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Rheology and compression characteristics of lactose based direct compression excipients

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Summary

This article compares the rheological and the fundamental direct compression properties of five lactose-based excipients for direct compression. The sequence observed, in decreasing order, of flow characteristics was: Ludipress®, Cellactose®, Tablettose®, Fast-Flo Lactose and anhydrous lactose. Granulometry of Ludipress®, Cellactose® and Fast-Flo Lactose demonstrated a clearly normal distribution with best fitting to straight lines on a probability scale. The compression characteristics of Cellactose® are better than those of the other lactose-based excipients which showed plasticity values from maximum to minimum as follows: Ludipress®, Fast-Flo Lactose®, Tablettose® and lactose. Fast-Flo Lactose showed a greater dependence of disintegration on crushing strength than did the other lactose-based excipients.

Introduction

Lactose is one of the diluents most widely used by tablet formulators. Because it lacks essential fluidity and compressibility in its regular form, common lactose cannot be used in direct compression of tablets without modification (Bossert and Stamm, 1978; Delacourte-Thibaut et al., 1983). The advent of direct compression as it is known today was made possible in the late 1950s with the commercial availability of spray-dried lactose, the first tablet filler possessing the fluidity and compressibility necessary to form compacts in high-speed tablet machines (Shangraw et al., 1981).

It is generally accepted that crystalline α-lactose monohydrate fragments on compaction (Cole et al., 1975; McKenna and McCafferty, 1982; Garr and Rubinstein, 1991), the extent of which depends, for example, on the speed of compaction and the particle size. Riepma et al. (1992) showed differences in consolidation and compaction between roller-dried β-lactose, anhydrous α-lactose, and non-granular lactose types. Vromans et al. (1986) concluded that compactibility is to a large extent determined by the amorphous component of the excipient, while consoli-

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dation is governed by the crystalline part. The fragmentation propensity of a substance increases along with its particle size (Hersey et al., 1973; McKenna and McCafferty, 1982; Alderborn and Nystrom, 1985), while the contribution of the plastic deformation decreases. The participation of particle rearrangement and plastic flow in the densification process of crystalline lactose has been reported (Fell and Newton, 1971a; Hersey et al., 1973). For mixtures of α-lactose monohydrate, anhydrous α-lactose and anhydrous β-lactose, it was possible to predict the strength of tablets from measurements of the strength of compacts prepared from the individual components (Fell and Newton, 1970a). Other studies point to possible plastic deformation properties of amorphous lactose (Fell and Newton, 1971a).

In general, the anhydrous lactose types yield stronger tablets than α-lactose monohydrate (Fell and Newton, 1970a). The same applies to spray-dried lactose (Gunsel and Lachman, 1963). However, there is a considerable number of conflicting results (Fell and Newton, 1968, 1970b, 1971b; Alpar et al., 1970).

After many unsuccessful attempts at improvement of spray-dried lactose, a much more compressible product was introduced in the early 1970s, Fast-Flo Lactose (Shangraw et al., 1981). At present, new forms of α-monohydrate lactose have been introduced into the market. However, it is often not clearly indicated which type of lactose has been used for the experiments. Minet et al. (1982) and Whiteman and Yarwood (1988) have reported an evaluation of different lactose-based products as direct compression tableting excipients. Rheological characteristics of Ludipress® and their mixtures with Compril® and Avicel® PH 101 have been published (Muñoz et al., 1992a).

This paper presents the results of an extended study on the fundamental rheological characteristics and tableting properties of five lactose-based excipients frequently used for direct compression.

Materials and Methods

In this study five excipients for direct compression were used; anhydrous α-lactose, batch 3227 (Acofarma, Barcelona, Spain), Tablettose®, batch X101 (α-monohydrate lactose) and Cellactose®, batch X945 (cellulose : lactose, 1 : 3) (Fher, Barcelona, Spain), Ludipress®, batch 56–0733 (lactose + 2.2% PVP C-30 + 3.4% crospovidone) (BASF, Madrid, Spain) and Fast-Flo® Lactose, batch 3RJ 701, (spray-dried lactose + amorphous lactose) (Foremost, WI, U.S.A.). A chloroformic solution of magnesium stearate (5% w/v) was used as a non-water soluble lubricant.

The methodology used for determining the rheological characteristics of repose angle and compressibility on tamping are described in detail in earlier studies (Borrero et al., 1988; Muñoz et al., 1988). Dynamic angle of repose was measured according to the rotating cylinder method (Hedge et al., 1985) (stainless-steel cylinder with an internal diameter of 80 mm). Particle size distributions were determined using mesh sieves of 500, 450, 400, 300, 250, 200, 175, 150, 125, 100, 75, 50 and 25 μm (CISA, Barcelona, Spain) in a vibrator sieve (Retsch, Rheil, Germany). The true density of each powder was determined using a pycnometer (Model stereopycnometer, Quantachrome, Syosset, U.S.A.); the gas employed was helium. Excipients were stored under controlled humidity conditions (RH = 40%).

Compression characteristics of the powders were investigated on an instrumented single punch tablet machine (Bonals AMT 300, Barcelona, Spain), equipped with HBM YL6 strain gauges and dynamic amplifiers (NEC Sanei, Tokyo, Japan), and inductive displacement transducers (HBM, Darmstat, Germany). A sufficient 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 fixed hardness (4, 6 and 8 kp). Also, to investigate the sensivity to lubrication, similar tablets were made after lubricating the die with a chloroformic solution of magnesium stearate (5% w/v).

The study of tablet weight variation was performed on a instrumented single punch tableting machine (Bonals, Model AMT 300, Spain) at 30 cycles/min and equipped with a forced feeding system. The uniformity in weight of the tablets was determined using a Mettler AE 100 analyti-

cal balance (Mettler Instrumentate, Geneva, Switzerland) according to European Pharmacopoeia II.

The tablet crushing strength was determined immediately after compression using a commercially available hardness tester (Schleuniger-2E, Dr K. Schleuniger, Geneva, Swizerland).

Friability was evaluated from the weight loss of 10 tablets tumbled for 100 revolutions using an Erweka ZT-3 (Erweka, Heusenstamm, Germany) friabilator.

Disintegration testing (six tablets) was performed at 37°C in 0.1 N HCl medium in accordance with the European Pharmacopoeia using an Erweka ZT-3 apparatus (Erweka, Heusenstamm, Germany), without discs.

Results and Discussion

The static angle of repose (σ_{st}), dynamic angle of repose (σ_{dy}), static friction coefficient (μ_{st}) and dynamic friction coefficient (μ_{dy}) are listed in Table 1.

Ludipress® has a lower static angle of repose (35.41) and dynamic angle of repose (31.30) than the other lactose-based excipients. This may be interpreted on the basis of its interparticulate friction being minimal due to its spherical form. Fast-Flo Lactose® has the largest difference (20.48) between dynamic angle of repose (32.3) and static angle of repose (51.78). This disparity may be explained according to the bulk solids flow theory (Johanson, 1987). In this way, an improved system to measure flow characteristics according to the bulk solids flow theoretical considerations has been described (Muñoz and Jiménez-Castellanos, 1992b).

TABLE 1

Angle of repose and friction coefficient of lactoses

Material	σ_{st} ± S.D.	μ_{st} ± S.D.	σ_{dy} ± S.D.	μ_{dy} ± S.D.
Lactose	62.90 ± 2.57	1.96 ± 0.22	51.6 ± 1.5	1.26 ± 0.04
Tablettose®	45.36 ± 0.36	1.01 ± 0.01	44.3 ± 1.15	0.98 ± 0.03
Cellactose®	42.17 ± 0.81	0.90 ± 0.03	34.5 ± 1.8	0.68 ± 0.05
Ludipress®	35.41 ± 1.49	0.71 ± 0.04	31.3 ± 0.57	0.61 ± 0.03
Fast-Flo Lactose®	51.78 ± 0.44	1.27 ± 0.02	32.3 ± 1.15	0.63 ± 0.03

Values for the true density (ρ), tap density (ρ_t), bulk density (ρ_b), Hausner ratio (H) and compressibility index (C) of excipients under study are shown in Table 2.

Fast-Flo Lactose® has a lower Hausner ratio and compressibility factor than those of the other lactose-based excipients. In a comparative study, Brittain et al. (1991) reported higher values for the compressibility parameters of anhydrous lactose and lower values for Fast-Flo Lactose® samples. This lower value of the compressibility factor suggests an intrinsic, strong tendency to maximum compactness (ratio between volume filled by the material and total volume) of the powder (Carr, 1965b). On the other hand, the value of the compressibility factor for this excipient (5.49) between 5 and 15 indicates an excellent flow (Carr, 1965) of the powders. Ludipress® and Cellactose® possess similar values of compressibility factor, lower than that of anhydrous α-lactose and higher than that of Tablettose®. This sequence observed for the compressibility factor was inconsistent with the order in the values of the Hausner index, since Ludipress® displayed lower values for this parameter as compared to Cellactose® and Tablettose®.

Typical parameters of normal distributions are represented in Table 3: geometric mean diameter (d_{gw}), standard deviation, and coefficient of variation, kurtosis and skewness.

Fast-Flo Lactose® has a minimum geometric mean diameter (107.2), and a minimum variation coefficient (0.2777). Also, together with Cellactose®, it exhibits the highest symmetry around the mean (coefficient of skewness closer to 0) and height of the curve more similar to the normal size distribution (coefficient of kurtosis closer to 0). Tablettose® and Ludipress® show similar symmetry around the mean and anhydrous α-lactose exhibits the highest asymmetry.

Granulometric data for the five lactose-based excipients are presented in Fig. 1. Ludipress®, Cellactose® and Fast-Flo Lactose® clearly demonstrate a normal distribution with best fitting to straight lines on a normal probability scale.

TABLE 2

True density (ρ), tap density (ρ_t), bulk density (ρ_b), Hausner ratio (H) and compressibility index (C) of lactoses

Material	$\rho \pm$ S.D. (g/cm^3)	$\rho_t \pm$ S.D. (g/cm^3)	$\rho_b \pm$ S.D. (g/cm^3)	H $\pm$ S.D.	C $\pm$ S.D. (%)
Lactose	1.527 ± 0.003	0.925 ± 0.000	0.576 ± 0.066	1.607 ± 0.021	15.09 ± 1.57
Tablettose®	1.526 ± 0.002	0.694 ± 0.000	0.530 ± 0.030	1.308 ± 0.014	7.92 ± 1.60
Cellactose®	1.628 ± 0.003	0.471 ± 0.020	0.373 ± 0.028	1.261 ± 0.009	8.62 ± 1.49
Ludipress®	1.469 ± 0.001	0.590 ± 0.015	0.490 ± 0.052	1.200 ± 0.017	8.46 ± 1.39
Fast-Flo Lactose®	1.483 ± 0.009	0.709 ± 0.020	0.608 ± 0.040	1.165 ± 0.018	5.49 ± 1.83

Fast-Flo Lactose® shows a narrow particle size distribution.

To evaluate the compressional properties of the excipients unlubricated (UN) and with lubrication of the die (L), the average of the parameters, maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient (R) and plasticity (Stamm and Mathis, 1976) in percent (% Pl) were calculated with values obtained for tablets of 4, 6 and 8 kp crushing strength. These parameters are listed in Table 4.

The data show that Cellactose® has greater compactibility as compared with the other excipients (lower applied forces to make tablets of similar crushing strength), since the cellulose component undergoes predominantly plastic deformation (Cellactose exhibits higher plasticity in unlubricated and lubricated tablets than the other lactoses; Table 4) and, therefore, the mechanical strength of the excipient is largelly controlled by the extent of hydrogen bonding. Simultaneously, the lactose component of the mixture undergoes extensive fragmentation and fills the void spaces during compression. Thus, the combination of fragmentation and plastic deformation in the cellulose-lactose excipient leads to improvements over the lactose excipient in the utilization of

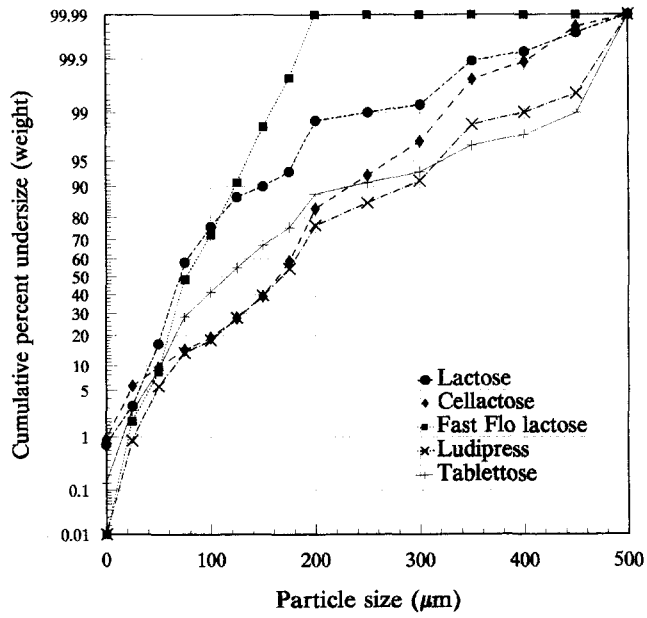

Fig. 1. Normal fitting on probability scale.

TABLE 3

Evaluation of normal size distribution geometric mean diameter (d_{gw}), standard deviation, coefficient of variation, kurtosis and skewness

Material	d_{gw} (μm)	Variation	Kurtosis or excess	Skewness
Lactose	107.2 ± 47.2	0.4401	7.21062	1.97130
Tablettose®	162.1 ± 93.1	0.5743	2.82308	1.58090
Cellactose®	187.0 ± 77.1	0.4123	0.23701	0.07390
Ludipress®	202.6 ± 93.1	0.5743	2.82308	1.58090
Fast-Flo Lactose®	107.2 ± 29.8	0.2777	0.07990	0.43700

compression force, consolidation, and bonding. The observed sequence in plasticity for the other lactose-based excipients (in descending order) was Ludipress®, Fast-Flo Lactose®, Tablettose® and anhydrous α-lactose. In all cases, lubrication of the die improved the parameter R (lower values) and diminished ejection and residual forces. Values for all these parameters in the lubricated tablets follow from minimum to maximum friction the sequence : Cellactose®, Tablettose®, Fast-Flo Lactose®, Ludipress® and anhydrous α-lactose.

The different tests for unlubricated tablets are detailed in Tables 5 and 6.

Tablets from all products passed the test for weight uniformity (Table 5), except as indicated (Henderson and Bruno, 1970) for tablets of anhydrous α-lactose (C.V. = 9.2%) which, due to poor flow, was unsuitable for making batches of tablets

TABLE 4

Average of maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient (R) and plasticity (% Pl) from tablets of 4, 6 and 8 kp crushing strength, unlubricated (UN) and with lubrication of the die (L)

Excipient	Die	MUF ± S.D.	EF ± S.D.	RLPF ± S.D.	R ± S.D.	% Pl ± S.D.
Lactose	UN	[a]	[a]	[a]	[a]	[a]
	L	29 850 ± 8 121	1 994 ± 435	1 637 ± 385	0.858 ± 0.006	63.88 ± 2.71
Tablettose®	UN	[a]	[a]	[a]	[a]	[a]
	L	21 685 ± 7 117	591 ± 103	479 ± 99	0.964 ± 0.019	75.65 ± 3.41
Cellactose®	UN	10 837 ± 2 340	982 ± 724	704 ± 336	0.862 ± 0.017	93.67 ± 0.94
	L	9 659 ± 2 134	296 ± 81	212 ± 107	0.984 ± 0.008	91.11 ± 1.86
Ludipress®	UN	[a]	[a]	[a]	[a]	[a]
	L	11 267 ± 2 215	1 210 ± 135	907.3 ± 104	0.848 ± 0.018	89.39 ± 1.58
Fast-Flo	UN	21 833 ± 7 830	3 138 ± 35	1 817 ± 188	0.741 ± 0.019	92.95 ± 1.29
Lactose®	L	16 266 ± 8 125	1 038.8 ± 129	655 ± 90	0.922 ± 0.007	82.79 ± 1.71

[a] Impossible to make the tablets.

TABLE 5

Weight uniformity of lactose tablets

Excipient	4 kp		6 kp		8 kp		Average C.V. (%)
	Weight ± S.D. (mg)	C.V. (%)	Weight ± S.D. (mg)	C.V. (%)	Weight (mg)	C.V. (%)	
Lactose	419.6 ± 38.6	9.20	[a]	[a]	[a]	[a]	9.20 ± 0.00
Tablettose®	365.4 ± 7.1	1.94	362.9 ± 4.7	1.30	367.6 ± 1.9	0.52	1.23 ± 0.70
Cellactose®	343.3 ± 3.4	1.00	323.6 ± 3.6	1.10	349.8 ± 3.3	0.90	1.00 ± 0.10
Ludipress®	364.5 ± 5.9	1.62	363.9 ± 3.3	0.91	375.7 ± 1.6	0.42	0.98 ± 0.52
Fast-Flo Lactose®	403.3 ± 4.3	1.10	398.2 ± 10.7	2.19	407.5 ± 7.1	1.75	1.85 ± 0.80

[a] Impossible to make tablets.

TABLE 6

Thickness, friability and crushing strength of lactose tablets

Excipient	Thickness ± S.D. (mm)			Friability (%)			Disintegration ± S.D. (s)		
	4 kp	6 kp	8 kp	4 kp	6 kp	8 kp	4 kp	6 kp	8 kp
Lactose	2.70 ± 0.41	[a]	[a]	34.21	[a]	[a]	26.0 ± 0.00	[a]	[a]
Tablettose®	2.41 ± 0.03	2.19 ± 0.01	2.05 ± 0.00	2.92	2.36	1.32	14.0 ± 0.00	18.0 ± 0.00	22.0 ± 0.00
Cellactose®	2.80 ± 0.08	2.45 ± 0.05	2.46 ± 0.03	3.12	1.73	0.68	1.3 ± 0.00	9.9 ± 1.34	15.2 ± 9.03
Ludipress®	2.40 ± 0.02	2.39 ± 0.04	2.33 ± 0.02	7.76	7.33	2.64	1.2 ± 0.10	1.2 ± 0.06	1.3 ± 0.11
Fast-Flo Lactose	2.74 ± 0.07	2.58 ± 0.05	2.44 ± 0.03	43.5	16.4	1.45	18.0 ± 0.00	26.0 ± 0.00	42.6 ± 3.1

[a] Impossible to make tablets.

with different crushing forces. In this sense, we do not agree with Batuyios (1966) who found excellent tableting properties for anhydrous α-lactose. As expected from the flow properties and narrow particle-size distribution, coefficient of weight variation values for other excipients were improved with respect to anhydrous α-lactose. Coefficient of weight variation values for Ludipress® were slightly lower than those of Cellactose® and lower than those of the other lactoses. Only the static angle of repose is in agreement with this sequence observed in coefficient of weight variation. This observation suggested the requirement of measuring flow characteristics with system simulating hopper with funnel or mass flow.

The thickness of the tablets decreased with increasing tablet strength. Only tablets of Cellactose® at 8 kp demonstrated an acceptable friability (less than 1%). Fast-Flo Lactose® and Tablettose® showed a clear dependence of the friability on crushing strength. Tablets at 8 kp crushing strength of these excipients exhibited friability values scarcely higher than 1%.

As pointed by Henderson and Bruno (1970), the disintegration time of lactose-based tablets was short. Tablets from all products demonstrated times shorter than 1 min. Tablet disintegration of Ludipress® was immediate and independent of crushing force. Fast-Flo Lactose showed a stronger dependence of disintegration on crushing strength than that of the other lactose-based excipients.

Conclusions

(1) Only the static angle of repose of lactose-based excipients under study agreed with the sequence observed in coefficient of tablet weight variation. The sequence observed in decreasing order of flow characteristics was: Ludipress®, Cellactose®, Tablettose®, Fast-Flo Lactose® and anhydrous α-lactose.

(2) Ludipress® and Cellactose showed a greater geometric mean diameter than the other lactose-based excipients. Moreover, Ludipress®, Cellactose® and Fast-Flo Lactose® demonstrated a clearly normal distribution. Fast-Flo Lactose® showed a narrow particle size distribution.

(3) Compression characteristics (compactability and plasticity) of Cellactose® are better than in the other lactose-based excipients which showed plasticity values from maximum to minimum as follows: Ludipress®, Fast-Flo Lactose®, Tablettose® and lactose.

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