

Sensitivity of dissolution rate to location in the paddle dissolution apparatus

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Abstract

The aim of the present study was to determine the apparent diffusion boundary layer and dissolution rate constant for various surfaces of compacts and at various locations in the USP paddle dissolution apparatus. Benzoic acid compacts were coated with paraffin wax leaving only the surface under investigation free for dissolution. The dissolution rates for various surfaces at varying locations in the paddle dissolution vessel were determined from the slope of the dissolution profile (amount dissolved (mg) versus time (min)). The apparent diffusion boundary layer and dissolution rate constant were calculated and were found to vary depending on the surface of the compact from which dissolution took place and also on the location and size of the compact. It may be concluded that, in developing models to describe the dissolution from solid dosage forms, it is not accurate to assume constant hydrodynamics and mass transfer rates at all surfaces of the system, or in different locations within the test device. A more exact description of the hydrodynamics would be necessary in order to precisely model drug dissolution in the paddle dissolution apparatus.

Introduction

In most cases, dissolution is convective–diffusion controlled and the dissolution rate is dependent on surface area (A), solubility (C_s), diffusion coefficient (D) and on the size of the apparent diffusion boundary layer (h), as described by the Nernst–Brunner equation (Brunner 1904; Nernst 1904):

$$dW/dt = (DA(C_s - C))/h \quad (1)$$

or, where sink conditions apply:

$$dW/dt = kAC_s \quad (2)$$

where k , the dissolution rate constant, is equal to D/h .

Models of dissolution have commonly used a single value of h for a drug delivery system under test and generally assume h to be constant for all aspects of the dosage form. The USP paddle dissolution apparatus (USP 24, Type 2 apparatus) has become the most widely used dissolution testing device in the pharmaceutical industry and is generally considered to be an accurate, precise and robust testing method. Despite the simple design of the USP paddle dissolution apparatus, the hydrodynamics are likely to be complex and variable at different sites in the vessel. Alterations in apparent diffusion boundary layer thickness, owing to altered hydrodynamics, may therefore significantly affect drug dissolution, and the

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dissolution rate may change depending on the location of the dissolving substance in the dissolution vessel. The dissolution rate of the dosage form may be dependent on its shape.

Precise modelling of in-vitro release profiles, which will in turn facilitate the development of in-vitro/in-vivo correlations, requires an understanding of the hydrodynamics of the particular dissolution test apparatus employed.

The objective of the present work was to estimate the apparent diffusion boundary layer thickness and dissolution rate constant, parameters reflective of the hydrodynamics of the systems, for single component compacts, at different surfaces and positions in the paddle dissolution apparatus.

Materials and Methods

Preparation of compacts

Benzoic acid (Merck) compacts were prepared by compression at 10 tonnes for 10 min in a hydraulic press using a 13-mm punch and die (Perkin-Elmer). Compacts were made using 1.5 g or 250 mg benzoic acid. The former, referred to as 'large compacts', had a mean height of 8.5 mm, whereas the latter, referred to as 'small compacts' had a mean height of 1.5 mm.

In some cases, compacts were coated using paraffin wax, leaving only the surface under investigation free for dissolution. Surface area measurements of the dissolving surface were performed on compacts before dissolution using a micrometer screw gauge.

In two cases, the 1.5-g compacts were raised by approximately 3 mm from the base of the dissolution vessel. This was achieved by moulding a portion of wax to the base of the compact. The compacts were affixed to the base of the dissolution vessel using molten wax.

Dissolution studies

Dissolution studies were performed using the USP paddle apparatus (USP 24, Type 2 apparatus), with a paddle rotation speed of 50 rev min⁻¹ and a dissolution medium of 0.1 M HCl (900 mL), which was de-aerated using the USP method and equilibrated at 37°C (n = 6 for each system studied). Samples were taken from the dissolution apparatus at 5, 10, 15, 20, 30, 40, 50 and 60 min. Filtered samples were analysed by UV spectroscopy using an absorbance wavelength of 274 nm.

The effective diffusion boundary layer thickness, *h*, was calculated from equation 1, where *dW/dt* was

calculated via linear regression from the slope of the straight line of the least squares fit of a plot of the amount dissolved versus time. The surface area was taken to be the initial surface area before dissolution, and the diffusion coefficient and saturated solubility of benzoic acid were taken to be 12.36 × 10⁻⁶ cm² s⁻¹ and 4.55 × 10³ g cm⁻³, respectively (Edwards 1951; Ramtoola & Corrigan 1987). The dissolution rate constant, *k*, was then calculated by dividing the diffusion coefficient, *D*, by *h*. One-way analysis of variance was carried out, using Minitab Statistical Software, to determine if there was a statistically significant difference between the resulting dissolution rate constants.

Results

The values of *k* and *h* were determined for different surfaces of benzoic acid compacts by coating the compacts with paraffin wax, leaving only the surface under investigation free for dissolution (see Figures 1 and 2). The linear regression parameters of the straight line of the least squares fit of plots of the mean amount dissolved (mg) versus time (min) of the systems studied are given in Table 1. As the corresponding correlation coefficient (*R*²) was greater than 0.997 for all systems (except system IV, which was releasing from the lower planar surface), the surface area was taken to be the initial surface area before dissolution. Using *dW/dt* from the regression slope parameters and the calculated surface area measurements, *A*, allowed calculation of *h* and *k* as shown in Table 2.

The calculated dissolution rate constants of individual compacts were then examined to allow comparison of

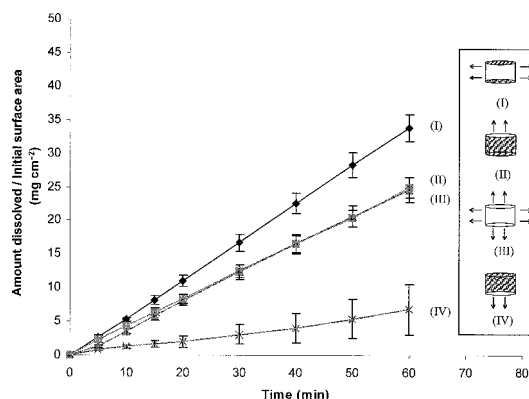


Figure 1 Dissolution of benzoic acid from different surfaces of a solid compact into 0.1 M HCl, with a paddle rotation speed of 50 rev min⁻¹.

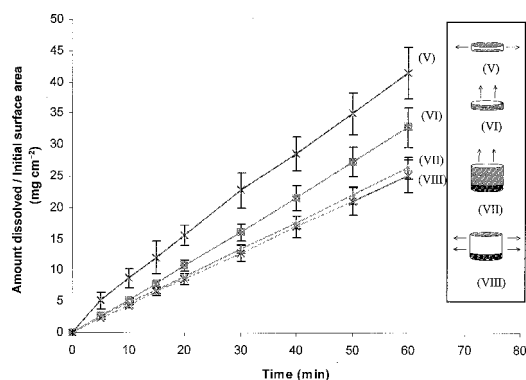


Figure 2 Dissolution of benzoic acid from different surfaces of solid compacts of varying size and location into 0.1 M HCl, with a paddle rotation speed of 50 rev min⁻¹.

Table 1 Values for linear regression parameters and correlation coefficients of the straight line of the least squares fit of plots of mean amount dissolved (mg) versus time (min) for the systems studied.

System investigated	Linear regression parameters $y = a + bx$ ($b = dW/dt$)	Correlation coefficient (R^2)
I	$y = -0.7639 + 1.975x$	0.9999
II	$y = +0.2771 + 0.5414x$	0.9997
III	$y = -2.4612 + 2.578x$	0.9993
IV	$y = +0.09 + 0.1412x$	0.9888
V	$y = +0.9698 + 0.4093x$	0.9972
VI	$y = -0.1704 + 0.7228x$	0.9997
VII	$y = +0.4735 + 0.5769x$	0.9997
VIII	$y = +0.7628 + 1.4647x$	0.9998

Table 2 Values for release rate, initial surface area of compacts and estimates of h and k for the systems studied.

System investigated	A (cm ²)	h ($\times 10^4$ cm)	k ($\times 10^4$ cm s ⁻¹)
I	3.48	59.7 ± 4.2	20.8 ± 1.4
II	1.33	83.0 ± 4.4	14.9 ± 0.8
III	6.15	80.9 ± 6.1	15.4 ± 1.2
IV	1.33	595.8 ± 573.0	3.9 ± 2.7
V	0.61	50.4 ± 5.3	24.7 ± 2.5
VI	1.33	62.5 ± 5.5	19.9 ± 1.8
VII	1.33	78.2 ± 5.2	16.2 ± 1.1
VIII	3.51	81.6 ± 7.8	15.3 ± 1.5

variation between systems with variation within systems (error) in a one-way analysis of variance test. The results of the analysis of variance test are given in Table 3. The low P value associated with the analysis of variance

($P < 0.001$) indicates that there is a highly significant difference in the dissolution rate constant depending on the system studied. To investigate which systems were significantly different, the least significant difference (LSD) was calculated using a pooled estimate of the variance based on all data. The LSD for a significance level, α , of 0.05 was calculated to be 1.6×10^{-4} cm s⁻¹. There were four separate groups of statistically different dissolution rate constants: system IV; systems II, VIII, and VII; systems VI and I; and system V.

Dissolution from different surfaces

The values k and h were determined for different surfaces of large benzoic acid compacts. The amount of benzoic acid dissolved per initial surface area over time is shown in Figure 1 for four different systems, with estimates of k and h given in Table 2. The dissolution rate constant for the curved surface (system I) was significantly greater than that for either the upper (system II) or lower (system IV) planar surfaces. There was a 5-fold difference in k between the curved surface and the lower planar surface, and a 1.4-fold difference between the curved surface and the upper planar surface.

Dissolution from different locations

When the large uncoated compacts (system III) were removed from the dissolution apparatus, a groove or indent was observed at the lower 3-mm region, suggesting that uniform hydrodynamics were not present at all surfaces of the compact. The same phenomenon was observed for compacts that were coated top and bottom (system I).

Dissolution from the curved or upper planar surface was then investigated for large compacts that were raised approximately 3 mm from the base of the dissolution vessel and for small compacts that were located within approximately 3 mm of the base of the vessel (Figure 2). There was no groove or indentation evident in the compacts that were raised from the base of the dissolution vessel. The dissolution rate constant for the curved surface was significantly greater when the compact was sitting on the base of the vessel (1.4-fold greater for system I compared with system VIII), whereas there was no significant change in k for the upper planar surface when the compact was sitting on the base of the vessel (system II) compared with when it was raised (system VII). The dissolution rate constants were also significantly greater for the small compacts than the large compacts raised from the base of the vessel, with a 1.6-fold difference in k when dissolution was from the

Table 3 The analysis of variance of k (cm s^{-1}) for the systems studied.

Source of variation	Sum of squares ($\times 10^6$)	Degrees of freedom	Mean squares ($\times 10^6$)	F	P value
Between systems	15.8	7	2.3	76.04	0.000
Error	1.1	40	0.0		
Total	16.9	47			

curved surface (system V compared with system VIII), and a 1.2-fold difference in k when dissolution was from the upper planar surface (system VI compared with system VII).

Discussion

The fluid flow patterns in an apparently simple apparatus such as the paddle dissolution vessel can be quite complex. It has been shown that different fluid velocities exist at different points in the dissolution vessel (Bocanegra et al 1990; Diebold 2000). In the present work, we have shown that minor location changes of the dosage form can give rise to quite significant differences in the rate of drug dissolution.

Fluid flow inwards, towards the compact, at the base of the dissolution vessel is thought to be responsible for the increased dissolution rate constant observed where a portion of the compact or the entire compact is located within approximately 3 mm from the base of the dissolution vessel, as shown in Figure 3 (Beckett et al 1996; Diebold 2000). This inward fluid flow may not be as significant when the compact is raised from the base of the vessel.

The fact that small changes in location can give rise to appreciably different dissolution rates is significant with regard to establishing precise models of dissolution. It would appear that an accurate model of dissolution from a solid system should take account of the variable hydrodynamics of the dissolution apparatus resulting in variable flow velocities and apparent diffusion boundary layers at different sites on the dosage form. This in turn will lead to different mass transfer rates from different surfaces/positions of a solid dosage form. If a dosage unit moves around during the dissolution test, this will introduce further complications, as the dissolution rate may vary, not only with location, but also with time.

Work is continuing to model the complex flow behaviour in the paddle dissolution apparatus using computational fluid dynamics to predict fluid velocities.

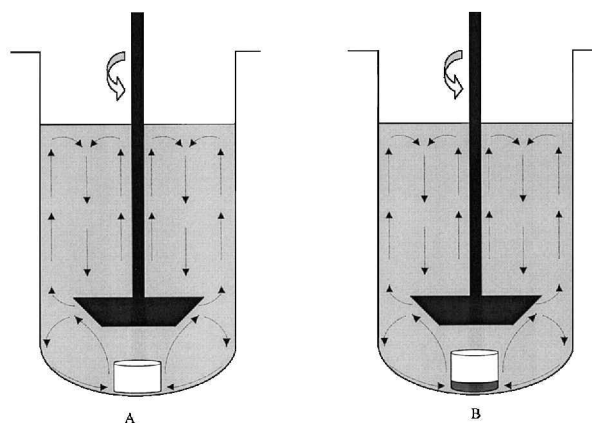


Figure 3 Diagram of postulated fluid flow patterns surrounding compacts that are located at the base (A) and raised up from the base (B) of the USP paddle dissolution apparatus vessel (modified from Beckett et al 1996 and Diebold 2000).

References

- Beckett, A. H., Quach, T. T., Kurs, G. S. (1996) Improved hydrodynamics for USP apparatus 2. *Dissolution Technol.* **3**: 7–18
- Bocanegra, L. M., Morris, G. J., Jurewicz, J. T., Mauger J. W. (1990) Fluid and particle laser Doppler velocity measurements and mass transfer predictions for the USP paddle method dissolution apparatus. *Drug Dev. Ind. Pharm.* **16**: 1441–1464
- Brunner, E. (1904) Reaktionsgeschwindigkeit in heterogenen systemen. *Z. Phys. Chem.* **47**: 56–102
- Diebold, S. M. (2000) Hydrodynamik und lösungsgeschwindigkeit. In: *Untersuchungen zum Einfluß der Hydrodynamik auf die Lösungsgeschwindigkeit Schwer Wasserlöslicher Arzneistoffe*. Shaker Verlag, Germany, pp 151–204
- Edwards, L. J. (1951) The dissolution and diffusion of aspirin in aqueous media. *Trans. Faraday Soc.* **47**: 1191–1210
- Nernst, W. (1904) Theorie der reaktionsgeschwindigkeit in heterogenen systemen. *Z. Phys. Chem.* **47**: 52–55
- Ramtoola, Z., Corrigan, O. I. (1987) Dissolution characteristics of benzoic acid and salicylic acid mixtures in reactive media. *Drug Dev. Ind. Pharm.* **13**: 1703–1720
- USP 24/NF19 (1999) The United States Pharmacopeial Convention, Inc., Rockville, MD, pp 1941–1943