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# THE EFFECT OF RECOMPRESSION ON THE DISSOLUTION OF WET MASSED TABLETS CONTAINING 'SUPER' DISINTEGRANTS

Philip L. Gould*+ and Soo Bin Tan$
Pharmaceutical Development Department,
Pfizer Central Research,
Ramsgate Road, Sandwich, Kent, U.K.

*Pharmaceutical Group,
Product Research and Development Laboratories,
Cyanamid of Great Britain Limited, Gosport, Hants, U.K.

$The School of Pharmacy,
The University of London,
29/39 Brunswick Square, London WC1, U.K.

+ Correspondence

## ABSTRACT

The effect of recompression on the disintegration and dissolution of tablets employing 'super' disintegrants within a wet-massed Avicel matrix is reported. Differences were found in the disintegration times of tablets containing intra-granular or extra-granular disintegrants (Polyplasdone XL, Explotab and Ac-di-sol), both between disintegrant type and within the same disintegrant system following rework.

In the case of extra-granular disintegrant, reworked compacts dissolved faster than the first compression tablets, irrespective of disintegrant type. Thus, milling and dispersion of the drug during rework appear to dominate over the effects of impaired disintegration when 'super' disintegrants are present. The control



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compacts (no disintegrant), however, dissolved less quickly following rework, indicating that dissolution was controlled by disintegration.

Tablets with intra-granular Polyplasdone XL and Ac-di-sol dissolved less quickly following rework. Both disintegrants have poor intra-granular rework efficiencies. However, for Explotab, which has better rework intra-granular efficiency, reworked tablets dissolved faster than first compression compacts.

## INTRODUCTION

The dissolution of a wet-massed tablet involves disintegration of the compact to granules which then deaggregate to primary particles. The generation of primary particles, thereby maximising drug surface area, then leads to efficient dissolution of the drug(1).

The modern, so called' super' disintegrants(2), which are added to tablet formulations at low levels(3) can assist tablet dissolution in two ways. Firstly, extra-granular incorporation assists tablet disintegration to granules and secondly, intra-granular incorporation assists granule deaggregation to primary particles. In cases where the rate of primary particle generation rather than particle dissolution is rate determining in the dissolution process, the addition of disintegrants have been shown to improve bio-availability(4).

Recently we investigated the effect of rework on the disintegration times(5) and swelling kinetics(6) of wet-massed tablets containing 'super' disintegrants. The formulation model used was a slowly eroding tablet system employing a high loading of a soluble drug within an insoluble matrix. It was found that rework caused a reduced rate of fluid penetration into and a

significant prolongation of the disintegration times of the compacts. As an extension of those studies we now report the influence of rework on the dissolution kinetics of the compacts.

## MATERIALS

Experimental compound (Pfizer Ltd., U.K.); Microcrystalline cellulose, Avicel PH101 (Honeywill & Stein Ltd., Surrey, U.K.); Sodium starch glycollate, Explotab (K&K Greeff, Croydon, U.K.); Cross-linked polyvinylpyrrolidone, Polyplasdone XL (GAF Chemicals, Manchester, U.K.); Croscarmellose sodium, Ac-Di-Sol (Honeywill & Stein LTD., Surrey, U.K.); Polyvinylpyrrolidone, Kollidon K30 (Blagden Campbell Chem. Ltd., Croydon, U.K); Magnesium stearate USP (Durham Raw Materials Ltd., Durham, U.K.); Sodium lauryl sulphate BP (Marchon Products Ltd., Whitehaven, U.K.).

## METHODS

### 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 10mm flat faced tooling. Compacts were produced over a range of compaction pressures 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 ( < 50um). They were then wet massed with an identical level of water (50%) as before. The resultant granules, of the same mean size and distribution as those produced originally, were relubricated with a further 1% of the lubricant blend and then recompressed.

## Disintegration Times

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

## Tablet Dissolution

Tablets undergoing dissolution studies were prepared using a compaction pressure of 200MPa and had a resultant tensile strength of 2.3-2.5MPa.

Tablet dissolution was conducted using the USPXXI paddle method (USP2) using a precalibrated dissolution bath (G.B. Caleva, Model 6ST) at 100 rev. $min^{-1}$. The dissolution process was monitored automatically using a Uvicon 810 spectrophotometer (Kontron Instruments, St. Albans, U.K.), fitted with a programmable cell-changer controlled externally by a Commodore PET 4032 microcomputer with an IEEE/RS232 interface (Small Systems Engineering Ltd). The dissolution medium (deaerated water), following passage through an in-line filter (sintered polypropylene, Frost Instruments, U.K.) was circulated by a peristaltic pump (Watson Marlow, Model S170) through flow cells in the spectrophotometer.

Solution absorbances were read automatically at the max for the drug (281nm) and stored in the microcomputer during the dissolution test. Following completion of the dissolution, profiles were generated by the microcomputer and a dissolution test report generated.

All dissolution studies were conducted on six tablets and mean values are reported.

## RESULTS AND DISCUSSION

The dissolution profiles for extra-granular disintegrant incorporation are shown in Figure 1. Tablet rework caused a prolongation of disintegration times (Table 1) which are caused by impaired fluid influx and reduced disintegrant efficiency(5).

Figure 1 indicates that impairment of tablet disintegration on rework retards dissolution for control tablets. Dissolution of reworked tablets containing Ac-Di-Sol is initially slower than first compression compacts, presumably through impaired tablet disintegration, but then have an increased rate of dissolution. Reworked tablets containing Polyplasdone XL and Explotab dissolve faster than first compression tablets and their dissolution profiles appear unaffected by impaired disintegration, suggesting that processing benefits on primary particle dissolution occur.

Overall tablet disintegration and dissolution were assessed using the method of Al-Yazigi(7, 8) assuming pseudo first-order kinetics for both processes, and tablet surface dissolution to be negligible(9). Disintegration and dissolution rate constants ($k_d$ and $k_s$ respectively) were determined and the disintegration or dissolution-time profile deduced from the relation:

$$f_d = 100(1-\exp(-k_{d,s}t)$$

where $f_d$ is the cumulative percent disintegrated at time t.

The times for 50% and 90% disintegration (t50%D and t90%D respectively), deduced using the values of $k_d$ in the above equation, together with the times for 10% and 50% dissolution (t10%S and t50%S respectively) were deduced using the method as

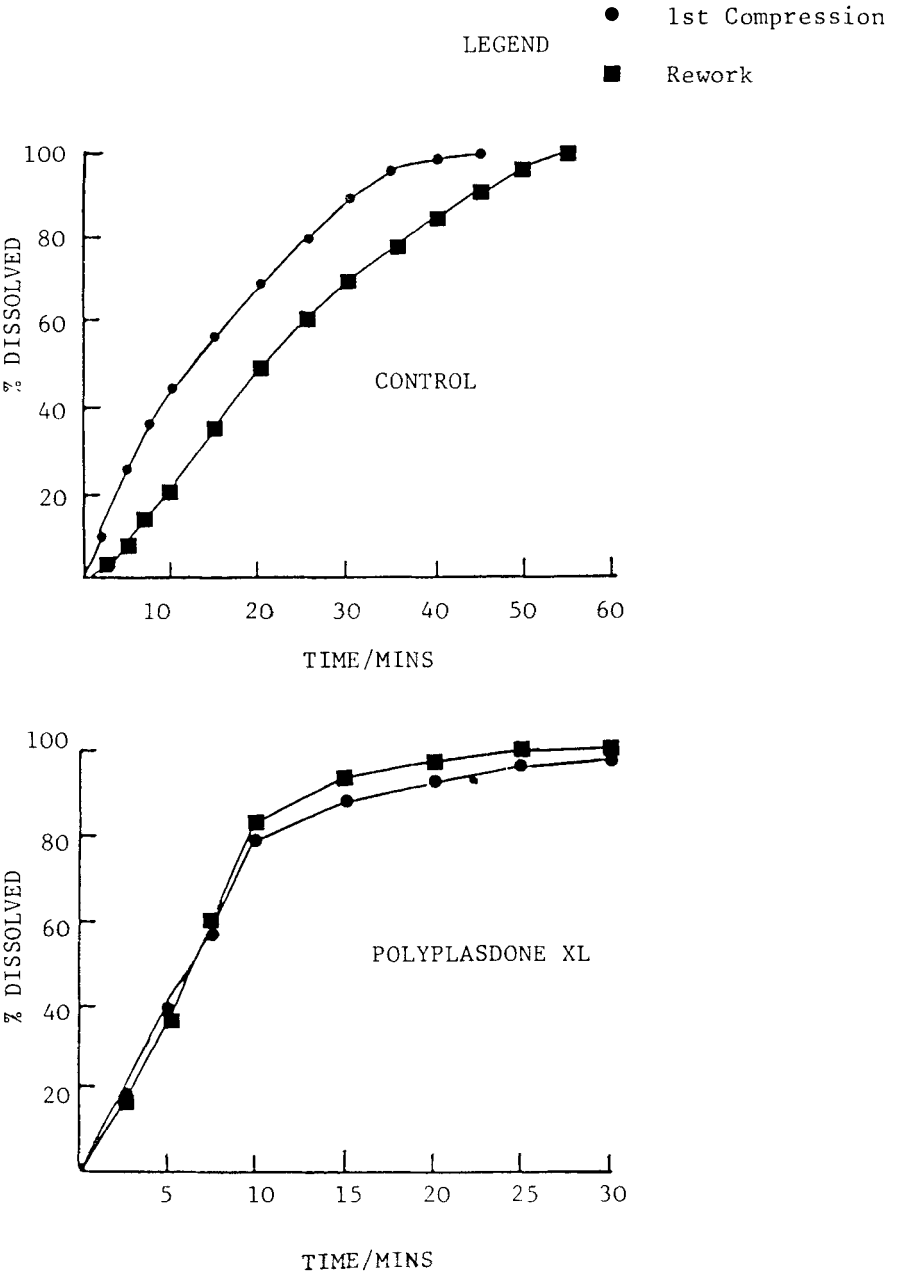
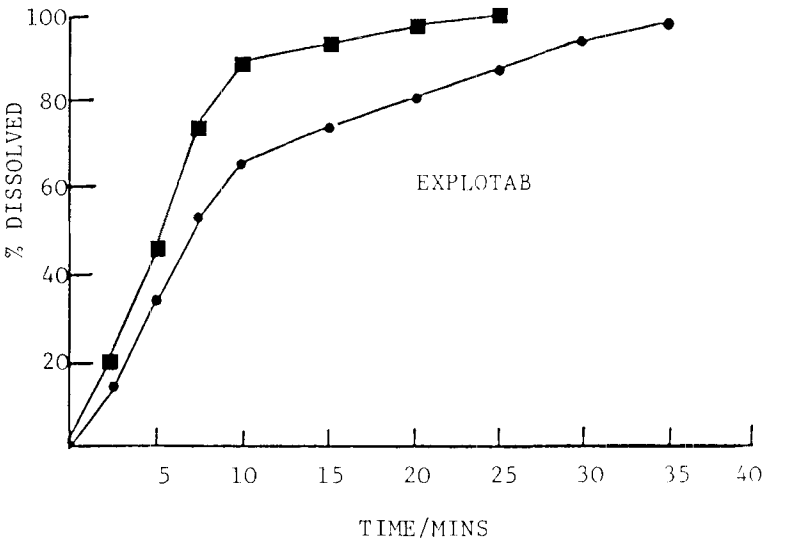



FIGURE 1 - DISSOLUTION PROFILES OF DRUG WHEN DISINTEGRANTS PLACED EXTRA-GRANULARLY



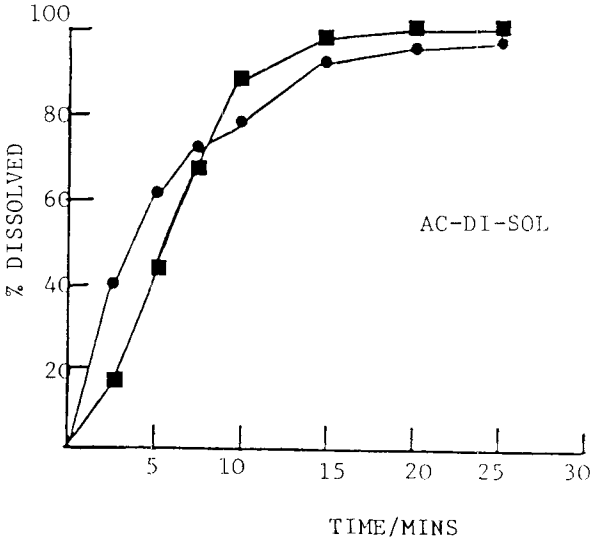




FIGURE 1 CONTINUED.

TABLE 1

Disintegration and Dissolution Data for Tablets Containing Extra-granular Disintegrants

| Disintegrant | Disintegration Time (mins) | Di (%) | t50%D (mins) | t90%D (mins) | t10%S (mins) | t50%S (mins) | Ds (%) |
|---|---|---|---|---|---|---|---|
| Control | 9.0 | 53.0 | 1.5 | 5.0 | 2.0 | 12.3 | 63.0 |
| Control - Rework | 17.0 | | 2.8 | 9.4 | 5.7 | 19.5 | |
| Polyplasdone XL | 5.2 | 69.3 | 0.86 | 2.9 | 1.5 | 7.9 | 100.0 |
| Polyplasdone XL - Rework | 7.5 | | 1.3 | 4.2 | 1.5 | 7.9 | |
| Explotab | 6.5 | 98.4 | 1.1 | 3.6 | 1.1 | 7.3 | 135.0 |
| Explotab - Rework | 6.6 | | 1.1 | 3.7 | 1.4 | 5.4 | |
| Ac-di-sol | 3.8 | 44.7 | 0.63 | 2.1 | 0.7 | 4.8 | 60.7 |
| Ac-di-sol - Rework | 8.5 | | 1.4 | 4.7 | 1.6 | 7.9 | |

shown in Figure 2 and are given in Table 1. Figure 3 shows the excellent correlation ($r=0.963$, $n=9$, $p < 0.05$) between t90%D and t50%S, indicating that tablet dissolution is highly dependant on the primary disintegration of the tablet matrix.

Since all compacts were produced at the same compaction pressure and possessed the same tensile strengths and porosities(6), the ratio of the disintegration times for Polyplasdone XL, Explotab and Ac-di-sol systems after rework

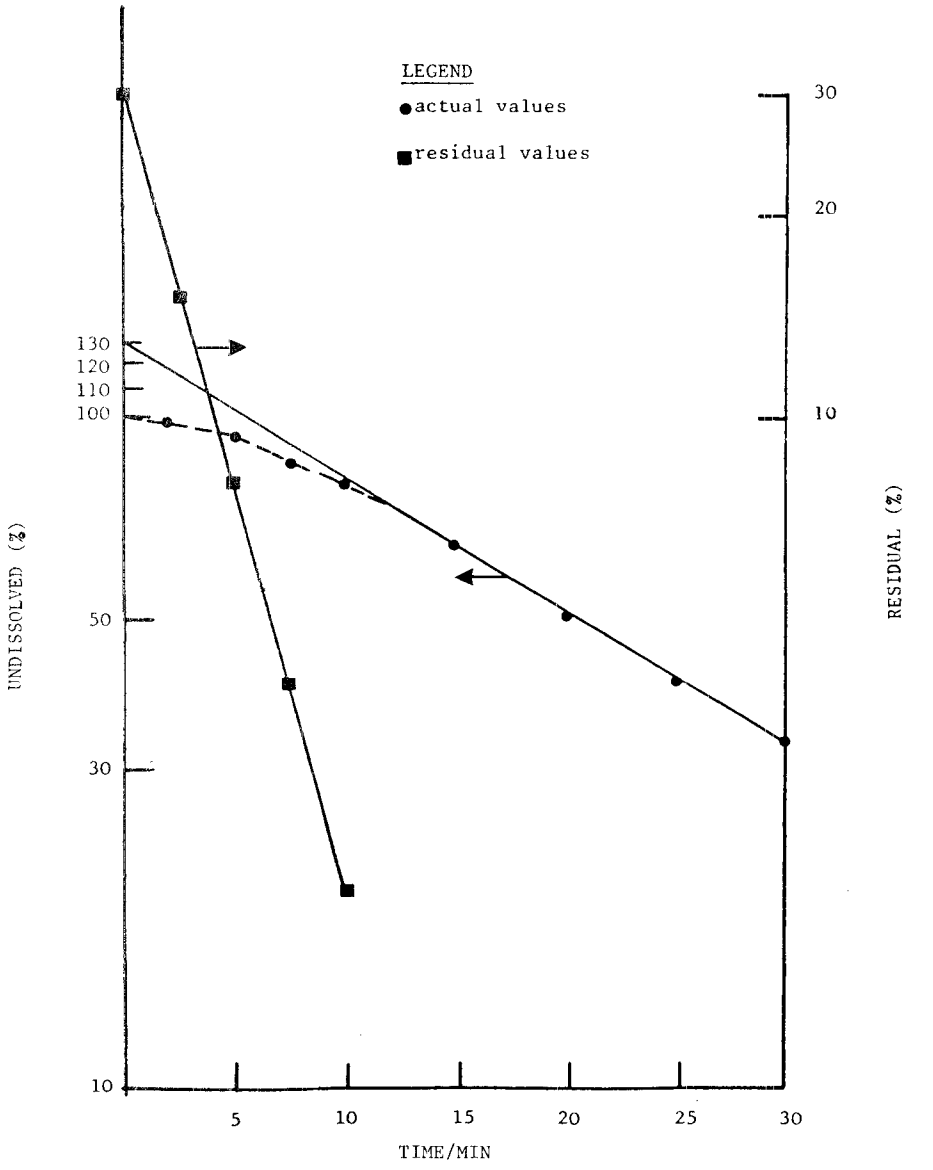



FIGURE 2 - SEMILOGARITHMIC PLOT OF CUMMULATIVE PERCENT DISSOLVED AGAINST TIME. EXAMPLE USED OF REWORK TABLET CONTAINING NO DISINTEGRANT.

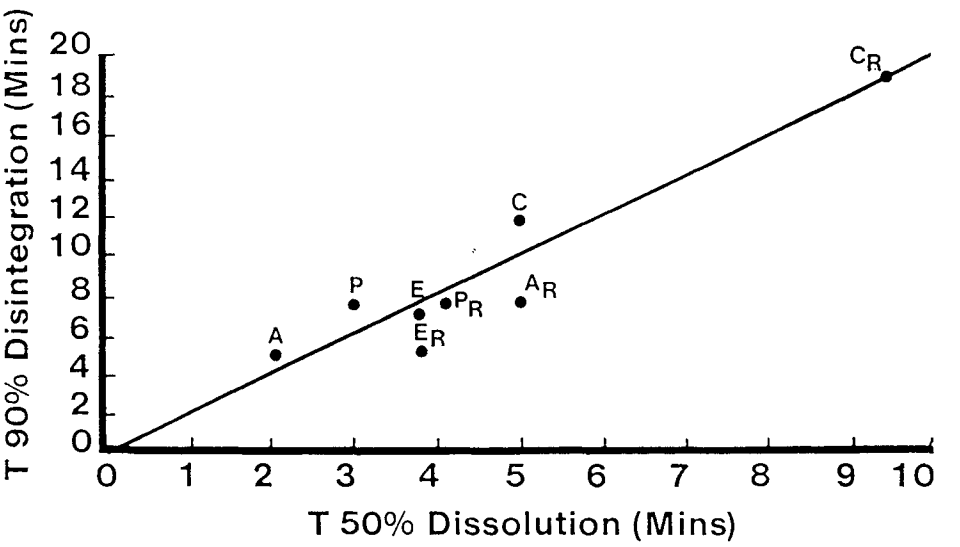



FIGURE 3

PLOT OF t50%S VS t90%D FOR TABLETS CONTAINING EXTRA-GRANULAR DISINTEGRANTS

to that initially can be defined as their disintegration rework efficiencies(5). The values of these efficiencies(Di), also given in Table 1, show that Explotab has full retention of Di, whereas that for Polyplasdone XL is reduced. A substantial reduction in Di occurs with Ac-di-sol. However, in reality both these latter two disintegrants give more than acceptable disintegration and dissolution performance when compared with the control.

On the basis of Figure 3 it would be expected, and is indeed found (Figure 4), that a change in Di results in a composite change in the dissolution performance of the tablets. Analysis of the data indicates this, and that approximately 70-75% retention of extra-granular disintegrant efficiency is required to maintain full dissolution performance following rework. Ac-di-sol, despite its excellent performance on first compression (fastest dissolution

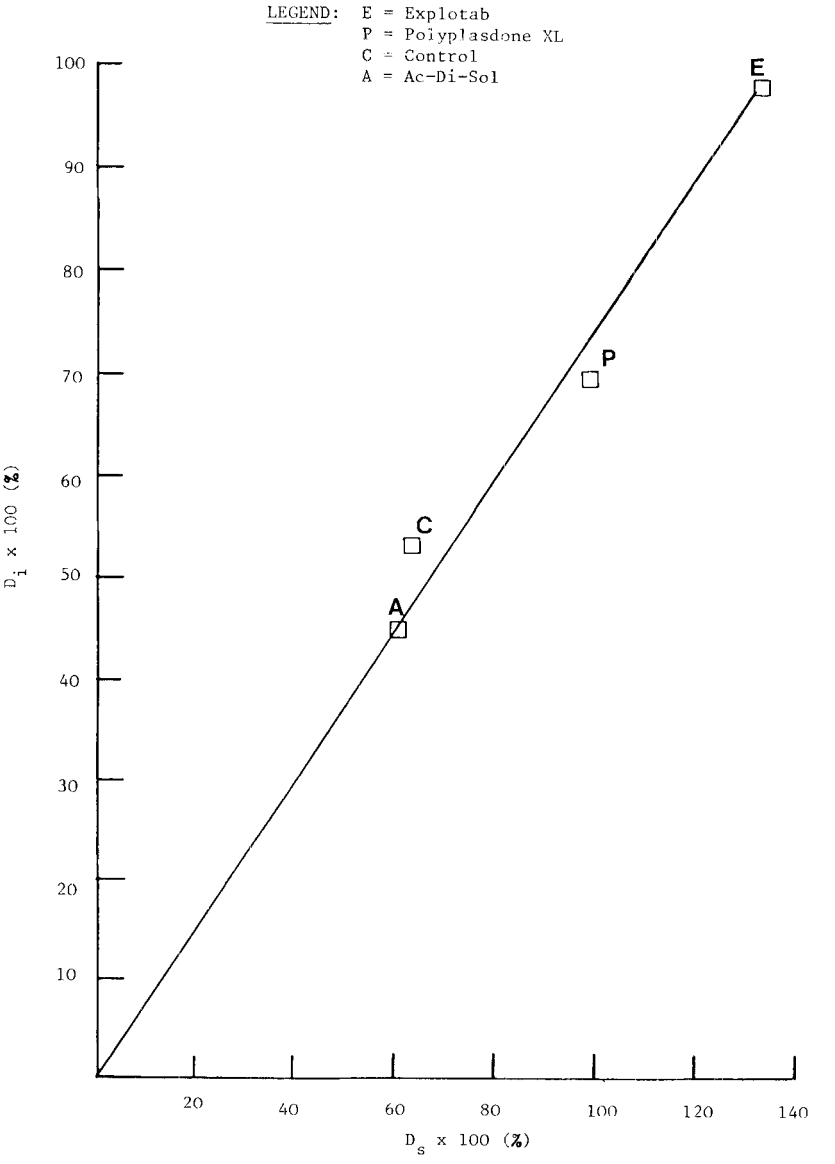



FIGURE 4

PLOT OF $D_i$ vs $D_s$ FOR TABLETS CONTAINING EXTRA-GRANULAR DISINTEGRANTS

rate), and the control tablets fall below this value and have impaired dissolution.

One further point of interest emerges from Figures 1 and 2. The rework process appears to cause a beneficial effect on primary drug particles that amounts to some 40% improvement in drug dissolution. This effect, leads to some compacts employing Explotab and Polyplasdone XL dissolving at an equivalent or faster rate than those produced by first compression. This indicates that the effects of comminution and more efficient dispersal of the drug during the rework process, thereby resulting in improved primary particle dissolution, appear to dominate over impaired tablet disintegration for compacts employing these disintegrants. This implies that the remaining Di's for these disintegrants allow initial tablet disintegration, and that this coupled with the intra-granular fluid wicking of the Avicel matrix for de-aggregation, is sufficiently fast that primary particle influences on the dissolution process can be observed.

The dissolution profiles for intra-granular disintegrant incorporation are shown in Figure 4. Once again tablet rework causes a prolongation of disintegration times (Table 2), which are caused by impaired fluid influx into the tablets due to lubricant effects(6) and to deterioration of disintegrant performance due to the additional wetting and drying in the re-granulation component of the rework process(5, 10, 11).

In the case of Polyplasdone XL and Ac-di-sol, the two disintegrants most affected by rework, prolongation of disintegration leads to slower dissolution. As with the extra-granular systems, a good correlation exists between tablet disintegration (T90%D) and dissolution (T50%S) indicating that tablet dissolution is highly dependent on disintegration. Analysis

TABLE 2

Disintegration and Dissolution Data for Tablets Containing Intra-granular Disintegrants

| Disintegrant | Disintegration Time (mins) | Di (%) | t50%D (mins) | t90%D (mins) | t10%S (mins) | t50%S (mins) | Ds (%) |
|---|---|---|---|---|---|---|---|
| Polyplasdone XL | 3.7 | 48.1 | 0.62 | 2.07 | 0.51 | 3.62 | 68.4 |
| Polyplasdone XL - Rework | 7.8 | | 1.29 | 4.29 | 1.01 | 5.29 | |
| Explotab | 3.9 | 61.4 | 0.66 | 2.18 | 1.02 | 6.83 | 102.0 |
| Explotab - Rework | 6.4 | | 1.01 | 3.54 | 1.02 | 6.69 | |
| Ac-di-sol | 2.01 | 42.3 | 0.33 | 1.11 | 0.66 | 3.17 | 63.0 |
| Ac-di-sol - Rework | 4.8 | | 0.79 | 2.63 | 0.98 | 5.03 | |

of the disintegrant efficiency data (Table 2) shows the high dependence of tablet dissolution on disintegration (Figure 6; $r = 0.9664$, $P < 0.05$) and indicates that at least 60% intra-granular disintegrant efficiency is required following rework to maintain full dissolution performance. Thus in comparison with the Di retention required for the extra-granular systems, granule disintegration appears fundamentally more important in the dissolution process than tablet disintegration. The Ac-di-sol and Polyplasdone XL systems, although giving acceptable disintegration and dissolution performance compared to the control, fall below the 60% value and have impaired dissolution over first compression tablets.

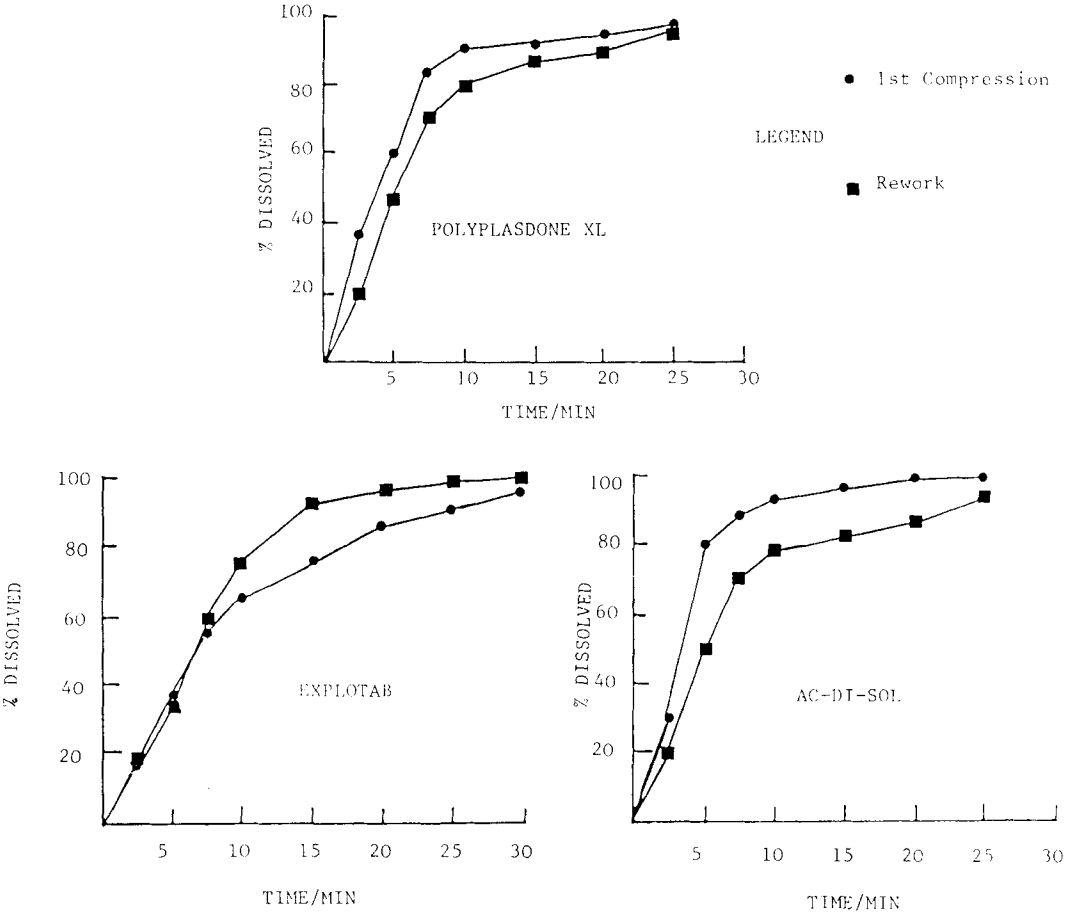



FIGURE 5 - DISSOLUTION PROFILES OF DRUG WHEN DISINTEGRANT PLACED INTRA-GRANULARLY

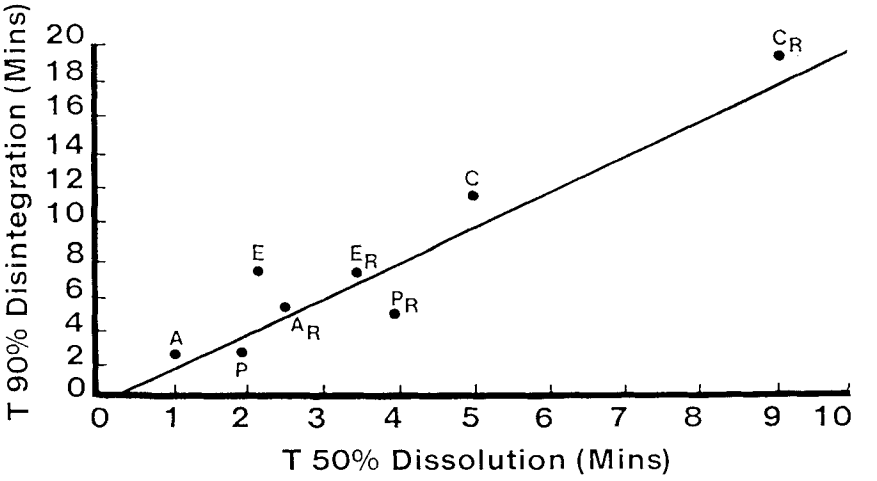



FIGURE 6 - PLOT OF t50%S VS t90%D FOR TABLETS CONTAINING INTRA-GRANULAR DISINTEGRANTS

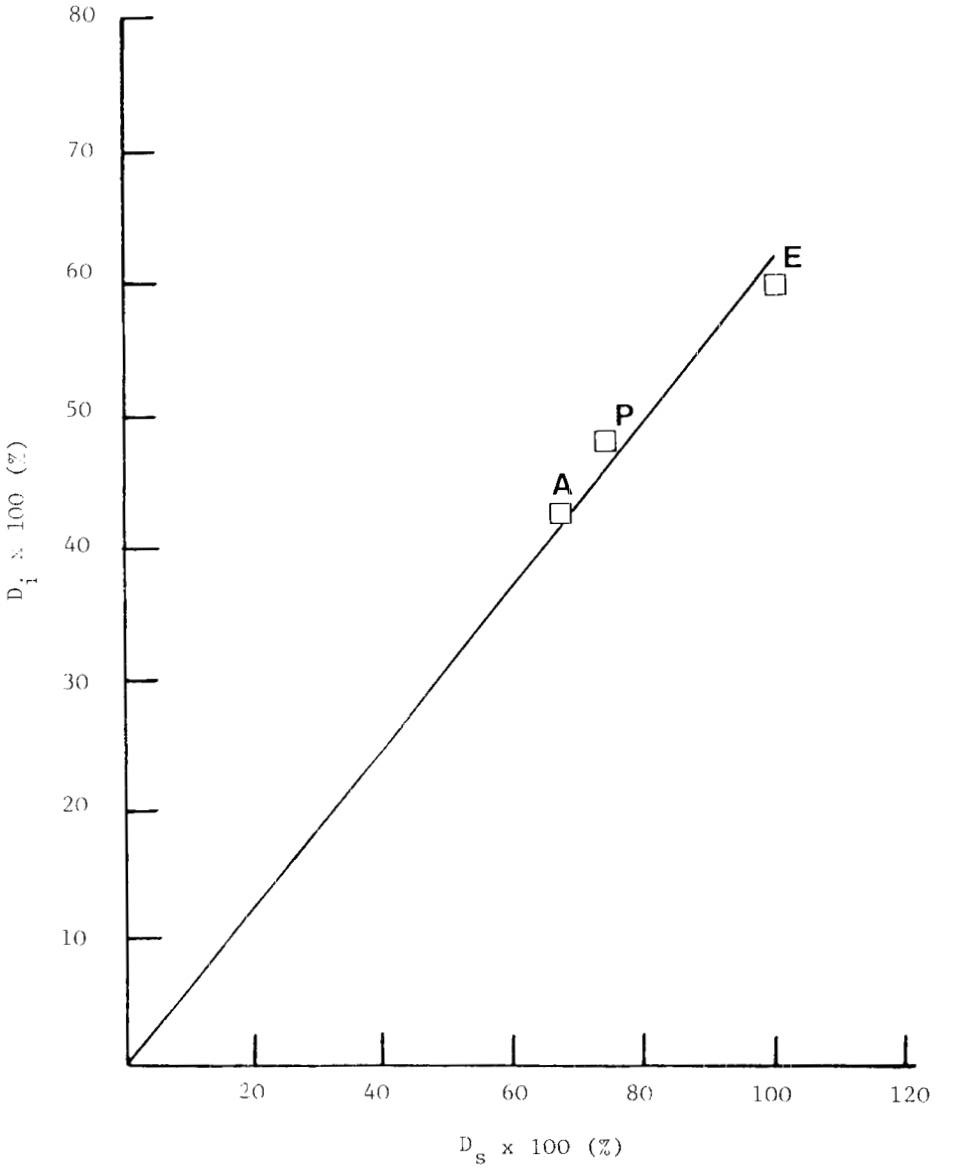



FIGURE 7

PLOT OF $D_i$ vs $D_s$ FOR TABLETS CONTAINING INTRA-GRANULAR DISINTEGRANTS

LEGEND AS FIGURE 4

Despite the impairment of disintegration for Explotab, tablet rework appears to improve drug dissolution. Consistent with the extra-granular systems, analysis of the Di data and retention in dissolution performance data (Figure 7) indicates that tablet rework has a beneficial effect on primary drug particles which leads to some 47% improvement in the rate of drug dissolution. Thus in this case, the high Di value for Explotab, together with the wicking component of the ungranulated Avicel facilitating initial tablet disintegration, allows primary particle effects to be observed.

## CONCLUSION

Tablets containing a 'super' disintegrant, intra- or extra-granularly, disintegrate and dissolve faster than tablets containing no disintegrant. Rework of the tablets involving the stages of regranulation, additional drying and relubrication leads to a loss in disintegrant efficiency. With extra- or intra-granular incorporation, approximately 70% and 60% of Di has to be retained respectively following rework to maintain full dissolution characteristics. In the experimental system investigated the Di for tablets incorporating Polyplasdone XL and Ac-di-sol, both intra- or extra-granularly, fall below these respective values and have some measure of impaired dissolution following rework. Explotab maintains its disintegrant efficiency above these values and has equivalent or improved dissolution following rework. This arises from the beneficial effect on primary drug particles resulting from the effects of comminution and better dispersal of the drug during the rework process. It is deduced that this effect leads to an approximate 40% increase in dissolution performance, irrespective of disintegrant location, within the system investigated.

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