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COMMUNICATION

Influence of Avicel PH-301 on the Compressibility of α-Methyldopa and Phenobarbitone in Direct Compression

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ABSTRACT

The aim of this work was to investigate the compressibility behavior of α-methyldopa and phenobarbitone using a Korsch EK0 instrumented eccentric tablet machine, with force-time and force-displacement curves constructed and applied to calculate different compressional values to study the compressional behavior. The results of this work revealed a difference in compressibility behavior between the two drugs during the compressional process. α-Methyldopa gave an abnormal compressional curve with high friction in the pre- and postcompressional phases. A residual force could be seen on the lower punch. Furthermore, capping and sticking were observed visually during tablet pressing, indicating poor compressibility behavior. In the case of phenobarbitone, no friction was observed in the precompressional phase, but there was higher friction in the postcompressional phase, especially in the ejection phase. The compressibility of the drugs was improved by the addition of Avicel PH-301 and magnesium stearate.

Key Words: *Compressibility; Compressibility behavior; Compressional curves; Direct compression; Plasticity.*

INTRODUCTION

Compression during tableting is a complex and irreversible dynamic process (1). Several methods can be used to study compressibility, among them the measurement of force-displacement curves (2–6). Higuchi et al. (7,8) initiated fundamental research on tableting problems in the early 1950s, introducing a displacement measuring system during a compression process by means of an inductive displacement transducer. Several authors have reported about the instrumentation of tableting machines (9–11).

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Phenobarbitone is widely used as a sedative and antiepileptic drug. It can be given orally in doses of 15–30 mg for sedation and 50–100 mg as an anticonvulsant (12,13). Phenobarbitone may exhibit polymorphism and pseudopolymorphism (12,14). The crystals are difficult to compress directly.

α-Methyldopa is an antihypertensive drug. It can be given orally in an initial dose of 250 mg and a maintenance dose of 500–3000 mg/day (12,13). The direct compression of α-methyldopa is especially advantageous because of its decomposition in the presence of water (15).

It is well known that excipients influence the compressibility of drugs. Microcrystalline celluloses are frequently used as dry binders in direct compression. It was earlier found that Avicel PH-301 has better flowability and compactibility parameters than those of Avicel PH-101 (16), and that Avicel PH-301 exerts a positive influence on the compactibility properties of α-methyldopa and phenobarbitone (17).

The aim of this work was to evaluate the influence of Avicel PH-301 on the compressional behavior of α-methyldopa and phenobarbitone.

The tableting process begins when the upper punch starts to move down in the die filled with a certain quantity of powder. Particle rearrangement takes place by the particles slipping past each other, reducing the distances of contact between the particles without causing excessive deformation (18), with energy E_1 being consumed to overcome the friction in this precompressional phase. As the applied stress is increased and the stage is reached at which there is no more room for particle rearrangement, elastic and plastic deformation of the particles occur, consuming further energy E_2. Part of this deformation energy, the effective work *EW*, is used for the binding of the particles after the friction work *FW* exerted on the die walls in this compressional phase has been overcome, that is, $EW = E_2 - FW$. When the tablet has been made in the die and the upper punch starts to change direction and move upward, tablet expansion takes place as a result of elastic recovery in this decompressional phase and continues even after tablet ejection (19). The elastic recovery energy E_3 is a measure of the work a tablet does on expansion. Capping and lamination are attributed to the inability of compacts to relieve localized internal stress without failure (18,20), and their incidence depends on the plastic and elastic behaviors of the material used (21). E_1 depends on the compaction parameters of the material. $E_2 + E_3$ together comprise the compressional work *CW* done by the upper punch, where E_2 is the energy needed to form the tablet, and E_3 depends on the degree of elastic springing-back (22).

The absolute values for the work terms describe the magnitudes of the different types of work done during the tableting process. However, as these values do not give a realistic impression of the states of the different compressional phases for tablet forming, relative work values can be used for this. The relative work values were calculated by dividing each type of work by the compressional work (23).

Plasticity can be calculated from the absolute values according to Stamm and Mathis (2):

$$Pl_{S\text{-}M} = \frac{E_2}{E_2 + E_3} \cdot 100 \qquad (\%) \tag{1}$$

In our work, the plasticity was calculated from the relative work values by applying the following formulas:

$$Pl_A = 100 - RExpW \tag{2}$$

$$Pl_B = REW + RFW \tag{3}$$

The ability of formulated powders to form satisfactory tablets depends on their plastic deformation during compression and on their elastic recovery during decompression (24). The use of force-displacement curves allows the calculation of the work involved during tablet compaction (25). The work is calculated using the equation

$$W = \int_{s1}^{s2} F \cdot ds \tag{4}$$

where F is the force, and s is the displacement (23).

Work is required for particle rearrangement, deformation of particles, friction on the die wall, and the formation of bonds between particles (26).

EXPERIMENTAL

Materials

Phenobarbitone (Ph. Eur. 3) (Alkaloida, Tiszavasvári, Hungary), α-methyldopa (EGIS Pharmaceuticals, Ltd., Budapest, Hungary), Avicel PH-301 (FMC Corp., Philadelphia, PA), and magnesium stearate (Ph. Eur. 3) were used.

Compression Procedures

Formulations containing 50% drug substance, 46.5% Avicel PH-301, 3% talc, and 0.5% magnesium stearate were mixed for 5 min by a Turbula mixer (W. A. Bacho-

fen Maschinenfabrik, Basel, Switzerland) operating at 50 rpm. They were then compressed into tablets with a Korsch EK0 instrumented eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The compression tools were single flat punches 10 mm in diameter and furnished with strain gauges and a displacement transducer. The strain gauges allow the pressure forces on the upper and lower punches to be followed with force-measuring equipment, which was calibrated with a Wazau HM-HN-30 kN-D cell (Kaliber, Ltd., Budapest, Hungary). The displacement transducer was fitted over the upper punch. The transducer distance accuracy was checked using five measuring pieces of different thickness (2.0, 5.0, 7.5, 10.0, and 15.0 mm) under zero load (Mitutoyo, Tokyo, Japan). The compression was carried out electrically at 36 rpm at an air temperature of 24°C and an air relative humidity of 45%. There were 10 tablets compressed at each compression force for each drug formula. Lots with relative standard deviation not exceeding 5% were accepted.

Force-time and force-displacement curves were plotted, and the different energy/work relations were calculated from the curves.

RESULTS

Figure 1a presents the force-displacement (*F-d*) curves of α-methyldopa. The curve is abnormal, and an unequal force effect can be observed, which means that the deformation was hindered because of the friction in the die in the precompressional phase. Later, after the limit of compaction was reached, the good plasticity behavior of the crystals can be seen.

The same can be stated on the basis of the force-time (*F-t*) curve (Fig. 1b). The curve of the upper punch reveals high friction in the die during the precompressional phase. The reason lies in part in the friction between the crystals and in part in the high friction between the upper punch and the die wall. It is clear that there is a relatively large difference between the forces of the lower and upper punches, so the *R* value is small. It can be observed further that a residual force can be measured on the lower punch (Fig. 1b), which means that too high friction is indicated by the ejection of the tablet from the die. This residual force is increased, particularly on top of the die. Further, capping and sticking were visually seen during tablet pressing.

These results demonstrate that the friction should be reduced in the pre- and postcompressional phases. Excipients that can reduce the friction between the crystals in the compaction phase should be chosen, and a suitable concentration of highly effective lubricant must be used. The problem-free tableting of α-methyldopa can be achieved using excipients that can correct such unsuitable compressional parameters. Tablets with good parameters can then be prepared.

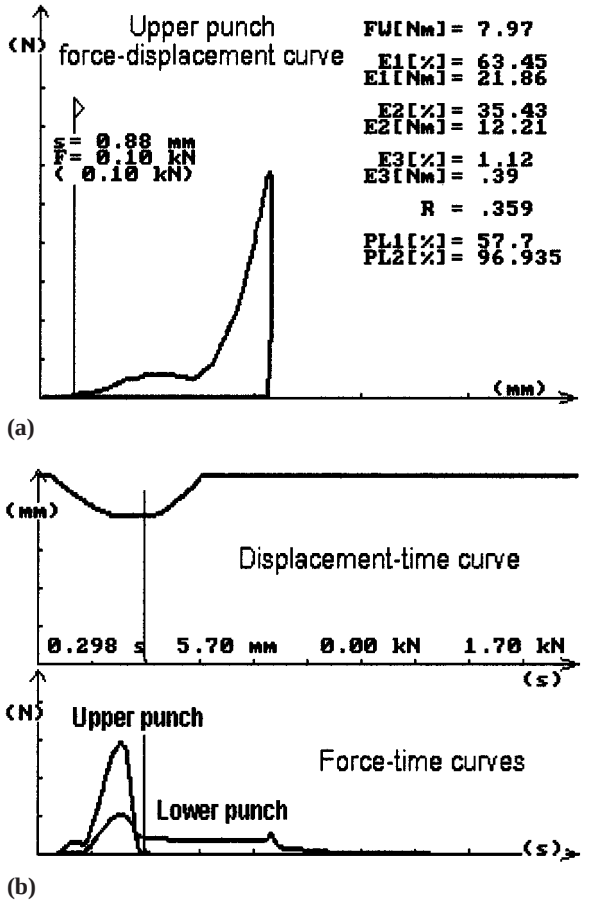

Figure 1. (a) Force-displacement curve of α-methyldopa comprimates; (b) force-time curve of α-methyldopa comprimates.

In the case of phenobarbitone, no friction was observed in the precompressional phase (Fig. 2a), but the small *R* value and high *FW* value (Fig. 2b) indicate that there was high friction in the postcompressional phase, especially in the ejection phase, as shown by the residual force on the lower punch.

The use of lubricants and antiadhesives with a higher lubrication effect is necessary for the tableting of phenobarbitone crystals. In addition, in practice, these crystals

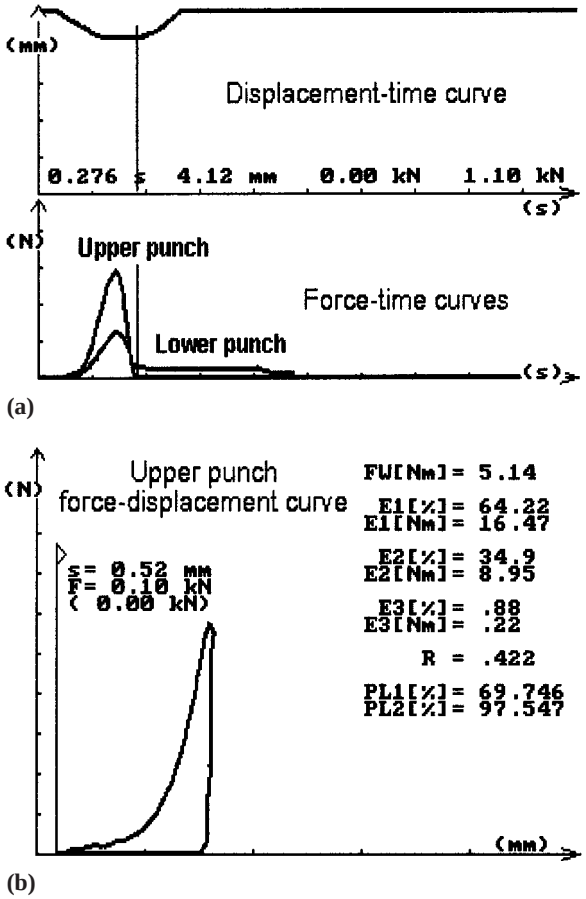

Figure 2. (a) Force-time curve of phenobarbitone comprimates; (b) force-displacement curve of phenobarbitone comprimates.

displayed an inclination to capping, but they did not tend to stick to the lower punch at the end of the ejection phase.

From these results, it can be concluded that there is a difference in behavior between the two drugs during the compressional process, and for tablet making, it is necessary to use excipients to reduce the elasticity and the friction and to enhance bond formation.

Avicel PH-301 was chosen as the binder and magnesium stearate as the lubricant and antiadhesive material.

The compressional processes are demonstrated in Figs. 3 and 4. In comparison with the compressional curves of the drugs, it can be seen that the shapes of the curves have become normal, and the excipients clearly have a positive influence on the compressional behavior of the drugs. The friction is decreased, and there

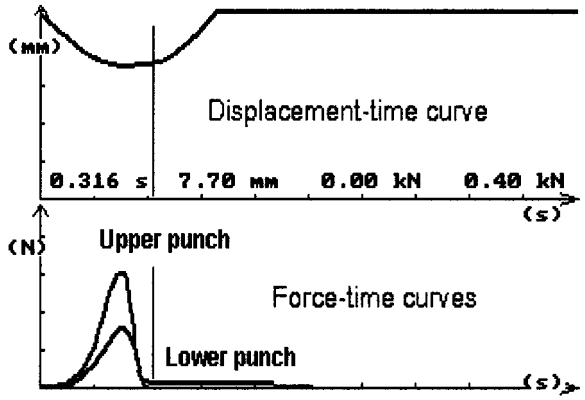

Figure 3. Force-time curve of α-methyldopa tablets.

is a sharp decrease in the residual force on the lower punch.

The compressional parameters of the tablets are shown in Table 1. It can be seen that the plasticity *Pl* of phenobarbitone is improved, while the friction of α-methyldopa is decreased, and the *R* values are therefore increased. In spite of this, *R* values of both drug formulations are still relatively low, which means that 0.5% magnesium stearate is not enough to induce sufficient lubrication. However, the compressional parameters of both drugs are generally improved by the use of Avicel PH-301, and capping was practically unnoticeable due to the marked increase in the effective work *EW*.

It can be stated, moreover, that the new formulas give the same results in plasticity (Pl_A and Pl_B), and thus the relative values can also be used in the calculations for characterization of the deformability of the materials.

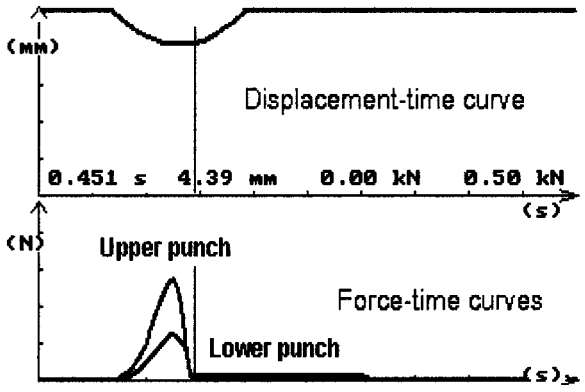

Figure 4. Force-time curve of phenobarbitone tablets.

Table 1

Compressional Parameters of Drug Formulas

Parameters	A301ph			A301md		
F_u (kN)	7.5 ± 0.5	10.5 ± 0.2	13 ± 0.5	7.5 ± 0.7	10.5 ± 0.2	13 ± 0.4
Wt (g)	0.3782	0.3775	0.3799	0.4003	0.3973	0.3981
E_1 (Nm)	13.57	20.19	23.80	18.52	25.31	31.40
E_2 (Nm)	7.53	10.90	13.72	10.56	12.58	14.71
E_3 (Nm)	0.10	0.31	0.55	0.20	0.32	0.48
CW (Nm)	7.63	11.21	14.27	10.75	12.89	15.18
EW (Nm)	3.79	5.09	6.06	5.94	6.86	7.90
FW (Nm)	3.74	5.81	7.66	4.62	5.72	6.81
R	.458	.447	.485	.523	.519	.512
$Pl_{S\text{-}M}$ (%)	98.70	97.24	96.17	98.18	97.53	96.87
Pl_A	98.70	97.24	96.17	98.18	97.53	96.87
Pl_B	98.70	97.24	96.17	98.18	97.53	96.87

CONCLUSIONS

From the results of this work, it can be concluded that both drugs have high friction work and also a high tendency toward capping due to high elasticity and expansion work, and they are therefore difficult to compress.

To make tablets of α-methyldopa and phenobarbitone, it is necessary to use suitable additives to correct such unsatisfactory characteristics to improve their compressibility behavior, reducing their elasticity and friction, and to enhance bond formation, so that these materials can be compressed successfully.

Avicel PH-301 exhibited a positive influence on the compressional behavior of the investigated drugs. The friction decreased in the pre- and postcompressional phases, with increases in the *R* values of both drugs. The residual force also decreased in the postcompressional phase, and the compressional behavior in general improved.

It can also be stated that the new formulas give the same results in plasticity (Pl_A and Pl_B), and thus the relative values can be used in the calculations for characterization of the deformability of the materials.

LIST OF ACRONYMS

CW	compressional work (Nm)
E_1	lost energy (Nm)
E_2	deformation energy (Nm)
E_3	expansion energy (Nm)
F_u	upper punch force (kN)
EW	effective work (Nm)
F-d	force-displacement
F-t	force-time
FW	friction work (Nm)
Pl_A	new formula for plasticity
Pl_B	new formula for plasticity
$Pl_{S\text{-}M}(Pl_2)$	Stamm-Mathis plasticity (%)
R	lubrication factor
*R*Exp*W*	relative expansion work
RFW	relative friction work
Wt	average mass

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