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Evaluation of an adequate method of estimating flowability according to powder characteristics

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Summary

An evaluation of different methods of investigating the flow properties of bulk solids has been carried out on two new direct compression excipients, Ludipress® and Maltrin® M150, in order to establish a better validation of the study of the flowability of pharmaceutical powders according to their characteristics. A good correlation among all the methods was found. Also, both excipients showed different behavior, maybe due to the stickiness of Maltrin® M150 and the size and shape of its particles. Finally, as far as an appropriate procedure is concerned, the most suitable method of estimating the flowability of powders is based on the flow rate system design, however, if it does not flow the shear cell method provides useful information about the reasons why this is so.

Introduction

The need on the part of the pharmaceutical industry for having tests to characterize the properties of bulk solids flow has led to the search for methods that make it possible to estimate this property. This parameter is of great importance for direct compression excipients, since they must be inherently free flowing without the requiring granulation (Ho et al., 1977). These tests could be used to characterize bulk solids routinely before compression, in order to diminish the time of filling on machinery or in the development laboratory, so that better optimization of flow properties can be achieved in experimental formulation. Such techniques can be classified into direct and indirect methods. With respect to the former, we have designed (Muñoz-Ruiz and Jiménez-Castellanos, 1993) a new integrated system of data acquisition for the measurement of flow characteristics that eliminates all external factors influencing the flow rate such as the operator, weight of powder and vessel. On the other hand, in relation to indirect methods, Train (1958) reported considerable variability in results as a consequence of the method applied to measure the angle of repose. Moreover, Carr (1970) pointed out that the compressibility index cannot be used

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as the only means of measuring flowability. This scheme has been accomplished recently by Brittain (1989).

Finally, Jenike cells have been used in pharmaceutical technology for several years (Ho et al., 1977; Cohard et al., 1984); however, the great number of devices (York, 1975; Ho et al., 1977; Sanz and Vazquez, 1986; Staniforth, 1988) as well as the diversity of methods (Hiestand and Wilcox, 1969; Nyqvist and Brodin, 1980; Irono and Pilpel, 1982; Sanz and Vázquez, 1987) necessitate prior validation of the method to be used.

In the light of the above, this work has been centered on the evaluation of methods using a new direct method, the classical indirect procedures of determining the angles of repose and compressibility index, and a device for shear measurement, in order to establish a better validation of the study of the flowability of pharmaceutical powders according to their characteristics.

Materials and Methods

In this study two new excipients for direct compression were used: Ludipress® batch 56-0733 (BASF,Spain), and Maltrin® M150 batch P-1251 (Grain Processing Corp., U.S.A.), which were stored under controlled temperature (20°C) and humidity conditions (RH = 40%).

The flow rate was measured by our data acquisition flowmeter system (Muñoz-Ruiz and Jiménez-Castellanos, 1993). The vessel used was a stainless-steel cylinder with a hole size of 12 mm. A balance with an interface connected to a personal computer (IBM PC compatible) constitute the whole system. A software program for data acquisition, graphics and calculations was used.

Static angle of repose was measured according to the fixed funnel and free standing cone method (Train, 1958). A funnel with the end of the stem cut perpendicular to the axis of symmetry is secured with its tip 2 cm height, H, above graph paper placed on a flat horizontal surface. Powder is carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of the funnel. The mean diameter, $2R$, of the base of the powder cone is determined and the tangent of the angle of repose is given by:

$$\tan \alpha = H/R \qquad (1)$$

where α is the angle of repose.

Dynamic angle of repose was measured according to the revolving cylinder method (Train, 1958). A sealed hollow stainless-steel cylinder having an internal diameter of 80 mm with one end transparent is made to revolve horizontally. It is half-filled with the powder, so that the free surface of the powder forms a diametrical plane. The maximum angle that this plane makes with the horizontal on rotation of the container is taken as the angle of repose. The data given are the means of 10 measurements.

To calculate the compressibility index (Carr, 1965), a sample of 100 g is placed in a 250 ml graduated cylinder and the occupied volume (V_0) is determined. After 10 and 500 tapping or vibrations, the occupied volumes are determined, V_{10} and V_{500}, respectively. The data given are the means of 10 measurements.

Mechanical parameters of shear were determined using a ring shear cell (Bromhead Ring Shear, Wykeham Farrance Engineering Ltd, Slough, U.K.) described previously (Velasco et al., 1992). In this apparatus, an annular sample, 5 mm thick with inner and outer diameters of 70 and 100 mm, respectively, is taken and confined radially between concentric rings. The sample is compressed between porous bronze loading platens by means of a counterbalanced 10:1 ratio lever loading system. Rotation is imparted to the base plate and lower platen by means of a variable speed motor and causes the sample to shear. Torque transmitted through the sample is reacted by a pair of matched load measuring proving rings bearing on a cross arm. A speed of 0.24 ° min^{-1} was selected to run the test in order to permit adequate data acquisition. It was necessary to use a different powder in every test. The pre-consolidation time was 10 min and the consolidation time was 15 min. The pre-consolidation loads used were 1000, 300, 260, 220, 180, 120 and 60 g and the reduced loads were 6 or 7 in order to obtain the yield loci.

Particle shapes were described using a scanning electron microscope (ISI-SS40). Particle size distributions were determined using mesh sieves of 500, 450, 400, 350, 300, 250, 200, 175, 150, 125, 100, 75, 50 and 25 μm (C.I.S.A., Barcelona, Spain) in a vibrator sieve (Retsch, Rheil, Germany).

Results and Discussion

Table 1 shows the results in relation to flow rate, angles of repose and compressibility index. A good correlation is evident among all the methods, since Ludipress® has a high flow rate, angles of repose below 40°, which many authors have indicated as the limit to flow (Delattre et al., 1973; Staniforth, 1988), a low compressibility index, less than 20%, which is indicative of good flow according to Carr (1965) and a Hausner ratio close to 1 (Hausner, 1972). In contrast, Maltrin® M150 does not flow in the flowmeter system, shows angles of repose higher than 40°, a compressibility index greater than 20% and a Hausner ratio inferior to that of Ludipress®.

Figs 1 and 2 show a single example of a plot of shear stress vs shear strain for Ludipress® and Maltrin® M150, respectively, although it was necessary to construct seven plots, one for every pre-consolidation load used. The shear strain is expressed as the speed of the motor (mm/min) multiplied by the time (min) during which the cell was rotating. The equation used to calculate shear strain was:

$$S = \text{sp} \cdot t \tag{2}$$

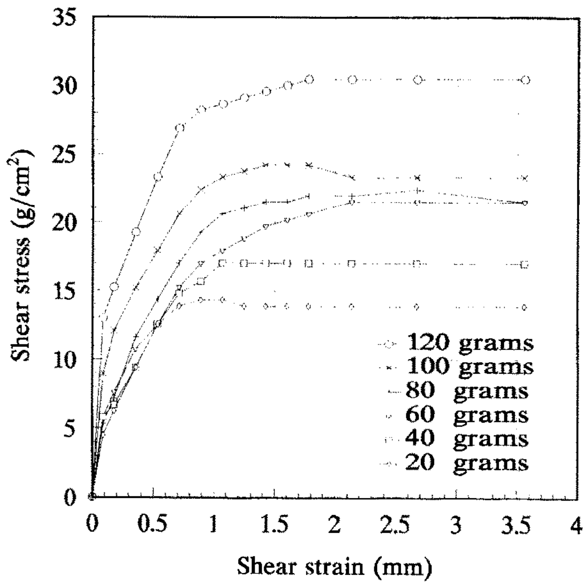

Fig. 1. Shear stress vs shear strain of Ludipress® at 120 g of pre-consolidation load.

where S is shear strain (mm), sp denotes speed (mm/min) and t is time (min).

In order to calculate the shear stress (τ), a uniform shear stress distribution across the sample was assumed. The distribution is more likely to be close to being uniform particularly when the sample is narrow in comparison to its diameter. The torque transmitted through the sample is given by:

$$T = \int_{R_1}^{R_2} \tau R^2 \pi \mathrm{d} R \tag{3}$$

TABLE 1

Values of flow rate for N-1 data corresponding to the excipients and the average of the static and dynamic angles of repose (°), compressibility index and Hausner ratio for Ludipress® and Maltrin® M150

Excipient	Flow rate (g/s)	Static angle of repose (°)	Dynamic angle of repose (°)	Compressibility index	Hausner ratio
Ludipress®	10.96	36.81 ± 0.69	31.3 ± 0.57	5.14	0.95
Maltrin® M150	–	65.23 ± 3.30	50.3 ± 0.5	36.11	0.73

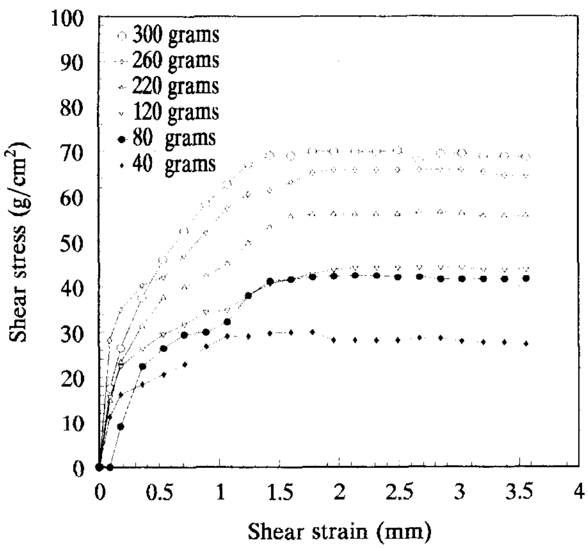

Fig. 2. Shear stress vs shear strain of Maltrin® M150 at 300 g of pre-consolidation load.

Since the torque is given by mean load on the proving rings (F), multiplied by the distance between them (L):

$$T = [(F_1 + F_2)L]/2 \tag{4}$$

thus

$$\tau = [3(F_1 + F_2)L] / [4\pi(R_2^3 - R_1^3)]$$
$$= 0.448(F_1 + F_2) \tag{5}$$

where F_1 and F_2 are the measurements on proving rings 1 and 2, respectively, L denotes the distance between the proving rings, and R_1 and R_2 are the inner and outer radii, respectively.

Figs 3 and 4 represent the yield loci of Ludipress® and Maltrin® M150, respectively, at a pre-consolidation load, as shear stress at failure vs normal stress. The shear stress at failure (τ_f) is the highest value of shear stress at every consolidation load. The normal stress (σ) corresponds to the stress due to the load applied in every test to the sample by means of the counterbalanced lever loading system. This load must be multiplied by 10 as it is 10:1 ratio system. This load is divided by the sample area, the equation to calculate the normal stress being:

$$\sigma = 10P/[\pi(R_2^2 - R_1^2)] = 0.25P \tag{6}$$

where P is the load applied, and R_1 and R_2 denote the inner and outer radii, respectively.

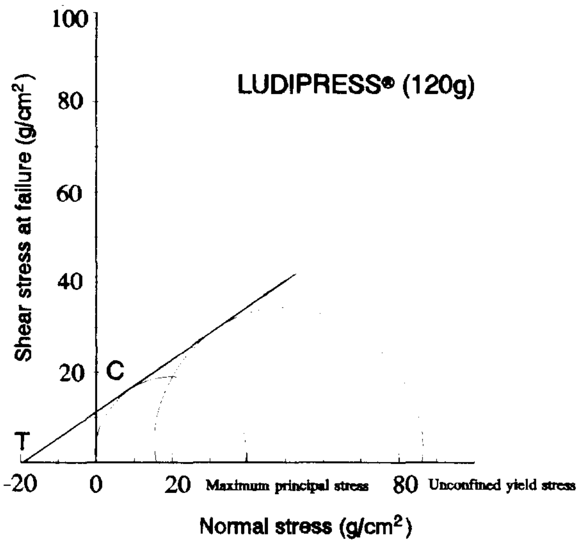

Fig. 3. Yield loci and Mohr circles of Ludipress® at 120 g of pre-consolidation load.

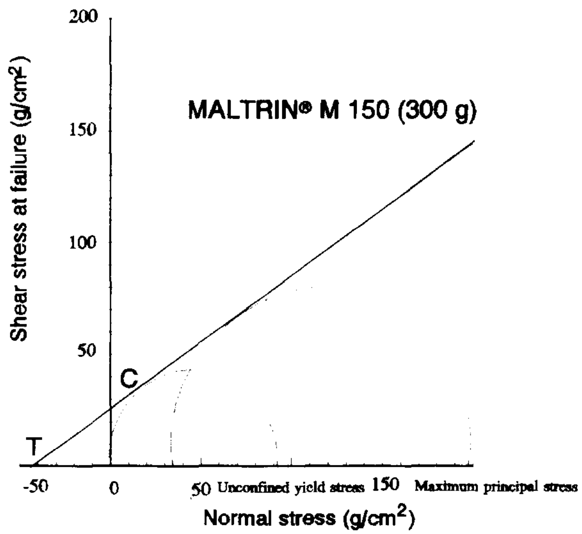

Fig. 4. Yield loci and Mohr circles of Maltrin® M 150 at 300 g of pre-consolidation load.

TABLE 2

Results for Ludipress® of the parameters corresponding to pre-consolidation stress (σ_{max}), cohesion (C), correlation coefficient (r), friction coefficient (μ), traction (T), maximum principal stress (σ_{1max}), angle of friction (Ø) and unconfined yield stress (f_c)

σ_{max}	C	r	μ	T	σ_{1max}	Ø	f_c
250	18.21	0.999	0.667	27.292	582.82	33.72	71.67
75	9.12	0.981	0.573	15.916	178.40	29.833	31.51
65	12.04	0.981	0.533	22.563	129.68	28.095	40.15
55	14.37	0.976	0.436	32.960	114.12	23.557	43.88
45	12.11	0.941	0.597	20.271	127.45	30.872	42.73
30	11.34	0.974	0.586	19.335	85.55	30.406	39.63
15	12.40	0.992	0.806	15.384	65.19	38.869	51.84

Although it was not possible to apply the Warren-Spring equation (Ashton et al., 1965; Farley and Valentin, 1968) to adjust the function of shear stress at failure vs normal stress, the high values of correlation coefficients obtained for the yield loci of the two excipients in this study (Tables 2 and 3), demonstrate the correct treatment of the data as a straight line (Terzaghi and Peck, 1980).

The parameters obtained from the yield loci at different pre-consolidation loads for Ludipress® and Maltrin® M150 are listed in Tables 2 and 3, respectively. These parameters are cohesion (C), friction coefficient (μ), traction (T) and angle of friction (Ø), which help us to justify the results obtained with the other method used.

It is well known that flow properties are influenced by cohesion and, at the same time, friction between particles. Ludipress® has lower values of cohesion and traction than Maltrin® M150 while similar values of friction coefficients are obtained for both excipients, as can be observed in Tables 2 and 3. Both phenomena can be explained as follows: the high cohesion of Maltrin® M150 may be justified by the stickiness of the excipient, and the similar friction values by the predominance in both samples of polyhedric particles.

In order to obtain only one factor representative of the shear cell, Figs 3 and 4 also show plots of Mohr semicircles. The first semicircle, tangential to the yield loci, with its center on the σ axis and passing through the origin, determines the value of unconfined yield stress (f_c). The second Mohr semicircle, also tangential to the yield locus, passing the point (σ_{max},τ_f) and with its center along the σ axis, determines the maximum principal stress (σ_{1max}). Values of unconfined yield stress and maximum principal stress for all pre-consolidation stresses are also listed in Table 2 for Ludipress® and Table 3 for Maltrin® M150.

In order to estimate the flowability, we follow the procedures employed previously by different authors. Two types of functions were constructed: (A) unconfined yield stress (f_c) vs maximum principal stress (σ_{1max}) (Crooks et al., 1977; Ho et al., 1977; Nyqvist and Brodin, 1980, 1982; Nyqvist,

TABLE 3

Results for Maltrin® M150 of the parameters corresponding to pre-consolidation stress (σ_{max}), cohesion (C), correlation coefficient (r), friction coefficient (μ), traction (T), maximum principal stress (σ_{1max}), angle of friction (Ø) and unconfined yield stress (f_c)

σ_{max}	C	r	μ	T	σ_{1max}	Ø	f_c
250	34.50	1	0.666	51.749	625.95	33.68	128.86
100	30.24	0.991	0.582	51.923	257.79	30.22	105.22
75	26.09	0.993	0.590	44.22	197.36	30.54	91.43
65	22.70	0.984	0.615	36.90	184.92	33.03	81.24
55	21.68	0.942	0.606	35.75	167.55	31.23	76.99
45	22.31	0.883	0.542	41.19	142.02	28.43	74.87
30	22.96	0.900	0.522	43.98	75.78	27.57	98.17

1982; Sanz and Vazquez, 1986); and (B) Unconfined yield stress (f_c) vs pre-consolidation stress (σ_{max}) (Nyqvist, 1982; Nyqvist and Brodin, 1982; Sanz and Vazquez, 1986).

The correlation coefficients of Ludipress® were slightly higher for $f_c = f(\sigma_{1max})$ (0.659) than $f_c = f(\sigma_{max})$ (0.639) while for Maltrin® M150 the difference between both coefficients was higher (0.941 and 0.849, respectively). Although correlation coefficients were low for both plots (options A and B) we decided to use $f_c = f(\sigma_{1max})$ like Nyqvist (1982) and Nyqvist and Brodin (1982) who prefer $f_c = f(\sigma_{1max})$ to calculate the flow factor, using the plot $f_c = f(\sigma_{max})$ when there is poorer linearity in the first plot.

After fitting the f_c vs σ_{1max} plots to the possible theoretical equations that follow this process, linear (Nyqvist, 1982) and geometric (Nyqvist and Brodin, 1980; López and Vázquez, 1986) regression, we found the same correlation coefficients (0.659 for Ludipress® and 0.941 for Maltrin® M150).

The high value of the flow factor of Jenike (ff) for Ludipress® (29.4) corresponds, according to this scale (Jenike, 1970), to an excipient with excellent flow while the flow factor of Jenike (ff) (8.326) of Maltrin® M150 is indicative of a cohesive excipient. These results are in accordance with the York factor (1/ff), which is high for Maltrin® M150 (0.12) and low for Ludipress® (0.034).

Typical parameters of a normal distribution are presented in Table 4: mean diameter in weight (d_w), standard deviation, coefficient of variation, and kurtosis and skewness coefficients. On the one hand, Maltrin® M150 has a minimum geometric mean diameter (99.3) although both excipients have the same coefficient of variation (0.43). On the other, Ludipress® also has the highest symmetry around the mean (coefficient of skewness closer to 0) and a height of the curve more similar to a normal size distribution (coefficient of kurtosis closer to 0). Therefore, the difference in the flow properties between Ludipress® and Maltrin® M150 can be explained due to the stickiness of Maltrin® M150 and as a result of the size and shape of its particles.

TABLE 4

Evaluation of normal size distribution

Material	d_w (μm)	Coefficient of		
		Variation	Kurtosis	Skewness
Ludipress®	202.6±88.7	0.4377	0.38249	0.6368
Maltrin® M150	99.3±42.9	0.4312	33.83606	4.88440

Conclusions

As a result of this study, we conclude that the most appropriate method to choose for evaluating the flowability of powders is the use of a flowmeter, since it allows this property to be determined quickly and precisely. If the powder does not flow, we consider a suitable alternative method to be the use of a shear cell since, despite being more tedious than other indirect methods, it undoubtedly provides more information to justify the flowability and does not depend on experimental factors such as the angle of repose and compressibility index.

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