RESEARCH PAPER

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Modification of Lactose for direct compression - I

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An attempt was made to provide cheaper, indigenous, directly compressible lactose by thermal modification of lactose I.P. The modified lactose (Thermally modified lactose, TML) was characterised for physico-chemical properties and flow behaviour and the results compared with those of Marketed directly compressible lactose (MDL). The direct compressibility of TML and MDL was also evaluated by compression on a rotary tablet compression machine. Results indicated TML to be a promising 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 providing cheaper, indigenous directly compressible lactose.

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, Baroda. 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[3].

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Preparation of thermally modified Lactose

One hundred g of lactose was accurately weighed and transferred to a 250 ml S.S. vessel containing 100 g of purified water to obtain 200 g of a supersaturated (50% w/w) solution of lactose. The solution was placed inside an insulated paraffin bath, the temperature increased gradually and then maintained at 110° ± 2°. The solution was stirred at 100 rpm using a single blade overhead stirrer. Stirring was discontinued after about 4 hours and the product was allowed to dry to a constant weight in the bath. The vessel containing the dried product was removed from the bath and the product passed through 44 mesh sieve and then was stored in a dessicator at room temperature till further use. The product was named thermally modified lactose (TML).

Characterization of thermally modified Lactose

TML was evaluated in comparison with MDL and LAC.

I) Pharmacopoeial tests : All the three products were subjected to the following pharmacopoeial tests as per the procedures given in the Indian Pharmacopoeia[3] : Identification; specific optical rotation; clarity, color and odor of solution; arsenic; heavy metals; acidity; alcohol-soluble matter; sulphated ash; water. Findings not consistent with pharmacopoeial limits are depicted in Table 1.

Fig. 1, 2 & 3

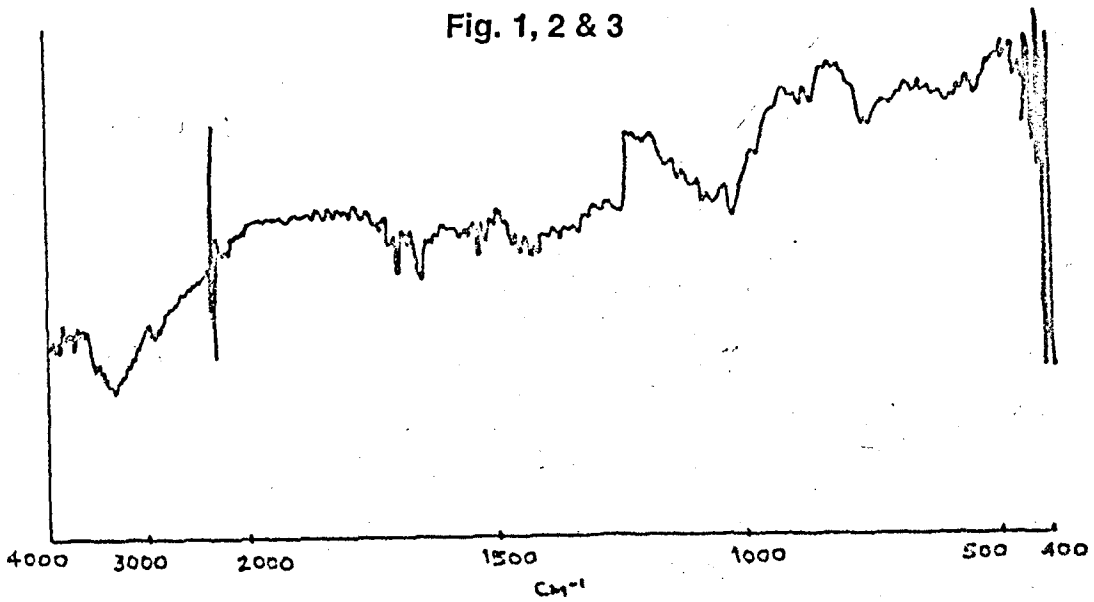

FIG. 1 MID INFRARED REGION SPECTRUM OF MDL

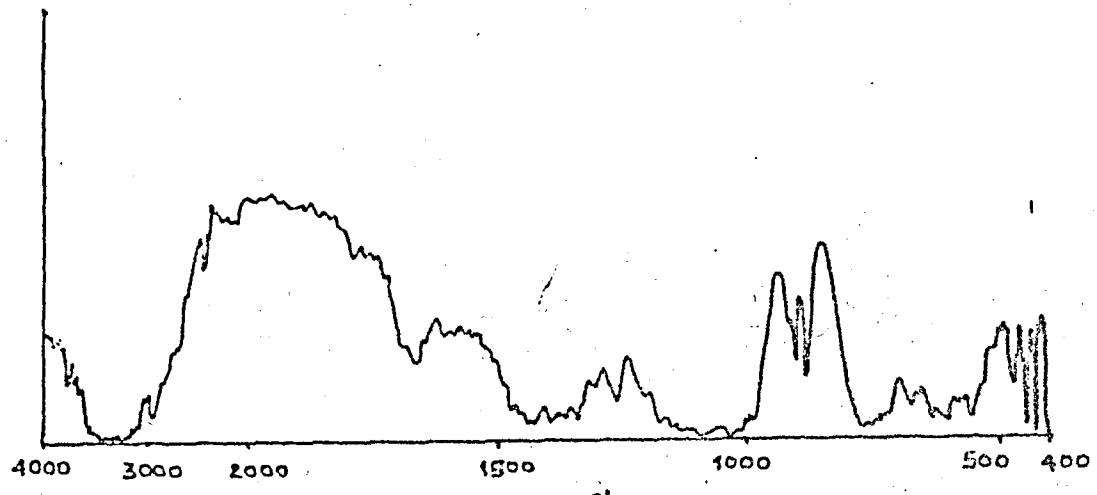

FIG. 2 MID INFRARED REGION SPECTRUM OF LAC

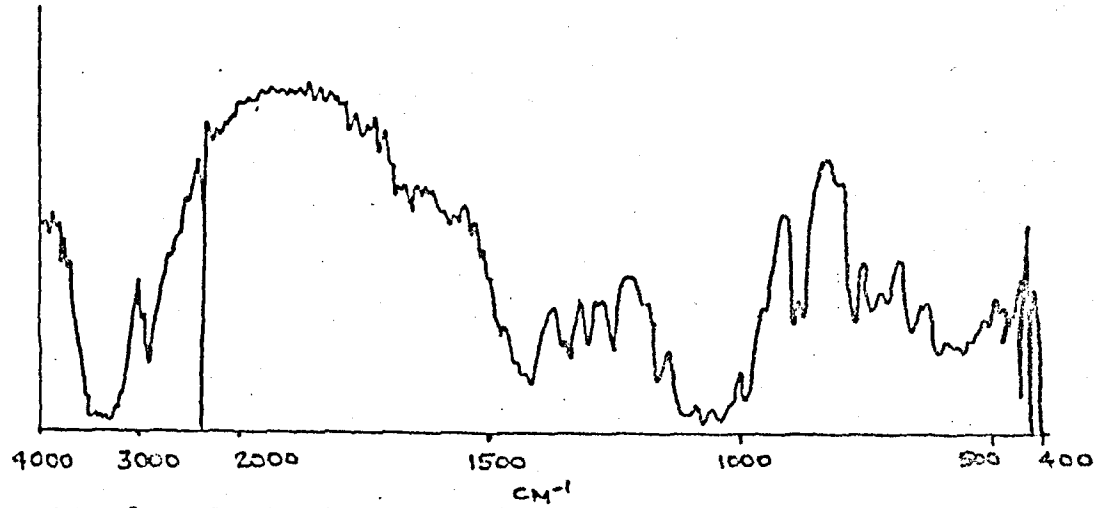

FIG. 3 MID INFRARED REGION SPECTRUM OF TML

Fig. 4, 5 & 6

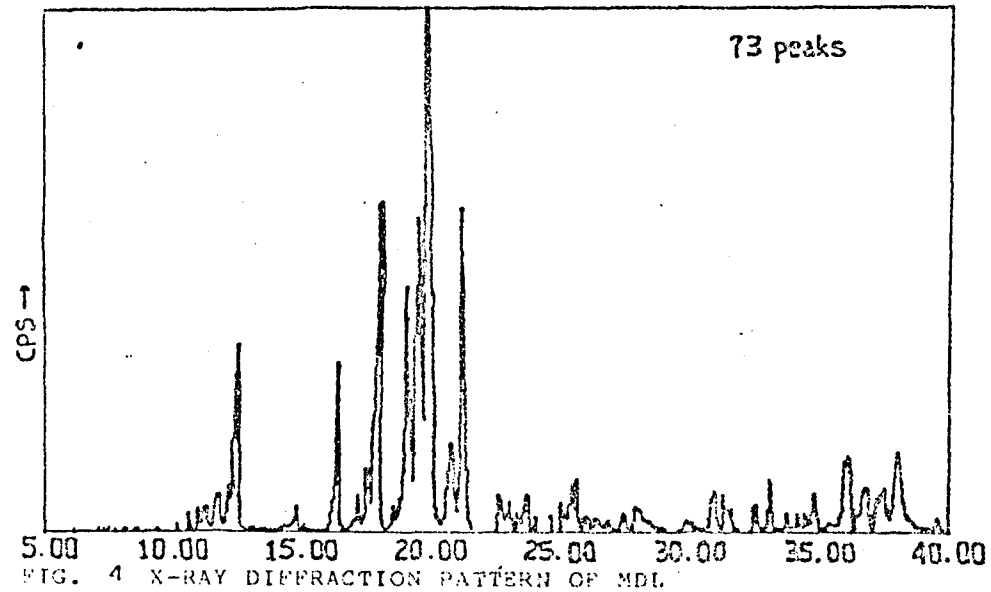

FIG. 4 X-RAY DIFFRACTION PATTERN OF MDL

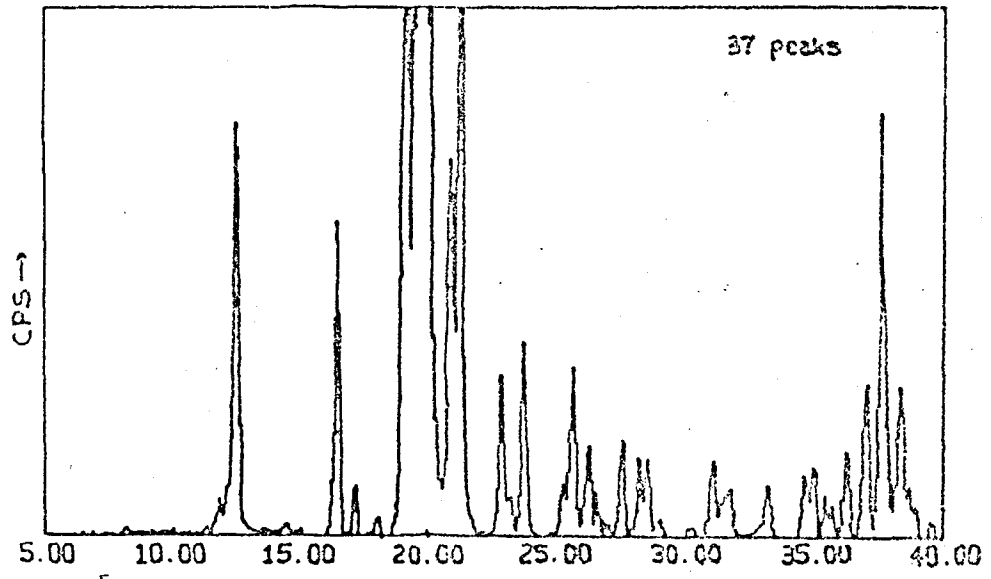

FIG 5 X-RAY DIFFRACTION PATTERN OF LAC

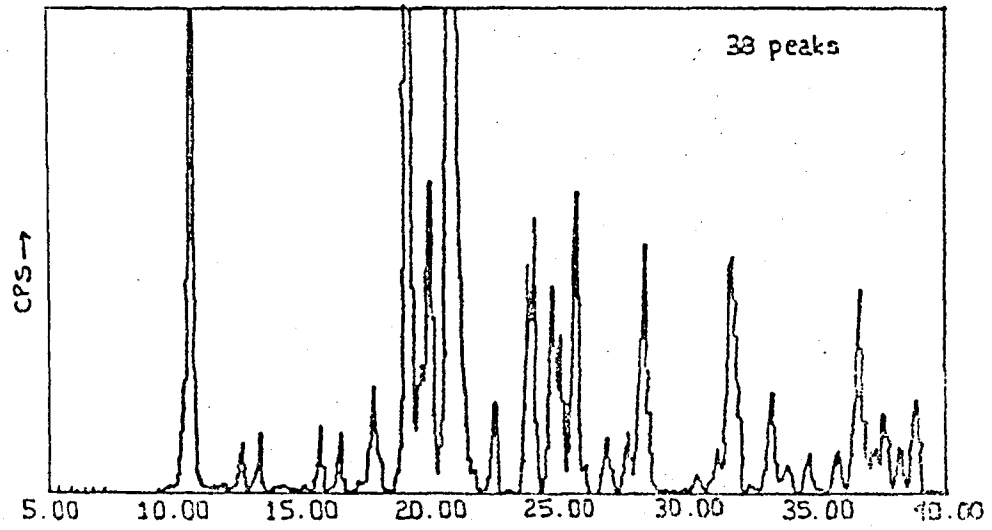

FIG 6 X-RAY DIFFRACTION PATTERN OF TML

Fig. 7 & 8

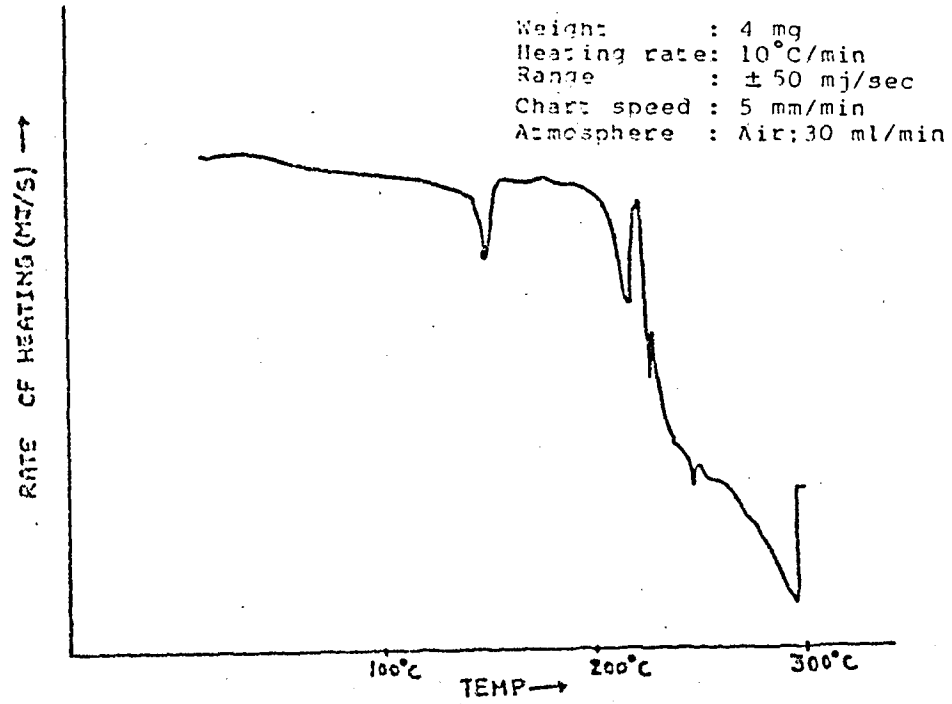

FIG. 7 DSC OF LAC

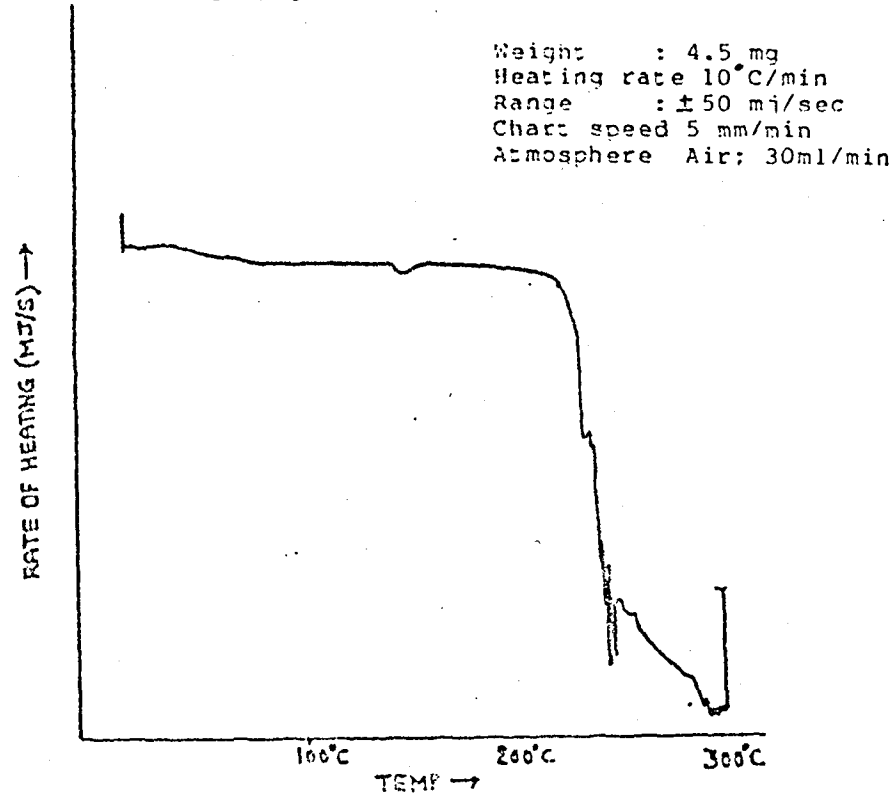

FIG. 8 DSC OF TML

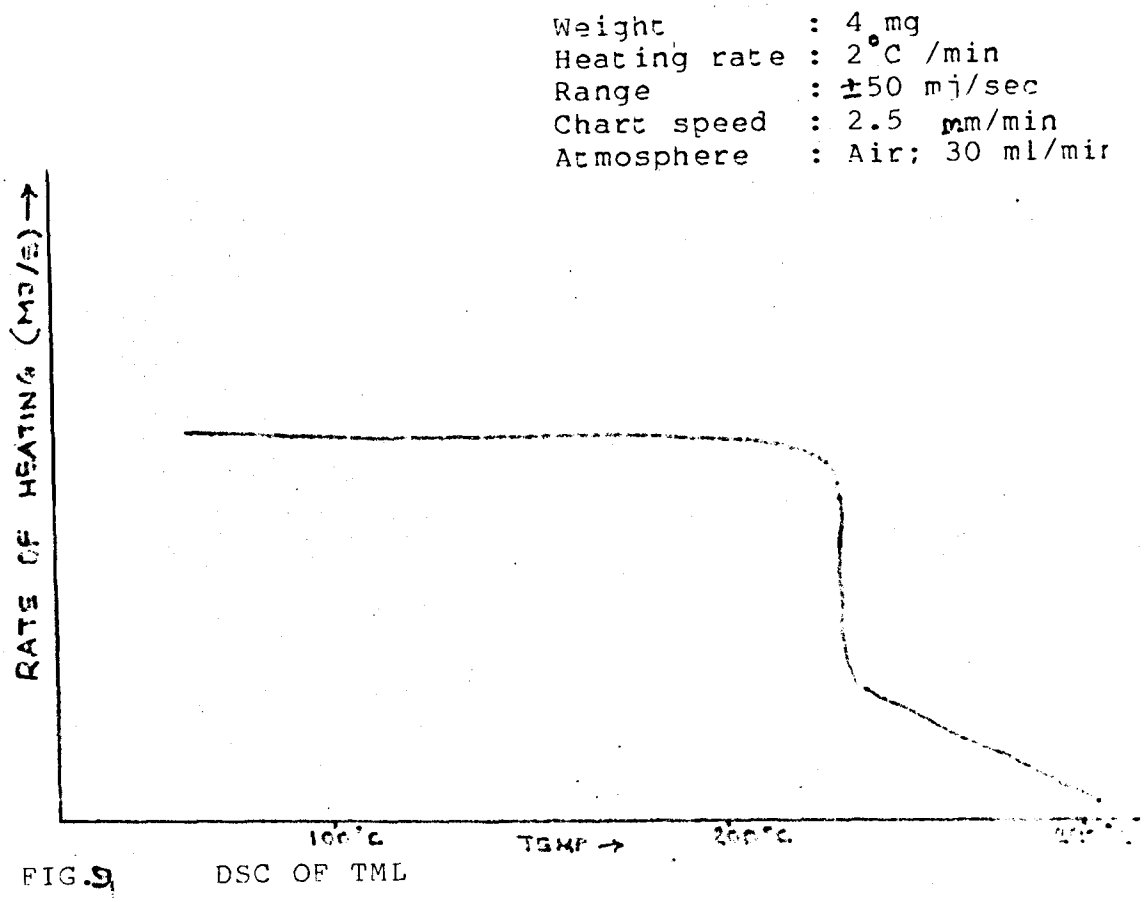

FIG. 5 DSC OF TML

Table 1: In consistent Pharmacopoeial test results

	Test	Pharmacopieal limits	MDL	LAC	TML
1	Specific optical rotation	+54.8° to +55.5°	+	+	(+52.6°)
2	Clarity, colour and odor of solution	Clear, Colourless, odorless	+	+	slight cream color
3	Water	5.5 % w/w	+	+	- (0.58 % w/w)

Key + = Passes, - = fails

2) Non-Pharmacopoeial tests: The mid infrared region (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 spectra are shown in figures 1 to 3. The X-ray Diffraction (XRD) patterns of the products were obtained using a Rigaku D-Max X-ray Diffractometer (Rigaku Corporation, Japan). These patterns are shown in figures 4 to 6. LAC and TML were subjected to Differential Scanning Calorimetry (DSC) studies using a Shimadzu Thermal Analyzer Model SC-30 (Shimadzu Corporation, Kyoto, Japan). The thermograms are depicted in figures 7-9. Particle shape was observed from photomicrographs taken through a Wild M3Z Stereomicroscope (Wild, Heerbrugg, Switzerland). Surface characteristics of the products were studied by Scanning Electron Microscopy (SEM) using a JEOL JSM-T300

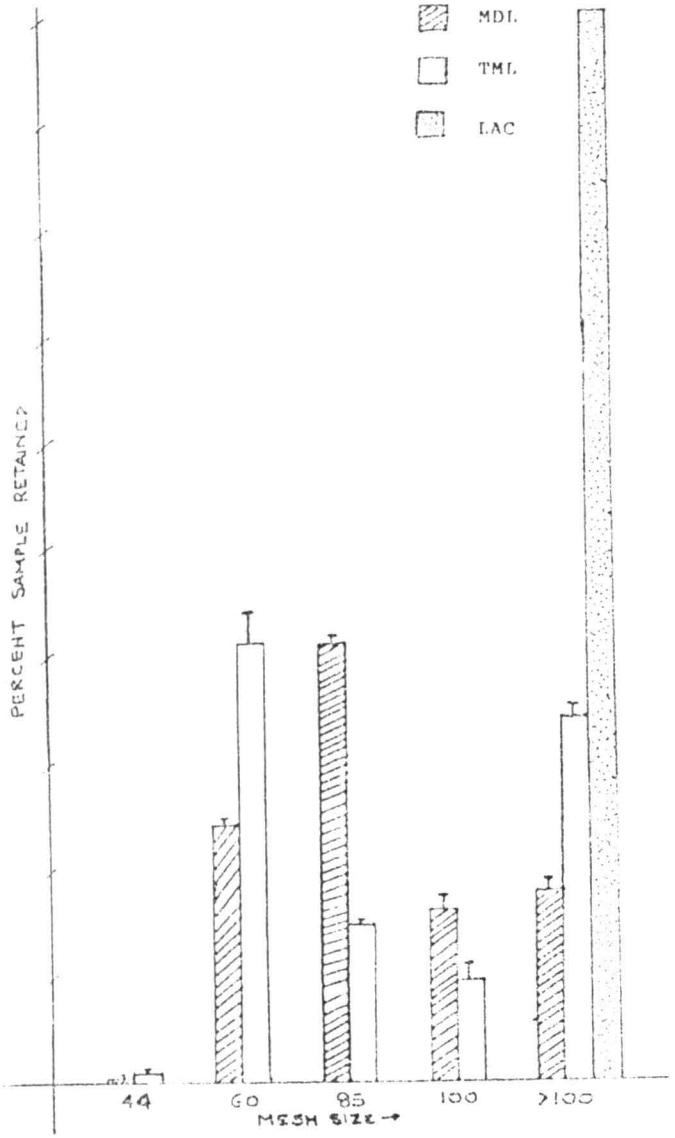

Fig. 10 Sieve Analysis Results

Plate 2: Photomicrograph of LAC (25x)

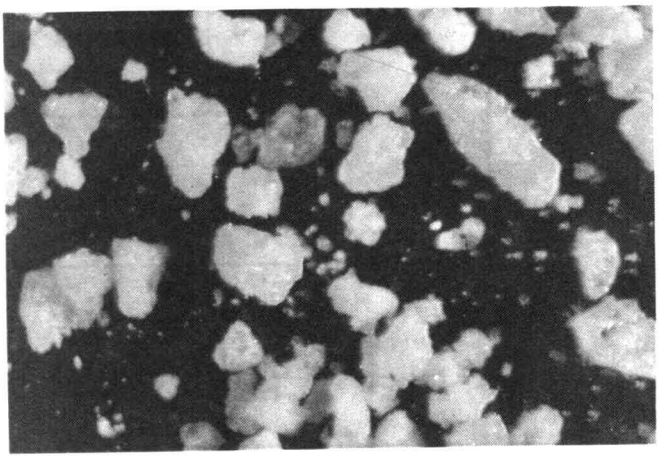

Plate 3: Photomicrograph of TML (25x)

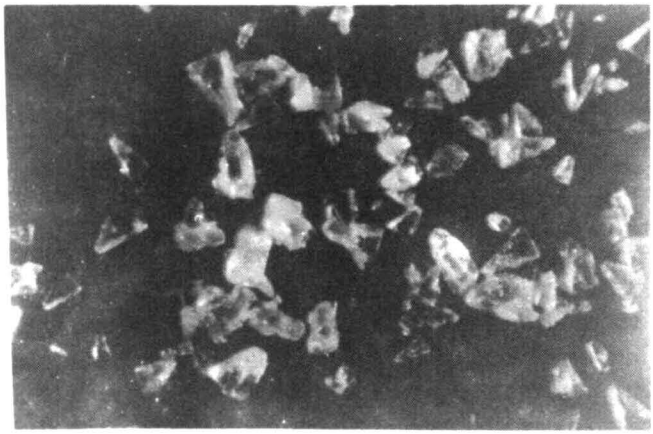

Plate 1: Photomicrograph of MDL (25x)

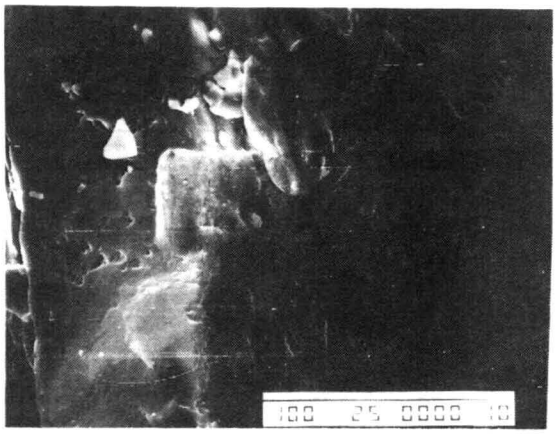

Plate 4: Scanning Electron Photomicrograph of MDL (500x)

Plate 5: Scanning Electron Photomicrograph of LAC (1000x)

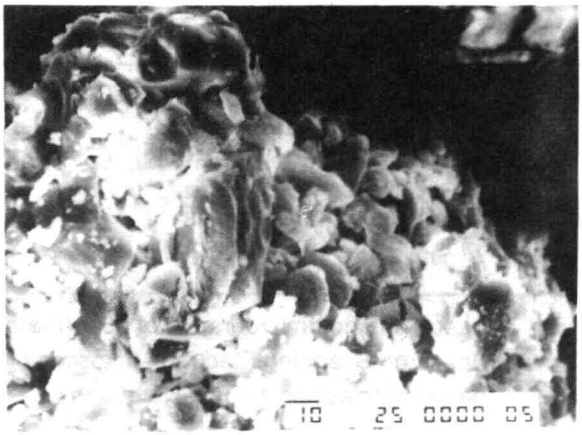

Plate 6: Scanning Electron Photomicrograph of TML(750x)

Scanning Microscope (JEOL Corporation, Tokyo, Japan). Plates 1-3 depict the photomicrographs while plates 4-6 reveal the surface details of the samples. Observations are given in Table 2. 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 Figure 10. Powder flow characteristics of the products were determined using the method suggested by Carr[4]. The Hausner ratio for the samples was also determined[5]. Table 3 summarises the results of these determinations.

Preparation of Chlorpheniramine Maleate Tablets

Eight mm standard concave tablets with a bisecting line on one side were prepared by direct compression of the ingredients listed in table 4 using a 16 station rotary table compression machine (Cadmach, Ahmedabad). The following tests were carried out on the tablets as per the procedure given in the Indian Pharmacopoeia[3] : Weight variation, disintegration, assay, content uniformity. Non-pharmacopoeial tests such as hardness and friability were performed. Results are summarised in table 5.

RESULTS AND DISCUSSION

Recrystallisation of lactose from a supersaturated (50% w/w) solution at temperatures above 93° using a boiling water bath was the technique first employed according to the available literature[6,7]. This method failed to give a product with the desired compression properties when tested on a single stroke tableting machine. It was assumed that the temperatures used had not led to the recrystallisation of the required β-form of lactose and so higher temperatures were used for the purpose. A temperature of 110° ± 2° obtained using an insulted heavy liquid paraffin bath gave a product which was found to exhibit good compression properties. In this process, a high viscosity of the solution prevailed in the later stages and so stirring was discontinued as it was not very effective. Agglomeration was prevented by mechanical means, initially with a glass rod and later with a spatula. Only the product that was passed through 44 mesh sieve had good flow properties when trials were taken on a running single stroke tableting machine.

A comparative evaluation of TML, MDL and LAC was attempted using pharmacopoeial tests. Findings not consistent with pharmacopoeial limits, depicted in Table 1 are discussed. The specific optical rotation of TML was found to be outside the pharmacopoeial limits. Literature review[8] shows this value (+52.6°) to be close to that reported for anhydrous α - and β-lactose (+52.3°). Therefore TML may be anhydrous lactose. The anomeric composition of LAC and TML was determined using the method suggested by Sharp and Doob[9]. LAC was found to consist of 79.9% of

Table 2: Particle Morphology

Property	MDL	LAC	TML
Shape+	Regular, tomahawk shaped	No shape	Irregular aggregates of small angular microcrystals*
Surface details*	Smooth, minute pits	Smooth	Highly rough
Class++	Non-porous smooth	Non-porous smooth	Porous rough

\+ - based on photomicrographs at 25 x (Plates 1-3)
* - based on Scanning Electron Microscopy (plates 4-6)
++ - based on classification by Neumann[13]

Table 3: Evaluation of flow properties

Property	MDL	LAC	TML
Angle of repose	25.7°	52.5°	28.2°
Compressibility	17.9%	33.1%	21.3%
Cohesion	9.0	50.0	12.0
Angle of spatula	26.3°	63.4°	26.6°
Flowability index	81.0	38.0	77.0
Angle of fall	21.8°	43.8°	20.7°
Angle of difference	3.9°	8.7°	7.5°
Dispersibility	4.0	9.0	7.2
Floodability index	53.0	46.0	59.5
Hausner ratio	1.22	1.50	1.27

Table 4 : Composition of CPM Tablets

	Per Tablet, mg	
Ingredient	I	II
CPM	4.0	4.0
TML	189.0	—
MDL	—	189.0
Sodium starch glycolate	4.0	4.0
Talc I.P.	1.5	1.5
Magnesium stearate I.P.	1.5	1.5
Total tablet weight in mg	200.0	200.0

Table 5 : Results of evaluation of CPM tablets

Test	MDL			TML		
	1	2	3	1	2	3
	+	+	+	+	+	+
Weight variation (mg)	208.6	211.9	208.2	204.7	207.3	206.1
(±S.E.)	(±0.318)	(±0.74)	(±0.667)	(±0.27)	(±0.53)	(±0.38)
Hardness (kg)	1.32	1.26	1.36	2.68	2.66	2.65
(±S.E.)	(±0.05)	(0.024)	(±0.04)	(±0.102)	(±0.062)	(±0.05)
Disintegration (min)	+	+	+	+	+	+
Friability (%)	-	-	-	-	-	-
	(All tablets capped)			(3±1 Tablets capped)		
Assay (%)	98.03	98.47	98.27	100.27	102.4	101.87
(±S.E.)	(±0.770)	(±1.21)	(±1.041)	(±0.997)	(±0.773)	(±0.869)
Content uniformity (No.)	+	+	+	+	+	+

Key + = passes - = fails S.E. = Standard Error

α-lactose and 21.2% of β-lactose while TML consists of 40.6% of α-lactose and 59.4% of β-lactose. A slightly creamish color is observed in a solution of TML which may be due to the presence of degradation products in it. The low moisture content of TML indicates that it may be an anhydrous form of lactose.

Comparison of the infrared spectra of MDL (figure 1) and LAC (figure 2) reveal the existence of common hydroxyl bands (like those at 3875cm^{-1}, 3385cm^{-1}) and carbonyl bands (like 1846 cm^{-1}, 1772 cm^{-1}, 1682 cm^{-1}) as well as other bands (1522 cm^{-1} and 1469 $^{-1}$ indicating MDL to be basically lactose. However, the presence of some bands like 1811.0 cm^{-1}, 1226 cm^{-1}, 953 cm^{-1}, which are not observed in the spectrum of LAC signify the presence of some other functional groups and thus of other compounds. Further investigation of this aspect was not carried out. A shift of bands to lower frequencies is noted in the spectrum of MDL as compared to that of LAC. The band due to the hydroxyl group is also sharper. This may be due to intramolecular hydrogen bonding indicating loss of water. However, since the moisture content in MDL is 5.25% (Table 1), this may be due to reduced free moisture. Comparison of the infrared spectra of TML (figure 3) and of LAC reveals TML to be basically lactose due to the presence of the same common bands mentioned before. Bands such as 1871 cm^{-1}, 1453 cm^{-1} and 1307 cm^{-1} may be due to degradation products in TML. A shift in the bands of the spectrum of TML to lower frequencies especially those due to hydroxyl group and carboxyl group along with the sharper hydroxyl band is suggestive on intramolecular hydrogen bonding. Due to the low moisture content (0.58% w/w) this phenomenon can be attributed to the loss of water of crystallization pointing to the anhydrous nature of TML.

Comparison of the XRD patterns of MDL (Figure 4) and LAC (Figure 5) reveal that both have similar patterns indicating that MDL is basically α-lactose monohydrate. The MDL pattern has an increased number of diffracting planes over those of the LAC pattern. This can be attributed to the presence of some other crystalline material (s) in MDL. Reduced peak amplitudes and lower intensity values of the MDL pattern over that LAC indicate reduced crystallinity of MDL as compared to that of LAC. Significant differences exist in the XRD patterns of LAC (figure 5) and TML (figure 6). Literature review[10] indicates similarity of the TML pattern to that of anhydrous lactose. The patterns show TML to have reduced crystallinity as compared to that of LAC which can be attributed to the anhydrous nature of TML.

Examination of the thermogram DSC of LAC (figure 7) reveals two endothermic peaks. The initial peak at 145° - 150° is a dehydration peak while the second peak at

210° - 220° is the melting endotherm. The observed increase in the melting point of LAC over that reported for α-lactose monohydrate (202°) has been explained by Lerk et al[11]. The DSC thermogram of sample C (figure 8) reveals a very weak dehydration endotherm at 140° to 145° (due to the low moisture content, 0.58% w/w). No melting endotherm was observed even when the heating rate and chart speed were reduced to 2° min. and 2.5 mm/min respectively (figure 9). However, the curve changes direction at a certain point and a certain amount of printer activity is seen at the same point in figure 8 indicating that this point marks the end of the melting of the sample. The melting point range was thus obtained as 225° - 230°. This value is close to the melting point reported for anhydrous lactose[11].

The tomahawk shape of the majority of the crystals of MDL agree with the shape describe 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 pulversation to which LAC was subjected. The shape of particles of TML agrees well with the particle morphology reported for anhydrous lactose[12]. The aggregation may be due to the process of recrystallization used for obtaining TML wherein small nuclei adhere to each other leading to crystal growth. Figure 10 show the results for sieve analysis performed on the three products. The small particle size of LAC is due to the pulverization process to which it was subjected.

Table 3 provides the full range of physical characteristics needed to characterise the flow bahaviour of the products. According to the scheme of Carr[4], among 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 spatula and high flowability index. This is further proved by the Hausner ratio which is nearest to one for MDL. This excellent flow bahaviour of MDL can be attributed to regular shape and smooth surface of the particles[13,14] (Table 2) and to the relatively less proportion of fines in it[15] (Figure 10). Conversely, the comparatively irregular shape and highly rough surface (Table 2) and the high proportion of fines (Figure 10) in TML leads to its flow behaviour being fair (Table 3). Addition of a glidant may improve flow in case of TML. The flow behaviour of LAC is extremely poor and can be due to the very small particle size of LAC (Figure 10). 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.

TML and MDL were subjected to a comparative evaluation for their use as directly compressible materials. Initially, few small lots were made on a single stroke tablet compression machine followed by direct compression of chlorpheniramine maleate (4 mg) tablets 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 5. Examination of the data reveals the following conclusions:

Both the products were compressed into tablets with weight variation within the pharmacopoeial limits. Analysis of variances 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. TML gave tablets with better hardness. The improved hardness of tablets of TML can be related to its high specific surface area[6]. The disintegration time of the tablets of both products was found to be below 15 minutes. 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. On the other hand, tablets made out of TML showed capping in 3-4 tablets per 20 tablets. This may be due to low compactibility of this material. We suggest that a few more trials be taken to optimise the process variables to achieve the product with the desired qualities. The tablets of both the products passed the assay test and the content uniformity of these tablets were within pharmacopoeial limits.

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 behavior amongst the three samples. TML (Thermally Modified Lactose) is an agglomerated mixture of crystalline, anhydrous α- and β-lactose with reduced

crystallinity as compared to that of MDL and LAC and having a melting point of 225° - 230°. The flow properties of TML were ranked below those of MDL but were better than the parent material LAC. Addition of a glidant may improve flow in case of TML.

The results of evaluation of direct compressibility of both products indicate that MDL has poor compactibility and should be used in conjuction with a dry binder for direct compressing. TML 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.

Presently, the Indian pharmaceutical industry is using traditional method of tableting or importing directly compressible excipient. Further research on the lines of the suggestions mentioned above may help in achieving commercial availability of indigenous directly compressible lactose.

ACKNOWLEDGEMENTS

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