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EFFECT OF MOISTURE CONTENT ON COMPRESSION PROPERTIES OF DIRECTLY COMPRESSIBLE HIGH BETA-CONTENT ANHYDROUS LACTOSE

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ABSTRACT

Moisture sorption characteristics and the role of moisture on the compression properties of direct compression anhydrous lactose was investigated. Anhydrous lactose sorbed little moisture even when exposed to very high relative humidities. The equilibrium moisture content of the diluent was less than 1% at 55% relative humidity, 1.66% at 80% relative humidity and 2.03% at 92% relative humidity. An increase in moisture content of lactose resulted in a reduction in hardness of the tablets and increased pressure requirements to achieve specified hardness values. Heckel plots obtained from the compression data of the diluent were linear for all moisture contents. Yield pressures calculated from the Heckel plots increased at moisture contents greater than that of the

original diluent. Differential scanning calorimetry performed on the diluent with 5.13% moisture showed that the added water was bound as the crystalline hydrate.

INTRODUCTION

Lactose has been a preferred tablet diluent for many years because of its low hygroscopicity and acceptable compression qualities. Several types of lactose as pharmaceutical diluents are commercially available, and studies on the compression properties of various types of lactose abound in the literature (1-12).

A survey of current literature shows that the role of moisture in lactose direct compression systems in general has not been thoroughly investigated despite a general consensus that moisture content can affect the compression properties of direct compression diluents (13-22). This investigation deals with the effect of moisture content on the compression properties of directly compressible high beta content anyhydrous lactose.

MATERIALS AND METHODS

The materials utilized in this investigation were used as received from the suppliers except as noted to adjust the moisture content. They were anhydrous lactose (Lot No. 8 NG 12, Humco-Sheffield Chemical, Memphis, TN), magnesium stearate (Lot No. 0710870, Amend Drug and Chemical Co., Inc., N.Y.) and Karl Fisher reagent and formamide (Fisher Scientific Co., Fairlawn, N.J.).

Moisture Content Determination

Initial moisture content of the diluent as received from the manufacturer was carried out by the Karl Fisher method. Formamide

was used as the solvent instead of methanol for the Karl Fisher titrations because of greater solubility of the diluent in the solvent.

Moisture Variability of the Powders

Once the initial moisture content of the diluent was determined, the diluent was dried in the oven at 80°C for one week (until no more moisture loss could be observed) in order to attain moisture contents below the manufacturer's specifications. The dried sample was stored in a dry glass bottle with a tight sealing screw cap and equilibrated for at least 24 hours before determining the exact moisture content of the powder by the Karl Fisher method.

Moisture content of the oven dried sample was increased to the reported values by spraying calculated quantities of water with a syringe fitted with a spray nozzle. The diluent was then blended for two minutes in a twin shell blender and equilibrated for at least 48 hours. Final moisture content determination of the diluent was carried out just before and soon after compression by the Karl Fisher method.

Moisture Sorption by the Diluents

Three grams of the dried diluent with the lowest moisture content was placed in tared 5 cm diameter petri-dishes and exposed to five different relative humidity chambers viz. 10%, 30%, 55%, 80% and 92% prepared with saturated salt solutions. The petri-dishes containing the powders were periodically taken out of the humidity chambers at specified intervals and accurately weighed to determine any changes in weights of the diluents. The

moisture content of the diluents was calculated on a dry weight basis established by Karl Fisher titration. The temperature was maintained at 23° + 2°C throughout the investigation. Equilibrium moisture contents of the diluent were also determined by exposing the powders to controlled humidity chambers for more than two weeks.

Density Determination

The density of the diluent was determined with an air comparison pycnometer (Beckmann Model 930, Beckmann Instruments Inc., Scientific and Process Instrument Division, Fullerton, CA.). The density of the sample was calculated from a mean of four readings.

Tablet Compression

Diluent with the desired moisture content (obtained by either oven drying or by addition of appropriate quantities of water to the oven dried sample and equilibration) ranging from 0.33% to 5.13% was blended with 0.75% magnesium stearate (lubricant) in a twin-shell blender for four minutes just prior to tableting. Tablets were compressed on a single punch machine (Stokes Model, F.J. Stokes Machine Co., Philadelphia, Pa.) on which compression pressure was measured with calibrated strain gauges on the upper punch and read out with an oscilloscope.

Since the temperature and the relative humidity of the room varied between 23° - 25°C and 20% - 60% respectively, minimal exposure of diluent to the atmospheric air was allowed during the compression process. This was accomplished by adding small

quantities of the diluent to the feed shoe and quickly covering it with aluminum foil. The compressed tablets were quickly transferred to tightly sealed dry containers. Weight of the tablets was constantly monitored during the compression period and at least two hundred tablets were punched for each batch. Moisture content analysis on the remaining diluent was performed in order to ascertain the amount of moisture that may have been lost or sorbed from the atmosphere by the diluent during the compression process. Other physical tests such as weight variation, hardness (Erweka Hardness Tester Type TBT, Erweka Apparatebau, Heusenstamm, West Germany) and thickness were carried out on random samples of 20 tablets within 6 hours after compression. The relative density of the tablets was calculated from the geometric parameters, the weights of the tablets, and the true density of the diluents.

Differential Scanning Calorimetry

An accurately weighed sample (15 mg) of lactose with added moisture (5.13%) was placed in a sample pan and heated at the rate of 20°C/minute in a differential scanning calorimeter (Differential Scanning Calorimeter Model DSC-1B, Perkin Elmer Co.). A sample of accurately weighed lactose monohydrate containing 5% moisture was also heated at the same rate for comparison.

RESULTS AND DISCUSSION

Moisture Sorption by the Diluent

Moisture uptake characteristics (Figure 1) and equilibrium moisture content (Table I) of anhydrous lactose at different

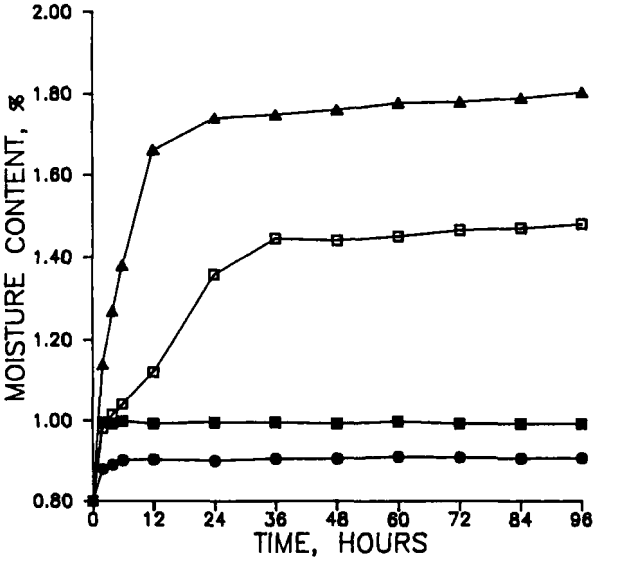

FIGURE 1: Moisture Sortion by Anhydrous Lactose at Different Relative Humidities

(●) - 30% RH; (■) - 55% RH; (□) - 80% RH; (▲) - 92% RH

Table I. Equilibrium Moisture Contents of Anhydrous Lactose at Different Relative Humidities

Relative Humidities (%)	Equilibrium Moisture Content (%)
10	0.90
30	0.88
55	0.95
80	1.66
92	2.03

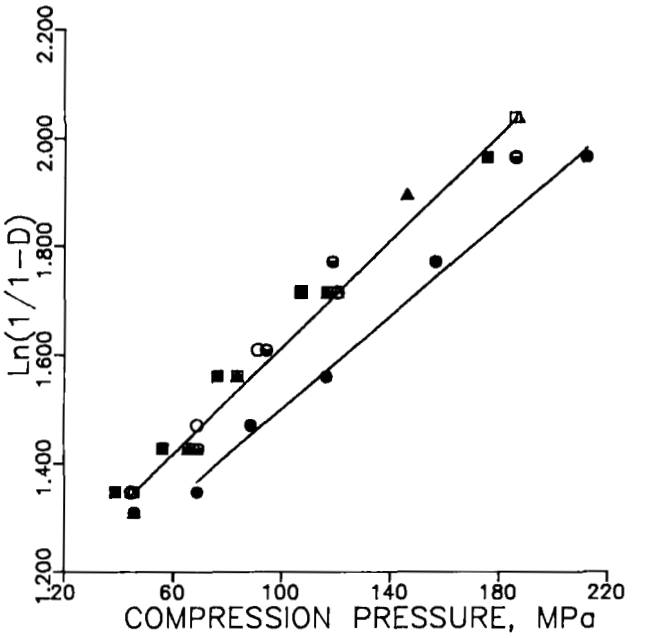

FIGURE 2. Heckel Plots for Anhydrous Lactose at Different Moisture Contents.

(▲) - 0.33%; (△) - 0.58%; (□) - 0.92%;
(■) - 2.05%; (○) - 3.30%; (◒) - 4.36%;
(●) - 5.13%

relative humidities showed that the diluent can be stored at humidities up to 55% without picking up an appreciable quantity of moisture. Up to 55% relative humidity, the equilibrium moisture content was less than one percent, but climbed to 2% at 92% R.H.

Moisture content analysis of the diluent before and after the compression process revealed no significant increase or decrease in the moisture content from the starting value inspite of the variations in the relative humidity of the room ranging from 20% to 60%.

Table II. Calculated Data for Heckel Plots

Moisture Content (%)	0.33%	0.58%	0.92%	2.05%	3.30%	4.36%	5.13%
Correlation Coefficient	0.998	0.997	0.998	0.993	0.974	0.978	0.996
Slope (K) x 10^3	5.75	4.91	4.98	4.55	4.33	4.76	4.30
Intercept (A)	1.056	1.122	1.123	1.190	1.180	1.127	1.071
Yield Pressure Megapascals (MPa)	174	204	201	220	231	210	233
D_o	0.400	0.400	0.400	0.400	0.400	0.400	0.400
D_a	0.634	0.675	0.675	0.696	0.693	0.676	0.658
D_b	0.234	0.275	0.275	0.296	0.293	0.273	0.258

Compression Properties of the Diluent

Each data point in all the figures represents an average value obtained from physical tests performed on 20 tablets. Heckel Plots (23, 24) were constructed from the compression data of the diluent at all moisture contents. In the compression range to produce viable tablets, these plots were linear (Figure 2) with correlation coefficients of 0.99 or better for five out of seven moisture contents (Table II). D_a values (the total densification due to the die filling) were greater than the D_b values (density contribution from individual particle movement and rearrangement), indicating that more densification occurred by granule deformation than by rearrangement and granule movement.

Figure 3 shows pressure - hardness profiles of lactose with moisture levels from 0.33% to 5.13%. As moisture level increased, tablet hardness decreased for given pressure levels. The decrease in hardness of lactose tablets as moisture level increased can be attributed to decreased binding strength between the particles because of the added water. Similar results have been observed by Lerk et. al. (25) who reported that dehydration increased the binding capacity of α-lactose monohydrate.

For the same tablet relative densities, tablet hardness values decreased when the moisture content was increased from 0.3% to 2% (Figure 4). Further increase in moisture content to 5.13% caused little further change in tablet hardness.

Figure 5 shows that to achieve a specified tablet hardness, the pressure required increased as moisture in the diluent was

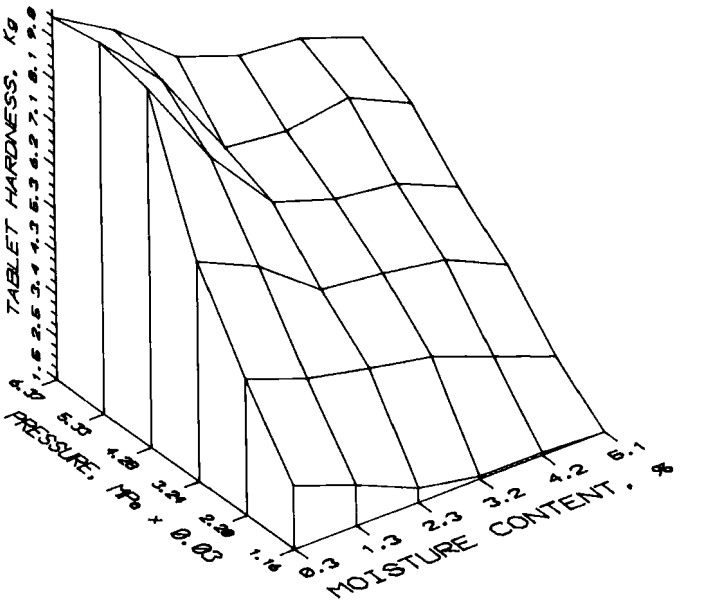

FIGURE 3. Effect of Moisture Content on the Relationship Between Tablet Hardness and Compression Pressure.

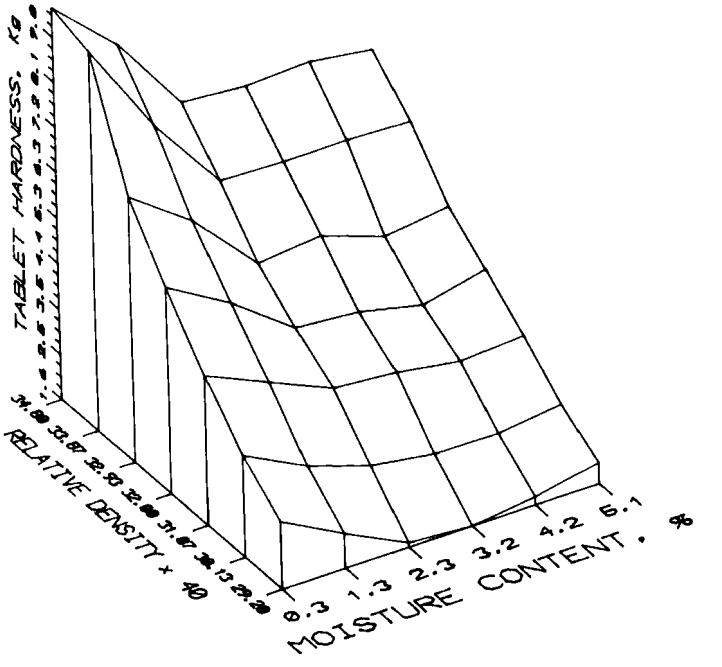

FIGURE 4. Effect of Moisture Content on the Relationship Between Tablet Hardness and Relative Density.

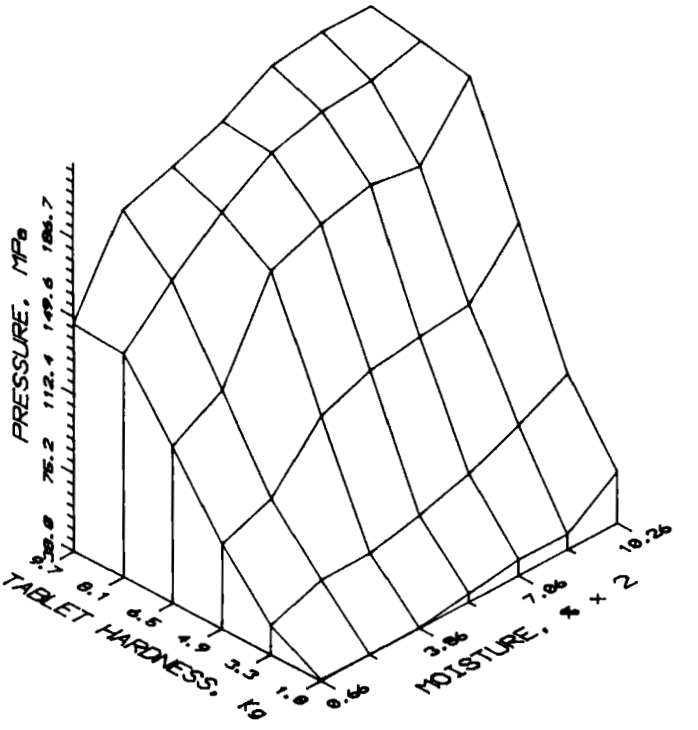

FIGURE 5. Effect of Moisture Content on Pressure Required to Achieve Specified Tablet Hardness.

increased. Yield pressures calculated from Heckel plots were generally higher for lactose with added moisture (233 MPa for 5.13% moisture) than for unmodified anhydrous lactose (174 MPa) indicating increased resistance to deformation of the diluent with higher moisture content. Both the increased yield pressure and decreased binding strength contributed to the poorer compression performance when moisture content of lactose was increased.

Differential Scanning Calorimetry

Figures 6 and 7 show the endotherms for bound water present in lactose with 5.13% moisture and lactose monohydrate with 5%

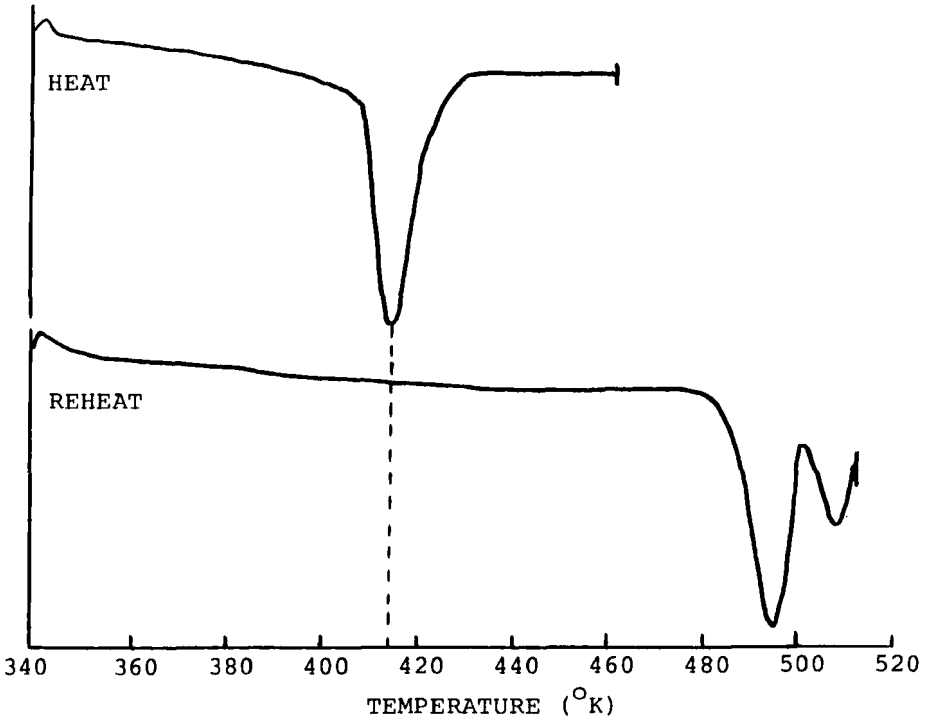

FIGURE 6. DSC Profile of Lactose Sample With 5.13% Moisture.

moisture content respectively. The loss of bound water in lactose with 5.13% moisture occurred at 415°K (142°C) as determined by the DSC technique, whereas, the loss of bound water in lactose monohydrate was 425°K (152°C), both values within the range reported by Vromans et. al. (7) for α- lactose monohydrate of different particle size fractions. A second endotherm evident at 496°K (223°C) in the lactose sample containing 5.13% moisture and at 500°K (226°C) for a sample of lactose monohydrate could be due to the presence of α- anhydrous lactose (12) after the bound water was removed from the lactose sample during the first heating cycle of the DSC scan. A third endotherm evident at 515°K (242°C) for

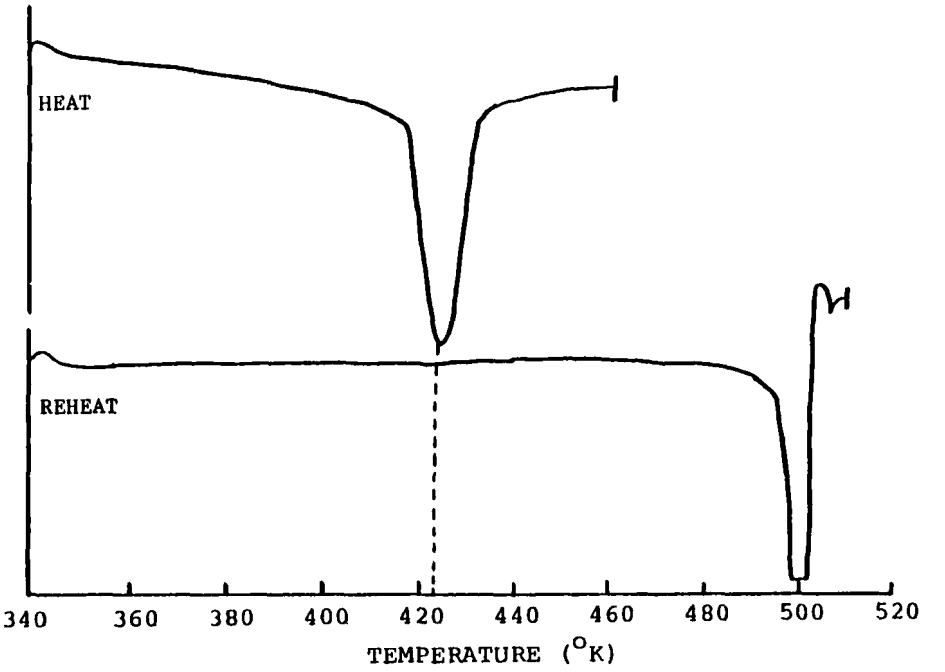

FIGURE 7. DSC Profile of Lactose Monohydrate Containing 5% Moisture.

the lactose sample containing 5.13% moisture (Figure 6) could be due to the presence of β-anhydrous lactose (12) after the bound water was removed from the lactose sample during the first heating cycle of the DSC scan.

CONCLUSION

When stored below 55% relative humidity, anhydrous lactose sorbs only small amounts of moisture and compression properties are insignificantly affected. Storage at relative humidities of 80% and above results in the sorption of sufficient moisture to affect the compression properties of the diluent, probably by the formation of the monohydrate with a change from the β-form to the α-form.

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