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Note

Using a particle counter to assess in vitro dissolution studies

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Abstract

The purpose of this work was to establish a comparison between the dissolution profiles obtained with the Coulter technique and the Paddle method, for a sparingly soluble drug. Four fractions of indomethacin were tested and the corresponding mean dissolution times were calculated and plotted against the fraction mean diameter (d_{sv}). A unique correlation was found for both methods. The importance of this correlation is also discussed.

Keywords: Mean particle size; Coulter Counter method; Paddle method; indomethacin; Dissolution profile; Mean dissolution time

In a previous work (Simões et al., 1996), a particle counter (the Coulter Multisizer II) was used to evaluate the dissolution profiles of sparingly soluble drugs. The main objective was to study the influence of the primary particle size on the dissolution rate. Several size fractions were tested and the conclusion was that a reduction in particle size causes an increase in the dissolution rate. An attempt was made to correlate the mean dissolution time with the mean particle size of each fraction, having in mind a future application on drug release control.

The Coulter method is an attractive method for dissolution studies, since it is the only one capable of providing information about the variation of size and number of suspended particles during the dissolution process. However, when the purpose is to simulate the physiological conditions, this method presents some limitations, namely those related to temperature and hydrodynamics. In fact, although in the Coulter sampling stand the particles were suspended in a mechanically agitated round-bottom beaker, it did not enable any temperature control. Therefore, only experiments at ambient temperature could be performed. Moreover, the agitation speed ($\approx$ 900 rev./min) could not have a wide range of variation since a uniform solids concentration was required in the beaker so that the sampled volume was representative of the suspension.

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Table 1
Mean size (d_{sv}) of indomethacin fractions and corresponding MDT values obtained with the Coulter and the Paddle methods

Fraction	d_{sv} (μm)	MDT_{80} (min) (Coulter method)	MDT_{80} (min) (Paddle method)
Micronized	4.81	0.53	0.66
5–15 μm	13.26	4.27	3.00
15–25 μm	19.20	8.50	7.00
25–35 μm	30.91	24.82	25.43

It was then decided to perform some tests with the same fractions used with the Coulter but making use of a reference method recommended for in vitro dissolution studies — the USP Paddle method — the purpose being the comparison of the dissolution profiles obtained by both methods.

The Paddle method was, with one exception, used under standard conditions (37°C and 100 rev./min) and the dissolved indomethacin was assayed by UV spectrometry at 265.8 nm (US Pharmacopeia XXII, 1990). In the Coulter method the dissolved fraction was calculated by the difference between the initial solids concentration and the corresponding value at a given instant (Simões et al., 1996). The same suspending medium was used in both methods: a phosphate buffer pH 6.2 (with 0.9% NaCl and 0.01% Tween 80). Also the initial solids concentration, corresponding to sink conditions, was kept the same in both experiments.

Three narrow sieved fractions and a micronized sample of indomethacin were used. Table 1 shows the mean sizes of these fractions in terms of d_{sv} (defined as $\Sigma n_i d_{vi}^3 / \Sigma n_i d_{vi}^2$, d_v being the equivalent volume diameter measured by the Coulter) (Allen, 1990). In this table, values of the mean dissolution time obtained for each fraction, as described later, are also presented. In order to eliminate the effect of temperature, one set of experiments was performed with the Paddle method at room temperature (23 ± 1°C) in an attempt to confront these results with those of the Coulter for the same fractions. The results are shown in Fig. 1. As expected, the curve correspondent to the Coulter method lies above that of the Paddle method, clearly demonstrating the importance of agitation.

The next step was to perform dissolution tests using the Paddle method at 37°C for all the fractions. Fig. 2 presents these results as well as those obtained with the Coulter for the same fractions.

Qualitatively it can be concluded that the effect of particle size on the dissolution profiles is similar for both methods, despite the differences in the operating conditions (agitation and temperature) and dosage techniques. The parameter used to compare both sets of results was the mean dissolution time (MDT) defined as (Brockmeier, 1986):

$$MDT = \frac{\sum_i \bar{t}_i \Delta M_i}{\sum_i \Delta M_i} \quad (1)$$

where $\bar{t}_i$ is the midpoint of the time interval corresponding to the released fraction ΔM_i.

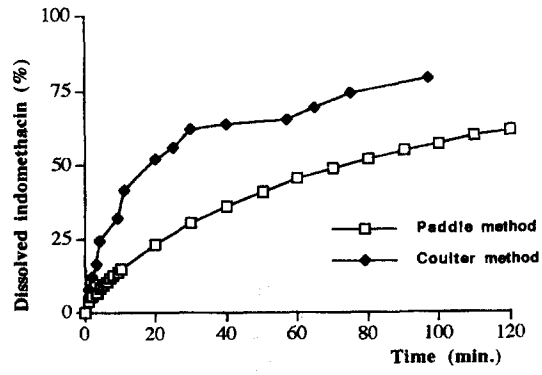

Fig. 1. Comparison of the dissolution profiles obtained with the Coulter and the Paddle method (at 900 and 100 rev./min, respectively) at the same temperature (23 ± 1°C) for the 25–35 μm indomethacin fraction.

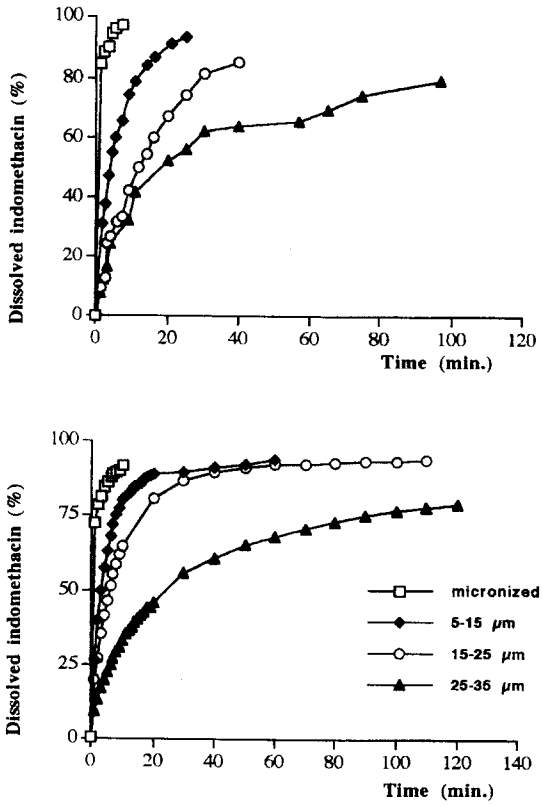

Fig. 2. Dissolution profiles of different fractions of indomethacin obtained with the Coulter (a) and the Paddle method (b). The magnitude of S.D. values on the points are less than 5%.

These results, calculated for 80% of the total dissolution (MDT_{80}) for each size fraction, are displayed in Table 1 and plotted in Fig. 3 as a function of d_{sv} in a semi-log scale. The analysis of this graph shows that both methods not only gave a linear relationship but, surprisingly, that this correlation was unique. This result suggests that the operating conditions of the Coulter simulate, somehow, those of the reference method.

Taking into account the results of Fig. 1, obtained for the same temperature, it follows that this coincidence can only be explained by a balance between temperature and agitation effects. However, a large number of size fractions should be tested to establish a precise correlation. Other drugs should also be investigated to check if this kind of correlation is also found. In order to test

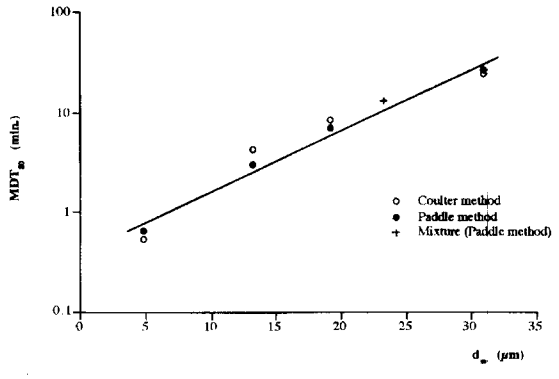

Fig. 3. Relationship between mean dissolution time (MDT) and fraction mean size ($d < \mathrm{INF} > \mathrm{sv} < /\mathrm{INF} >$) obtained by the Coulter and Paddle methods (+ , corresponds to a mixture of the coarsest and finest fraction of indomethacin).

this correlation it was decided to perform one experiment with a mixture (in equal proportions) of the finest and coarsest fraction. The resulting dissolution profile, evaluated using the Paddle method, is shown in Fig. 4 together with those corresponding to the primary fractions. As expected, the profile representative of the mixture lies in between those of the individual fractions. The MDT_{80} was calculated for this profile and plotted against the d_{sv} of the mixture. As can be seen in Fig. 3, the resulting point also fits the correlation well.

In conclusion, it can be said that these results look quite promising and encourage further investigation. It is believed that this type of correlation (if generally applicable) will be of greatest use

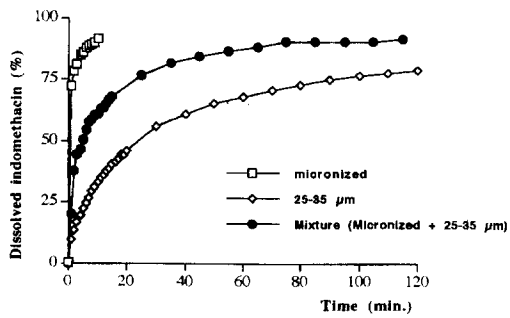

Fig. 4. Dissolution profiles of two indomethacin fractions and their mixture (in equal proportions) obtained by the Paddle method. The magnitude of S.D. values on the points are less than 5%.

when used in a predictive way. In this manner, it will be possible to manipulate particle size so that a required dissolution profile is obtained. This may be regarded as an interesting alternative to solve bioavailability problems of sparingly soluble drugs.

On the other hand, this study has shown that the Coulter technique, besides providing information about the way particles dissolve (Simões et al., 1996), produces, for the present operating conditions, results comparable with those of the reference method (Paddle method).

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