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The angle of internal flow as an indicator of filling and drug release properties of capsule formulations

J. M. NEWTON* AND F. BADER†

The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, †Department of Pharmacy, University of Nottingham, Nottingham NG7 2RD, UK

The cohesiveness of size fractions of acetylsalicylic acid and lactose alone and in various combinations has been determined by estimation of the rate of decrease in volume as a function of tamping under standard conditions. The cohesiveness was quantified in terms of empirically derived characteristic, the angle of internal flow φ. The value of φ was found to decrease with the particle size of acetylsalicylic acid, but not lactose, and was found to be dependent on the relative proportion and particle sizes of acetylsalicylic acid and lactose when blends of powder were studied. The value of the time for 50% of the drug content to be released from a hard gelatin capsule in an in-vitro dissolution test, T50, was found to decrease with decreasing values of φ for capsules containing acetylsalicylic acid alone. For capsules containing powder blends there was no consistent relationship between the value of T50 and φ.

The characterization of blends of powders to provide an indication of their ability to fill into and be released from hard gelatin capsules, presents problems for the formulator. For single component systems filling performance of hard gelatin capsules has been shown to depend on the particle size and extent of consolidation used in the filling process (e.g. Newton & Rowley 1970; Jolliffe & Newton 1982b). For multi-component systems, the particle size of each component and their relative proportions influence the filling (Newton & Bader 1981) and release (Newton & Bader 1980). The characterization of flow properties of powders by shear cell techniques does offer a theoretical and practical approach to the characterization of powders for filling by the dosator nozzle system (Jolliffe et al 1980; Jolliffe & Newton 1982a) but such studies are time-consuming and subject to some variability. Simple methods of the characterization of powder flow have been considered by Newman (1967) and could be used for capsule formulations, but many require the powders to have some degree of flowability. Verthalis & Pilpel (1976) described a measure of powder flow and packing in terms of the 'angle of internal flow' φ, an empirically derived parameter, from the rate of change of bulk density with tamping. As such the technique is useful in providing an equilibrium value for bulk density of a powder mixture. The question arises as to whether the value of φ derived from the rate of reaching the equilibrium value is also a useful characteristic of powder blends and, in particular, whether it can characterize capsule filling performance.

* Correspondence.

MATERIALS AND METHODS

The six acetylsalicylic and four lactose particle size fractions were those used previously (Newton & Bader 1980). Blends of these samples were prepared with each size fraction of acetylsalicylic acid and each size fraction of lactose to give a 20, 40, 60 and 80% w/w of acetylsalicylic acid in lactose. The volume of 30 g powder placed in a 100 mL measuring cylinder was determined initially and at intervals of 10 tamps, when moved through a vertical distance of 2·5 cm at a rate of 43 taps min^{-1} until no further decrease in volume was noted on additional tamping. From a knowledge of the apparent particle density of the powder blends (determined with a Beckman air comparison pycnometer, Model 920), the porosity ε of the powder beds was derived. The angle of internal flow φ was obtained from a plot of K as a function of the number of tamps, n, where $K = n\varepsilon^2/(1 - \varepsilon)$ and ε is the porosity of the powder bed (Verthalis & Pilpel 1976). The results were obtained from four replicate determinations and provided values with a coefficient of variation of less than 2%. Size 0 hard gelatin capsules were filled with the various powder blends and their in-vitro drug release assessed by the methods described by Newton & Bader (1980).

RESULTS AND DISCUSSION

The extent and rate at which particles pack into an equilibrium position has been shown to be related to their cohesiveness (e.g. Verthalis & Pilpel 1976). In general, the finer the particle, the greater is their cohesiveness, but the size at which the domination of surface as opposed to gravitational forces takes place, is material-dependent. This is illustrated by the results for the angle of internal flow for the size fractions of acetylsalicylic acid and lactose (Fig. 1). The former shows not only greater cohesiveness for a given particle size, but also a greater increase as the particle size decreases. In fact, the value of φ for changes in lactose varies little over the range of sizes studied. This agrees with shear cell measurements where the angle of internal friction for lactose remained constant over the size range covered here (Jolliffe & Newton 1982b). When the results for mixtures of powders are being considered, the experimental design may be viewed as a 6 × 4 × 4 factorial experiment and hence the influence of a given factor can be derived from the average of the results for that factor and the significance of the effects assessed by analysis of variance (Snedecor & Cochrane 1980). The analysis of variance indicated that there were interactions between the factors, preventing exact quantification of the effects. Nevertheless, certain general conclusions may be drawn. Thus the influence of acetylsalicylic acid particle size (F ratio significant at the 1% level), is shown in Fig. 2. As is to be

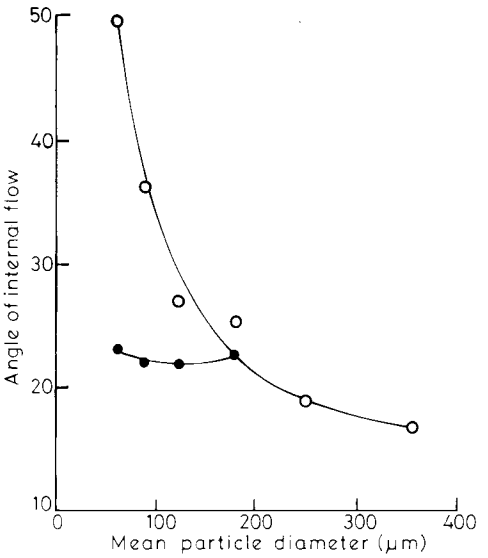

FIG. 1. Angle of internal flow φ of particle size fractions, of acetylsalicylic acid, ○, and lactose, ●.

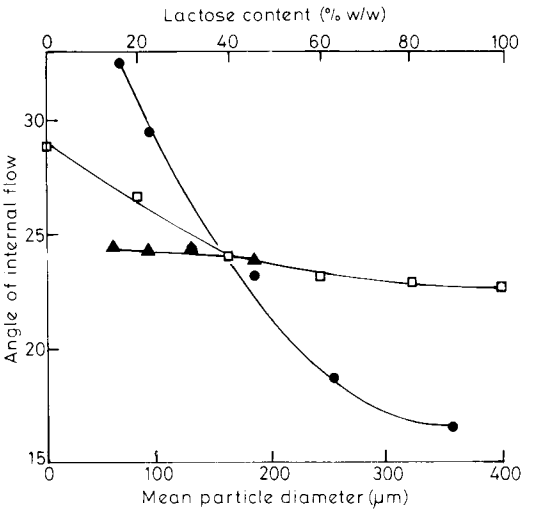

FIG. 2. Overall average value of the angle of internal flow φ of blends of acetylsalicylic acid and lactose averaged as a function of: (a) acetylsalicylic acid particle size, ●, (b) lactose particle size, ▲ and (c) proportion of lactose □.

expected, formulations containing the small particle size fractions of acetylsalicylic acid were generally the most cohesive and had the higher values of φ. The influence of particle size of lactose was not significant (F ratio not significant) and the value of φ for the range of mixtures only changed marginally with particle size (Fig. 2). When considered as a function of the proportion of lactose, the value of φ decreased significantly (F ratio significant at 1% level) as the proportion of lactose increased (Fig. 2). When expressed as individual blend results (Fig. 3), the ability of lactose to change the value of φ, especially for small particle size fractions of acetylsalicylic acid with increased concentration is clearly demonstrated (cf. Fig. 3a, d). Although there is only a small variation in the value of φ for the largest and smallest size fractions of lactose, these two size fractions differed considerably in their ability to reduce the value of φ, and hence the cohesiveness. The smallest size fraction of lactose had much less effect on the smaller size fractions of acetylsalicylic acid, although it did significantly reduce the value of φ for the larger size fractions of drug at 20 and 40% lactose concentrations (cf. Fig. 3a, b).

The final bulk density of the blends achieved is related to the particle size of the components and their relative proportions (Newton & Bader 1981). The relationship between this final value and φ for mixed systems does not appear to have been previously reported. The results in Fig. 4 clearly show for the current powder mixtures that the higher

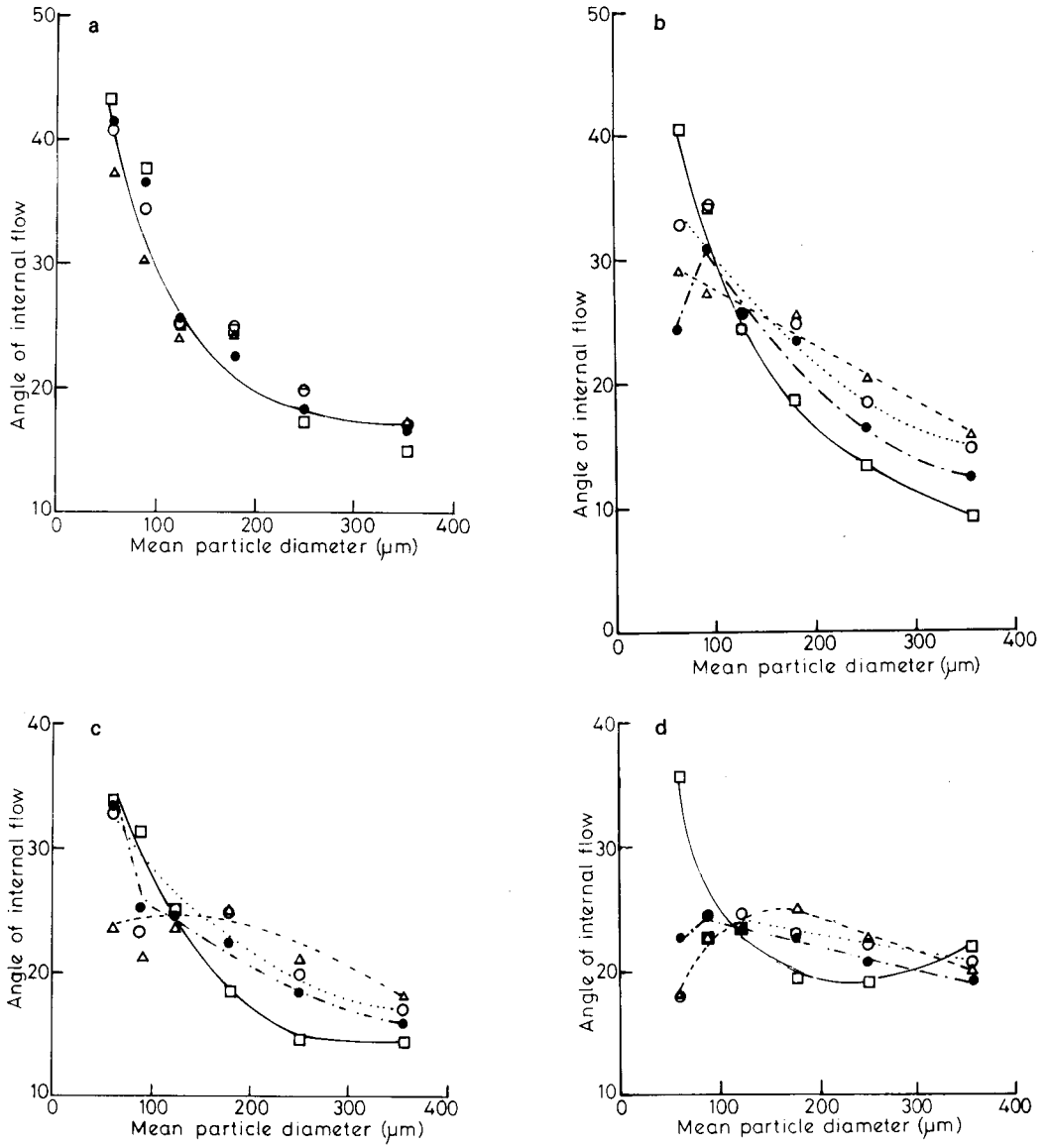

FIG. 3. The influence of particle diameter of acetylsalicylic acid on the angle of internal flow of blends of particle size fractions of acetylsalicylic acid and (a) 20% (b) 40% (c) 60% and (d) 80% lactose. Mean particle diameter of lactose size fractions. 180 μm △——△, 125 μm ○·····○, 90 μm ●—·—●, 63 μm □——□.

the value of φ, the lower the maximum bulk density achievable by tamping. As the maximum bulk density has been found to be related to the capsule fill weight, for capsules filled by tamping, the relationship between the value of φ and capsule fill weight shown in Fig. 5a could be anticipated (correlation coefficient r = 0·98). When the capsules are filled by applying compression to the powder bed, the relationship between φ and the capsule fill weight shows a lower correlation coefficient (r = 0·78) and a lower slope (Fig. 5b). Nevertheless blends with lower values of φ do provide a greater capsule fill weight.

The clear indication the value of φ gives to the cohesiveness of the blends of powders might be an indicator of their drug release properties. It could be anticipated that cohesive formulations would show poor drug release properties. This is supported for

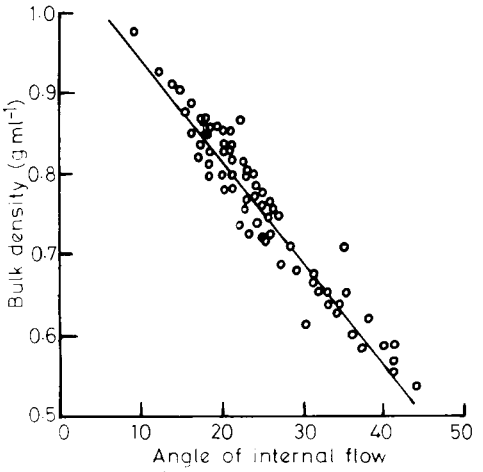

FIG. 4. The relationship between the angle of internal flow φ of blends of particle size fractions of acetylsalicylic acid and lactose and the tapped bulk density.

capsules filled with different particle size fractions of acetylsalicyclic acid alone (Fig. 6). Capsules filled by both simple tamping and compression show the reliance of the value of T50 being greater for the compression filled capsules. However, when blends of powders are considered, the relationship is usually not so clear. Plotting the values of T50 as a function of φ produces a random scattering of points with usually no clear relationship emerging (correlation coefficients never significant). When the results are considered separately for each of the contents of lactose, a pattern does emerge. For high lactose content, i.e. 80%, there are only small variations in the values of both T50 and φ and the results generally are clustered closely together in Fig. 7a for both tamp and compression filled capsules. As the content of lactose decreases, the scatter of results increases from capsules containing 60% (Fig. 7b) to those containing 40% (Fig. 7c) and then 20% (Fig. 7d) lactose. In these latter two systems, i.e. 40 and 20% lactose, quite large variations in the value of T50 can occur for blends which have the same values of φ and there appears to be no specific relationship. It would appear, therefore, that for blends which are dominated by the properties of a swamping effect of lactose, the drug release is not controlled by the cohesiveness of the blend. When there is sufficient lactose present to reduce the value of φ, the drug release may not be enhanced. Similarly, even when insufficient lactose has been added to reduce the value of φ, the drug release may be improved by its presence. The results appear, therefore, to indicate that determination of φ alone cannot provide a reliable indicator of the drug release from capsule formulations of mixed components. Nevertheless the relationship between the value of φ and the capsule

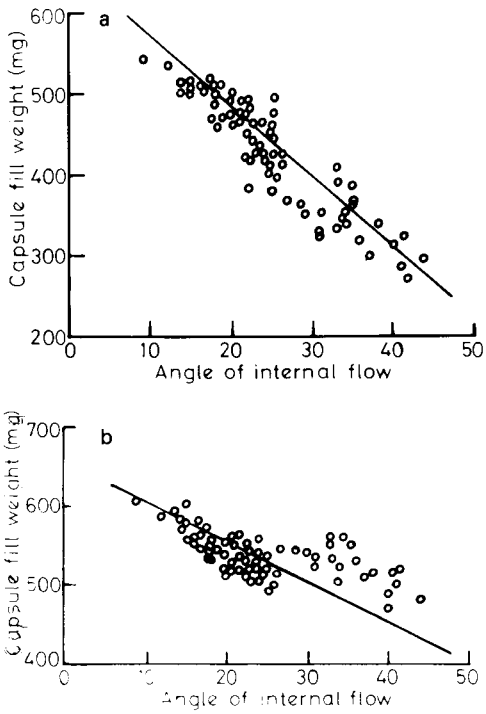

FIG. 5. The relationship between the angle of internal flow φ and the fill weight of capsules containing blends of particle size fractions of acetylsalicylic acid and lactose for capsules filled by (a) tamping (b) compression.

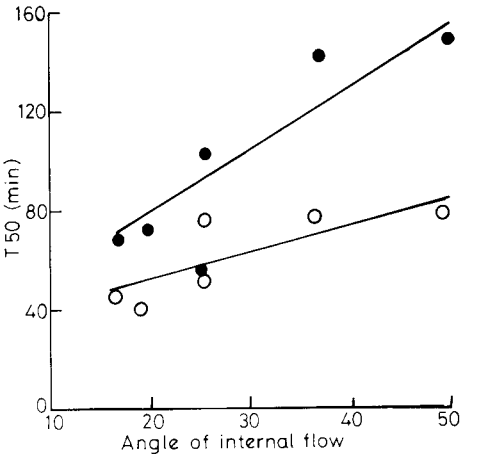

FIG. 6. The in-vitro release, T50, of capsules filled with particle size fractions of acetylsalicylic acid by tamping ○ and compression ●.

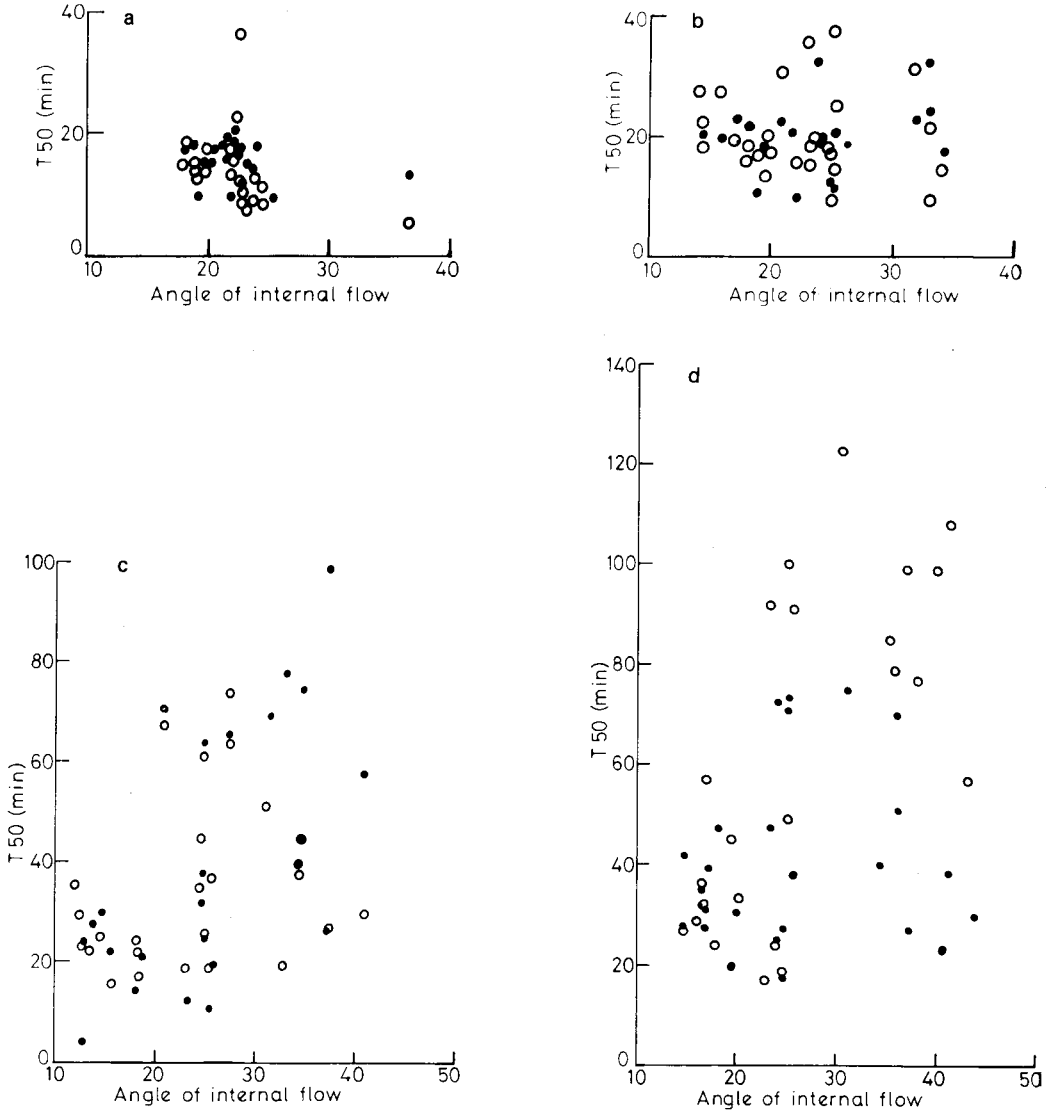

FIG. 7. The Scatter diagrams for the relationship between the angle of internal flow φ and the in-vitro drug release, T50 for capsules containing blends of particle size fractions of acetylsalicylic acid and (a) 80%, (b) 40%, (c) 60% and (d) 20% lactose. Capsules filled by tamping ○ and compression ●.

filling performance does represent a worthwhile measurement, which can be made readily.

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