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ORIGINAL ARTICLE

Investigation of the Compressibility Characteristics of Paracetamol using "Compaction Simulator"

"Compaction Simulator" Kullanılarak Parasetamolün Basılabilirlik Özelliklerinin İncelenmesi

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ABSTRACT

Objectives: This study was performed to understand the behavior of poorly compressible paracetamol powder using a compaction simulator (CS), equipment that records data during the compaction process. The aim was to investigate the compressibility of paracetamol tablets using a dry granulation (slugging) process, with different formulation compositions.

Materials and Methods: Formulations were prepared to observe the effect on compressibility with two different lactose-based fillers, Flowlac®100 and Granulac®70, and a binder, Kollidon® K90. In each combination, a total of four formulations were prepared with paracetamol to filler ratios of 1:1 and 0.8:1. Tablets were produced by single punch (11.28 mm) CS at six different pressures (152, 210, 263, 316, 400, and 452 MPa). During compression, upper punch displacement and force data were produced by the CS equipment. The compressed tablets were tested for hardness, thickness, and weight variation and compared with each other.

Results: All formulations reached maximum tensile strength at compaction pressures between 263 and 316 MPa. In the formulations without binder, those containing Granulac®70 had higher tensile strength than those containing Flowlac®100 at both filler ratios. The results obtained indicated that the addition of binder to the formulations (F-45-1, F-45-2, F-50-3, and F-50-4) improved the compressibility of paracetamol. Formulation F-45-2, containing Flowlac®100 and binder, showed better compressibility at 2.9 MPa tensile strength. Data from the CS were used to compare Young's modulus and work of compaction on selected formulations (F-45-1 and F-45-2).

Conclusion: The proposed lactose-based filler, Flowlac®100, with low pressure can be successfully applied for improving the compressibility of paracetamol. An optimum formulation can be designed with smaller amounts of materials using a compaction simulator.

Key words: Compaction simulator, tableting, compactibility, paracetamol, alpha-lactose

ÖZ

Amaç: Bu çalışmada basım sırasında verileri kaydeden "Compaction Simulator (CS)" cihazı kullanılarak sıkışabilirlik özellikleri zayıf olan toz parasetamolün basılabilirlik davranışları incelendi. Çalışmanın amacı, kuru granülasyon (slugging) yöntemi ile hazırlanan farklı formülasyonlardaki parasetamol tabletlerin basılabilirlik özelliklerinin incelenmesidir.

Gereç ve Yöntemler: Laktoz bazlı iki değişik dolgu maddesi olarak Flowlac®100 ve Granulac®70 ile bağlayıcı olarak Kollidon®K90 kullanılarak hazırlanan farklı formülasyonların basılabilirliği üzerine bu maddelerin etkisi gözlendi. Her kombinasyon için parasetamol: yardımcı madde oranı 1:1 ve 0.8:1 olan toplam 4 formülasyon hazırlandı. Tabletler tek zımbalı (11,28 mm) CS'de altı farklı basınçta (152, 210, 263, 316, 400, 452 MPa) üretildi. Sıkıştırma sırasında üst zımba ötelemesi ve zımba kuvvet verileri CS cihazı çıktılarıdır. Basılan tabletleride sertlik, kalınlık ve ağırlık sapması testleri yapıldı ve sonuçlar birbirleri ile mukayese edildi.

Bulgular: Bütün formülasyonlar en büyük gerilme direncine 263-316 MPa sıkıştırma aralığındaki basınçta ulaştılar. Bağlayıcı olmayan ve aynı oranda dolgu maddesi içeren formülasyonlarda Granulac®70 içerenler, Flowlac®100 içerenlere göre daha yüksek gerilme direnci göstermiştir. Sonuçlara göre, formülasyonlara bağlayıcı ilavesi (F-45-1, F-45-2, F-50-3 ve F-50-4), parasetamolün basılabilirliğini iyileştirmiştir. Flowlac®100 ve bağlayıcı içeren F-45-2 formülasyonu 2,9 MPa basınçta daha iyi bir basılabilirlik göstermiştir. CS verileri belli formülasyonlarda (F-45-1 ve F-45-2) Young modülleri ve basım çalışmaları sonuçlarını karşılaştırmada kullanılmıştır.

Sonuç: Parasetamolün düşük basınçta basılabilirliği laktoz bazlı dolgu maddesi olan Flowlac®100 ile başarıyla sağlanabilmiştir.

Anahtar kelimeler: Compaction simulator, tablet hazırlama, sıkışabilirlik, parasetamol, alfa-laktoz

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INTRODUCTION

During the manufacture of pharmaceutical tablets, there are certain problems that may arise, such as poor flowability, mixing, compactibility, and compressibility, and inconsistent die filling. The need to avert such problems in manufacturing may include the use of different tableting methods such as granulation.[1,2]

Slugging, an old conventional method, is chosen for research purposes in respect to the roller compactor, which is a more modern and efficient method used for dry granulation (DG).

The effect of DG often results in decreased tensile strength in tablets in comparison to other processes. This outcome is due to the loss of binding potential, which occurs after the first compression.[3,4,5]

The ability to transform powder into tablets involves certain factors and these factors, such as compactibility (tensile strength vs pressure) and other tableting measures, give a perspective on powder tableting characteristics.[1,6]

In the tableting process, three important stages are paramount for understanding the characteristics of powders. The stages are die filling (powder blends are loaded into the die under gravity, which applies to powder flowability), compaction (where compression is applied between two punches), and ejection (when the tablet is ejected from the die). These three stages determine the powder behavior and tableting parameters.[7]

The compaction behavior can be assessed using stress strain graphs to obtain Young's modulus, which gives insight into the plastic, elastic, or brittle nature of powders. Data obtained from measurements of macroscopic dimensional variations during the compaction cycle give information about the compressibility and compactibility of powder material.[8]

In formulating a poorly compressible active ingredient, the choice of excipient is important for the outcome. Therefore, finding the best tableting parameters is essential for further production and can also be used as an outline in fixing production problems.

To understand and characterize the compaction behavior and tableting parameters, instrumented single stations and multistations have been widely used. As observed, powders with good performance in a laboratory tablet press sometimes perform differently, with problems during scale up. However, with a compaction simulator these problems can be predicted with data used to analyze the compaction behavior of pharmaceutical materials. A compaction simulator provided advantages, limitations, and modifications by using methods such as F-D curve, tensile strength, and hardness measurement to improve the design and development of solid dosage forms.[9,10]

The use of a compaction simulator as a mimicking machine that emulates scale-up production gives real time data on every tablet pressed. These data can be analyzed and powder behavior and characteristics can be observed.[11]

In the present study, data obtained from a compaction simulator were used from an industrial perspective to determine and evaluate the tableting parameters to obtain improved compactibility of poorly compressible paracetamol.

MATERIALS AND METHODS

Materials

Paracetamol was used as the model drug in the present study, USP grade (Kimetsan). Two types of lactose-based fillers from Meggle, milled alpha-lactose monohydrate (Granulac® 70) and spray dried lactose (Flowlac®100), were used in the formulation at different concentrations to understand the effect of fillers on tableting parameters using the slugging process. Stearic acid (Kimetsan) was used as lubricant; it was kept at a constant concentration of 2% in every formulation.

The reason for addition of a binder from BASF (Kollidon® K90) to specific formulations was to further understand certain variables that may influence tablet behavior during compaction.

Methods

Slugging

Tablets (slugs) were made containing API, filler, and lubricant mixture, with ratios 1:1 and 0.8:1 (paracetamol to filler loading). The slugs were made with a mixture of paracetamol powder and filler (both Flowlac® 100 and Granulac® 70, at different ratios) with the addition of 1% of the lubricants to the mixture (Tables 1a and 1b).

The slugs were produced using an 18 mm single punch (Korsch XP1), milled using an Erweka oscillating mill granulator, and passed through a sieve with sieve size of 0.68 mm.

Mixing

The granules obtained from the DG slugging process were mixed with the binder and the remaining 1% lubricant (w/w) (according to each concentration variation in different formulation composition and ratio).

Tableting

Formulations were compressed at different compaction pressures: 152, 210, 263, 316, 400, and 452 MPa. Tablets were produced with a flat-faced Euro B punch of 11.28 mm diameter using a compaction simulator (Stylcam 200R). Tablets of eight different formulation mixtures were pressed to understand and characterize formulations of each compaction force.

For die filling, each powder was weighed individually using a Mettler Toledo AB 104-S/PH analytic balance and hand-filled in the die for compaction. From the tablets pressed, tablets from each formulation and batch were selected randomly and immediately characterized for weight variation and thickness.

Tensile strength

Tensile strength was calculated from crushing force (TBH 225; Erweka) and thickness.

Tensile strength was calculated using the following equation:

$$TS = \frac{2F}{\pi Dt}$$

where F is the crushing force in N; D the diameter and t the thickness of the tablet, both in mm.

Table 1a. Formulation composition with paracetamol to filler ratio 0.8:1

Formulation	Paracetamol	Flowlac® 100	Granulac® 70	Kollidon® K90	Stearic acid
F-45-1	45%	-	51%	2%	2%
F-45-2	45%	51%	-	2%	2%
F-45-3	45%	-	53%	-	2%
F-45-4	45%	53%	-	-	2%

Table 1b. Formulation composition with paracetamol to filler ratio 1:1

Formulation	Paracetamol	Flowlac® 100	Granulac® 70	Kollidon® K90	Stearic acid
F-50-1	50%	-	48%	-	2%
F-50-2	50%	48%	-	-	2%
F-50-3	50%	-	46%	2%	2%
F-50-4	50%	46%	-	2%	2%

Stress-strain graph

A graph was obtained using both upper and lower punch displacement data derived from the compaction simulator. Young's modulus was obtained from slope of the line of the stress-strain graph.

F-D curve

Compression force vs punch displacement profiles (F-D curve) can be obtained in order to assess the compaction behavior of materials and to calculate the work involved during tablet compaction.

Statistical analysis

Analysis of variance was applied for prediction using a one-way ANOVA model. The software package IBM SPSS Statistics v26 was used for calculation. The level of significance was defined as $p<0.05$.

RESULTS

Figure 1 shows the tensile strength for the set of formulations with different filler types at different ratios (1:1 and 0.8:1).[11,12,13] The formulations containing Granulac® 70 (F-45-3 and F-50-1) gave higher tensile strength in comparison to those containing Flowlac® 100. The effect of the filler ratio is seen in Figure 1, with formulations F-45-3 and F-45-4 showing better compressibility than formulations F-50-1 and F-50-2, respectively. Granulac® 70-containing formulations improved the compressibility of paracetamol more than Flowlac® 100-containing formulations at both ratios. Analysis of variance indicated that both filler ratio and filler type exert statistical significance ($p<0.05$).

Figure 2 shows the effect of binder on the tensile strength of the formulations. There was an increase in the tensile strength of all different formulation compositions. Formulation F-45-2 containing Flowlac® 100 had a higher tensile strength at lower compaction pressure than F-45-1 containing Granulac® 70 at a similar filler ratio (0.8:1). Flowlac® 100 had more improved tensile strength with addition of binder in comparison to Figure 1. The significant difference ($p<0.05$) with a confidence level of 95% indicates clear variation with the addition of binder.

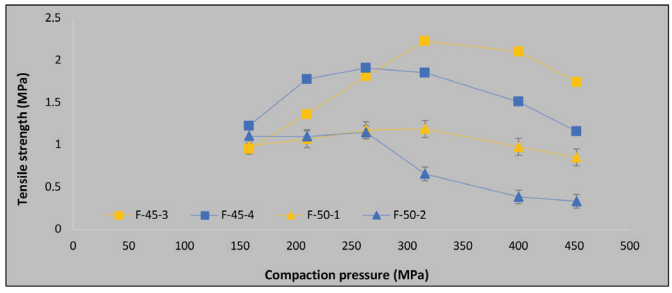

Figure 1. Effect of Flowlac® 100 and Granulac® 70 in different ratios on tensile strength (n=3)

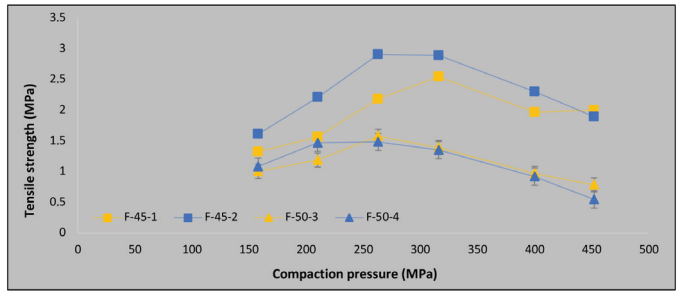

Figure 2. Effect of Flowlac® 100 and Granulac® 70 composition with binder (Kollidon® K90) on tensile strength (n=3)

In Figure 3, both tablets' results are derived from similar compaction conditions, having been selected from tensile strength resulting data to be the optimum tablets from different filler type formulation compositions. Figure 3 shows the variation in stress-strain for F-45-1 and F-45-2. There was a linear increase in F-45-2, but a different result was observed in F-45-1, which takes more loading capacity to see a significant change in the strain of F-45-1. The Young's modulus results were given at 60 for F-45-1 and 98 for F-45-2. As calculated from Figure 3, Young's modulus for F-45-1 is lower than that for F-45-2, indicating that F-45-1 has greater elastic recovery.

Figure 4 shows the total of work compaction for the selected formulations. The area under the curve shows the energy required during the compaction process. F-45-2 is seen to require more energy in comparison to F-45-1.

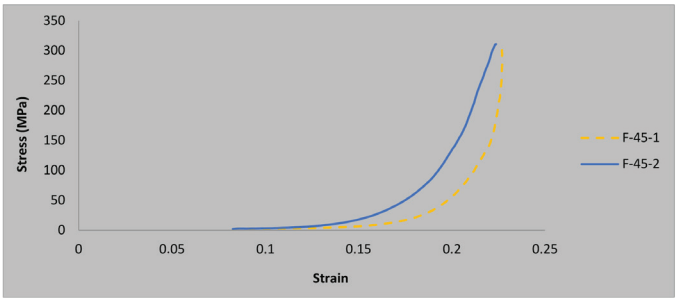

Figure 3. Stress vs strain for selected formulations (F-45-1 and F-45-2)

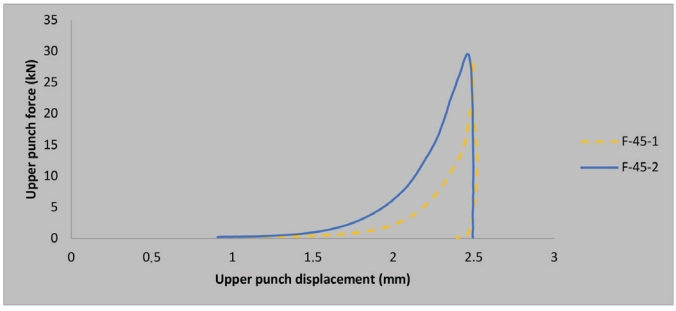

Figure 4. Determination of energy for selected formulations (F-45-1 and F-45-2)

DISCUSSION

As seen in the results in Figure 1, Granulac® 70 displayed better loading capacity than Flowlac® 100. In both filler ratios, Granulac® 70-containing formulations performed better under higher compaction pressure. However, Flowlac® 100 had better tensile strength at lower pressures. The particle structure and size difference of filler affects the bonding and may show different results under identical compaction conditions.[14,15,16] All formulations had a significant decline in tensile strength as compaction pressures increased above 316 MPa.

Figure 2 shows the change in formulation composition with the addition of binder. From the tensile strength results, both filler types at ratios 1:1 and 0.8:1 improved in compressibility when compared with the results in Figure 1. It is seen that binder effect has a more significant impact in Flowlac® 100 than in Granulac® 70. Formulation F-50-3 containing Granulac® 70 maintained a slightly better higher tensile strength than formulation F-50-4 containing Flowlac® 100. This indicates the need for higher filler loading ratio for Flowlac® 100 to exhibit proper bonding, increasing the tensile strength. Granulac® 70, however, has more compactibility at different loading ratios. It was observed that with the addition of binder and tensile strength increase, the tableting behavior of all formulations at different filler ratios and formulation compositions had a distinctive pattern in respect to compaction pressure. These results suggest that lactose-based fillers may have unpredictable compression behavior, giving more deviations when lubricated.[16,17]

As seen in the stress-strain curve, the variation in deformation of both formulations with similar tableting parameters may have many reasons. A factor that may give rise to these variations is density distribution in the tablets as a result of stress transmission, which is dependent on internal friction, contact powder, and lubrication.[18,19,20] The relationship between Young's modulus and tablet strength is that the higher the elastic recovery, the lower the tablet strength.[21,22] This can be further supported by the results that F-45-1 has lower tensile strength than F-45-2 because of its greater elastic recovery, shown by higher Young's modulus. Flowlac® 100-containing formulations showed lower elastic recovery because of its spray-dried property, which results in harder tablets.[23]

Results from the F-D curve show that the work of compaction gives a detailed assessment of the characteristics of tableting parameters due to differences in packing characteristics of individual formulation powders.[10,24] Powders with different plastic and elastic deformational properties and different packing characteristics will absorb varying amounts of energy,[25] as seen by differences in compaction energy between formulations F-45-1 and F-45-2.

CONCLUSION

With a compaction simulator it is possible to obtain:

- the mechanical properties of powders,
- optimum tabletability profile for designed formulations,
- compaction data such as stress strain and F-D curves, which can help in optimizing a formulation.

Granulac® 70 is seen to have better loading capacity than Flowlac® 100. However, it needs more pressure during the compaction process. The addition of binder has more effect on Flowlac® 100 in improving the compressibility of paracetamol at lower compaction pressure.

The most robust formulation, F-45-2, is selected from the set of formulations due to its superior compaction characteristics. Based on the information obtained from the compaction simulator, large-scale manufacturing can be reproduced.

Conflicts of interest: No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

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