DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(14-16), 2455-2474 (1989)

VOLUME/SURFACE WEIGHTED MEAN DIAMETER AS AN INDICATOR OF DISSOLUTION RATE

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ABSTRACT

The dissolution rate of a batch of drug substance is related to its intrinsic dissolution rate and particle size distribution. For dissolution purposes, the volume/surface weighted mean diameter (d_{vs}) appears to be the best descriptor of a batch.

Knowledge of the intrinsic dissolution rate of a compound allows the formulator to set a particle size specification for that compound. This ensures batch to batch consistency of *in vitro* dissolution performance and affords a high degree of assurance that bioavailability will be maximised.

Examples cited are phenacetin, nitrofurantoin, griseofulvin, methylprednisolone and cromakalim.

INTRODUCTION

There are numerous examples of relationships between the particle size of a drug and its bioavailability[1]. Commonly cited drugs include phenacetin, nitrofurantoin, griseofulvin, coricosteroids and digoxin.

During the development of a new chemical entity, increasing quantities of drug are required and the batch size must be increased. The greater bulk of the crystallising solution often means that cooling is relatively slow, resulting in an increase in both the size and quality of the product crystals. Both factors tend to decrease the dissolution rate of the drug.

For poorly soluble materials, some point will be reached at which it is deemed necessary to size reduce crystals because of potential dissolution rate limited bioavailability problems. Presented here is a simple means of assessing particle size data and identifying batches of drug substance which require reprocessing. Such treatment should increase the effective surface area of the material, thereby accelerating dissolution from the chosen dosage form. Proper formulation is also critical to the dissolution performance of a drug. The effective surface area can be substantially less than the measured surface area if poor wetting occurs due to agglomeration and air entrapment[1].

A calculated volume/surface weighted mean diameter can be added to the drug substance specification. This ensures batch to batch consistency of *in vitro* dissolution performance and affords a high degree of assurance that bioavailability will be maximised.

One of the drugs studied, cromakalim, is a new chemical entity from Beecham Research Laboratories currently being evaluated for the treatment of asthma and hypertension.

EXPERIMENTAL

Materials

Phenacetin, nitrofurantoin, Triton X100 and Tween 80 were obtained commercially from the Sigma Chemical Co.Ltd. (Poole, England). Cromakalim was obtained from Beecham Pharmaceuticals (Harlow, England). All materials were used as received.

Methods

Intrinsic Dissolution Rates

These were determined in duplicate for cromakalim, nitrofurantoin and phenacetin from rotating disc experiments according to the method described by Nicklasson et al.[2]. Sink conditions in water at 37°C were employed throughout.

Solubilities

These were determined for phenacetin and cromakalim in water at 37°C. The solubility of the latter in 0.1% w/v aqueous Tween 80 at 37°C was also determined.

An excess of drug was suspended in the solvent and allowed to equilibrate at 37°C for 24 hours. Filtration was followed by dilution and quantitation by ultraviolet absorbance.

Absolute Densities

A Beckman Model 930 Air Comparison Pycnometer was used to determine the true densities of cromakalim, nitrofurantoin and phenacetin. Air was the medium in each instance and duplicate determinations were made according to the manufacturers standard operating procedure.

Particle Size Distribution

Batches of cromakalim were particle sized using a Malvern 2200/3300 Particle Sizer. 50 to 100 mg of drug was added to 50 ml of a saturated aqueous solution of cromakalim. Three drops of Triton X100 (wetting agent) were added to the suspension and the mixture sonicated for 4 minutes. After shaking, a sample was introduced into the Malvern cell and the data collected in the range 1.9 to 188 μm. Duplicate determinations were made in each case. D_{vs} values were determined in the usual way[3].

Cromakalim Dissolution Rates

About 25 mg of cromakalim was added to 1000 ml of 0.1% w/v Tween 80 solution in dissolution Apparatus II of the B.P. operating at 50 rpm. The amount of drug dissolved was monitored at 252 nm, from duplicate experiments.

RESULTS

TABLE 1

Summary of relevant Physical Constants for Drug Substances

Drug	Intrinsic Dissolution Rate ($mgcm^{-2}\ min^{-1}$)	Aqueous Solubility at 37°C ($mgcm^{-3}$)	Density (gcm^{-3})
Phenacetin	0.22	1.3	1.23
Nitrofurantoin	0.029	0.30[4]	1.55
Griseofulvin	0.0065[5]	0.012[1]	1.44[5]
Methylprednisolone (Form I)	0.010[6]	0.072[6]*	1.28[7]
Cromakalim	0.074	0.60 0.70**	1.25

* At 30°C

** In 0.1% w/v Tween 80 solution.

TABLE 2

Particle Sizes of Cromakalim Batches

Batch Number	D_{vs} (μm)
HP5	4.6
HP8	9.3
HP11	7.2
HP13R	19.0

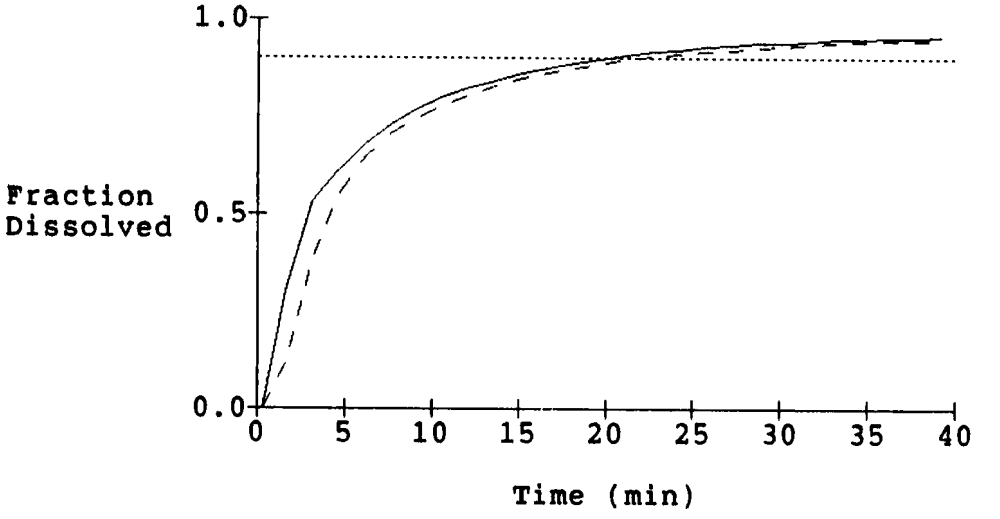

FIGURE 1

Cromakalim (Batch HP13R)

Dissolution of Crystals

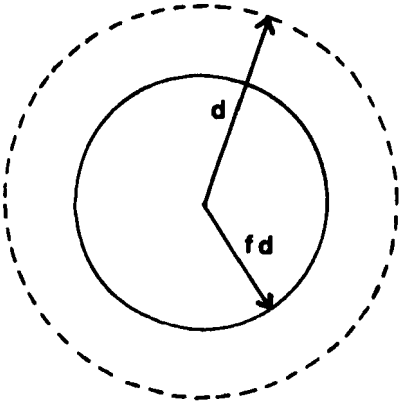

FIGURE 2

Dissolution of Pharmaceutical Spheres

THEORY

Powder distributions can be described in terms of their pharmaceutical diameters, the mean surface (d_S), mean volume (d_V) and mean volume/surface (d_{VS}) diameters. Assume that a powder distribution can be represented by single particles with these diameters. Assume also that, during dissolution, the diameter of these particles is some fraction, f, of the original value.

Using d_V, the weight, W, dissolved after time, t is given by:

$$W = \frac{p \pi d_V^3 (1 - f^3)}{6} \qquad (1)$$

where p = particle density

Under mild to high agitation and sink conditions[8]:

$$W = G A t \qquad (2)$$

where G = intrinsic dissolution rate
A = surface area
t = time

From the average surface area exposed, the weight dissolved after time, t, is:

$$W = \frac{G \pi d_S^2 (1 + f^2) t}{2} \qquad (3)$$

Combining 1 and 3 affords

$$\frac{d_V^3}{d_S^2} = d_{VS} = \frac{3 G t (1 + f^2)}{(1 - f^3) p} \qquad (4)$$

If d_{vs} decreases linearly with time (this is true for monodisperse or narrow distributions), then:

$$d_{vs}\,(1 - f) = kt$$

where k = a constant

At the moment of complete dissolution, $t = t_t$ and $f = 0$. It follows that:

$$t = (1 - f)\,t_t$$

Substituting for t in equation 4 affords

$$d_{vs} = \frac{3\,G\,t_t\,(1 + f^2)\,(1 - f)}{(1 - f^3)\,p}$$

In the range $f = 1$ to 0.5, representing up to 90% of sample dissolution, this approximates to:

$$d_{vs} = \frac{20\,G\,t_t}{p} \qquad (5)$$

with d_{vs} in μm
G in mg cm^{-2} min^{-1}
t_t in min
p in g cm^{-3}

SUPPORTING THEORY

Carstensen[9] and Brooke[10] derived dissolution profiles of log-normally distributed powders assuming cube root kinetics for the individual particles. For the narrowest size distribution with a geometric mean diameter of 40 μm, t_t = 44.0 min[9], d_{vs} = 40.1 μm. Hence, $20.G/p = 0.91$ from Equation 5 .

TABLE 3

Characteristics of Different Log-normally Distributed Powders with a Geometric Mean Diameter of 40 μm[1,9,10]

Log (Sigma)	95% Size Range (μm)	d_{vs} (μm)	Predicted t_t (min)
0.01380	37.5 - 42.6	40.1	-
0.04343	32.8 - 48.9	41.0	45.1
0.13029	22.0 - 72.9	50.1	55.1
0.21715	14.7 - 109	74.7	82.1
0.47036	4.6 - 349	751	825

From the d_{vs} values for the wider distributions, t_t can be predicted from Equation 5 , and the dissolution profiles modelled assuming cube root kinetics. In general, there is good agreement with other theoretical data (Table 3 and Figures 3 to 6).

Thus, d_{vs}, which increases dramatically as the distribution broadens, reflects the overriding influence of large particles on the dissolution profile.

APPLICATIONS

For data on intrinsic dissolution rates, solubilities, densities etc. please refer to Table 1.

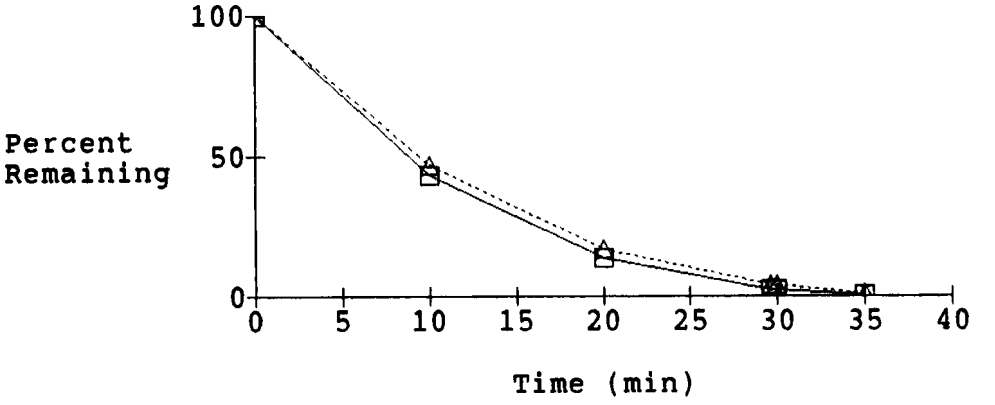

FIGURE 3

Theoretical Dissolution Curves for a Log-Normally Distributed Powder with Log(sigma) = 0.04343

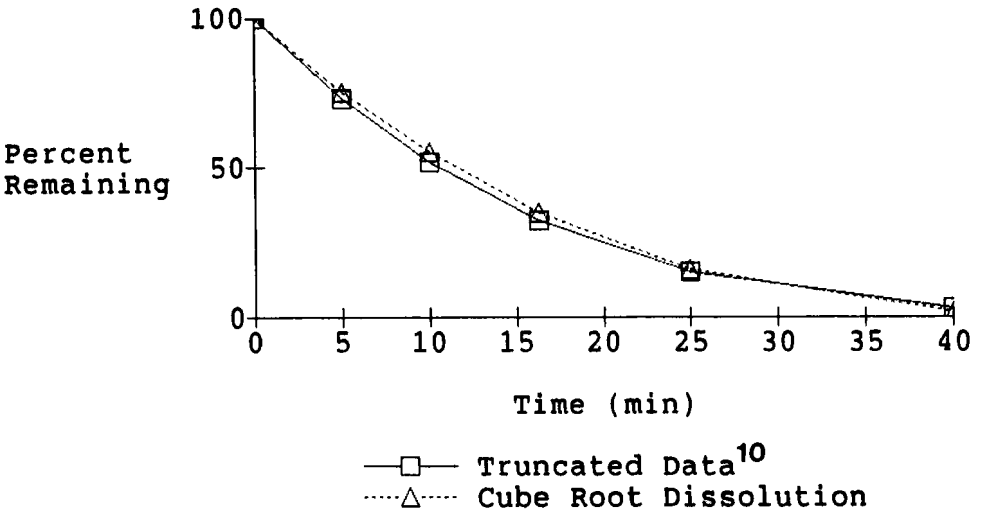

FIGURE 4

Theoretical Dissolution Curves for a Log-Normally Distributed Powder with Log(sigma) = 0.13029

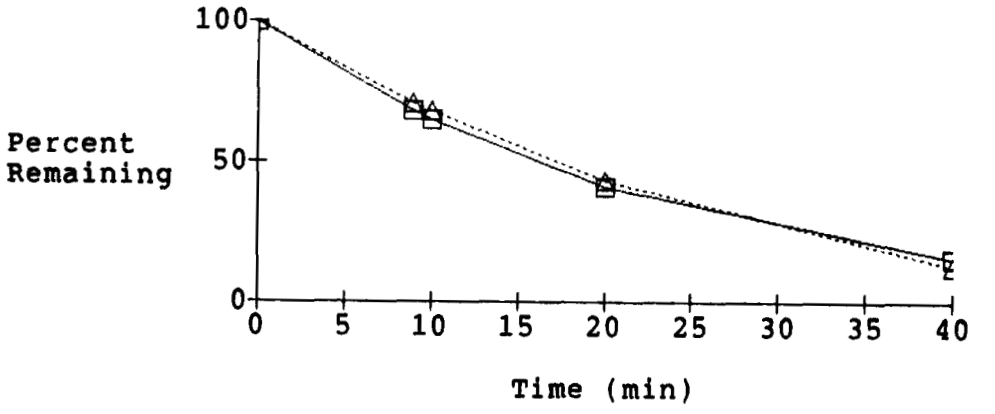

FIGURE 5

Theoretical Dissolution Curves for a Log-Normally Distributed Powder with Log(sigma) = 0.21715

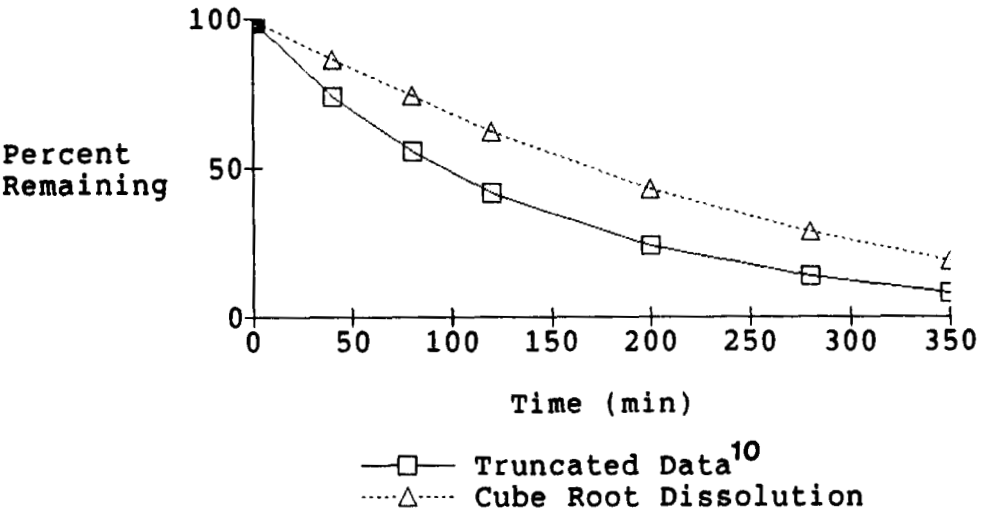

FIGURE 6

Theoretical Dissolution Curves for a Log-Normally Distributed Powder with Log(sigma) = 0.47036

In-vitro Systems

One of the few systems to be examined experimentally is that of methylprednisolone[6,7]. The volume/surface diameter of the micronised material used is estimated to be 8.2 μm. From Equation 5 , the estimated total time for dissolution of such a sample is 18 minutes. This is in good agreement with other theoretical values, and experimental data where a sample of the powder took 30 minutes to dissolve at 25°C[7].

For cromakalim batch HP 13R, d_{vs} was 19.0 μm according to Malvern analyses. From Equation 5 , that batch should dissolve in 16 minutes. Dissolution curves of samples are shown in Figure 1 (note that the solvent had little effect on drug solubility). Ninety percent of the sample had dissolved in 22 minutes under relatively mild agitation conditions. In addition, all capsules of cromakalim prepared by admixing with Starch 1500 have disintegration times of 5 minutes and invariably afford greater than 90% dissolved within 15 minutes in a standard in vitro dissolution test.

In-vivo Systems

According to the USP XXI, "There is no known medically significant bioinequivalence problem with articles where 75 percent is dissolved in water at 37°C in 45 minutes with the use of either official apparatus at usual speed". If drug absorption in the small intestine is good and dosage form disintegration takes 15 minutes, there should be no bioinequivalence problem for a drug which dissolves completely in 30 minutes. To guide the formulator through the early days of development of poorly soluble drugs, the following equation can be applied, by setting t_t = 30 min.

$$d_{vs} = \frac{600\ G}{p} \qquad (6)$$

This should allow a critical particle size specification to be set and facilitate batch selection for toxicology or clinical use. A suitable means of size reduction can also be chosen.

a) Phenacetin

From Equation 6 the volume/surface diameter should not exceed 107 μm. The situation is generally misrepresented by reproduction of the plasma phenacetin time profile[11]. A truer picture of the particle size/absorption relationship may be gained by considering the drug plus metabolite profile (Figure 7).

For narrow size distributions (sieve fractions) d_{vs} is approximately equal to the mid point of the size range. Hence, the fine sample, which is the only one with d_{vs} less than 107 μm, should be the only one which is completely bioavailable. Its bioavailability is increased with respect to the other two particle size fractions though, for some reason, the bioavailability of the finest fraction can be increased by administering it as a suspension in Tween 80 solution.

b) Nitrofurantoin

From Equation 6 , d_{vs} = 11 μm. With the volume/surface diameter assumed equal to the mid point of the sieve size range, the medium and coarse materials used in rat studies should dissolve too slowly to render them fully

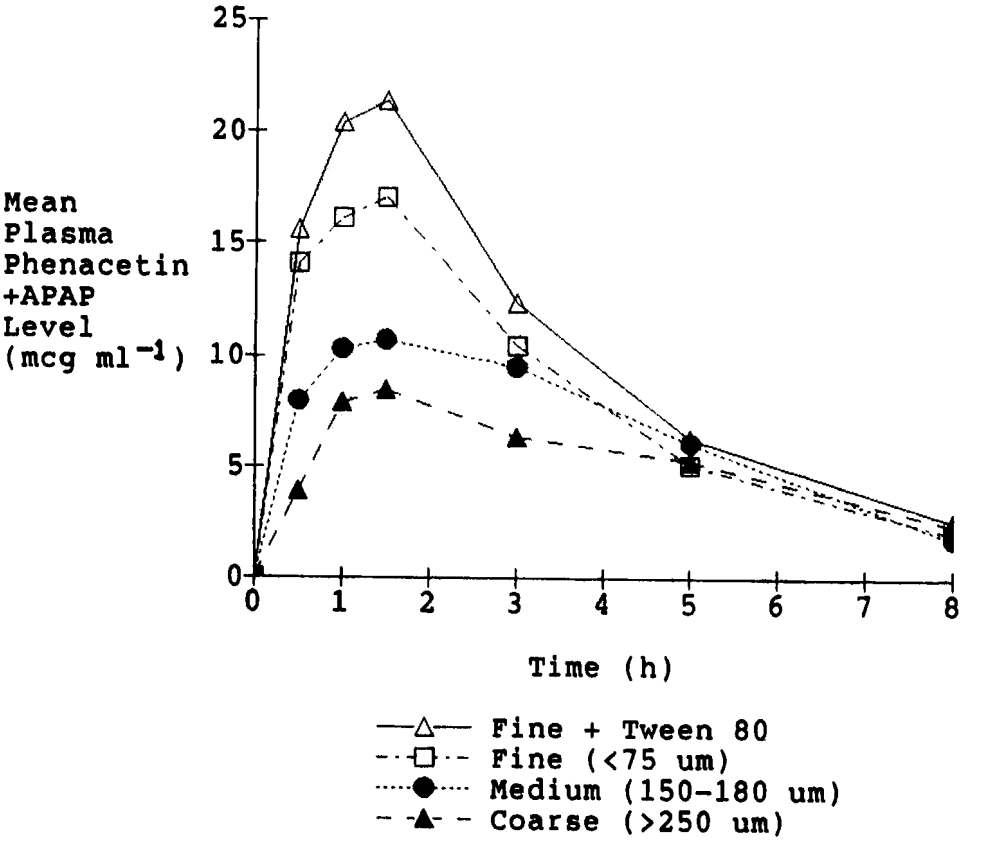

FIGURE 7

Dissolution Rate Limited Bioavailability of Phenacetin[11]

bioavailable[12]. This appears to be the case , though some evidence of distal GI tract absorption is evident. In human subjects, particle sizes up to 58 µm appear bioequivalent[12] (Figure 8). This might also be due to colonic drug absorption.

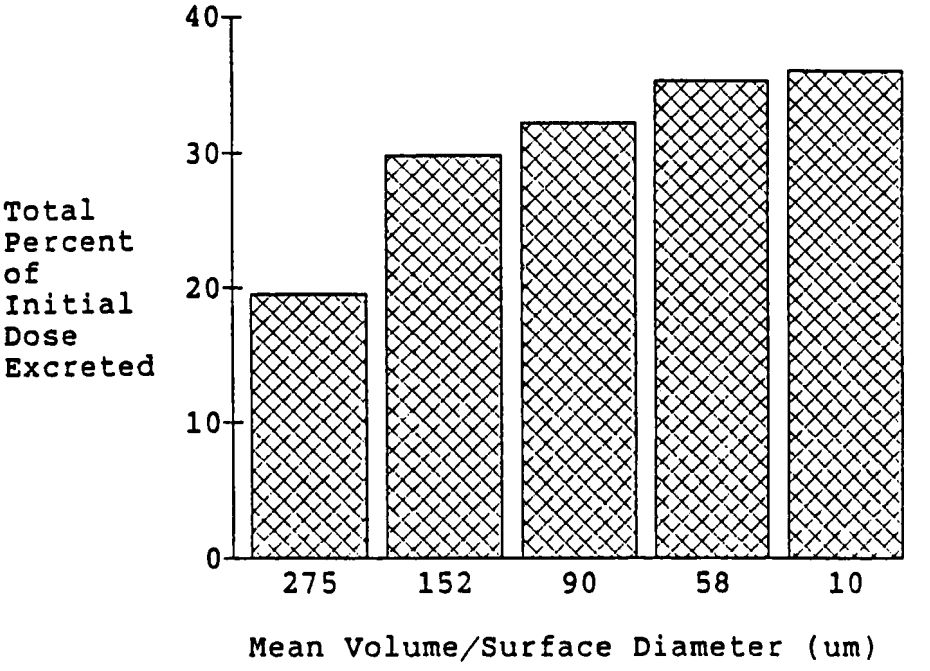

FIGURE 8

Dissolution Rate Limited Bioavailability of Nitrofurantoin[12]

c) Griseofulvin

According to Equation 6 , d_{vs} should not exceed 2.7 μm. If micronised particles are assumed to be spherical, which is very nearly the case[13], then:

$$d_{vs} = \frac{6}{p\ SSA}$$

where SSA = specific surface area ($m^2\ g^{-1}$).

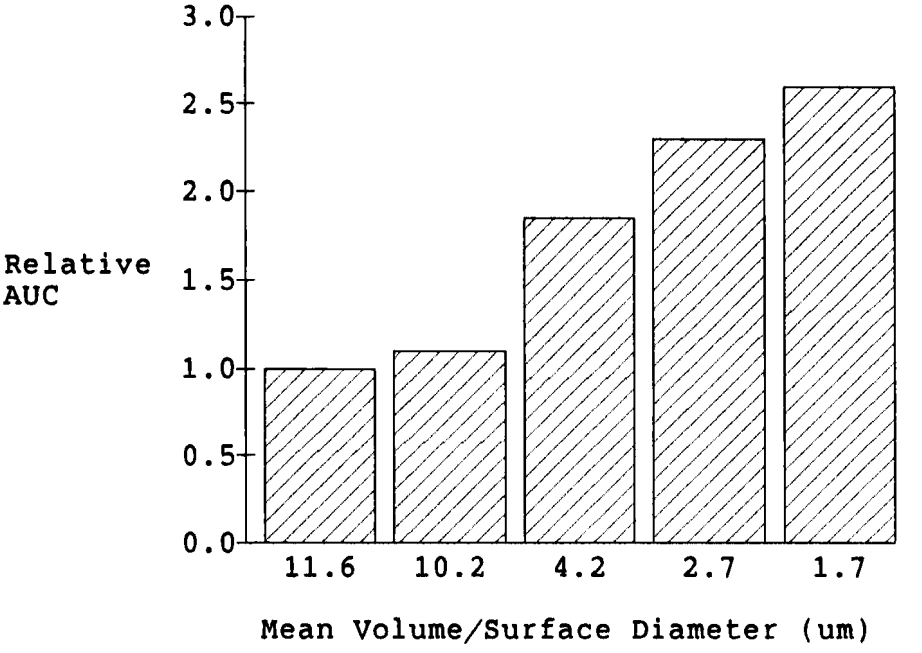

FIGURE 9

Dissolution Rate Limited Bioavailability of Griseofulvin[14]

From Atkinson et al.[14] we obtain:

SSA	d_{vs}
0.36	11.6
0.41	10.2
1.00	4.2
1.56	2.7
2.43	1.7

Bioavailabilities of different particle sizes of griseofulvin were shown to be different. There was,

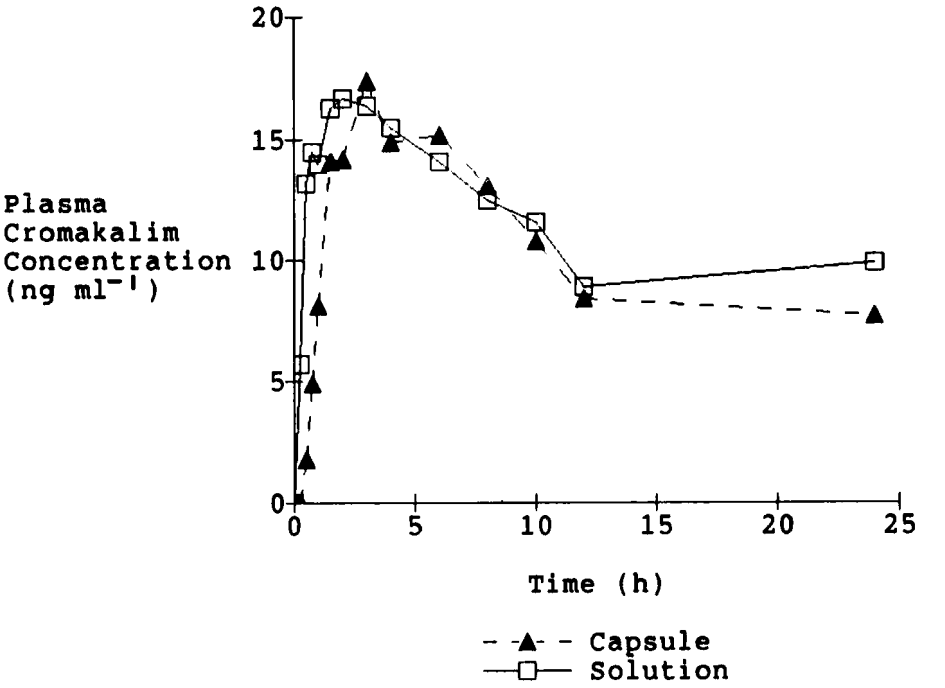

FIGURE 10

Bioavailability of Cromakalim Capsules and Oral Solution

however, little difference between the highest two specific surface area samples (Figure 9).

d) Cromakalim

From Equation 6 , d_{vs} should not exceed 35 μm. Preliminary in vivo studies reveal that drug from capsules prepared to date is well absorbed, bioavailability being similar to that of an oral solution (Figure 10).

USE OF SOLUBILITY DATA

Nicklasson et al. derived a log/log relationship between intrinsic dissolution rate and solubility[2].

$$\log (G) = 0.98 \log (S) - 0.552$$

with G in mg $cm^{-2}min^{-1}$.

and S = aqueous buffer solubility at 37°C ($mgcm^{-3}$).

Assuming the slope to be unity and taking antilogs affords:

$$G = \frac{S}{3.56} \qquad (7)$$

Substituting for G in Equation 6 gives:

$$d_{vs} = \frac{170\ S}{p} \qquad (8)$$

Thus an estimate of the maximum acceptable particle size of a drug can be gleaned from its aqueous solubility at 37°C. Because of the assumptions involved in deriving Equation 8, it can only be considered as approximate, and d_{vs} values derived from it will be subject to error. This is highlighted in Table 4, where up to three-fold discrepancies are evident, though all estimates appear sensible and could be used.

TABLE 4

Comparison of Critical d_{vs} Values Derived from Intrinsic Dissolution Rates and from Solubilities

Drug	d_{vs} from IDR (μm)	d_{vs} from S (μm)
Phenacetin	107	180
Nitrofurantoin	11	33
Griseofulvin	2.7	1.4
Methylprednisolone	4.7	9.6
Cromakalim	36	82

Kaplan has suggested that drugs with intrinsic dissolution rates greater than 1 mg cm^{-2} min^{-1} are generally not prone to dissolution rate limited absorption problems[1]. Using Equation 7 and building in a three-fold margin for error, drugs with aqueous solubilities of 10 mg cm^{-3} or greater at 37°C should not exhibit such problems. This solubility limit is in accordance with Kaplan's rule of thumb[1].

CONCLUSIONS

Use of the mean volume surface diameter for batches of drug substances allows the formulator to decide what pharmaceutical processing is necessary to provide satisfactory dosage forms. These should comply with current pharmacopoeial dissolution requirements and be maximally bioavailable in the first instance.

Depending on the magnitude of d_{vs} for rapid dissolution, the drug might be screened, milled, micronised or molecularly dispersed.

ACKNOWLEDGMENTS

I wish to thank Dr. I.I. Al-Janabi for his invaluable advice and assistance throughout, Miss W.J. Pennington for her high quality experimental work, and Mrs E. Robe for her excellent typographical skills.

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