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FLOW PROPERTIES OF COMPRESSIBLE LACTOSE CONTAINING SMALL QUANTITIES OF DRUG SUBSTANCES

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ABSTRACT

The flow behaviour of direct compressible lactose after addition of small quantities of drug substances was studied by different laboratory methods. Determination of the limiting unconfined yield pressure, [f_c], in an annular shear cell was found to be a material saving technique suitable for use in early formulation work. Estimation of the flow behaviour in a multiple punch machine by means of coefficient of tablet weight variation at high tabletting speed in a multiple punch machine was also performed with a material saving technique and was found to reflect the differences in flow behaviour as measured with the shear cell technique and also angle of repose. Water adsorption to the added drug substances was found to be an important factor for explaining the sometimes significant changes in flow behaviour.

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INTRODUCTION

During the development of tablet formulations for direct compression the evaluation of flow properties of powder mixtures is an essential part. Excipients to be used for direct compression must possess excellent flow and compaction properties, and different lactose qualities have been the subject of investigations in this respect (1 - 8). However, the flow behaviour of tablet excipients for direct compression after addition of drug substances has not been studied thoroughly (8).

Laboratory methods available for determining the flow behaviour of pharmaceutical powders such as angle of repose and bulk density have been evaluated in different investigations (6 - 9) but to some extent they seem to have limited value (6). Shear cell measurements have, however, been shown to be able to correlate with good precision to the flowability at tabletting estimated as the coefficient of tablet weight variation both in pilot plant and full scale production (6, 8, 10).

The purpose of this work has been to study, with different laboratory techniques, the flow behaviour, for some direct compressible lactose qualities after addition of small amounts of drug substances. The water adsorption to the added substances and its influence on the flow behaviour has been given special attention. The aim has also been to test a combination of a shear cell and a tabletting technique for testing flow behaviour which can be used in early formulation work when limited quantities of drug substance are available.

EXPERIMENTAL

Materials

Three qualities of spray dried lactose were studied, i.e. lactose DC[1], Fast-Flo[2] and Zeparox[3]. Anhydrous lactose[4] was also included in the tests (Table 1).

Three drug substances were investigated and they were all obtained from Astra Pharmaceutical Production, Södertälje, Sweden. Alaproclate with a particle size of 250 - 300 µm and 105 - 150 µm were obtained by sieving. A fraction with a mean surface volume diameter d_{sv} = 37 µm as determined by permeametry[5] was also included in the study. Amiflamine was used in two powder qualities precipitated as an anhydrate (d_{sv} = 9.5 µm) and a 0.5 hydrate (d_{sv} = 10.5 µm). The third substance was a substituted benzamide derivative, UH 106, in two different precipitations UH 106:I, d_{sv} = 2.2 µm and UH 106:II, d_{sv} = 3.6 µm.

Methods

Particle size

The particle size of the lactose qualities and the drug substances was determined by sieve analysis in an air jet sieve[6] or by permeametry[5]. The true density (D_t) was determined in an air comparison pycnometer[7].

Flow properties

All measurements of the flow properties were performed with addition of 0.5 % magnesium stearate to the powders.

The drained angle of repose was determined using an apparatus described by Dahlinder et al. (5). The reported values are the mean of ten measurements.

The aerated (D_A) and tamped bulk densities (D_p) were determined on powder samples of 100 ml^8, and the Hausner quotient (D_p/D_A) calculated from the mean of 10 measurements.

The unconfined yield pressure, f_c, was determined on 75 mg samples of the powders in an annular shear cell at consolidation loads, σ_{max}, of 0.98, 1.97, 2.95 and 3.93 kPa. Five measurements of each yield locus were performed and the limiting unconfined yield pressure, [f_c], was determined as the intercept from the plot of f_c versus the applied consolidation load, σ_{max} (10).

Mixing

The drug substances were blended with the lactose qualities in concentrations of 1.25 and 5.00 % (w/w). The mixing was performed in a double cone mixer for 10 minutes and was followed by addition of magnesium stearate 0.5 % for another 2 minutes. Apart from the pure lactose qualities, two 50/50 binary mixtures of lactose DC DMV and Fast-Flo with anhydrous lactose were studied. The respective lactose qualities were blended in a double cone mixer for 10 minutes prior to addition of the drug substances and the magnesium stearate as above.

Tablet compression

Tablets with a weight of 200 mg corresponding to a drug content of 2.5 and 10 mg were compressed on a Beta-press multiple

punch machine[9]. Round, slightly convex tablets with a diameter of 8 mm were compressed at 47 000 and 63 000 ± 3 000 tablets per hour. The tablet machine was run with four punches using an open feed frame. The tabletting was performed for five hours at each speed and every 10 minutes 16 tablets were sampled by an automatic sampling device[10] for calculation of the coefficient of tablet weight variation C.V., (n = 480).

RESULTS

Lactose Fast-Flo exhibited the best flowability of all the lactose qualities as demonstrated by the lowest Hausner quotient, angle of repose, limiting unconfined yield pressure ([f_c]) and coefficient of tablet weight variation at both tabletting speeds (Table 1).

The 50/50 blend of Fast-Flo and anhydrous lactose was the second best as shown by all the flow parameters. The preceeding ranking order given by the angle of repose, [f_c] and C.V. at 63 000 tablets per hour ($C.V._2$) was DC DMV, Zeparox, DC DMV/ anhydrous lactose 50/50 and finally the anhydrous lactose (Table 1). Looking at the Hausner quotient and C.V. at 47 000 tablets per hour ($C.V._1$) a slightly different ranking was obtained, however, still with Fast-Flo considered as exhibiting the best flowability. This is in accordance with previous results where it was found that the Hausner quotient gave diverging results compared to both angle of repose, [f_c], and C.V. (8).

Addition of the drug substances brought about significant changes in the flow properties for some of the lactose qualities

TABLE 1
Powder characteristics of lactose qualities studied and coefficients of tablet weight variation.

Lactose	d_g (μm)	σ_g	D_A g · ml^{-1}	D_p g · ml^{-1}	D_p/D_A	Angle of Reporse (deg.)	[f_c]	C.V.$_1$ (%)	C.V.$_2$ (%)
Fast-Flo	140	(1.45)	0.69	0.76	1.10	39.0	0.093	0.51	0.98
DC DMV	80	(1.60)	0.80	0.93	1.16	53.1	0.210	0.84	2.79
Zeparox	90	(1.28)	0.57	0.70	1.24	54.2	0.242	0.55	2.87
Anyhydrous	125	(2.30)	0.74	0.88	1.19	56.1	0.274	0.95	3.84
DC DMV/Anhydrous 50/50	–	–	0.76	0.91	1.20	55.6	0.243	0.89	3.52
Fast-Flo/Anhydrous 50/50	–	–	0.73	0.83	1.14	46.4	0.103	0.52	1.24

as demonstrated with the shear cell data in Fig. 1a for Alaproclate/DC DMV mixtures. Similar changes were recorded also for the anhydrous lactose and the 50/50 blend of DC DMV/anhydrous lactose after addition of the drug substances. The fine particle quality of alaproclate (d_{sv} = 37 µm) impaired the flow behaviour, especially at the high amount added (5 %). On the other hand, addition of the coarse powder quality of alaproclate improved the flow behaviour slightly as refelcted by the lower intercepts ([f_c]) in Fig. 1. The flow behaviour of the Fast-Flo and the Zeparox lactose qualities was only slightly affected by addition of the drug substances but the same tendencies were observed also for these i.e. slightly improved flowability after addition of a coarse powder quality and slightly impaired by the presence of fine powder quality of the drug substance (Fig. 1b).

The water adsorption properties of the drug substances used in this study were different as shown in Fig. 2. The alaproclate and

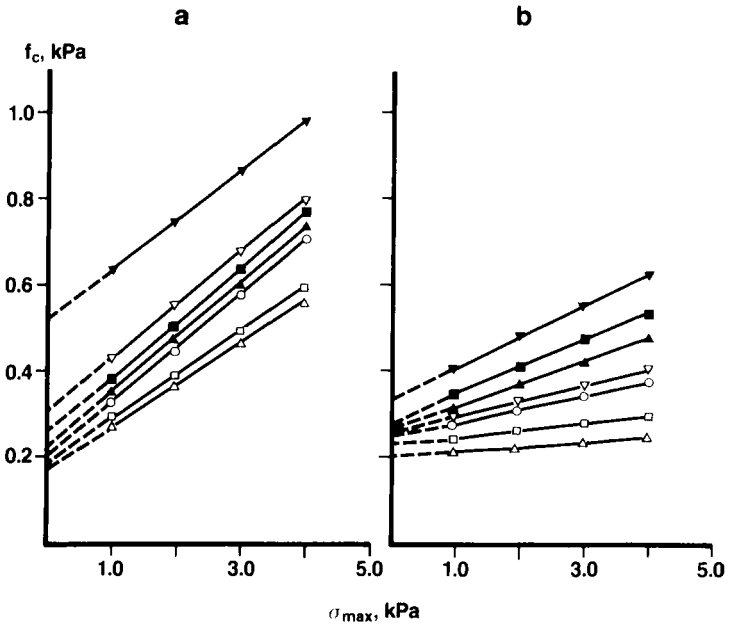

Fig. 1 Unconfined yield pressure, f_c, as a function of applied consolidation pressure, σ_{max}, for lactose-DC DMV (a) and Zeparox (b) in mixtures with alaproclate 1.25 % (open symbols) and 5.00 % (closed symbols). ○ = lactose per se, △ = Alaproclate 250 - 300 µm, □ = Alaproclate 105 - 150 µm, ▽ = Alaproclate d_{sv} = 37 µm.

the 0.5 hydrate of amiflamine adsorb water by simple surface binding, while the anhydrate binds the water as a 0.5 hydrate (Figs. 2a and 2b). The difference in isotherms between the three powder qualities is due to different surface areas. Both the two precipiations of UH 106 bind the water by surface adsorption (Fig. 2c)

The amount of water adsorbed to the surface of the drug substance was found to be of importance for the flow behaviour of the lactose mixture as shown in Fig. 3. At higher relative humidities the mixtures of UH 106:II and lactose DC DMV showed an impaired flowability as demonstrated by the higher [f_c]-values. The

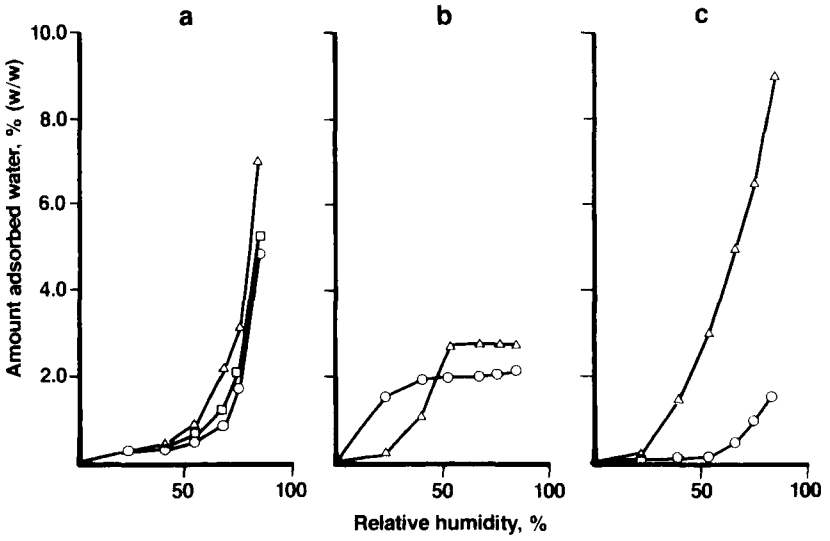

Fig. 2 Water sorption isotherms at 25°C for (a) Alaproclate: ○ = 250 - 300 µm, □ = 105 - 125 µm, △ = 37 µm, (b) Amiflamine: ○ = 0.5 hydrate, △ = anhydrate, (c) UH 106: ○ = Precipitation I, △ = Precipitation II.

mixtures of UH 106:I and lactose DC DMV showed the same tendencies but the effects were much weaker. The same type of changes were recorded also with the other flowability parameters and a similar behaviour was observed also for the alaproclate mixtures. Taking into consideration that the lactose per se does not change the amount of surface adsorbed water considerably in the 10 - 75 % RH range (less than 0.5 % w/w), one can conclude that the water adsorption to the admixed drug substances is responsible for the change in flow behaviour of the lactose mixtures at different relative humidities.

The Fast-Flo and Zeparox mixtures with UH 106 did not show any substantial changes in flow behaviour at different relative humidities (Fig. 3), in contrast to i.e. lactose DC DMV. This might be

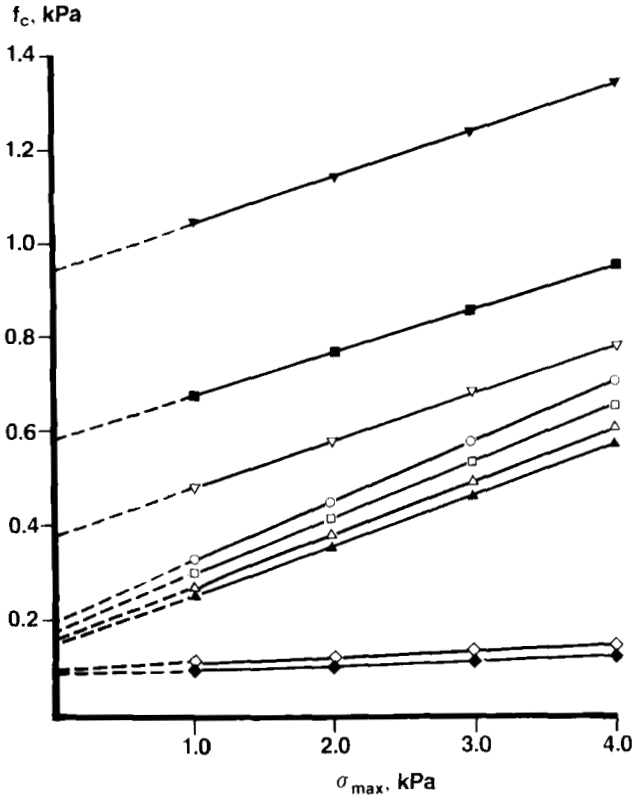

Fig. 3 Unconfined yield pressure, f_c, as a function of applied consolidation pressure, σ_{max}, for lactose DC DMV (○) and Fast-Flo (◇) per se and with addition of 1.25 % UH 106:I (open symbols) and UH 106:II (closed symbols). △ = DC DMV 10 - 20 % RH, □ = DC DMV 35 - 45 % RH, ▽ = DC DMV 70 - 75 % RH, ◆ = Fast-Flo 70 - 75 % RH.

explained by the different shape of these lactose qualities. Both Fast-Flo and Zeparox consist of large spherical aggregates consisting of small crystals with many pores and irregularities on the surface. This will enable small particles such as those of UH 106 ($d_{sv} \leq 3.6$ μm) to be entrapped in these pores in accordance with a model proposed by Staniforth and Rees (11). The DC DMV quality, on the other hand, consists of smooth spherical par-

ticles, single or in irregular agglomerates, and in this system the small UH 106 particles cannot be hidden. Thus, the more open exposure of the drug substance particles enables a stronger influence on the flow behaviour.

Water adsorption to the coarse powder quality of alaproclate did not bring about any substantial changes in any of the flow parameters for the lactose qualities studied while similar changes as with UH 106:I were observed for the fine alaproclate powder quality.

In the case of a drug substance where the adsorbed water is not bound on the surface but as crystal water, water uptake at high relative humidities may not bring about any substantial changes in flow-behaviour of a direct compressible lactose system. This is illustrated by the two crystal qualities of amiflamine in Table 2. Both qualities consist of needle-like crystals with a length of 20 - 40 µm and a thickness of about 10 µm. The 0.5 hydrate adsorbs water on the surface of the crystal while the anhydrate binds it in the crystal lattice. The surface adsorption of the water brings about a substantial decrease in flowability at higher relative humidities as demonstrated by the increase in Hausner quotient, [f_c] and angle of repose in Table 2. For the anhydrate on the other hand, no substantial changes are recorded at the high relative humidity compared to the low. The significance of these changes is demostrated by the relationship between the coefficient of tablet weight variation and the angle of repose as well as [f_c] for mixtures of different lactose qualities

TABLE 2
Hausner quotient (D_p/D_A), limiting unconfined yield pressure ([f_c]) and angle of repose for different lactose qualities with addition of amiflamine 1.25%. Mean values with 95% confidence intervals for [f_c] and angle of repose.

Amiflamine	RH (%)	Powder mixture	D_p/D_A	[f_c] (kPa)	Angle Repose (deg.)
0.5-Hydrate	10–20	DC DMV	1.21	0.423 ± 0.0091	57.3 ± 1.31
		Fast-Flo	1.10	0.115 ± 0.0092	41.0 ± 1.25
		Anhydrous	1.26	0.487 ± 0.0082	59.6 ± 2.74
		DC DMV/Anhydrous 50/50	1.26	0.382 ± 0.0079	59.4 ± 3.10
		Fast-Flo/Anhydrous 50/50	1.17	0.259 ± 0.0098	47.5 ± 1.88
	70–75	DC DMV	1.28	0.578 ± 0.0090	63.5 ± 5.40
		Fast-Flo	1.19	0.197 ± 0.0098	45.9 ± 1.53
		Anhydrous	1.29	0.582 ± 0.0085	62.7 ± 3.88
		DC DMV/Anhydrous 50/50	1.31	0.527 ± 0.0097	61.5 ± 2.95
		Fast-Flo/Anhydrous 50/50	1.24	0.453 ± 0.0061	54.1 ± 2.15
Anhydrate	10–20	DC DMV	1.23	0.425 ± 0.0058	57.5 ± 1.89
		Fast-Flo	1.12	0.118 ± 0.0065	40.5 ± 1.18
		Anhydrous	1.25	0.501 ± 0.0125	57.5 ± 2.31
		DC DMV/Anhydrous 50/50	1.27	0.374 ± 0.0097	58.6 ± 2.95
		Fast-Flo/Anhydrous 50/50	1.18	0.295 ± 0.0079	48.8 ± 1.25
	70–75	DC DMV	1.20	0.419 ± 0.0052	55.8 ± 2.51
		Fast-Flo	1.10	0.118 ± 0.0090	39.0 ± 0.88
		Anhydrous	1.25	0.478 ± 0.0081	56.8 ± 2.11
		DC DMV/Anhydrous 50/50	1.25	0.394 ± 0.0078	57.3 ± 3.10
		Fast-Flo/Anhydrous 50/50	1.18	0.265 ± 0.0067	47.5 ± 1.15

lactose and amiflamine 1.25 and 5.00 % at 10 - 30 and 35 - 45 % RH (Fig. 4).

At the high tabletting speed (63 000 tablets/hour) the increase in angle of repose and [f_c] are reflected by an increase in C.V. Both angle of repose and [f_c] give good correlations (r = 0.919 and r = 0.958 respectively, n = 20). However, the variation is larger for the angle of repose measurements compared to [f_c] and it seems like the shear cell method is less operator dependent (12).

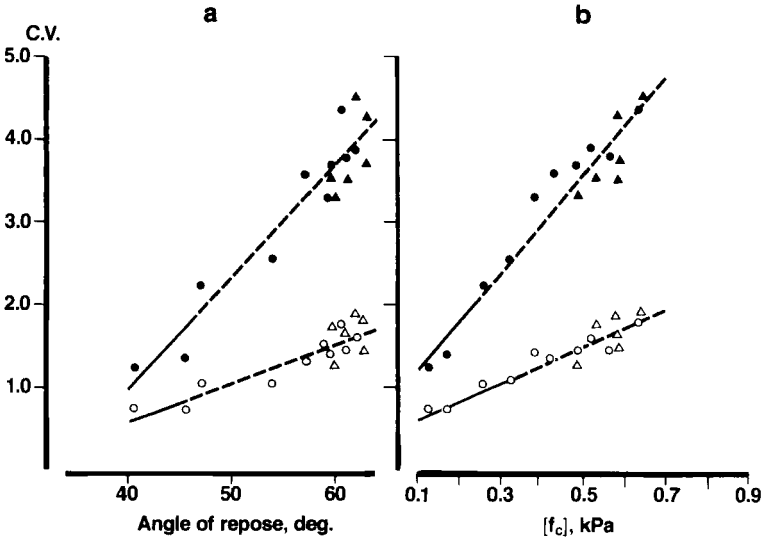

Fig. 4 Coefficient of tablet weight variation, C.V., as a function of angle of repose (a) and limiting unconfined yield pressure, [f_c], (b) for lactose mixtures with amiflamine 0.5 hydrate 1.25 and 5.00 %. Open symbols denote 47 000 tablets/h, closed 63 000 tablets/h. ○ = 10 -20 % RH, △ = 35 - 45 % RH.

DISCUSSION

The results obtained in this study show that for all the lactose qualities studied, additon of small amounts of drug substances can bring about substantial changes in the flow behaviour. In some cases the changes can be explained by water adsorption to the added drug substances. However, it is essential to survey the flow behaviour of a new drug substance in different tablet formulations as early as possible in the formulation work. This will enable the selection of an optimal powder quality of the drug substance also from the flowability point of view which is essential in the case of direct compressible systems. The shear cell method used here appears to be suitable for this purpose and it

seems to be less operator dependent compared to the angle of repose. The powder quantity required is small, about 75 g, corresponding to 0.94 and 3.75 g of the drug substances for the 1.25 and 5.00 % level used here.

By performing tablet compression in a rotary tabletting machine at high speed with a reduced number of punches for a long time, a view of the flow behaviour at tabletting as measured by the coefficient of tablet weight variation could be obtained. Thus, with a powder quantity of 16.5 kg containing 206 or 825 g of the drug substance (1.25 % and 5.00 % w/w, respectively), five hour tabletting at a speed of the die table corresponding to 63 000 tablets per hour could be performed. The C.V. determined were found to correlate well with both the limiting unconfined yield pressure, [f_c], from the shear cell measurements and also the angle of repose.

FOOT NOTES

1., 4. DMV, Veghet, The Netherlands

2. Fast-Flo, Foremost-McKesson, USA

3. Zeparox, Diary Crest, England

5. Fisher Sub Sieve Sizer

6. Alpine Air Jet Sieve A 200

7. Beckman Model 930

8. According to DIN 53192 and 53194

9. Manesty Ltd., England

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