International Journal of Pharmaceutics, 55 (1989) 217–220
Elsevier

IJP 01874

Comparative study of two dissolution methods for indomethacin suppositories from fatty and water-soluble bases

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(Received 16 December 1988)
(Modified version received 7 April 1989)
(Accepted 10 April 1989)

Key words: Continuous flow-through bead bed apparatus; Rotating paddle method; Dissolution; Indomethacin; Suppository; Release

Summary

The continuous flow-through bead bed dissolution apparatus was compared to the rotating paddle method used by USP XXI for the dissolution testing of indomethacin suppositories. The comparison of the two dissolution techniques showed that the continuous flow-through bead bed technique is more suitable for experimental studies, while the rotating paddle method is suitable for routine dissolution testing. Also, it was noted that the suppositories containing a mixture of PEG 400 and 4000 in a ratio of 5 : 1 presented the highest rate of drug release.

Indomethacin is a well established analgesic, anti-inflammatory and anti-rheumatic, anti-arthritic agent. Its physicochemical characteristics (weak acid) are responsible for the high incidence of adverse effects on the gastrointestinal tract resulting in an increased danger of gastric irritation.

The drug, if administered orally may also cause various side-effects, i.e. anorexia, nausea, vomiting, diarrhea, dizziness, etc. Rectal administration of indomethacin in the form of suppositories is often prefered, in particular when dealing with patients suffering from intestinal disturbances and generally patients who do not tolerate medication well.

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Up to now, several techniques have been applied for the dissolution study of active substances from suppositories, these include: the beaker method (Pagay et al., 1974), rotating basket method (Parrot et al., 1971), the membrane dialysis method (Thomas et al., 1971), and also various techniques using continuous flow-through systems (Baichwal et al., 1970) where the dosage form is placed on a woolen or wire screen or where dialyzing tubing with a natural or artificial membrane is used (Puffet et al., 1973; Bhavnagri et al., 1976).

This study compares the continuous flow-through bead bed dissolution technique (Roseman et al., 1981; McElnay et al., 1984); a technique used exclusively to study the drug dissolution from suppository bases compared to the rotating paddle method (USP XXI, 4th Suppl.). The two techniques were compared for the dissolution testing of both commercially available drugs and suppositories prepared in the laboratory containing 100

mg indomethacin were incorporated in various water-soluble polyethylene glycol bases.

The diagrammatic representation of the flow-through bead bed dissolution apparatus is shown in Fig. 1.

The suppositories are prepared by melting the water-soluble base and adding the active substance with continuous mixing. The mixing was continued until all of the drug was incorporated. The molten mixture was poured into a metal mould (2 ml) and was left to cool at room temperature. The suppositories were then stored in a refrigerator at 4 °C.

The following suppository formulations were prepared using this method:

A: 5% indomethacin in PEG 6000

B: 5% indomethacin in PEG 4000

C: 5% indomethacin in a combination of PEG 400 and 4000 (5 : 1)

D: 5% indomethacin in PEG 1500

The **D** suppository formulation could not be maintained in a solid form at room temperature (20–30 °C).

The dissolution profiles of suppositories containing indomethacin incorporated in a water-soluble base with the two techniques is given in Fig. 2.

The results showed that the continuous flow-through bead bed dissolution technique prolongs significantly the rate of release of indomethacin from the suppositories. This prolongation does not affect the results of this technique compared with the results obtained with the rotating paddle technique.

On the other hand, the noted differences during the dissolution procedure become more characteristic. In this way an easier and more accurate estimation of the release rate profiles is achieved. Also, it should be noticed that this method, though more complicated than the rotating paddle method, gives almost the same reproductive results. This method therefore is much more suitable for the study of the effect of different parameters on the dissolution profiles.

With this method a better correlation may be obtained with the in vivo absorption of the drug from the suppository base.

The release rate of the drug with the rotating paddle technique is faster, a fact that makes the estimation of the quality of the suppository under examination easier.

In conclusion, the rotating paddle technique may be considered a suitable method for routine dissolution testing but the continuous flow-through

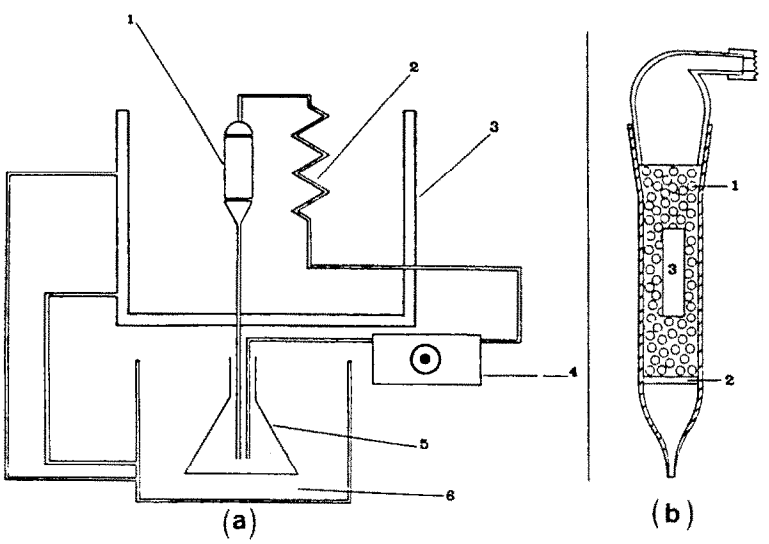

Fig. 1. Diagrammatic representation of flow-through bead bed dissolution apparatus. (a) 1 = flow-through bead bed chamber; 2 = glass coil; 3 = thermostated waterbath with double external walls; 4 = peristaltic pump; 5 = conical flask; 6 = thermostat. (b) 1 = glass beads; 2 = Buchner filter disk; 3 = suppository.

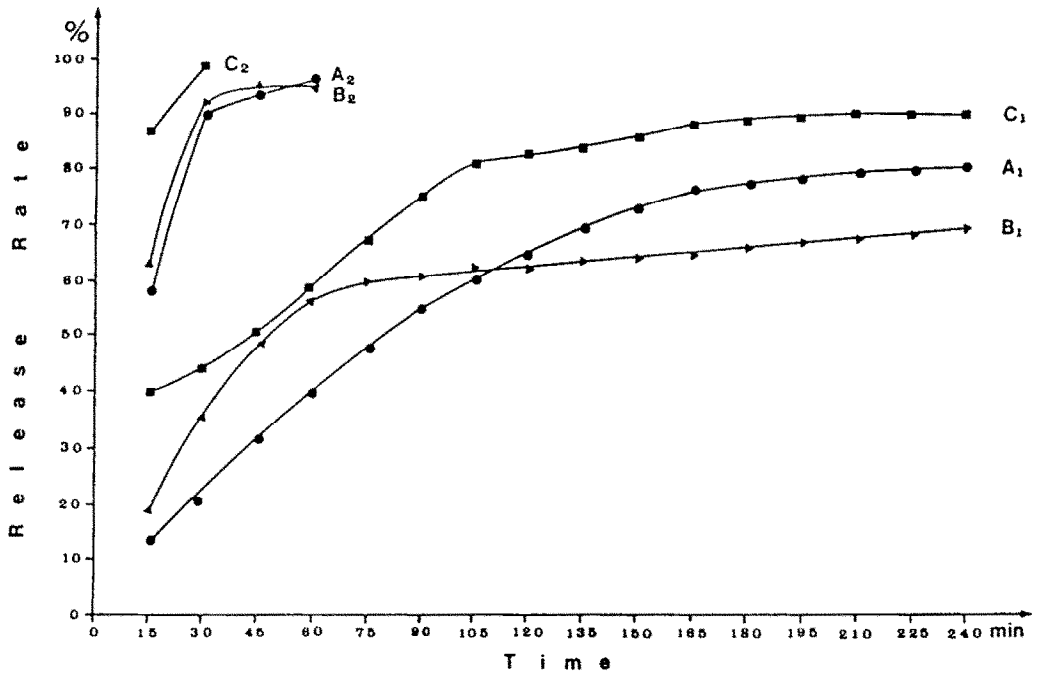

Fig. 2. Dissolution profiles of suppositories prepared in the laboratory consisting of indomethacin incorporated in a water-soluble base. A_1 = suppositories composed of 5% indomethacin incorporated in PEG 6000. Continuous-flow bead bed apparatus technique. B_1 = suppositories composed of 5% indomethacin incorporated in PEG 4000. Continuous-flow bead bed apparatus technique. C_1 = suppositories composed of 5% indomethacin incorporated in a combination of PEG 400 and 4000 (5 : 1). Continuous-flow bead bed apparatus technique. A_2 = suppositories composed of 5% indomethacin incorporated in PEG 6000. Rotating paddle technique. B_2 = suppositories composed of 5% indomethacin incorporated in PEG 4000. Rotating paddle technique. C_2 = suppositories composed of 5% indomethacin incorporated in a combination of PEG 400 and 4000 (5 : 1). Rotating paddle technique.

bead bed dissolution apparatus is more suitable for the experimental study of suppositories.

The polyethyleneglycol water-soluble bases give faster release rates of indomethacin compared to the fatty bases. Also it is of notable interest that the mixture of PEG 400 and 4000 in a ratio of 5 : 1 presented an extremely fast dissolution rate, a fact which could lead to an increase in the bioavailability of the drug.

Finally the release rate of indomethacin from fatty bases increases significantly when a surface-active agent is present.

Acknowledgement

The authors wish to thank the Pharmaceutical Laboratories UNI-PHRMA-KLEON TSETIS, Kifissia, Athens, for the experimental help that they offered during this study.

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