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International Journal of Pharmaceutics 152 (1997) 45–52

international journal of pharmaceutics

Compaction simulator study of a novel triple-layer tablet matrix for industrial tableting[1]

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Received 2 December 1996; received in revised form 30 January 1997; accepted 31 January 1997

Abstract

The compression behavior and compactibility of a novel triple-layer tablet formulation has been studied and the effect of punch velocity (50 mm s^{-1}, 125 mm s^{-1}, 250 mm s^{-1}, and 500 mm s^{-1}) on the compaction properties was also investigated using compaction simulator. The main formulation components were poly(ethylene oxide) (PEO), lactose, and theophylline. Heckel profiles of each layer as well as the combined layers were constructed, the porosity and tensile strength of the compacts were determined, and strain rate sensitivity (SRS) values were calculated. Results indicate that the formulation of each layer and the combined triple-layer tablet exhibited similar compression behavior, and the consolidation mechanism was shown to follow predominantly plastic deformation as evidenced by the shape of Heckel plots and high SRS values. The strain rate sensitivity for layer 1, 2, and 3 and combined triple-layer tablet was 16.2%, 26.1%, 19.3% and 10.7%, respectively. The degree of compact densification and resistance to compressibility within the die cavity was influenced by production rate as evidenced from percent porosity reduction with increasing compaction pressure as well as varying punch velocity. Compact lamination was only observed at both high punch velocity (500 mm s^{-1}) and compaction pressure. Furthermore, changes in tensile strengths and residual porosity as compression force was increased showed similar trends at constant punch velocities. It might be concluded that a successful design of triple-layer tablet formulation necessitates careful selection of plastic, brittle, and other desirable components to ensure comparable compactibility profiles. © 1997 Elsevier Science B.V.

Keywords: Triple-layer tablet; Compaction simulator; Compactibility; Poly(ethylene oxide) (PEO); Heckel equation; Mechanism of densification; Three-layer matrix system; Industrial tableting

1. Introduction

Oral solid dosage forms based on triple-layer matrix principle have been well explored as an

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[1] Presented in part at the 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Miami Beach, FL, November, 1995.

PII S0378-5173(97)04911-9

approach to achieve controlled delivery of drugs (Conte et al., 1993; Fassihi and Ritschel, 1993; Yang and Fassihi, 1996), and are now commercially available. Triple-layer tablets for controlled release usually consist of drug core layer sandwiched by the external layers which may contain different amounts of drug to form concentration gradient matrix or just act as a barrier layer. In general, drug release modulation from the triple-layer matrix system can be accomplished via the following geometric modification: (1) formation of drug concentration gradient and differential erosion of the matrix layers (Fassihi, 1988; Fassihi and Ritschel, 1993), (2) restriction of release surface of swellable matrix by barrier layers (Conte et al., 1993), (3) the swelling and differential erosion of external layers to maintain constant surface area and constant release (Yang and Fassihi, 1996), and (4) differential layer dissolution for pulsatile or rapid-slow release purposes (Yang and Fassihi, 1997). Some of the advantages of a triple-layer matrix system over other delivery systems and devices include the maximum flexibility in drug release patterns, ease of manufacturing, and total system solubility and drug release.

In terms of manufacturing technology, the triple-layer tablet dosage form design require a more in-depth understanding of compactibility process. Generally speaking, the compaction of powdered or granular material into a compact (i.e. tablet) is a complex and irreversible process. The compression behavior exhibited is a consequence of primary particle reorientation, elastic deformation, plastic deformation, or particle fracture, formation and breaking of interparticulate bonding and at high applied pressure even asperity melting. Thus, the characteristics of finished tablet are expected to be influenced by the viscoelastic properties of formulation components, production rate, and the resultant stresses during decompression and ejection from the die. The production of a triple-layer tablet is accomplished by successively filling the die with compression mixes forming successive layers followed by precompression or tamping after each filling, and finally compressing the powder bed in the die to achieve tablet of desired thickness and tensile strength. The formulation of triple-layer tablet is therefore more demanding than that of conventional tablets. For example, prevention of layer separation, lamination, capping and differential thermal expansion between layers when the dosage form is to be coated as well as more stringent storage requirements need to be met.

Presently triple-layer tablets are commercially available, however, the compaction characteristics of individual layers as well as the combined triple-layer tablet has not been reported in the past. It is our hypothesis that individual layers of the triple-layer tablet should possess similar compression properties in order to form quality tablets, although the individual component in different layers may significantly differ in their compaction characteristics. The precompression or tamping force applied after each filling should be carefully optimized and monitored to prevent powder diffusion across layers and to achieve enough cohesion between the surfaces of different layers. Therefore, the objectives of this study were (i) to investigate the compression behavior of each layer and the combined triple-layer tablet, and (ii) the effect of punch velocity on the compaction properties of this system, and the role of material viscoelasticity in the formulation will be discussed. The model tablet matrix used is a novel 'asymmetric configuration drug delivery system' which was described in detail previously (Yang and Fassihi, 1996).

2. Materials and methods

2.1. Materials

Polyethylene oxides (Polyox-WSR®NF) (PEO) with declared average molecular weight of 1×10^6 (WSRN-12K) and 7×10^6 (WSR-303) were obtained from Union Carbide Corp. (Danbury, CT). Theophylline anhydrous USP and magnesium stearate were purchased from Amend Co. (Irving, NJ). Calcium carbonate (Pharma-Carb®) and lactose NF anhydrous were supplied by Crompton and Knowles Corp. (Mahwah, NJ) and Sheffield Products (Norwich, NY), respectively. Other excipients were all USP or NF grades. All materials were used as received.

Table 1
Formulation components of asymmetric configuration drug delivery system[a,b]

Layer	Components	% (w/w)
1	Polyethylene oxide	50
	Sodium bicarbonate	~10
	Calcium carbonate	~20
	Lactose	~10–20
2	Polyethylene oxide	50
	Theophylline anhydrous	~34
	Lactose	~16
3	Polyethylene oxide	50
	Lactose	~50

[a] Formulation components were optimized for the required release rate.
[b] 1% Magnesium stearate was used as lubricant in each layer.

2.2. Matrix formulation

The three types of particulate systems used for direct compression of a desirable matrix are shown in Table 1. All the powders were screened through a # 20 US standard sieve and components of each layer were mixed in cube-mixer for 15 min, 1% magnesium stearate was added and mixed for an additional 5 min, prior to compaction studies.

2.3. True density

The true density of each layer powders was determined on a helium Pycnometer AccuPyc 1330 (Micromeritics, Norcross, GA), and the average of two runs was recorded. The values are given in Table 2.

2.4. Compaction profiling

Compaction profiling was carried out using a compaction simulator which has been described in detail elsewhere (Celik and Marshall, 1989). In brief, the system consists of a Mand Compaction Simulator (Abacus Industries Ltd., formerly Mand Testing Machines Ltd, Stoubridge, UK), Nicolet Model 440 Oscilloscope, and a personal computer. The compaction cycle used to drive the simulator was that of a Manesty Betapress, i.e. double-ended compaction (both punches moving) with subsequent automatic ejection. The punch velocity was 50 mm s^{-1}, 125 mm s^{-1}, 250 mm s^{-1}, and 500 mm s^{-1}, respectively. The elastic deformation of the punches and related parts

Table 2
Physical parameters for individual layers, combined three-layer tablet, and PEO[a]

Layer	True density (g cm^3)	Punch velocity (mm s^{-1})	Tensile strength (MPa)	P_y (MPa)
1	1.5015	50	0.80	118
		125	0.82	134
		250	0.58	142
		500	0.58	190
2	1.3634	50	0.66	102
		125	0.61	125
		250	0.52	138
		500	0.36	200
3	1.4354	50	1.04	159
		125	0.87	193
		250	0.77	197
		500	0.70	270
3 Layers[b]	1.4329	50	0.99	125
		125	0.83	135
		250	0.73	140
WSRN-12K	1.2479	250	0.55	88
WSR-303	1.2492	250	0.55	88

[a] These parameters were derived from compacts of 3 mm thick.
[b] The combined three layers have identical proportions with the total thickness of 3 mm.

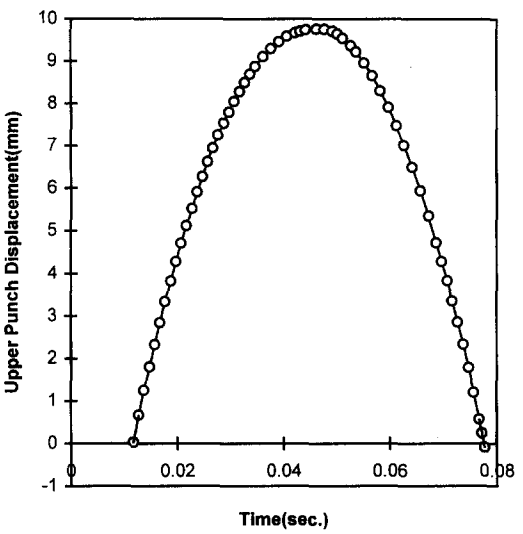

Fig. 1. Representative upper punch displacement as a function of time at punch speed of 250 mm s^{-1}.

under load were also determined and utilized to correct the compact heights in the die.

The required time-displacement profiles (i.e. a full compression cycle) were calculated according to the Rippie and Danielson equation derived for rotary tablet press (Manesty Betapress) (Rippie and Danielson, 1981):

$$Z = [(r_1 + r_2)^2 - (r_3 \sin \omega t - x)^2]^{1/2} \quad (1)$$

where Z is the vertical displacement of the upper or lower punch at time t; r_1 and r_2 are the radii of the compression roller and the vertical curvature of the punch head rim respectively, r_3 is the radial distance between the turret center and die cavity center (so called 'pitch circle'); x is the horizontal distance between the center of the upper punch and the center of vertical curvature of the punch head rim; while ω is the turret angular velocity. This equation and the waveform do not take into consideration the punch head flatness as has been discussed in our previous report (Yang et al., 1996). Typical upper punch displacement profile as a function of time generated from this study is presented in Fig. 1.

Compacts were prepared using a constant volume of solid in the die equivalent to 0.225 cm^3 (compact weight = true density × 0.225 cm^3) and flat faced, 1 cm, round tooling. The nominal thickness of compacts to be produced was set at 2.8, 3.0, 3.2 and 3.5 mm in order to obtain a residual porosity of 2–20% and seven compacts were prepared at each condition. Thickness, weight and hardness (Tablet Hardness Analyzer VK 2000, Vankel Corp.) of ejected tablets were determined immediately after production. The data (loads and displacements of upper and lower punches as a function of time) were down-loaded from the Nicolet oscilloscope to the PC and converted into Microsoft Excel (version 5.0) for further manipulation.

2.5. Data analysis

The compaction force-porosity data were analyzed with Heckel equation (Heckel, 1961a,b):

$$\ln \frac{1}{1-D} = KP + A \quad (2)$$

where D is the relative density of the compact at compression pressure P, K is the slope of the linear portion of the plot, and its reciprocal is taken as the yield pressure P_y; A is constant.

The tensile strength of the compact was calculated using the following equation (Fell and Newton, 1970):

$$\text{Tensile strength} = \frac{2F}{\pi D t} \quad (3)$$

where F is the crushing force, D and t are the diameter and thichness of the compact, respectively.

Apparent strain rate sensitivity (SRS) of the compact was computed based on the equation proposed by Roberts and Rowe (1985):

$$\text{Apparent SRS} = \frac{P_{y2} - P_{y1}}{P_{y2}} \times 100\% \quad (4)$$

in this equation, P_{y1} is the yield pressure obtained at low punch velocity, P_{y2} is the yield pressure obtained at high punch velocity.

3. Results and discussion

3.1. Compactibility of individual layers and their combination

The primary consolidation mechanism of powder or the mixture of powders can be often deduced from Heckel plot (Heckel, 1961a,b). Usually the value of $\ln[1/(1-D)]$ changes rapidly with compression pressure if the material deforms plastically, while changes in density-pressure plots are relatively less sensitive for brittle materials.

In this study, the force-density data of individual layer formulations and their combination were subjected to Heckel analysis, and the representative results at a punch velocity of 250 mm s^{-1} are presented in Fig. 2. The porosity changes as a function of applied pressure for individual layers as well as the triple-layer tablet derived at 250 mm s^{-1} are presented in Fig. 3. All the layer formulations and their combination exhibited similar compression and consolidation characteristics with increasing compaction pressure. This is understandable in view of the fact that these formulations consisted of both plastically deforming and brittle fracture materials in high proportions.

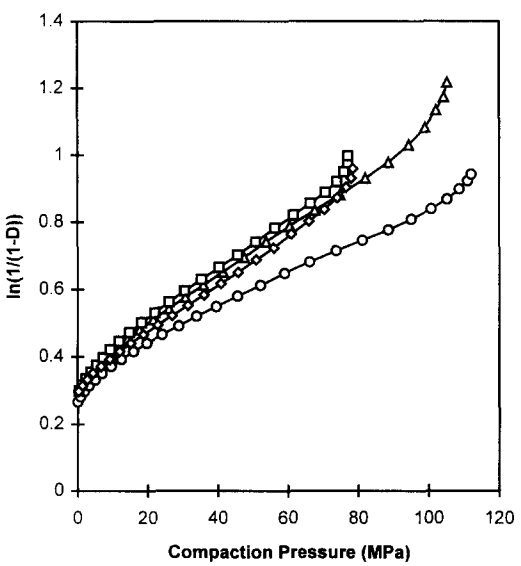

Fig. 2. Representative Heckel plot for the individual layer as well as their combination. Punch velocity equals 250 mm s^{-1} and the in-die thickness is 3.0 mm; (◇) layer 1; (□) layer 2; (○) layer 3; (△) triple-layer tablet.

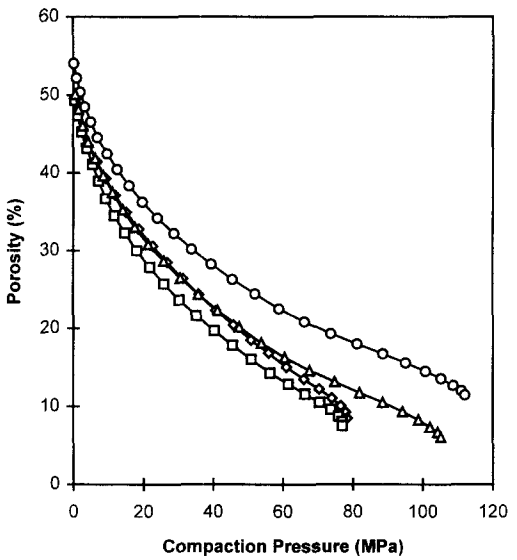

Fig. 3. The relationship between the porosity and compaction pressure. Punch velocity 250 mm s^{-1} and the in-die thickness 3.0 mm; (◇) layer 1; (□) layer 2; (○) layer 3; (△) triple-layer tablet.

The data also suggest that these powder mixtures predominantly undergo plastic deformation as indicated by their low yield pressure and slope of the Heckel plots. Note that the slope of the Heckel plot for layer 3 containing a high proportion of lactose (at 50% w/w), a moderately hard, brittle fracture excipient, is smaller than those of layer 1 and 2 and the combined layer. The differences in the yield pressure do not seem to be significantly different for these formulations, suggesting that the plastically deforming PEO at a level of 50% or more dominates the initial compression behavior of these formulations. However, as compression pressure increases, curves approach the linear region, plastic deformation of particles and particle fragmentation may occur. In this study the compression pressure was controlled by thickness of the compact, therefore the maximum pressure to reach the required thickness varied for different powder mixtures, and the minimum porosity achieved was also different for each layer. The typical force-time curves (upper punch force as a function of time at a punch velocity of 50 mm s^{-1}) for individual layers and their combination are presented in Fig. 4. Inspection of Fig. 3 and 4 indicate that layer 1 and 2

require similar compression pressures to produce similar residual porosities, while layer 3 and combined triple-layer tablet need significantly higher compaction pressures to attain similar residual porosity.

3.2. Role of plastic or brittle material on compact formation

The resultant mechanical strength of the compacts is partly dependent on the particle size, size distribution as well as the physicomechanical properties of individual formulation components. Therefore, the consolidation behavior mainly reflects the summation of the compression properties of individual components. As shown in Table 1, the polymer used in this formulation is poly(ethylene oxide) (PEO), a high molecular weight, linear polymer, which exhibits plastic deformation under compression pressure (Yang et al., 1996). Knowing that the compaction properties of PEO of various molecular weight display little variation and the proportion of PEO in each layer is approximately constant, the observed differences in Heckel plots are likely to be due to other formulation components. Table 2 summarizes the physical parameters of individual layer, triple-layer tablet, and pure PEO. It is apparent that layer 3 forms the strongest compacts as evidenced from the tensile-strength values. It should be noted that layer 3 contains 50% lactose (brittle material), a moderately compressibile/compactible diluent. From these results it is apparent that when brittle and plastic materials are blended and compressed together they may have synergistic effect on tablet strength. This is in agreement with previously published report (Fassihi et al., 1995).

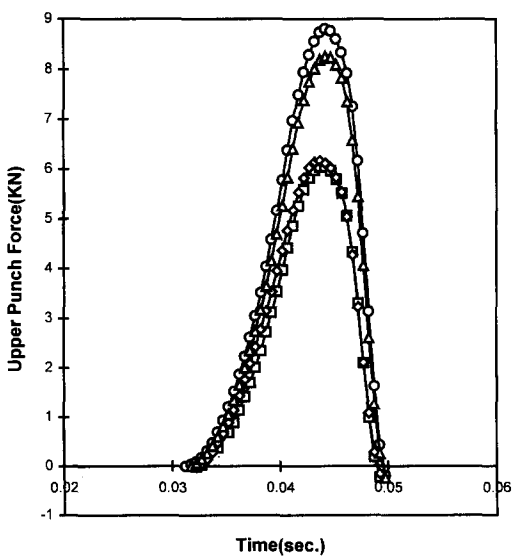

Fig. 4. Representations of upper punch force versus time at punch speed of 50 mm s^{-1} and the in-die thickness of 2.8 mm; (◇) layer 1; (□) layer 2; (○) layer 3; (△) triple-layer tablet.

3.3. Apparent strain rate sensitivity

Apparent strain rate sensitivity (SRS) is an additional parameter that characterizes the main consolidation mechanism when powders are compressed at different punch velocities and can be calculated according to the Eq. (3). The SRS value would be greatly affected by the punch velocity used for compression. In this study, P_{y1} is determined at 50 mm s^{-1}, P_{y2} was determined at 250 mm s^{-1}. The SRS values of layer 1, 2, 3, and combined tablet are 16.2%, 26.1%, 19.3% and 10.7%, respectively. These values indicate that all layers are strain rate sensitive, and therefore dominantly follow plastic deformation. In their original work, Roberts and Rowe (1985) ranked a series of pharmaceutical solids in terms of their SRS, the two compression rates chosen were 0.033 mm s^{-1} and 300 mm s^{-1}. They demonstrated that materials with fragmentation mechanism have low SRS values ($< 2\%$) while plastically deforming materials possess high SRS values.

3.4. Influence of dwell time on compact strength

It is established that powder consolidation by plastic deformation is a time-dependent phenomenon. At comparable tableting conditions (i.e. at a nominal thickness setting), both the reduction in porosity and mechanical strength of the compressed tablets decrease with increasing rate of tablet output (i.e. decreasing dwell time) (Roberts and Rowe, 1986; Armstrong and Palfrey, 1989; Marshall et al., 1993). It is evident from Fig. 5, which presents a typical strain rate sensitivity profile of the 50:50 PEO/lactose blend.

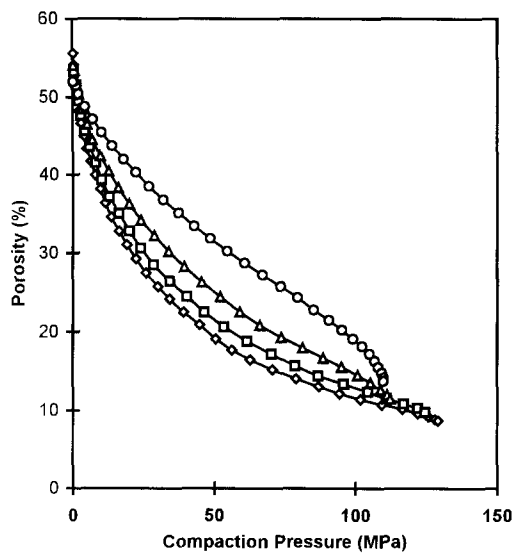

Fig. 5. The relationship between the porosity of layer 3 and punch velocity. The in-die compact thickness 3.0 mm; (◇) 50 mm s^{-1}; (□) 125 mm s^{-1}; (△) 250 mm s^{-1}; (○) 500 mm s^{-1}.

At low punch velocities, the presence of viscoelastic PEO helps relieve the applied stress and hence achieve lower porosities and higher strengths than at higher punch velocities. As shown in Table 2, the compacts produced at four different speeds clearly demonstrate different degrees of densification (i.e. residual porosities), bonding and resultant tensile strength. It is also known that the yield pressure, P_y of the plastically deforming materials increases with increasing punch velocity (refer to Table 2). At highest tablet output rate (i.e. at the extremely short dwell time), structure failures were occasionally observed during tableting for layer 2, which contains 16% w/w of a brittle fracture material, namely lactose. However, it should be noted that such short dwell times are not encountered in routine production, and therefore capping and/or lamination is not an issue in this particular triple-layer tablet formulation.

In conclusion, based on the evidence presented in this work, the individual layer of the triple-layer tablet appear to possess fairly well balanced proportions of ingredients (both brittle fracture and plastically deforming excipients/actives). Overall, the major formulation components primarily consolidate by plastic deformation as evidenced by a relatively high SRS values and exhibit comparable but low elastic recoveries during decompression and ejection. In general, it is essential for a trouble free production of tablets that individual layers used in the design of triple-layer tablet formulation should preferably have similar consolidation characteristics, i.e. predominantly consolidate by brittle fracture or plastic deformation. Alternatively, a well balanced proportions of both brittle and plastic materials may be necessary for a acceptable tablet quality and production.

Acknowledgements

Union Carbide Corp. is gratefully acknowledged for supplying Polyox-WSR® samples and we like to thank Dr. Nagesh Palepu of SmithKline Beecham Pharmaceuticals for his encouragement and support, and Mr. David Spiese for technical assistance.

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