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Effect of slugging pressure on the properties of granules and tablets prepared from potassium phenethicillin

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The mechanism of preparing compacts by precompression has been investigated. The influence of slugging pressure on the bulk and tapped density, particle size distribution and the surface area of precompressed granules has been examined. The slugged granules have been tableted and the effect of compaction force on the weight uniformity, friability, crushing strength, disintegration time, dissolution rate and internal surface area of the tablets has been studied. The results show that the granules obtained from 15·9 mm slugs manufactured at low compaction forces (e.g. 49 MNm^{-2}) had a lower bulk density, higher friability and larger surface area than those made at higher compaction pressures (e.g. 196 MNm^{-2}). The lighter granules compacted into stronger tablets over a range of compaction forces and the effect was attributed to greater intergranular bonding caused by increased plastic flow.

The mechanism by which precompression facilitates bonding in tablet manufacture is not fully understood. Gunsel & Kanig (1976) hypothesized that slugging was just an elaborate method of subjecting material to an increased dwell time during tableting. However, it is difficult to imagine that the act of slugging followed by milling/screening and subsequent compression can be equivalent to an extended dwell time, since many of the bonds are never subjected to increased compression time but are in fact formed, broken and new and old ones formed again.

Several workers have included the precompression process in comparative studies on granulation methods and have examined the effect of processing methods on tableting properties (Levy et al 1963; Selkirk & Ganderton 1970; Chalmers & Elworthy 1976). For example, Levy et al (1963) found that increasing the slugging pressure increased the dissolution rate of tablets. It was suggested that fragmentation at the higher pressure was the reason. Selkirk & Ganderton (1970) noted that granules produced by wet and dry methods behaved differently upon compression. These workers found that granules formed by wet granulation were most robust and possessed a coarser, wider pore size distribution which persisted to the highest tableting pressure used. However, with the tablets made from slugged granules, the pore structure in the tablets was destroyed by high tablet pressures.

Langridge & Wells (1980) have recently shown that precompression of a mixture of microcrystalline cellulose (Avicel PH 102) and dicalcium phosphate dihydrate (Emcompress) significantly reduced compressibility of these excipients. The reason for this behaviour was attributed to work-hardening.

To help elucidate the bonding mechanisms in a precompressed system, the behaviour of potassium phenethicillin, a moisture sensitive penicillin, has been investigated by examining the influence of slugging pressure on granule and tablet properties. Since, in practice, materials are often subjected to repeated precompression to improve flow and or compaction, the process of double slugging has also been investigated.

MATERIALS AND METHODS

Materials

Potassium phenethicillin Batch No. Bx 4277 and Bx 4340 (Broxil*, Beecham Pharmaceuticals, Worthing). Microcrystalline cellulose, Avicel PH 102 (Honeywill & Stein Ltd, Surrey, U.K.). Magnesium stearate (Durham Chemical Ltd, Durham, U.K.). Colloidal silica, Aerosil 200 (Bush Beach & Segner Bayley Ltd, London). Sodium starch glycolate, Explotab (Kingsley & Keith, Croydon, Surrey, U.K.).

Methods

Single slugging (Formulation A). The initial work was carried out using the slug formulation: potas-

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sium phenethicillin batch 4277 89%; microcrystalline cellulose (MCC) 10% and magnesium stearate 1%. These ingredients were mixed in a planetary mixer (Hobart, U.K.) and then compressed on a single punch instrumented tablet machine (F3, Manesty, Speke, Liverpool, U.K.) using 5/8" flat punches at 49, 98, 147 and 196 MNm^{-2}. The slugs were milled using an Apex comminuting mill (Apex Construction Ltd, Northfleet, Kent) at slow speed with hammers forward and fitted with 0·077" aperture screen. After determining the granule properties (described below), the granules were mixed with the following ingredients before compression into tablets (% refer to w/w granules); granules 83·5%, MCC 10%, sodium starch glycolate (Explotab) 5%, magnesium stearate 1% and Aerosil 0·5%. The blending was carried out in a Kenwood mixer, operating at slow speed for 15 min. Tablets contining 125 mg phenethicillin were compressed using 5/16" flat punches at applied pressures of 82, 162, 327 and 490 MNm^{-2}.

Double slugging (Formulation B). The first precompression was carried out at 147 MNm^{-2} using the granule formulation described for formulation A. The slugs were milled using hammers at slow speed and 0·5% extragranular magnesium stearate was included before the second slugging. The milling, mixing and tableting procedures were identical to those described above except that a further 0·5% extragranular magnesium stearate was used to assist compression into tablets. Thus a total of 2% magnesium stearate was incorporated at various stages, for both single and double slugging.

Compression of sieve fraction (Formulation C). Since the milling of slugs compressed at lower and higher pressure yielded granules of different size distributions (see Fig. 1), the same sieve cuts from the lower and higher pressure slug systems were tableted to eliminate the effect of granule size variation. The slug formulation A was precompressed at 49 and 196 MNm^{-2}. The slugs were milled using knives at slow speed and granules produced were separated into 355 to 500 μm sieve fractions. Fines from these fractions were removed using an air jet sieve (Alpine Air Jet, M. and M. Equipment Ltd, Herts., U.K.). As for formulation A, 10% MCC and 1% magnesium stearate was added to the sieve fraction before compression into tablets.

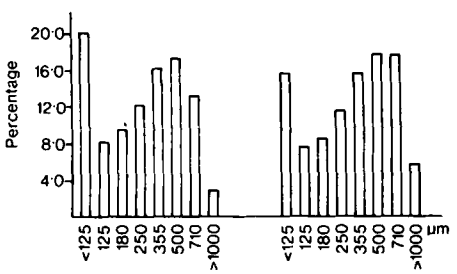

FIG. 1. Particle size distribution of granules obtained after milling slugs compressed at 49 and 196 MNm^{-2}.

Granule properties

The true density of the granules and some compression mixes were determined using an air comparison pycnometer (Beckman Model 930, Beckman Instruments, London) with air as reference. Bulk and tapped densities were determined using an automatic tapping device similar to that described by Neumann (1967). One hundred taps were used to obtain the final tapped density. Particle size distributions were determined by sieve analysis. The friability of the granules was assessed using a Roche friabilator incorporating polythene spheres as described by Rubinstein & Musikabhumma (1978). The mean granule diameter was calculated before and after each determination. Scanning electron photomicrographs of the granules were also taken.

Tablet properties

Uniformity of weight was measured by weighing ten tablets and the coefficient of variation (c.v.) calculated and found to be generally below 1% (maximum 2%); batch to batch variations were insignificant. Apparent tablet density was determined from tablet weight and volume measurements. The tablet porosity was calculated from the knowledge of the true density of the compression mix and the apparent tablet density. The crushing strengths of at least ten tablets were determined using a Schleuniger hardness tester and a mean value was obtained. The friability of five tablets from each batch was determined using the Beecham friabilator which consists of six screw capped cylinders 3·8 cm in diameter and 8·7 cm long, rotating at 1 Hz. The apparatus was run for 1000 revolutions and the percentage of weight lost was calculated. The tablets produced were relatively non-friable (below 2%) and interbatch differences were insignificant. Disintegration time of tablets was measured using the B.P. 1973 method except that two tablets were tested in each tube and the mean of three determinations obtained. The dissolution rates of the tablets were measured using an apparatus similar to that described in the U.S.P. and the concentration of potassium phenethicillin in

the dissolution medium was determined, at 268 nm (Khan & Rooke 1976). The surface area of both granules and tablets was measured using multipoint analysis on a Quantasorb surface area machine (Quantochrome Corporation, New York) using a mixture of nitrogen and helium.

To ensure that the results were not peculiar to the batch of potassium phenethicillin used, compressional properties of another batch of potassium phenethicillin (4340), slugged at 49 and 198 MNm^{-2}, were also examined. Scanning electron photomicrographs of the surface of tablets prepared from slugs compacted at 49 and 196 MNm^{-2} were also taken.

RESULTS AND DISCUSSION

The packing density (PD = tapped bulk density/true density) of granules obtained from formulation A and B after milling single and double compressed slugs at four pressures show (Fig. 2) that an increase in slugging pressures increased the packing densities of the granules. The packing densities of double slugged granules were also greater than those prepared by single slugging. Similar results were reported by Selkirk & Ganderton (1970), who found that higher slugging pressures reduced the porosity of slugs and milling of these slugs produced granules with similar variations in intragranular porosity (Porosity = 1 − PD).

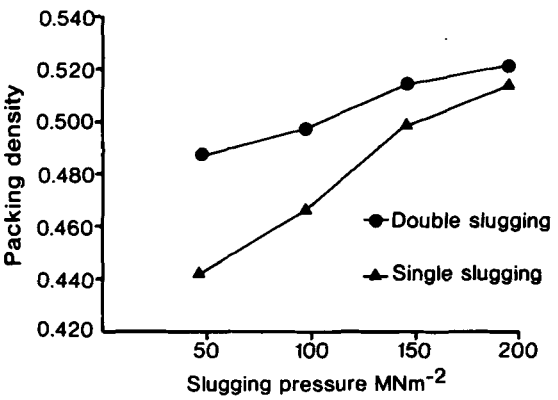

FIG. 2. Effect of the slugging pressure on the packing densities (P.D.) of granules.

Fig. 3A shows the crushing strength applied pressure profiles of tablets prepared from formulation A, single slugged at four compaction pressures. The tablets manufactured from granules prepared from slugs made at lower pressures were stronger than those made from granules obtained from slugs prepared at higher pressures. In fact, there was a progressive decrease in compressibility with increasing slugging pressure. Fig. 3B shows the crushing strength/pressure profiles of granules (Formulation B) prepared by double slugging. Here again, although the differences were small, the behaviour was similar to that observed for single slugging.

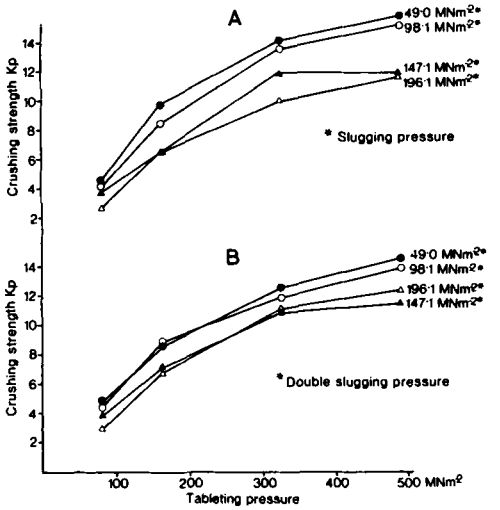

FIG. 3. Crushing strength compaction pressure profiles of tablets prepared from granules obtained from slugs single compressed (A) and double compressed (B) at various pressures.

The crushing strengths of tablets prepared from granules obtained from single slugging at 49 and 98 MNm^{-2} were slightly higher than those of tablets prepared from granules obtained from double slugged material at these pressures (cf Figs 2 and 3A). However, at higher slugging pressures (147 and 196 MNm^{-2}) granules produced from both single and double slugging processes yielded granules of similar compressibilities and packing densities (see Fig. 2). The better compressibility of granules obtained from single slugging especially at low pressures, could be the result of their lower strength and packing density, which permitted more consolidation, fragmentation and stronger bond formation in compression. The tablet porosity also varied to some degree with the slugging pressure (Table 1). The granules obtained from slugs compressed once at low pressure, which would be expected to have higher intergranular porosity (Selkirk & Ganderton 1970), produced compacts of higher porosity at lower tableting pressures. However the tablets produced from the granules obtained from double slugging were less porous at lower tableting pressures than those prepared from single slugs. This difference in porosities may be attributed to the higher packing

Table 1. The effect of applied pressure on the properties of potassium phenethicillin prepared by single and double slugging (Formulations A and B).

Applied compression pressure (MNm^{-2})		Single slugging		Double slugging	
Slugging	Tableting	Porosity %	Disintegration time min	Porosity %	Disintegration time min
	82	29·77	3·62	23·94	4·07
49	162	20·47	3·70	18·73	4·15
	327	12·44	3·73	11·37	4·17
	490	10·03	3·97	9·16	4·43
	82	27·49	3·92	24·48	4·33
98	163	19·53	4·03	18·66	4·27
	327	11·84	4·32	12·37	4·45
	490	9·36	4·55	9·03	4·45
	82	29·48	4 05	23·95	4·42
147	163	17·46	4·08	18·66	4·20
	327	12·64	4·50	12·84	4·30
	490	9·50	4·57	9·30	4·37
	82	23·81	4·25	21·87	3·98
196	163	16·79	4·43	20·07	4·30
	327	12·24	4·55	11·71	4·53
	490	9·63	4·67	9·36	4·57

density (Fig. 2) and, probably, lower intergranular porosity of double slugged granules. However, at higher tableting pressure, the slugging pressure had little effect on the compact porosity. Also, there was little difference between the porosities of compacts produced at 490 MNm^{-2} from single or double slugged granules. These results are similar to those reported by Selkirk & Ganderton (1970) who found that granulation by slugging destroyed the pore structure of tablets made at higher pressure. Because of the high water solubility of potassium phenethicillin and the presence of hydrophilic components (e.g. MCC and sodium starch glycolate), the disintegration times were generally unaffected by the variation in porosity produced by the increase in slugging or tableting pressures (Table 1). The dissolution results followed the same pattern and showed no real differences between tablets compacted at various pressures, and are therefore not reported.

Table 2. The effect of compression pressure on the properties of potassium phenethicillin tablets prepared from single slugging (Formulation C, sieve fraction 355 μ–500 μ).

Applied compression pressure (MNm^{-2})		Crushing Strength	Porosity
Slugging	Tableting	Kp	%
	82	7·7	23·55
49	163	10·3	15·85
	327	18·2	10·3
	490	19·3	8·36
	82	3·6	22·21
196	163	7·0	16·39
	327	11·9	10·84
	490	13·1	8·63

To determine if the differences in granule compressibility reported earlier (Fig. 3A, B) were influenced by particle size, sieve fractions of slug formulation C, were compacted and their crushing strength and porosities are shown in Table 2. For tablets of similar porosities, the crushing strength of tablets produced from a given granule size fraction obtained from slugs made at a lower pressure, was significantly higher than that of tablets produced from the same granule size fraction but obtained from slugs made at higher pressures. Therefore, the differences in the compressibilities of the granules obtained from slugs made at lower and higher pressures do not appear to be a function of the granule size, but may be influenced by other granule properties, e.g. strength and structure.

Table 3. Friability of granules produced by single slugging potassium phenethicillin at various pressures (Formulation A).

Slugging Pressure MNm^{-2}	Friability %
49	15·7
98	11·7
187	9·4
196	9·0

To determine if the strengths of granules produced by lower and higher pressure systems were different, the friability of the granules was measured (Table 3). As expected, the granules from slugs made at lower pressures were more friable than those from slugs made a higher pressures. Because lower granule

strength and higher intragranular porosity would permit more granule fragmentation and stronger bond formation, the lower pressure granule/slug system produced stronger tablets. Rue (1978) has shown that plastically deforming sodium chloride undergoes work-hardening and then behaves as a brittle material. It is possible that potassium phenethicillin granules also undergo some work-hardening especially when prepared at higher slugging pressure.

The results of surface area measurements of tablets prepared from Formulation C (Table 4), showed that the overall reduction in the surface area caused by an increase in the tableting pressures, was greater for the tablets made from softer granules than that shown by tablets made from the harder granules. These results support the hypothesis that the harder granules yield to a lesser degree and thus expose fewer new surfaces for bonding.

Table 4. The effect of slugging pressure on the specific area of potassium phenethicillin tablets (Formulation C).

Tableting pressure MNm^{-2}	Specific surface area $m^2\ g^{-1}$	
	Slugging pressure (MNm^{-2})	
	49·0	196
82	6·46	4·43
163	5·32	4·56
327	1·98	1·51
490	1·30	1·30

The scanning electron photomicrographs did not reveal any differences in the structure of granules obtained from slugs made at lower and higher pressure. However, the surface of compacts prepared from soft and harder granules were different. The surface of tablets compressed at 49 MNm^{-2} made from lower pressure slug system were the more uniform whereas compacts prepared at the same pressure from denser and harder granules showed more surface cracks which can be attributed to elastic deformation.

Fig. 4 shows the crushing strength/pressure profiles of tablets prepared from two different raw material batches of potassium phenethicillin. It is evident that there is good agreement between these two batches and that in both cases, softer slugs produced stronger compacts.

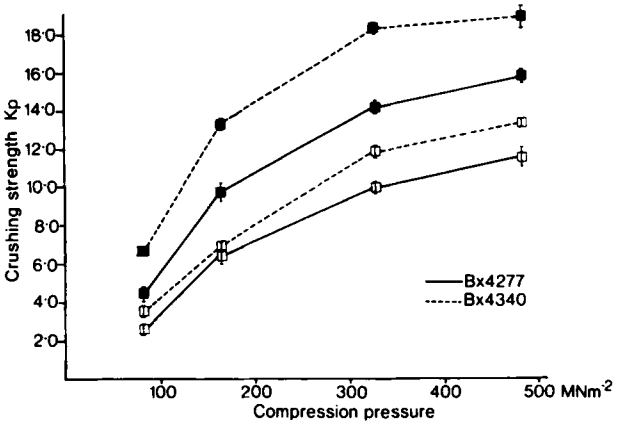

FIG. 4. Crushing strength compaction pressure profiles of tablets prepared from granules obtained by slugging two different batches of potassium phenethicillin at 49 and 196 MNm^{-2} compaction pressures.

In conclusion, this investigation emphasizes the need for full compressional studies and the optimization of slugging pressures for the manufacture of tablets by pre-compression. It also suggests that for some formulations lower slugging pressures may produce compacts of higher strength and quality.

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