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The influence of agitation intensity, particle size and pH of dissolution fluid on the in-vitro release of drug from hard gelatin capsules

J. M. NEWTON*, N. A. H. MUHAMMAD†, *Pharmacy Department, Chelsea College, University of London, Manresa Road, London SW3 6LX, U.K. and †Pharmacy Department, University of Nottingham, Nottingham NG7 2RD, U.K.*

The influence of agitation intensity on the in-vitro release of controlled particle size fractions of acetylsalicylic acid from hard gelatin capsules into buffered dissolution fluids has been investigated employing a dissolution technique. The value of T50 decreased as the stirring rate increased from 120 to 320 rev min^{-1} for all particle size fractions and pH values. A further increase in the stirring rate had a limited effect on the value of T50 and the changes were particle size dependent. The influence of the drug solubility, induced by changing the pH of the dissolution fluid, was decreased by increased agitation. When the capsules were filled at bulk densities above the maximum tapped bulk density, the value of T50 was increased, the extent of increase being greater the smaller the particle size of the drug. The kinetics of the solution process were influenced by agitation intensity and particle packing.

The in-vitro rate of release of drug from solid dosage forms is greatly influenced by the conditions of the test procedure. The variables involved include the type of dissolution apparatus, composition and volume of the dissolution fluid, temperature, the type and rate of fluid movement, and the solubility of drug in the dissolution fluid. For hard gelatin capsules, the drug, its particle size, the presence of other additives and method of filling are particularly important. By simplifying the formulation some elucidation of the mechanism involved in the process can be obtained. For single component formulations, Newton & Rowley (1970) demonstrated the importance of drug particle size and packing within the capsule and their relationship to powder bed permeability. Muhammad & Newton (1983) have demonstrated the importance of the interaction between solubility and the particle size of the drug in controlling release. By changing the test conditions, in terms of agitation intensity, drug solubility, drug particle size and the packing conditions, the present work investigates how these factors are involved in controlling the in-vitro drug release process.

* Correspondence.

Materials and methods

Materials. The acetylsalicylic acid and chemicals used to prepare the buffer were as described previously (Muhammed & Newton 1983).

Methods. Capsules were filled to a maximum tapped bulk density as described previously with the controlled particle sizes of drug (Muhammad & Newton 1983). To increase the packing to a level above the maximum tapped bulk density, capsules were initially filled to this level and then consolidated by placing a plate with pegs of the same dimensions as the internal diameter of the capsule, on top of the powder. A 5 kg weight was placed on this plate to compress the powder within the capsule. The plate was removed and further drug filled into the capsule. The process was repeated until application of the load produced no further compression of the powder. The fill weight of the capsules was determined by weighing 10 capsules and allowing for the weight of the shell. The dissolution test was that described by Muhammad & Newton (1983) undertaken at additional stirring speeds of 320 and 450 rev min^{-1}. The time for 50% of the drug to dissolve, T50, was estimated from a plot of percentage of drug released from the capsule as a function of time.

Results and discussion

The experimental design allows treatment of the results by analysis of variance. The results can be considered in two sets, firstly a 3-way design with 7 pH values for the dissolution fluid, 7 particle size fractions and 3 stirring speeds and secondly, a 4-way design with 7 pH values for the dissolution fluid, 4 particle size fractions, 3 stirring speeds and 2 capsule filling conditions. When subjected to analysis of variance the factors all had significant influence on the value of T50. There are however significant interactions between the factors which limits the conclusions which can be drawn as to the magnitude of the effects. It is more useful therefore

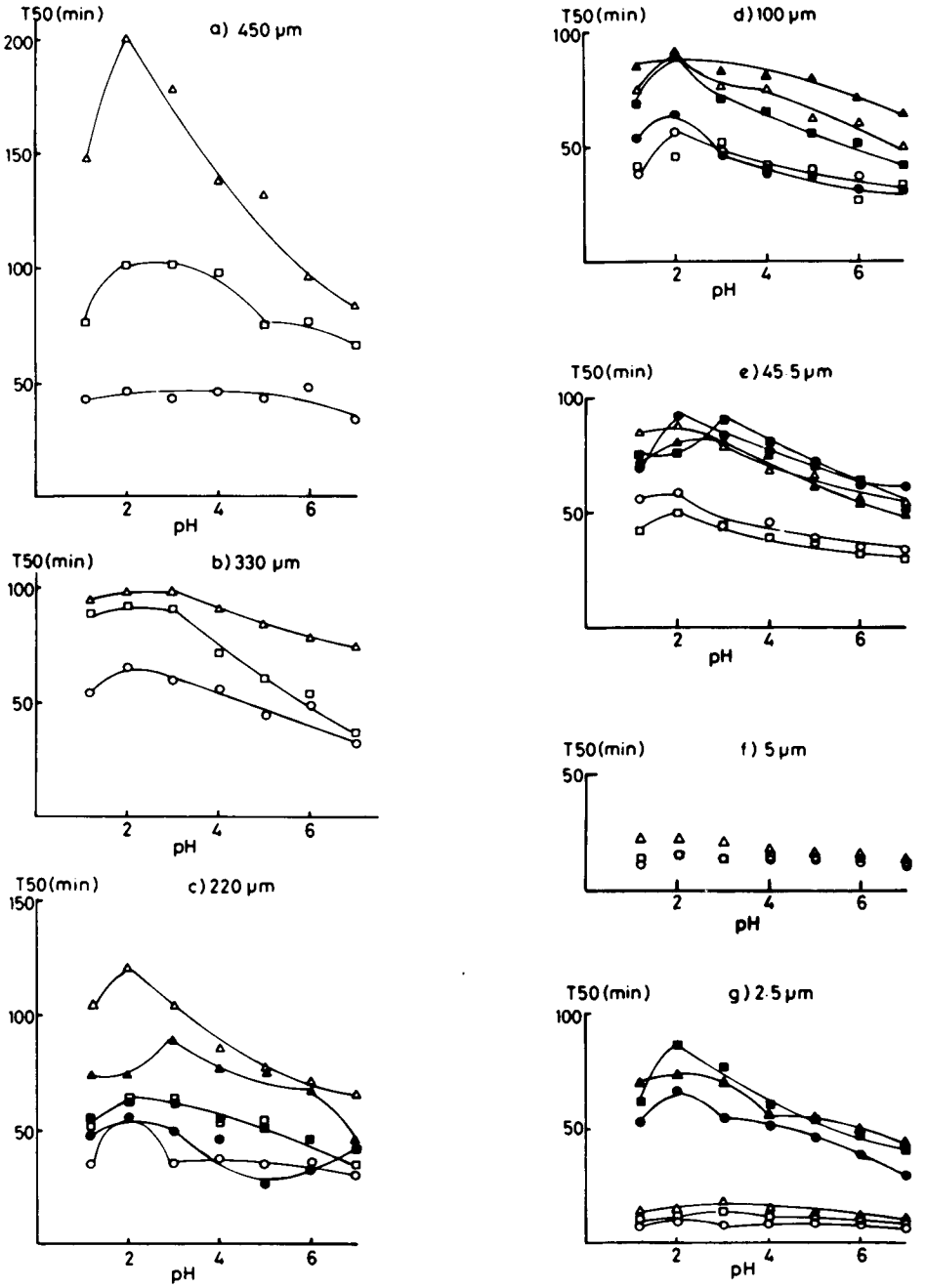

FIG. 1. The T50 value of capsules containing particle size fractions of acetylsalicylic acid tested in fluids at differing pH and with differing intensity of agitation. Size fractions (a) 450, (b) 330, (c) 220, (d) 100, (e) 45·5, (f) 5·0 and (g) 2·5 μm. Agitation intensities △, 120; □, 330; and ○, 450 rev min^{-1}, particle size fractions packed at maximum bulk density. Agitation intensities ▲, 120; ■, 330; and ●, 450 rev min^{-1}, particle size fractions packed with 5 kg loading in excess of maximum bulk density.

to consider the results individually rather than averages for a given factor.

The gross changes in the in-vitro release of the drug from the capsules which occur with agitation intensity are shown as a function of the pH of the dissolution media in Fig. 1. At the slowest stirring speed, changes in the pH of the dissolution fluid provide changes in the value of T50 which are particle size-dependent, the

greatest change being observed with the largest particle size fraction. When the stirring speed is increased to 320 rev min^{-1}, the value of T50 decreases for all but the two smallest particle size fractions, and the dependence on pH is generally decreased. On further increase in the stirring speed to 450 rev min^{-1}, the value of T50 decreases even further, except for those particle size fractions which already have very high dissolution rates. The dependence of T50 on the pH of the dissolution fluid almost disappears. Except for the two smallest size fractions, the value of T50 is virtually independent of particle size and the pH of the dissolution fluid. That the T50 value is greater than the constant value of T50 for the two smallest size fractions, implies that there is still some surface area effect involved in controlling the rate of dissolution.

The increase in stirring rate is obviously involved in disruption of the powder mass from the capsule as well as increasing the dissolution rate by increased fluid movement over the surface of the particles. The ease of deaggregation is related to the degree of packing within the capsule and in general, the tighter the powder packing the slower the drug release (Newton & Rowley 1970). There is certainly a decrease in porosity with increase in particle size for the capsules considered in these experiments (see Fig. 2). For a given particle size the packing density can be changed by loading the powder mass during the filling process. This was achieved for the particle size fractions 2·5, 45·5, 100 and 220 μm, resulting in the modified porosities illustrated in Fig. 2. The influence of this increased packing on selected particle size fractions is shown in Fig. 1. Loading has least effect on the porosity and drug release of the larger particle size fraction but the greater effect on the dissolution of the smallest size fraction. The porosity and drug release do not correlate exactly and do not give a total answer to the controlling mechanism of dissolution. The more tightly packed systems do show some pH dependence but not to the same extent as the large particle size fractions at the lowest stirring speed.

Changes in pH exert the greatest effect in terms of drug solubility (a factor which changes approximately 65 fold for the current system). For the systems studied here, as previously (Muhammad & Newton 1983), there was however no correlation between drug solubility and the T50 value and hence solubility cannot be considered to be the rate controlling step in the dissolution process.

Employing the slowest speed of stirring, Muhammad & Newton (1983) observed a zero order dissolution rate for the larger particle size fractions implying a constant

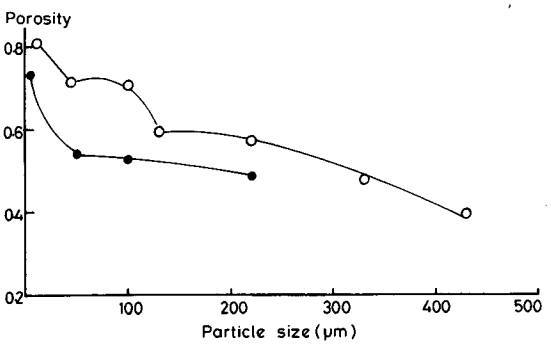

FIG. 2. Porosities within capsules for different particle size fractions, ○ at maximum bulk density and ● packed with 5 kg loading in excess of bulk density.

rate of dissolution and hence production of new surface. At the two higher speeds tested here, dissolution for the capsules filled by tamping followed apparent first order kinetics. This suggests that the rate of production of new surface by deaggregation is less than that by dissolution, hence dissolution decreases exponentially as the test proceeds (Wagner 1969).

These apparent first order dissolution rates are associated with systems that have a higher dissolution rate than those which have apparent zero order. This suggests that higher agitation intensities are capable of generating a greater surface area available for dissolution in the early stages of the test, and that the subsequent decline in dissolution rate is associated with the loss of surface by the dissolution process.

The results clearly establish that even for capsule formulations containing a drug whose solubility is pH dependent, it is the degree of agitation which has the greatest influence on the in-vitro drug release. An approximately four fold change in stirring rate thus produces a greater change than an approximately 65 fold change in solubility. The magnitude of the changes are associated with break up of the powder mass within the capsule. Hence the agitation conditions for capsule dissolution tests would appear to require greater control than the solubility of the drug in the dissolution fluid.

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