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Modification of Lactose for Direct Compression-II

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An attempt was made to provide cheaper, indigenous, directly compressible lactose by spray drying a slurry of lactose I.P. The modified lactose (spray-dried lactose, SDL) was characterised by evaluating physico-chemical properties and flow behaviour and the results obtained were compared with those for marketed directly compressible lactose (MDL). The direct compressibility of SDL and MDL was also evaluated by compression on a rotary tablet compression machine. Results indicated that SDL has the potential to be used as a directly compressible excipient which can replace imported directly compressible lactose.

The advent of direct compression was made possible by the commercial availability of directly compressible tablet vehicles that possess both fluidity and compressibility[1]. One of the most important directly compressible excipients is the directly compressible filler binder which can constitute over 95% of the weight of a direct compression formulation. Good flow, good binding and blending properties, low cost and compatibility with other ingredients are some of the requirements of directly compressible filler binders[2]. Different kinds of lactose, to meet the demands listed above, are currently available internationally for direct compression. This study was aimed at developing a cheaper, indigenous directly compressible lactose. An earlier attempt in this regard has already been reported[3].

EXPERIMENTAL

Lactose I.P, pulverized (LAC) and marketed directly compressible lactose (MDL) were courtesy Lactose India Ltd., Bombay. Chlorpheniramine maleate I.P. (CPM) was a gift from Alembic Chemical Works Co. Ltd., Vadodara. All other chemicals were of analytical grade and obtained from standard manufacturers. All the reagents were prepared according to the procedures given in the Indian Pharmacopoeia[4].

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Preparation of spray-dried lactose

Two hundred and twenty five grams of lactose was accurately weighed and transferred to a 1000 ml glass beaker containing 775 g of purified water I.P. The mixture was stirred at 2000 rpm using an overhead twin-blade stirrer. Two hundred and fifty milligrams of guargum was accurately weighed and dispersed in about 10 grams of purified water. This dispersion was then added to the lactose suspension. Two kilograms of this slurry was spray dried at a rate of 30 g/min using a Niro spray dryer at an air pressure of 6.0 kg/cm^2 keeping the inlet air temperature at 190°. The outlet air temperature was found to be 90°. The spray dried lactose was subjected to various evaluations along with MDL and LAC.

Pharmacopoeial tests : All the three products were subjected to the pharmacopoeial tests for lactose as per the procedures given in the Indian Pharmacopoeia[4]. Findings inconsistant with pharmacopoeial limits are depicted in Table 1.

Non-Pharmacopoeial tests: The anomeric composition of LAC and SDL was determined by the method suggested by Sharp and Doob[5]. The mid infrared region

Table I - Comparative evaluation of MDL, SDL and LAC

	Test/ Property	MDL	LAC	SDL
		Inconsistent Pharmacopoeial test results		
1	Clarity, colour & odor of solution	+	+	slight haze
2	Water	+ (5.25% w/w)	+ (5.3% w/w)	+ (4.11% w/w)
			Particle Morphology	
3	Shape[a]	Regular, tomahawk shaped	No shape	Spherical as well as angular
4	Surface details[b]	Smooth, minute pits	Smooth	Ridged with minute pits
5	Class[c]	Non-porous smooth	Non-porous smooth	Porous smooth

+ indicates that the material passed the test

a - based on photomicrographs at 25X (Plates 1) and Ref. 3

b - based on Scanning Electron Microscopy (plate 2) and Ref. 3

c - based on classification by Neumann[12]

(4000 cm^{-1} to 400 cm^{-1}) spectra of the products were obtained using a Shimadzu Infrared Spectrophotometer IR-460 (Shimadzu Corporation, Kyoto, Japan). The X-ray diffraction (XRD) patterns of the products were obtained using a Rigaku D-Max X-ray Diffractometer (Rigaku Corporation, Japan). The pattern for SDL is shown in figure 1. LAC and SDL were also subjected to differential scanning calorimetry (DSC) studies using a Shimadzu Thermal Analyzer Model SC-30 (Shimadzu Corporation, Kyoto, Japan). The thermogram for SDL is depicted in Figure 2.

Particle shape was observed from photomicrographs taken through a Wild M3Z Steremicroscope (Wild, Heerbrugg, Switzerland). Surface characteristics of the products were studied by scanning electron microscopy (SEM) using a JEOL JSM-T300 Scanning Microscope (JEOL Corporation, Tokyo, Japan). Plate 1 depicts the photomicrograph for SDL while plate 2 reveals the surface details of SDL. Observations are given in Table 1. The particle size distribution of the product was obtained by sieve analysis using 100 g of the products and a nest (44-, 60-, 85- and 100 mesh) of sieves. The results of the analysis are depicted in Table 2. Powder flow characteristics of the products were determined using the method

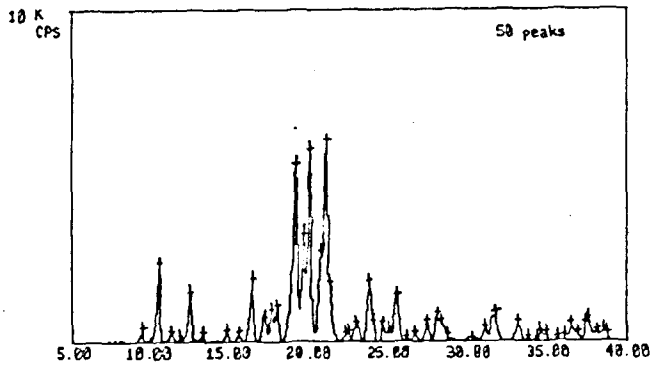

Fig. 1 : 1 XRD pattern of SDL

suggested by Carr[6,7]. The Hausner ratio for the samples was also determined[8]. Table 3 summarises the results of these determinations.

Preparation and evaluation of Chlorpheniramine Maleate Tablets

Eight millimeter standard concave chlorpheniramine maleate (4 mg) tablets with a bisecting line on one side were prepared by direct compression, to a weight of 200

Table II - Sieve Analysis Results

	Mesh size	MDL		SDL	
		%	Cumulative	%	Cumulative
Retained on	44	0.32-0.36	-	32.0-34.3	-
	60	24.2-24.8	24.52 - 25.16	10.8 - 12.1	42.8 - 46.4
	85	39.5 - 41.9	64.02 - 67.06	8.0 - 11.3	50.8 - 57.7
	100	14.9 - 17.6	78.92 - 84.66	6.6 - 9.8	57.4 - 67.5
Through	100	17.4 - 18.6	-	35.4 - 37.4	-

The entire LAC sample passed through 100 mesh size.

mg, of 189 mg of SDL or MDL, 0.75% w/w of talc and magnesium stearate and 2% w/w of sodium starch glycolate using a 16 station rotary tablet compression machine (Cadmach, Ahmedabad). LAC was not investigated further since it had poor direct compression properties. The following tests were carried out on the tablets as per the procedures given in the Indian Pharmacopoeia[9]: weight variation, disintegration, assay and content uniformity. Non-pharmacopoeial tests such as hardness and friability were also performed. Results are summarised in Table 4.

RESULTS AND DISCUSSION

Initial trials of spray drying involved the use of a 20% w/w solution of lactose in which 10% w/w of lactose was suspended. However, the solids settled when the slurry was fed to the spray dryer. To overcome this problem, the suspended lactose content was reduced to 2.5% w/w from 10% w/w. It was assumed that guar gum would lead to the production of agglomerates of fine spray dried particles. Thus, a product with improved flow properties would be obtained. Therefore, guar gum was added to the slurry. Addition of guar gum further prevented the settling of the suspended lactose crystals during spray drying the slurry. Spray drying of the slurry was successfully carried out at an air pressure of 6.0 kg/cm^2, an inlet air temperature of 190° and a feed rate of 30 g/min. The spray dried product exhibited a tendency to stick to the walls of the spray dryer. A lesser feed rate and/or a higher air pressure may be the solution to this problem.

Findings of pharmacopoeial tests were significantly different from the pharmacopoeial limits and are depicted in Table 1. A slight haze is observed in a solution of SDL which may be due to the presence of guar gum (0.025%

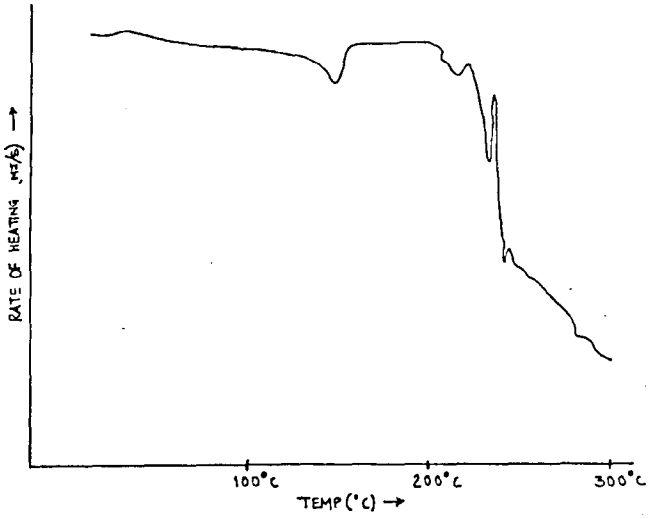

Fig. 2: DSC Thermogram of SDL

w/w) in it. SDL had slightly lower moisture content than MDL (5.25% w/w) or LAC (5.30% w/w). Using the method suggested by Sharp and Doob[5], the anomeric composition of LAC & SDL was found to be 79.9% and 60% of α-lactose and 21.2% and 40.0% of β-lactose respectively. This proportion of β-lactose in SDL, which is anhydrous, may explain the lower moisture content of SDL.

The infrared spectra and XRD patterns of MDL and LAC have been compared in our earlier communication[3] and it was observed that MDL is basically α-lactose monohydrate admixed with some other crystalline material(s). Comparison of the infrared spectra of SDL and of LAC reveal a shift in frequency to the lower side and a sharper hydroxyl band is also seen in the spectrum of SDL indicating intramolecular hydrogen bonding. The reduced moisture content (Table 1) may account for

Table III - Evaluation of flow properties

Property	MDL	LAC	SDL
Angle of repose	25.7°	52.5°	27.3°
Compressibility	17.9%	33.1%	21.1%
Cohesion	9.0	50.0	17.0
Angle of spatula	26.3°	63.4°	24.0°
Flowability index	81.0	38.0	78.0
Angle of fall	21.8°	43.8°	23.0°
Angle of difference	3.9°	8.7°	4.3°
Dispersibility	4.0	9.0	3.6
Floodability index	53.0	46.0	52.0
Hausner ratio	1.22	1.50	1.27

Table IV - Results of evaluation of CPM tablets

Test	MDL			SDL		
	1	2	3	1	2	3
	+	+	+	+	+	+
Weight variation (mg) (±S.E.)	208.6 (±0.32)	211.9 (±0.74)	208.2 (±0.67)	211.4 (±0.48)	211.4 (±0.89)	212.5 (±0.60)
Hardness (kg) (±S.E.)	1.32 (±0.05)	1.26 (±0.02)	1.36 (±0.04)	4.29 (±0.06)	4.26 (±0.11)	4.22 (±0.11)
Disintegration (min)	+	+	+	+	+	+
Friability (%)	-	-	-	-	-	-
		(All tablets capped)			<0.1%	
Assay (%) (±S.E.)	98.03 (±0.77)	98.47 (±1.21)	98.27 (±1.04)	99.73 (±1.30)	101.5 (±1.26)	101.9 (±0.87)
Content uniformity (No.)	+	+	+	+	+	+

Key + = passess - = failsS.E. = Standard Error

this. The presence of additional bands (1809 cm^{-1}, 1445 cm^{-1} and 1398 cm^{-1}) may be due to impurities or due to guar gum present in SDL.

The XRD pattern of SDL (figure 1) point to reduced crystallinity of this sample which may be due to amorphous lactose which is reported to be present in spray-dried lactose[10]. The pattern exhibits peaks common to those of the pattern of LAC[3]. This points to the presence of α-lactose monohydrate (LAC) in SDL which agrees with the information reported[10]. Peaks corresponding to anhydrous β-lactose[11] were also found to be present in the SDL pattern. Additional peaks shown by the pattern of SDL can be attributed to guar gum present in it.

The DSC thermogram of LAC has already been explained[3]. The DSC thermogram of SDL (Figure 2) reveals a relatively weak (compared to LAC) dehydration endotherm at 140 to 145°, explained by the reduced moisture content of SDL (Table 1), and a melting endotherm

at 205-215°. The reduction in melting point over that shown by the thermogram of LAC may be due to the presence of amorphous lactose which is the most unstable form of lactose and consequently has the lowest melting point. No SDC studies were performed on MDL. However, its melting point was found to be 215-220°.

The tomahawk shape of the majority of the crystals of MDL (Table 1) agree with the shape described for α-lactose monohydrate[2]. No shape could be attributed to the particles of LAC. This loss of crystal shape may be due to the pulverisation to which LAC was subjected. The spherical shape of the particles of SDL is the direct result of the process of spray drying which is known to produce spherical particles.

Table 2 shows the results for sieve analysis performed on the three products. The small particle size of LAC is due to the pulverisation process to which it was subjected. The high proportion of particles less than 44 mesh found in SDL may be due to the aggregation of particles that may have occured in the spray dryer when particles stuck to the walls of the spray dryer.

Table 3 provides the full range of physical characteristics needed to characterise the flow behaviour of the products. According to the scheme of Carr[6,7], amongst the products, the flow behaviour of MDL is the best as evidenced by its comparatively low angle of repose, low compressibility index, low angle of spatuala and high flowability index. This is further proved by the Hausner ratio which is nearest to one for MDL. This excellent flow behaviour of MDL can be attributed to the regular shape and smooth surface of the particles[12,13] (Table 1) and to the relatively less proportion of fines in it[14] (Table 2). The spherical shape of the particles of SDL is responsible for its fair flow behaviour but the greater surface details of these particles (Table 1) and the higher proportion of fines (Table 2) contribute to the ranking of its flow behaviour below that of MDL. Addition of a glidant may improve flow in case of SDL. The flow behaviour of LAC is extremely poor and can be due to the very small particle size of LAC (Table 2). Since the more flowable a material is, the more floodable it is, the observed values of the floodability index are in agreement with the flow behaviour ranking.

SDL and MDL were subjected to a comparative evaluation for their use as directly compressible materials. Direct compression of chlorpheniramine maleate (4 mg)

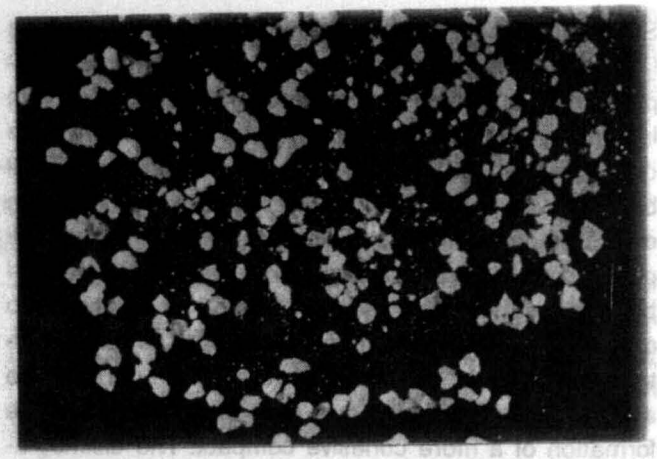

Plate 1. Photomicrograph of SDL (6.5 X)

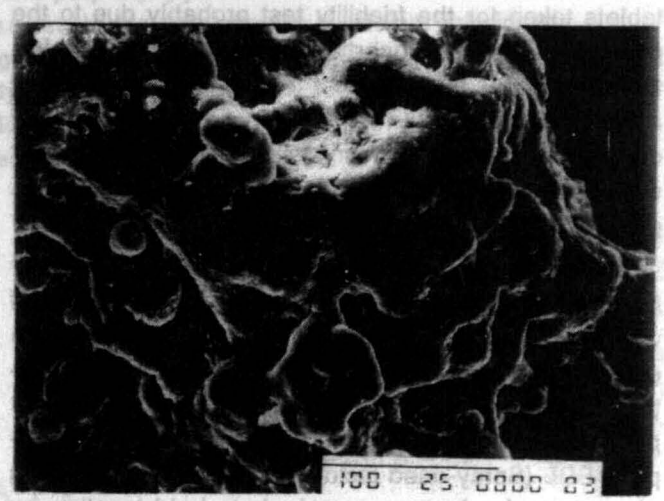

Plate 2. Scanning Electron Photomicrograph of SDL (350 X)

tablets was done using these materials on a 16-station rotary tablet compression machine. All the batches were subjected to evaluation using the pharmacopoeial and non-pharmacopoeial tests for tablets. The results are shown in Table 4. Examination of the data reveals the following conclusions:

Both the products were compressed into tablets with weight variation within the pharmacopoeial limits. Analysis of variance showed no significant differences between the products. However, significant differences were obtained in the hardness of tablets of the two products. MDL gave tablets with exceptionally poor hardness and hence it cannot be used without mixing it with a dry binder. SDL gave tablets with good hardness. This is because

SDL comprises of α-lactose monohydrate (crystalline lactose) and amorphous lactose. So, during direct compression, the number of binding points will increase with increasing fragmentation of the α-lactose monohydrate crystals under compression and the binding surface will be increased at the binding points by plastic deformation of the amorphous lactose present. Fragmentation and plastic deformation will consequently result into increased binding capacity of spray dried lactose as compared to α-lactose monohydrate crystals (which is a major portion of MDL) only[10]. The comparatively large particle size and the presence of guar gum may also contribute to the formation of a more cohesive compact. The disintegration time of the tablets of both products was found to be below 15 min. MDL tablets showed capping in all the 20 tablets taken for the friability test probably due to the poor compactibility properties of this material. This further strengthens our argument for use of this material as a directly compressible material only as a mixture with dry binders such as microcrystalline cellulose and other such materials known for this type of behaviour. SDL gave tablets with friability <1%.

In conclusion, MDL (Marketed Directly compressible Lactose) is α-lactose monohydrate crystals admixed with some unknown crystalline material(s). The sample exhibited reduced crystallinity as compared to LAC (lactose I.P.) and had a melting point of 215-220°. The sample had the best flow behaviour amongst the three samples. SDL (Spray-dried lactose) consists of aggregates of crystals of α-lactose monohydrate held together by amorphous lactose and guar gum with reduced crystallinity as compared to that of MDL and LAC and exhibiting a melting point of 205-215°. Flow behaviour tests indicate SDL to have fair flow behaviour which can be improved by adding a glidant. The results of evaluation of direct compressibility of both products indicate that MDL, compared to SDL, has poor compactibility and should be used in conjunction with a dry binder for direct compressing. SDL had improved compactibility as compared to MDL indicating its suitability for use as a direct compression excipient. However, the process variables of the method used for producing this product need to be optimized. Trials should be followed by the scale up process before going on to commercial lots.

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