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Studies on the simultaneous dissolution and degradation of progabide powders

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Summary

The simultaneous dissolution and degradation of progabide multiparticulate powders was examined using the U.S.P. Apparatus II. A reduction in particle size increased the dissolution rate particularly when the initial wettability of the powders was enhanced. A reduction in pH increased the dissolution rate but also increased the degradation rate of Progabide in solution. Fitting the data to a modified dissolution model allowed the evaluation of the rate constants of the simultaneous processes occurring.

Introduction

Progabide is an anticonvulsant compound which has undergone clinical trials for the long-term treatment of epilepsy (Musch et al., 1987). The in vitro dissolution of progabide powders is important in predicting the bioavailability of its formulations in vivo. In this paper, the dissolution of progabide powder is examined under conditions of varied particle size, varied pH, and in the presence of surfactants. There is a growing body of evidence (Withey, 1971; Carstensen et al., 1977; Cabana and O'Neill, 1980) indicating that Apparatus I (basket) of the U.S.P. dissolution systems suffers from severe deficiences, the most important being that the basket is inherently inadequate as a stirring device which may result in a high degree of non-homogeneity in the system. Such irregularities are overcome in Apparatus II (paddle) although both systems have disadvantages and shortcomings that were pointed out by Koch (1982). Nevertheless, the simplicity of the paddle method was capitalized upon in this study to test the dissolution of progabide powders.

Materials and Methods

Materials and instrumentation

Progabide micronised (lot 11129) and coarse (lot 11040) powders, supplied by L.E.R.S. (Paris, France), were used with an Alpine Augsburg A200LS air-jet sieve or with an Endecott 1MKII test sieve shaker to obtain the powder fractions. Where applicable, the particle-size distributions

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were determined on a Coulter Counter model TA in a low-sensitivity balanced electrolyte solution (Isoton II; Coulter). The particles were dispersed with the aid of the non-ionic surfactant Nonidet P42 (Coulter). P.D.V.B. Latex particles (Coulter) of 14.6 μm number median particle diameter were used to calibrate the instrument. Filtration was performed on Nuclepore polycarbonate membrane filters of 0.4 μm pore size. Tween 80 (Honeywill-Atlas) and sodium dodecyl sulphate (SDS) of special pure grade (B.D.H.) were used as supplied. The automated dissolution system consisted of a Copley (Erweka) DT-D6 six-unit dissolution apparatus conforming to the specifications of Apparatus II (U.S.P., 1984). For each of the 3 dissolution flasks used, the buffered medium was continually circulated, by a 4-channel LKB 2115 Multiperpex peristaltic pump, through a 1 ml Kontron stream analysis cell in a 6-cell thermostated holder in the Kontron Uvikon 810 double-beam spectrophotometer. Particulate matter was prevented from entering the sampling circuit by use of a cylindrical filter probe, commercially available (no. 178-3985-PO1; Technicon), fitted at the solvent entry point in the dissolution flask. The sampling circuit was made of 0.74 mm i.d. PTFE tubing (Jencons Scientific) with 1.3 mm i.d. LKB silicone tubing inside the pump. A Grant FH15 thermocirculator was used to maintain the cell's holder at 37 °C as in the dissolution apparatus. The spectrophotometer allowed automatic change-over of the cell in the beam path so that alternate measurements could be made of all 3 cells in the thermostated holder. A single measurement cycle only took 15 s which, coupled with a pump flow rate of 5 ml/min, allowed an almost continuous measurement of the dissolution in each flask. The spectrophotometer was interfaced with a Commodore CBM8032 computer and a 4022P tractor printer. Following each cycle, the data was transferred to the computer memory and a printout was made immediately.

Methods

Preparation of powder fractions. The 212–300 μm fraction was prepared on the Endecott sieve shaker and the 40–63 μm fraction on the air-jet sieve, from the coarse progabide powder. The micronised powder supplied was used after passage through a 32 μm sieve on the air-jet sieve. On average, 30 min sieving time was sufficient to ensure a good representative sample of the nominal range.

Particle size analysis. The volume size distribution of the powder fractions was measured on the Coulter counter. Since the size range over which the instrument may be used is generally quoted (Coulter Counter Manual, 1974) as from 2% to 40% of the orifice diameter, only the smaller two fractions were analysed by this method with the available 200 μm orifice tube. The instrument was calibrated by the simple version of the half-count technique (Coulter Counter Manual, 1974). The progabide powder was prewetted by shaking it in a solution of Nonidet P42, well below its C.M.C. value, and a small quantity of the powder was then added to the sample beaker of the instrument for analysis. As a precaution against possible dissolution of the particles, the electrolyte solution was presaturated with progabide.

Dissolution testing. The effect of pH on the dissolution of the powder fractions was investigated in pH 7 (phosphate) and in pH 1.5 (hydrochloric acid/potassium chloride) buffers (Dawson et al., 1986) at 37 °C. The effect of surfactants was only examined at pH 7. For SDS and Tween 80, concentrations of 0.025% and 5% w/v were used, respectively. In each of the dissolution flasks 900 ml of the dissolution medium was allowed to equilibrate at 37 °C with the paddle rotating at 100 rpm. The sampling circuit was operated and allowed 30 min to equilibrate. The sampling probes were positioned in the recommended position for manual sampling (Cox et al., 1978). 150 mg of the powder in question was added to each of the three dissolution flasks and the change in absorbance of the dissolution medium at the determined λ_{max} was automatically recorded at 1 min intervals for 120 min. Calibration curves were constructed by running known standard solutions of progabide through the stream analysis cells and were then used to obtain the dissolution curves of the powder fractions tested.

Progabide solubility in dissolution media. The solubility of progabide in the buffers used was estimated from previous data (Farraj et al., 1988a).

For the surfactant systems used, the solubility of progabide was determined at 37 °C by the procedure developed earlier (Farraj et al., 1988a).

Results and Discussion

It was observed that the method of sampling and dispersion was as important to the particle size measurement as the parameters relating directly to the measurement. The guidelines given by Matthews (1971) on the use of the Coulter Counter were closely adhered to. The particle size distributions of the two powder fractions tested are presented in Fig. 1 showing the log-normality of the distributions. This is a useful fact because for a log-normal distribution, only the geometric mean and the standard deviation are needed (Beaubien and Vanderwielen, 1980) to define the whole distribution function. Using the equations given by Beaubien and Vanderwielen (1980), the geometric volume mean diameter (M_v), the geometric standard deviation (d) and the geometric count mean diameter (M_c) of the powders can be determined; the micronised powder values were 11.5 μm $\pm$ 1.53 and 6.68 μm, respectively. The corresponding values for the 40–63 μm fraction were 53.5 μm $\pm$ 1.14 and 50.8 μm. These values are close to the arithmetic mean of the upper and lower nominal particle size of the sieve fraction collected. Thus, although it was not determined experimentally, the M_v of the 212–300 μm sieve fraction is expected to be close to 256 μm. The solubility of Progabide in 0.025% SDS was found to be 104.8×10^{-6} M whereas its solubility in 5% Tween 80 was 6789×10^{-6} M. Baggesen and Bechgaard (1980) reported that 0.025% SDS and 0.1% Tween 80 caused a surface tension reduction from 69 mN/m to 34 mN/m and 40 mN/m, respectively. This means that both surfactants reduce the surface tension thereby increase wetting and promote deflocculation but only Tween 80 increases progabide solubility. Thus, by using these two surfactants with progabide, the dominant mechanism by which surfactants alter the dissolution curve can be elucidated. The dissolution of progabide powder fractions in pH 7 buffer is shown in Fig. 2. Because of the low solubility limit of progabide (Farraj et al., 1988a), the dissolution proceeded under non-sink conditions. Even so, the particle size reduction produced an increased dissolution rate. Because the dissolution was examined under non-sink conditions, the data could not be easily fitted to any of the commonly applied dissolution models (Gibaldi and Feldman, 1967; Langenbucher, 1972; Carstensen, 1977). Further, a log-normal probability plot (Wagner, 1969) did not yield straight lines for all of the dissolution curves (Fig. 3) although useful information such as the $t_{16\%}$ or the $t_{50\%}$ can be extracted from such a plot. The plot also indicates that the micronised powder is initially slow to wet and deflocculate but once wetted its dissolution is faster than the other two fractions.

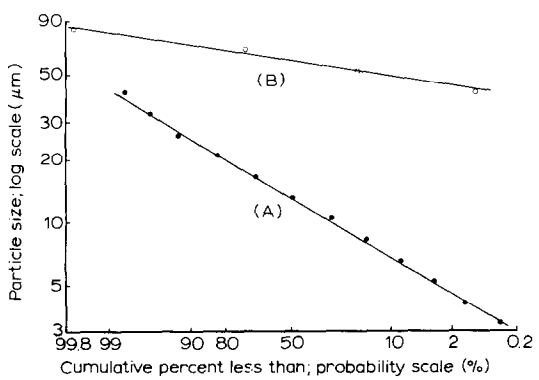

Fig. 1. Plots of the particle size of progabide vs probability demonstrating log-normality. A: micronised fraction. B: 40–63 μm sieve fraction.

The effect of adding SDS was to increase the initial dissolution rate and hence reduce the time required to approach the solubility limit, S_t (Fig. 4). In effect, the SDS appears to exhibit more clearly the differences in the dissolution rates of the three powder fractions by reducing the initial wetting and deflocculation time.

Recently, Matsuura (1982a and b) described how the cube-root model (Carstensen, 1977) can be modified into a complex mathematical function to account for non-sink conditions. Although such a method can be applied to the dissolution of progabide, an easier alternative is to convert non-sink conditions to sink conditions. Two methods of achieving this are by either using a high concentration of Tween 80 or by reducing the pH of

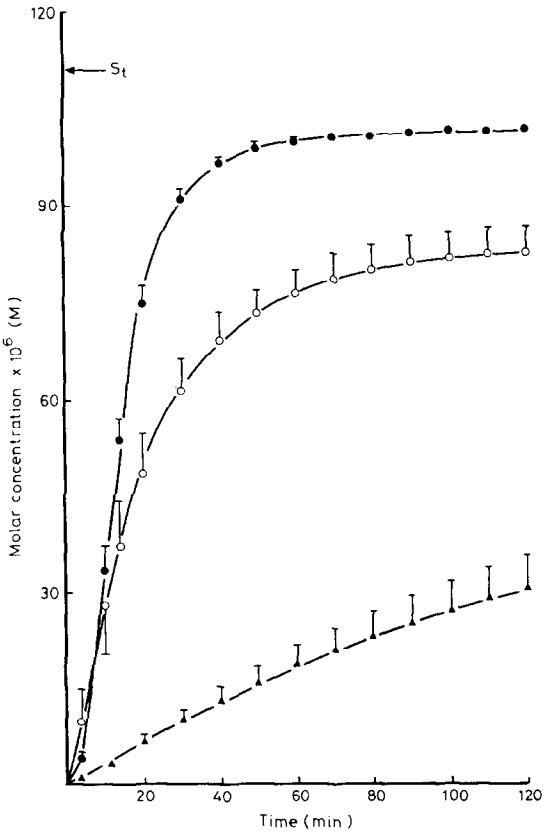

Fig. 2. Effect of particle size on the dissolution of progabide under non-sink conditions at pH 7. Each point represents the mean ± S.D. The solubility limit, S_t, is indicated. Key: ●, micronised powder; ○, 40–63 μm sieve fraction; and ▲, 212–300 μm sieve fraction.

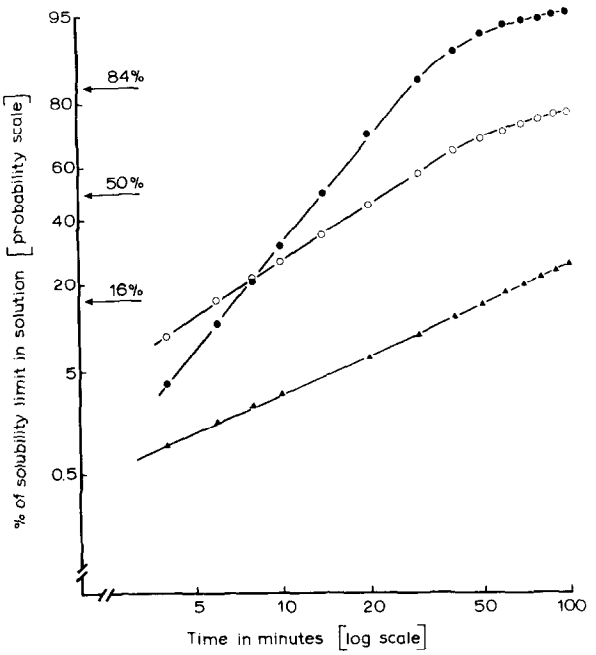

Fig. 3. Log-normal probability plots for progabide dissolution under non-sink conditions. Key: ●, micronised powder; ○, 40–63 μm sieve fraction; and ▲, 212–300 μm sieve fraction.

the dissolution medium to increase progabide solubility (Farraj et al., 1988a). Fig. 5 shows the effect of using 5% Tween 80 in the dissolution medium at pH 7. The high percentage of Tween 80 caused the pH of the buffer to drop to 6.9 but this was left unadjusted. If the whole dose of the added powder was to dissolve, then the maximum concentration would have been equal to 497.5×10^{-6} M, indicated by C_∞ in Fig. 5. This value, which is about 7% of the solubility limit of progabide, was approached rapidly by the micronised and the 40–63 μm fractions but not maintained because the effect of degradation on the high concentrations present in solution. Nevertheless, the increase in solubility produced a marked increase in the dissolution rate of all the powder fractions.

The dissolution models developed for non-reactive conditions (Gibaldi and Feldman, 1967; Langenbucher, 1972; Carstensen, 1977) would not be expected to describe exactly the whole of the dissolution curve, for any of the powders tested. This is because of the simultaneous processes occurring in the system, namely, dissolution and degradation. Because the former is dependent on the amount of solid drug remaining in the system whereas the latter is dependent on the amount of drug present in solution, the initial part of the dissolution curve will approximate to that controlled by a single process; this explains the data fit to first-order kinetics (Gibaldi and Feldman, 1967) as presented in Fig. 6 although it is clear from the plot that deviations do occur at later times. In other words, the shape of the dissolution curve is dependent on the relative magnitude of the simultaneous processes in the system. This explains the shape of the dissolution curves of Fig. 7 obtained at pH 1.5. At such low pH values, the

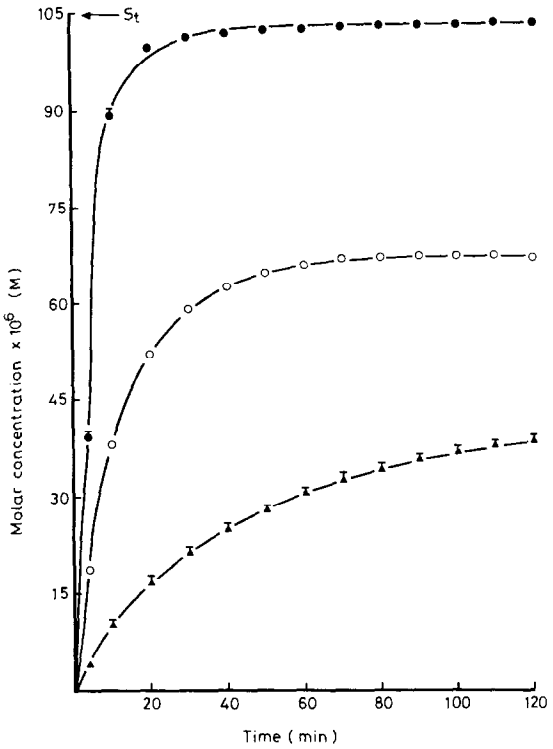

Fig. 4. Effect of 0.025% w/v SDS on the dissolution of progabide under non-sink conditions at pH 7. Each point represents the mean ± S.D. The solubility limit, S_t, is indicated. Key: ●, micronised powder; ○, 40–63 μm sieve fraction; and ▲, 212–300 μm sieve fraction.

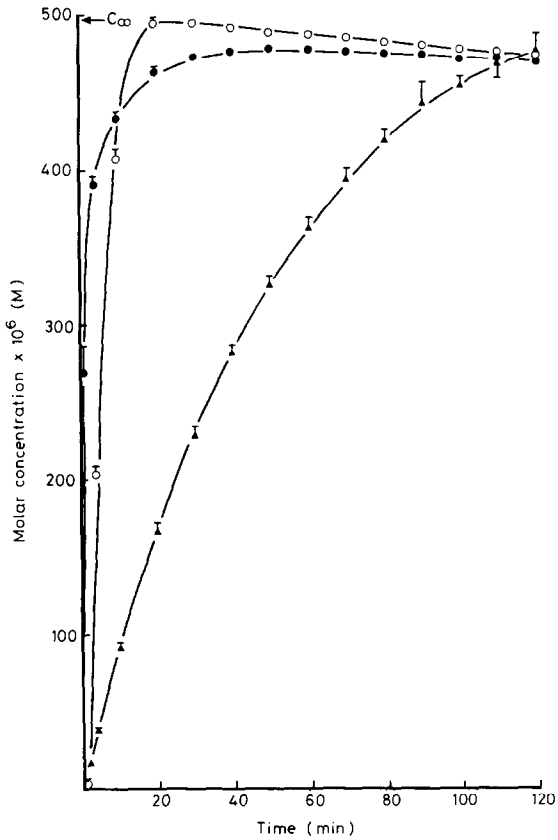

Fig. 5. Effect of 5% w/v Tween 80 on the dissolution of progabide under sink conditions. Each point represents the mean ± S.D. The theoretical concentration at infinity, C_∞, is indicated. Key: ●, micronised powder; ○, 40–63 μm sieve fraction; and ▲, 212–300 μm sieve fraction.

value of C_∞ represents only 3.6% of the solubility limit and the contribution of the degradation process is much larger than in the Tween 80 system (Farraj et al., 1988a and b). In fact, the ratio of the first-order degradation rate constants is about 70 : 1.

George Chen and colleagues (1980) modified the aforementioned dissolution models to account for reactive conditions. In particular, the modified first-order dissolution model can be described by:

$$m = m_0 \cdot k\left[\exp(-k' \cdot (t - t_0)) - \exp(-k \cdot (t - t_0))\right]/(k - k')$$

or

$$C = C_\infty \cdot k\left[\exp(-k' \cdot (t - t_0)) - \exp(-k \cdot (t - t_0))\right]/(k - k')$$

where m = mass of drug dissolved at time t, m_0 = initial mass present in dosage form, k = first-order dissolution rate constant, k' = first-order degradation rate constant, t_0 = lag time of dissolution, C = concentration of drug present at any time t, and C_∞ = maximum theoretical concentration achieved at infinity under non-reactive conditions.

This model was applied to the reactive dissolution of Progabide. For the curve-fitting procedures, the non-linear least-squares program (MULTI) developed by Yamaoka and others (1981) for microcomputers was used. Very slight modifications to the program, originally written in BASIC language for the CBM computers, were required to execute it on the available Commodore CBM 8032 computer. The Gauss-Newton

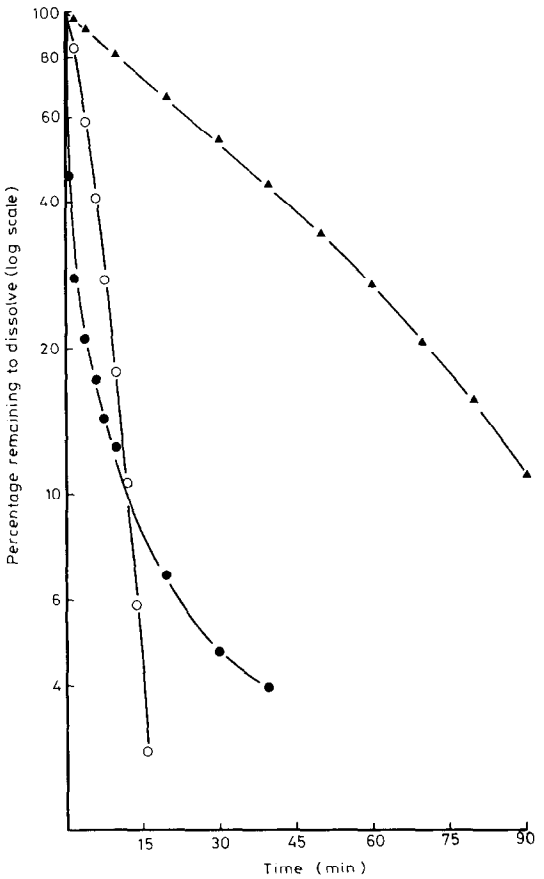

Fig. 6. Data from Fig. 5 plotted in a first-order kinetic fashion. Key: ●, micronised powder; ○, 40–63 μm sieve fraction; and ▲, 212–300 μm sieve fraction.

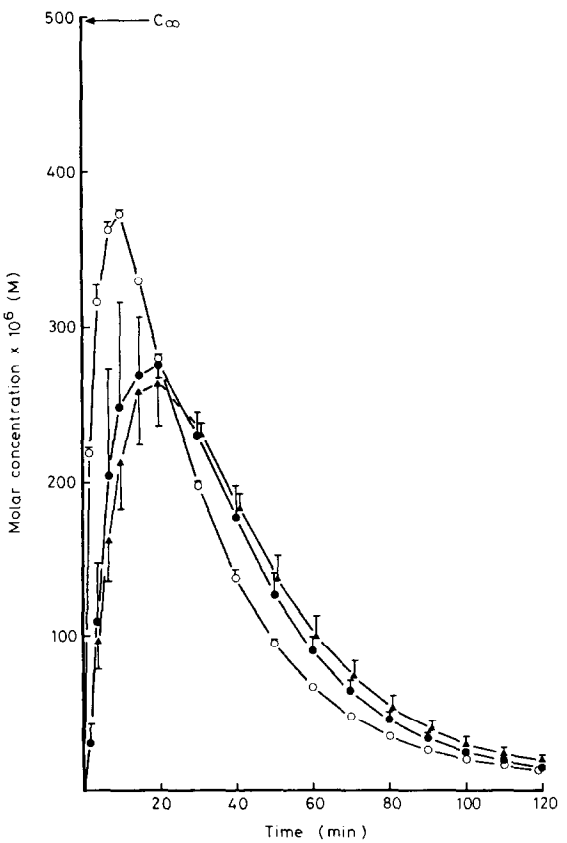

Fig. 7. Simultaneous dissolution and degradation of progabide at pH 1.5 and 37 °C. Each point represents the mean ± S.D. The theoretical concentration at infinity under non-reactive conditions, C_∞, is indicated. Key: ●, micronised powder; ○, 40–63 μm sieve fraction; and ▲, 212–300 μm sieve fraction.

method was used because it showed an excellent degree of convergence to the final values of k and k' and because it was the least time-consuming of the algorithms offered. As a typical example, Fig. 8 shows the type of fit achieved by the program using the above equation. The fitting-procedure was repeated for the other powder fractions used and also for the results obtained with Tween 80 in Fig. 5. The estimated values of k and k' are summarised in Table 1. In 5% Tween 80, the dissolution rate constant, k, increased with a decrease in particle size; however, in pH 1.5 buffer, this type of relationship did not hold; the 40–63 μm fraction had a much larger k value than the micronised fraction. This apparent anomaly can be explained in terms of surface tension. Tween 80 greatly reduces the surface tension of the dissolution medium whereas the hydrochloric acid/potassium chloride buffer does not (Baggesen and Bechgaard, 1980). Hence, the micronised powder does not readily wet in the pH 1.5 buffer and, because of surface charges, remains agglomerated for a longer period than in the Tween 80 system. A similar trend was previously observed (Figs. 2, 3). In Tween 80-containing system, progabide degraded very slowly with the result that the error in estimating the degradation rate constant was large. In fact, the negative value shown for the 212–300 μm fraction is an artifact because, in reality, the k' value cannot be estimated from the data collected as there are no post-peak data points. However, the estimated value of k' for the

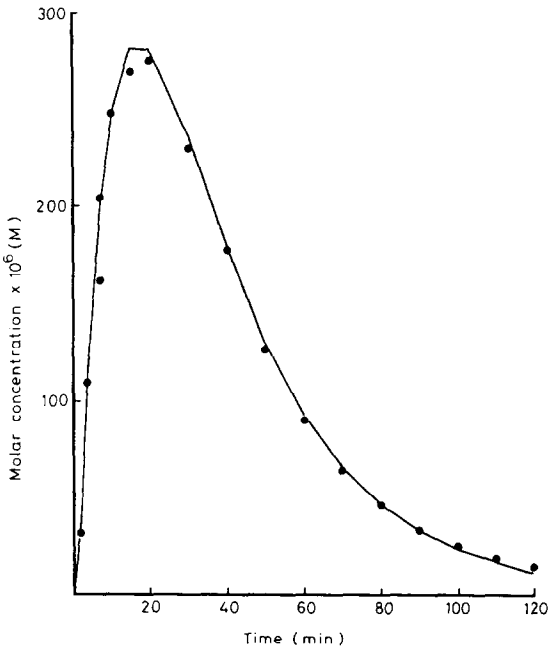

Fig. 8. Non-linear least-squares curve fitting of the simultaneous dissolution and degradation of progabide micronised powder fraction. The data points (●) are indicated.

pH 1.5 buffer was consistent and showed a low standard deviation. Further, it showed a remarkable agreement with the independent value obtained earlier (Farraj et al., 1988a). In terms of half-life, a value of 19.9 min obtained here compared favourably with the previous value of 18 min.

TABLE 1

Estimated parameters obtained, using MULTI, from the experimental results of Figs. 5 and 7

Powder fraction and dissolution medium	$k \pm$S.D. ($\times 10^2$)	$k' \pm$S.D. ($\times 10^4$)
Micronised		
5% Tween 80 (pH 7)	66.7 ± 8.7	6.1 ± 2.72
Buffer of pH 1.5	10.3 ± 0.23	354 ± 3.8
40–63 μm		
5% Tween 80 (pH 7)	14.4 ± 0.82	3.1 ± 2.88
Buffer of pH 1.5	66.2 ± 9.7	343 ± 12.8
212–300 μm		
5% Tween 80 (pH 7)	2.0 ± 0.03	−8.2 ± 1.13
Buffer of pH 1.5	8.4 ± 0.31	348 ± 6.64

The analysis of progabide was done in accordance with the assay procedure developed (Farraj et al., 1988a). However, for continuous measurement of progabide in pH 1.5 buffer, λ_{max} of 363 nm was used which is in apparent contradiction with the principles of specific analysis of progabide in the presence of SL79.182. Even so, by allowing the dissolution experiments to proceed for about 4 h, the value of the final absorbance of the solution at 363 nm (caused by SL79.182) was found to be 0.055. Although this can result in a significant error towards the end of the 120 min run, its effect on the calculated rate constants can be ignored. The advantages gained by using 363 nm were judged to heavily outweigh the disadvantages. In particular, the initial phase of the dissolution curve would have been difficult to follow if intermittent sampling was implemented.

Overall, the results obtained have highlighted the importance of particle size and pH to the simultaneous processes of dissolution and degradation of progabide. On the basis of the present studies, it is anticipated that factors such as gastric pH, intestinal pH, and the particle size of the administered dosage form will play important roles in controlling the oral bioavailability. The application of protective measures such as enteric-coating to prevent gastric degradation may not be very useful because in the absence of gastric dissolution, intestinal dissolution alone may prove insufficient to achieve an acceptable bioavailability.

References

Baggesen, S. and Bechgaard, H., In vitro evaluation of two controlled release propoxyphene hydrochloride formulations – influence of the composition of dissolution media on drug release. *Pharm. Acta Helv.*, 55 (1980) 312–315.

Beaubien, L.J. and Vanderwielen, A.J., Particle-size analysis of pharmaceutical powders. *J. Pharm. Sci.*, 69 (1980) 651–655.

Cabana, B.E. and O'Neill, R., FDA's report on drug dissolution. *Pharmacopeial Forum*, 6 (1980) 71–75.

Carstensen, J.T., Lai, T. and Prasad, V.K., USP dissolution test I: adequacy of mixing. *J. Pharm. Sci.*, 66 (1977) 607–608.

Carstensen, J.T., *Pharmaceutics of Solids and Solid Dosage Forms*, Wiley, New York, 1977, pp. 75–84.

Coulter Counter Model TA Instruction Manual, Coulter Electronics, Luton, Beds., U.K., 1974, pp. 36–40.

Cox, D.C., Douglas, C.C., Furman, W.B., Kirchhoefer, R.D., Myrick, J.W. and Wells, C.E., Guidelines for dissolution testing. *Pharm. Technol.*, 2 (1978) 41–53.

Dawson, R.M.C., Elliott, D.C., Elliott, W.H. and Jones, K.M., *Data for Biochemical Research*, Clarendon, Oxford, 1986, pp. 417–448.

Farraj, N.F., Davis, S.S., Parr, G.D. and Stevens, H.N.E., The stability and solubility of progabide and its related metabolic derivatives. *Pharm. Res.*, 5 (1988a) 226–231.

Farraj, N.F., Davis, S.S., Parr, G.D. and Stevens, H.N.E., Modification of the aqueous solubility and stability of progabide. *Int. J. Pharm.*, (1988b) in press.

George Chen, H.-S., Chang, S.Y., Evans, T.L. and Gross, J.F., Concentration profile for the dissolution of drug tablets undergoing simultaneous degradation. *J. Pharmacokin. Biopharm.*, 8 (1980) 621–631.

Gibaldi, M. and Feldman, S., Establishment of sink conditions in dissolution rate determinations. Theoretical considerations and application to nondisintegrating dosage forms. *J. Pharm. Sci.*, 56 (1967) 1238–1242.

Koch, H.P., The rotation flask method: choice of an alternative methodology in dissolution testing. *Pharm. Ind.*, 44 (1982) 838–842.

Langenbucher, F., Linearization of dissolution rate curves by the weibull distribution. *J. Pharm. Pharmacol.*, 24 (1972) 979–981.

Matsuura, I., Dissolution of drug powders. 1. Dissolution of monodisperse powders. *Yakugaku Zasshi*, 102 (1982a) 264–271.

Matsuura, I., Dissolution of solid drugs. 2. Dissolution of polydisperse powders. *Yakugaku Zasshi*. 102 (1982b) 678–689.

Matthews, B.A., The use of the coulter counter in emulsion and suspension studies. *Can. J. Pharm. Sci.*, 6 (1971) 29–34.

Musch, B., Cambier, J., Loiseau, P., Fournier, V., Beaussart, M., Benoit, C., Broglin, D., Centraud, M., Chatel, M. and Deville, M.C., Long-term treatment of epilepsy – open multicentre trial with progabide in epileptic patients. Eur. Neurol., 26 (1987) 113–119.

United States Pharmacopeia, 21st rev., U.S. Pharmacopeial Convention, Rockville Md, 1984, pp. 1243–1244.

Wagner, J.G., Interpretation of percent dissolved–time plots derived from in vitro testing of conventional tablets and capsules. *J. Pharm. Sci.*, 58 (1969) 1253–1257.

Withey, R.J., The kinetics of dissolution for a non-disintegrating standard substrate. *J. Pharm. Pharmacol.*, 23 (1971) 573–582.

Yamaoka, K., Tanigawara, Y., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobio-Dyn.*, 4 (1981) 879–885.