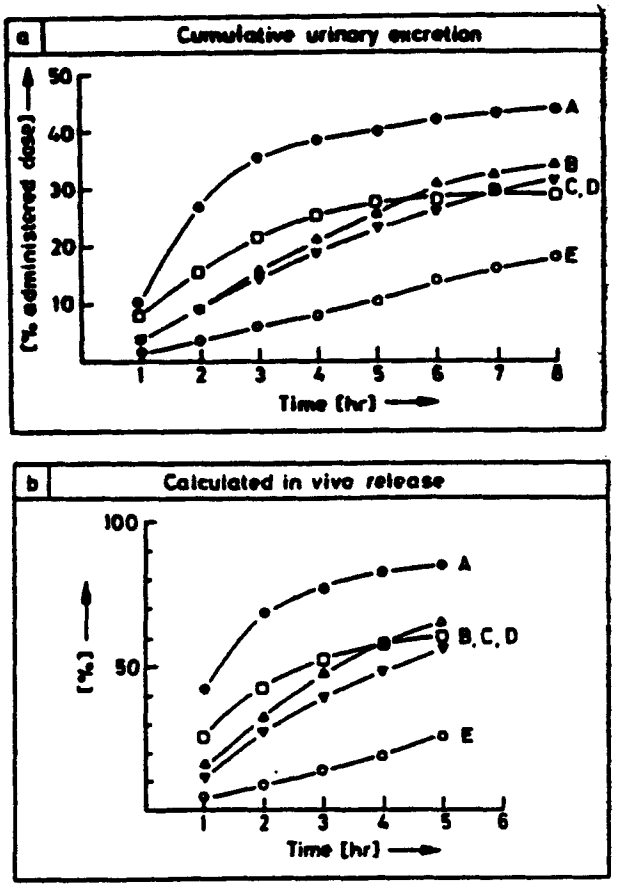

FIGURE 2 a,b

Cumulative urinary excretion and calculated in vivo release after oral administration of commercial preparations of nitrofurantoin

A, Tabl. 100 mg B, Caps. 100 mg
C, Caps. 100 mg D, Tabl. 50 mg (2x)
E, Caps. 150 mg

Calculated release profiles

The renal excretion of nitrofurantoin after administration of medizinal preparations can give only indirect information about the dissolution pattern of various preparations in the gastrointestinal tract. The urinary excretion profile is influenced not only by the release of active ingredient, but also by, for example, by the individual pharmacokinetics of the drug in man.

To obtain analogous data for comparing and evaluating the results of in vitro tests, the in vivo release profiles of the clinically tested preparations are calculated by approximation (9). As shown in Fig. 2 b, the calculations were undertaken over only a limited time of 5 hrs. Absorption of the drug is reduced after a few hours, so it is correspondingly not excreted in the urine to such an extend as in the first hours. Thus the in vivo release of nitrofurantoin is only represented by its urinary excretion for the initial period following its administration.

In vitro tests

When attempting to correlate the results of in vitro studies with comparative clinical investigations, it is always necessary to use drugs from the same manufacturing process for both experiments. For this reason the commercial preparations used in these investigations were of the same batch employed in in vivo studies.

Paddle Method

In the Paddle Method, the dissolution of the drug is tested in a specified amount of buffer solution under agitation with a special rotating blade (10). The Paddle Method is being discussed as the method to be adopted by the European Pharmacopoeia.

The results of the present study (figs. 3 a and 3 b) show that, in the case of nitrofurantoin, this method could not give release profiles, under two different conditions of pH, which would enable suitable evaluation of the various commercial preparations investigated. Thus preparations which show practically no differences in vivo, give quite different results in vitro with this method.

The limited predictive ability of the Paddle Method for nitrofurantoin is reflected in the correlation coefficients calculated for the comparison of the amount of the drug released after 5 hrs in vitro and that released in vivo. At pH 3.0, $r = 0.69$, at pH 7.2, $r = 0.56$.

Rotating Basket Method USP

The conditions used for studying the release of nitrofurantoin from commercial preparations using the Rotating Basket Method at a pH of 7.2 were those specified in the USP for tablets. The results given in Fig. 3d show that the release of active ingredient from all preparations is extremly rapid. The inappropriate rank order of preparations given by this test indicates that this method is also not

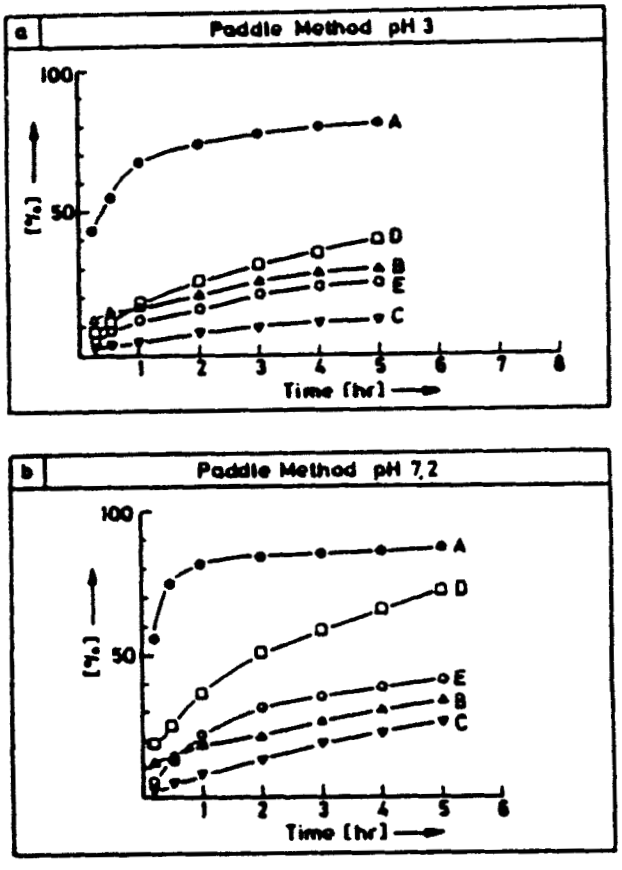

FIGURE 3 a,b
In vitro release of nitrofurantoin from commercial preparations

suitable as an accelerated dissolution test. Comparison of the release after one hour in vitro with the cumulative urinary excretion after 5 hrs gives a correlation coefficient of only 0.39.

Flow Through Cells

The rate of flow and pH development in flow through cells can be adjusted according to the

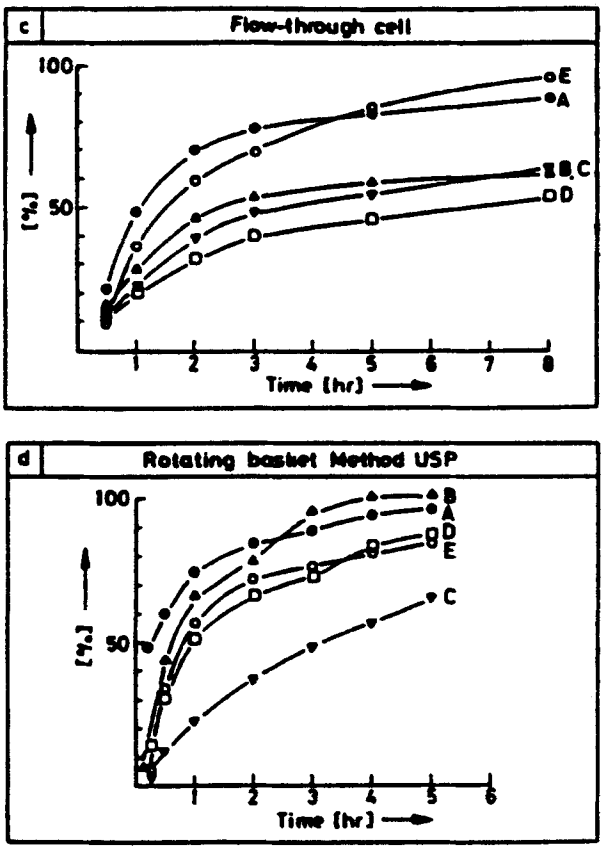

FIGURE 3 c,d
In vitro release of nitrofurantoin from commercial preparations

desired rate of dissolution (9). As shown in Fig. 3 c, it was possible using flow through cells to obtain closely similar release profiles in vitro and in vivo for four out of the five preparations tested. Thus the comparison of the amount of drug released after 7 hours in vitro with the cumulative urinary excretion gives a correlation coefficient of 0.97. The limitations of the flow through technique in

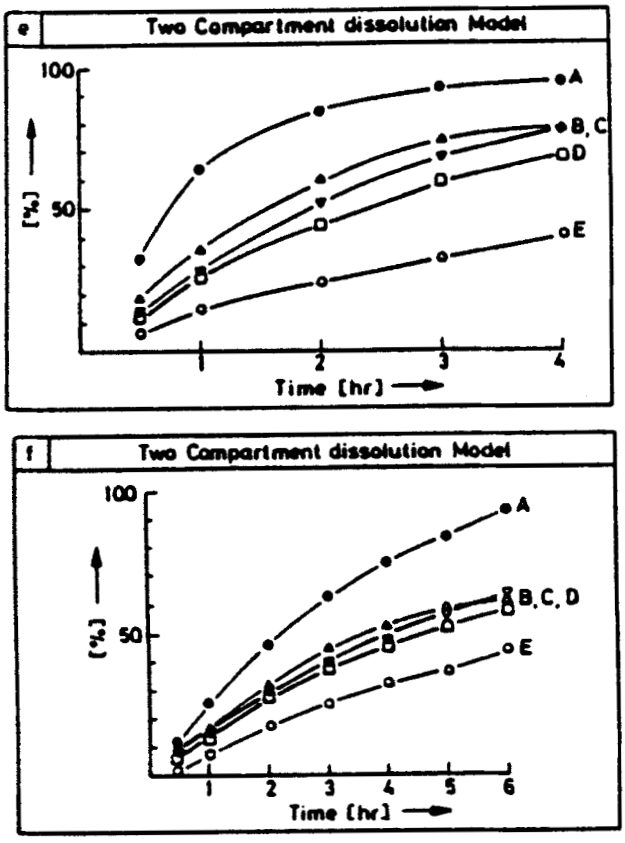

FIGURE 3 e,f
In vitro release of nitrofurantoin from commercial preparations

testing release are however demonstrated by preparation E, where there is a large discrepancy between in vitro and in vivo results.

Development and evaluation of a multi-compartment release model

The comparative studies of release of active ingredient from commercial preparations of nitro-

furantoin show that a correlation can be obtained between in vitro and in vivo results using standard flow through cells for four of five dosage forms tested. For another preparation where an important requirement for drug release is transport of the coated drug from the stomach into the small intestine no correlation is obtained.

During the course of the present investigations attempts were therefor made to see if multi-chamber systems would give correlateble release data in evaluating drug forms based on different formulation principles.

The multi-compartment system developed in this study consists of two or more flow-through cells joined together. By regulating the in and outflows it is possible to achieve a controlled transfer of dissolution medium with drug particles from one chamber to the next. A diagram of the simplest construction of a "gastrointestinal" model is shown in Fig. 4. The drug disintegrates at the start of the experiment in cell A. The exchange of dissolution medium containing dissolved and suspended drug is regulated in the present example by variable speed pumps. By this means the limited buffer capacity of the isotonically adjusted artificial gastric juice is guaranteed so that no significant pH fluctuations occur in cell B. A rotatory movement of the flow through cells, and if necessary, the addition of glass beads to cell A may be required to standardise parameters such as eg the mixing of the solution, suspension of particles, as well as the mechanical stress of the drug.

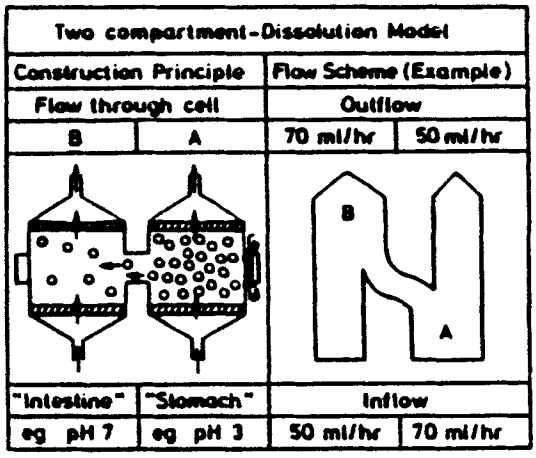

FIGURE 4

Construction principle and flow scheme of a multi-compartiment dissolution model

The results of the in vitro test of commercial preparations (Fig. 3e) shows that after standardization of the flow rate, this method gives in vitro release profiles which are in agreement with in vivo data for all the preparations tested, even those based on different formulation principles. The slow passage of acid-resistend, coated drug carrier particles from cell A to cell B leads, even for preparation E, to release rates which correlate with in vivo data. A comparison of the time axis shows that the flow rates chosen in vitro correspond to an accelerated release test. Thus a correlation coefficient of 0.99 is achived between the amount of drug released after 3 hrs in vitro and the urinary excretion after 5 hrs. The comparison of the in vivo release after 4 hrs with the in vitro release after

2 hrs gives a correlation coefficient of 0.98, which shows that dissolution after these conditions in vitro proceeds at an acceleration factor of 2.

As the results in Fig 3f predict, by reducing the flow rate it is also possible to match the time axes, and so preserve the rank order of the preparations. When in vivo and in vitro release times are equalised, a correlation coefficient of 0.96 can be obtained for comparison of amounts of drug released in vitro and in vivo after 5 hrs.

DISCUSSION

In the present study it has been shown that in the case of nitrofurantoin preparations, release tests most frequently proposed as Pharmacopoeial Methods, eg the Paddle Method or the USP Rotating Basket, do not provide results which correlate with the corresponding in vivo data. A correct evaluation of the test preparations using the in vitro data is thus not possible.

Although, for various reasons, simple release tests are currently preferred for Pharmacopoeial methods, more complex techniques may be necessary in drug research and development. The new type of test apparatus described in this study was developed in an attempt to solve problems encountered in the in vitro/in vivo correlation of preparations of nitrofurantoin. A model was constructed in which those factors could be simulated which actually alter the release of drug from drug forms in vivo. Among these factors for oral dosage forms is the change in

dissolution conditions for some of the drug as it passes from the stomach to the small intestine. Such conditions cannot be simulated in the usual dissolution tests. The pH of the dissolution medium is normally kept constant and/or the pH conditions are changed for the entire dosage form.

However in the multi-compartment model, two or more flow through cells are joined together. In each individual cell, specific dissolution conditions, eg in respect of pH can be programmed by adjustment of in and outflow. It is possible to achive passage of particles of drug from one cell to the next through connections between the cells by regulating the inflow and outflow rates. On the basic of this principle, complex 'gastrointestinal' models can be constructed which can help to solve biopharmaceutical problems.

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