The influence of drug and diluent particle size on the in vitro release of drug from hard gelatin capsules

J. M. NEWTON* AND F. BADER**

Department of Pharmacy, Chelsea College, London University, Manresa Road, London SW3 6LX* and Department of Pharmacy, Nottingham University, Nottingham,** U.K.

The in vitro release of a drug from capsules containing different proportions of controlled particle size fractions of acetylsalicylic acid and lactose, has been assessed in terms of the time for 50% of the drug content of the capsule to be released into solution during a dissolution test (T50), and by a standard disintegration test. In general the two types of test gave closely related responses although some discrepancies existed with certain systems. For capsules containing only the drug, the value of T50 increased as the particle size of the drug decreased. The addition of lactose generally reduced the T50 value, the extent of the reduction showing greater dependence on the proportion of lactose added than its particle size. Capsule formulations containing 80% w/w of lactose had values of T50 which were independent of drug or diluent particle size. Capsule formulations containing lower proportions of lactose usually had an optimum combination of particle size fractions of drug and diluent for maximum drug release. The relationship between drug release and the porosity within the capsule was dependent on the particle size of the drug.

The release of drugs from hard gelatin capsules has been shown to be dependent on such factors as the type of drug, the particle size of the drug, the preparation and type of various additives, such as diluents, lubricants, wetting agents and the way in which the capsules are filled (Newton 1972). The factors are related in a complex manner as a number of rate-limiting processes appear to be involved in drug release. For capsules containing only a drug, the particle size and its degree of consolidation was shown to be the controlling feature (Newton & Rowley 1970). The next stage in increasing complicity is the addition of a second component, and as a diluent is the most commonly used additive, this was chosen as the second component in this study. The model diluent used was lactose while acetylsalicylic acid was the model drug.

MATERIALS AND METHODS

Materials

The acetylsalicylic acid was B.P. crystalline grade obtained from Monsanto Chemicals Limited. The initial particle size of the sample exceeded 353 μm and therefore to obtain a range of particle sizes, down to $-125 +90$ μm, the original crystals were ball milled, then sieved to obtain a range of particle size fractions. For a size fraction in the sieve range $-90 +63$ μm, the smallest size fraction from

* Correspondence.

ball milling was subjected to vibratory milling (McCrone Vibratory mill). 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. The size fractions of lactose were obtained by sieving a sample of B.P. quality, Whey Products, regular grade. Again number/length median diameter was determined for each particle size fraction by microscope counting.

Methods

Capsule filling. The size 1 opaque white capsules (Elanco) were filled by the method described by Newton & Razzo (1974). This method provides the filling of the shell under conditions in which a maximum tapped bulk density is obtained. The various combinations of acetylsalicylic acid and lactose were prepared by hand blending, followed by rotation in a horizontal cylinder at 60 rev min^{-1} for 15 min.

Determination of apparent porosity within the capsule. The apparent particle density of each particle size fraction of drug and diluent and of each of the powder blends was determined with a Beckman air pycnometer. The apparent porosity was calculated from this value, the weight of powder within the capsule, and the volume of the capsule.

Dissolution test. The dissolution test was the modified Levy & Hayes (1960) beaker method described by Newton & Razzo (1974) using a stirring rate of 45

rev min^{-1} and 2 litres of 0·1 M hydrochloric acid as the dissolution fluid with four replicate determinations of each formulation. The content of acetylsalicylic acid in the dissolution fluid was determined by hydrolysing a known sample volume of the dissolution fluid by heating in a boiling water bath for 30 min. The solution was allowed to cool and made up to a known volume before determination of the optical density at 302·5 μm spectrophotometrically. The time for 50% of the drug content of the capsule to appear in the dissolution fluid, T50, was determined from a graph of % of the drug content of the capsule in solution as a function of time.

Disintegration test. The test used a single capsule in each of 5 stations of a B.P. disintegration test apparatus. The end point was taken as that when all the sample had passed through the mesh and values given are the average of the 5 samples.

RESULTS AND DISCUSSION

The experimental design involves the variation of 3 factors: 1. The particle size of acetylsalicylic acid. 2. The particle size of lactose. 3. The relative proportions of acetylsalicylic acid and lactose. There were 6 particle size fractions of acetylsalicylic acid and 4 particle size fractions of lactose. Powder blends were prepared and filled into capsules to provide the capsules which contained each particle size fraction of acetylsalicylic acid and lactose and also capsules containing 20, 40, 60 and 80% w/w of acetylsalicylic acid in lactose. This cannot be considered as a complete factorial design unless the two extremes of 0 and 100% lactose are excluded. The presence of these extremes would not allow all possible combinations of particle size fraction as required by a factorial design. It was considered necessary to obtain these extremes as a basis of comparison.

An estimate of the effects of the 3 factors can be obtained by averaging all results for that factor, for all levels of the other 2 factors, Fig. 1 shows the influence of the particle size of acetylsalicylic acid on the 2 methods of assessing drug release. Two particle size fractions appear to show greatest resistance to drug release as indicated by the T50 value. The two methods of assessment do not correspond for all particle size fractions. Fig. 2 illustrates that, on average, the particle size of lactose used as the diluent is not an important factor in drug release. The proportion of lactose, however, shows considerable effect, Fig. 3. As the quantity of lactose present increases, so does the drug release, as indicated by both dissolution and disintegration. The averaging of results in this manner can cause problems if the
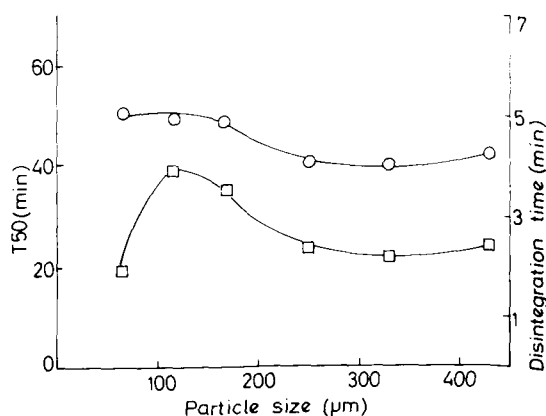

Fig. 1. Overall average effect of the particle size of acetylsalicylic acid on in vitro drug release. □ T50. ○ Disintegration time.

factors interact. As this is a strong possibility it could help to look more closely at the individual results for each factor at different levels of the other factor.

The results illustrating the influence of the particle size of acetylsalicylic acid on the value of T50 and the disintegration time are shown in Fig. 4. The decrease in the value of T50 as the particle size increases confirms the previous findings of Newton & Rowley (1970) for single component systems. Thus it appears even at the maximum tapped bulk density, the fine particles agglomerate to prevent access of the dissolution fluid to the total surface area available. The porosity within the capsules, also shown in Fig. 4, indicates that the smaller particle size fractions provide a more porous system within the capsule. Porosity only represents the total voidage of this system and although porosity is here seen to increase with a decrease in particle size, it is likely that the
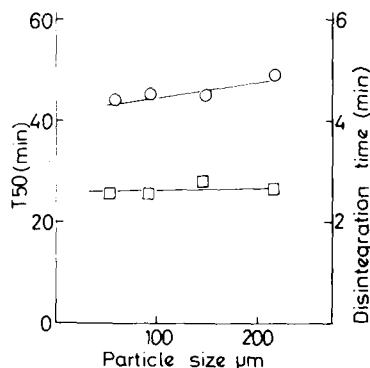

Fig. 2. Overall average effect of the particle size of lactose on in vitro drug release. □ T50. ○ Disintegration time.
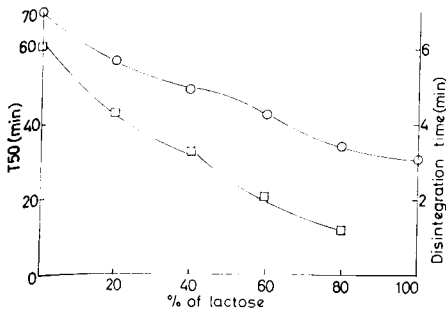
FIG. 3. Overall average effect of the proportion of lactose on in vitro drug release. □ T50. ○ Disintegration time.

dimensions of the space between the particles is much less when smaller particles are packed in the capsules. Hence, it appears that this increased porosity is not available to the dissolution fluid. The results for disintegration, Fig. 4, illustrate that the smaller particle size fractions are more difficult to break down, resulting in the extended T50 values.

The effect of including various proportions of lactose of different particle size fractions on the T50 value of capsules containing different particle size fractions of acetylsalicylic acid is shown in Fig. 5. With only 20% lactose present (Fig. 5a) there is a varying effect, depending on the particle size fraction
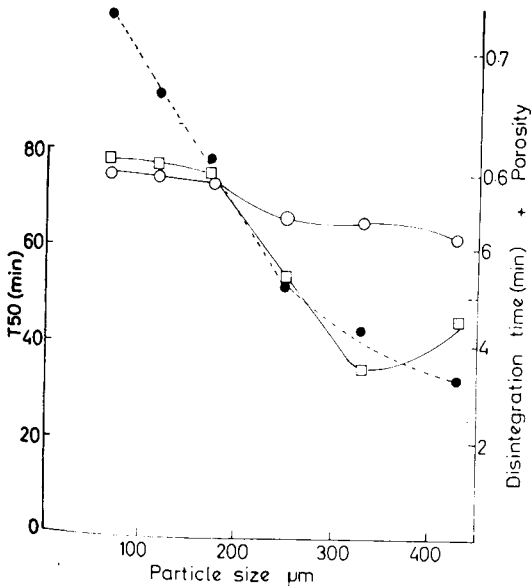

FIG. 4. Effect of the particle size of acetylsalicylic acid on in vitro drug release and powder porosity in the absence of lactose. □ T50. ○ Disintegration time. ● Porosity.
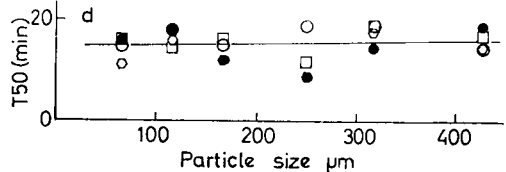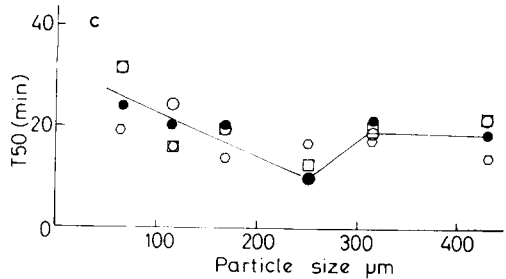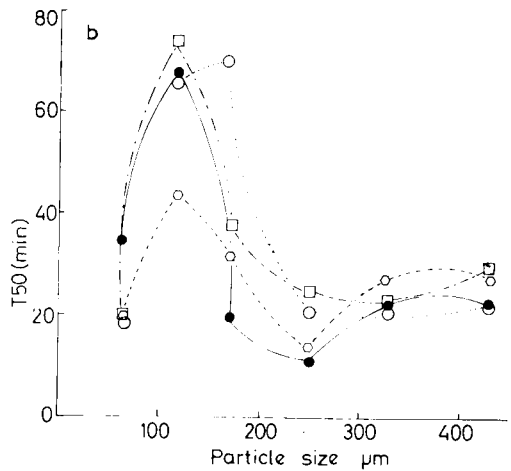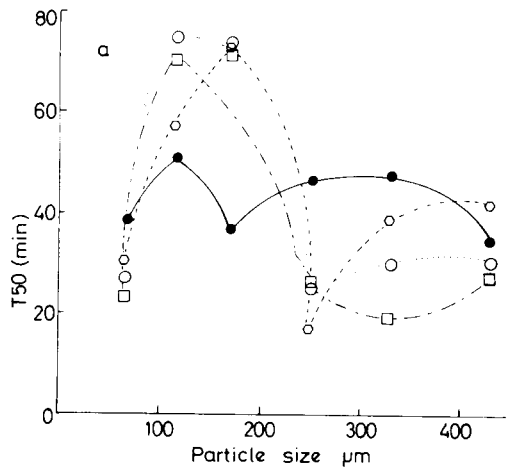

FIG. 5. Effect of the particle size of acetylsalicylic acid on the in vitro dissolution of drug from capsules in the presence of (a) 20%, (b) 40%, (c) 60%, and (d) 80% of lactose. Lactose particle size: 217 μm ○. 150 μm □. 94 μm ●. 65 μm ◯.

of lactose. Except for two smaller particle size fractions of acetylsalicylic acid mixed with the two larger particle size fractions of lactose, there is generally an improvement in drug release. It appears somewhat surprising that incorporation of lactose is capable of improving the accessibility of the dissolution media to the smallest particle size fraction of drug yet does not assist the next two larger particle size fractions. It would appear therefore that accessibility of fluid is not the only feature of the dissolution process. As the lactose content increases to 40% (Fig. 5b) there is a general improvement in drug release from the capsules containing the larger particle size fractions of the drug. The difficulty in obtaining good drug release from the 115 μm median diameter acetylsalicylic acid remains. With further increase in lactose content to 60% (Fig. 5c) and then 80% (Fig. 5d) drug release is further improved until it appears impossible to distinguish between the different particle size fractions of drug and diluent. The choice of which diluent particle size to use in formulations containing less than 60% of lactose would vary with the acetylsalicylic acid particle size and also the proportion of lactose. For larger and the smallest particle size fractions of drug, the 125 μm diameter lactose is better when 20% lactose is used, but the 90 μm diameter lactose is better for those drug sizes if 40% lactose is present. For intermediate particle size fractions of drug, it would appear preferable to incorporate one of the two smaller particle size fractions of lactose.

An important feature of the capsule filling process is how the presence of the diluent influences the packing of the particles. As observed in Fig. 4 the drug release of the single component capsule decreases as the porosity increases. If the drug release, as indicated by the T50 value, is plotted as a function of the porosity within the capsules when varying proportions and particle size fractions of lactose are incorporated, for each particle size of acetylsalicylic acid there is linear relationship (statistically significant at the 5% level) between the value of T50 and the apparent porosity of the powder bed within the capsule. The nature of this relationship is dependent on particle size of the drug, Fig. 6. In the case of the smallest acetylsalicylic acid size fraction, there was a significant difference between the blends containing the smallest particle size fraction of lactose, hence this is shown separately from the other blends. For all other particle sizes of drug, a common regression line was obtained for all the particle size fractions of lactose. For the two largest particle size fractions of acetylsalicylic acid,
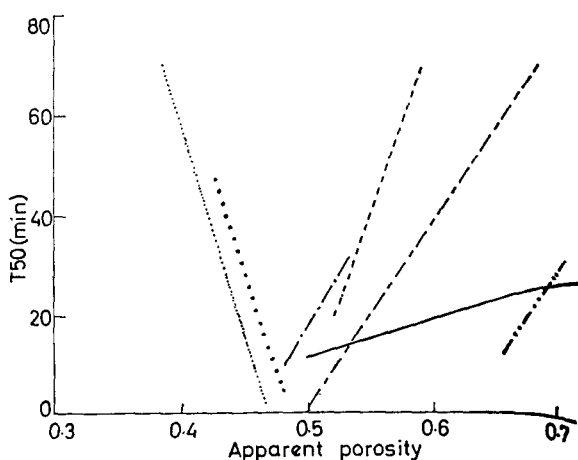

FIG. 6. In vitro dissolution of acetylsalicylic acid as a function of the apparent porosity within the capsules. The linear regression lines are for mixtures of varying proportions and particle sizes of lactose mixed with acetylsalicylic acid of median particle diameter ········· 430 μm, ●●●● 330 μm, ——·—— 250 μm, ———— 170 μm, ——————————— 117 μm, ———— 64 μm (with 3 particle size fractions of lactose), ——·——·· 64 μm with 65 μm particle size fraction of lactose.

the drug release increases as the apparent porosity increases. For the four remaining particle size fractions, the reverse is true, i.e. increasing porosity results in a decrease in drug release. The extent of the change varies with the drug particle size, as shown by the differing slopes. The changes in relationship are associated with a different range of apparent porosity values and it is probable that not only is the overall porosity different but so is the nature of the space between the particles. For the larger particles, the dissolution fluid is presumably less able to penetrate the tightly packed system, whereas an alternative phenomenon occurs with the smaller particle sizes of the drug. These results suggest that for the smaller particle size fractions of acetylsalicylic acid, the presence of lactose alters the basic mechanism of access of the fluid to the drug particles and their subsequent break up. For the larger drug particle size fractions, however, the presence of lactose does not appear to alter the system to one in which the drug release is related to the degree of close packing of the particles in the powder bed.

A further insight into the possible control of drug release from these systems can be obtained by a consideration of the disintegration times. Although the variation in the values of disintegration time was not as large as anticipated, there is a significant linear correlation between the T50 value and the disintegra-

tion time, for each particle size fraction of acetylsalicylic acid mixed with the varying proportions of the four size fractions of lactose, Fig. 7. The relationship for capsules containing the smallest particle size fraction of drug shows an increase in the value of T50 with increasing disintegration time, for all combinations of drug and diluent. For capsules containing the
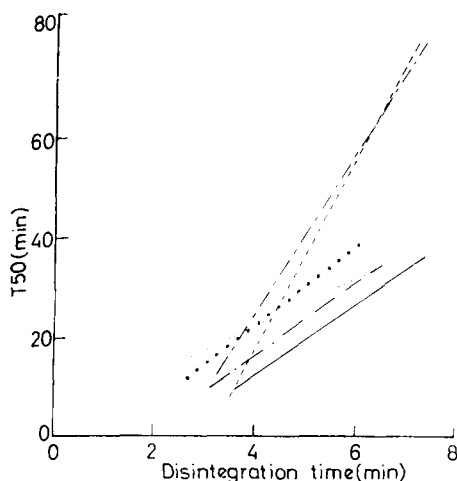

FIG. 7. The relationship between dissolution and disintegration of capsules containing varying proportions of acetylsalicylic acid and lactose. The linear regression lines are for mixtures of varying proportions and particle sizes of lactose mixed with acetylsalicylic acid of median particles diameter of · · · · · 430 μm, ●●●● 330 μm, —— · —— 250 μm, – – – 170 μm —— – —— 115 μm, ———— 64 μm.

next larger size of acetylsalicylic acid i.e. 115 and 170 μm there is a larger variation in the T50 values for similar changes in disintegration time. These two size fractions of acetylsalicylic acid proved to be the

size range which was the most difficult to ensure drug release, and it would appear that this difficulty is not related to the ability of the capsules to disintegrate. For capsules containing the next two larger particle size fraction of drug i.e. 250 and 330 μm the relationship between T50 and disintegration time, is similar in the rate of change of T50 with disintegration time to that which exists for the smallest size fraction of drug. For the capsules containing the largest particle size of drug, changes in disintegration produce the smallest changes in the T50 value for any drug particle size. These results imply that disintegration varies in its control of the dissolution process for different particle size fractions of drug in the presence of differing proportions and particle sizes of lactose.

The results presented here clearly show that the addition of a second component, in the form of the diluent lactose, to a drug in a capsule can change the mechanism and hence the pattern of drug release. In the present case, the change in mechanism appears more closely associated with the particle size of the drug than that of the diluent, if drug release is judged by dissolution characteristics. It appears possible to overcome the inherent resistance of all particle size fractions of this drug to dissolution from a capsule if sufficient lactose can be incorporated into the formulation. The effect is not solely related to ensuring disintegration of the powder mass.

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