

In vitro dissolution of dapsone

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Log normal samples of dapsone (DDS) were prepared in which the geometric mean diameter ranged from 20 to 50 μm while the geometric standard deviation was in the range 1.62 to 1.88. Using a simple in vitro flow-through dissolution cell at 37 °C, the data obtained were found to fit the Hixson-Crowell cube root dissolution law up to a critical time, T_c , where a distinct break occurred. Such a biphasic phenomenon has been predicted by other workers and is related to the time at which the smallest particles present have undergone dissolution. The initial slopes of the cube root dissolution plots were shown to be directly related to the reciprocal of the geometric mean diameter.

Dapsone is a widely used orally effective antileprotic drug. The long term use of dapsone often results in poor patient compliance and this can lead to sub-therapeutic plasma levels (Ellard et al 1974; Ellard 1975). This in turn can result in the development of resistant strains of the causative organism, *M. leprae*. As part of the development of a sustained release intramuscular preparation of dapsone we wished to study the in vitro dissolution rate of dapsone as a function of particle size distribution in order to quantitate the relationship and see if such data agreed with prior theoretical predictions made for polydisperse powders (Carstensen & Musa 1972).

MATERIALS AND METHODS

Materials

Dapsone (Aldrich Chemical Company, Milwaukee), *NN'*-dimethylformamide (DMF, Omnisolv grade, MCB Manufacturing Chemists, Cincinnati, Ohio), sodium chloride, sodium phosphate monobasic, sodium phosphate dibasic anhydrous (Mallinckrodt Inc., St Louis, Missouri), Tween 80 (J. T. Baker, Phillipsburg, New Jersey) and carboxymethylcellulose (CMC, medium grade, Atlas Chemical Company, Wilmington, Delaware) were used as received, except as noted below.

Preparation of dapsone samples of various mean diameters

Approximately 250 mg dapsone was dissolved in 1.5 ml DMF at room temperature (24 °C) and added slowly, with stirring, to 62.5 ml of water held at 36 °C. Precipitation of dapsone was instantaneous. The temperature was allowed to fall back to ambient

conditions and the vessel refrigerated overnight. The precipitate was filtered, washed with water and placed in a vacuum desiccator (GCA/Precision Scientific, Chicago, Illinois) at 45 °C for 2 h.

Samples of different mean particle size were obtained by placing each dispersion of precipitated material in an ultrasonic generator (Bransonic 52, Branson Instruments, Shelton, Connecticut) for varying periods of time (Table 1). Particle size analysis was undertaken using a Coulter Counter (model T_{AII} , Coulter Electronics, Haileah, Florida) fitted with a 400 μm aperture tube. Isoton II (Coulter Diagnostics, Haileah, Florida), saturated with dapsone at room temperature, was used as the electrolyte vehicle into which the several dapsone dispersions were diluted for analysis. With each sample, at least three replicates were performed and the mean data calculated.

Dissolution of dapsone samples

The dissolution cell was a 25 mm diameter clear plastic filter holder (Curtin Matheson Scientific, Houston, Texas) with a capacity of approximately 1.7 ml and fitted with a 5 μm membrane filter (Metrical GA-1, Gelman Instrument Company, Ann Arbor, Michigan). The filter holder was connected in series with a peristaltic pump (Buckler Instruments, Fort Lee, New Jersey) and a reservoir containing pH 7.4 buffer.

A known volume of dapsone suspension containing 20 mg ml⁻¹ in a Tween 80 (0.5%) - CMC (0.3%) - sodium chloride (0.9%) vehicle was added directly to the filter holder. Buffer solution at 37 °C was passed through the system at a flow rate of 2.70 ± 0.30 ml min⁻¹, and the total effluent was collected at known times and assayed spectrophotometrically at 290 nm (E1%, 1 cm for dapsone in

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Table 1. Particle size characteristics and dissolution data of dapsone powder samples.

System	Method of Preparation	Geometric mean diameter, d'_g and s.d. σ'_g	Corr. coeff. r	Initial slope from Hixson-Crowell Cube Root Plot	Second slope from Hixson-Crowell Cube Root Plot	Critical time T_c , min
I	Dapsone powder used as received; ultrasonified for 5 min	19.35 (1.62)	0.992	0.153 \pm 0.016	0.084 \pm 0.009	7.75
II	Dapsone ppt ^d from DMF into water at 36 °C; ultrasonified for 10 min	26.19 (1.86)	0.989	0.084 \pm 0.002	0.058 \pm 0.008	8.61
III	Dapsone ppt ^d from DMF into water at 36 °C; ultrasonified for 5 min	33.11 (1.88)	0.994	0.048 \pm 0.010	0.029 \pm 0.006	6.23
IV	Dapsone ppt ^d from DMF into water at 36 °C; no ultrasonification	49.44 (1.78)	0.953	0.026 \pm 0.007	0.015 \pm 0.002	8.55

pH 7.4 buffer = 996). At the end of a dissolution run, the weight of dapsone added initially was determined by thoroughly rinsing the filter holder and tubing down-stream from the filter holder with buffer and soaking the filter in buffer for at least 24 h. An aliquot was assayed for dapsone and this weight was added to that in the effluent. The total weight of dapsone injected initially into the cell ranged from 0.700 to 4.300 mg.

RESULTS

Particle size of dapsone samples

Samples of differing particle size distributions were obtained as a result of the preparative procedure described. The distributions were found to be log-normal and are summarized in Table 1. Owing to the common method of preparation, the geometric standard deviations, σ'_g , for systems II, III and IV are close, showing that the log-normal distribution profile was similar in all cases.

Dissolution of dapsone samples

The dissolution profiles (per cent dissolved against time) of the various samples investigated showed good reproducibility and were independent of the amount of dapsone initially added. The dissolution data were expressed in terms of the Hixson-Crowell (1931) law, namely: $W_0^{1/3} - W^{1/3} = Kt$ where W_0 is the initial weight (expressed as 100%) of dapsone present and W is the per cent remaining undissolved at time t . K is an apparent dissolution rate constant. Typical data are shown in Fig. 1 where it is apparent that a break in the relationship occurs some time within the first 10 min. Linear regression analyses were carried out on the dissolution data from each individual experiment. In every case, the points included in the regression analysis were increased

stepwise until the correlation coefficient reached a maximum. The slope calculated from these points was taken as the initial dissolution rate conforming to the Hixson-Crowell cube root dissolution law. The next several data points, up to an elapsed time of 20 min, were then used in a second regression analysis that provided the second slope immediately above the point at which deviation from the Hixson-Crowell law occurred. Mathematical interpolation of the two slopes allowed calculation of the average time at which the break in the slope took place. This was designated as T_c , the critical time. The calculated slopes and values of T_c are presented in Table 1. Depending on the system under study, the per cent DDS dissolved at T_c ranged from 10 to 50% of the amount present initially.

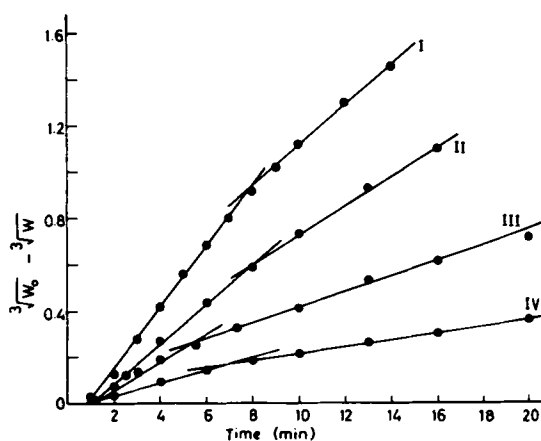


FIG. 1. Representative cube root dissolution plots for samples of dapsone with different geometric mean diameters. I, $d'_g = 19.35 \mu\text{m}$; II, $d'_g = 26.19 \mu\text{m}$; III, $d'_g = 33.11 \mu\text{m}$; IV, $d'_g = 49.44 \mu\text{m}$. Vertical bars indicate standard deviations.

With systems II, III and IV the maximum per cent saturation reached in the effluent did not exceed 11.2%, even transiently; in most instances it ranged from 2 to 10%. Sink conditions, generally felt to exist below 15% of saturation (Carstensen 1977), were thus observed in all cases. With system I the dissolution rate was such that the per cent saturation of the effluent rose to between 18.3 and 26.5% for a few minutes. However, this did not appear to unduly affect the dissolution process.

DISCUSSION

It is well known that pharmaceutical powders prepared by milling or precipitation invariably exhibit log normal distributions (Herdan & Smith 1953; Beyer 1959). System I was a commercial sample of dapsone, used as received and presumably milled at some time during its preparation. Systems II, III and IV were all produced from I by precipitation. It is not therefore unexpected that all four systems studied in this work exhibited a log normal distribution. In addition, since systems II and III were derived from system IV by ultrasonification, it would also be anticipated that the geometric standard deviations of these three systems would be similar. This was found to be the case. Coincidentally the geometric standard deviation for system I was close to the other systems (Table 1). This does allow comparisons to be made between all four systems, particularly in terms of dissolution, since they can be said to have similar standard deviations but different mean diameters.

Carstensen & Musa (1972) predicted that the Hixson-Crowell cube root dissolution law is obeyed by some polydisperse powders only up to the time T_c where the smallest particles present have undergone dissolution, thereby changing the initial distribution. Using computer-generated particle size data, these workers found that the cube root plot changed slope at T_c . Later, Carstensen & Patel (1975), working with particles of oxalic acid dihydrate, found the predicted cube root dependence in log normal populations that had been obtained by sieving and then reblending various fractions in ratios that were log normal on a number basis. These workers were unable to detect a biphasic cube root dissolution pattern due, it was postulated, to the particles being either too small and/or having too large a standard deviation. Other workers (Pedersen & Brown 1975a,b, 1976a,b) have developed and investigated several models for the dissolution of powders. They found the dissolution of a 60–85 mesh fraction of tolbutamide to be best described by the cube root dissolution model of Hixson and Crowell.

In the present study, powder samples of dapsone with geometric mean diameters ranging from approximately 20 to 50 μm consistently exhibited biphasic dissolution behaviour, with T_c 's in the range of 6 to 8 min. It may well be that this observed difference in behaviour between DDS and oxalic acid is due to the relatively low solubility of DDS (0.30 mg ml⁻¹ in pH 7.4 buffer at 37 °C) which results in a slower dissolution process.

Brooke (1973, 1974) also used computer simulated data to devise an exact expression for the dissolution rate profile of non-truncated log normal particle size distributions. As shown by Carstensen & Patel (1975), Brooke's work predicts a linear log-log relationship between the cube root slope and the reciprocal of the geometric mean diameter. Such a relationship (based on the initial cube root slope) was found to hold for the real powders used in the present work ($r = 0.996$), even though the average standard deviation was somewhat higher than quoted in the other works. Overall, these results indicate that dissolution from real powder samples of DDS can be quantitated in a meaningful manner and conform to previously predicted behaviour.

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