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Predicting dissolution via hydrodynamics: salicylic acid tablets in flow through cell dissolution

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Abstract

A model was established for the dissolution of non-disintegrating salicylic acid tablets as a function of hydrodynamic conditions in the Flow Through Cell system (USP Apparatus 4). The approach was to model the dissolution rate of the material as a function of the Reynold's number, the dimensionless engineering term that describes the degree of turbulence. The dissolution rate of USP calibrator salicylic acid tablets was measured as a function of tablet size, orientation within the cell, dissolution media flow rate, and cell size. All of these variables were found to have an effect on dissolution rate, consistent with theory. An equation to predict this dissolution was established as: $N_{SH} = -21.1 + 12.6 \times N_{RE}^{0.5}$, $R^2 = 0.99$; $10 < N_{re} < 292$.

Keywords: Dissolution; Hydrodynamics; Reynold's number; Flow through cell dissolution

1. Introduction

Dissolution is a critical parameter of pharmaceutical dosage forms. Dissolution testing is used by the pharmaceutical scientist for a number of reasons, including the guidance of pharmaceutical development to ensure acceptable in vivo performance, and quality control to ensure that manufactured product matches product design. Accordingly, much of the focus of dissolution method development has focused on simulating in vivo performance (Nelson, 1957; Levy et al., 1965, 1967; Mannin et al., 1972), and on reducing the variability of the dissolution method (Cox et al., 1978, 1982a,b; Hanson, 1991). Less emphasis, however, has been placed upon understanding the underlying physical chemistry considerations that affect dissolution. If the physical chemistry were to be better understood, a number of benefits could result, such as: (1) improved guidance of formulation development to obtain specific dissolution parameters; (2) improved modeling of in vivo performance; (3) improved development of dissolution devices; and (4) further reduction in the variability of the dissolution methods.

Dissolution of a solid object in a moving fluid involves simultaneous momentum transport (i.e.

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the shear imparted by the moving fluid) and mass transport (i.e. the diffusion of the dissolving material into the bulk media). Although each of these can be modeled by differential equations, simultaneous solution of these equations can be quite complex. This is particularly true if the model involves non-steady-state performance, as occurs with dissolution.

An alternate approach involves modeling this performance via dimensionless analysis. The approach of using dimensionless numbers to describe behavior is common in the field of chemical engineering. Garner and Grafton (1954), Garner and Suckling (1958) used this approach to describe the dissolution of benzoic acid spheres in a moving stream of water, and found that a relationship between the mass and momentum transfer could be established, of the form:

$$N_{SH} = 2 + 0.95 \times N_{RE}^{1/2} \times N_{SC}^{1/3}$$

where N_{SH}, Sherwood number, the ratio of mass diffusivity to molecular diffusivity; N_{RE}, Reynold's number, the ratio of momentum forces to viscous forces in a moving fluid, commonly interpreted as the degree of turbulence in the fluid; N_{SC}, Schmidt number, the ratio of kinetic viscosity to molecular diffusivity and $100 < N_{re} < 700$.

The above dimensionless terms are defined mathematically as:

$$N_{SH} = k' \times d/(c \times D_{ab})$$

$$N_{RE} = d \times v \times \rho/\nu$$

$$N_{SC} = \nu/(D_{ab} \times \rho)$$

where d, sphere diameter; v, linear fluid velocity around the object; ρ, fluid density; ν, fluid viscosity; c, saturation concentration of solute; D_{ab}, diffusivity of benzoic acid moving through stagnant water; k', mass transfer coefficient or film coefficient.

Under the conditions of identical solvent and solute, then density (ρ), viscosity (ν) and diffusivity (D_{ab}) would be constant, as would be the Schmidt number. The equation of Garner, Grafton, and Suckling then reduces to the form:

$$N_{SH} = a + b \times N_{RE}^{0.5}$$

where a and b are constants.

The findings of Garner, Grafton, and Suckling suggested that dissolution rate increases with the square root of fluid velocity. This was similarly established by findings by Cooper et al. (1962).

The intent of this work was to determine if a similar relationship could be established in pharmaceutical dissolution. This requires modeling the dissolution of pharmaceutical dosage forms using established pharmaceutical dissolution techniques.

2. Materials and methods

2.1. Materials

Salicylic acid calibrator tablets, from USP, were used for dissolution materials. These were chosen because: (1) salicylic acid calibrator tablets are non-disintegrating, and therefore surface area would remain relatively constant; (2) these tablets contain no binders, which ensures the Fickian assumptions were followed (e.g. the rate-limiting step would be transport from the film to the bulk media, not internal to the dosage form); and (3) these tablets provide the additional benefits of no other excipients, and high content uniformity. USP non-disintegrating calibrators, salicylic acid tablets 300 mg Lot N, were purchased from the United States Pharmacopeia (Rockville MD). Similarly, salicylic acid reference standard for calibration of the spectrophotometers was also purchased from USP. Sodium hydroxide pellets and Potassium Phosphate, Monobasic, Crystals, for media preparation were purchased from JT Baker (JT Baker, Phillipsburg NJ).

2.2. Methods

2.2.1. Media preparation

Media was prepared as per directions from USP (USP, 1997). This specified 0.05 M phosphate buffer (pH 7.4). Immediately prior to use, media was filtered through a 3 micron filter, and dearated via sonication under vacuum for 30 min.

2.2.2. Extinction coefficient determination

The extinction coefficient of salicylic acid in the compendial media was determined by dissolving salicylic acid reference standard in the media at concentrations from 8.4 to 531 mg/l. Absorption of each solution at 296 nm was determined. The extinction coefficient was determined from the slope, and found to 0.235 l/mg per cm.

2.2.3. Dissolution equipment

The Flow Through Cell (USP Apparatus 4) was selected as the dissolution system for several reasons, including:

- The model for dissolution of linear flow past stationary objects had been established;
- The similarity of the system to the configuration of Garner, Grafton, and Suckling;
- The acceptance of the Flow Through system in the pharmaceutical industry;
- The ability to run multiple experiments simultaneously through cell configuration changes.

The configuration of the dissolution and sampling system is shown in Fig. 1. A 'continuous double loop arrangement' was used, in which the media is continuously cycled between the flow cell apparatus, the media pumps, and the media flasks. Simultaneously, media samples were continuously cycled to the uv for continuous sampling.

Media (900 ml) was maintained in each of six 1000 ml Erlenmeyer flasks, kept under gentle agitation via magnetic stirrers. Media was pumped via the Sotax CY-750 Media pump to the Sotax CH 4008 Flow Cell unit (Sotax, Basel Switzerland). Six cells were operated in parallel, and the flow rate to each cell was checked prior to each experimental run to ensure the variability was less than 5%. The temperature of the Flow Cell unit bath was kept at 37.5 ± 0.5°C. Unless otherwise noted, the cell configuration followed compendial recommendations for Apparatus 4 (USP XXIII, 1995).

UV sampling and data collection was controlled automatically using the IDIS software system (Icalis Data Systems). Sampling frequency for each cell was set at 90 s, for a period of up to 90 min. The extinction coefficient was entered into the IDIS system, allowing the percentage dissolution to be calculated directly from the absorption results. Results were provided as percentage dissolved versus time in both tabular and graphical form.

2.2.4. Cell and tablet configuration

As noted previously, cell configuration followed compendial guidelines. Both 12 and 22.6 mm cells were used during the studies. A total of 2.5 g of 1 mm glass beads were placed in each 12 mm cell, and 8.0 g of 1 mm glass beads were placed in each 22.6 mm cell.

Salicylic acid tablets were mounted in place using tablet clips. This ensured control over the placement of the tablet, and therefore the flow regimes around the tablet. Three different mountings were used: (1) **vertical**, in which the tablet was placed vertically between the clip faces; (2) **double vertical**, in which two tablets were glued together (using acrylic cement) and then mounted vertically between the clip faces; and (3) **horizontal**, in which the tablet was glued horizontally to the bottom of the clip, using rubber cement. Diagrams of vertical and horizontal mounting of tablets are shown in Fig. 2.

2.2.5. Experimental design

The dissolution rate was measured at various Reynold's numbers. The Reynold's number, in turn, was controlled by varying the following experimental conditions: (1) the mass flow rate, and therefore the linear velocity; (2) cell diameter, which altered the linear velocity around the tablet; (3) tablet mounting, which changed the effective tablet diameter; and (4) tablet thickness (by gluing two tablets together). A summary of the experimental design for this study is given in Table 1.

2.3. Calculations

2.3.1. Dissolution rate k'

As noted previously, the IDIS program provides the results as the percentage dissolved over time. The dissolution rate (k') is simply the slope of this line, normalized for molecular weight and surface area of the tablet. Since the surface area of the tablet is only known at time zero, the dissolution rate can only be accurately calculated

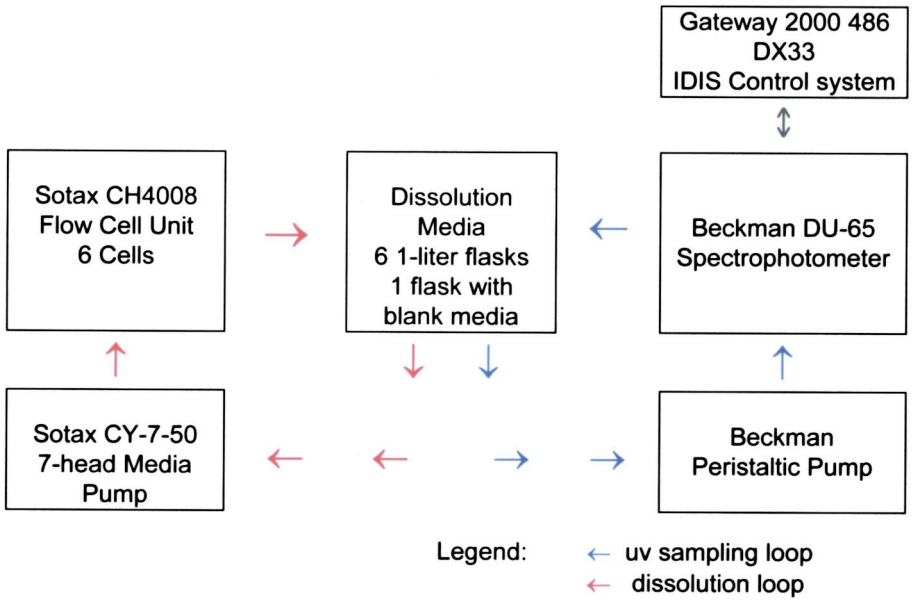

Fig. 1

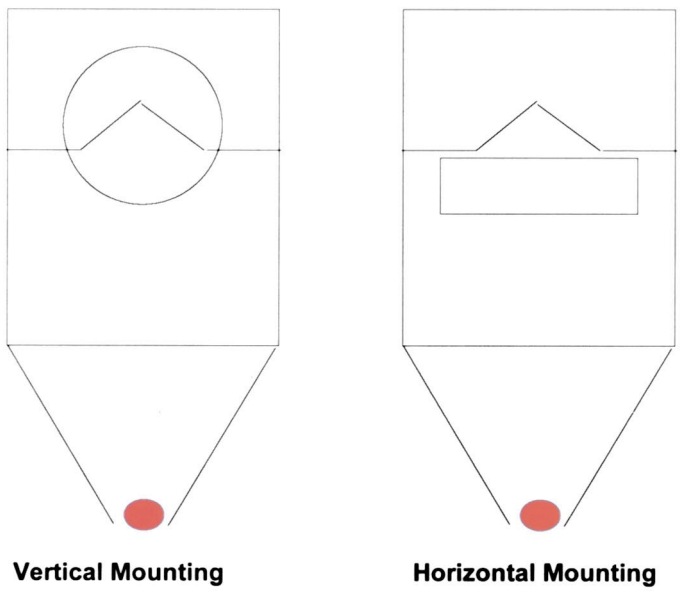

Fig. 2

Fig. 1. Dissolution apparatus configuration.
Fig. 2. Mounting of salicylic acid tablets in the cells.

Table 1
Experimental design

Experiment	No. cell replicates	Flow rate (ml/min)	Cell diameter (mm)	Tablet mounting	Tablet size
1A	3	20.3	12	Vertical	Single
1B	3	20.3	22.6	Vertical	Single
2A	3	51.2	12	Vertical	Single
2B	3	51.2	22.6	Vertical	Single
3A	3	10.4	12	Vertical	Single
3B	3	10.4	22.6	Vertical	Single
4A	3	38.4	12	Vertical	Single
4B	3	38.4	22.6	Vertical	Single
5A	3	38.4	12	Vertical	Double
5B	3	38.4	12	Horizontal	Single
6A	2	52.9	12	Vertical	Double
6B	2	52.9	12	Horizontal	Single
6C	2	52.9	22.6	Horizontal	Single

prior to any significant loss of surface area. Therefore, the slope of the line is taken over the initial time period to determine the initial dissolution rate (typically when percentage dissolved $< 10\%$). For each given cell, the slope was determined by regression using SAS JMP, and residuals plotted to assure linearity. The slope was divided by the surface area of the tablet and molecular weight to provide final units of grams per mole dissolved per cm^2 per min.

The effect of each hydrodynamic condition (cell diameter, linear velocity, tablet size, and tablet orientation) was determined by a comparison of the dissolution rates. The dissolution rate for each condition was determined by pooling the data from multiple cells and establishing a single estimated slope from the pooled data. To compare the effect of each condition, Student's t-test was used, with Bonferroni's modification for multiple comparisons (Neter et al., 1996). Parameters included $\alpha = 0.05$, 20 comparisons, and therefore $(1-\alpha_{BON}) = 0.999$.

2.3.2. Diameter d

Diameter of the round salicylic acid tablet is 9.6 mm and the thickness is 3.15 mm. When the tablet is mounted horizontally, this diameter is used for velocity and Reynold's number calculations, as this is the diameter that is across the flow of media. However, when the tablet is mounted vertically, the tablet is asymmetric in the radial dimension, and the diameter must be approximated. The tablet was therefore approximated as a cylinder of identical volume, and of the same mean height of the tablet. For single vertical tablets, this gave a cylinder with a diameter of 5.8 mm and a height of 8.5 mm.

2.3.3. Linear velocity v

Linear velocity is the velocity of the media in the annular area around the tablet. This is calculated as:

$$\text{media flow rate/media density/area for flow}$$

where

$$\text{area for flow} = \text{cross sectional area of cell} - \text{cross sectional area of tablet}$$

2.3.4. Reynold's number

The Reynold's number can be calculated from the linear velocity, the diameter, the media density and media viscosity. Media density was measured experimentally via pycnometry and found to be 0.977 g/cm^3 at 37°C. Media viscosity at 37°C was assumed to be that of water at 37°C, and was interpolated from published data as 0.00697 g/cm per s (Handbook of Chemistry and Physics, 1991).

2.3.5. Sherwood number

The Sherwood number can be calculated from the dissolution rate, the tablet diameter, the satura-

tion concentration of the solute, and the diffusivity. The saturation concentration of salicylic acid in the media at 37°C was determined experimentally, and found to be 6.24 mg/ml. The diffusivity of salicylate in water at 25°C was determined from published data. This was converted to diffusivity at 37°C using the method of Treybal, yielding a value of 7.35×10^{-4} cm^2/min (Handbook of Chemistry and Physics, 1998).

3. Results

The dissolution curves for single vertical salicylic acid tablets in 12 mm cells at various flow rates are shown in Fig. 3. As can be seen in the graph, the dissolution rate progressively increases with increasing flow rate in the 12 mm cell. Regression was used to determine the dissolution rates at each flow rate. The dissolution rates in the 12 mm cell at 10.4, 20.3, 38.4, and 51.2 ml/min were found to be 1.95 ± 0.07, 2.75 ± 0.03, 4.12 ± 0.23, and 4.76 ± 0.08 μmol/cm^2 per min, respectively. Statistical comparison of the data showed that these dissolution rates at 10.4, 20.3, 38.4, and 51.2 ml/min in the 12 mm cell are all significantly different from one another.

The dissolution curves for single vertical salicylic acid tablets in 22.6 mm cells are shown in Fig. 4. As can be seen in the graph, the dissolution rates are much lower than those seen in the 12 mm cells. The dissolution rates in the 22.6 mm cell at 10.4, 20.3, 38.4, and 51.2 ml/min were found to be 1.71 ± 0.11, 1.80 ± 0.04, 1.71 ± 0.17, and 2.05 ± 0.11 μmol/cm^2 per min, respectively. Statistical comparison indicated that the dissolution rates in the 22.6 mm cells are significantly lower than those in the 12 mm cells at each flow rate. Moreover, the dissolution rate is insensitive to flow rate in these larger cells. Statistical comparison indicated that only the dissolution rate at 51.2 ml/min flow rate was different from the dissolution rates at other flow rates. There are no significant differences in the dissolution rates at 10.4, 20.3, and 38.4 ml/min. As will be shown later, this is thought to be due to the extremely low Reynold's numbers in these cells. Therefore, further work in 22.6 mm cells was discontinued after obtaining these results.

A comparison of the dissolution curves for horizontally versus vertically mounted salicylic acid tablets in 12 mm cells are shown in Fig. 5. As can be seen in the figure, mounting the tablets horizontally increases the dissolution rate at the nominal flow rates of 38 and 52 ml/min. The dissolution rates for horizontally mounted tablets in the 12 mm cell at 38.4 and 52.9 ml/min were found to be 5.82 ± 0.33 and 6.29 ± 0.46 μmol/cm^2 per min, respectively. Statistical comparison indicated that both of these dissolution rates were significantly higher than those seen for vertical tablets at similar flow rates (4.12 ± 0.23 and 4.76 ± 0.09 μmol/cm^2 per min). This is believed to be due to the higher Reynold's number (i.e. degree of turbulence) associated with the larger diameter and higher linear velocity around the horizontal tablets.

The dissolution curves for single and double vertical salicylic acid tablets are shown in Fig. 6. As can be seen in the graph, the dissolution rate increases with larger tablet diameter. The dissolution rates for doubled tablets, mounted vertically, at 38.4 and 52.9 ml/min were found to be 4.89 ± 0.07 and 6.12 ± 0.09 μmol/cm^2 per min, respectively. Statistical comparison indicated that dissolution rates for doubled tablets are significantly higher than those for single vertical tablets at similar flow rates (4.12 ± 0.23 and 4.76 ± 0.09 μmol/cm^2 per min). This is expected, due to the larger tablet diameter yielding an increased Reynold's number.

Table 2 gives a summary of the results of these studies. Dissolution rates are reported for each individual cell, as well as for the pooled data for multiple cells. Reynold's numbers are also reported.

Figs. 7 and 8 are graphs of dissolution rates compiled for all experiments. Dissolution rates from each cell are reported, rather than pooled dissolution results. Fig. 7 displays dissolution rate as a function of volumetric flow rate. As can be seen in the figure, there is little correlation between volumetric flow rate and dissolution rate ($R^2 = 0.23$). Fig. 8 displays dissolution rate as linear fluid velocity around the tablet. There is a far superior correlation between linear fluid velocity and dissolution rate ($R^2 = 0.95$), confirming the importance of this parameter.

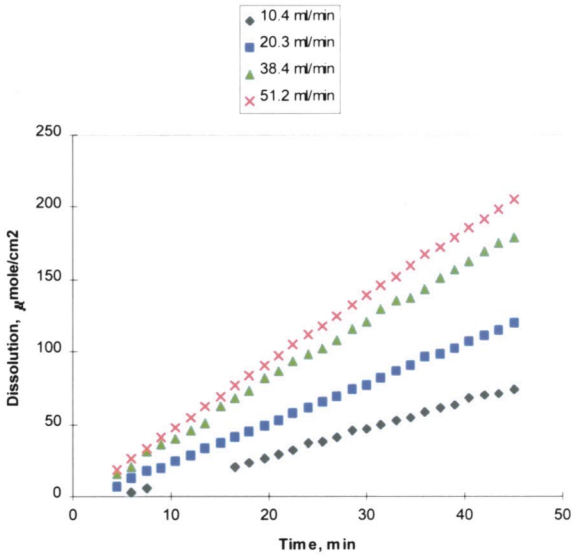

Fig. 3

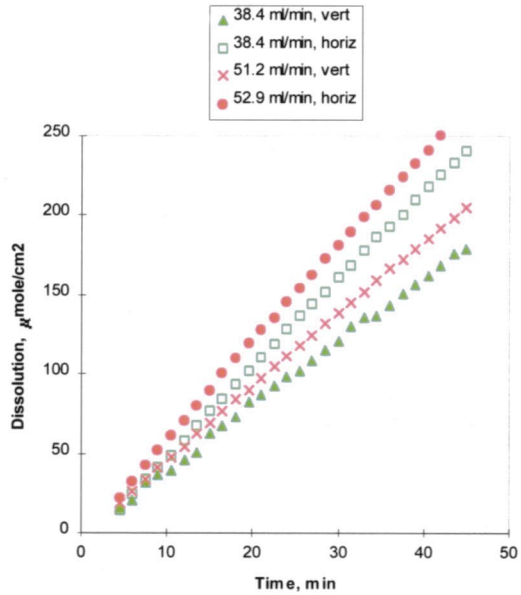

Fig. 5

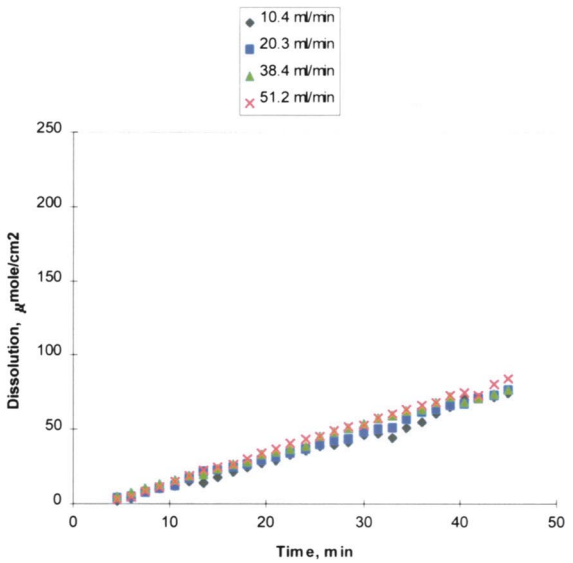

Fig. 4

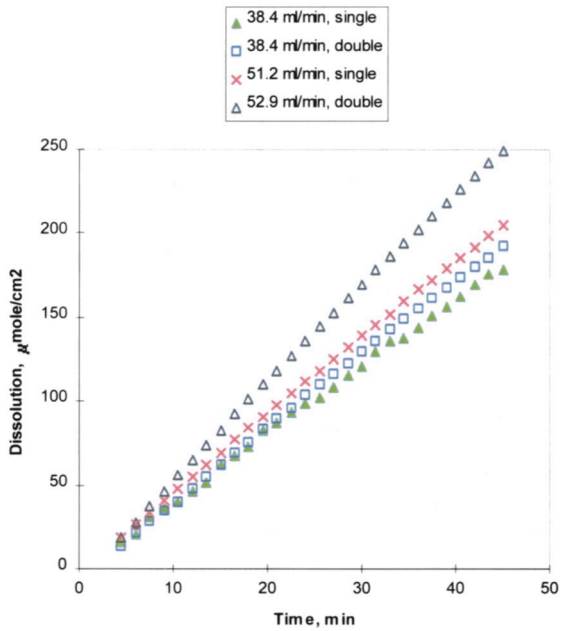

Fig. 6

Fig. 3. Dissolution rate in 12 mm cells, vertical tablets: effect of media flow rate.
Fig. 4. Dissolution rate in 22.6 mm cells, vertical tablets: effect of media flow rate.
Fig. 5. Dissolution rate in 12 mm cells: effect of tablet orientation and media flow rate.
Fig. 6. Dissolution rate in 12 mm cells: effect of tablet size and media flow rate.

Table 2
Summary of results

Experiment	Conditions	Reynold's number	Individual cell dissolution rates, μmol/min per cm^2	Mean dissolution rates and 95% confidence intervals, μmole/min per cm^2
1A	20.3 ml/min, 12 mm cell, single vertical	31.7	2.78, 2.74	2.75 ± 0.03
1B	20.3 ml/min, 22.6 mm cell, single vertical	7.3	1.73, 1.87	1.80 ± 0.04
2A	51.2 ml/min, 12 mm cell, single vertical	79.9	4.85, 4.56, 4.65	4.76 ± 0.08
2B	51.2 ml/min, 22.6 mm cell, single vertical	18.3	1.98, 1.90, 2.14	2.05 ± 0.11
3A	10.4 ml/min, 12 mm cell, single vertical	16.3	1.86	1.95 ± 0.07
3B	10.4 ml/min, 22.6 mm cell, single vertical	3.7	1.57, 1.86	1.71 ± 0.11
4A	38.4 ml/min, 12 mm cell, single vertical	59.9	4.05, 4.05, 4.33	4.12 ± 0.23
4B	38.4 ml/min, 22.6 mm cell, single vertical	13.7	1.56, 1.81	1.71 ± 0.17
5A	38.4 ml/min, 12 mm cell, double vertical	126.8	4.77, 4.90	4.89 ± 0.07
5B	38.4 ml/min, 12 mm cell, single horizontal	212.6	5.55, 6.09, 5.95	5.82 ± 0.33
6A	52.9 ml/min, 12 mm cell, double vertical	173.0	6.07, 6.17	6.12 ± 0.09
6B	52.9 ml/min, 12 mm cell, single horizontal	292.0	6.37, 6.72	6.29 ± 0.46
6C	52.9 ml/min, 22.6 mm cell, single horizontal	36.1	1.97, 2.09	2.03 ± 0.03

Fig. 9 displays the relationship between the Sherwood number and the Reynold's number to the one-half power, for Reynold's number's > 10. As expected from the work by Garner, Suckling, & Grafton, there is a linear relationship between the Sherwood number and Reynold's number to the one-half power.

Regression was done to establish the equation for the relationship between the Sherwood number and the Reynold's number$^{0.5}$ ($N_{RE} > 10$), and it was found to be:

$$N_{SH} = -21.1 + 12.6 \times N_{RE}^{0.5}$$

$$R^2 = 0.99$$

$$10 < N_{re} < 292$$

4. Discussion

4.1. Hydrodynamic considerations

Using the Flow Through Cell to measure the dissolution of salicylic acid tablets, the form of the relationship between Reynold's number and the Sherwood number was found to closely match that found by Garner, Grafton and Suckling. Although one might expect that to be the case, there were a number of significant hydrodynamic differences between the Flow Through Cell and the equipment used by the previous investigators. These include:

- Garner, Suckling and Grafton used a constant

velocity of fluid, whereas the Flow Through Cell uses a sinusoidal pulse pump. Therefore, the Reynold's number established for the Flow Through Cell is not constant, and the value reported is that of the mean flow rate.

- Entrance effects (i.e. turbulence associated with rapid changes in pipe diameter at an orifice) can cause the Reynold's number to underestimate the degree of turbulence. Therefore, when conducting any hydrodynamic experiments, it is generally recommended to allow a distance of 20 pipe diameters between any orifice and the site of interest. This was done in the work by Garner, Suckling, and Grafton, but is not feasible with the Flow Through Cell.
- The glass beads used in the Flow Through Cell would be expected to increase the amount of turbulence experienced, thereby causing an underestimation of the true degree of turbulence.
- Finally, Garner, Suckling, and Grafton used a sphere of benzoic acid. However, since spheres are not typically used as pharmaceutical dosage forms, disk-shaped tablets were used. This could also alter the model.

Resolution of these above issues could be accomplished by repeating the above experiments, using a benzoic acid:water system as done by previous researchers. However, as this has no utility to the pharmaceutical scientist, this has not been attempted.

An alternate approach to resolving the above uncertainty would be to establish a model with different solute–solvent systems, thereby including the Schmidt number in the model, as had been done by Garner, Grafton and Suckling. Therefore, further experimentation will need to be done to establish the effect of the Schmidt number (i.e. diffusivity) on dissolution.

The cause of the inflection point at $N_{re} < 10$ is not known. It is postulated that, at these low flow rates, the convection of dissolved solid away from the tablet may be negligible, and that dissolution is controlled by molecular diffusion, which would be constant. This would need further experimentation to evaluate.

4.2. Cell size

It was somewhat surprising to observe the relative insensitivity of dissolution rate to media ve-

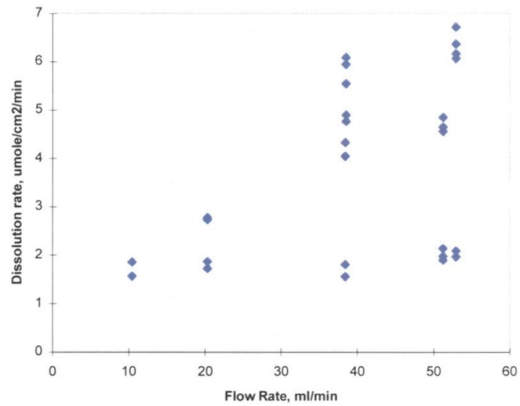

Fig. 7

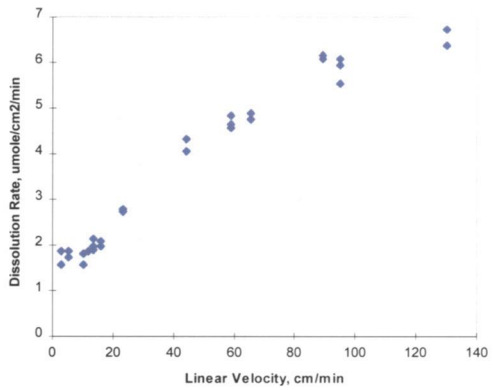

Fig. 8

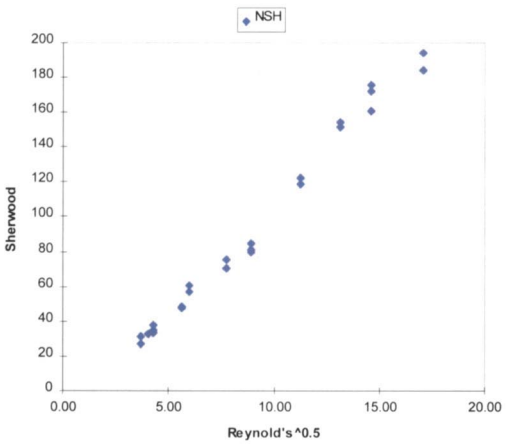

Fig. 9

Fig. 7. Dissolution rate versus flow rate.
Fig. 8. Dissolution rate versus linear velocity.
Fig. 9. Sherwood number versus Reynold's number$^{0.5}$.

locity in the 22.6 mm cell. However, calculations of the Reynold's numbers explain this. These show that the Reynold's numbers are very low, due to the very low linear velocity.

Another consideration is the lack of discriminatory ability of the larger cells. These cells do not show differences in dissolution rates due to a parameter as critical as flow rate. Therefore, it is possible that these cells would not be able to distinguish formulation differences in vitro that may be critical in vivo. An alternative is to develop flow cell pumps that deliver higher flow rates, but this is not currently available with commercial flow cell equipment. Therefore, due to the lack of discriminatory ability of these cells, this could be a limitation of the utility of these larger cells in dissolution method development.

4.3. Tablet orientation

There were significant differences in dissolution rate as a function of tablet orientation. Again, this can be readily explained by calculation of the linear velocity and the Reynold's number. Tablets in a horizontal orientation cause a higher velocity around the tablet, and have a higher cross-sectional area blocking flow, both increasing turbulence and thereby the dissolution rate. This also suggests that lack of control over tablet orientation can be a major factor in the variability of dissolution results. It is recommended that future researchers control the orientation of the dosage forms through the use of the clips provided with the Sotax cells.

4.4. Surface area

Results showed the increase in dissolution rate with increased size. Again, this is likely due to the increased linear velocity around the dosage form, and increased cross-sectional area blocking the flow. This would suggest that shape factor of the dosage form – the relationship between thickness, length and width – may affect in vitro dissolution rates per unit area. It is unlikely that this affects in vivo performance, as the much larger volume of gastrointestinal fluid is not expected to impart a higher linear velocity. Therefore, the pharmaceutical scientist would be wise to consider shape factor of dosage forms when establishing in vitro–in vivo correlations.

4.5. Sink conditions

Dissolution rate can only assumed to be constant if sink conditions (i.e. concentration of the media is $< 10\%$ of saturation concentration). The saturation concentration of salicylic acid in the media was experimentally found to be 6.24 mg/ml. Therefore, sink conditions are maintained at concentrations below 0.624 mg/ml, which is equivalent to 562 mg of salicylic acid in the 900 ml media. As this is beyond the maximum concentration of the media at 100% dissolution, sink conditions are maintained throughout the entire run.

4.6. In vitro correlation between USP 2 and USP 4

Documentation from USP specifies this lot of tablets (Lot N) are expected to achieve 17–26% dissolved in 30 min in USP 2 (Paddles) at 100 rpm[12]. This is equivalent to dissolution rates of 5.1–7.8 μmol/cm^2 per min. Dissolution results in USP 4 (the flow through cell) suggests that this is equivalent to approximately 52 ml/min with tablets in the horizontal position in the 12 mm cells. This high of a dissolution rate could not be achieved with tablets in the vertical orientation in 12 mm cells, or in any orientation in the 22.6 mm cells at the maximum velocity available on the pump. This suggests that dissolution rates in USP 2 at 100 rpm are generally beyond those capable in USP 4. More work would be required to establish a definitive correlation between USP 2 and USP 4.

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