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A STUDY ON THE INTERACTION BETWEEN SOME SUSTAINED RELEASE PREPARATIONS AND PHYSIOLOGICAL SALINE BY A MICROCALORIMETRIC METHOD

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Abstract

The thermal curves and the enthalpy changes of the interaction between some oral sustained release preparations (Contac, Fenbid and Benza sustained release capsules) and physiological saline have been measured at 298.15 K with a MS-80 standard Calvet microcalorimeter. The curves that recorded the changes of heat effect with time have clearly shown the sustained release action and process of the above preparations. A method for examining the sustained release action of sustained release preparations can be developed from the above experiments. The principle of application and the experimental procedure of this method have been expounded, and some results of the above experiments have also been discussed.

Keywords: microcalorimetry, physiological saline

Introduction

The controlled release action of compounds has become a new and developing technique in the field of the pharmacy, chemical fertilizers, breeding in water, and so on. Two methods are now in use for studying and examining the oral sustained release preparations of medications. One is the examination of the medicine concentration in vivo, and the other. Another is an in vitro method in which the concentration of the drug released from the pellets of the sustained release capsules is traced by some experimental technique like spectrophotometry at regular hours in physiological saline.

On the basis of the thermal effect caused by interactions between drugs and physiological saline, a microcalorimetric method can be employed as a technique for studying and examining oral sustained release preparations. Because the heat effect is proportional at to the quantity of drug released from the sus-

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tained release pellets in a period, the duration of therapeutic effect and the changes in efficacy of a drug with the time can all be examined and checked by recording the thermoanalytical curves of the interaction between sustained release preparations and physiological saline and analyzing the thermokinetic curves [1–5]. The experimental results have shown that as one of the methods for examining the sustained release and action of sustained release preparations, the microcalorimetric method exhibits some distinguished features and advantages, such as easy operation, visual results and continuous and reliable data, over the in vitro methods used.

Experimental

All the oral sustained release preparations (Contac, Fenbid and Benza) were obtained from the Chinese market. Contac and Fenbid were made by Tianjin Smith Kline & French Laboratories Ltd. The beads of Benza were made by Takeda Chemical Ind. Ltd., Osaka, Japan and packing by Lisheng Pharmaceutical Factory, Tianjin, China.

The curves and the enthalpy changes of the interaction between the above preparations and physiological saline were recorded with a MS-80 standard Calvet microcalorimeter at 298.15 K [3, 6]. The 25 μV range of the amplifier was selected and the base-line deviation of the instrument was ±1 μW/48 h. The experimental errors of enthalpy changes were within 2%. The speed of the recorder chart was 1 mm/min. The measurements were made on each sample in duplicate or triplicate.

For comparing the quick dissolution reaction of compounds with the controlled release process, all the pellets in a Contac sustained release capsule were smashed and grained, and the curve of the interaction between the powdery contents and 5 ml of physiological saline was recorded under the same experimental conditions as those of the interaction between all the pellets in a whole Contac sustained release capsule and 5 ml of physiological saline at 298.15 K (Fig. 1).

Results and discussion

Figure 1 is the curve of the interaction between the powdery contents in a whole Contac sustained release capsule and 5 ml of physiological saline at 298.15 K. The thermokinetic curve shows that the time to return to the base-line needed for the recording pen is about 20 min. On the other hand, the time required by a quick dissolution reaction is about 20 min as shown by curve measured by the MS-80 standard Calvet microcalorimeter. Therefore, as a kind of time correction, 20 min during heat equilibration should be deduced from

the time of complete dissolution of the drug from the pellets of the sustained release preparation.

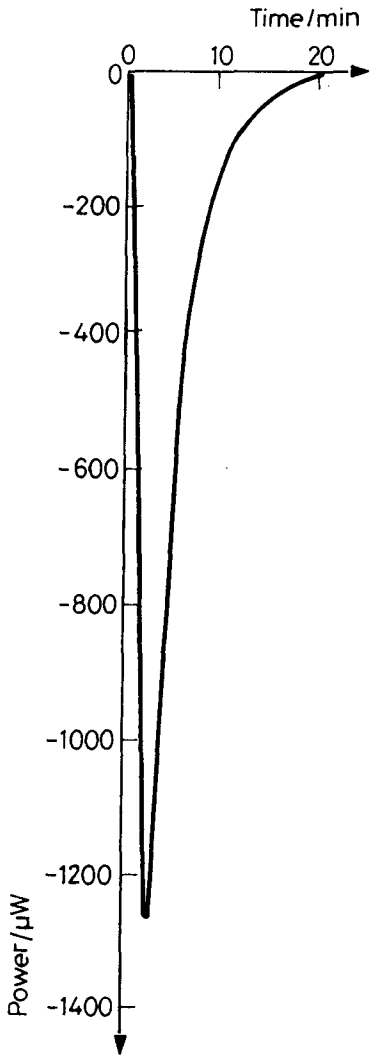

Fig. 1 Calorimetric curve of the interaction between 71.3 mg of the powder contents in Contac sustained release capsules and 5 ml of physiological saline at 298.15 K

Figure 2 shows the curve of the interaction between all the pellets in a whole Contac sustained release capsule and 5 ml of physiological saline at 298.15 K. It shows the release time of all the ingredients from the Contac pellets to be about 6.0 h.

Figure 3 shows the calorimetric curve of the interaction between three different kinds of 200 pellets in Contac sustained capsules and 5 ml of physiological saline at 298.15 K respectively. It shows that the release times of the

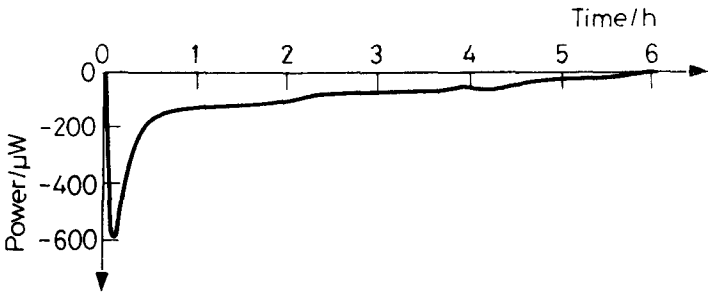

Fig. 2 Calorimetric curve of the interaction between all the pellets (293.5 mg) in a whole Contac sustained release capsule and 5 ml of physiological saline at 298.15 K

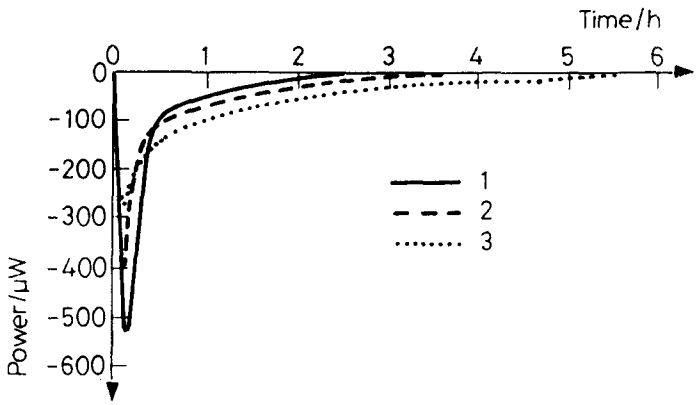

Fig. 3 Calorimetric curve of the interaction between three different kinds of 200 pellets in Contac sustained capsules and 5 ml of physiological saline at 298.15 K respectively: (1)yellow pellets (84.9 mg); (2) white pellets (83.6 mg); (3) red pellets (87.4 mg)

ingredients from three different kinds of Contac pellets are different. The release time of the ingredients from the pellets with the slowest release red pellets, is about 5.2 h, from the pellets with the quickest release yellow pellets, about 2.2 h and from the pellets with medium release speed, while pellets, about 4.1 h.

Figure 4 shows the calorimetric curve of the interaction between all the pellets in a whole Fenbid sustained release capsule and 5 ml of physiological saline at 298.15 K. It shows that the release time of the ingredients from the Fenbid pellets, only one kind of pellet, is about 5.5 h.

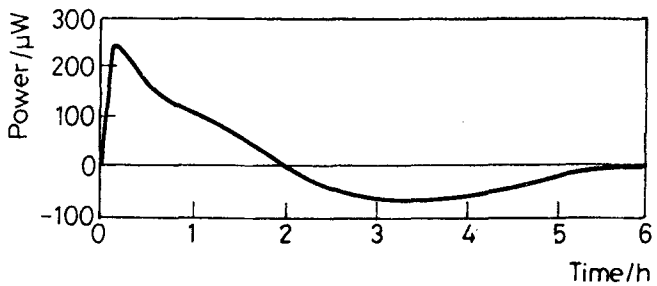

Fig. 4 Calorimetric curve of the interaction between all the pellets (349.4 mg) in a whole Fenbid sustained release capsule and 5 ml of physiological saline at 298.15 K

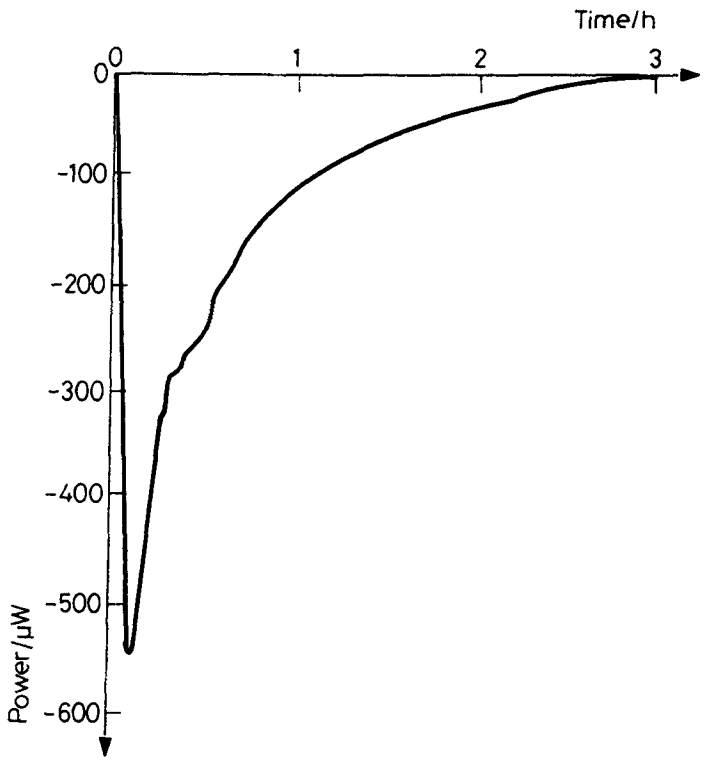

Fig. 5 Calorimetric curve of the interaction between all the pellets (398.2 mg) in a whole Benza sustained release capsule and 5 ml of physiological saline at 298.15 K

Figure 5 represents the calorimetric curve of the interaction between all the pellets in a whole Benza sustained release capsule and 5 ml of physiological saline at 298.15 K. It shows the release time of all the ingredients from the Benza pellets to be about 2.7 h.

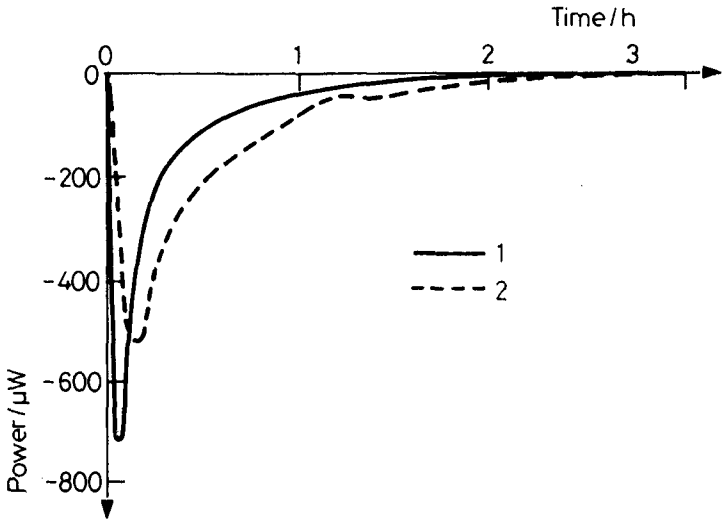

Fig. 6 Calorimetric curve of the interaction between two different kinds of 200 pellets in Benza sustained capsules and 5 ml of physiological saline at 298.15 K respectively: (1) greyish white pellets (107.8 mg); (2) white pellets (110.4 mg)

Figure 6 is the calorimetric curve of the interaction between two different kinds of 200 pellets in Benza sustained release capsules and 5 ml of physiological saline at 298.15 K respectively. It shows that the release times of the ingredients from two different kinds of Benza pellets are different too. The release time of the ingredients from the pellets with slower release the white pellets, is about 2.7 h and from the pellets with faster release the greyish white pellets, about 1.5 h.

The enthalpy changes of the interaction between the contents of a single pellet in three sustained release capsules and 5 ml of physiological saline at 298.15 K are listed in Table 1.

Table 1 Enthalpy changes of the interaction between the content of a single pellet in three sustained release capsules and physiological saline at 298.15 K

Different kinds of pellets	Average weight of a single pellet mg /pellet	Enthalpy changes for a single pellet 10^{-3} J /pellet
red (Contac)	0.437	4.58
white (Contac)	0.418	4.30
yellow (Contac)	0.425	4.37
white (Fenbid)	1.14	–0.21(–2.59+2.38)
white (Benza)	0.552	5.51
greyish white (Benza)	0.539	4.05

From the above experimental results it can be seen that all the calorimetric curves recording the changes of thermal effect with time clearly show the sustained release action and process of the above preparations. Whether or not a preparation has a sustained action, how the released amount of the ingredients changes with time and how long the release of the ingredients takes, can all be concluded from the experimental curves. Therefore, a microcalorimetric method can be developed for studying and examining the sustained release action of oral sustained release preparations. This method is also suitable for studying and examining of the controlled release action of all compounds that can be dissolved in water or other solvents.

In addition, it should be pointed out that the microcalorimetric method may yield quantitative data for a sustained release preparation with a single ingredient, but a combined result for medicines made of two or more ingredients. The experiments for each ingredient in the medicines made of two or more ingredients should be carried out separately so that the results can be discussed accurately. Due to the difficulty of making the outer thin coating of sustained release pellets, the experiments for each ingredient in the pellets of the preparations mentioned above could not be carried out in this study.

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Zusammenfassung — Mittels eines MS-80 Standard-Calvet-Mikrokalorimeters wurden bei 298.15 K die thermischen Kurven und die Enthalpieänderungen der Wechselwirkung zwischen einigen oralen Retard-Präparaten (Contac, Fenbid und Benza Retard-Kapseln) und physiologischer Kochsalzlösung gemessen. Die Kurven, in denen die zeitliche Änderung der Wärmeeffekte aufgezeichnet wurden, zeigen klar die Retard-Aktivität obiger Präparate. Anhand obiger Experimente kann eine Methode zur Untersuchung der Retard-Aktivität von Retard-Präparaten entwickelt werden. Die Anwendungsprinzipien und das experimentelle Vorgehen dieser Methode wurde erläutert und einige Ergebnisse obiger Experimente wurden ebenfalls diskutiert.