Interpretation of dissolution rate maxima: dependence upon tablet compression force

The relation between the dissolution rates of drugs from tablets and the force used to compress the tablets has not been well defined. Studies in this area have provided a variety of results which have not led to a simple or straightforward interpretation. Jacob & Plein (1968) demonstrated that the dissolution rates of several phenobarbitone tablets decreased with increasing tablet hardness. In a study of phenindione tablets by Ganderton, Hadgraft & others (1967) at least one maximum in the dissolution rate as a function of compression force was reported for each formula studied. Yen (1964) studied several formulations of Triamterene tablets. Both maxima and minima in the dissolution rates as a function of tablet hardness may be noted in his data. Armstrong & Griffiths (1970) measured the specific surface area of compacts of several different granulations as a function of compression force and found that maxima existed in this function for each of these granulations. This demonstrates the existence of a non-linear relation between force and the ratio of bonding to cleavage occurring during the compression event.

Non-linear data of this type are frequently described as complex because they do not lend themselves to a simple mechanistic interpretation. We suggest that one of the more logical interpretations of these data is in terms of dissolution dependency upon changes in particle size or specific surface area during tablet compression. When particle bonding is the predominating phenomenon during the compression event, dissolution rates should diminish. When, at another compression force, particle cleavage is predominant, the dissolution rate would increase. Further, the ratio of bonding to cleavage would not be linearly related to the compression force. Because of the scarcity of data to support this thesis, and of the possibility that some other phenomena occurring during compression might be responsible for the observed dissolution behaviour, there has been no general recognition of this possible explanation.

We have set out to directly assess the roles of tablet hardness, compression force used and resulting dissolution characteristics using Li_2CO_3 as the drug of choice with various concentrations of polyvinylpyrrolidone (PVP) as binder.

Tablets were prepared by fluid granulating the solid with six concentrations of PVP in ethanol. The basic formula was 300 mg of Li_2CO_3, 80 mg of lactose, 60 mg of corn starch and 5 mg of magnesium stearate per tablet. The PVP solutions were of a strength that provided tablet granulations containing from 4 to 16 mg of PVP per tablet. Each of the granulations was compressed using standard concave 7/16 inch punches on a Model F Stokes Machine maintaining constant tablet weight over a range of compression settings. This produced a series of tablets with constant weights and varying thicknesses for each of the binder concentrations. Tablet thickness is used as an inverse measure of tablet compression force.

Dissolution rates of batches of six tablets for each of the tablet series were determined in 0·1N HCl according to the USP XVIII. The rotational speed was 100 rev/min. Samples were collected every 2 min for 2 h and assayed for lithium. Thickness was measured with a micrometer. Hardness was determined as the crushing force with the Stokes Hardness Tester.

Dissolution curves, obtained by plotting the amount of Li_2CO_3 dissolved as a function of time, resulted in smooth lines for all tablets. The mg of Li_2CO_3 dissolved after 20 min was used as a measure of the initial dissolution rate. These rates were plotted as a function of tablet thickness (a measure of compression force) for tablets containing each of the six levels of PVP. The typical plot for the tablets containing 8 mg per tablet of PVP is given in Fig. 1.

These plots exhibited two maxima when sufficient data were available for completely characterizing them between thickness of 0·19 and 0·24 inches. One at lower compression forces (greater thickness) and a second at higher compression forces. It is suggested that the low compression force maxima are related to the structure and crushing characteristics of the granules and, therefore, to the concentration of the PVP binder. Fig. 2 is a plot of the PVP concentration as a function of the tablet

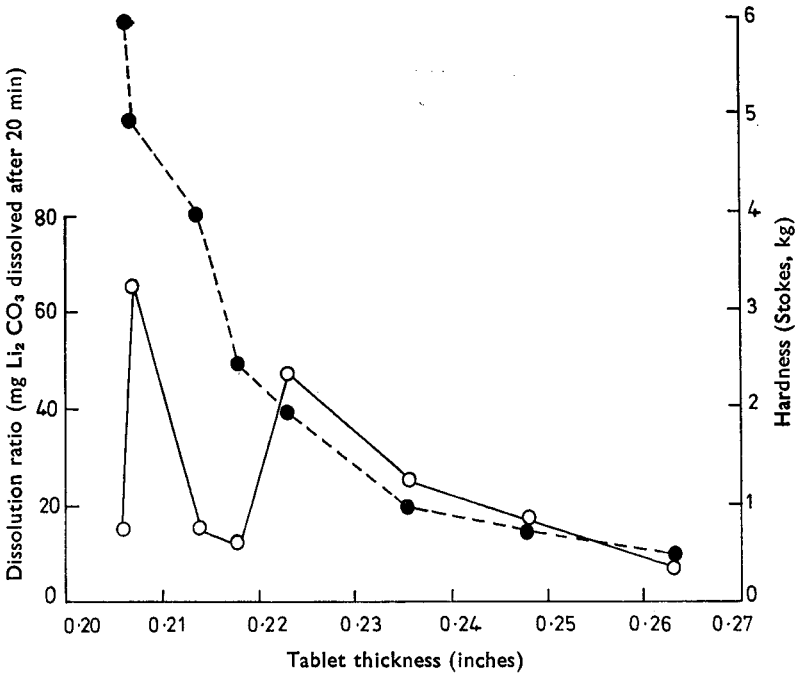
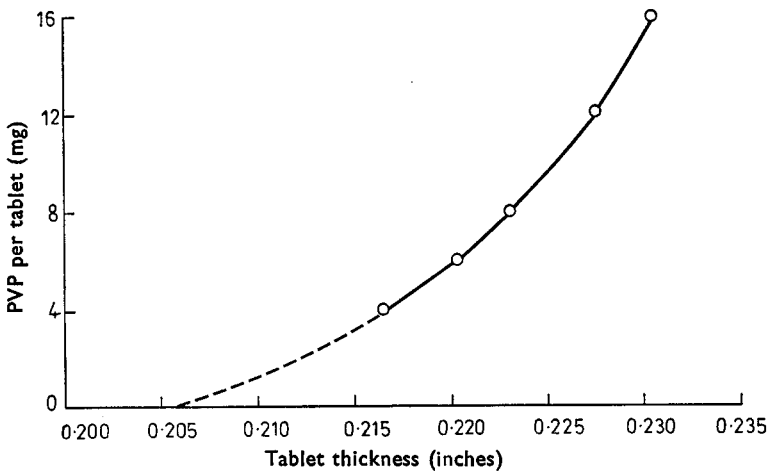


FIG. 1. Dissolution rate (○—○) of Li_2CO_3 tablets containing 8 mg per tablet of PVP as a function of tablet thickness for tablets of constant weight (left-hand scale). Hardness (●—●) of same tablets with varying thickness (right-hand scale),



FIG, 2. Tablet thickness for maximum in dissolution rate (low compression force) for Li_2CO_3 tablets with varying quantities of PVP for tablets of constant weight.

thickness at which the low compression force maxima occurred. Up to this maximum, fission of the granular structure results in increased dissolution release rate with increasing pressure. Further pressure results in a compact fusion or bonding which markedly reduces dissolution rate. At pressures higher again, there is an increased dissolution rate, indicating a new relative dominance of a cleavage component. It is further suggested that the high compression force maxima are related to the inherent compression characteristics of the basic formulation components and, therefore, should be essentially independent of the binder concentration. This holds for the values for the high compression maxima since at concentrations of PVP of 4, 6, 8, 12, 14 and 16 mg/tablet, dissolution rate maxima (expressed as thickness in inches for tablets of constant weight) are respectively: $\leqslant$0·205, $\leqslant$0·203, 0·208, $\leqslant$0·205, 0·208, 0·203 (mean 0·205). It should follow that the value for the low compression maximum should coalesce with that of the high compression maximum at zero concentration of PVP. The dotted line which is extrapolated to zero percent of PVP in Fig. 2 indicates this to be a reasonable assumption.

From Fig. 1 it is apparent that hardness increases as the tablet thickness decreases. The increases are slow in that area of compression that has been cited above as predominately cleavage rather than fusion. Where dissolution rates decrease as a result of fusion becoming the primary process, the hardness rises more rapidly.

From this and, by implication from the cited references, it is apparent that a full compressional study for a given granulation formulation is essential to determine the compression parameters that will assure adequate bioavailability.

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