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The comparison of a novel continuous-flow dissolution apparatus for suppositories with the rotating basket technique

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Summary

The dissolution rate of a drug from a solid dosage unit is an important parameter affecting drug bioavailability. While dissolution testing has received much attention in the cases of tablets and capsules, it has received much less attention with suppositories. It was for this reason that the performance of a novel flow-through bead-bed apparatus was assessed in our laboratories. A flow-through dissolution chamber based on a published American design was constructed. It was tested in two ways: firstly using fatty based benzocaine suppositories, dissolution rates were determined at different temperatures. The data obtained agreed well with original published data indicating that the apparatus can be easily fashioned from standard laboratory equipment and can give reproducible results in different laboratories. For comparison the benzocaine suppositories were also tested using a rotating basket method. Similar dissolution profiles were obtained using the two methods at 37°C. Secondly the dissolution profiles of two commercially available indomethacin suppositories were measured using both the flow-through bead-bed apparatus and the more established rotating basket method. Although both products contained the same dose of indomethacin in a polyethylene glycol base, clear differences were noted between the dissolution profiles of the two products. The difference, however, was much more marked when using the flow-through bead-bed apparatus. These data therefore indicate that the latter technique may be a more precise tool for monitoring the effects of subtle formulation changes on dissolution profiles. In the case of indomethacin, from a pharmacological standpoint, a slower release rate is

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advantageous as such a product is likely to be more effective at relieving early morning stiffness after an evening dose.

Introduction

The use of suppositories is a helpful alternative to the oral route in those cases where a drug gives gastrointestinal irritation, when it is largely destroyed by first pass metabolism, when the patient is unable or unwilling to swallow or when a local effect on the rectal mucosa is required. Like all other solid dosage forms the active drug must first be released from the suppository base and dissolve (in this case in the rectal fluids) before systemic absorption can take place. Also, as is the case with other solid dosage forms, it is recognized that a dissolution testing procedure would be useful in both formulation design and also in quality control procedures relating to the products, both in the industrial and hospital settings. Several techniques have been used in the past for the study of drug release rates from suppositories including the beaker method (Pagay et al., 1974), the rotating basket method (Parrott, 1975), and methods involving dialysis across membranes (which are used in an attempt to control the interfacial area, by restricting the area exposed to the dissolution medium; Thomas and McCormack, 1971; Bhavnagri and Speiser, 1976).

Flow-through systems have also been used with the dosage unit being placed on a cotton or wire screen (Baichwal and Lohit, 1970; Puffer and Crowell, 1973). More recently Roseman et al. (1981) have described a continuous-flow bead-bed dissolution apparatus for monitoring drug dissolution rates from suppository bases. They assessed the performance of their apparatus using the model drug benzocaine.

Wagner (1971) has laid down requirements for test dissolution procedure for both research and quality control. Two such requirements were: (a) the apparatus should be capable of being fashioned from standard laboratory equipment or purchasable at low cost; and (b) there must be the capability of reproducing definable results from one copy of the apparatus to the next.

The aim of the present work was to assess the performance of an apparatus fashioned in this laboratory utilizing the specifications outlined by Roseman et al. (1981) and to compare the results obtained for benzocaine with those reported by the latter authors, and with rotating basket data obtained in this laboratory. A further aim was to determine the dissolution rate of two commonly used indomethacin suppositories (Imbrilon and Indocid [1]) using both dissolution methods. These latter products each contain 100 mg of indomethacin in a polyethylene glycol base.

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[1] Imbrilon and Indocid are the two most popular proprietary indomethacin suppositories in the United Kingdom.

Methods

(a) Flow-through apparatus

A schematic diagram of the continuous-flow bead-bed dissolution apparatus is shown in Fig. 1. While the flow-through cell matched that of Roseman et al. (1981) closely (slight dimension changes were made according to the availability of glassware), the experimental set-up did not include a continuous monitoring spectrophotometer. Intermittent samples were therefore taken from the insulated reservoir. Temperature control was facilitated using a thermostated water bath.

During experimental runs 3 rows of beads (chemically resistant; 3 mm in diameter) were placed in the release chamber and a suppository inserted into the centre of the chamber using a stainless steel cork borer. The remaining glass beads were poured into the chamber around the cork borer before it was removed. This ensured that the suppository was positioned reproducibly on all occasions. Having placed 500 ml preheated dissolution medium in the reservoir, the peristaltic pump was started in the reverse direction allowing the fluid to fill the release chamber from the bottom up. As soon as the entire system was filled with dissolution fluid the flow was reversed so that the fluid flowed from the top to the bottom of the chamber. The reservoir (1 litre in volume) was insulated with polystyrene and stirred using a magnetic stirrer. Before reaching the release chamber the dissolution fluid passed through a glass coil to ensure that ambient temperature was reached. The flow rate was maintained at 30 $ml \cdot min^{-1}$; 3 ml samples were removed at 15-min intervals. These samples were replaced with fresh dissolution fluid on all occasions.

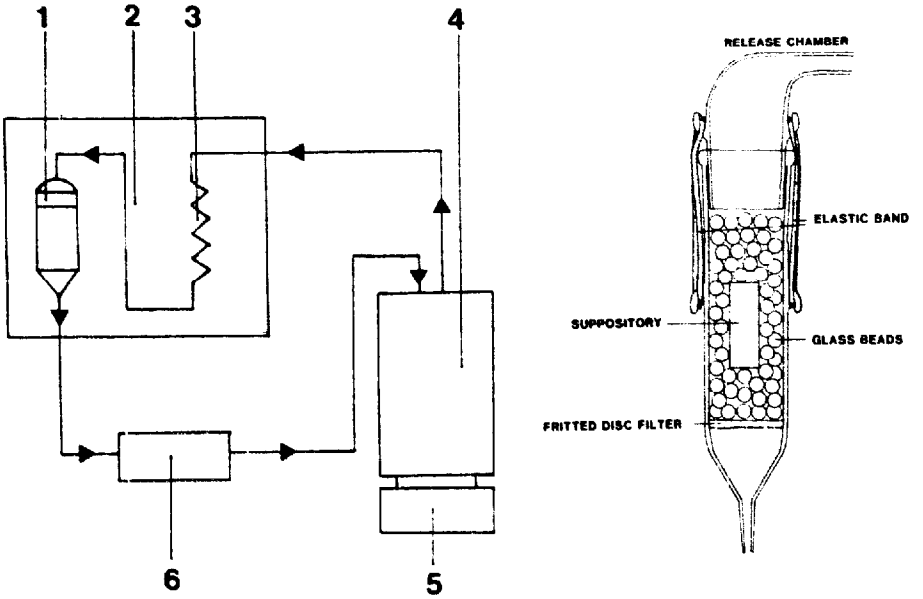

Fig. 1. Diagrammatic representation of flow-through bead-bed dissolution apparatus. (Internal dimensions of bead holding section is 30 mm × 52 mm). 1 = flow-through bead-bed chamber (see enlarged inset to right); 2 = thermostated water bath; 3 = glass heating coil; 4 = insulated reservoir; 5 = magnetic stirrer; 6 = peristaltic pump.

(b) Rotating basket apparatus

This apparatus, manufactured by Hanson Research (California) was in accordance with the USP-NF design with the exception that the reservoir vessels were flat-bottomed and not slightly concave. The baskets were made from 40 mesh woven wire cloth. The rotation rate used was 50 rpm and as in (a) above, 3 ml samples were removed for analysis at 15-min intervals; as before these were replaced with fresh dissolution medium. The volume of dissolution fluid used in each chamber was 500 ml.

(c) Dissolution of benzocaine suppositories

Dosage units containing 0.481% w/v benzocaine in Witespol E75 were prepared and used for experimentation. The dissolution medium used for benzocaine was distilled water. Three benzocaine suppositories were tested at each of 4 temperatures (33, 37, 40 and 45°C) using the flow-through apparatus and at 3 temperatures (33, 37 and 40°C) in the rotating basket apparatus. Each experimental run was carried out for 2 h. Benzocaine release from the suppositories was monitored spectrophotometrically at 282 nm (LKB Biochrom Ultrospec 4050).

(d) Dissolution of indomethacin suppositories

While a range of temperatures were required for benzocaine, to allow comparisons with the published results of Roseman et al. (1981), a single temperature (37°C) was chosen for work with the indomethacin suppositories. The dissolution medium used in this case was Sørensen phosphate buffer (pH 7.2). Dissolution of indomethacin was monitored spectrophotometrically at 320 nm (LKB Biochrom Ultrospec 4050) over 3-h periods. All experiments in this and the previous section were repeated in triplicate.

Results

Typical dissolution profiles for the benzocaine suppositories are shown in Figs. 2 and 3. In comparing the data at 37°C there is little difference between data generated by the different dissolution apparatuses. At the end of the 2-h test period using the rotating basket procedure, $29.9 \pm 0.9\%$ of benzocaine had dissolved which compared very closely with the $27.0 \pm 2.8\%$ dissolved value obtained using the flow-through bead-bed apparatus. The shape of the curves was also superimposible.

Major differences between the two dissolution methods was, however, apparent when different dissolution temperatures were used. There was a gradual increase in dissolution with rise in temperature in the rotating basket technique. This was not the case for the flow-through bead-bed apparatus. Using this latter technique the dissolution rate increased with increasing temperature between 33 and 37°C; however, on changing the temperature from 37 to 40°C the measured dissolution rate decreased. This inflection was, however, overcome by increasing the temperature of the dissolution medium to 45°C.

The indomethacin data (Figs. 4 and 5) showed less variation within the triplicate data at each sampling time than was shown for benzocaine. Both methods indicated

Fig. 2.

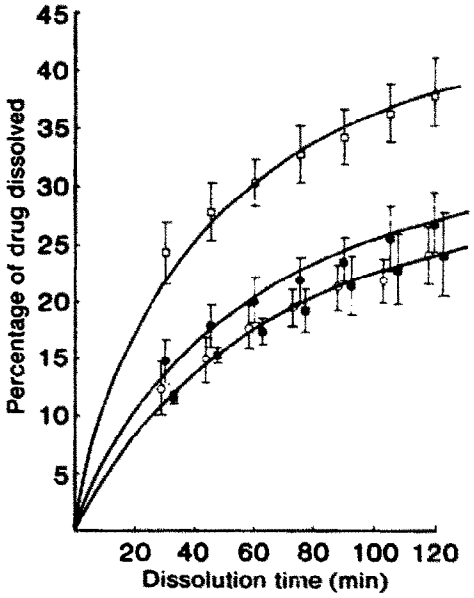

Fig. 3.

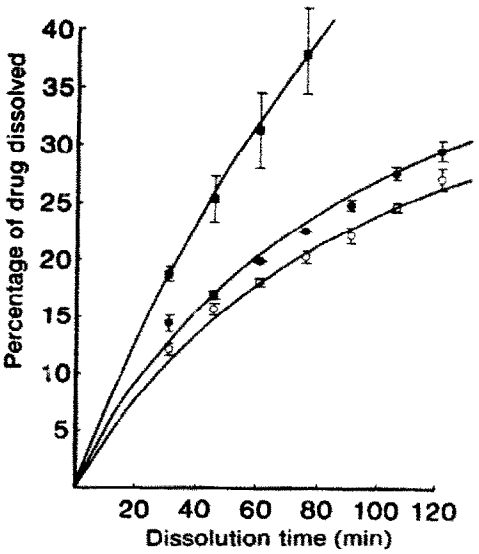

Fig. 2. Changes in dissolution profile of benzocaine suppositories as a function of temperature obtained using the flow-through bead-bed apparatus: □, 45°C; ■, 40°C; ●, 37°C, ○, 33°C. (Data for 33°C and 40°C have been displaced slightly to avoid overlap of the S.E. bars.)

Fig. 3. Changes in dissolution profiles of benzocaine suppositories as a function of temperature obtained using the rotating basket apparatus: ■, 40°C; ●, 37°C; ○, 33°C. Mean ± S.E. data presented.

Fig. 4.

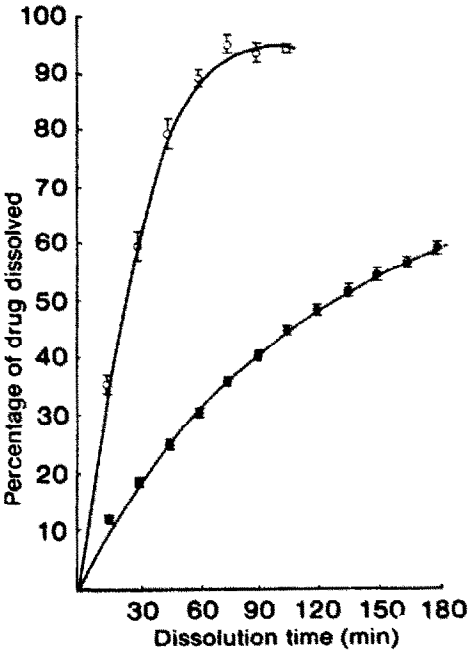

Fig. 5.

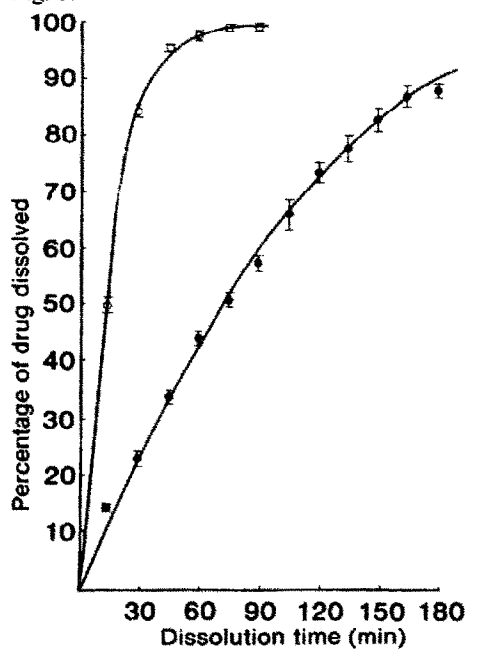

Fig. 4. Dissolution profiles of indomethacin suppositories obtained using the flow through bead-bed apparatus: ●, Indocid; ○, Imbrilon. Mean ± S.E. data presented.

Fig. 5. Dissolution profiles of indomethacin suppositories obtained using the rotating basket apparatus: ●, Indocid; ○, Imbrilon. Mean ± S.E. data presented.

an interesting and unexpected difference in the dissolution rate of the two commercially available indomethacin products, since they both contained 100 mg of indomethacin in a polyethylene glycol base. The difference (a much slower release rate for the Indocid suppositories) was demonstrated more clearly using the flow-through bead-bed apparatus. Using this latter technique only $59.7 \pm 1.2\%$ (S.E.) of the indomethacin from Indocid had dissolved at the end of the 3-h experimental period (as compared with $88.4 \pm 1.3\%$ in the case of the rotating basket technique). In both cases Imbrilon suppositories showed complete dissolution by 90 min.

Discussion

A major aim of the present study was to assess the performance of the flow-through bead-bed dissolution apparatus and to compare it with the rotating basket technique. During the dissolution testing, anticipated problems arose with the rotating basket apparatus. The rotation speed used (50 rpm) tended to give less than the required agitation to maintain homogeneity in the bulk dissolution fluid. By standardizing the sampling level as suggested by Bathe (1975), this problem was largely overcome. Although there was no problem with the polyethylene glycol base suppositories, those containing benzocaine formulated in a fatty base tended to give rise to clogging of the mesh of the basket. This was obviously responsible for variation within the results obtained.

Lack of homogeneity was not a problem with the flow-through bead-bed apparatus since the bulk dissolution fluid was kept in a stirred reservoir in which the rate of stirring did not influence the rate of drug dissolution. One slight problem with this apparatus, however, was getting the complete apparatus filled with dissolution fluid. When filling the apparatus and then reversing the flow direction of the peristaltic pump, a small pocket of air was trapped near the bend at the top of the dissolution cell. Although this undoubtably changed flow characteristics within the cell it did not appear to influence the resulting dissolution data, since the variation between the triplicate experimental runs was small (Figs. 2 and 4). The use of the flow-through bead-bed apparatus was of course much more time-consuming than the rotating basket method in which 6 tests could be carried out simultaneously. This problem could of course be overcome by having a series of flow-through bead-bed apparatuses.

The apparatus manufactured in our own laboratory gave rise to reproducible dissolution data for benzocaine when compared to the results of Roseman et al. (1981). This temperature dependence was not observed with the rotating basket apparatus (compare Figs. 2 and 3). The temperature dependence shown by the flow-through bead-bed apparatus was explained by Roseman et al. (1981), after close examination of the physical state of the suppository during dissolution testing. As the dosage unit softened, the beads became impressed within the suppository. At 39 and 40°C the beads penetrated the surface of the suppository thereby reducing the surface area available for drug release. Once the base melted completely (e.g. 45°C) release increased again due to the spreading of the oil in the bead-bed.

Although this temperature dependence is important in the present context for testing the reproducibility of data obtained from different laboratories using copies of a particular dissolution apparatus, it is not a consideration during routine dissolution testing. In routine testing 37°C should be used.

The flow-through bead-bed apparatus was designed to provide greater constancy of the exposed suppository for dissolution, thus increasing reproducibility and indeed it is clear that reproducible results were obtained under normal testing (37°C). It must be pointed out, however, that the rotating basket method also gave a very reproducible and almost identical dissolution profile for benzocaine at 37°C, even though clogging of the baskets did occur while using the fatty base products.

The major difference between the two methods was seen while examining dissolution of the indomethacin suppositories. A marked increased rate of dissolution was noted for Indocid suppositories when examined using the rotating basket technique and this led to a decreased distinction between the two products (compare Figs. 4 and 5). These data suggest that the flow-through bead-bed apparatus may be a more precise tool for distinguishing between the effects of subtle formulation changes on dissolution profiles. If this is the case, and if these changes in dissolution profiles are reflected by changed serum levels of the formulated drug in patients, then undoubtedly the latter method would be advantageous. We have not compared the in vivo serum profiles of indomethacin at present but hope to carry out such experiments in the near future. From a pharmacological standpoint a slower release of the non-steroidal anti-inflammatory drug would be advantageous to the patient, i.e. in preventing early morning stiffness after an evening dose.

In conclusion therefore similar data were obtained using the two dissolution techniques for the fatty base suppositories at 37°C; the results obtained in this laboratory for benzocaine corresponded well with data obtained in Michigan (Roseman et al., 1981) and therefore rapid replication of the apparatus is possible. The bead-bed apparatus, however, led to greater discrimination between the two commercially available indomethacin suppositories and thus, based on the present results, in the method of choice for the dissolution testing of suppositories.

Acknowledgements

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