J. Pharm. Pharmacol. 1983, 35: 345–349
Received August 26, 1982

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

N. A. H. MUHAMMAD* AND J. M. NEWTON†

* *Pharmacy Department, University of Nottingham, Nottingham, NG7 2RD, U.K.,*
† *Pharmacy Department, Chelsea College, University of London, Manresa Road, London SW3 6LX, U.K.*

The influence of pH of the dissolution fluid on the in-vitro release of acetylsalicylic acid from hard gelatin capsules has been studied for a series of particle size fractions of the drug. Generally, the time required for 50% of the drug content of the capsule to appear in solution during a dissolution test, T50, increased as the pH increased from 1·2 to 2·0; thereafter the value of T50 decreased as the pH increased from 3 to 7. These changes were found to be related to the apparent solubility of the drug. The extent of the changes was found to be further dependent on the particle size of the drug. For capsules filled with particle size fractions of 2·5 and 5·5 μm median diameter, the changes were small. Larger changes were observed with particles of median diameters of 45, 100, 220 and 330 μm while the largest changes (greater than two-fold) were obtained with particles of median diameter 130 and 430 μm. The type of kinetics that could be used to express the release rates was found to be particle size-dependent. For particles of 45 μm and larger, the release rate followed an apparent zero order process while an apparent first order process represented the release for the two smallest particle size fractions.

The release of drugs from hard gelatin capsules has attracted attention in the last two decades. This is because of bioavailability differences which have been observed in capsule formulation (Glasko et al 1968; Brice & Hammer 1969). The variation in release of drugs from capsules has been shown to arise from the type of drug, other additives present and the method of preparation of the capsules (Withey & Mainville 1969; Samyn & Jung 1970; Newton et al 1971a,b; Khalil & Ali 1972; Newton & Razzo 1974, 1977; Newton & Bader 1980).

An orally administered solid dosage form such as a capsule, will be subjected to a gradient of pH change ranging from acidic in the stomach (the average pH of gastric fluid in men is about 1·9, while it is reported to be approximately 2·6 for women, Dotevall 1961) to neutral medium in the intestine (the pH of the duodenal secretion for both men and women varies from 5·8 to 7·6 Altman 1961). This change in pH will change the solubility and degree of ionization of acidic or basic drugs, and consequently the dissolution rate and the rate of absorption. The objective of the work described in this study is to investigate the influence that the pH of the dissolution fluid will produce on the dissolution rate of a model drug, presented as controlled particle size fractions within gelatin capsules.

† Correspondence.

MATERIALS AND METHODS

Materials

Acetylsalicylic acid, B.P., crystalline grade was supplied by Monsanto Chemicals Limited. Hydrochloric acid, boric acid, potassium dihydrogen orthophosphate, citric acid and sodium hydroxide were all analar grade obtained from BDH Chemicals Limited. To obtain acetylsalicylic acid of different particle size fractions, the sample drug was ground in a ball mill and sieved, producing particles down to a −106+90 μm size fraction. A McCrone vibratory mill was used to obtain particles of sieve size less than 90 μm. An even smaller size of drug was produced by subjecting a quantity of the powder which had passed through a 90 μm aperture sieve to fluid energy milling. The micronized powder was separated into two particle size fractions with an Alpine multiplex classifer. The particle size range of each sieve fraction was determined by microscopic counting

with an eye piece graticule to give a number/length median diameter. This method can be used for all the size fractions whereas different methods would be required to cover the different size ranges involved. The counts were undertaken in a manner described by BS 3406 Part 4 1963. To take into account possible variations in shapes elongation ratios were determined in each size fraction on about 200 particles. The results in Table 1 illustrate that while there is a general reduction in elongation ratio, as the median diameter decreases, the various size fractions are not dissimilar, bearing in mind the considerable variation in elongation ratio.

Methods

Capsule filling

The size 2 opaque hard gelatin capsules (LOK-CAP) were supplied by Elanco Division of Eli Lilly and Co. and were filled by using the Cap III Tevopharm (Schiedam—Holland). The shell was filled by tapping until a maximum tapped bulk density was obtained.

Determination of the apparent equilibrium solubility

Solutions of known pH were prepared with either 0·1 M hydrochloric acid (pH 1·2) or a suitable universal buffer (Britton 1958) omitting the barbital. the resulting buffer solutions were 0·0285 M with respect to hydrochloric acid, potassium dihydrogen orthophosphate, boric acid and citric acid. The buffer system was chosen because its change in pH was a linear function of the volume of base added. A series of vials were immersed and agitated in a shaking water bath at 37 ± 0·1 °C for one week. The pH of the solution in each vial was readjusted at regular intervals. When equilibrium had been achieved, the solution was filtered rapidly into a previously warmed container, to remove excess particles of drug. The acetylsalicylic acid content of the filtrate was determined as described by Newton & Bader (1980). The values of the solubility of acetylsalicylic acid as a function of pH are given in Fig. 1.

Table 1. Elongation ratio and its variation for size fractions of acetylsalicylic acid.

Median number/length particle diameter (μm)	Elongation ratio	Coefficient of variation
430·0	2·84	28·8
330·0	2·69	32·1
220·0	2·59	39·7
130·0	2·50	35·0
100·0	2·49	34·0
45·5	2·34	31·6
5·5	2·25	30·8
2·5	2·20	29·2

Dissolution test

The dissolution was based on the beaker method of Levy & Hayes (1960). Two litres of appropriate dissolution fluid were placed in a 2 litre beaker. The fluid was agitated by a triangular section stirring rod rotating at a speed of 120 rev min^{-1} immersed to a depth of 30 mm into the dissolution fluid, and situated half-way from the side to the centre of the beaker. The capsule, held by a spiral of stainless steel wire (2 cm long, 0·8 cm diameter and 4 turns cm^{-1}) was placed centrally at the bottom of the beaker. The acetylsalicylic acid content of the filtered samples of the dissolution fluid was determined as described by Newton & Bader (1980). The time required for 50% of the drug content of the capsules to appear in the dissolution fluid, T50, was determined graphically from a plot of the percentage of drug released from the capsule as a function of time. Each T50 value represents the mean of three determinations.

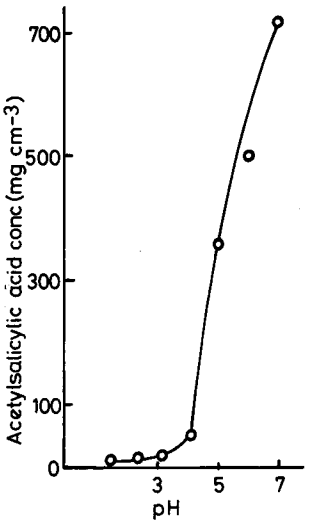

FIG. 1. The solubility of acetylsalicylic acid as a function of pH.

RESULTS AND DISCUSSION

Capsules were filled with acetylsalicylic acid of number length median diameters of 2·5, 5·5, 45·5, 100, 130, 220, 330 and 430 μm. The value of T50 for the capsules, as a function of pH, is shown in Fig. 2.

In general, the influence of the pH of the dissolution fluid was of the same general form for all particle size fractions. There was a maximum T50 at pH 2 to 3, with lower values of T50 below and above these pH values. Exception to this general rule occurred with particle size fractions 330 and 2·5 μm in that the values of T50 were higher at pH 3 than pH 2. The magnitude of the change in the value of T50 with pH is seen to be dependent on the particle size of the drug. The two micronized samples show low T50 values which are not greatly influenced by the pH of the dissolution fluid. The largest particle size fraction, 430 μm and intermediate size fractions 220 and 130 μm, show approximately two-fold change in the value of T50, over the range of pH values. The other size fractions, namely 330, 100 and 45·5 μm, show less variation with pH. It would appear that the controlling mechanism of release differs with the differing particle size fractions.

capsules filled with each particle size fraction. The influence of solubility is clearly particle size-dependent. In the case of those particle size fractions which show considerable change in T50 with solubility, the relationship shows least change in the value of T50 over the range of most rapid change in solubility. In this region it appears that some factor other than solubility is the rate-controlling step of the dissolution process. If, however, the solubility was the only factor controlling the release of drug from the capsules, the rate of change of T50 with solubility would be independent of particle size. This is not the case as can be seen in Fig. 3, nor is there a consistent change in the value of T50 with the drug particle size, at different pH values (see Fig. 4), confirming that differing dissolution controlling mechanisms operate to different extents with different particle size systems.

Dissolution of dosage forms is a complex function

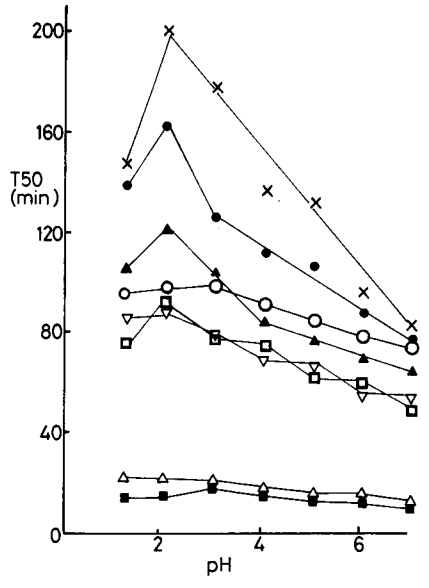

FIG. 2. The influence of pH on the in-vitro release (T50) of acetylsalicylic acid of different particle size fractions from hard gelatin capsules. The mean particle diameters (μm): 430, ×; 330, ○; 220, ▲; 130, ●; 100, □; 45·5, ▽; 5·5, △ and 2·5, ■.

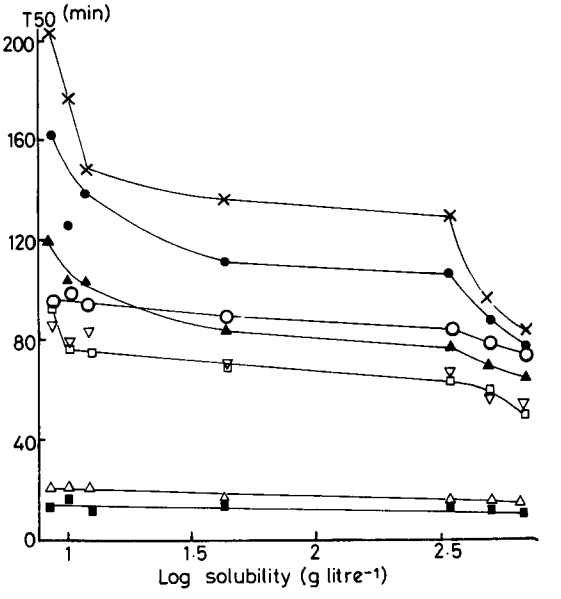

FIG. 3. The relationship between the apparent solubility of acetylsalicylic acid at different pH values and its in-vitro release from hard gelatin capsules (T50), containing different particle size fractions of drug. Symbols as Fig. 2.

A significant factor in the dissolution process is the saturation solubility of the drug in the dissolution fluid, which in the present system will be pH-dependent. The influence of solubility on the dissolution can be seen in Fig. 3 where the value of T50 is shown as a function of the apparent solubility, for

of the test conditions and the dosage form. Usually the percentage of drug dissolved as a function of time, in most dissolution test procedures, is non-linear. Thus representation of dissolution by a T50 value will not characterize the whole process, but merely provide a single value by which formulations

may be compared. To obtain an improved characterization the ability to express the quantity released as a function of time would provide an improved characterization of the dissolution process plus a possible insight into the mechanism of the dissolution.

In the present experiments it was found in certain instances that the percentage of drug released was a linear function of time. This linear relationship was shown by capsules containing particles with median number/length diameters of 45·5, 100, 130, 220, 330 and 430 μm. The release of acetylsalicylic acid from capsules in these cases can be considered to follow apparent zero order kinetics over the time studied. Fig. 5 shows the dissolution rates of acetylsalicylic acid capsules determined by using linear regression analysis, as a function of pH. The dissolution rate is clearly pH-dependent but not in a completely regular manner. Although dissolution rate is particle size-dependent, again there is no regular order of dependence. For capsules filled with micronized powder, median number/length particle diameters 5·5 and 2·5 μm, the percentage release time relationship was not linear over the time studied, which suggests that a different mechanism controls the dissolution process.

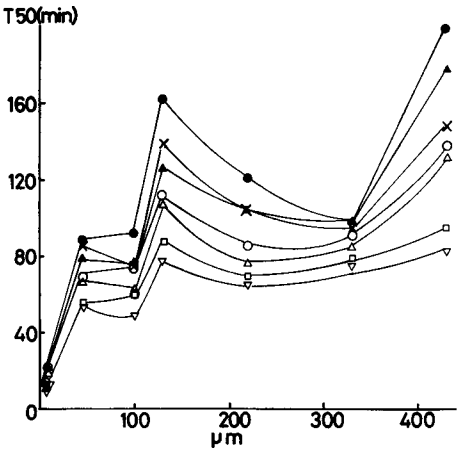

FIG. 4. The influence of particle size of acetylsalicylic acid on its in-vitro release (T50) from hard gelatin capsules in dissolution fluids pH: 1·2, X; 2·0, ●; 3·0, ▲; 4·0, ○; 5·0, △; 6·0, □ and 7·0, ▽.

The high release rate for capsules containing micronized drug is in contrast to the trend of reduction of drug release with particle size observed with capsules containing acetylsalicylic acid (Newton & Bader 1980) and capsules containing ethinamate (Newton & Rowley 1970). In the present experimental systems it was observed that after disintegration of the capsule, powder aggregates floated to the surface of the dissolution fluid due to the presence of entrapped air. This allowed dissolution to take place from the surface and within the beaker and appears to allow access of the dissolution fluid to the greater surface area of the fine particles, which apparently did not occur in the previous systems. To examine the kinetics of the dissolution process of capsules containing micronized drug, the log of the percentage undissolved in the capsule was plotted as a function of time, i.e. an apparent first order process. A linear relationship was obtained indicating an apparent first order process.

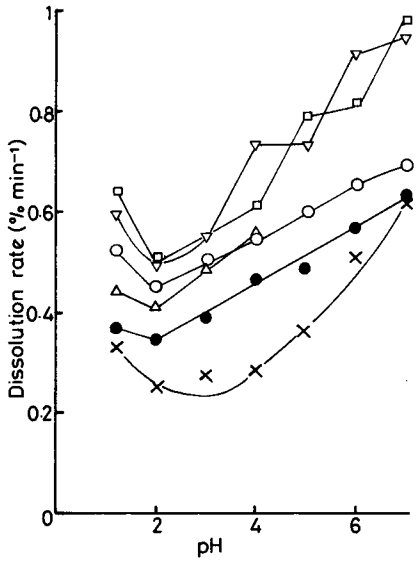

FIG. 5. The influence of pH on the in-vitro zero order dissolution rate of different particle size fractions of acetylsalicylic acid from hard gelatin capsules. Symbols as Fig. 2.

It has been suggested by Wagner (1969) that pharmaceutical dosage forms which show first order dissolution kinetics have a system in which the rate of solution exceeds the rate of generation of new surface and that there is an exponential decay in surface area and hence rate of dissolution. The zero order process observed with the larger particle size implies a constant surface area available for dissolution and suggests therefore that the rate of loss of surface by dissolution is matched by the rate of creation of surface by some mechanism other than

dissolution. The rate of generation of surface is associated with the deaggregation of particles which is controlled by the particle/particle adhesion and the forces of dispersion induced by the agitation procedure.

The results indicate, therefore, that even under conditions which provide large changes in drug solubility, this is not the only factor that controls the in-vitro release of drug from hard gelatin capsules. This is also likely to be true of the in-vivo situation where differences in physical environment are likely to be even more diverse.

REFERENCES

Altman, P. L. (1961) in: Ditter, D. S. (ed.) Blood and other body fluids. Biological Handbooks, Federation of American Societies for Experimental Biology, Washington D.C., pp 416–417

Brice, G. W., Hammer, F. H. (1969) J.A.M.A. 208: 1189–1190

Britton, H. T. (1958) Hydrogen ion Vol. I, D. Van Nostrand, New York, p. 368

Dotevall, G. (1961) Acta. Med. Scand. 170: 56–69

Glasko, A. J., Kinkel, A. W., Algenani, W. C., Holmes, B. D. (1968) Clin. Pharmacol. Ther. 9: 472–483

Khalil, S. A., Ali, L. M. M. (1972) Acta Pharm. Suec. 9: 563–572

Levy, G., Hayes, B. A. (1960) New Eng. J. Med. 262: 1053–1058

Newton, J. M., Bader, F. (1980) J. Pharm. Pharmacol. 32: 167–171

Newton, J. M., Razzo, F. N. (1974) Ibid. 26 Suppl.: 30P–36P

Newton, J. M., Razzo, F. N. (1977) Ibid. 29: 205–208

Newton, J. M., Rowley, G. (1970) Ibid. 22 Suppl.: 163S–168S

Newton, J. M., Rowley, G., Tornblom, J-F. V. (1971a) Ibid. 23: 452–453

Newton, J. M., Rowley, G., Tornblom, J-F. V. (1971b) Ibid. 23 Suppl.: 156S–160S

Samyn, J. C., Jung, W. L. (1970) J. Pharm. Sci. 59: 169–175

Wagner, J. G. (1969) Ibid. 58: 1253–1257

Withey, R. J., Mainville, C. A. (1969) Ibid. 1120–1126