DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(9&10), 1819-1836 (1985)

THE EFFECT OF RECOMPRESSION ON THE SWELLING KINETICS OF WET MASSED TABLETS, CONTAINING 'SUPER' DISINTEGRANTS

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ABSTRACT

The effect of recompression on the swelling force kinetics of tablets employing a wet massed Avicel matrix and those containing extra-granular super disintegrants has been investigated. Explotab, unlike the Ac-Di-Sol and Polyplasdone XL systems, was found to give a high initial compact swelling force at low tablet porosities, but the rework process reduced the maximal swelling forces for all systems. However, the measured maximal swelling forces did not correlate with tablet disintegration time.

The rate of fluid penetration into the compacts was found to be controlled by tablet porosity but the penetration rates for all disintegrant systems were essentially identical. However the penetration rates for reworked compacts were significantly lower than those for tablets produced by first compression possibly due to the effects of increased lubricant distribution and relubrication causing poorer wettability.

0363-9045/85/1109-1819$3.50/0

Tablet disintegration times were found to correlate with a fluid penetration kinetic function involving lag time and time for 50% tablet swelling. Also, the retention of disintegration efficiency following rework correlated with the retention of the rate of fluid penetration. It is concluded that lubricants can play an important role in the efficiency of compact disintegration following tablet rework.

INTRODUCTION

Disintegrants are used in tablet formulations to promote their dispersion in dissolution fluids[1]. The modern, so called super disintegrants[2] operate by a process of wicking[3] and/or swelling[4]. These disintegrants are effective at low levels[5] and have been shown to improve bioavailability[6].

Many workers have pointed out that both the rate and extent of disintegrant swelling is related to their efficiency[5,7]. List and Muazzam[8,9] related the increase in disintegrant efficiency (De) to a greater swelling force, whereas Gissinger and Stamm[7] concluded that improved De was related to the rate of disintegrant swelling.

Recently we investigated the effect of rework on the De values of wet massed tablets, containing super disintegrants[10]. It was found that rework caused a significant reduction in the De values of the compacts. In this study we report the influence of the rework process on the rate and extent of tablet swelling, and correlate them with the previously reported disintegration data.

MATERIALS

Experimental compound (Pfizer Ltd., UK); Microcrystalline cellulose, Avicel PH101 (Honeywill & Stein Ltd., Surrey, UK);

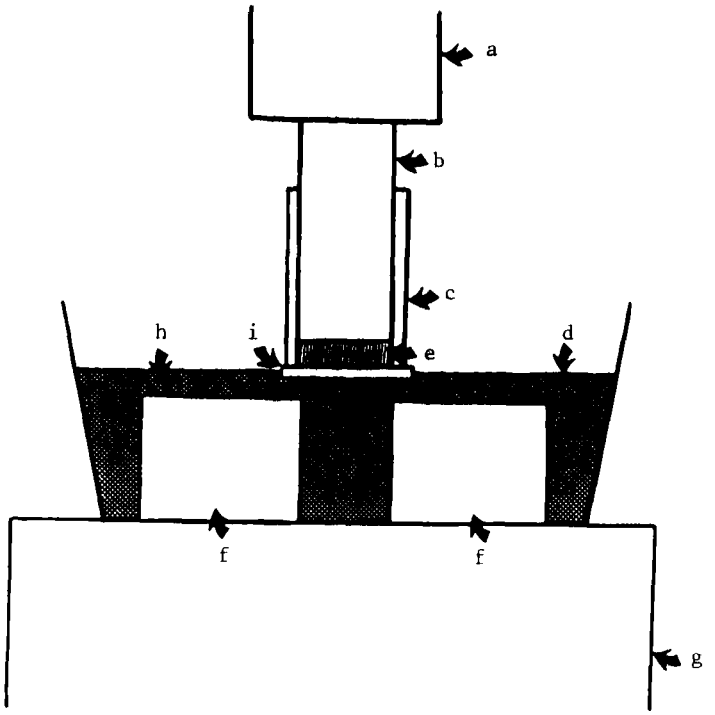

Figure 1

Apparatus for Measurement of Tablet Swelling Force.

(a) upper platen of tensile strength apparatus;
(b) flat faced 10 mm steel punch; (c) 10 mm perspex die;
(d) disintegrating medium; (e) 10 mm tablet under test;
(f) perspex annular ring; (g) lower platen of tensile strength apparatus;
(h) wire gauze, 8#; (i) sintered polypropylene filter

Sodium starch glycollate, Explotab (K&K Greeff, Croydon, UK); Cross-linked polyvinylpyrrolidone, Polyplasdone XL (GAF Chemicals, Manchester, UK); Croscarmellose sodium, Ac-Di-Sol (Honeywill & Stein Ltd., Surrey, UK); Polyvinylpyrrolidone, Kollidon K30 (Blagden Campbell Chem. Ltd., Croydon, UK); Magnesium stearate USP (Durham Raw Materials Ltd., Durham, UK); Sodium lauryl sulphate BP (Marchon Products Ltd., Whitehaven, UK).

METHODS

Measurement of Swelling Force

Water penetration into, and the swelling of tablets is a simultaneous process[11]. Therefore an ability to study the rate and extent of the tablet swelling force was deemed to be important in the design of the apparatus. Gissinger and Stamm[7] developed an apparatus, based on an original design by List and Muazzam[8,9] using a force and displacement transducer to dynamically measure the swelling of powder compacts. We have used an adaptation of this method (Figure 1).

A tablet was loaded into the perspex die and the punch inserted; both punch and tablet exactly fitting the die. This was placed on a sintered polypropylene disc of 17 mm diameter (Godax Labs, USA), and then loaded on the gauze disc (8#, 70 mm diameter) located centrally on a perspex annular ring (40 mm external diameter, 17 mm internal diameter) contained in a perspex beaker on the lower platen of a calibrated tensile strength apparatus (G.B. Caleva, Ascot, UK). The lower platen of the apparatus was then raised to a force of 0.023 kg (0.226N) to ensure contact between the top of the punch and the upper platen. Water was then introduced quickly and uniformly into the beaker and the resultant swelling force phenomenon followed using a chart recorder. All determinations were conducted in duplicate.

Tableting

The disintegrants at 2% were compared extra-granularly with a control (no disintegrant) in a formulation containing Avicel PH101 (59%) and an extremely soluble, plastically deforming experimental compound (33%) that was wet massed with an aqueous binder solution (PVP K30) to give 5% w/w binder in the finished product. All granules were lubricated (5 minutes; Turbula T2) with 1% of a blend of 9 parts magnesium stearate and 1 part sodium lauryl sulphate prior to compression.

Each disintegrant system was tableted using an instrumented single punch tablet press (Manesty, F3) fitted with 10 mm flat faced tooling. Compacts were produced over a range of compaction pressures (CP) from 50 to 250 MPa.

Following characterisation, the tablets were milled (Fitz mill; hammers forward, 0.02" screen) to a fine powder similar to the original blend (<50 μm). They were then wet massed with an identical level of water (50%) to that used before. The resultant granules, which were of the same mean size and size distribution as those produced originally, were relubricated with a further 1% of the lubricant blend and then recompressed.

Tablet Tensile Strength

Tablet crushing strength and hence tensile strength[12] was obtained through single point fracture using a calibrated tensile strength apparatus (G.B. Caleva, Ascot, UK). Tablet tensile strengths varied over the range 0.11-2.98 MPa.

Tablet Porosity

Since all tablets were of the same weight (300 mg) and diameter (10 mm), tablet porosities were deduced from relative

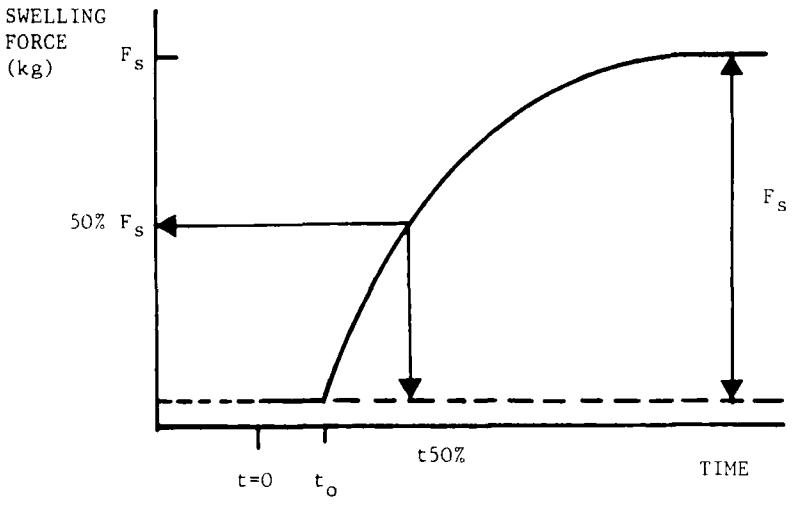

Figure 2

Typical tablet swelling-time profile.
t_o refers to the lag time prior to swelling, F_s to the maximal swelling force and t50% for the time taken to achieve one half this value.

tablet thicknesses. The minimum tablet thicknesses, i.e. at zero porosity, were deduced from the linear relationships between tablet thickness and tensile strength as described by Newton and Grant[13]. Tablet porosities varied over the range 9.4-48.8%.

Disintegration Times

Tablet disintegration times were measured using the BP disintegration test using one tablet per tube with water as the immersion fluid.

RESULTS AND DISCUSSION

A typical swelling profile is shown in Figure 2. Profiles were interpreted in terms of the maximal swelling force, F_s, and

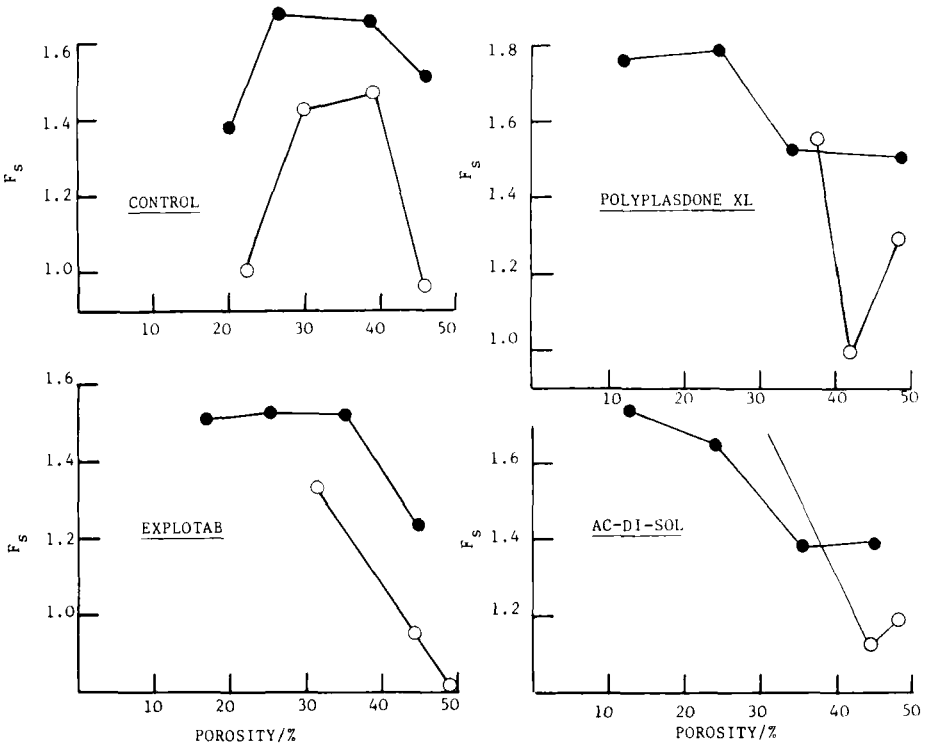

Figure 3

Plot of maximal swelling force (F_s/kg) vs tablet porosity. Closed symbols are tablets on first compression and open symbols for second compression (reworked) tablets.

the time (minutes) taken for one half of the total swelling force to occur (t50%). With some compacts the swelling force was seen to build up immediately, whereas others showed a distinct lag phase presumably associated with the initial wetting of the tablet surface.

The maximal tablet swelling forces are displayed as a function of tablet porosity in Figure 3. The inclusion of disintegrant increases Fs for tablets of low porosity, and the systems containing different disintegrants show slightly different Fs-Porosity profiles. The wicking disintegrants Polyplasdone XL and Ac-Di-Sol produce sigmoidal curves with the value of Fs

slightly greater than the control. The Explotab (swelling disintegrant) system however, quickly reaches a lower but constant Fs value over a wide range of tablet porosities. This indicates that as long as water penetrates the tablet, and as long as the particles are in close proximity, i.e. below ~25% porosity its power as a swelling disintegrant is manifested. The sigmoidal curves for Polyplasdone XL and Ac-Di-Sol arise because tablets of high porosity rapidly wick water[14], but the large pore diameters, and a lack of a swelling component result in only a low swelling force. However, at low porosity (below 25%) the wicking power of these disintegrants maintain effective fluid uptake and allow swelling of the Avicel matrix resulting in a larger swelling force.

However, the Fs values of the compacts are at variance with the disintegration times which decrease exponentially with tablet porosity[10]. This is in accord with the conclusion of Gissinger and Stamm[7] and suggests that tablet swelling force alone does not control tablet disintegration.

One further feature is clearly evident (Figure 3). The Fs values of nearly all systems are reduced by tablet rework (recompression). The greatest reduction in Fs is for tablets relying on the Avicel matrix to assist fluid uptake (Explotab and control), whereas the wicking disintegrant systems have lower Fs values only at high tablet porosities. Table 2 gives the relative swelling forces of tablets at two porosities, 35 and 40%, for tablets produced by first and second compression.

However, the retention of maximal tablet swelling force on rework is converse to their disintegrant rework efficiencies[10] also given in the table. This result again suggests that the disintegration process is not controlled by the final swelling (disintegrating) force produced by the compacts.

TABLE 2

Relative retention of maximal swelling forces (F_s following rework for compacts at two porosities; 35% and 40%

Disintegrant	Relative F_s P = 35%	Relative F_s P = 40%	RE %
Control	0.842	0.848	45
Polyplasdone XL	0.941	0.926	64
Explotab	0.737	0.863	86
Ac-di-sol	1.045	0.951	45

RE = Disintegrant Rework Efficiency (Gould and Tan, ref. 10)
Relative F_s = F_s (2nd compression)/F_s (1st compression)

The swelling velocity of the compacts, presented as the time for 50% of the maximal swelling force (t50%) when plotted against tablet porosity, yielded the linear plots shown in Figure 4. Little difference is seen between the compacts containing the various disintegrants, which show essentially similar rates of swelling to the controls, over the range of compact porosities investigated. This suggests that the Avicel component controls the rate of swelling, with the linearity of the porosity-t50% plots indicating that the swelling rate is controlled by the rate of fluid penetration.

Figure 4 also shows that there are marked differences between the porosity-t50% relationships for reworked tablets over tablets produced by first compression; the rate of penetration of fluid into tablets on first compression at unit porosity being 2.33, 3.90 and 3.09 times the rate for reworked tablets for Ac-Di-Sol, Explotab and Polyplasdone XL compacts respectively.

Since the reduced swelling rates of reworked tablets are not due to differences in the total porosity of compacts on second

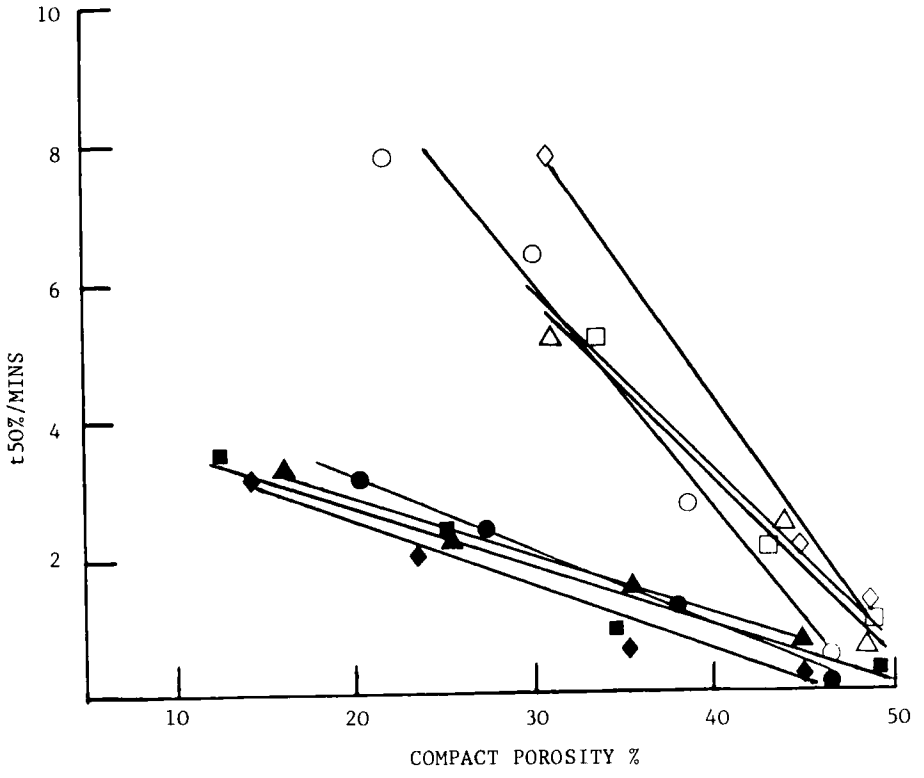

Figure 4

Plot of swelling velocity (t50%) vs. compact porosity for compacts produced on 1st and 2nd compression (rework)

▲ Explotab
△ Explotab-rework
◆ Ac-Di-Sol
◇ Ac-Di-Sol-rework
● Control
○ Control-rework
■ Polyplasdone XL
□ Polyplasdone XL-rework

compression, the differences may be due to impaired wetting of the capillaries that conduct the water into the tablet[15]. The formulations under investigation were lubricated with magnesium stearate, a material well known to render the capillaries in the tablet mass hydrophobic. The effect of the lubricant on the formulation is dependent on its level and distribution by mixing[15]. Thus, the differences in water penetration rates, and hence swelling rates, seen for reworked compacts in Figure 4 are possibly due to the effects of lubricant. The rework process enhances the effect of the lubricant, firstly because the original extra-granular lubricant in the tablet mass undergoes further distribution during the rework process and secondly, by the incorporation of a further 0.9% of magnesium stearate immediately prior to recompression. The deduced pooled slope from Figure 4 for 1st and 2nd compression tablets (0.224 ± 0.014 and 0.077 ± 0.021 respectively), suggests[16] that pore wettability decreases by a factor ~3 (2.9 ± 0.9) on tablet rework.

Although swelling velocity appears dependent on tablet porosity, it might be expected that the rate of tablet swelling is important for tablet rupture[11,17]. In the model system used here, the tablet matrix, i.e. the Avicel, appears to control water penetration, with all disintegrants yielding essentially identical swelling rates at unit porosity. However, tablet disintegration times between disintegrants are significantly different suggesting that the disintegration process is not completely rate-limited by water penetration into the compacts.

The t50% for swelling vs. the logarithm of the tablet disintegration times yields the biphasic plot shown in Figure 5. The first phase covers systems disintegrating in less than ~6 minutes and appears common for tablets produced by 1st and 2nd compression. The latter phase is dominated by reworked tablets having disintegration times greater than 6 minutes. Regression

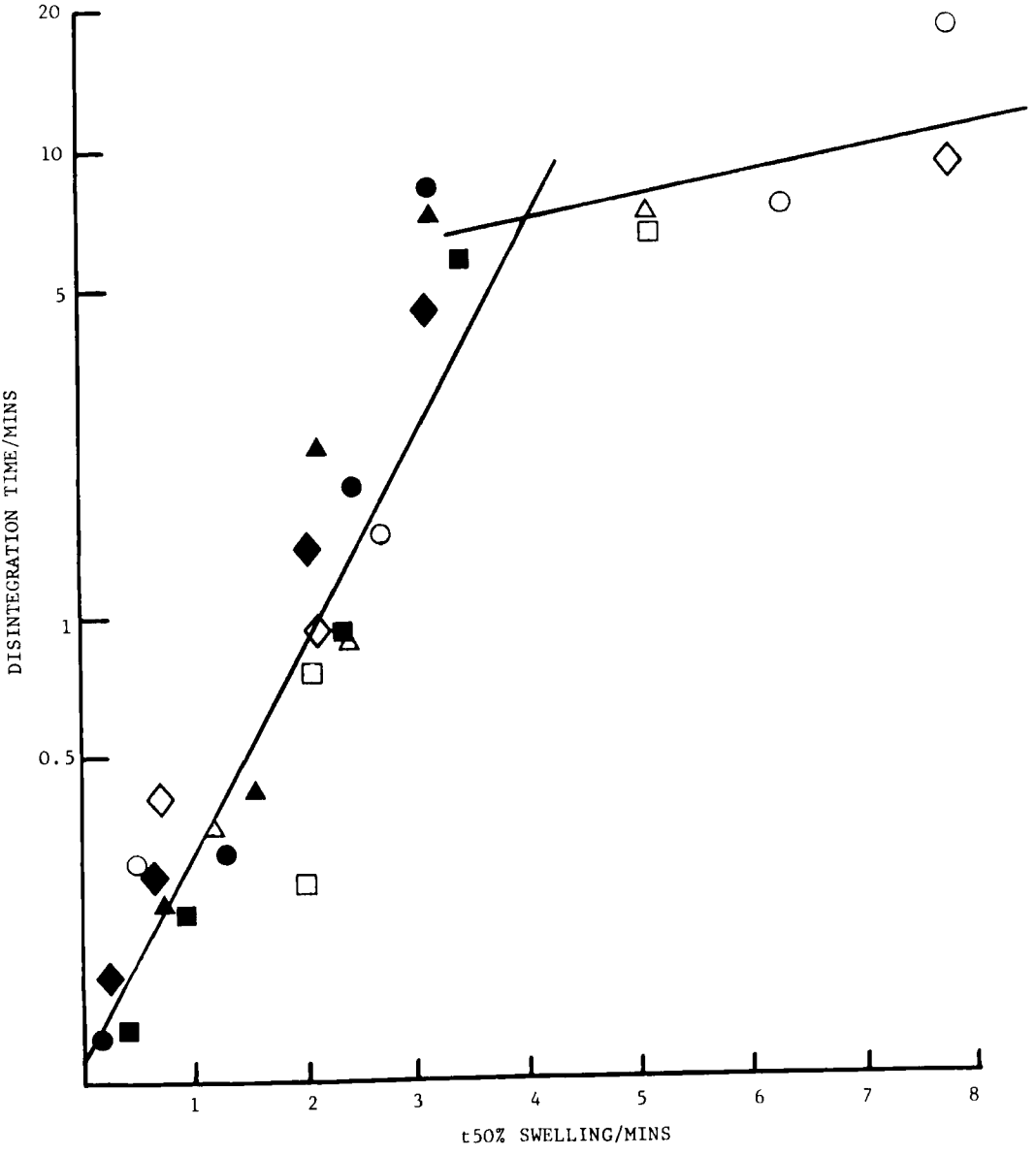

Figure 5

Plot of $\underline{\text{Log}}_{10}$ disintegration time (minutes) vs. t50% swelling for compacts produced on 1st and 2nd compression
Legend as Figure 4.

analysis of the data shows that the slope for the second phase process is ~5-10 times lower than that of the first phase (0.049 ± 0.025 vs. 0.446 ± 0.047). The first phase occurs for disintegration times controlled by initial tablet wetting and rapid fluid penetration caused by high compact porosity and partially lubricant coated capillaries. Analysis of the disintegration time-porosity data suggested that this occurred with compact porosities of >25-30%. The second phase corresponds to compacts with narrow, hydrophobic capillaries which results in impaired wetting, low rates of water penetration and prolonged disintegration times.

Columbo and co-workers[17] have also shown that the rate of generation of the disintegrating (swelling) force determines the disintegration characteristics of the compacts. They correlated, on a logarithmic basis the disintegrating force kinetics, using a composite time function of t63.2% and the lag time prior to generation of the swelling force (t_o), with the disintegration time (DT).

Plotting our data in the form DT vs. (t50% + t_o), (Figure 6) gives an excellent correlation ($r = 0.9368$, $n = 29$, $p < 0.001$) for tablets produced both on first and second compression. This result, which is common for all disintegrant systems, indicates that fluid penetration kinetics dominate the disintegration of the compacts, and that reworking increases tablet disintegration times by lowering the rate at which the tablets wick fluid and swell. The lag times are only significant in the kinetic function for highly porous tablets which disintegrate quickly (<0.5 minutes), suggesting that the initial wetting of the tablet surface limits tablet disintegration. The relationship between the DT and the swelling force kinetics function follows the form

$$DT = -0.672\ (\pm\ 0.068) + [(t_o + t50\%)]^{2.15} \pm 0.15$$

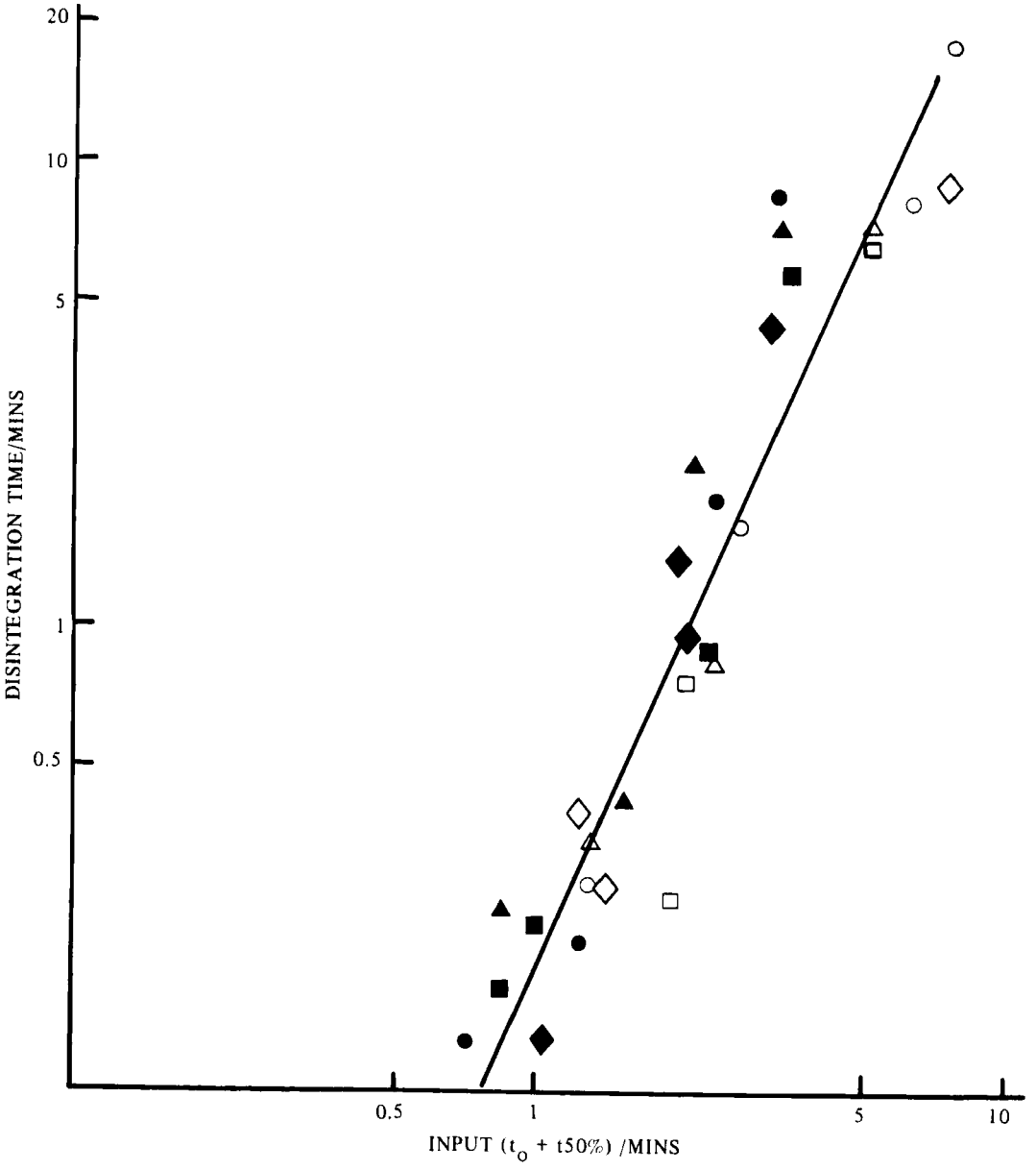

Figure 6

Plot of Log_{10} DT vs Log_{10} (t_o + t50%)

Legend as Figure 4

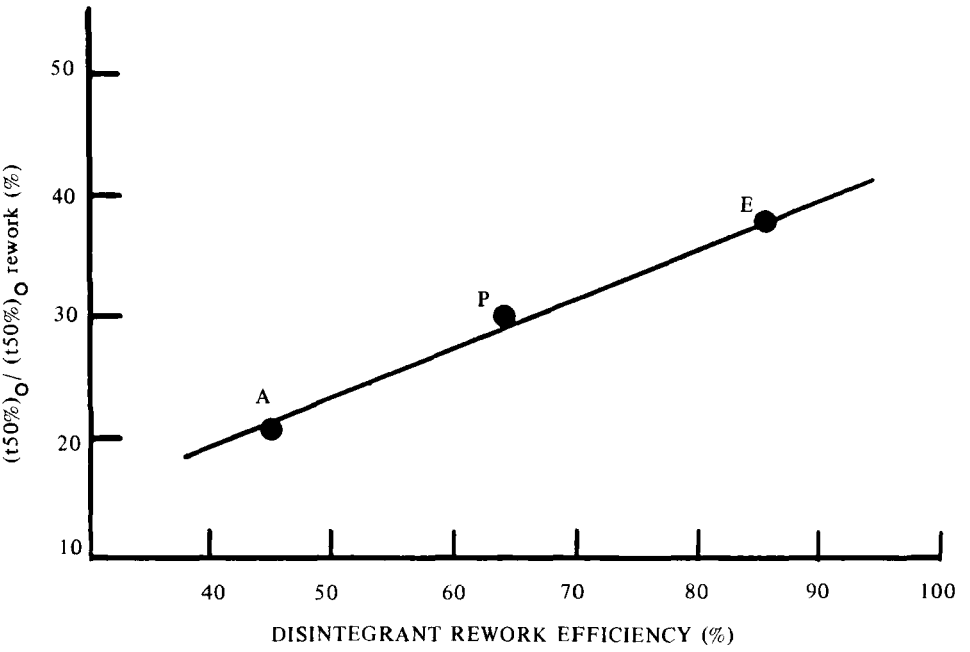

Figure 7

Plot of the percentage ratios of swelling rates at minimum porosities vs. disintegrant rework efficiency (%) for extra-granular polyplasdone XL (P Explotab (E) and Ac-di-sol (A) in standard tablet system

indicating that the reduction in disintegration time of the compacts is proportional to the square of the overall penetration kinetics. This result is consistent with the Washburn equation[14] defining the rate of penetration of fluid into compact(ed) powder beds, and supports the conclusion that the swelling/ disintegration process is largely controlled by the penetration of the fluid into the compacts.

The t50%-Porosity data was then compared under conditions at the minimum rate of water penetration (zero porosity) where the disintegration is potentially controlled by the disintegrant rather than the matrix. The ratio of the respective $(t50\%)_o$

values (the ratio of the intercept values in Figure 4) are plotted against the measured rework disintegrant efficiencies, deduced in our previous work, in Figure 7.

Inspection of the figure shows that there is a good correlation ($r = 0.9971$), $p < 0.05$) indicating that for full retention of disintegrant efficiency, the swelling rate of reworked compacts has to be at least ~44% of that of compacts produced on 1st compression.

CONCLUSION

The maximal swelling force-porosity profiles of compacts in the model tablet system are different for the various disintegrants investigated. Explotab maintains a high compact swelling force at low tablet porosities. However, the rework process in general reduces maximal swelling forces possibly due to comminution, regranulation and recompression[10].

The rate of fluid penetration into tablets is controlled by tablet porosity which is governed by the Avicel matrix, and the penetration rates for all first compression and all second compression tablet systems are similar, irrespective of the disintegrant employed. However the rate of fluid penetration into reworked compacts is significantly lower than for tablets produced by first compression, possibly through poorer wettability due to the effects of lubricant.

Tablet disintegration times correlate, on a logarithmic basis with a fluid penetration kinetic function involving a lag time and a time for 50% tablet swelling. For systems where $t_o \ll t50\%$, i.e. where initial tablet surface wettability is not limiting, this result is consistent with the Washburn equation.

The retention of disintegrant efficiency following rework correlates with the retention of the rate of fluid penetration. This supports the view that lubricants play an important role in tablet disintegration[18,19], and can affect disintegrant rework efficiency by reducing the rate at which they allow fluid to penetrate compacts prior to disintegration. Formulators should consider carefully the effects of lubricants, and indeed the implications of relubrication, on disintegration when reprocessing tablet formulations.

ACKNOWLEDGEMENTS

The authors would like to thank Miss S.L. Darling and Mr. I.L. Smales for technical assistance and Mrs. K.J. Mills for typing the manuscript.

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