DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(14), 2323-2331 (1994)

THE CHANGES IN THE MECHANIC PROPERTIES OF A DIRECT TABLETING AGENT MICROCRYSTALLINE CELLULOSE BY PRECOMPRESSION

Deniz Bilge BETEN[*1], Nilüfer YÜKSEL[*2], Tamer BAYKARA[*2,#]

***1 Université Libre de Bruxelles, Laboratoie de Pharmacie Galénique et Biopharmacie, CP 207, Boulevard de Triomphe, 1050 Brussels, Belgium**

***2 Department of Pharmaceutical Technology Faculty of Pharmacy, University of Ankara Tandoğan - Ankara - Turkey**

ABSTRACT

In the manufacturing of tablets, direct tableting agents are not only used in direct compression, but are also used in wet granulation and slugging methods. These agents are effective only if their particle size and form is appropriate. However, the precompression, milling and grinding which are applied in the slugging method changes the particular properties of these agents.

In this study, microcrystalline cellulose tablets were prepared both by direct compression and slugging. The consolidation, compressibility and flow properties of the two mixed powders were compared. Finally, it was observed that the compressibility of the mixed powder was influenced negatively by the slugging method.

[#]Author to whom correspondence should be addressed

INTRODUCTION

Direct tableting agents are used in the production of solid dosage forms not only by direct compression (DC), but also by wet and dry granulation. For example, microcrystalline cellulose (MCC) is used in both wet granulation and slugging process as it offers several advantages like rapid tablet disintegration due to its wicking action and optimization of tablet hardness without applying excessive compression force. As a result, the percentage of MCC to be used is at least 3 or 4 times less than that needed for direct compression (1).

The success of the direct compression formulations are closely associated with the manufracturing process of the direct tableting agent such as its particle size and crystal form (2).

During the slugging process, uniform slugs are formed by applying precompression and then these slugs are reduced to appropriate granule size for compression by grinding or milling which is responsible for the change in the particle size of the direct tableting agent thus influencing negatively its compressibility that is its dilution potential (3). The dilution potential is a non parametric value which by definition is low or high. Dilution indicates that the decrease of the percentage of the direct tableting agent in the tablet formulation depends on the amount of other ingredients in the formulation. One important advantage of these agents is that even at very low quantities they are compressible. However, when a certain dilution value is reached the direct tableting agent can no longer become compact; this value corresponds to the dilution potential of that agent. It is very difficult to determine this value for each agent and for this reason their compressibility is taken as reference.

In this study, tablets containing 20 % (MCC) and 75 % acetyl-salicylic acid (ASA) were prepared using direct compression and slugging process. In both methods the same quantity of (MCC) was used and the influence of precompression and grinding procedures on the compressibility of the powder blend and the dilution potential of the direct tableting agent was investigated, under these conditions.

EXPERIMENTAL

Materials :

Acetylsalicylic acid (Bayer, geometric sieve diameter; 0.167 mm) Microcrystalline cellulose (Avicel PH 101, FMC Corp., Humidity 5.5 %), Crospovidone (Kollidon CL, BASF AG), as lubricant mono-diglyceride and triglyceride mixture (BOESON VP, Boehringer Ingelheim GmbH) (4). Colloidal silicon dioxide (Aerosil-200, Deggusa AG).

Methods :

The formulation used is shown below :

ASA	0.300 g	75 %
MCC	0.080 g	20 %
Kollidon CL	0.016 g	4 %
Running Powder*	0.004	1 %

* Running Powder :

Boeson VP	50 g
Kollidon CL	30 g
Aerosil-200	20 g

The quantities indicated are calculated for 1500 tablets.

1- Direct Compression :

The first three powders indicated in the formulation were mixed during 20 min. at 20 rpm in a cubic mixer (Erweka) and then for another 5 min. after the addition of the running powder.

2- Slugging Process :

The powder mixture was prepared the same way as described for direct compression. Then slugs were prepared with a 20 mm flat face punch, in a single punch machine (Korsch EK-0). Afterwards these slugs were crushed (Erweka) and reduced to the appropriate granule size by using a sieve having apertures of 1 mm.

3- The Control for Powder and Granules :

3.1- Determination of Consolidation Properties of Powder and Granules :

The consolidation of 10 ml of each powder mixture was realized in a 10 ml graduated cylinder with a funnel, so that percolation could be avoided. Then the weight of 10 ml was determined, the bulk density (BD) being calculated thereafter. The graduated cylinder was tapped from a height of 25 mm and the resulting reduction in volume was measured after repeating this procedure 5, 10, 20, 30, 50, 75, 100, 120, 200, 300 and 500 times. The natural logarithm of the tapping values (N_T), thus obtained was plotted against the double (1n) of the relative density change (A) (Equa. 1) (5) and the parameters of the regression lines were investigated. Also, the ratio ID/BD and the Hausner Index (HI) were calculated.

$$A = \frac{TD - BD}{TD} \qquad \text{(Equation 1)}$$

A : Relative density change
TD : Tapp density
BD : Bulk density

3.2- Determination of the Compressibility of Powder and Granules :

The compression properties of each mixed powder were investigated using the HECKEL and KAWAKITA equations (6-9). For this purpose a 12 mm flat face punch and a hydraulic press were used. Equal volumes of powder or granules (1357.17 mm3) were pressed at 30.08, 75.21, 112.8, 150.5, 188.0, 225.7, 263.2, 300.1 and 376.1 mPa. When the desired pressure was reached, it was kept at this value for 20 sec. (10). The volume of the tablet; V_p, formed at each pressure level was calculated. Results were calculated with a computer programme written using the equation of HECKEL and KAWAKITA (11).

Heckel equation is;

$$1n \frac{V_p}{V_p - V_\infty} = kP + \frac{V_o}{V_o - V_\infty} \qquad \text{(Equation 2)}$$

V_o : Initial powder volume
V_p : The volume at each pressure value
V_∞ : The true volume of the solid (without pores)
k : Constant. HECKEL correlated the slope of the compaction curves, k, with the yield strength of the material being compressed ($k = 1/P_y$).

Kawakita equation is;

$$\frac{V_o - V_p}{V_o} = \frac{abP}{1 + bP} \qquad \text{(Equation 3)}$$

$$\text{or,} \quad \frac{P}{C} = \frac{1}{ab} + \frac{1}{a} \cdot P \qquad \text{(Equation 4)}$$

C : Degree of volume reduction (V_o-V_p/V_o = C)

V_o : Initial apperent volume of powder.

V_p : Powder volume under applied pressure (P).

a,b : Constants, characteristic of the powder.

In the KAWAKITA equation (a) is a numeric parameter indicating the initial porosity of the compressed powder mass and (b) is the compression coefficient (12).

3.3- Determination of the Flow Properties of Powder and Granules :

The flow rate was determined with Erweka flow tester by weighing each time the same quantitiy (40 g) of powder or granules (n = 5). In order to avoid segregation, the angle of repose was determined with the rotating drum method instead of the dynamic angle of repose method. The value of the angle of repose was calculated using a glass jar containing 25 ml of powder mass or granules which was rotated 4 times before each measurement (13).

RESULTS AND DISCUSSION

The consolidation parameters of granules (SLG) and powder mass (DC) are shown in Table 1. According to these results, the (r^2) value of (SLG) is closer to 1, thus indicating a regular bulk density. However, for (DC) the slope value of the consolidation line and (HI) is lower. These are expected results for a powder mass and granules (14). For granules a high (r^2) and slope value is normal (15), as the abundance of interparticular spaces result in a better compressibility (Fig. 1) (16).

According to the HECKEL equation, the powder mass of (DC) has a (r^2) value of 0.9758 which is higher than the (r^2) value of granules (SLG). Although

TABLE 1

(DC) and (SLG) consolidation parameters according to equation 1.

Type of Granules	r^2	Slope	Intercept	HI
DC	0.8696	0.0848±0.00978	-0.842±0.0831	1.28
SLG	0.9209	0.0920±0.00953	-0.672±0.0348	1.38

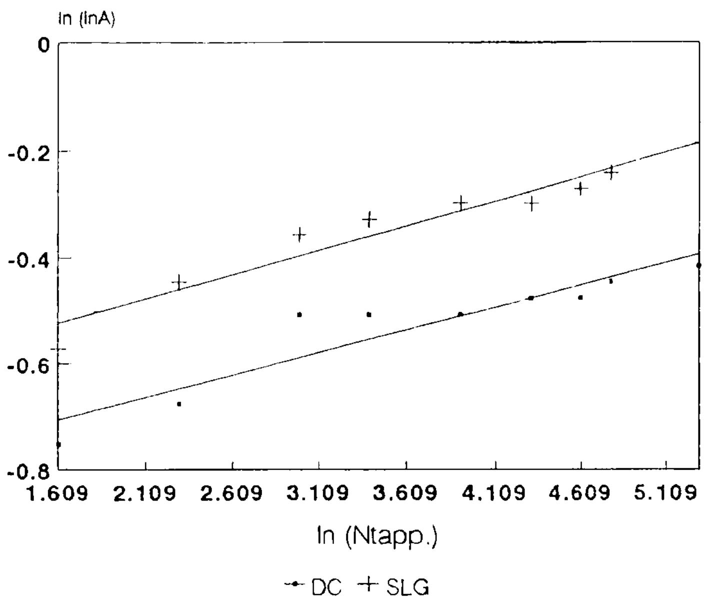

FIGURE 1

Consolidation of (DC) and (SLG) according to equation 1.

the same quantity of MCC is used for both methods, the yield pressure value (P_y) for (SLG) 569.0 mPa is five times higher than the value of (DC) 106.8 mPa. This is expected as in the (SLG) method the particle size and form of MCC is modified which results in changes of the (P_y) values (17).

The HECKEL equation shows that the powder mass (DC) is compressible at lower pressure values. In other words, the precompression applied in (SLG) influences negatively the dilution potential of MCC (Table 2).

TABLE 2

The compressibility parameters of (DC) and (SLG) according to HECKEL and KAWAKITA equations.

Type of Granules	Heckel Equation r^2	Heckel Equation P_y (mPa)	Kawakita Equation r^2	Kawakita Equation a	Kawakita Equation b
DC	0.9758	106.8	0.9999	0.9572	0.2174
SLG	0.7936	569.0	0.9997	0.5862	0.02258

TABLE 3

Flow rates and angle of repose of (DC) and (SLG).

Type of Granules	Flow rate (g/sec.) $X_1 \pm (S_x \cdot t_{0.05})$	Angle of repose $X_2 \pm (S_x \cdot t_{0.05})$
DC	11.56±0.109	26.9±0.864
SLG	13.61±0.0850	26.6±0.706

The (a) values in Table 2 are very similar to values in Table 1. The ratio between the consolidation values of (DC) and (SLG) are in parallel with their (a) values (8). The (b) values calculated by KAWAKITA equation is a parameter related to the elastic coefficient of the system (14). The ratio between the (b) values (0.2174 and 0.02258) (DC) and (SLG) is 1/10. These important differences in (Py) and (b) parameters of the granules of (SLG) indicate that the compressibility parameters of MCC are modified by recompression.

On the other hand, the flow rates of (DC) and (SLG) are significantly different ($p > 0.05$), as in each case the particle size and its distribution is very different (Table 3).

However, there is no significant difference between the values of angle of repose ($p < 0.05$).

The results of this study indicate that milling and grinding as well as precompression applied during slugging significantly modifies the (Py) value and the elastic coefficient of MCC.

REFERENCES

1- J.N. Staniforth, A.R. Baichwal, J.P. Hart & P.W.S. Heng, *Int. J. Pharm.*, 41, 231 (1988).

2- R.F. Shangraw, "Compressed Tablets by Direct Compression", Lieberman, H.A., Lachman, L. & Schwartz, J.B. (Eds.), "Pharmaceutical Dosage Forms : Tablets", Marcel Dekker Inc., New York, Vol. 1, 2nd Edition, 1989, P : 203-214.

3- C. Nyström & M. Glazer, *Int. J. Pharm.*, 23, 255 (1985).

4- G.K. Bolhuis, C.F. Lerk & P. Broersma, *Drug Dev. Ind. Pharm.*, 6 (1), 15 (1980).

5- T. Baykara, G. Duman & M.M. Süleyman, "Stampf-Kompressionseigenschaften von pharmazeutischen Pulvern und Pressmassen", Presented at the 49th Int. Pharm. Sci. Congress of F.I.P., Munich, September 4-9, 1989, P : 167.

6- R.W. Heckel, *Trans Met. Soc. A.I.M.E.*, 221, 671 (1961).

7- E.L. Parrott, "Compression", Lieberman, L. & Lachman, L. (Eds.), "Pharmaceutical Dosage Form : Tablets", Marcel Dekker Inc., New York, Vol. 2, 1981, P : 154.

8- M. Sheikh-Salem & J.T. Fell, *J. Pharm. Pharmacol.*, 33, 491 (1981).

9- K.H. Lüdde & K. Kawakita, *Die Pharmazie*, 21, 393 (1966).

10- K. Marschall, *Drug Dev. Ind. Pharm.*, 15 (13), 2153 (1989).

11- M.M. Süleyman & T. Baykara, "A microcomputer programme series for use in tablet technology", presented at the 3rd Int. Pharm. Technology Symposium, Ankara, September 9-11, 1986, P : 89.

12- P.J. James, *Powder Metall. Int.*, 4, 1 (1972).

13- J.N. Staniforth, *Int. J. Pharm. Tech. & Prod. Mfr.*, 3, (Supp.), 1 (1982).

14- E. Doelker, D. Mordier, H. Iten & P. Humbert-Droz, *Drug Dev. Ind. Pharm.*, 13 (9-11), 1847 (1987).

15- T. Baykara, G. Duman, K. Özşener, Ş. Ordu & B. Özateş, *Drug Dev. Ind. Pharm.*, 17 (17), 2359 (1991).

16- T. Baykara & F. Acartürk, *Drug Dev. Ind. Pharm.*, 15 (9), 1341 (1989).

17- D. Sixsmith, *J. Pharm. Pharmacol.*, 34, 345 (1982).