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THE EFFECT OF RECOMPRESSION ON DISINTEGRANT EFFICIENCY IN TABLETS PREPARED BY WET GRANULATION

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ABSTRACT

The efficiency of three modern disintegrants, Explotab, Ac-Di-Sol and Polyplasdone XL, has been investigated following rework of a wet massed, slowly eroding, tablet formulation. When the disintegrants were placed extra-granularly it was found that only Explotab retained good efficiency following rework. All disintegrants placed intra-granularly had rework efficiencies that were essentially the same as the control (no disintegrant). However, the addition of 2% extra-granular disintegrant prior to the second compression restored tablet disintegration behaviour for Polyplasdone XL and partially for Ac-Di-Sol.

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Two of the factors potentially affecting the reworkability of disintegrants (comminution and regranulation) were also investigated. Regranulation caused Ac-Di-Sol and Explotab to significantly lose disintegrant efficiency. However milling alone caused no reduction in efficiency of any disintegrant.

INTRODUCTION

Disintegrants are routinely used in tablet systems to promote moisture penetration within compacts and subsequently assist dispersion in dissolution fluids(1). The newer types of disintegrants(2) have been shown to be effective at low levels(3) and to improve bioavailability(4,5).

Reworking of tablet systems is an accepted practice within the pharmaceutical industry and although a few studies on the reworkability of compression in tablet systems(6,7) have been recently reported, little if any attention has been given to the retention of disintegrant efficiency following rework. We have investigated this for three modern disintegrants; Explotab (sodium starch glycollate), Polyplasdone XL (cross-linked polyvinylpyrrolidone) and Ac-Di-Sol (croscarmellose sodium). The formulation model used was a slowly eroding tablet system employing a high loading of a soluble drug with insoluble excipients.

Explotab is a partially soluble material, deriving most of its disintegrant power by swelling(2). Polyplasdone XL and Ac-Di-Sol are, on the other hand, matrix (sponge) like materials which assist disintegration by absorbing water through capillary action (wicking), with a secondary swelling effect(2). In the case of the latter material, Ac-Di-Sol, its fibrous nature allows intra-particulate as well as inter-particulate wicking of the dissolution fluid into the powder compact.

EXPERIMENTAL

Materials

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

Method

The disintegrants at the 2% level were compared to a control (no disintegrant), both intra and extra-granularly, 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 result in 5% binder in the finished product. All granules were lubricated 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 the determination of the disintegration times (DT) (BP method, one tablet per tube), the DT-CP profile was constructed and the area under the curve (AUC, 0 - 220 MPa) determined by the trapezoidal rule. This value was then termed the 'disintegrant index' (Di) for the tablet system.

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 were relubricated with a further 1% of the lubricant blend and then recompressed. The new DT-CP profiles were then constructed and the Di values redetermined. The rework efficiencies of the disintegrant systems were then calculated by taking the ratio of the Di of the

DT-CP profile for the first compression to that for recompression (Figure 1) expressed as a percentage, viz

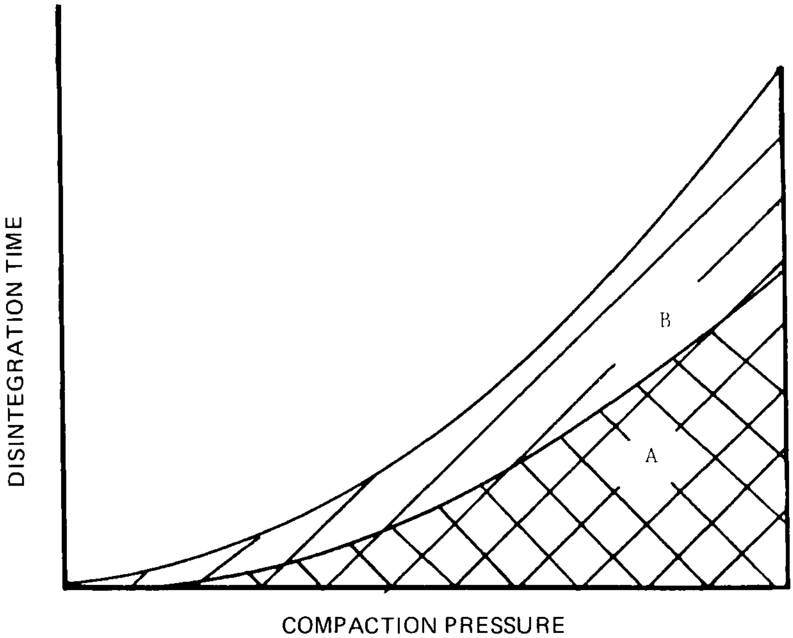
$$\text{Rework Efficiency of disintegrant (\%) (RE)} = \frac{(Di)_{\text{first compression}}}{(Di)_{\text{second compression}}} \times 100$$

RESULTS AND DISCUSSION

The disintegrant indices of all three disintegrants, incorporated intra- and extra-granularly are given in Table 1 and the rework efficiencies in the form of histograms in Figure 2. Disintegration times for tablets made under all experimental conditions at a compaction pressure of 200 MPa, are given in Table 2.

Table 1 shows Ac-Di-Sol to be the most effective disintegrant, both extra- and intra-granularly producing the lowest Di. Explotab and Polyplasdone XL behave fairly similarly producing comparable but higher Di values in the same locations. However, all disintegrant materials signficiantly reduce the disintegrant index vs. the control; by at least a factor of 2 intra-granularly and a factor of 1.5 extra-granularly.

One feature is clearly evident from Table 1; under all conditions tablet rework increases disintegration times and Di



$Di_{(1st\ Compression)} = AUC(A)$

$Di_{(2nd\ Compression)\ rework} = AUC(B)$

$$RE = \frac{AUC(A)}{AUC(B)} \times 100\%$$

Figure 1

Diagramatic representation of interpretation of disintegration indices (Di) and rework efficiencies (RE)

TABLE 1

Disintegrant indices (Di) and Rework Efficiencies (RE) of Tablet Systems. Di_1 and Di_R refer to 1st and 2nd compression respectively.

Location:	Intra-granular			Extra-granular		
Disintegrant:	Di_1 min	Di_R MPA	RE %	Di_1 min	Di_R MPA	RE %
Control (no disintegrant)	579	1291	45	579	1291	45
Polyplasdone XL	259	565	46	380	593	64
Explotab	277	516	54	432	502	86
Ac-Di-Sol	144	364	40	277	614	45

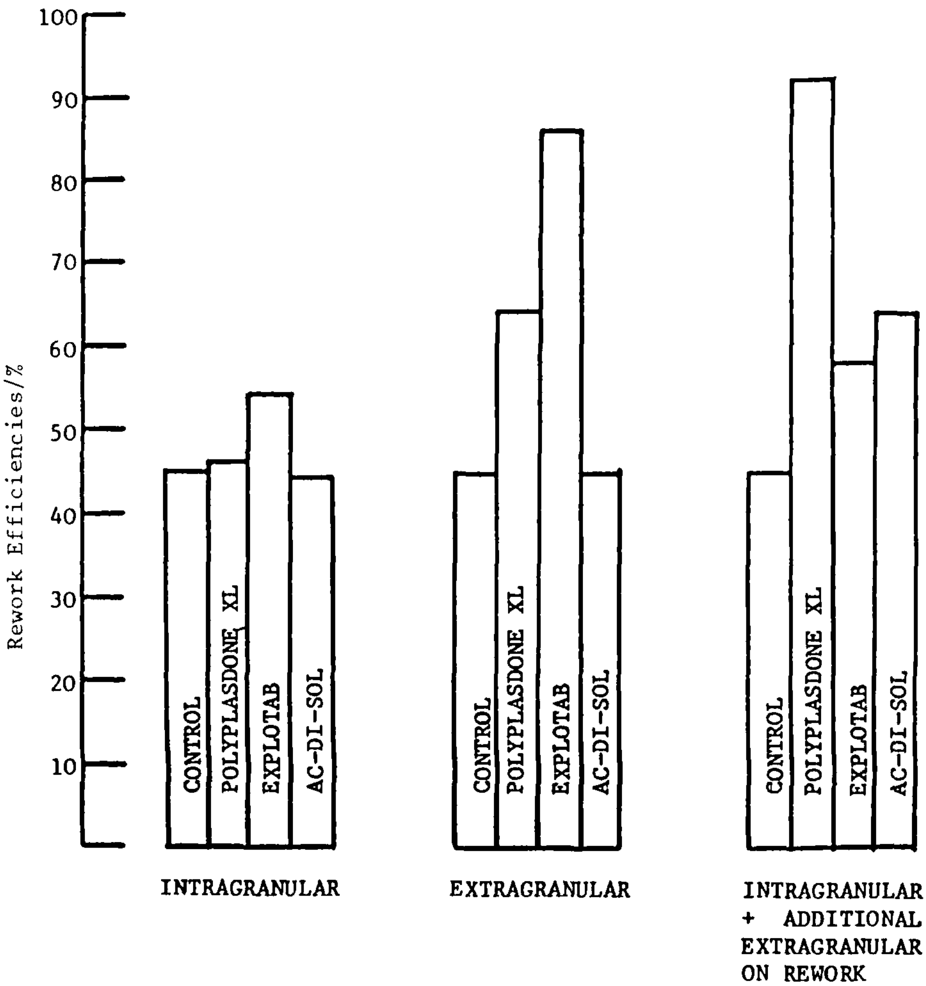


Figure 2

Rework Efficiencies of Tablet System when Polyplasdone XL, Explotab and Ac-Di-Sol placed intra- and extra- granularly

values. At the same time rework also results in weaker compacts produced at the same compression force (Figure 3). Compression rework efficiencies(7) for all systems were in the range 60-78%; the reduction in compressibility presumably occurring through work hardening and lubricant poisoning of bonding surfaces. Since reworked tablets are weaker, and are in principle more

TABLE 2

Disintegration times (mins.) for tablets prepared at a compaction pressure of 200 MPa

	Intra-granular	Extra-Granular
Control	9	9
- rework	17	17
Polyplasdone XL	4.0	5.2
- rework	8.9	7.5
Explotab	3.9	6.5
- rework	6.1	6.6
Ac-Di-Sol	1.9	3.8
- rework	4.4	8.5

porous, they should potentially disintegrate more quickly. However, the significant increases in disintegrant indices and low rework efficiencies shown in Figures 4 and 5 suggest a fundamental loss in performance or change in nature of the disintegrant material following rework.

In the extra-granular case (Figure 4), the rework efficiencies of Explotab (86%) and Polyplasdone XL (65%) were greater than the control (45%). Ac-Di-Sol, having the same RE as the control, appears to have lost all of its disintegrant

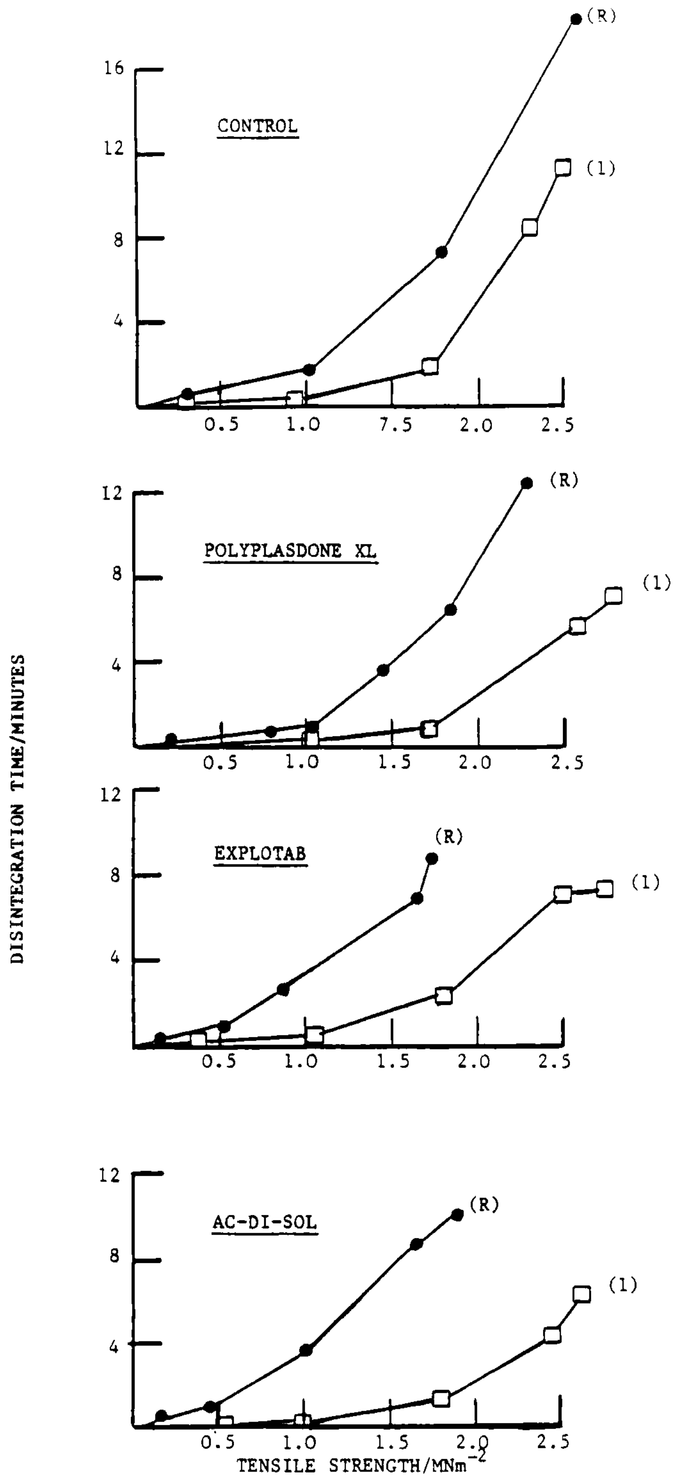


Figure 3: Disintegration Time vs. Tensile strength profiles of Tablet systems, on first compression (1) and second compression (R), when disintegrants placed extra-granularly. Tensile strengths determined from force for single point fracture using equation of Fell and Newton (J.Pharm.Sci. 59 (1970) 688).

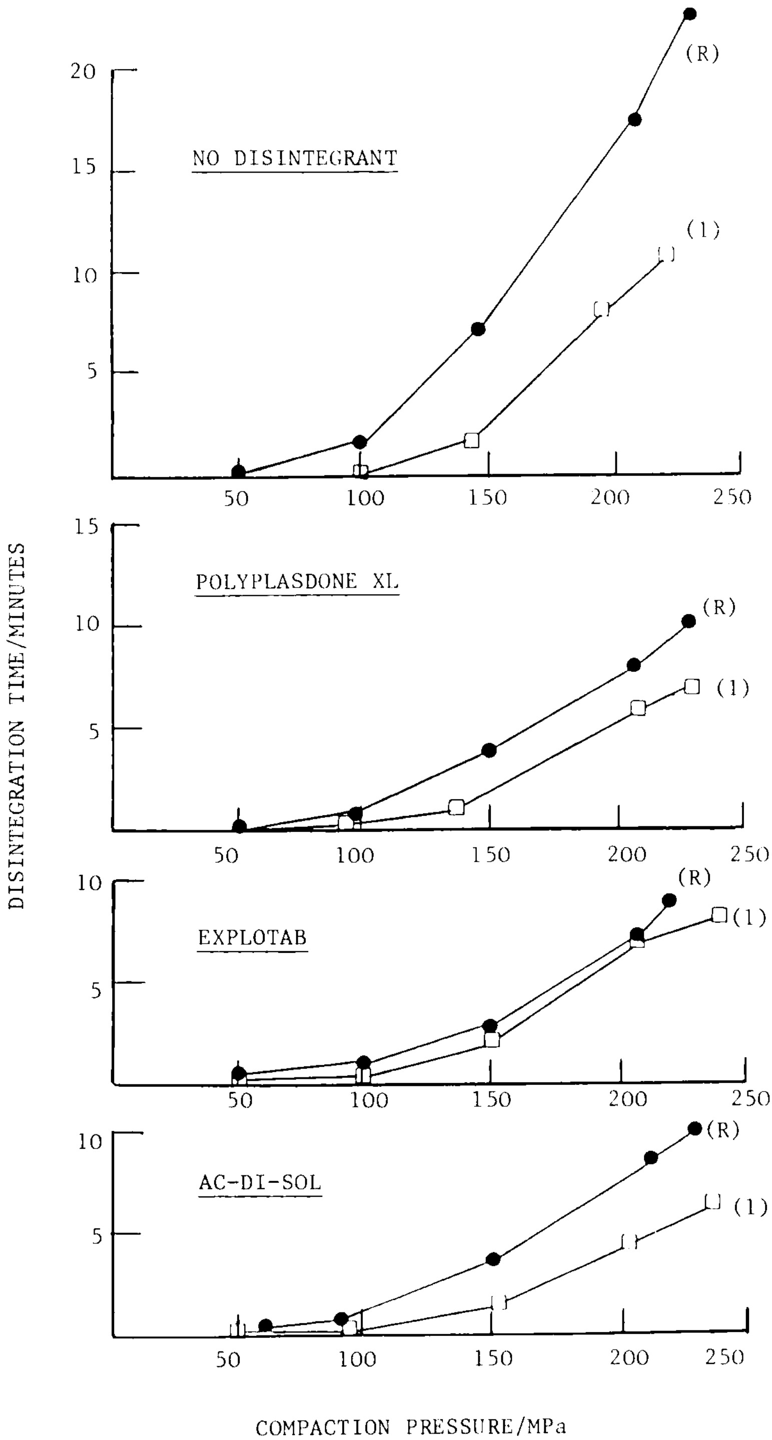


Figure 4: Disintegration Time vs. Compaction Pressure profiles of Tablet systems, on first compression (1) and second compression (R), when disintegrants placed extra-granularly

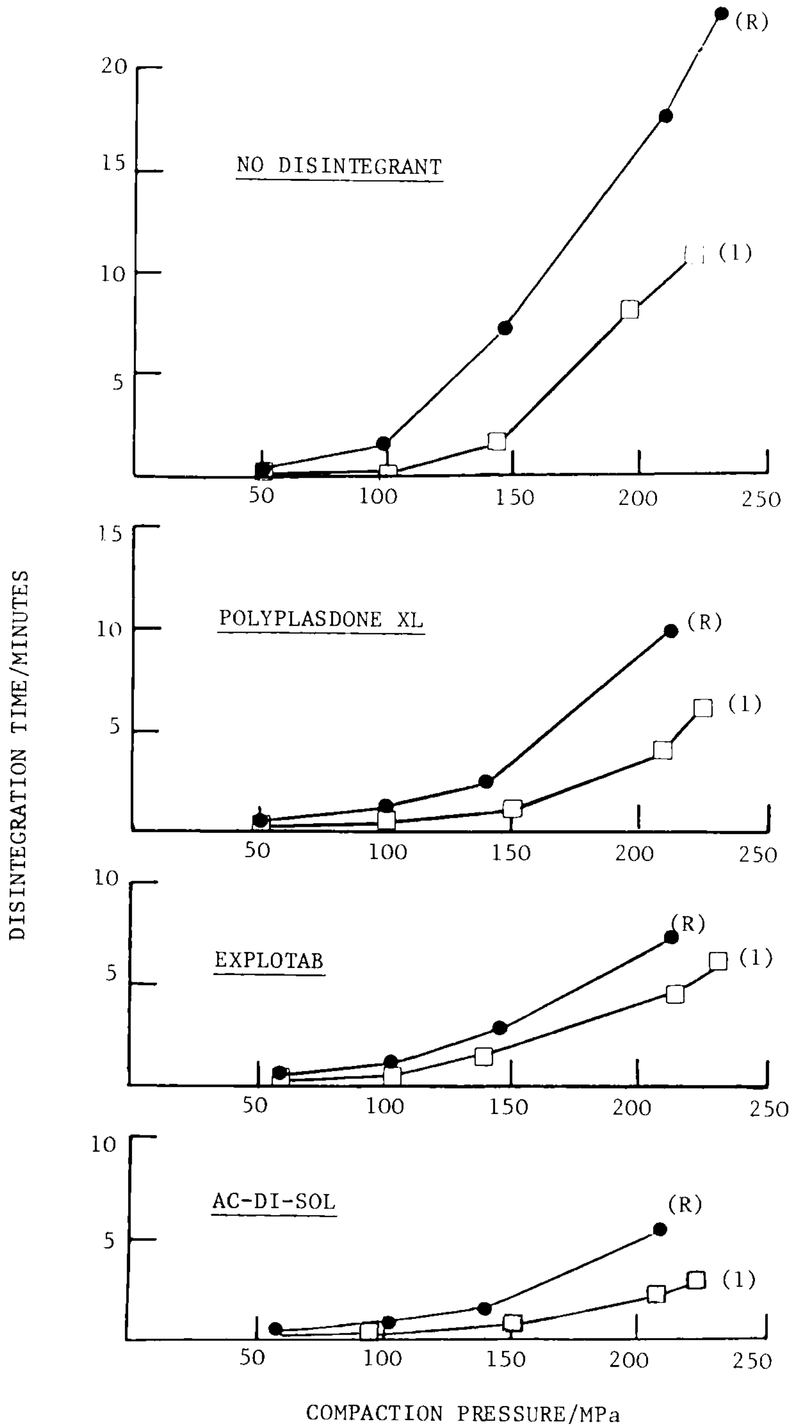


Figure 5: Disintegration Time vs. Compaction Pressure profiles of Tablet Systems on first compression (1) and second compression (R) when disintegrants placed intra-granularly

efficiency following rework. This loss in efficiency of the wicking disintegrants can possibly be explained by the breakdown of their solid state structure during the rework process; the matrix sponge-like Polyplasdone XL and the 'spaghetti'-like fibrous Ac-Di-Sol being broken down by the compaction and comminution processes into much smaller, more highly dispersed particles within the reworked tablets. Local concentrations of the disintegrant may then be too low within the compact to allow the formation of an efficient capillary network, thereby preventing effective wicking and the subsequent swelling to aid tablet disintegration. This hypothesis is supported by the work of Rudnic et al.(8), who showed that in a comparative evaluation of three different particle size grades of cross-linked PVP, the finest material had the lowest disintegrant efficiency. However, List and Muazzam(9) have shown that the lubrication of a weakly swelling disintegrant (potato starch) with magnesium stearate causes the disintegration time of compacts to increase with decreasing particle size of the disintegrant. This effect has been attributed(10) to the lubricant film formed on the disintegrant particles decreasing wettability, thereby retarding liquid penetration into the tablets. These features are clearly present in the rework process, especially since the lubricant present from the first compression becomes trapped within the reworked granules. Further reduction in wettability may then result from relubrication on rework. This feature potentially explains the increase in disintegration index and low RE of the control tablet system.

The primarily swelling disintegrant, Explotab, retains its disintegrant efficiency well following rework. This may be a result of its morphology, where the majority of the starch grains remain unaffected by the rework process, and the retention of their individual integrity leads to a maintenance of localised swelling in the powder compacts. In addition, Smallenbroek and coworkers(10) and Proost et al.(11) have shown that strongly swelling disintegrants such as sodium starch glycollate are unaffected by magnesium stearate and retain their swelling properties well following lubrication. However some RE is lost and possibly slightly impaired wetting, together with some of the Explotab grains splitting open on compression(12) causes a reduction in the effectiveness of the disintegrant.

When the disintegrants were placed intra-granularly (Figure 5), the rework efficiencies of all three disintegrant systems were substantially reduced. Polyplasdone XL and Ac-Di-Sol had RE values of 46% and 43% respectively, which were essentially the same as the control (45%). The RE of Explotab was reduced to 54%. For the wicking disintegrants the same explanations for loss of disintegrant efficiency following rework would still seem to apply, i.e. reduction in capillary effects due to increased dispersal of finer material throughout the solid matrix and impaired wetting due to the lubricant. However, in this case the greater loss in RE for Polyplasdone XL (64% to 46%) and the substantial reduction for Explotab (86% to 54%) may be due to the additional wetting and drying processes of the rework granulation. Indeed, Khan and Rhodes(13) have shown that Explotab shows considerable structural changes on absorbing water, leading to pre-swelling and partial dissolution. In a separate study Mitrevej and Hollenbeck(14) found that drying of swollen Explotab particles was not reversible and that permanent structural modification to the disintegrant grains took place. However, Ac-Di-Sol showed a complete reversal of swelling and the dried material closely resembled the initial material. Thus regranulation 'ageing' of the disintegrant (lack of recovery following moisture challenge), possibly explains the loss in RE for Explotab, but is less likely to be the cause of the loss in RE for Ac-Di-Sol.

The potential factors affecting the reworkability of disintegrants were further investigated. 'Stressed' disintegrants were prepared simulating two of the components of the rework process; comminution using a Fitzmill (fast hammers, 0.02" screen), and also slurrying with a suitable level of water. The 'stressed' disintegrants were then incorporated in the normal way extra-granularly (2%) into the standard tablet system. The disintegration time-compaction pressure profiles vs. a control (standard disintegrant) are given in Figure 6 and resultant disintegrant indices in Table 3.

As was anticipated from the intra-granular rework, the moisture stress with Explotab caused a significant reduction in its disintegrant efficiency and a subsequent increase in its Di value. Ac-Di-Sol showed identical behaviour, again presumably the result of incomplete reversal of the structural changes brought about by the absorption of moisture during the slurrying process. Milling has a negligible effect on the Di value of Explotab and causes a relatively small reduction in Di value with Ac-Di-Sol. The results with Polyplasdone XL show that both milling (which reduces the particle size by 15-20% but with similar width of distribution) and slurrying significantly increases the disintegrant efficiency and reduces the Di values. These latter results imply that other features in the rework process such as lubrication or compaction must be responsible for reducing the disintegrant efficiency of Polyplasdone XL.

Further work was conducted attempting to improve the intra-granular systems following rework. Additional disintegrant (2%) was added extra-granularly prior to recompression and the disintegrant indices and rework efficiencies redetermined. The

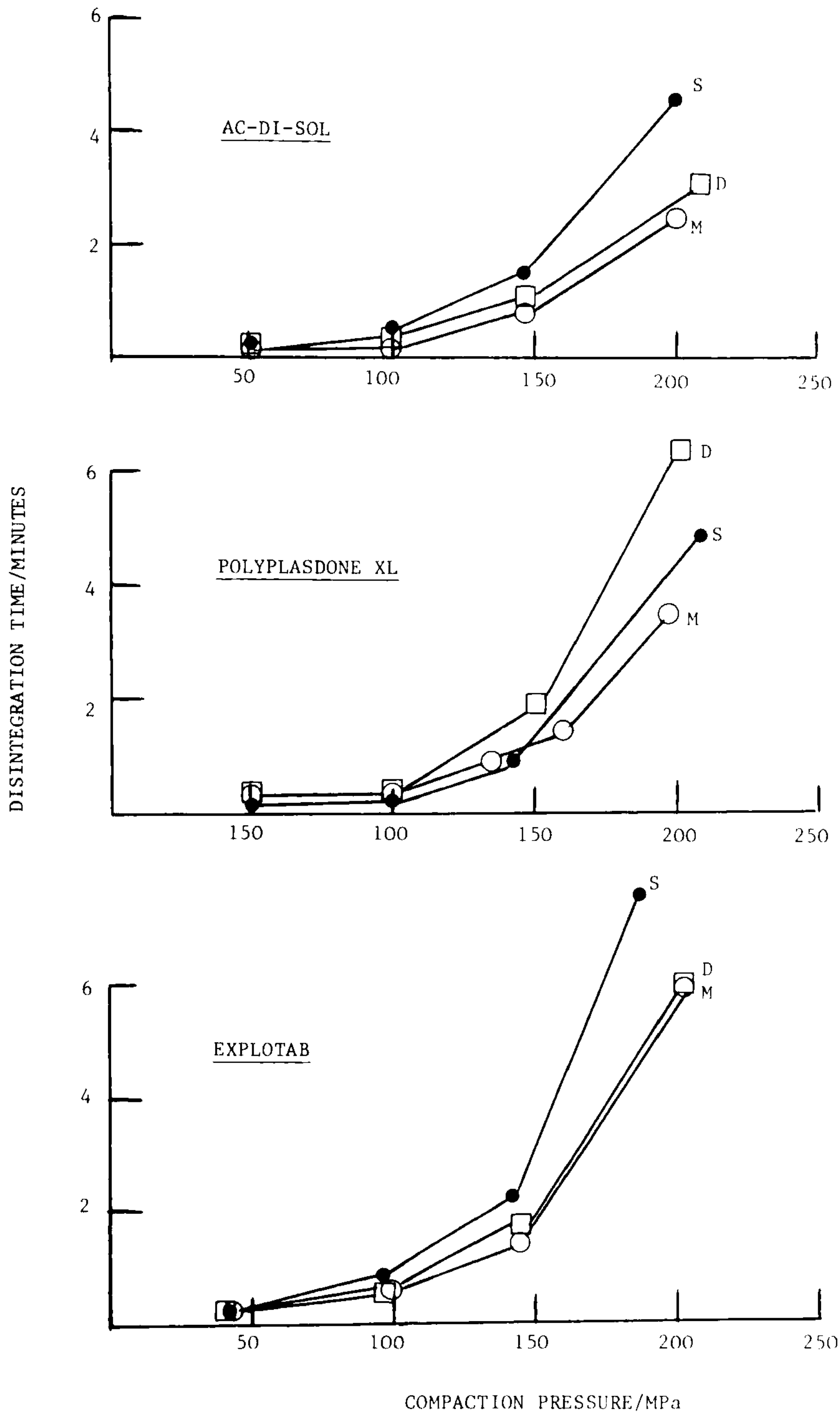


Figure 6 : Disintegration Time-Compaction Pressure profiles for 'stressed' (slurried (S) and milled (M) and normal (D) disintegrant in tablet system

TABLE 3

Disintegrant Indices (Di) and Relative Disintegrant Indices for ´stressed´ disintegrants in tablet system

Disintegrant:	Polyplasdone XL		Explotab		Ac-di-sol	
Stress	Di min MPa	$Di/Di_{(control)}$	Di min MPa	$Di/Di_{(control)}$	Di min MPa	$Di/Di_{(control)}$
Control	271.1	1.000	291.6	1.00	159.5	1.000
Milled	177.6	0.655	271.2	0.930	139.6	0.875
Slurried	193.3	0.713	374.8	1.285	215.2	1.349

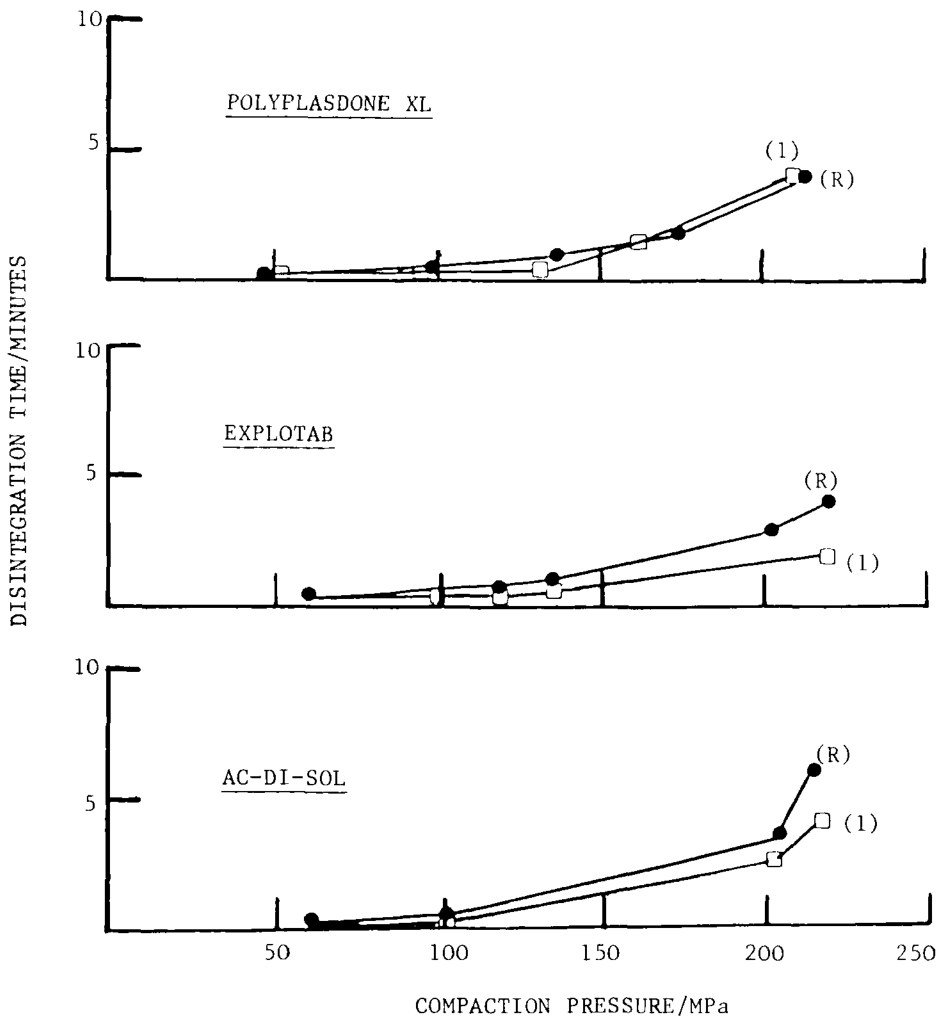


Figure 7: Disintegration Time vs. Compaction Pressure profiles of tablet systems when disintegrant placed extra-granularly on first compression (1) and addition 2% added extra-granularly on second compression (R)

results (Figure 7) show that the RE is virtually re-established with Polyplasdone XL to 92%, improved for Ac-Di-Sol (68%), but only slightly improved with Explotab (57%). The latter results suggest a failure in intra-granular disintegration for the reworked systems.

CONCLUSIONS

The disintegrant efficiencies of extra- and intra-granular Polyplasdone XL, Explotab and Ac-Di-Sol in the model tablet system are reduced by tablet rework. When included extra-granularly, the higher rework efficiency of the strongly swelling disintegrant, Explotab, may be a result of the retention of its morphological character, or a failure to be perturbed by lubricant during the rework process. The results also suggest that for intra-granular Explotab and Ac-Di-Sol, regranulation ageing may be the most likely cause for their loss in rework efficiency.

Finally, on rework of wet granulation tablet systems, the results suggest particularly with Polyplasdone XL, that additional disintegrant should be added immediately prior to recompression in order to maintain tablet disintegration characteristics.

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