MODELLING DISSOLUTION OF SPARINGLY SOLUBLE POWDERS

L. Pereira de Almeida[1], P. Brito[2], A. Sousa[1], A. Portugal[2] and M. Figueiredo[2]

[1]Laboratório de Galénica e Tecnologia Farmacêutica,
Faculdade de Farmácia
[2]Departamento de Engenharia Química,
Faculdade de Ciências e Tecnologia
Universidade de Coimbra, 3000 Coimbra, Portugal

ABSTRACT

The present work deals with the simulation of the dissolution process of polydisperse powders. Three different size fractions of Ibuprofen were used to develop a model which assumes a diffusion layer thickness proportional to the particle diameter, up to a critical value, beyond which it is considered constant. The application of the resultant integrated equations to each size class of the primary particle size distribution leads to an almost perfect agreement between simulated and experimental dissolution profiles.

1 INTRODUCTION

A previous study of the dissolution of Ibuprofen using a particle counter - which allows the monitorization of the size and number of the particles in suspension throughout the time - enabled to test the applicability of the Hixson-Crowell model to multisized powders [1]. Although reasonable fittings were achieved (especially for the fine fractions) these were only apparent. In fact, this model is based on the premise that the number of particles remains constant, which was not found experimentally [1,2]. Besides, allowing the boundary layer thickness (h) to vary with particle size (d) seems physically more realistic than to assume a constant value of h during the whole dissolution process [3]. Furthermore, the polydispersity nature of the drug powder must also be taken into consideration [4,5,6].
An integrated form of the Noyes-Whitney equation, assuming h proportional to d, was recently applied to each size class of the primary particle size distribution of one of the fractions (the finest), and an almost perfect agreement between the simulated and experimental profiles was obtained, using a value of h approximately equal to half of the particle radius [7].

Since dissolution data are available for various fractions, the present work intends to study the model quality of fit when applied to larger particles.

2 EXPERIMENTAL

2.1 Physical characterisation of Ibuprofen fractions

Three different size fractions of Ibuprofen, a widely used NSAID, were

utilised for dissolution testing. Table 1 summarises the most relevant physical characteristics with regard to this study. Particle size distribution was evaluated using a Coulter Multisizer II in a previously saturated solution being the results shown in figure 1. A particle shape factor was calculated from the powder specific surface area (BET), as described elsewhere [8]. Density was measured by helium picnometry. The diffusion coefficient was evaluated using the rotating disk method by the Levich equation [9]. The Ibuprofen solubility was determined by spectrophotometric assay of saturated solutions at 221 nm [10].

Table 1 - Physical characteristics of Ibuprofen samples

Fraction (nominal size)	Volume median diameter μm	Shape factor ($\alpha_{s,dv}$)	Solubility (C_S) $\mu g/ml$	Diffusion coefficient (D) cm^2/s	Density (ρ) g/cm^3
25	22.9	4.1	72	6.6×10^{-6}	1.112
38	27.3	3.6	72	6.6×10^{-6}	1.112
50	52.6	3.2	72	6.6×10^{-6}	1.112

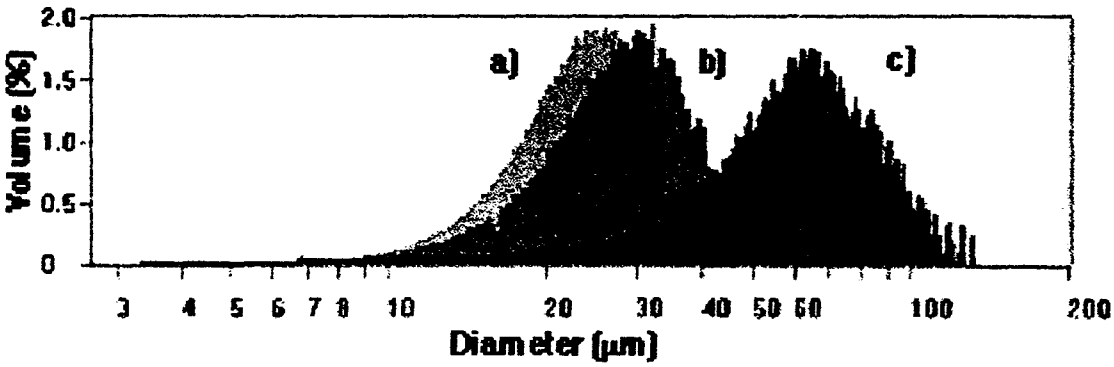

Figure 1 Primary particle size distribution of the Ibuprofen fractions obtained with the Coulter Multisizer II: a) fraction 25; b) fraction 38; c) fraction 50.

2.2 Experimental dissolution profiles

The experimental procedure adopted in this work was to follow the suspended solids concentration, as a function of time, with the Coulter Multisizer II, and using potassium dihidrogen phosphate buffer solution of pH=4.5 (European Pharmacopoea), complemented by 0.01% Tween 80, under sink conditions.

3 MODELLING

Assuming the boundary layer thickness proportional to particle diameter, the integrated equation, takes the form:

$$w_{t+\Delta t,i}^{2/3} = w_{t,i}^{2/3} - N_i^{2/3} K t \quad \text{, where} \quad K = \frac{2}{3}\frac{D}{k}\alpha_{s,dv}\left(\frac{6}{\pi\rho}\right)^{1/3} C_s \qquad (1)$$

being

$w_{t+\Delta t,i}$ – suspended particles weight at time $t+\Delta t$, for the size class i,

$w_{t,i}$ – suspended particles weight at time t, for the size class i,
N_i – number of particles at time t for the size class i,
k – constant=h/d.

The rest of the variables are defined in Table 1.

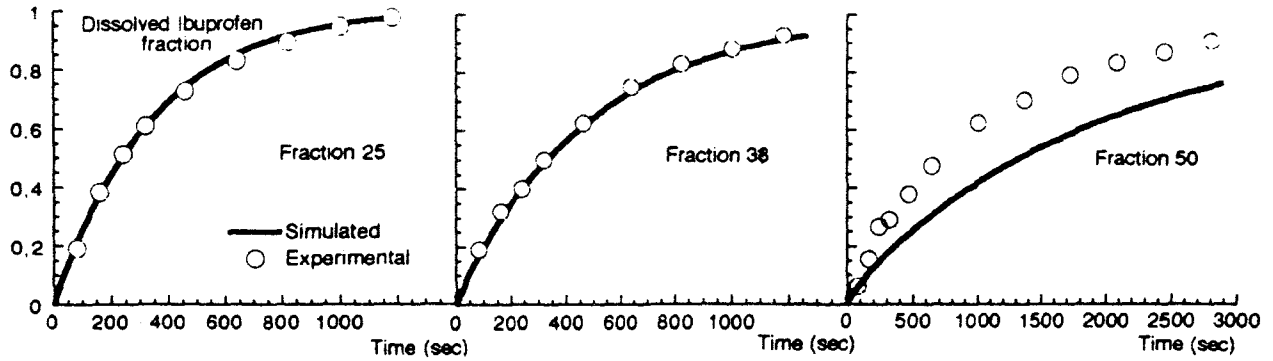

Figure 2 Experimental *versus* simulated dissolution profiles of the various fractions of Ibuprofen ($k=0.282$, adjusted for fraction 25).

As can be seen from figure 2, the simulated and experimental profiles obtained using the value of k, optimised for the fraction 25 ($k=0.282$), clearly deviate for the largest fraction. An additional condition was then imposed to the model: beyond a certain size, designated as critical diameter (d_{crit}), h is considered constant [5,11]. In this case, equation (1) is no longer valid and the following equation has to be used

$$w_{t+\Delta t,i}^{1/3} = w_{t,i}^{1/3} - N_i^{1/3} K t \quad , \text{ where } K = \frac{1}{3}\frac{D}{k d_{crit}} \alpha_{s,dv} \left(\frac{6}{\pi \rho}\right)^{2/3} C_s \qquad (2)$$

These equations (eq. (1) for $d<d_{crit}$ and eq. (2) for $d>d_{crit}$) were applied to each size class (in a total of 64 classes) of the primary particle size distribution, the total mass of suspended solids, at a given time, being equal to the summation of the calculated values. The number of particles in each size class was constantly updated taking into consideration the correspondent mass decrease, computed at every time interval.

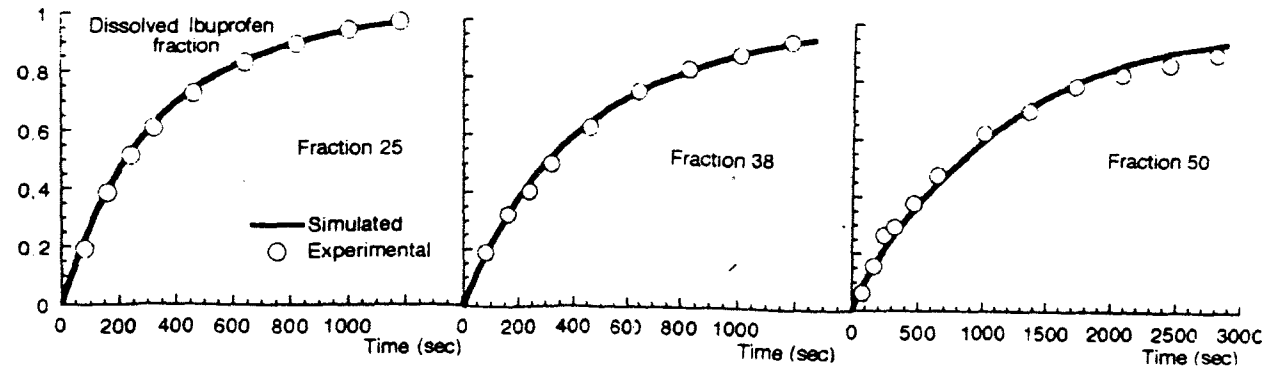

Figure 3 Experimental *versus* simulated dissolution profiles of the various fractions of Ibuprofen ($k= 0.263$, and $d_{crit}=22\ \mu m$).

Figure 3 shows the new simulated profiles, after optimisation of k and d_{crit}. As the new value of k (0.263) is close to the previous one, it can be concluded that the condition added concerning the larger particles ($d>d_{crit}$)

was the main responsible for the good fittings.
Additional experiments were carried out with mixtures of the finest and coarsest fractions and equally good fittings were obtained.

4. CONCLUSIONS

The almost perfect agreement between the simulated and experimental profiles leads to the conclusion that the model developed here is valid to describe the dissolution process of Ibuprofen, regardless of the size of the fraction. The relationship between the diffusion layer thickness and the particle radius was not equal to unity, as mentioned by other authors [3,5], but inferior. Similar relationships can, nevertheless, be evaluated from the results published in the literature [12].
Besides being straightforward, one of the greatest advantages of this model is that it uses the real particle size distribution of the powder drug and not an assumed one as frequently found in the literature [3,4,11]. However, it requires in principle, at least two size fractions of the drug (one finer and one coarser) in order to adjust both k and d_{crit}.

REFERENCES

[1] Pereira de Almeida L., Simões S., Sousa A. and Figueiredo M., Testing the applicability of the cube root law to the dissolution of ibuprofen using a particle counter, 1st World Meeting on Pharmaceutics, Biopharmaceutics, and Pharmaceutical Technology, Budapest, 9-11 May 1995

[2] Simões S., Sousa A. and Figueiredo M., Dissolution studies of pharmaceutical powders using the Coulter Multisizer II - influence of particle size, Symposium on Solid Oral Dosage Forms, Stockholm, 1994.

[3] Higuchi W.I. and Hiestand E.N., Dissolution rates of finely divided drug powders I- effect of a distribution of particle sizes in a diffusion-controlled process, J.Pharm.Sci., **5 2** 67-71 (1963)

[4] Pederson P.V. and Brown K.F., Dissolution profile in relation to initial particle distribution, J.Pharm.Sci., **6 4** 1192-1195 (1975)

[5] Hintz R.J. and Johnson K.C., The effect of particle size distribution on dissolution rate and oral absorption, Int.J.Pharm., **5 1** 9-17 (1989)

[6] Hoffman A., Donbrow M., Gross S.T., Benita S. and Bahat R., Fundamentals of release mechanism interpretation in multiparticulate systems: determination of substrate release from single microcapsules and relation between individual and ensemble release kinetics, Int.J.Pharm., **2 9** 195-211 (1986)

[7] Pereira de Almeida L., Brito P., Portugal A., Sousa A. and Figueiredo M., Modelling the dissolution kinetics of Ibuprofen, 1st Spanish-Portuguese Conference on Controlled Drug Delivery, Santiago de Compostela, Spain, 25-27 September 1995

[8] C. Nyström, J. Mazurt, M.I. Barnett and M. Glazer, Dissolution rate measurements of sparingly soluble compounds with the Coulter Counter model TA II, J. Pharm. Pharmacol., 37 217-221 (1985)

[9] Levich V.G., Physico-chemical Hydrodynamics, Prentice Hall, Englewood Cliffs, New Jersey, 1962

[10] Smidt J.H. , Offringa J.C.A. and Crommelin D.J.A., Dissolution rate of griseofulvin in bile salt solutions, J.Pharm.Sci., **8 0** 399-401 (1991)

[11] Lu A.T.K., Frisella M.E. and Johnson K.C., Dissolution Modeling: factors affecting the dissolution rates of polydisperse powders, Pharm.Res., **1 0** 1308-1314 (1993)

[12] Mauger J.W., Howard S.A. and Amin K., Dissolution for finely divided drug suspensions, J.Pharm.Sci., **7 2** 190-193 (1983)