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Report

Dependence of Dissolution Rate on Surface Area: Is a Simple Linear Relationship Valid for Co-Compressed Drug Mixtures?

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A quantitative analysis of the dependence of dissolution rate on the relative surface area occupied by two non-interacting drug mixtures from co-compressed slabs is described. The results from the experimental dissolution rates of each component from naproxen/phenytoin co-compressed slabs under laminar flow conditions, when corrected for the area occupied by that component in the slab, contradict the stagnant layer model predictions, where dissolution rates are assumed to be directly proportional to the occupied surface area. Simulations from non-mixed co-compressates of naproxen and phenytoin indicated that dissolution rates are proportional to $bL^{2/3}$, as reported for pure compounds in the laminar dissolution apparatus by Shah and Nelson. However, for a well mixed co-compressate, which differs with the non-mixed case only in the distribution of particles, this proportionality did not hold. The deviation was explained by 'carryover' of material from one section of the component to the next due to fluid flow, resulting in an increase in apparent effective length of the component in the slab (L_{eff}).

KEY WORDS: carryover; co-compressate; convective-diffusion; dissolution; laminar flow; surface area.

INTRODUCTION

Dissolution of solids in liquids is usually described in the pharmaceutical literature using the stagnant layer model and the Noyes-Whitney relationship (1–6). Although a good practical approximation, the stagnant layer model does not specifically consider the hydrodynamics of the dissolution medium. The model also assumes a linear dependence of dissolution rate on the surface area available for dissolution. However, it has been found that under forced convection, in laminar as well as turbulent flow, the dissolution rate from regular, non-disintegrating surfaces of a pure compound can be treated mathematically using the general expression of Grijseels et al. (7), as given in Eq. 1:

$$R = K\, C_s\, D^{\beta}\, \nu^{\gamma}\, u^{\epsilon}\, F \tag{1}$$

where the exponents β, γ, and ϵ and the proportionality factor K depend on the hydrodynamic conditions; C_s is the intrinsic solubility and D is the diffusion coefficient of the compound, while ν is the kinematic viscosity of the medium. Here, as in the stagnant layer models, the dissolution rate is dependent on the exposed surface area. In a flow system, however, the dependence may be non-linear; F is a function of the slab and the dissolution apparatus dimension (same as A in Ref. 7 and does not indicate surface area) and dependent on the system hydrodynamics. In one of several hydrodynamic studies, Shah and Nelson (8) reported that the dissolution rate of a neutral compound (R) under laminar flow conditions in a rectangular channel is proportional to $bL^{2/3}$, where b and L are the width and length of a rectangular slab, respectively, or in area terms, the dissolution rate is proportional to Area/$L^{1/3}$, as given in Eq. 2 below:

$$R = \left(\frac{1.468\, D^{2/3}\, C_0\, b\, L^{2/3}}{(H^2\, W)^{1/3}}\right) Q^{1/3} \tag{2}$$

where D is the diffusion coefficient, C_0 is the saturated solubility, H and W are channel dimensions and Q is the volumetric flow rate.

Tablets are rarely formulated as pure drug, but are co-compressed with one or more excipients (inert or otherwise). It has been shown that models for the dissolution of pure components like that of Shah and Nelson, cannot be applied to multicomponent formulations. Rather, surface area ratios of the drug and excipient affect the drug dissolution rate. Because the dissolution process of either solid component is complicated by the presence of the other, it has not been feasible to develop an algebraic expression such as Eq. 1, and numerical methods must be used (9).

A study to quantitatively determine the dependence of dissolution rate on the relative surface area occupied by two non-interacting drugs in a co-compressed slab is described in this communication. Dissolution rates from co-compressates consisting of naproxen and phenytoin in a dissolution apparatus exhibiting laminar flow were determined both experimentally and numerically in a previous study (9). Here, the dissolution rates were corrected for an effective area function and evaluated for varying weight proportions of the components. The results demonstrate that the dissolution rates are *not* linearly proportional to the relative surface area occupied by the two components of the compressate.

METHODS

Simulation for a Non-Mixed Co-Compressed, Two Component Slab

To understand the effect of the occupied surface area on the dissolution behavior in the micro-environment next to the dissolving surface, a formulation was simulated where the components are not mixed i.e., for a two component system containing drugs A and B, it was assumed that all of A occupies one section of the slab and all of B occupies the other section. The surface areas of A and B are proportional to their respective weight proportions in the slab (densities for the two materials are essentially identical). For example, the length of A (LA) in a slab containing 50% w/w of A will be 50% of the total length of the slab, as depicted in Fig 1A. This situation can also be explained as two pure slabs of A

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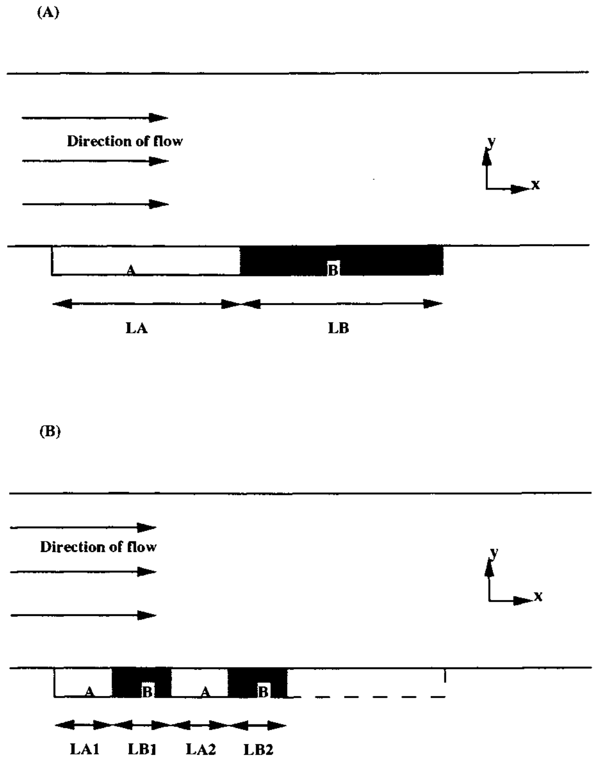

Fig. 1. Schematic diagram of a two component co-compressed pellet in laminar dissolution apparatus. (A) non-mixed co-compressate (B) partial representation of well mixed co-compressate showing repeating units of compounds A and B with lengths LA and LB respectively.

and B with differing lengths (constant width is assumed) being placed side by side to form a continuous slab. Hence, Shah and Nelson's analytical expression for dissolution rate, which assumes a linear velocity profile within the boundary layer, could be applied and the theoretical effect of the relative slab dimensions on dissolution rate can be verified (simulated). A numerical convective diffusion model also was developed as before (9), by incorporating the actual parabolic velocity profile to calculate dissolution rates of A and B. Although the numerical model requires computer solution (and is of little extra value for this simple case), it can be used to compare surface area effects in non-mixed and well mixed co-compressates.

Dissolution from Well Mixed Co-Compressates

The dissolution rates (R) of naproxen/phenytoin mixtures from co-compressed slabs at various weight proportions were determined experimentally from a laminar dissolution apparatus, as a function of flow rate and particle size as reported earlier (9). These values correlated very well with the numerical model developed concurrently.

In order to delineate the effects of component surface area and understand them better, the dissolution rates were modified and corrected for the actual area occupied by the component in the compressed slab. The actual area occupied by the component was calculated by taking the slab densities of the two components (reported in Ref. 9) into account, as follows:

$$\begin{array}{c}\%\text{ actual area}\\ \text{occupied by A}\end{array} = \frac{\dfrac{\text{weight of A}}{\text{density of A}}}{\dfrac{\text{weight of A}}{\text{density of A}} + \dfrac{\text{weight of B}}{\text{density of B}}} \times 100$$

The 'area-corrected' dissolution rate (R_{ac}) is calculated as shown below in order to examine the dependence of the dissolution rate on the actual area occupied by the component in the slab:

$$\text{'Area-Corrected' Dissolution Rate} = \text{Dissolution Rate} \times \left(\frac{100}{\%\text{ actual area occupied}}\right)$$

Also, the result of Shah and Nelson, that dissolution rate is proportional to $bL^{2/3}$ rather than area (bL) for pure compounds, was tested for co-compressed slabs by calculat-

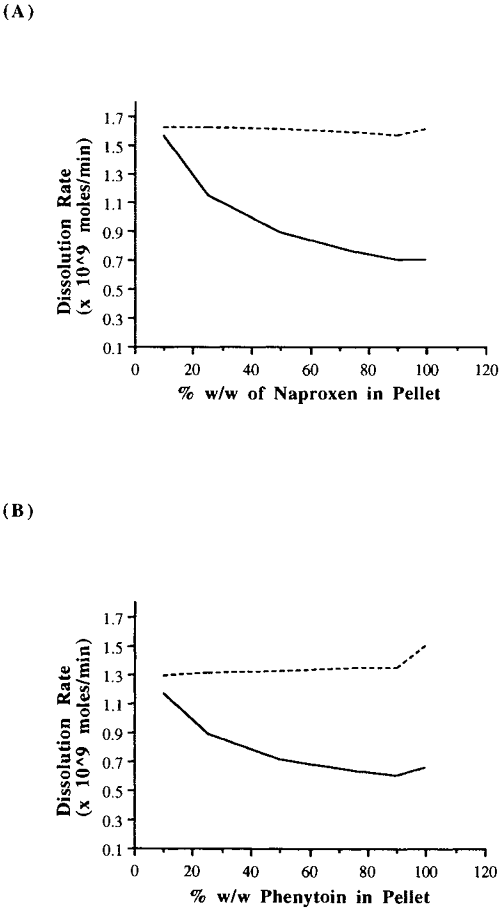

Fig. 2. Simulated plot of dissolution rate of (A) Naproxen and (B) Phenytoin at various weight proportions from non-mixed co-compressates. The dissolution rates were corrected for surface area (——, R_{ac} = R/% area) and area/$L^{1/3}$ (----, R_L = R/b$L^{2/3}$), where R is the dissolution rate, b is the width and L is the length of the pellet, respectively.

ing dissolution rates corrected for $bL^{2/3}$ (R_L), as given by Eq. 3 below:

$$R_{L,i} = {}^{R_i}\!/_{bL_i^{2/3}} \qquad (3)$$

where b is the width of the slab, L_i is the actual cumulative length of component i in the slab based on its weight proportion (LA1 + LA2 + LA3 + . . . for component A in Fig. 1B) and R_i, its dissolution rate. The simulated dissolution rates from non-mixed co-compressates also were corrected for area and $bL^{2/3}$ as above, so that the effects of mixing and distribution of particles in the slab could be studied.

RESULTS AND DISCUSSION

The simulated dissolution rates for non-mixed co-compressates of naproxen and phenytoin at a flow rate of 3.45 ml/min corrected for area (R_{ac}) and $bL^{2/3}$ (R_L) are shown in Fig. 2. As expected, the data indicate that the dissolution rate is proportional to $bL^{2/3}$, since R_L is independent of the % w/w of the component in the slab, whereas, the 'area-corrected' dissolution rate (R_{ac}) is dependent on the weight proportion.

For the well-mixed co-compressate dissolution, the effect of hydrodynamics of the bulk medium was similar to that of pure compounds, showing dependence of dissolution rate on cube-root of flow rate (constant slope of around 0.33 in a Log dissolution rate − log flow rate plot) for any weight ratio of the components, as shown in Fig. 3. Thus, as the proportion of the component in a slab is changed and exposed to a given flow rate, the dissolution rate is affected only by changes in the occupied relative surface area (total length, since component width in the slab, b, is assumed constant in the model), as indicated by the change in the intercept only. As a first approximation, it might be expected that the same area-related correlations simulated in non-mixed co-compressates would hold for the mixed compressates since the cumulative surface area occupied for a particular ratio of naproxen to phenytoin, is the same as in the non-mixed slab; the only difference being the distribution of the particles. However, the experimental as well as the numerical dissolution rates for co-compressates consisting nominally of 112 μm particles and exposed to a flow rate of 3.45 ml/min, when corrected for area (R_{ac}) and $bL^{2/3}$ (R_L) indicated (Fig. 4) that dissolution rate is *not* directly proportional to either the area occupied or the actual cumulative length (L) of the component in the slab. The log R versus log Q plots in Fig. 3 indicates that as weight proportion of a component is varied, the intercept changes. The log trans-

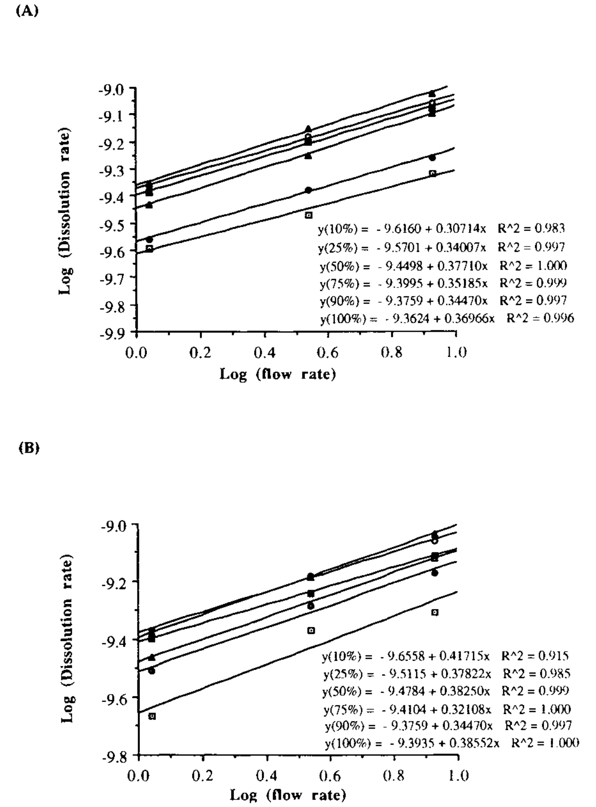

Fig. 3. Log-log plots of dissolution rate vs the flow rate of (A) Naproxen and (B) Phenytoin showing the linear fits for various weight proportions: (⊡), 10% w/w; (●), 25% w/w; (△), 50% w/w; (■), 75% w/w; (○), 90% w/w; (▲), 100% w/w.

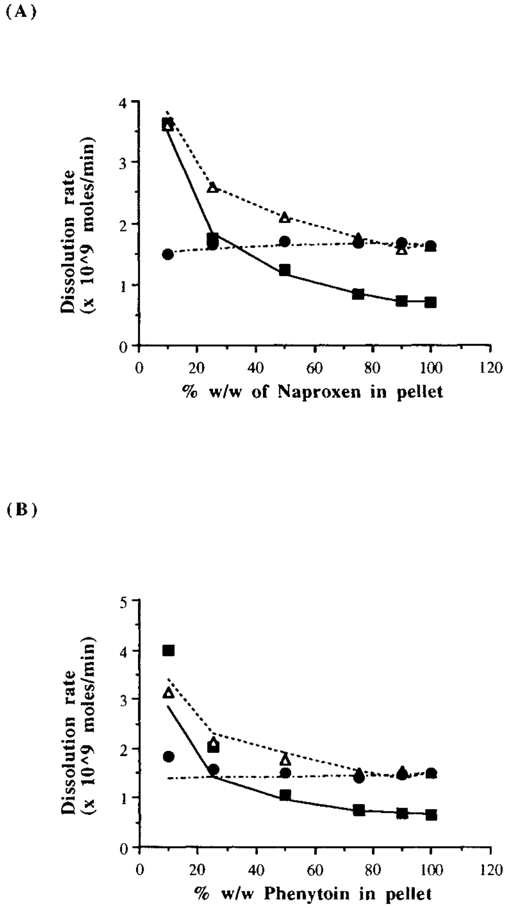

Fig. 4. Plot of dissolution rate of (A) Naproxen and (B) Phenytoin from well mixed co-compressates with a nominal particle size of 112 μm exposed to a flow rate of 3.45 ml/min, at various weight proportions of A to B. The dissolution rates were corrected for surface area (■, ——, R_{ac}); area/$L^{1/3}$ (△, ----, R_L); and $bL_{eff}^{2/3}$ (●, ----, $R_{Leff} = R/bL_{eff}^{2/3}$), where L_{eff} is the effective particle length due to fluid carryover. Symbols represent experimental dissolution data and lines represent theoretical results from the model solved numerically.

formation of Eq. 2, as shown in Eq. 4, indicates that the only parameter that varies with weight proportion of a component is the length (L) in the intercept, since the width b was assumed constant in the model.

$$\text{Log } R = \text{Log}\left(\frac{1.468\, D^{2/3}\, C_0\, b\, L^{2/3}}{(H^2\, W)^{1/3}}\right) + 0.33 \text{ Log } Q \qquad (4)$$

The length calculated with the intercept function from the above equation and the intercept from the plots in Fig. 3 for various weight proportions of the components was termed effective length, L_{eff}. Statistical analysis indicated that this effective length is significantly different than the actual cumulative length. L_{eff} became larger than L as the weight proportion of the component is lower, as shown in Table 1. This was explained by a 'carryover' hypothesis, where material from one section of a component is carried over to the adjacent section of the other component due to convective transport, thus increasing the apparent length of the components. A visual representation of a well mixed formulation (Fig. 5), generated by the model computer simulation, shows the carryover of one component in the direction of flow. In the present study, the effects of this carryover on dissolution from co-compressed slabs were evaluated by normalizing the dissolution rate data with $b(L_{eff})^{2/3}$, as given in Eq. 5, below:

$$R_{L_{eff},\, i} = {R_i}\Big/{b(L_{eff,i})^{2/3}} \qquad (5)$$

Fig. 4 indicates that $R_{L_{eff}}$ (both experimental and numerical) is independent of the weight proportion for either component. Hence, the dissolution rates are proportional to $b(L_{eff})^{2/3}$ rather than $bL^{2/3}$. This dependence of dissolution rate on L_{eff} rather than the actual cumulative length suggests that L_{eff} is a more meaningful parameter for evaluating drug dissolution characteristics from a formulation. Because L_{eff} is a result of fluid flow and composition of the formulation, it is evident that convective transport and proportion of active ingredient play a very important role in the dissolution process. Effectively, these results suggest that under laminar flow conditions, dissolution rate varies disproportionally to the effective surface area exposed to the dissolution media.

The model has some limitations and as mentioned earlier (9), the dissolving compounds under study should both be sparingly soluble in water and have similar intrinsic solubility. Also, the L_{eff} dependence, as described above, holds only for the rectangular geometry of the tablet in the laminar hydrodynamic conditions. Independent but similar evaluations have to be made for co-compressed tablets in other geometrical shapes and for other hydrodynamic systems in order to understand the effects of the 'carry-over' phenomenon.

Table I. Comparison of Actual Length Occupied in the Pellet and the Effective Diffusional Length (L_{eff}) for the Components Calculated from the Log-Log Plots of Dissolution Rate Versus the Flow Rate (Fig. 3)

% w/w of component in pellet	Total component lengths in pellet, cm			
	Naproxen		Phenytoin	
	Actual length	Effective length	Actual length	Effective length
10	0.157	0.60	0.157	0.64
25	0.394	0.70	0.394	1.05
50	0.788	1.06	0.788	1.17
75	1.18	1.26	1.18	1.49
90	1.42	1.37	1.42	1.57
100	1.575	1.575	1.575	1.575

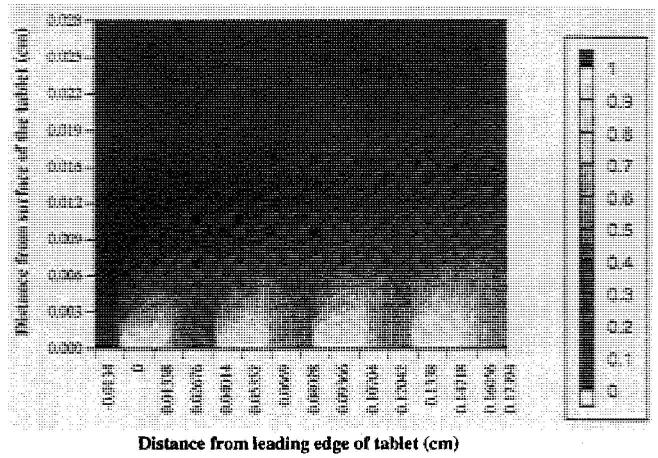

Fig. 5. Simulated naproxen concentration profile from a 50% w/w naproxen/phenytoin co-compressed pellet. The concentrations were normalized with respect to saturated solubility and range from saturated solubility (1, lighter section) at the solid surface-media interface to sink conditions (0, darker section) in the bulk solution.

Grijseels et al. (7) have summarized the geometric factors that influence dissolution of pure compounds in different hydrodynamic conditions. However, for pharmaceutical formulations where excipients are added to the active agent(s), the effects of other factors such as the 'carryover' phenomenon described earlier (9) and re-emphasized in this communication, on the geometric parameters should be understood. The dissolution of drugs in complex compressed mixtures will vary depending on the hydrodynamics at the dissolving surface, the number of components present on the surface and also on the interaction (chemical or physical), if any, between the components. A simple direct proportionality relationship between dissolution rate to area of drug exposed to a dissolution media, especially in complex co-compressed mixtures, appears to be invalid.

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