ELSEVIER

International Journal of Pharmaceutics 110 (1994) 203–210

international journal of pharmaceutics

Research Papers

An evaluation of microcrystalline cellulose and lactose excipients using an instrumented single station tablet press

Nagin K. Patel [a,*], Ajay H. Upadhyay [a], James S. Bergum [b], George E. Reier [b]

[a] *Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, Brooklyn, NY, USA*
[b] *Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ, USA*

(Received 27 July 1992; Modified version received 6 December 1993; Accepted 11 January 1994)

Abstract

The objective of this study was to evaluate the effects of microcrystalline cellulose of two particle sizes from two suppliers at two concentration levels, in combination with anhydrous lactose or Fast-Flo lactose on various properties of hydrochlorothiazide tablets. The powder blends before compression were evaluated for flow, density and compressibility. Tablets were compressed at three hardnesses and evaluated for friability, disintegration and hydrochlorothiazide dissolution. Powder blends containing Fast-Flo lactose exhibited a flow rate predicted to be sufficient for high-speed tableting whereas only when anhydrous lactose was used with the larger particle size microcrystalline cellulose was the same degree of flowability obtained. Density was affected by the concentration of microcrystalline cellulose. Fast-Flo lactose markedly increased density at the lower level of microcrystalline cellulose concentration. No difference was found in blend compressibility as a result of microcrystalline cellulose particle size or supplier source at medium to high tablet hardness levels, however, anhydrous lactose blends were more compressible than Fast-Flo lactose blends. At all hardness levels, tablets from all blends exhibited excellent friability. In most instances, tablet disintegration seemed to be more rapid when Fast-Flo lactose was present. Hydrochlorothiazide dissolution from all tablets easily met USP specifications. The microcrystalline cellulose from the two sources are interchangeable within particle size classification. Anhydrous lactose is more compressible than Fast-Flo lactose but Fast-Flo lactose is more flowable and its use results in more rapid drug dissolution at the higher microcrystalline cellulose levels.

Key words: Microcrystalline cellulose; Lactose; Direct compression tableting; Excipient evaluation

1. Introduction

The advantages of the direct compression process of tablet manufacture are well known. The wide-spread applicability of the method on a large scale can be traced to the development in the early 1960's of one excipient – microcrystalline cellulose – and the modification of another – lactose. These two materials, each of which can be used alone in a direct compression tablet formulation as a filler/binder with appropriate disintegrants and lubricants, have some disadvantages. Microcrystalline cellulose, while it is ex-

* Corresponding author.

SSDI 0378-5173(94)00013-U

tremely compressible and possesses disintegrant properties, does not flow adequately for high-speed production of tablets having uniform weight. Lactose, in some of its forms, is highly flowable but only moderately compressible and has no disintegrant properties. However, these two materials when used in combination make them an almost ideal mixture for direct compression tablet formulations.

For any material to be useful in a manufacturing operation, it must be consistent in it properties from batch to batch and vendor to vendor. In the case of microcrystalline cellulose, there was for many years only one supplier (FMC Corp.), and history of use indicates that the product supplied was indeed constant in its properties. The supplier recognized the flow problem present in the original product, Avicel PH 101, and developed a larger particle size product, Avicel PH 102, to address this problem. In 1986 a report appeared (Pesonen and Paronen) comparing a 'new' microcrystalline cellulose product, Emcocel, manufactured by Edward Mendell Co., with Avicel PH 101. The authors concluded that these products were equivalent. Subsequently, a number of reports have appeared comparing Avicel PH 101 with Emcocel and Avicel PH 102 with its larger particle size counterpart, Emcocel 90M (Doelker et al., 1987; Staniforth et al., 1988; Pesonen et al., 1989; Pesonen and Paronen 1990a,b; York et al., 1990). The products from the two manufacturers were found comparable in the properties evaluated.

It is perhaps not surprising that lactose, because it is a much older excipient than microcrystalline cellulose, is produced by many manufacturers in a variety of forms, both hydrous and anhydrous, some marketed specifically for direct compression applications. Koparkar et al. (1990) noted that hydrochlorothiazide dissolution was equivalent from tablet formulations containing either hydrous (Fast-Flo Lactose) or anhydrous lactose. Earlier, Whiteman and Yarwood (1988) recommended anhydrous lactose of the six direct compression lactoses they tested as the best for direct compression, followed by Fast-Flo. High-speed mixing has been found to alter the characteristics of tablet produced from some commercial grades of direct compression lactose through its direct effect on particle size (Thwaites et al., 1991). Differences in tablet hardness of a direct compression formulation were attributed to differences in particle size and surface area of powdered hydrous lactose obtained from two sources (Whiteman and Yarwood, 1990). In contrast, Ishino et al. (1990) found no differences in compact hardness or density as a result of differences in lactose particle size or compression speed.

It is widely recognized that mixtures of microcrystalline cellulose and direct compression grades of lactose are excellent vehicles for direct compression tablet formulation and production. With reference to microcrystalline cellulose, the studies cited above deal with mechanistic and powder properties of the material alone. With the emergence of a second source of supply, interest has been generated to determine the equivalency of these products in formulations. Both the hydrous and anhydrous forms of lactose are used in direct compression formulations but the authors are unaware of any published reports regarding a comparison of formulation properties when they are used in conjunction with microcrystalline cellulose.

Powder blend properties and tablet characteristics of formulations containing microcrystalline cellulose from the two sources and anhydrous and hydrous lactose were studied to provide information as to the equivalency of the two sources of microcrystalline cellulose and the superiority, if any, of the two types of lactoses in practical direct compression formulations.

2. Materials and methods

2.1. Materials

Avicel PH 101 and Avicel PH 102 (microcrystalline cellulose, NF) were obtained from FMC Corp., Philadelphia, PA. Emcocel 50M (formerly known only as Emcocel) and Emcocel 90M (microcrystalline cellulose, NF) were obtained from Edward Mendell Co., Inc., Patterson, NY. Anhydrous lactose (lactose, NF, anhydrous) was obtained from Sheffield Products, Norwich, NY.

Fast-Flo lactose (lactose, NF, hydrous) was obtained from Foremost Ingredients Group, Baraboo, WI. Magnesium stearate, NF was obtained from Mallinckrodt, St. Louis, MO. Hydrochlorothiazide, USP was obtained from Vinchem, Inc., Chatham, NJ.

2.2. Experimental design

A full $2 \times 4 \times 2$ factorial design was used. The factors considered were microcrystalline cellulose level (25 and 50%), microcrystalline cellulose particle size and source (Avicel PH101, Avicel PH 102, Emcocel 50M, Emcocel 90M) and lactose type (anhydrous lactose, Fast-Flo lactose). 16 formulations (3 kg batch size each) were prepared utilizing a planetary mixer (Hobart Corp., Troy, OH) containing drug (hydrochlorothiazide), microcrystalline cellulose, lactose, and magnesium stearate. One series of formulations contained 25% microcrystalline cellulose and 62% lactose while the second series contained 50% microcrystalline cellulose and 37% lactose. In both series the drug concentration was held constant at 25 mg per 200 mg of formulation (the tablet weight) and the magnesium stearate was kept constant at 0.5%.

2.3. Powder blend properties

The flow rate of each powder blend was determined according to a previously described method (Patel et al., 1987). A Vanderkamp Tap Density Tester (VanKel Industries, Edison, NJ) was used to determine tap density (15 taps).

2.4. Tablet compression

Tablets (5/16 inch round standard concave) were compressed in three hardness ranges (9–11 SCU, 14–16 SCU and 19–21 SCU) on a Stokes F single punch tableting machine instrumented as described by Jerzewski and Rudnic (1986).

2.5. Tablet characteristics

A model HT-300 hardness tester (Key International, Englishtown, NJ) was used for hardness testing. Thickness was determined using a hand-held Ames gauge (Ames Co., Waltham, MA). 20 tablets were dropped 100 times in a Vanderkamp Friabilator to evaluate friability. Disintegration times were determined as described in the USP. The USP dissolution test for hydrochlorothiazide tablets was employed except that 50 rpm was used as the basket rotational speed. Where appropriate, procedure GLM of SAS was used in the analysis of a response variable (tablet characteristic). For each target hardness, a model which included all main effects and two-way interactions was run for each response variable. In some cases, specific contrasts were used to compare the microcrystalline celluloses for statistical significance.

3. Results and discussion

The flow rates and the tap densities of the powder blends are given in Tables 1 and 2. From these tables several observations can be made. The use of Fast-Flo lactose in place of anhydrous lactose increases flowability. Density is increased in the 25% microcrystalline cellulose blends by the use of Fast-Flo lactose but is approximately equal in the 50% microcrystalline cellulose blends. Increasing the percentage of microcrystalline cellulose in the blend decreases flow and density. Larger particle size microcrystalline cellulose improves flow but has little if any effect on tap density. The source of microcrystalline cellulose of a given particle size does not influence flow or density in any consistent manner.

Table 1
Flow rates (g/s) of formulation blends [a]

	25% MCC [b]		50% MCC [b]	
	Anhydrous lactose	Fast-Flo lactose	Anhydrous lactose	Fast-Flo lactose
Avicel PH101	3.5	7.8	2.1	5.7
Avicel PH102	5.6	8.4	5.7	7.1
Emcocel 50M	3.9	8.4	2.8	5.7
Emcocel 90M	5.9	9.4	6.0	6.7

[a] All values are the mean of three determinations.
[b] Microcrystalline cellulose.

Table 2
Tap densities (g/cm^3) of formulation blends [a]

	25% MCC [b]		50% MCC [b]	
	Anhydrous lactose	Fast-Flo lactose	Anhydrous lactose	Fast-Flo lactose
Avicel PH101	0.58	0.63	0.49	0.51
Avicel PH102	0.60	0.65	0.52	0.52
Emcocel 50M	0.59	0.64	0.50	0.50
Emcocel 90M	0.59	0.64	0.50	0.52

[a] All values are the mean of three determinations.
[b] Microcrystalline cellulose.

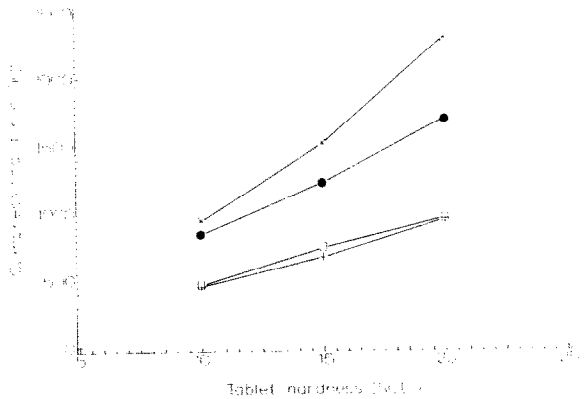

Fig. 1. Compressional force-hardness relationships for blends of 25% Avicel PH101 with Fast-Flo lactose (∗), anhydrous lactose (●) and 50% Avicel PH101 with Fast-Flo lactose (□) and anhydrous lactose (+).

These observations are to be expected assuming that the microcrystalline celluloses from the two sources are identical. Fast-Flo lactose particles are spherical and tend to exhibit improved flow and better packing than anhydrous lactose particles which are irregular in shape. Increasing the size of microcrystalline cellulose particles, which tend to interlock because of their needle-like shape, improves flow.

Experience with various formulations in these laboratories has shown that a flow rate of at least 4.0 g/s is necessary to obtain minimum tablet weight variation during high-speed tableting. On this basis, it would appear that Fast-Flo lactose, in the concentrations studied, with both particle size microcrystalline celluloses would result in satisfactory formulations whereas anhydrous lactose would need to be limited to use with only the larger particle size microcrystalline cellulose.

Compression force-hardness profiles are given in Fig. 1–4. From these and Table 3, it can be seen that those formulations containing 50% microcrystalline cellulose are more compressible than those containing 25%. That is, to produce a tablet having hardness in the ranges studied (mid-points plotted), less compression force is needed when 50% microcrystalline cellulose is present as compared to 25%. Similarly, anhydrous lactose is more compressible than Fast-Flo lactose over the range of hardness studied, particularly in the 25% microcrystalline cellulose formulations. At the low hardness level (both levels of microcrystalline cellulose), the effect of interaction between lactose type and microcrystalline cellulose percent on compressibility is marginal ($p = 0.10$) but at medium to high hardnesses the interaction is significant ($p < 0.05$).

The particle size of the microcrystalline cellulose has a significant effect on compressibility ($p < 0.02$) at the low hardness level. Also at the low hardness level, there is a marginal interaction ($p = 0.09$) between the effect of microcrystalline cellulose particle size and level on compressibility. In the 50% blends, Emcocel 50M gives rise to about the same effect on compressibility as Avicel PH101, and Emcocel 90M produces about the same effect as Avicel PH102. At the 25% level,

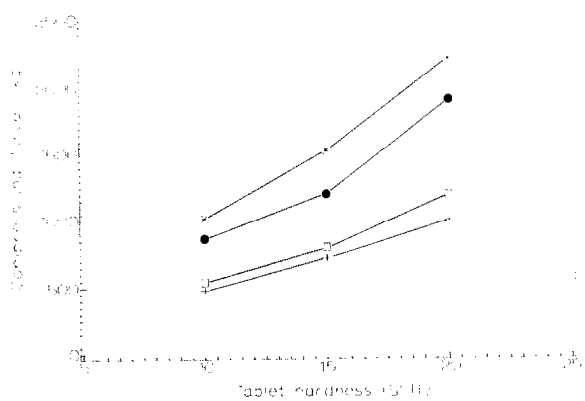

Fig. 2. Compressional force-hardness relationships for blends of 25% Avicel PH102 with Fast-Flo lactose (∗), anhydrous lactose (●) and 50% Avicel PH102 with Fast-Flo lactose (□) and anhydrous lactose (+).

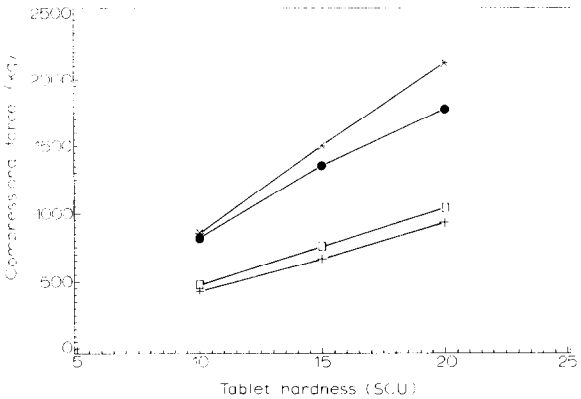

Fig. 3. Compressional force-hardness relationships for blends of 25% Emcocel 50 M with Fast-Flo lactose (*), anhydrous lactose (●) and 50% Emcocel 50 M with Fast-Flo lactose (□) and anhydrous lactose (+).

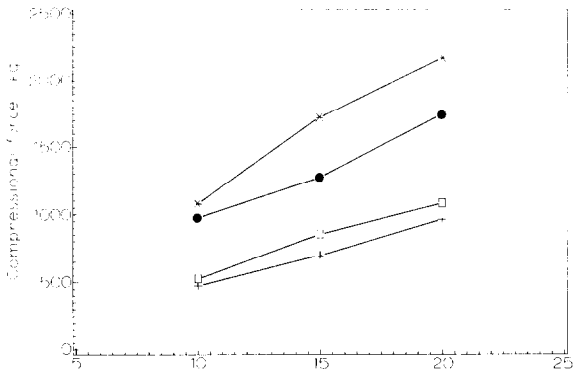

Fig. 4. Compressional force-hardness relationships for blends of 25% Emcocel 90 M with Fast-Flo lactose (*), anhydrous lactose (●) and 50% Emcocel 90 M with Fast-Flo lactose (□) and anhydrous lactose (+).

Table 3
Upper punch compression force (kg)

	Anhydrous lactose			Fast-Flo lactose		
Hardness (SCU):	9–11	14–16	19–21	9–11	14–16	19–21
25% microcrystalline cellulose						
Avicel PH101	843	1226	1693	943	1512	2300
Avicel PH102	865	1198	1901	1017	1524	2210
Emcocel 50M	822	1352	1776	852	1499	2116
Emcocel 90M	974	1273	1745	1079	1726	2164
50% microcrystalline cellulose						
Avicel PH101	451	668	948	461	738	957
Avicel PH102	478	715	999	541	793	1187
Emcocel 50M	428	664	929	470	754	1035
Emcocel 90M	473	695	964	523	853	1080

Table 4
Tablet thickness (inches) [a]

	Anhydrous lactose			Fast-Flo lactose		
Hardness (SCU):	9–11	14–16	19–21	9–11	14–16	19–21
25% microcrystalline cellulose						
Avicel PH101	0.160	0.154	0.150	0.158	0.152	0.148
Avicel PH102	0.158	0.153	0.147	0.159	0.152	0.148
Emcocel 50M	0.159	0.153	0.148	0.159	0.153	0.148
Emcocel 90M	0.160	0.154	0.150	0.157	0.151	0.147
50% microcrystalline cellulose						
Avicel PH101	0.170	0.161	0.155	0.171	0.160	0.156
Avicel PH102	0.169	0.161	0.155	0.168	0.160	0.153
Emcocel 50M	0.172	0.162	0.156	0.173	0.163	0.156
Emcocel 90M	0.169	0.160	0.155	0.170	0.159	0.154

[a] All values are the mean of six determinations.

Table 5
Tablet disintegration time (s) [a]

	Anhydrous lactose			Fast-Flo lactose		
Hardness (SCU):	9–11	14–16	19–21	9–11	14–16	19–21
25% microcrystalline cellulose						
Avicel PH101	101	334	683	43	344	798
Avicel PH102	109	358	719	28	114	518
Emcocel 50M	176	420	673	33	216	736
Emcocel 90M	164	457	729	34	290	884
50% microcrystalline cellulose						
Avicel PH101	29	77	194	18	30	78
Avicel PH102	23	58	214	13	23	49
Emcocel 50M	27	80	197	26	32	57
Emcocel 90M	26	80	288	15	26	103

[a] All values are the mean of two determinations.

Avicel PH102 may be slightly more compressible than Emcocel 90M and Emcocel 50M may be slightly more compressible than Avicel PH101. However, at the medium and high hardness levels, there is no significant effect on compressibility due to microcrystalline cellulose source ($p > 0.19$).

It can be seen in Table 4, as one would expect, that tablet thickness decreases as compression pressure increases (hardness increases). Lactose type and microcrystalline cellulose particle size and source have no effect on tablet thickness. The use of 50% microcrystalline cellulose significantly increases tablet thickness ($p < 0.05$), perhaps as a result of needing less compression force and therefore less consolidation to obtain a given hardness,

When the microcrystalline cellulose level was at 25%, the friability of the tablets ranged from 0.01 to 0.04%. At 50% microcrystalline cellulose, the friability was zero in all cases except for the Emcocel 90M/anhydrous lactose combination compressed at the 9–11 hardness range where the value was 0.02%. There is no practical difference between the 25 and 50% microcrystalline cellulose levels. None approached values of friability considered unacceptable (> 0.5%).

From an inspection of the data in Table 5, it can be seen that tablets containing Fast-Flo lactose, in most cases, disintegrate more rapidly than those containing anhydrous lactose. This may be related in part to the internal structure of the tablets since, as noted above, to achieve the same hardness more compressional force is

Table 6
Amount (%) of hydrochlorothiazide released in 30 min from tablets [a]

	Anhydrous lactose			Fast-Flo lactose		
Hardness (SCU):	9–11	14–16	19–21	9–11	14–16	19–21
25% microcrystalline cellulose						
Avicel PH101	93.5	93.6	91.8	97.0	94.8	89.5
Avicel PH102	95.6	95.4	92.1	87.1	87.1	93.4
Emcocel 50M	93.5	92.7	90.5	86.3	85.8	83.0
Emcocel 90M	93.5	93.6	92.2	94.1	93.7	89.6
50% microcrystalline cellulose						
Avicel PH101	92.2	90.7	81.6	94.8	93.3	89.7
Avicel PH102	94.0	94.5	85.7	95.1	94.2	93.7
Emcocel 50M	92.0	83.0	71.5	92.2	88.7	80.7
Emcocel 90M	94.4	92.1	73.9	94.4	90.6	86.0

[a] All values are the mean of six determinations.

needed for formulations containing Fast-Flo lactose. The surface properties of Fast-Flo lactose may also lead to faster wetting.

An increase in microcrystalline cellulose content decreases disintegration times as would be expected, since this material functions as a swellable disintegrant. However, no clear trend regarding particle size or material source is apparent.

The 30 min dissolution values are listed in Table 6. For the harder tablets (19–21 SCU), Fast-Flo lactose and anhydrous lactose have about the same dissolution rate at the 25% microcrystalline cellulose level, however, at the 50% level tablets containing Fast-Flo lactose are about 10% faster than those containing anhydrous lactose.

The times for 60% of the hydrochlorothiazide to dissolve in the dissolution test are shown in Table 7. It is not possible to make comparisons between the formulations at the low tablet hardness level, since greater than 60% of the drug was in solution at the first sampling point (5 min). At the intermediate hardness level, the 50% microcrystalline cellulose tablets were marginally faster releasing and those formulations containing Fast-Flo lactose tended to be slightly more rapid in their release than those with anhydrous lactose. The source or particle size of microcrystalline cellulose seems not to be a factor.

At the high hardness level it is difficult to make comparisons among formulations, since the results for the 25% microcrystalline cellulose tablets containing both lactoses and the 50% microcrystalline cellulose tablets containing anhydrous lactose are similar. Dissolution times for the 50% microcrystalline cellulose tablets with Fast-Flo lactose are more rapid than the others, and the Avicels at this hardness level appear to promote the most rapid dissolution. However, as a practical matter, all of the results in Table 7 are within the USP specification of 60% dissolution within 60 min and therefore all formulations are satisfactory with regard to dissolution.

4. Conclusions

Based on the study of powder properties, combinations of either particle size microcrystalline cellulose with Fast-Flo lactose would flow at a rate predicted to be sufficient for high-speed tableting. The use of anhydrous lactose with larger particle size microcrystalline cellulose would also be satisfactory. Blend density is decreased by increasing microcrystalline cellulose content. Only at the lower microcrystalline cellulose content does the type of lactose have an effect on density. Under that condition, Fast-Flo lactose increases density compared to anhydrous lactose. Blends containing anhydrous lactose are more compressible than those containing Fast-Flo lactose and blends containing 50% microcrystalline cellulose are more compressible than those containing 25%. The smaller particle size microcrystalline cellu-

Table 7
Time (in min) for 60% release of hydrochlorothiazide from tablets [a]

	Anhydrous lactose			Fast-Flo lactose		
Hardness (SCU):	9–11	14–16	19–21	9–11	14–16	19–21
25% microcrystalline cellulose						
Avicel PH101	< 5	8.70	13.82	< 5	8.28	17.85
Avicel PH102	< 5	6.91	12.99	< 5	< 5	9.40
Emcocel 50M	< 5	8.56	14.37	< 5	8.61	15.90
Emcocel 90M	< 5	8.64	13.32	< 5	6.27	17.60
50% microcrystalline cellulose						
Avicel PH101	< 5	< 5	11.55	< 5	< 5	15.00
Avicel PH102	< 5	< 5	11.42	< 5	< 5	< 5
Emcocel 50M	< 5	9.71	18.09	< 5	5.19	19.42
Emcocel 90M	< 5	< 5	19.25	< 5	< 5	17.67

[a] All values are the mean of six determinations.

lose is more compressible than the larger at the low tablet hardness level. At medium to high tablet hardnesses there is no significant effect on compressibility due to microcrystalline cellulose source.

The tablets produced from all blends exhibited excellent friability at all hardness levels. While particle size or source of microcrystalline cellulose seems to have no effect on tablet distintegration, those tablets containing Fast-Flo lactose and the Avicel products, in some cases, had more rapid disintegration times than those containing anhydrous lactose. However, dissolution of hydrochlorothiazide from all tablet formulations easily met USP specifications.

In the formulations studied, the microcrystalline celluloses from the two sources are interchangeable within particle size classification. While anhydrous lactose is more compressible than Fast-Flo lactose, the latter is more flowable and its use in tablets containing 50% microcrystalline cellulose compressed at high tablet hardnesses results in more rapid drug dissolution.

Acknowledgements

This work was presented at the 1991 Meeting of the American Association of Pharmaceutical Scientists, Washington, DC. The presentation was supported by a grant from Edward Mendell Co., Inc.

References

Doelker, E., Mordier, D., Iten, H. and Humbert-Droz, P., Comparative tableting properties of sixteen microcrystalline celluloses. *Drug Dev. Ind. Pharm.*, 13 (1987) 1847–1875.

Ishino, R., Yoshino, H., Hirakawa, Y. and Noda, K., Influence of tabletting speed on compactibility and compressibility of two direct compressible powders under high speed compression. *Chem. Pharm. Bull.*, 38 (1990) 1987–1992.

Jerzewski, R.L. and Rudnic, E.M., The development of a low-cost intelligent tablet compression monitor using a personal computer. *Pharm. Technol.*, 10 (1986) 32–41.

Koparkar, A.D., Augsburger, L.L. and Shangraw, R.F., Intrinsic dissolution rates of tablet filler-binders and their influence on the dissolution of drugs from tablet formulations. *Pharm. Res.*, 7 (1990) 80–86.

Patel, N.K., Patel, B.R., Plakogiannis, F.M. and Reier, G.E., An evaluation of tricalcium phosphate excipients particularly using instrumented rotary and single station tablet presses. *Drug Dev. Ind. Pharm.*, 13 (1987) 2693–2718.

Pesonen, T. and Paronen, P., Compressional behavior of an agglomerated cellulose powder. *Drug Dev. Ind. Pharm.*, 16 (1990b) 591–612.

Pesonen, T. and Paronen, P., Evaluation of a new cellulose material as binding agent for direct compression of tablets. *Drug Dev. Ind. Pharm.*, 12 (1986) 2091–2111.

Pesonen, T. and Paronen, P., The effect of particle and powder properties on the mechanical properties of directly compressed cellulose tablets. *Drug Dev. Ind. Pharm.*, 16 (1990a) 31–54.

Pesonen, T., Paronen, P. and Ketolainen, J., Disintegrant properties of an agglomerated cellulose powder. *Int. J. Pharm.*, 57 (1989) 139–147.

Staniforth, J.N., Baichwal, A.R., Hart, J.P. and Heng, P.W.S., Effect of addition of water on the rheological and mechanical properties of microcrystalline celluloses. *Int. J. Pharm.*, 41 (1988) 231–236.

Thwaites, P.M., Mashadi, A.B. and Moore, W.D., An investigation of the effect of high speed mixing on the mechanical and physical properties of direct compression lactose. *Drug Dev. Ind. Pharm.*, 17 (1991) 503–517.

Whiteman, M. and Yarwood, R.J., The evaluation of six lactose-based materials as direct compression tablet excipients. *Drug Dev. Ind. Pharm.*, 14 (1988) 1023–1040.

Whiteman, M. and Yarwood, R.J., Variations in lactose NF from two different sources and their influence on tablet properties. *Drug Dev. Ind. Pharm.*, 16 (1990) 1815–1827.

York, P., Bassam, F., Rowe, R.C. and Roberts, R.J., Fracture mechanics of microcrystalline cellulose powders. *Int. J. Pharm.*, 66 (1990) 143–148.