109 Lukens Drive. New Castle, DE 19720

In Vitro Dissolution Testing of Oral Controlled Release Preparations in the Presence of Artificial Foodstuffs. (1) Exploration of Alternative Methodology: Microcalorimetry

L. J. Ashby
A.E. Beezer
The University, Canterbury, Kent, England

G. Buckton
School of Pharmacy University of London Brunswick Sq, London

Instrument: *Isothermal Heat Conduction Microcalorimeter*

Field of application: *Material Science*

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INTRODUCTION

The rate at which pharmaceutical preparations and indeed pharmaceutical excipients dissolve are important in pre-formulation studies. Conventional methods for dissolution testing have been shown to be labour intensive and extremely elaborate. Although results from these techniques clearly show the rate of dissolution in buffer solutions, they do not reflect feeding and fasting conditions that occur in-vivo. The use of media which mimics the in-vivo state as closely as possible would be advantageous. However, such media would include suspended matter and coloured preparations which are difficult to remove, prior to spectrophotometric analysis without labour intensive separation.

Therefore the possibility of using microcalorimetry as an analytical method to monitor dissolution in complex media mimicking feeding and fasting regimes was explored and compared to results obtained from conventional techniques.

EXPERIMENTAL

Conventional dissolution experiments were carried out using the USP paddle method at 37°C stirring at 100rpm. The pH was controlled using 'universal' buffer and changed from 2.5 to 5.6 after 3 hours. Two complex media were used: Ensure containing essential foodstuffs to represent a fed patient, Intralipid mimicked a high lipid diet and simple buffer solution was used to simulate a fasting regime. However, difficulties were encountered in removing suspended matter from the complex media in order to use the UV spectrophotometer for conventional dissolution testing. Phyllocontin continus tablets (controlled release aminophylline 225mg) was used for the study. For microcalorimetric experiments where complex,

non optically transparrent solutions were used, a LKB 10700 microcalorimeter was employed. However, it is important to note that 2277 Thermal Activity Monitor, TAM, the successor to the LKB 10700 can be used for such studies.

RESULTS

USP dissolution studies

The rate of dissolution was found to be independent of pH (table 1). Rate constants further showed that dissolution in universal buffer followed two first order processes separated by a mixed order region in which the transition states ranged from 100-120min.

Table 1. *Apparent first order rate constants for the dissolution of Phyllocontin continus in the USP dissolution apparatus.*

	First stage (min^{-1})	Second stage (min^{-1})
Buffer at pH 2.5	0.0174	0.0021
Buffer at pH 2.5 then 5.6	0.0173	0.0022
Halved tablet in buffer at pH 5.6	0.0215	0.0019
Halved tablet in Ensure buffer mixture at pH 5.6	0.0635	0.0023

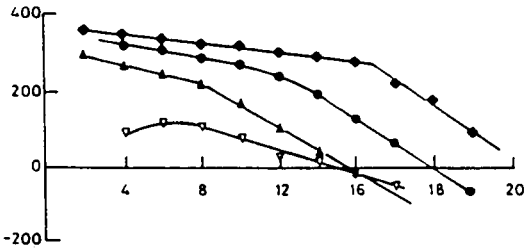
Microcalorimetric dissolution studies

Microcalorimetric rate constants (table 2; fig 1) were inevitably different from USP dissolution studies because of the different flow characteristics between the two techniques. It therefore follows that direct numerical comparisons cannot be made with the USP dissolution results. The behaviour observed in the microcalorimetric results is, however, similar in form to the USP results. Internal comparisons of dissolution rates under fasting, feeding and high lipid diet regimes can only be made via the microcalorimeter. The results show, again, two sequential 1st order rate constant processes with different rate constants. Microcalorimetry is capable therefore, of revealing direct data on dissolution kinetics in complex media.

Table 2. *Apparent first order rate constants from the ln(displacement) as a function of time plots obtained from the microcalorimeter.*

	Apparent first-order rate constants		Time of onset of second stage (min)
	First stage (min^{-1})	Second stage (min^{-1})	
Placebo in buffer	-	0.41	540
Active in buffer	0.148	0.47	720
Active in buffer/Ensure	0.216	0.46	480
Active in buffer/Intralipid	0.129	0.61	1050

Fig. 1. *Dissolution results obtained by microcalorimetry, presented as ln(deviation from baseline) as a function of time. Axes: x = time (hours); y = ln(deviation). Dissoultion of Phyllocontinus tablets in: (◆) Intralipid/buffer mixture; (●) buffer; and (▲) Ensure/buffer mixture. Dissolution of placebo Phyllocontin continus tablets: (▽) buffer.*



DISCUSSION

Results have clearly shown that the presence of different media affects aspects of the dissolution process. This is evident in both techniques especially over the initial first order release period (table 1). Microcalorimetric results showed that not only did rate constants differ but so did the timing of onset of the second dissolution process (table 2). Furthermore, the time taken for the second first order process to start was affected by the presence of different media constituents. A possible explanation for these effects is the differential wetting of the drug surface which necessarily influences the rate of dissolution.

CONCLUSION

It is evident that results from microcalorimetric techniques compare favourably with those from conventional techniques. In addition, it is possible to survey the effect on the rate of dissolution of pharmaceutical preparations in the presence of different complex media before undergoing human trials. Microcalorimetric data can thus, in principle, be used to observe the effects of different tablet formulations on the rate of dissolution.

REFERENCE

L.J. Ashby, A.E. Beezer, G. Buckton - International Journal of Pharmaceutics 51:245-251 (1989).

NOTE

This application note is written by M. Shafiq, Thermometric AB.