DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(3), 349-361 (1983)

EFFECT OF RE-COMPRESSION ON THE PROPERTIES OF TABLETS PREPARED BY MOIST GRANULATION

S. Malkowska, K.A. Khan*, R. Lentle, J. Marchant and G. Elger
Beecham Pharmaceuticals,
Biosciences Research Centre,
Great Burgh, Yew Tree Bottom Road,
Epsom, Surrey. KT18 5XQ

ABSTRACT

The effect of re-compression on the properties of tablets prepared by moist granulation using various binding agents was examined. The results show that re-working by dry granulation and re-compression (i.e. a slugging process) caused a reduction in tablet strength, which was related to the initial compaction pressure. This loss of compressibility was attributed to work hardening of granules during the compaction process. However, when compacts were milled, re-wetted and then re-compressed, the tablets produced were of similar strength to those obtained on initial compaction. Re-wetting reversed the effect of work hardening by reactivating the binder to produce granules more porous than those obtained by dry granulation.

---

*Present address: Head of Pharmaceutical Formulation, The Boots Company Limited, Nottingham.

This paper is based on a presentation made to the 31st National meeting of the Academy of Pharmaceutical Sciences, American Pharmaceutical Association, held at Orlando, Florida, U.S.A. on November 15-19th, 1981.

 0363-9045/83/0903-0349$3.50/0

INTRODUCTION

Recently Malkowska and Khan[1] reported that re-working reduced the compressibility of some direct compression excipients. A method for estimating the re-working potential was proposed and it was suggested that some excipients undergo work hardening during the compaction process. This study extends the investigation to formulations prepared by moist granulation, which are also re-worked in practice. The effects of dry granulation and re-wetting on the properties of tablets initially prepared by moist granulation with various binding agents were evaluated.

Paracetamol was chosen as a model drug as it exhibits poor compression properties and lactose for its widespread use as a diluent in moist granulation.

MATERIALS

Paracetamol B.P. (Graesser Salicylates Ltd., Clwyd, U.K.). Lactose B.P. (Whey Products, Unigate Foods Ltd., Trowbridge, U.K.). Sodium starch glycolate, Explotab (K. & K. Greeff, Croydon, U.K.). Hydroxypropyl methylcellulose, Pharmacoat 603 (Shin-Etsu Chemical Company, Tokyo, Japan). Hydrolysed gelatin, Protein S (Croda Colloids Ltd., Plymouth, U.K.). Polyvinyl pyrrolidone, Kollidon 25 (Blagden Campbell Chemicals Ltd., Croydon, U.K.). Maize starch (Laing National Ltd., Manchester, U.K.). Magnesium stearate (Durham Raw Materials Ltd., Durham, U.K.).

METHOD

The following two formulations were used:

A. Paracetamol Formulations

	%
Paracetamol	92
Sodium starch glycolate	2.5

Binder *	5
Magnesium stearate	0.5

* Hydroxypropyl methylcellulose (HPMC), polyvinyl pyrrolidone (PVP), hydrolysed gelatin or maize starch paste.

B. Lactose Formulation

	%
Lactose	92
Sodium starch glycolate	2.5
HPMC	5
Magnesium stearate	0.5

Paracetamol or lactose was mixed with sodium starch glycolate in a planetary mixer (Hobart, U.K.) and then granulated with an aqueous solution of the binder. This mass was then passed through a 2000µm screen on a rotorgranulator (Mark III, Manesty Machines Ltd., Speke, U.K.). The granules were dried in a tray oven at 45°C for about 18 hours and the moisture content, determined by loss of weight on drying, ranged from 0.5 - 1%. The granules were separated to obtain the -400 +1400µm sieve fraction. 0.5%w/w magnesium stearate, prescreened through a 250µm sieve, was incorporated into the granule sieve fraction by mixing in a planetary mixer at slow speed for five minutes.

Granule Properties

The tapped densities of the granules were determined using the procedure described by Neumann[2] and one hundred taps were used to obtain the final tapped volume.

Tableting

The granules were compressed into 200mg compacts on an instrumented single punch machine (F, Manesty, Speke, U.K.) using 8mm flat faced punches at a range of pressures (33-263MNm^{-2}).

Tablets made at two pressures (e.g. 79 and 263MNm^{-2} for paracetamol granulated with HPMC) were then milled for re-processing by the following two methods:

1. Dry granulation and re-compression

This re-working process was similar to the conventional slugging process and involved milling of tablets followed by re-compression. The tablets were milled using an Apex comminuting mill (Apex Construction Ltd., Northfleet, Kent, U.K.) fitted with an 0.107 inch aperture screen operating at slow speed with knives forward. The granules obtained were separated into the same sieve fraction used for initial compaction. These were then re-compressed under the same conditions used for initial compaction (e.g. tablet weight, pressures). No further magnesium stearate was added.

2. Re-wetting and re-compression

The effect of re-wetting followed by re-compression was examined using paracetamol granulated with HPMC and PVP and lactose granulated with HPMC. Tablets were milled using an Apex comminuting mill fitted with a 0.027 inch aperture screen operating at fast speed with hammers forward. The milled powder was re-granulated with water and the wet mass was passed through a 2000µm screen on the rotorgranulator. The granules were then dried as described above, separated into the -400 +1400µm sieve fraction and re-compressed under the same conditions used for initial compaction (e.g. tablet weight, pressures). 0.5% extra-granular magnesium stearate was incorporated as previously described.

Tablet Properties

The uniformity of tablet weight was measured by weighing five tablets and the coefficient of variation calculated. The apparent tablet density was calculated from tablet weight and volume

$$\text{Reworking potential} = \frac{\text{Area under recompression curve (A)}}{\text{Area under 1st compression curve (A+B)}} \times 100$$

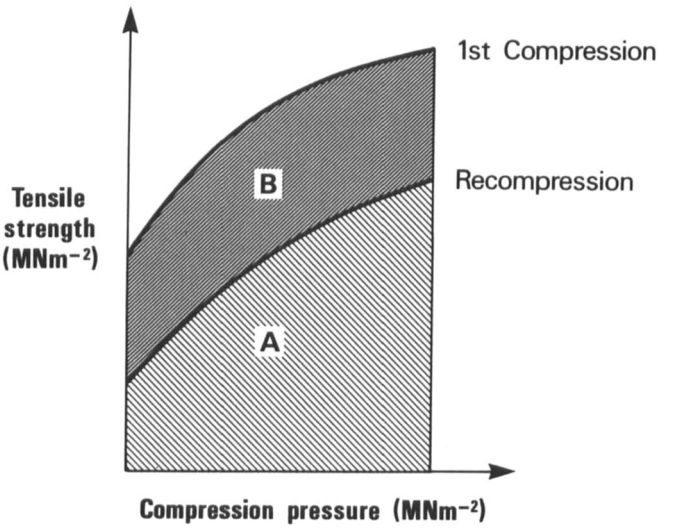

FIGURE 1

The determination of re-working potential

measurements. Tablet tensile strength was determined from the force required to fracture tablets by diametral compression on a motorised hardness tester (G.B. Caleva Ltd., Ascot, U.K.) using the method described by Fell and Newton[3]. The tablet friability was determined using a Beecham Friabilator[4]. The disintegration time of tablets was measured using the B.P. method with one tablet in each tube. The re-working potential of granules prepared by moist granulation was calculated by determining the area under the tensile strength/re-compression pressure profile as a percentage of the area under the initial tensile strength/compression pressure profile (Fig. 1).

RESULTS AND DISCUSSION

Table 1 shows the effect of compression on the tapped density of paracetamol and lactose granules. The granules

TABLE 1

The effect of compression on the tapped density of granules

MATERIAL/BINDER	RE-WORKING GRANULATION METHOD	APPLIED COMPRESSION PRESSURE (MNm^{-2})	TAPPED DENSITY (gcm^{-3})
Paracetamol/HPMC	Initial	-	0.50
	Dry	79	0.62
	Dry	263	0.69
	Wet	79	0.46
	Wet	263	0.47
Paracetamol/PVP	Initial	-	0.50
	Dry	85	0.64
	Dry	263	0.67
	Wet	85	0.46
	Wet	263	0.44
Paracetamol/ hydrolysed gelatin	Initial	-	0.48
	Dry	33	0.57
	Dry	131	0.65
Paracetamol/starch	Initial	-	0.46
	Dry	33	0.56
	Dry	131	0.63
Lactose/HPMC	Initial	-	0.55
	Dry	66	0.70
	Dry	263	0.80
	Wet	66	0.66
	Wet	263	0.65

obtained by dry granulation have higher tapped densities compared to the initial uncompressed granules and as before[1], the tapped density increases with an increase in compaction pressure. The tapped densities of paracetamol granules obtained after re-wetting are not affected by the initial compaction pressure and the granules produced are more porous than those obtained after dry granulation.

The coefficient of tablet weight variation was well below 2% and the apparent tablet densities of initial and re-compressed paracetamol and lactose tablets at given compaction pressures were virtually identical (range 0.9 - 1.4gcm^{-3}). Therefore, as for direct compression excipients[1], re-compression has little or no effect on tablet weight variation or density.

Fig. 2 shows the effect of re-compression (dry granulation) on the tensile strength/compression pressure profiles of paracetamol tablets containing HPMC. These results are typical of those obtained with PVP, hydrolysed gelatin and starch paste and show a reduction in compressibility upon re-working. Granules, obtained from compacts initially made at a low pressure

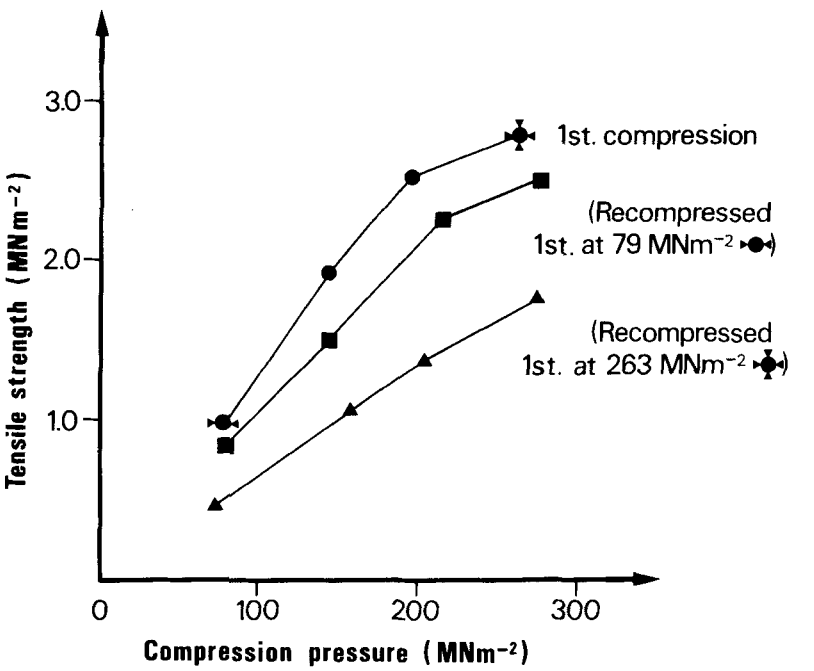

FIGURE 2

The effect of re-compression on the tensile strength/compression pressure profiles of paracetamol tablets containing HPMC

($79MNm^{-2}$), produce stronger tablets than those derived from compacts made at a higher pressure ($263MNm^{-2}$). Similar data was obtained with direct compression excipients[1]. HPMC and PVP produce stronger tablets than hydrolysed gelatin and starch paste but the re-working potentials of these formulations are almost identical and thus not affected by the type of binder used (Fig.3). The tensile strength/compression pressure profile of lactose tablets containing HPMC (Fig. 4) shows a reduction in tensile strength on re-compression (dry granulation). This decrease in the re-working potential of both paracetamol and lactose systems (Figs. 3 and 4) may be caused by work hardening of formulation components. The wet massed granules initially consist of paracetamol (or lactose) particles entrapped within the binder matrix[5]. The porous granules produced fragment and deform readily and the binder contributes predominantly to the inter-granular bonding process. However re-processed, work hardened granules resist deformation and fragmentation and thus fewer new binder surfaces for bonding are generated. In contrast, the structure of granules produced after re-wetting is essentially similar to the initial granules and thus the difference in their compressibilities is also small. The data presented in Table 2 shows a slight increase in tablet strength which may be caused by better binder distribution in both systems and improved salt bridging in lactose granules during the re-wetting process.

It has previously been shown that a comparison of the friability values of tablets before and after re-compression provides an indication of work hardening[1]. Table 3 shows some typical results of the effect of re-compression on the friability of tablets prepared by moist granulation. As before[1], re-working by dry granulation increases the friability of tablets; the effect is more pronounced when the initial compaction is carried out at higher pressures. On the other hand, re-wetting

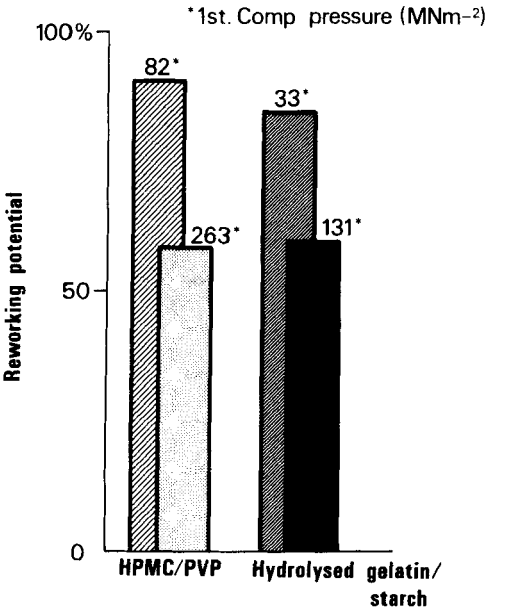

FIGURE 3

Re-working potential of paracetamol granulated with various binders

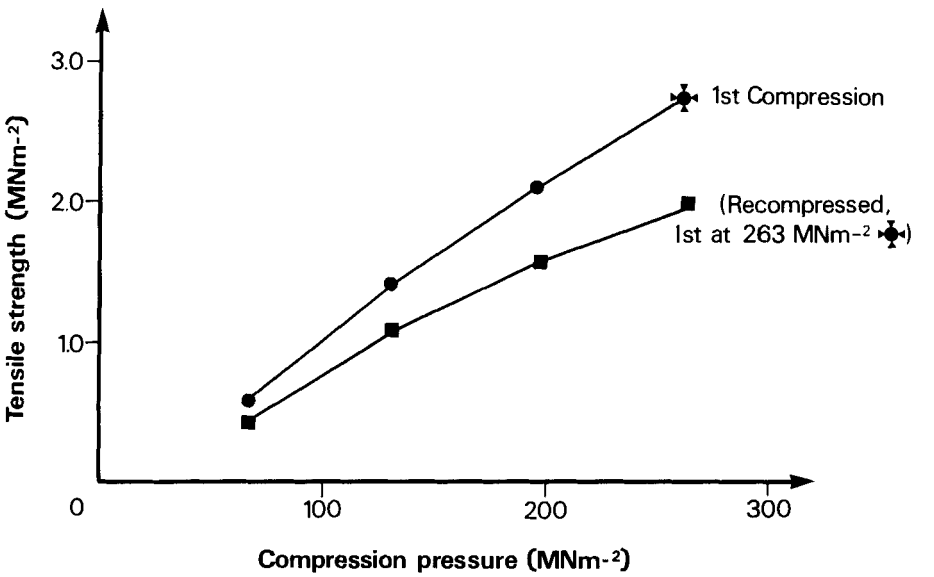

FIGURE 4

The effect of re-compression on the tensile strength/compression pressure profiles of lactose tablets containing HPMC as binder

TABLE 2

Effect of re-wetting on tablet tensile strength

MATERIAL/ BINDER	APPLIED COMPRESSION PRESSURE (MNm^{-2})	TABLET TENSILE STRENGTH (MNm^{-2})		
		INITIAL	RE-COMPRESSED, INITIALLY AT LOW PRESSURE*	RE-COMPRESSED, INITIALLY AT HIGH PRESSURE*
Paracetamol/ HPMC	72	1.05	0.98	1.36
	125	2.26	2.70	2.45
	197	2.93	3.61	3.46
	256	3.11	4.38	3.98
Paracetamol/ PVP	66	1.08	0.84	1.05
	144	2.67	2.05	2.50
	210	3.77	3.08	3.98
	275	3.61	3.34	3.86
Lactose/HPMC	66	0.57	0.79	0.77
	131	1.43	1.53	1.65
	197	2.10	2.37	2.87
	263	2.79	2.98	3.73

*The low and high initial pressures for Paracetamol/HPMC are 72 and 256MNm^{-2}, for Paracetamol/PVP:66 and 275MNm^{-2} and Lactose/ HPMC:66 and 263MNm^{-2}.

TABLE 3

Effect of re-compression on the friability of lactose tablets

APPLIED COMPRESSION PRESSURE (MNm^{-2})	FRIABILITY %				
	INITIAL	RE-COMPRESSED, INITIALLY COMPRESSED AT 66MNm^{-2}		RE-COMPRESSED INITIALLY COMPRESSED AT 263MNm^{-2}	
		DRY	WET	DRY	WET
66	3.54	3.36	2.85	6.27	2.57
131	1.91	1.88	1.51	2.34	1.51
197	1.56	1.58	1.31	1.63	1.31
263	1.42	1.43	1.19	1.65	1.20

TABLE 4

Effect of re-compression on the disintegration time of tablets compressed at 131MNm^{-2}

MATERIAL/BINDER	RE-WORKING GRANULATION METHOD	INITIAL COMPRESSION PRESSURE (MNm^{-2})	DISINTEGRATION TIME (MIN)
Paracetamol/HPMC	Initial	-	13.4
	Dry	79	11.3
	Dry	263	12.9
	Initial	-	19.2
	Wet	72	18.3
	Wet	256	22.8
Paracetamol/PVP	Initial	-	13.1
	Dry	85	16.6
	Dry	263	17.9
	Initial	-	17.0
	Wet	66	15.9
	Wet	263	16.4
Paracetamol/ Starch	Initial	-	0.9
	Dry	33	0.5
	Dry	131	0.7
Paracetamol/ hydrolysed gelatin	Initial	-	9.6
	Dry	33	6.0
	Dry	131	11.0
Lactose/HPMC	Initial	-	10.4
	Dry	66	11.4
	Dry	263	10.4
	Initial	-	10.4
	Wet	66	14.8
	Wet	263	16.7

followed by re-compression produces tablets of slightly lower friability than the initial compacts.

The tablet disintegration times appear to be affected by both formulation and re-processing factors (Table 4) although

further work in this area is necessary before any general conclusions can be drawn. The disintegration times of paracetamol tablets containing PVP increase after re-working by dry granulation but there is no effect on the disintegration times of paracetamol or lactose tablets containing HPMC. Similarly, re-processing by re-wetting has little effect on the disintegration times of paracetamol tablets containing PVP or HPMC but causes an increase in the disintegration time of lactose tablets containing HPMC, probably due to greater salt bridging and a reduction in granule porosity (cf. Table 1). In practice, the effect of re-processing on tablet disintegration may be difficult to predict as it will vary with the type of formulation and, in particular, the efficiency of the tablet disintegrant.

CONCLUSIONS

Re-working by dry granulation appears to cause work hardening which reduces the compressibility of granules derived from tablets prepared by both moist granulation and direct compression[1]. In contrast, re-processing by re-wetting reactivates the binder, producing porous granules which are essentially similar in structure and compressional characteristics to the original systems. Although the re-working potential of formulations produced by the re-wetting process is superior to those obtained by dry granulation, other tablet properties (i.e. stability, disintegration, dissolution) should also be considered.

ACKNOWLEDGEMENTS

The authors wish to thank M.J. Benton and M. Connor for the drawings and visual aids used in the talk.

REFERENCES

1) S. Malkowska and K.A. Khan, Drug Dev. Ind. Pharm. (submitted for publication).

2) B.S. Neumann, "H.S. Bean, A.H. Beckett, J.E. Carless (eds) Advances in Pharmaceutical Sciences, Vol. 2, Academic Press, London (1967).

3) J.T. Fell and J.M. Newton, J. Pharm. Sci., 59, 688 (1970).

4) K.A. Khan and P. Musikabhumma, J. Pharm. Pharmacol., 33, 627 (1981).

5) H. Seager, Paper presented to Postgraduate School on the Theory and Practice of Solid Dosage Form Manufacture, London, April 1981.