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X-ray tablet and raw diffraction as a method to study compression parameters in a direct compression excipient, Compril®

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Abstract

Compressional behavior of a direct compression excipient, Compril®, composed of a lipopolysaccharide, was studied on the basis of binding properties, plasticity, densification plot and X-ray diffraction of powder and tablet surfaces. The ratio between breaking force and mean applied force as well as plasticity of Compril® decreased when applied force was increased. The densification plot of Compril® demonstrated a non-linear relationship between $\ln 1/(1 - D_r)$ and applied pressure from low applied pressures. The increase in the slope of Heckel plot above 50 MPa may be due to densification by cold-hardening. The differences observed in integrated peak areas and full width at half maximum (FWHM) of raw material and tablets demonstrated changes in the microdomains. X-ray diffraction showed that the peaks of the tablets were narrower than in the case of the raw material, therefore a higher degree of the crystallinity of Compril® was observed when it is compacted. In this sense, the application of X-ray diffraction can clarify the consolidation mechanism of materials that deform by cold-hardening. Copyright © 1996 Elsevier Science B.V.

Keywords: Tableting; X-ray diffraction; Direct compression excipients; Lipopolysaccharide; Consolidation mechanism; Friction

1. Introduction

The advantages of direct compression with regard to other methods of tablet production are evident. However, low flowability of a powder (Bertulli et al., 1976) is very often one of the

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limiting factors in direct compression. The flow properties of Compril® and their mixtures with Avicel® PH 101 and Ludipress® were investigated in an earlier study (Muñoz-Ruiz et al., 1992).

Evaluation of the excipients in relation to compression characteristics is an important technological process, especially in the case of direct compression excipients because the characteristics of the excipient determine the properties of the tablet formulations.

In this paper, the next parameters were used to evaluate the compressional properties of Compril®: friction parameters; compactibility, ratio between tensile strength and net work (York and Pilpel, 1973); plasticity, ratio between apparent net work and apparent net work plus expansion work (Doelker, 1978); and elastic work, obtained from the second compression.

The goal of this work is to study the variation of tabletability of Compril® with applied pressure as well as to use X-ray diffraction in order to determine cristallinity or other changes during compression.

2. Experimental

2.1. Materials

For this study a direct compression excipient Compril®, lipopolysaccharide complex in micronized state and later cohesioned, batch 90584 (Glyco, Barcelona, Spain) was used. Also, Helium N-50 (SEO, Sevilla, Spain) was employed to determine true density of the powder. Powder was stored under humidity controlled conditions (RH = 40%).

2.2. Methods

2.2.1. Material density

The true density of the material was measured by a pycnometer Stereopycnometer SPY-2 (Quantachrome, Syosset, NY, USA) using helium as an inert gas.

2.2.2. Compression properties

Compression properties of the powders were investigated on an instrumented single punch tablet machine Bonals AMT 300 (Bonals, Barcelona, Spain) with strain gauges HMB YL6 (Hottinger Baldwin Messtechnik, Darmstadt, Germany) connected to strain dynamic amplifiers (NEC San-ei, Tokyo, Japan) and inductive displacement transducer HBM TS 50 linked to digital dynamic amplifiers HBM AB 12. Data acquisition was performed using a Metrabyte DAS 16-G1 A/D Converter (Metrabyte, MA, USA). Displacement measurements were corrected with punch deformation (Muñoz-Ruiz et al., 1995). A quantity of powder to produce tablets of thickness 2.5 mm at zero theoretical porosity was manually filled into the die (12 mm). Flat compacts were prepared at forces between 20 and 60 kN to study the variations in the compression properties.

2.2.3. Breaking strength

The tablet breaking strength was determined immediately after compression using commercially available breaking strength tester (Schleuniger-2E, Dr. K. Schleuniger, Geneve, Switzerland).

2.2.4. X-ray diffraction

X-ray diffractograms were obtained in a Siemens Kristalloflex D-500 diffractometer with a Ni-filtered Cu Kα radiation at a goniometer speed of 1° (2θ)/min. X-ray diffractogram of the tablet was procured scraping the tablet surface and depositing the powder in the diffractometer cell.

3. Results and discussion

To evaluate the compression properties of the raw material without lubrication of the die, five tablet batches corresponding to breaking forces from 20 to 60 N were carried out. The average of six tablets was calculated for each batch. The following parameters were measured: maximum upper force (F_u); ratio between breaking force (F_b) and mean applied force (F_m) to make the tablet; lubrication coefficient (R); ejection force (F_e); residual lower punch force (RLPF); friction work (W_f); work of ejection (W_e); compactibility, ratio

Table 1
Compressional properties of Compril®

F_u (N)	F_b/F_m	R	F_e (N)	RLPF (N)	W_f (J)	W_e (J)
17384 ± 565	$1.13e^{-3}$ ± 0.03	0.991 ± 0.015	436.6 ± 39.4	130.8 ± 9.8	0.502 ± .070	0.395 ± 0.119
28324 ± 326	$1.05e^{-3}$ ± 0.01	0.988 ± 0.003	338.2 ± 45.2	135.6 ± 10.5	0.721 ± .025	0.153 ± 0.032
43253 ± 365	$0.91e^{-3}$ ± 0.01	0.982 ± 0.002	229.4 ± 17.9	124.7 ± 27.2	0.939 ± .064	0.033 ± 0.000
52404 ± 2402	$0.89e^{-3}$ ± 0.03	0.990 ± 0.005	341.5 ± 25.3	180.7 ± 16.1	0.648 ± .056	0.105 ± 0.010
67089 ± 2713	$0.88e^{-3}$ ± 0.04	0.992 ± 0.002	457.0 ± 11.2	224.8 ± 14.5	0.547 ± .283	0.096 ± 0.007
σ/W_n	W_{ex} (J)	W_{el} (J)	W_{an} (J)	W_n (J)	R_{ela}%	Pl%
0.128 ± 0.020	2.644 ± 0.012	3.206 ± 0.088	4.620 ± 0.792	3.700 ± 0.594	18.34 ± 2.81	62.67 ± 5.06
0.142 ± 0.011	6.402 ± 0.612	6.944 ± 0.535	5.103 ± 0.617	4.801 ± 0.496	25.21 ± 2.80	53.61 ± 2.15
0.154 ± 0.014	9.311 ± 0.700	8.503 ± 0.896	7.754 ± 0.742	6.144 ± 0.579	29.37 ± 3.12	45.40 ± 2.08
0.158 ± 0.007	15.231 ± 1.562	16.405 ± 1.752	9.802 ± 0.884	8.204 ± 0.742	35.43 ± 3.10	40.15 ± 3.42
0.161 ± 0.002	19.385 ± 2.576	21.064 ± 2.667	12.273 ± 0.632	9.671 ± 0.130	42.59 ± 5.41	36.25 ± 7.01

between tensile strength and net work (σ/W_n); expansion work (W_{ex}); elastic work as obtained from the second compression (W_{el}); apparent net work (W_{an}); net work (W_n) (Doelker, 1978); elastic recovery (R_{ela}); and plasticity in percent (%Pl). These parameters are shown in Table 1.

The low values of ejection force, residual lower punch force, friction work and work of ejection agreed with the high lubrication coefficient close to 1. These parameters demonstrated the ability of this excipient to be compressed without lubricant. However, the poor flow characteristics (Muñoz-Ruiz et al., 1992) of Compril® determined the necessity of adding Aerosil® 200 or mixing it with other direct compression excipients. Low values of friction parameters are normally related with plastic materials, while high values are associated with brittle fracture materials (Muñoz-Ruiz et al., 1993). In this sense, Compril® seems to be a material that undergo compression deforms plastically.

Plasticity and ratio between breaking and mean applied forces of Compril® tend to decrease when applied force was increased. Whereas, compactibility showed the opposite trend. Thus, these results demonstrated an anomalous behavior of Compril® in relation with those results obtained (Doelker, 1988) for substances such as microcrystalline celluloses, lactoses, dibasic calcium phosphates and other materials used as direct compression excipients, which showed values of these parameters independent of applied force.

Fig. 1 displays Heckel tablet-in-die plots (Paronen, 1986) for several tablets replicates of Compril®. Materials that undergo compression deform plastically or materials with an extensive brittle fracture exhibit, at high pressures, a good fitting to Heckel equation (Humbert-Droz et al., 1982; Rue and Rees, 1978). Whereas, behavior of Compril® shows a non-linear relationship between $\ln 1/(1-D_r)$ and applied pressure over the range of applied pressures. For this reason, is not possi-

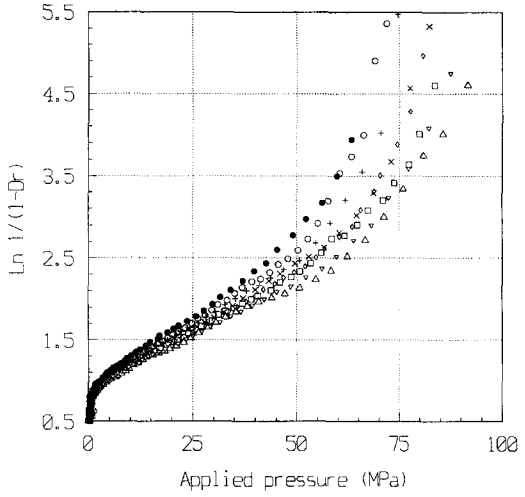

Fig. 1. Heckel in tablet die method.

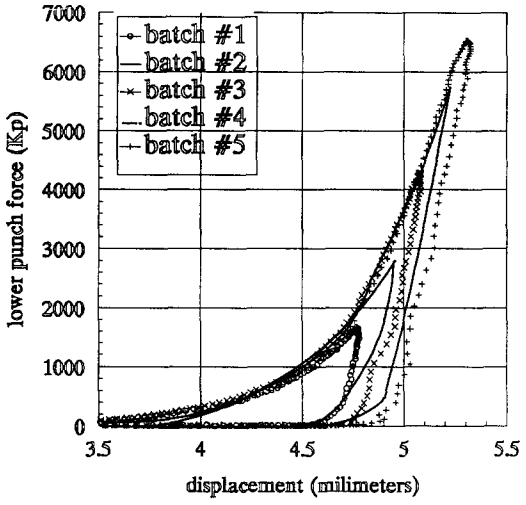

Fig. 2. Force–displacement profiles of tablet batches.

ble to estimate the yield pressure (P_y) and the density due to particle rearrangement and fragmentation (D_b) computing the densification in the whole range of applied pressures. Only, data reduction below 50 MPa with a correlation coefficient (0.9988), permitted to obtain values of yield pressure (33.9 MPa). This value of yield pressure less than 100 MPa (Paronen, 1986) suggests that Compril® has a high tendency to deform plastically. Futhermore, D_b-value (0.011 g/cm^3) (Hersey et al., 1972) was in concordance with this consolidation mechanism. However, a transformation of the excipient can take place from 50 MPa. These results support the finding of Pirttimäki et al. (1993) for anhydrous caffeine which was transformed from the metastable form I to the stable form II by using a compression pressure of 50 MPa.

Fig. 2 exhibits force–displacement profiles of the tablet batches at several pressures. This figure, as expected, shows how apparent net work increases as applied force increases. A non-linear relationship between applied force and the apparent net work was observed (Table 1). These results implied a limit in the linear relation between these two magnitudes upto a fixed pressure above which, the expansion originates friction phenomenon and therefore supplementary energy does not increase the cohesion of the compacts (Aulton and Marok, 1981). The high values of net work to make the tablets (Table 1) indicated the incapacity to create agglomerate by particulate bonding. In this sense, materials that deform plastically are normally related with a higher energy necessary for compression (Gillard et al., 1977). The force–displacement curves demonstrated high expansion work for all batches, especially at high pressures. The decrease in the force–displacement hysteresis loops at high pressures supports the finding of Travers and Cox (1978) who explained this fact for some pharmaceutical materials during the second compression in terms of work-hardening.

In order to elucidate consolidation mechanism in the Compril® and take into account the values of compactibility, apparent net and net work, plasticity and also parameters from Heckel equation that showed an unusual behavior, an X-ray diffraction analysis was performed.

The X-ray diffractograms were obtained not only for the raw material but also for tablet batches. Fig. 3 shows the X-ray diffractograms of raw material and the tablet batch at the highest pressure (# 5 batch), being the results similar for the other batches (# 1 – # 4). In this figure can be observed similar X-ray diffraction patterns for raw and tablet. This X-ray diffractogram showed the presence of strong peaks in decreasing order of intensity at 31.7, 32.8 and 25.9° 2θ.

An analysis of these strong peaks is shown in Table 2, in which the same diffraction 2θ peak, integrated peak areas and full width at half maximum (FWHM) of raw material and tablets at the highest pressure were different. Tablets at the

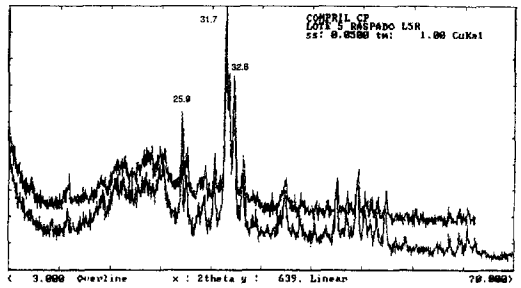

Fig. 3. X-ray diagrams of raw material and tablet batch at the highest pressure.

Table 2
Diffraction 2θ peak, background in peak areas, integrated peak areas and full width at half maximum of raw material and tablets at the highest pressure

2θ peak	Material	Background	Area	FWHM
25.9	Raw	0.0	31.79	0.2736
	#5	0.0	49.32	0.2021
31.7	Raw	6.25	207.56	0.5059
	#5	3.65	125.91	0.2747
32.8	Raw	8.35	78.64	0.2995
	#5	2.45	48.73	0.2746

highest applied pressure showed lower values FWHM than raw material. Futhermore, areas were lower in the tablet with regard to the raw material, except in the 25.9° 2θ peak that was higher in the raw material. The values obtained of these parameters in the #1–#4 batches were between both extremes. The differences observed in these parameters pointed out a modification in the microdomains. This change is associated with mechanical properties of the particulate matter (Klug and Alexander, 1974). The peaks of the tablet X-ray diffractograms, narrower than in the raw diffractogram (Table 2), demonstrated that the applied pressure produces a higher degree on the crystallinity of Compril®. Therefore, the modification in the slope of Heckel equation and the changes in binding parameters and plasticity may be explained due to the fact that applied pressure alters the microdomains. These results demonstrated the usefulness of quantitative X-ray diffraction analysis for the understanding of the behavior of tablet excipients in addition to the investigaton of polymorphic transformation of drug substances under compression (Pirttimäki et al., 1993; Ketolainen et al., 1995).

4. Conclusions

Quantitative X-ray diffraction analysis may be used to explain densification behavior on the basis of differences between the areas and the FWHM of the raw and tablet X-ray diffractograms. This application is quite interesting in materials as Compril®, with modifications in mechanical properties during compaction (work-hardening) and difficult to characterize in a typical consolidation mechanism.

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