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MEASUREMENT OF THE SURFACE AREA CHANGES DURING THE DISSOLUTION OF POORLY SOLUBLE DRUGS USING A WIDE ANGLE PHOTOSEDIMENTOMETER

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ABSTRACT

Using a Wide Angle Photosedimentometer, surface area changes during the dissolution of suspended particles of frusemide, glibenclamide and bendrofluazide have been measured. The method consisted of recording the change in optical density that occurs whilst the drugs are agitated in water in a 4cm square photosedimentometer cell. It was found that initially a high surface area was recorded which diminished exponentially with time and obeyed first order kinetics. From the surface area measurements, graphs of percentage drug dissolved against time were calculated and plotted and these profiles were found to correlate with similar plots of dissolution rate produced by analysing the amount dissolved spectrophotometrically. It was concluded that the surface area method offers an alternative technique for the measurement of the dissolution rate of poorly water soluble drugs, particularly when no adequate method exists for analysing the dissolved fraction.

INTRODUCTION

The measurement of dissolution rate conventionally involves the chemical analysis of the amount of drug achieving solution at various time intervals. Normally, ultraviolet spectrophotometry is used to assay the drug, but for many very poorly water soluble drugs, such as griseofulvin, the ultraviolet spectroscopic technique is not sensitive enough. Other drugs, like digoxin, have no ultraviolet spectra and therefore alternative assay techniques have to be developed

(Rubinstein & Wells 1977). In an attempt to monitor the dissolution of drug particles liberated after tablet deaggregation, Rubinstein & Wells (1977) measured particle size changes and evaluated surface areas using a modified Model T Coulter Counter. Nyström et al (1985) used a similar technique to determine both the solubility and dissolution rate of suspensions of griseofulvin and hydrocortisone acetate. The Coulter Counter is somewhat complex and tedious and measures the particle size distribution of the dissolving particles. No direct method of measuring surface area is possible. In the present study a wide angle photosedimentometer has been used to measure directly the surface area changes that occur as particles of frusemide, bendrofluazide and glibenclamide dissolve. The method provides a simple and convenient method for monitoring dissolution rate where no adequate technique exists for analysing the dissolved fraction.

MATERIALS AND METHODS

Materials

The drugs used were Glibenclamide B.P., Frusemide B.P. and Bendrofluazide B.P. (Sigma Chemicals, Poole, Dorset).

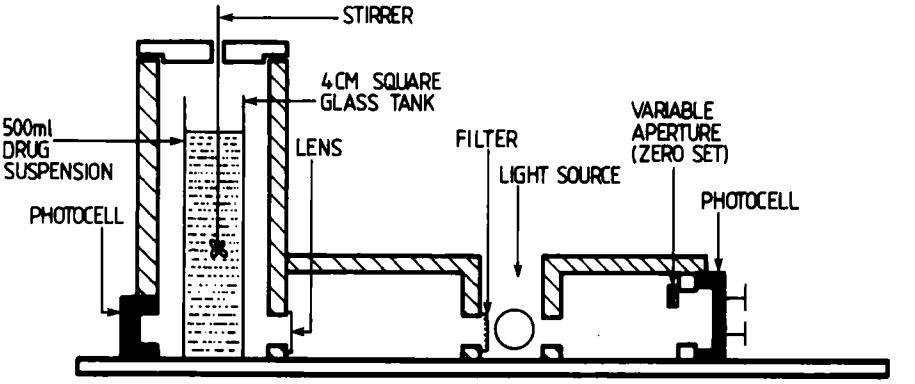
The Wide Angle Photosedimentometer

The instrument is shown in Fig. 1 and is produced by Microscal Ltd., London. It consists of two parallel beams of light of circular cross-section which are produced from a common light source. One passes through the working part of the instrument and the other through a reference arm onto a pair of matched photocells coupled in opposition. The measurement beam passes through a small circular aperture and is made parallel by a convex lens. It then passes through a similar aperture, through the tank containing 500ml of drug suspension and onto the photocell. The reference arm consists of a parallel light beam with an adjustable aperture and photocell. The output, fed to a chart recorder from the measuring arm, may thus be balanced before commencing an experiment. Plots of optical density against time are recorded on the flat bed recorder.

Method

500ml of distilled water was placed in the 4cm square glass photo-sedimentometer tank and the chart recorder adjusted to zero optical

THE WIDE ANGLE PHOTOSEDIMENTOMETER



LIGHT BEAM SYSTEM OF THE WIDE ANGLE PHOTOSEDIMENTOMETER

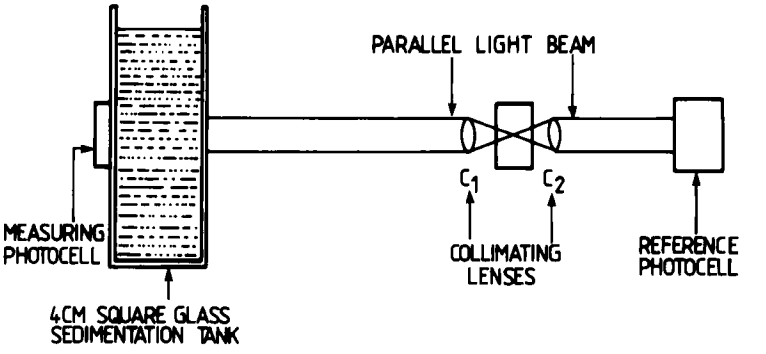


FIGURE.1.

density. A quantity of powder was weighed out and dispersed in the 500mls of distilled water in the tank, so as to give an optical density of between 0.2 and 0.3. The amounts suspended were: frusemide 40mg, bendrofluazide 70mg and glibenclamide 40mg. The weighed powder was first introduced into 30ml of distilled water from the tank and well dispersed using an ultrasonic bath. This concentrated suspension was then quickly added to the bulk of the distilled water in the photosedimentometer tank. The suspension was continuously stirred at 100 R.P.M. with an impeller, positioned above the light beam. A record of optical density against time was automatically recorded on the chart recorder. At the start of the experiment, 5ml of the suspension was withdrawn from the tank with a syringe; fitted with a 1.2μm membrane filter and the absorbance determined at the specified wavelength of maximum absorbance for the particular drug under investigation. This procedure was repeated every 10 minutes for three hours. A calibration graph of absorbance against concentration was obtained for each drug which resulted in a linear plot. Linear regression was used to find the best fit straight line.

Results and Discussion

Assuming that at time O the drug suspension is fully dispersed then the weight specific surface area (S_w) may be determined from the optical density (D_o) and the concentration (c) of the suspension:

$$S_w = \frac{9.21}{L} \frac{Do}{c} \qquad (1)$$

where L is the path length of the light beam in the suspension (4cm). The assumption is made that the total surface area of individual particles is four times their random projected area and that this holds for non re-enterant particles, that is the specific surface so measured does not include surface concavities. Dissolution takes place from the enveloping surface area, so this assumption is valid in the case of dissolving particles. Graphs of S_w against time, together with the corresponding dissolution results for the three drugs are shown in Figures 2, 3 and 4. The means of 4 determinations are depicted and variability between runs was within experimental error. Initially a high surface area was recorded for the drugs,

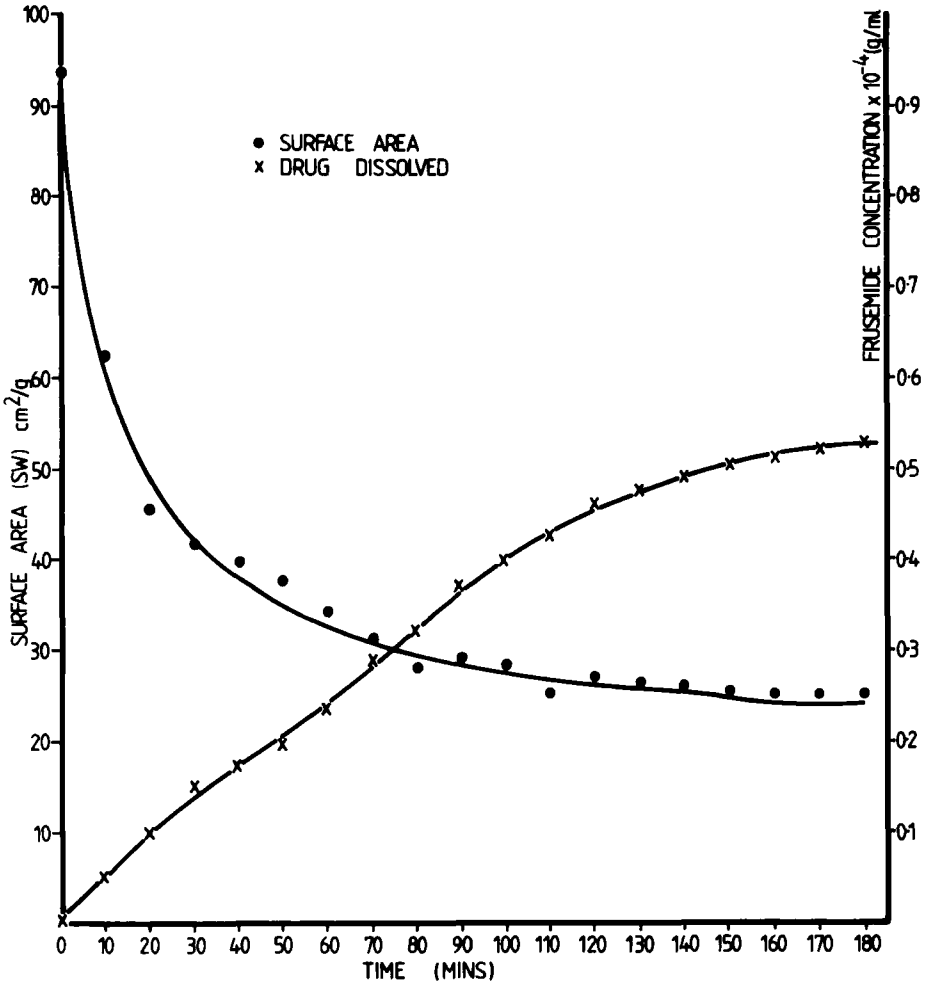


FIG. 2.

RELATIONSHIP OF SURFACE AREA AND DRUG CONCENTRATION WITH TIME FOR FRUSEMIDE POWDER

which exponentially decreased with time. The results indicate that first-order kinetics have been obeyed as suggested, but not experimentally proved, by Wagner (1969).

$$S_w = S_o e^{-K_s(t-t_o)} \qquad (2)$$

Where S_w is the surface area at time t and S_o is the initial surface area at time t_o. K_s is the rate constant. Taking logarithms of both sides of equation (2) will give a linear relationship.

$$\text{Log } S_w = \text{Log } S_o - K_s \, t \, \text{Log } e \qquad (3)$$

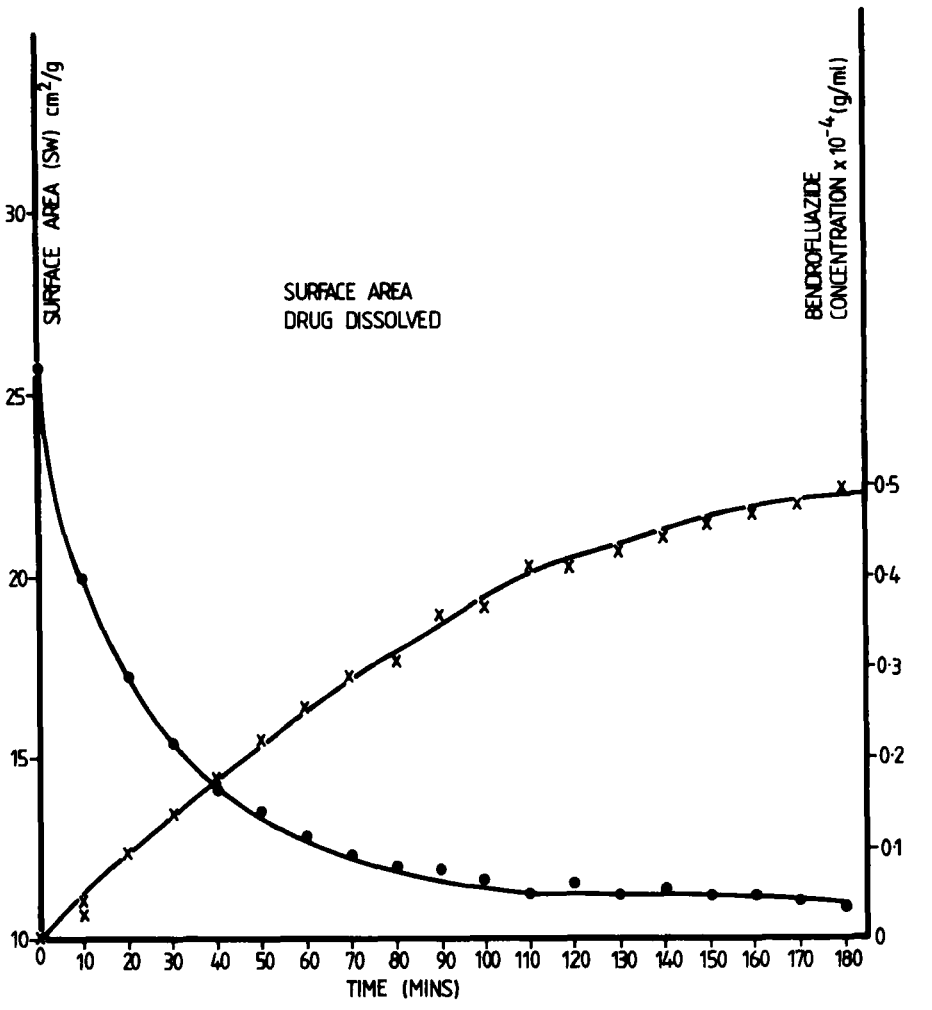


FIG. 3.
RELATIONSHIP OF SURFACE AREA AND DRUG CONCENTRATION WITH TIME FOR BENDROFLUAZIDE POWDER

Plots of Log S_w against time should thus produce a straight line with intercept Log S_o and slope $-K_s/2.3$. Straight line graphs were indeed found as can be seen from Fig. 5, confirming that as particles dissolve, the surface area decays in accordance with first-order kinetics.

Assuming that the drug particles are spherical and that the number of particles remains constant throughout the dissolution process

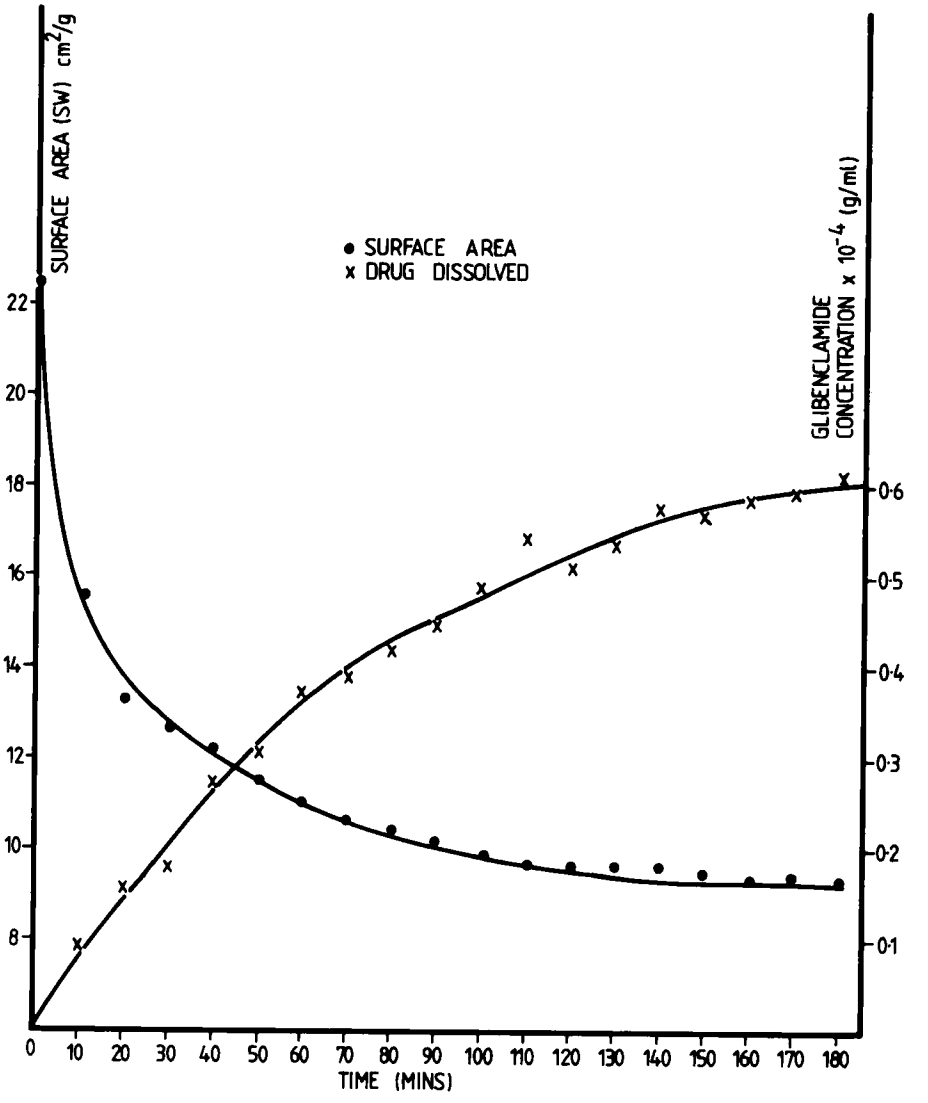


FIG. 4.
RELATIONSHIP OF SURFACE AREA AND DRUG CONCENTRATION WITH TIME FOR GLIBENCLAMIDE POWDER.

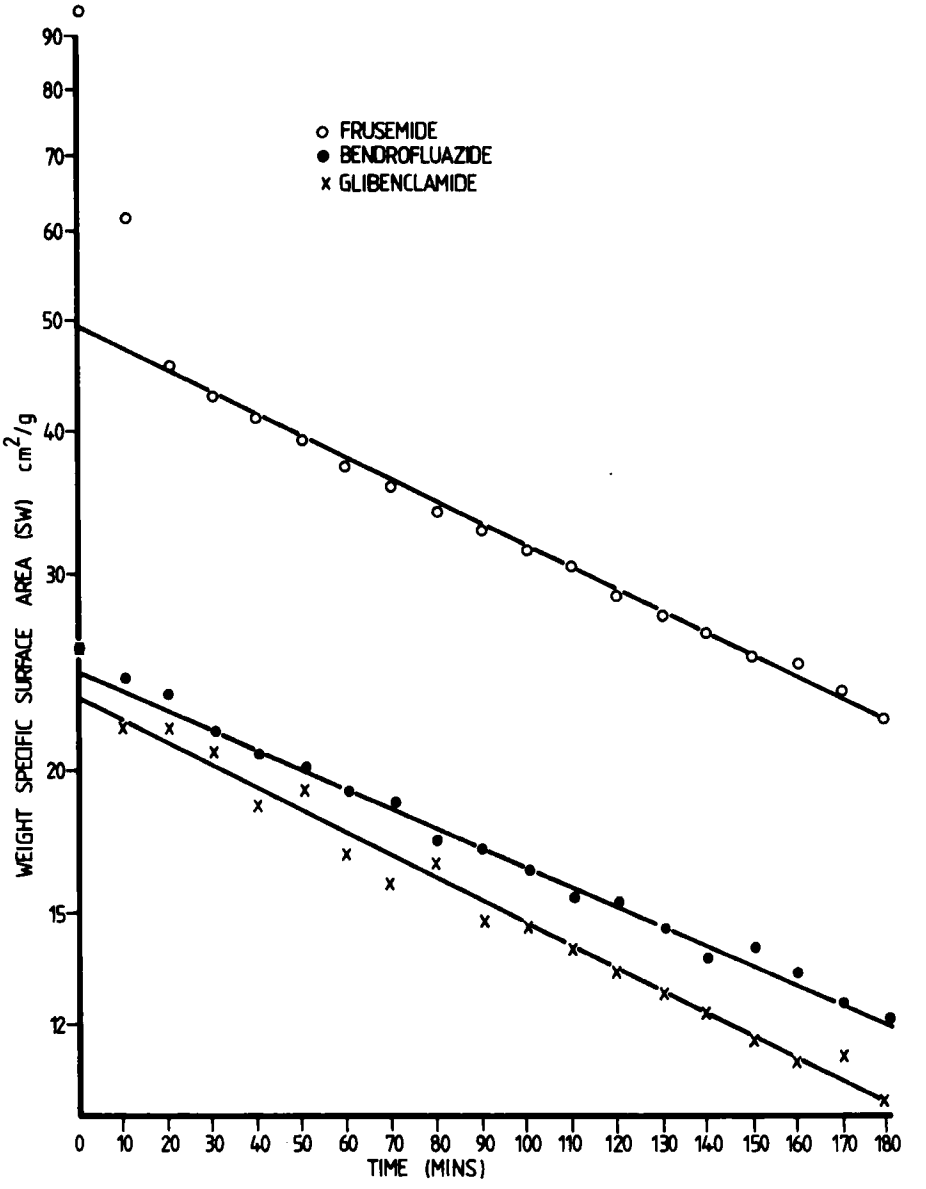
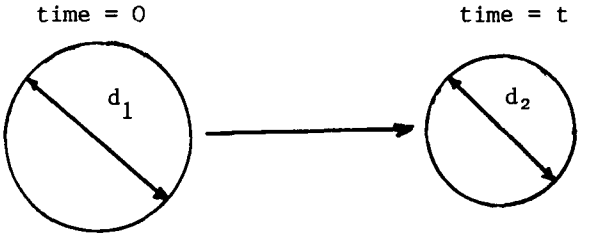


FIG. 5.
LOGARITHMIC PLOTS OF WEIGHT SPECIFIC SURFACE AREAS (SW) AGAINST TIME FOR THE THREE DRUGS.

(no flocculation or deaggregation), then a decrease in surface area with dissolution occurs due to a reduction in the diameter of the drug particles. The percentage amount of drug dissolving after time t can thus be calculated from surface area changes.



If S_1 is the surface area of a drug particle of diameter d_1 at time 0 and S_2 is the reduced surface area after t minutes of the same particle of smaller diameter d_2, D is the particle density and N is the total number of particles suspended then:

$$\text{At time} = 0 \quad \text{Mass of particle} = \frac{d_1^3 - D\pi}{6}$$

$$\text{At time} = t \quad \text{Mass dissolved} = \frac{D\,(d_1^3 - d_2^3)\pi}{6}$$

$$\% \text{ dissolved} = \frac{d_1^3 - d_2^3 \times 100\%}{d_1^3} \qquad (4)$$

At time 0, $S_1 = \pi d_1^2$ At time = t, $S_2 = \pi d_2^2$ and

$S_o = S_1 N$ and $S_w = S_2 N$, then substituting for d_1 and d_2 in equation (4) produces :

$$\% \text{ dissolved} = \frac{S_o^{3/2} - S_w^{3/2}}{S_o^{3/2}} \times 100\ \% \qquad (5)$$

Graphs of % dissolved evaluated from surface area measurements according to equation 5 are shown in Figure 6, 7 and 8. Also shown in the figures are corresponding graphs produced by analysing the

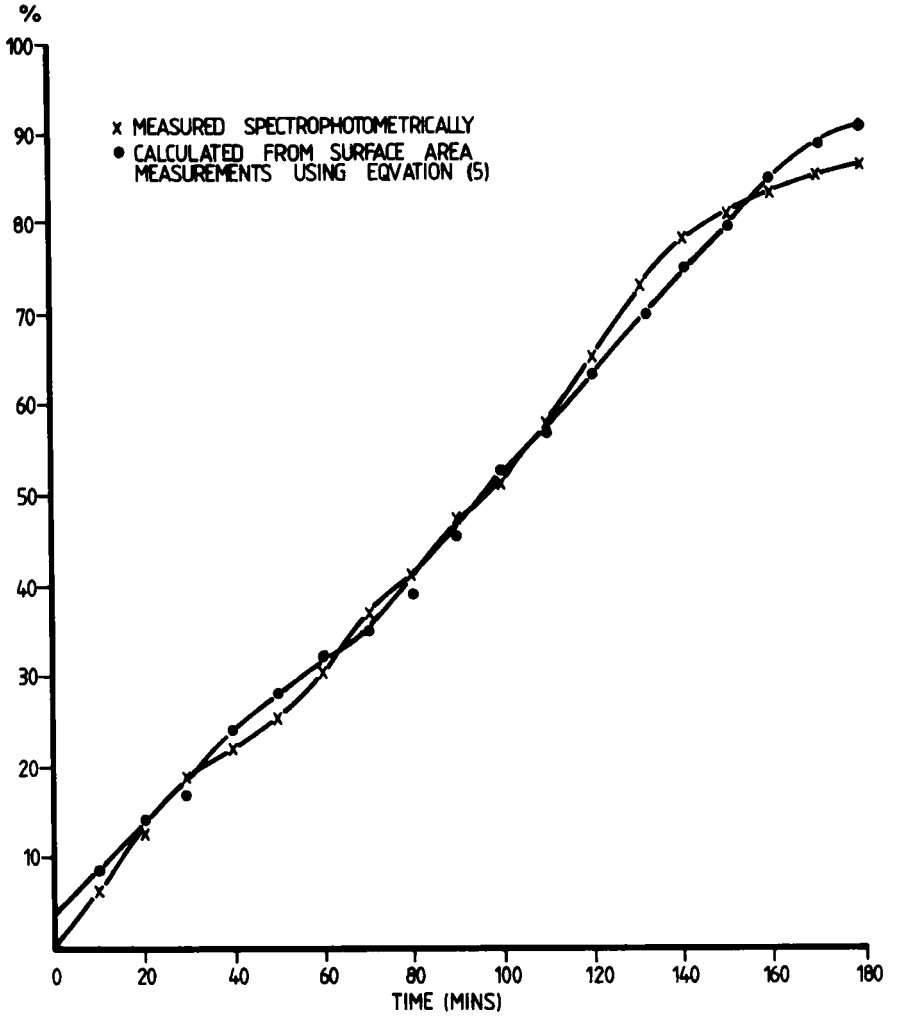


FIG. 6.

DISSOLUTION RATE OF FRUSEMIDE POWDER IN THE PHOTOSEDIMENTOMETER CELL.

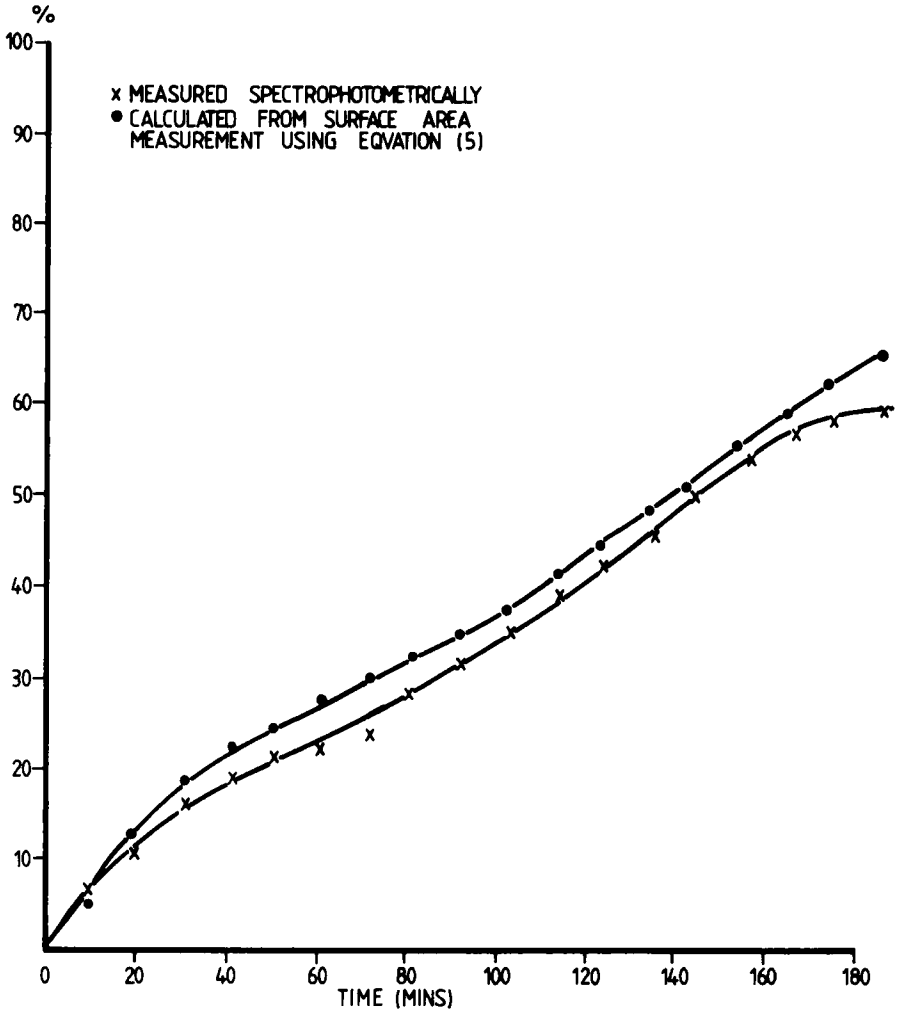


FIG. 7. DISSOLUTION RATE OF BENDROFLUAZIDE POWDER IN THE PHOTOSEDIMENTOMETER CELL.

amounts dissolved by ultraviolet spectrophotometry. The latter dissolution curves show a very close correlation with the graphs produced from surface area measurements. In effect dissolution measurements are monitoring the amount of drug going into solution, whereas surface area measurements are effectively recording the amount left suspended. It can therefore be concluded that this photo-sedimentometer method of measuring changes in surface area as drug

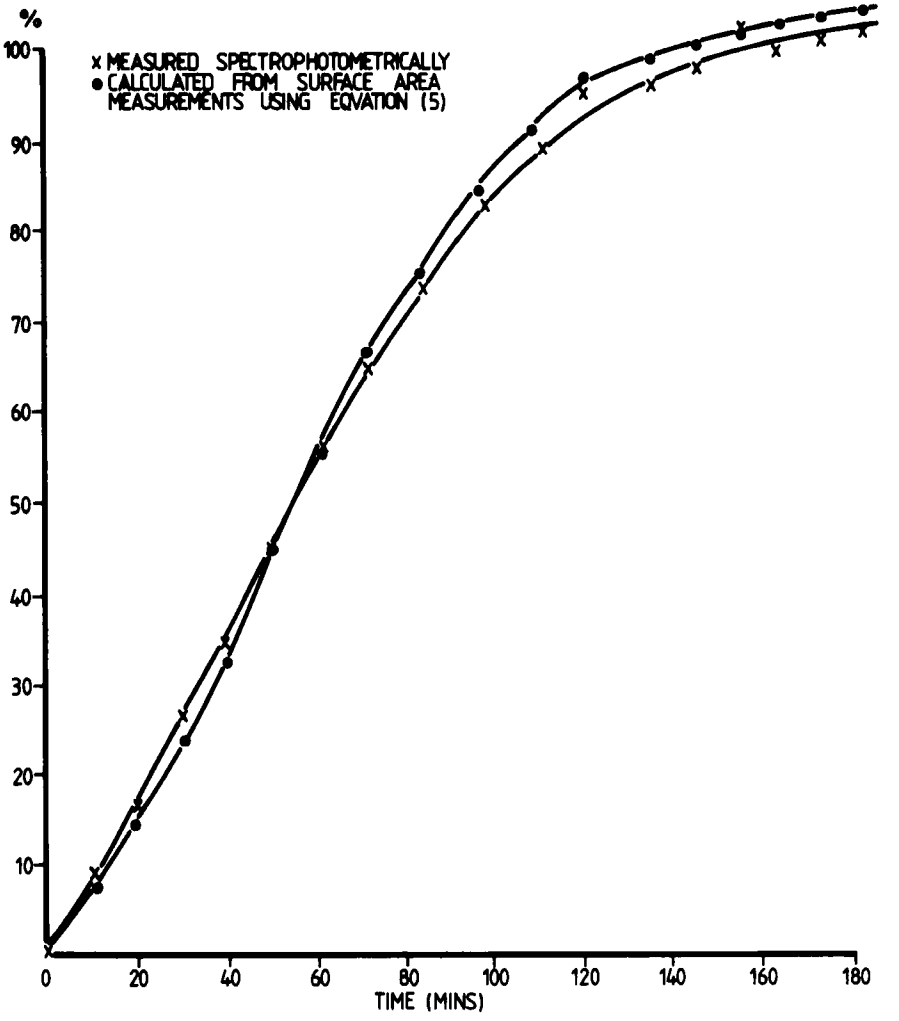


FIG. 8. DISSOLUTION RATE OF GLIBENCLAMIDE POWDER IN THE PHOTOSEDIMENTOMETER CELL.

particles dissolve is a simple method that can be employed in place of chemical analytical methods for the measurement of the dissolution rate of poorly water soluble drugs during pre-formulation. Since the effective surface area of the suspended particles is directly measured, the method may prove useful for comparative evaluations of different size fractions of the same drug or for evaluating particle-particle interactions.

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