The Effect of Crystalline and Amorphous Lactose on Mechanical Properties of Roller Compaction Ribbon and Tablets

By

Kim Gochioco

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Prof. Berkland

Prof. Stobaugh

Dr. Alvarez-Núñez

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The Thesis Committee for Kim Gochioco certifies that this is the approved version of the following thesis:

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Prof. Berkland

Date approved:

Abstract

Lactose is a widely used excipient in the pharmaceutical industry. It exists as anhydrous, α- and β- monohydrate forms, which can be either crystalline or amorphous. Commercially available lactose comes in various grades differentiated by physical forms as well as modifications such as particle size. These characteristic modifications enable formulation and processing. Lactose grades for direct compression applications for example, contain various concentrations of crystalline and amorphous content. The mixture of forms exhibit unique material compaction properties that facilitate performance within formulations.

Lactose is infrequently used in large concentrations for dry granulation processes because α-lactose monohydrate exhibits relatively poor binding properties and consolidates mainly by fragmentation due to its 'brittleness'[1]. Though this is true of *crystalline* lactose, previous direct compaction research has found that *amorphous* lactose is known to be more compressible than its crystalline form[1, 15, 17, 28]. This research aims to characterize the material properties of a directly compressible lactose monohydrate, Flowlac 100 containing high crystalline and high amorphous content; and to compare the fundamental differences in mechanical properties when manufactured by dry granulation via a roller compaction emulator. Ribbon properties such as tensile strength and solid fraction were measured, and the subsequent mechanical properties of tablets evaluated. Additionally, model drug formulations containing a very brittle drug, paracetamol, were manufactured into ribbons with high crystalline and high amorphous lactose. Subsequent tablettability was also evaluated.

Results from this research suggest that amorphous lactose offers advantages over its crystalline counterpart such as an increased ribbon tensile strength under lower compression forces. A formulation containing amorphous lactose and a poorly compressible model drug manufactured through a roller compaction process resulted in acceptable tablets with improved friability over the crystalline formulation.

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Introduction

Theoretical Background and Significance: Lactose

Lactose is a natural disaccharide produced from cow's milk. It has various isometric forms depending on the manufacture: α- lactose monohydrate, β- and α-lactose anhydrous- that exist as stable crystalline or amorphous forms.

Lactose monohydrate is an excipient commonly used as a tablet and capsule diluent, a binding agent, and carrier for dry-powder inhalers[26]. The general properties of lactose that contribute to its popularity as an excipient are cost effectiveness, availability, low hygroscopicity, excellent physical and chemical stability, and water solubility[26]. Commercially available lactose comes in various grades depending on the method of manufacture and exhibit modified physical properties such as particle size distribution, flow, density, moisture content, and surface area. They can be milled, sieved, micronized, granulated/agglomerated, or spray dried.[19]

Grades of spray-dried lactose monohydrate are available for direct compression and dry granulation purposes. Qualities available on the market consist of only around 12-15% amorphous lactose, while the remaining consists of α-lactose monohydrate[28]. These direct compression (DC) grades contain a mixture of crystalline and amorphous content and offer good flowability and compressibility.

Compaction Properties of Lactose

A Few Key Definitions:

Compactibility is the ability of a powder bed to cohere into or to form a compact. Usually described in terms of tablet strength as a function of applied compaction stress.[1]

Compressibility is the ability of a powder bed to be compressed (be reduced in volume) due to the application of a given stress.[1]

Compaction is the transformation of a powder into a coherent specimen of defined shape by powder compression.[1]

Compression is the reduction in volume of a powder bed due to the application of a stress.[1]

Ductile materials such as microcrystalline cellulose, will allow small amounts of plastic deformation within the particles.

Brittle materials fracture at relatively low stresses. Since they cannot yield to a significant extent, the material will fracture instead. Lactose is considered a brittle material.

Many pharmaceutical excipients occur naturally in the amorphous or partially amorphous state and many have been found to possess improved handling and mechanical properties. When compared to other excipients such as microcrystalline cellulose, crystalline α- lactose monohydrate exhibits relatively poor binding and compaction properties. It consolidates mainly by fragmentation and is more brittle[1]. Amorphous lactose is known to be more compressible than its crystalline form

A study by Hancock found "that spray dried lactose used mainly for DC processes, had compression characteristics optimized by manipulating its amorphous content. During manufacturing, the fast cooling of a solution and a high rate of crystallization produced solids with a concentration of amorphous content, generated by rapid cooling and crystallization. These spray dried particles are porous, spherical agglomerates that are fairly uniform in size and had superior binding ability when compared with α-lactose monohydrate." Its binding ability was mainly attributed to the amorphous lactose content which exhibits a higher degree of plastic deformation. A decrease in particle size also increased the compactibility of spray-dried lactose. While crystalline lactose fragments to a considerable extent during compression (Eriksson and Alderborn, 1995), amorphous lactose undergoes only limited fragmentation.[33]

In a direct compression study by Sebhatu et al., amorphous lactose yielded tablets with higher tensile strength than crystalline lactose. He concluded that crystalline lactose consolidated by brittle fracture whereas spray dried lactose consolidated by plastic deformation due to the binding of amorphous content. Studies by Heistand et al, (1984) and Vroman (1986) found that spray-dried lactose deforms mainly by plastic deformation and with accompanying mercury porosimetry data, concluded that "In contrast to lactose with crystalline concentrations, tablet pore surface did not change with increasing compaction forces which concluded that amorphous lactose deforms mainly by plastic flow." In addition, compressibility studies performed by Ilic et al. demonstrated that compared to milled or agglomerated types, the most compressible lactose is the spray-dried grade. Various tabletting and compression studies have been performed with various direct compression spray-dried grades of lactose. However, few relevant dry granulation studies via roller compaction are available.

Theoretical Background and Significance: Dry Granulation via Roller Compaction Process

Direct compression, dry granulation and wet granulation are the most widely used manufacturing processes for solid dosage forms in the pharmaceutical industry[1]. Generally speaking, the direct compression process is the simplest, most efficient and requires the fewest components and processing steps. The DC process however, is susceptible to segregation resulting in non-uniform distribution of API as the process is highly dependent on the flow of material.

Dry granulation in contrast has important advantages over direct compression. It employs a compaction stage that densifies the blend to form aggregates of small powder particles called 'granules'. These granules improve material flow, content uniformity and prevent segregation.

The pharmaceutical industry employs two methods of dry granulation: slugging and roller compaction. Both methods involve compressing the material under some pressure to make 'compacts or slugs' or 'ribbons' under an applied pressure. The applied pressure increases contact area between particle surfaces and overall bonding strength, to form a solid aggregate. The aggregates are subsequently milled to reach desired granule size and are further processed into capsules, powders for oral suspension/solution or tablets.

Principles of Roller Compaction

Dry granulation (DG) via roller compaction (RC) is a pharmaceutical manufacturing process whereby particles are consolidated by exerting a mechanical pressure on two compacting rolls to produce a densified sheet or 'ribbon' of product. The resulting ribbon is then milled to form granules of a particular particle size distribution, which can be filled into capsules or compressed into tablets.

Dry granulation via roller compaction is an efficient technique employed to increase material density, creating granules with good powder-flow and material characteristics without the application of heat. It is therefore the preferred manufacturing process for heat sensitive drugs. It also offers a simpler manufacturing process requiring less material and energy, and provides a readily scalable process with a higher production throughput[4,25,35].

Key critical parameters in roller compaction are: Screw speed and configuration, Roll Force (kN), Roll Gap (mm), Roll Speed (rpm), Roll Diameter, Roll Surface and the type of mill. Roll Force is the most important parameter in roller compaction. This is the force the rolls are imparting on material. Roll force and roll gap are material dependent and is manipulated in order to reach key ribbon attribute targets of tensile strength and solid fraction.
More information on the principles of roller compaction can be found in the Appendix.

Roller Compaction Emulator

The roller compaction portion of this research will be performed using the Presster (Metropolitan Computing Corporation) (Figure 1). The Presster is a linear tablet press emulator that has been modified to run simulations of various roller compactors. In this study, the roller compactor emulation was based on the Gerteis Minipactor. Surrogate ribbons were manufactured using rectangular D-tooling.

The Presster enables a prediction of 'ideal' ribbons by emulating critical parameters such as roll force, roll pressure, roll speed, and roll radius- allowing a representative measurement of its effects on ribbon properties using only a small fraction of material. This technique can be seen as a material sparing alternative for feasibility studies at bench top scale. It cannot however

emulate certain roller compaction aspects such as non-homogenous ribbon density, the powder feeding mechanism, and other shear forces the powder experiences as it travels through a conventional roller compactor.[20,37]

Figure 1. The Presster and Ribbon Tooling[20]

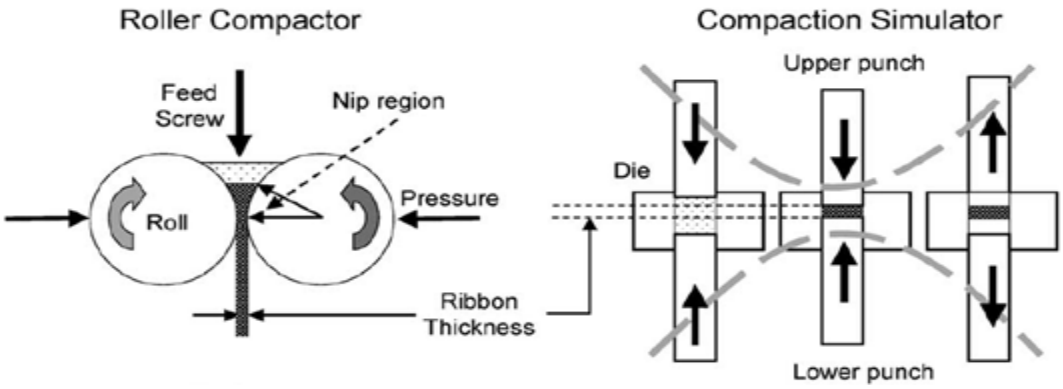


Figure 2. Linear Roller Compaction Simulation/Emulator[38]. Instead of two counter-rotating rolls, the compact is manufactured with a rectangular die in a linear compaction simulator.

Roller Compaction Measurements of Key Ribbon Attributes

Solid Fraction (SF) and Tensile Strength (TS) are key ribbon attributes that measured after processing. They are considered primary indicators of material behavior during roller compaction.

Solid Fraction

Solid fraction (SF) is the materials relative density and can be used to characterize powders at different stages of densification. SF increases as the material is densified and processed from powders into ribbons and then subsequently, into tablets. The SF of ribbons is affected by roller compaction factors such as compaction force, and roll speed and is an indicator to the degree of compaction of the powder. It is measured by:

$$\mathbf{SF = \rho_e / \rho_t = (100- P) / 100} \qquad \text{(eqn. 1)}$$

Where ρ_e is the envelope density of the sample, ρ_t the true density of the material and P is the porosity. [6,38]

Envelope density is defined as:

$$\mathbf{\rho_e = m / V_e} \qquad \text{(eqn. 2)}$$

Where m is mass of sample and V_e the apparent volume. It is the mass of an object divided by its volume where the volume includes pores and small cavities. Envelope density can be measured with a caliper or using a Geopyc 1360 Micromeritics Envelope Density Tester.

Tensile Strength

Tensile Strength is a mechanical property measurement after compression. The degree of densification affects the mechanical properties of materials and directly affects tensile strength. It is defined as the minimum tensile stress required for fracture initiation within a compact, and therefore an indicator of bond strength within the specimen. It is typically used to gauge tablet strength. In this case the tensile fracture strength of ribbons will be indicative of the properties of the material and its behavior in the subsequent processing steps[6,38].

TS of a ribbon is calculated by the following:

$$\sigma_T = \frac{3}{2}\frac{F \times L}{W \times t^2} \qquad \text{(eqn.3)}$$

Where F is the load, L is the distance between the supports, W is the width of the sample, and t is the thickness of the sample.

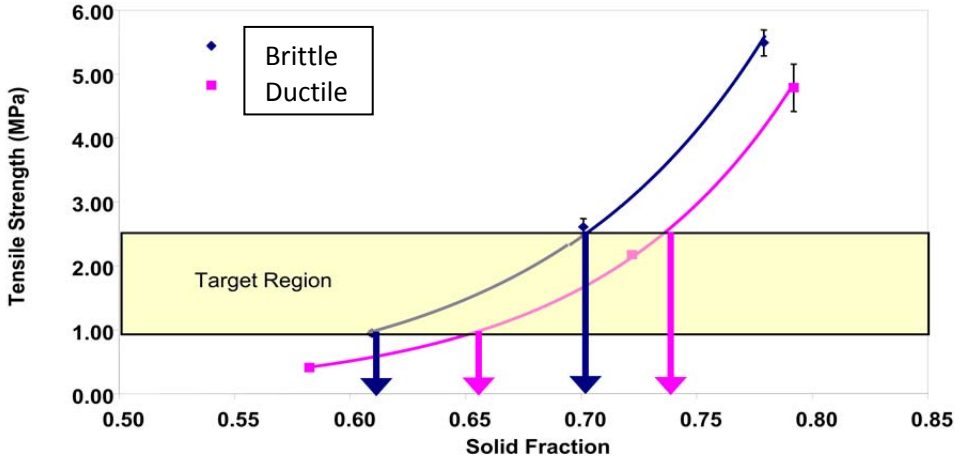


Figure 3. Tensile Strength and Solid Fraction Curves of Brittle and Ductile Materials[4].A target solid fraction of 0.6-0.75 and a tensile strength range of 1.2-2.5 is ideal for most formulated ribbons [4]. Brittle materials (◇) behave differently compared to ductile materials. Brittle materials such as lactose reach higher tensile strengths at lower solid fraction values while ductile materials, such as Microcrystalline cellulose reach a target TS at higher solid fraction values.

Aims of the Study

Crystalline lactose is an excipient used in a wide variety of pharmaceutical dosage forms. However, it is not usually utilized in large concentrations for roller compaction because of its 'brittle' nature and poor compressibility. Commercially available spray dried (SD) lactose for direct compression and dry granulation processes on the other hand, contains a mixture of crystalline and amorphous content. The amorphous portion offers advantages over its crystalline counterpart and exhibit properties that make it more amenable for an RC Process.

Tabletting and compression studies have been performed with various direct compression (DC) grades of lactose. Spray dried lactose qualities available on the market consist only of about 12-15% amorphous lactose, while the remaining consists of α-lactose monohydrate[28]. Few dry granulation relevant studies are available on spray-dried lactose grades and no comprehensive study on roller compaction employing this new grade of high amorphous lactose has been performed thus far.

This research aims to:

- Characterize the material properties of a directly compressible lactose monohydrate- Flowlac 100, containing high crystalline and high amorphous content;
- To compare the fundamental differences in mechanical properties of the two when manufactured by dry granulation via a roller compaction emulator.

A non-commercial spray-dried grade of lactose- Flowlac 100 amorphous containing an amorphous concentration of ~96%, along with its crystalline counterpart Flowlac 100, ~92% crystalline was compared in this study. Ribbon properties such as tensile strength and solid fraction were measured, and the subsequent mechanical properties of tablets evaluated. In addition, model drug formulations containing a very brittle drug paracetamol, were manufactured into ribbons with high crystalline and high amorphous lactose. Subsequent compressibility and compactibility of tablets were also evaluated. Ultimately, if this new high amorphous grade lactose show improved mechanical properties over its crystalline lactose counterpart, then incorporating amorphous lactose in a formulation may offer functional advantages that make it suited for a roller compaction process.

Materials and Methods

Placebo Early Feasibility Studies

Materials

Flowlac 100 crystalline and Flowlac 100 amorphous provided by Meggle Pharma (Wasserburg Germany) were investigated. Microcrystalline cellulose, Avicel PH102 was used as a diluent and dry binder, and magnesium stearate as lubricant.

Flowlac 100 is the trade name of a directly compressible spray-dried α-lactose monohydrate. The spray drying process leads to an excellent compressible excipient that has fast disintegration in water, superior flowability with exceptional hardness yield (Meggle). It is also used in lyophilized and aerosol formulations. Commercially available Flowlac 100 crystalline is composed of roughly <10% amorphous α-lactose monohydrate. The new spray dried Flowlac 100 amorphous is composed of ~96% amorphous lactose.

Microcrystalline cellulose, Avicel PH102 is a common diluent in pharmaceutical manufacturing. It is frequently used for dry granulation applications because it exhibits excellent compressibility. "The fibrous structure offers excellent compressibility and a high capacity to accommodate co-processed ingredients to produce granules with suitable mechanical properties for tablets"[6]. The behavior of Avicel PH102 ribbons will be compared to lactose ribbons.

Preparation of Powders

The following blends were dispensed:

Table 1. Formulation Composition

Formulation	#1	#2	#3
lactose monohydrate, Flowlac 100 crystalline	100	--	--
lactose monohydrate, Flowlac 100 amorphous	--	100	--
microcrystalline cellulose, Avicel PH102	--	--	100
Total (%)	100	100	100

Materials were weighed using an analytical balance. Each material was passed through a U.S. size#18 mesh screen to break up agglomerates. The components were then collected and transferred into a 250mL HDPE bottle. All blends were kept in sealed double bags with 100g of silica gel desiccants to maintain a low humidity/moisture environment and stored in ambient conditions.

Material Characterization

Full material characterization was performed on Flowlac 100 crystalline, Flowlac 100 amorphous and microcrystalline cellulose, Avicel PH102. This includes material identification, form identification, determination of particle size distribution, moisture sorption analysis, bulk and tapped density, true density, surface area, flow and flow behavior.

XRPD

Upon receipt of raw materials, Flowlac 100 crystalline and amorphous were identified by x-ray powder diffraction (XRPD). A 15 min normal scan was run on a Philips X'pert XRPD.

Differential Scanning Calorimetry

A modulated DSC run was performed on Flowlac 100 crystalline and Flowlac 100 amorphous using TA DSC Q2000 with Tzero Aluminum Pans. The modulated temperature was amped at 1°C/min, the temperature range from -10.0°C to 200.0°C.

Moisture Analysis

A VTI-SA+ Vapor Sorption Analyzer by TA Instruments-Waters was used to measure moisture sorption from 0 to 90%RH in 5% RH steps. The equilibrium condition was set to dm/dt = ±0.002% in 5 min. Each step had a minimum duration of 5 min and a max of 360 min. Samples were place on an open aluminum pan and the temperature was set at 25°C.

Microscopy

Microscope images were taken using a Nikon Eclipse E600 Polarized Light Microscope. A polarized lens was used to identify bifringence. A Zeiss Scanning Electron Microscope was used to take magnified images of the materials surface at various magnifications.

Bulk and Tapped Density

Bulk density and tapped density was measured using the USP <616> Bulk Density and Tapped Density method.

Bulk Density measured in g/ml by the formula: $\mathbf{M / V_{original}}$ (eqn. 4)

Tapped Density measured in g/ml by the formula: $\mathbf{M / V_{final}}$ (eqn. 5)

Carr's Index, Hausner's Ratio

Compressibility Index (Carr's Index) and the Hausner Ratio are measures of powder compressibility. In poorer flowing materials, there are greater interparticulate interactions and the difference between bulk and tapped densities are greater.

Compressibility or Carr's Index Formula: $\mathbf{100(V_o - V_{final}) / V_o}$ (eqn. 6)

Hausner's Ratio: $\mathbf{V_o / V}$ (eqn. 7)

A table with Compressibility Index, Hausner's Ratio and Flow Characterization guide can be found in the Appendix.

True Density

True density was determined using a Micromeritics Accupyc 1330 Helium Pycnometer following manufacture recommended procedures. True density was measured n=3 and standard deviations were recorded.

Particle Size Distribution

Particle size distribution was measured using a laser diffraction method. The samples were analyzed with a Sympatec HELOS/BF system with an ASPIROS feeder, an R5 lens and 0.5bar pressure. The average d10, d50, d90 values from three measurements were recorded.

Flow properties

Flow measurement using Ring Shear Tester

Flow functions were generated using the Schulze Ring Shear Tester RST-XS with RSV95 with a Size#1 Cell. The shear cell was assembled and uniformly filled with sample. A spatula was used to scrape off the top of the shear cell to remove the excess material evenly without applying force to the surface of the material. The material was filled ensuring that there were no 'void pockets'. Flow function values (FFc) were measured at 1, 2, 3 and 6 kPa consolidation forces for each material. The standard classification of powder flowability measured as Flow Functions (FFc) can be found in the Appendices.

Powder Flow Behavior from Powder Flow Rheometer

The FT4 Powder Rheometer measures the bulk, flowability and processability characteristics of powders. Sample material was loaded into a 25mm cell. This instrument measures the bulk powder's response to aeration, consolidation, flow rate; and measures bulk properties of density, compressibility and permeability after the powder bed is pre-conditioned.

Using the Freeman Technology FT4 Powder Flow Rheometer the following were measured:

Basic Flowability Energy (BFE) - BFE is the energy required to establish a particular flow pattern in a conditioned, precise volume of powder. It was calculated from the work done in moving the blade through the powder from the top of the vessel to the bottom.

Stability Index, SI - SI measures the how the powder is affected by a number of reasons, including de-aeration, agglomeration, segregation, moisture uptake or electrostatic charge.

Specific Energy, SE (mJ/g) - SE is a dynamic measurement that measures how powder will flow in an unconfined or low stress environment. It is calculated from the work done in moving the

test blade through the powder bed from the bottom to top of the vessel, and normalized against mass.

Compressibility Test - Compressibility is determined by how density changed as a function of applied normal stress. The instrument measures compressibility as the percentage change in volume after compression (%).

Permeability Test - The test is represented as a pressure drop across the powder bed versus the normal stress for a constant air velocity. Pressure drop through powder bed was measured at a constant 2mm/s air velocity as a function of applied normal stress.
Detailed information on the FT4 Powder Rheometer Tests can be found in the Appendix.

Placebo Roller Compaction Studies

Manufacturing of Placebo Ribbons via a Roller compaction Emulator: The Presster

A roller compaction emulation of placebo blends were performed using MCC's The Presster. The roller compactor simulation was based on a Gerteis Minipactor. Ribbons were manufactured with a 1"rectangular D-tooling (0.3937 x 0.9303) (Figure 4) to simulated smooth rectangular ribbons. A 250cm roll radius and a roll speed of 5 rpm was used to replicate typical settings in a Gerteis Minipactor roller compactor. No pre-compression was utilized. Simulated ribbons were manufactured to a weight of 1g and were produced to a thickness required to reach a range of TS values by setting the distance between upper and lower tooling (mm).

A range of ribbon tensile strengths from ~0.5MPA to 3.5MPA were initially investigated to evaluate the formulations processability. A final ribbon TS range of 1.2-2.0 MPa as well as a solid fraction range of 0.65-0.70 was targeted for manufactured ribbons. Three ribbons were

produced for each compression force target (n=3). The diameter, length, thickness, mass of ribbons were measured immediately after compaction. Solid Fraction (SF) and Tensile Strengths (TS) were calculated. True densities of roller compacted blends were determined with three replicates on the Micromeritics Accupyc Pyctnometer.

Measurement of Ribbon Solid Fraction

Solid fraction (SF) was calculated from equation 1.

Measuring Envelope Density

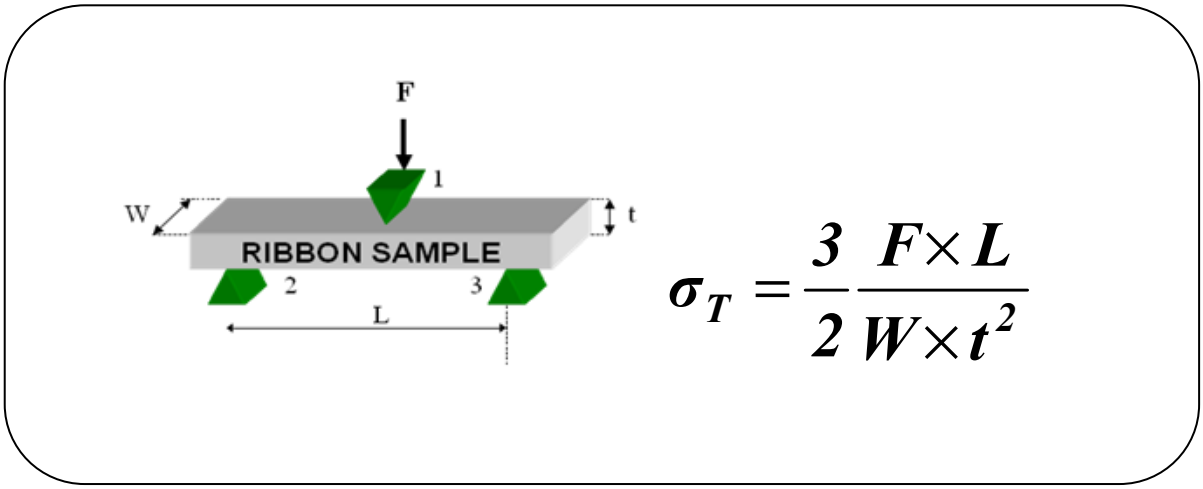
Envelope density was measured using both the caliper method and the envelope density method. The caliper method utilized a VWR caliper to measure ribbon thickness, width and length. The weight of the ribbon was measured with an analytical balance. The Geopyc 1360 Micromeritics Envelope Density Tester allows for accurate envelope volume measurements by a method analogous to volume measurement by fluid displacement. The sample mass was first measured using a Mettler Toledo AB-265-S analytical balance and the envelope volume automatically measured by the Geopyc. A 25.1mm chamber was used and filled with 3cm of Dry Flo, a free flowing quasi-fluid material composed of small, graphite lubricated glass micro-spheres.

During the test, the chamber with Dryflo was agitated and gently consolidated. The volume of the medium was determined at a certain plunger consolidation pressure. The ribbon sample was then added into the chamber, making sure that it was fully covered and surrounded with Dry flo. The volume was determined again using the same consolidation pressure. The Geopyc collects the displacement data, performs calculations and displays the volume and density results of the sample. All Geopyc measurements were performed in triplicate (n=3) and 3 samples from each

compression force was measured. The standard deviation of each measurement was recorded. The envelope density method of measuring SF was found to be more accurate than the caliper method.

Measurement of Ribbon Tensile Strength

Tensile strength of ribbons was calculated from break force values measured using a TA Texture Analyzer's three-point beam bend test. The ribbons were placed on a stand atop 2 beams separated by a known distance. A load cell was then applied to the top-middle section of the sample until the sample fails or 'breaks'. The speed of the applied force was fixed at 2mm/s. The load or force (measured in kg) required to break the sample was recorded and TS calculated using the formula in (Figure 4). Three samples were measured per compression setting (n=3), standard deviation and %RSD was calculated. Area under the curve, which is indicative of the materials mechanical behavior was also calculated per sample (n=3).



$$\sigma_T = \frac{3}{2}\frac{F \times L}{W \times t^2}$$

Figure 4. Calculating Tensile Strength- Three point bend test. Where F is the load, L is the distance between the supports, W is the width of the sample, and t is the thickness of the sample[4].

Measurement of Compactibility

The most common way to assess powder compactability is to study the effect of compaction pressure on the strength on the resulting compact, measured by the force needed to fracture the compact. This is represented by its tensile strength value. TS (in MPa) values were plotted against Compaction Pressure measured in MPa.

Roller Compaction Studies with a Model Drug at 25% Drug Load

Formulation Performance of an Active Formulation

To evaluate roller compaction performance of the different forms of Flowlac 100 (crystalline vs amorphous), active formulations were manufactured using a model drug substance at a 25% drug load. Paracetamol (acetaminophen) Form I was chosen for this study because of its brittle nature. This poorly compressible drug poses many formulation manufacturing challenges.

Preparation of 25% DL Model Drug Blends for Roller Compaction: Dispensing, Blending, True Density Measurements

Excipients and the model drug were dispensed into an appropriate sized container and blended in a Turbula mixer at 67rpm for 2 minutes. Microcrystalline cellulose, Avicel PH102 was used to serve as a ductile excipient for comparison. Intragranular magnesium stearate was added as lubricant. In addition, true density was determined and standard deviations recorded for each formulation blend using a Micromeritics Accupyc 1330 Helium Pycnometer at n=3.

Table 2. Formulation Composition for Model Drug Experiment

	#0001	#0002
Intra-Granular	**Theo (%)**	**Theo (%)**
Paracetamol/ Acetaminophen	**25**	**25**
Flowlac 100 crystalline	**37.00**	**-**
Flowlac 100 amorphous	**-**	**37.00**
MCC PH102	**37.00**	**37.00**
Mg Stearate	**0.50**	**0.50**
Extra-granular		
Mg Stearate	**0.50**	**0.50**
TOTAL	**100**	**100**

Manufacturing of 25%DL Model Drug Ribbons via a Roller Compaction Simulator: The Presster

Preparation of Ribbons for Roller Compactor Simulation

Formulations listed above were roller compacted using the Presster in roller compaction simulation mode. A 250cm roll radius and a roll speed of 5 rpm was used for a Gerteis Minipactor simulation. The D carriage, equipped with a 1" (0.3937 x 0.9303) ribbon tooling was used to simulate smooth rectangular ribbons. Approximately, 20g of ribbons from each formulation were manufactured at a target ribbon TS of 1.2Mpa. Ribbons of consistent quality were manufactured and no sticking issues were observed. Manufactured ribbons were kept in sealed 75cc HDPE bottles and stored with silica gel desiccants in sealed double bags.

Preparation of Tablets and Determination of Tensile Strength

Milling and Lubrication

Ribbons manufactured via the roller compaction simulator were milled in a Quadro Comil U3 – 0039 with a 7B050G03119(1270) Screen, 7B160110000 Impeller, and at 2200 mill speed. The milled granules were collected and weighed. A calculated amount of pre-sieved magnesium stearate was added and placed into a 100cc HDPE bottle. The following was blended in a Turbula mixer for 2 minutes at 67rpm to create a final lubricated blend.

Tablet Compression Conditions

Tablettability of the 25% drug load Paracetamol formulations manufactured with crystalline and amorphous Flowlac 100 was evaluated after compression. Compacts were manufactured using The Presster in tablet press simulation mode.

The Presster simulated a Korsch XL200 tablet compression machine with a 30rpm speed, ¼ "flat faced round tooling and target tablet weight of 150mg. Tablets were manufactured at 36k tablets/hr; 20.8 ms dwell time; 0.448 linear speed m/sec., 250mm roll with no precompression. Three compacts were manufactured at each target upper compression force of 3, 5, 10, 15, 20 kN (n=3). The weight, diameter, thickness and hardness of each tablet was measured immediately after tabletting using a caliper and a Vankel Hardness tester.

Figure 5. Ribbons were milled into granules then compacted into tablets.
(Actual images from experiments)

Tablettability Measurement

Tablettability was illustrated by plotting the tensile strength of tablet compacts versus the compaction forces required to make them. The tablet tensile strength or "tablet breaking force" can be calculated by:

$$\sigma_x = 2 \times F_b \; / \; \pi \times D \times H \qquad \text{(eqn. 8)}$$

Where F_b is the Tablet Breaking Force (N); D is the tablet/compact diameter (cm); H is the tablet thickness (cm).

Compacts were manufactured using flat faced round tooling at various compaction forces. Three compacts were produced at each compaction force. Weight, diameter, thickness and hardness (kP) of each tablet was measured immediately after tabletting using a caliper and a Vankel Hardness tester.

Tablet Friability Test

Friability of tablets was measured per USP<1216> using a Varian Inc. Percent mean weight loss was calculated from weight of tablets before and after 50 and 100 revolutions.

Results and Discussion

Material Characterization of Lactose Types

XRPD

XRPD results displayed distinct peaks characteristic of crystalline materials for Flowlac 100 crystalline. In comparison, Flowlac 100 had a distinct 'halo' that is characteristic of amorphous materials.

A sample of both Flowlac 100 crystalline and Flowlac 100 amorphous were exposed to 40°C/75%RH conditions in a stability chamber. After 3 days, Flowlac 100 amorphous had completely converted to the crystalline form. It is well known that amorphous lactose will eventually convert to its crystalline form upon exposure to moisture. Due to this observation, all samples were kept in desiccated sealed containers and stored in ambient conditions.

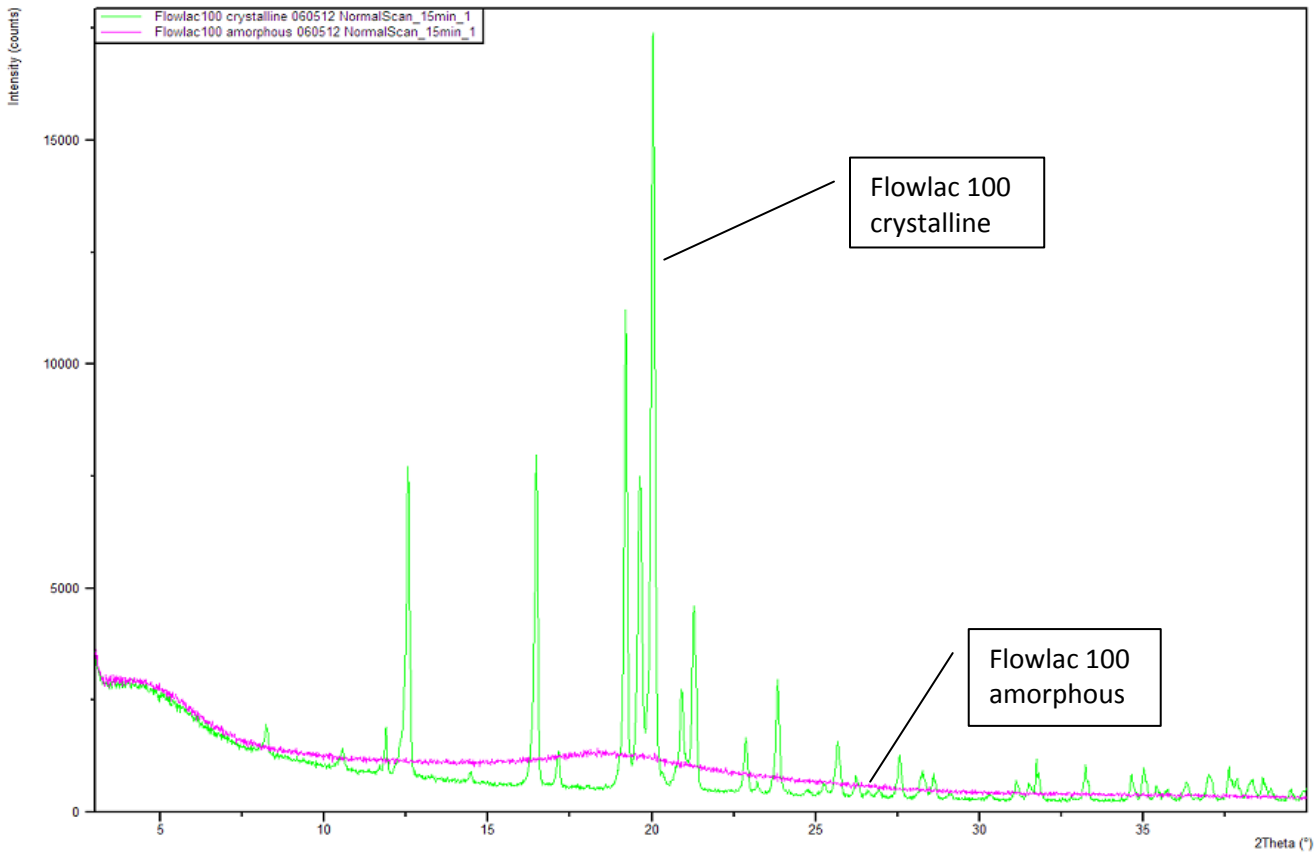


Figure 6. XRPD 15min Normal Scan of Flowlac 100 crystalline and Flowlac 100 amorphous. Flowlac 100 crystalline displaying distinct crystalline peaks, while Flowlac 100 amorphous displaying an amorphous halo.

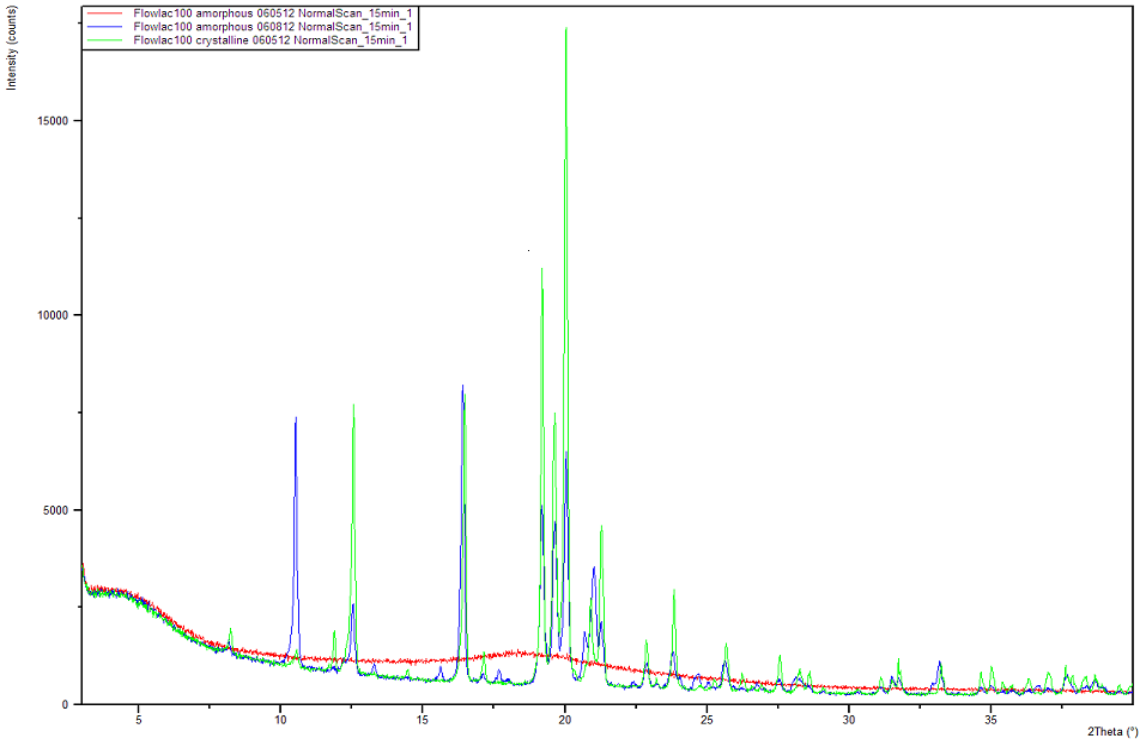


Figure 7. XRPD 15min Normal Scan after Exposure to 40°C/75%RH condition, 3 days. Amorphous lactose (060512) re-crystallized to (060812) in three days.

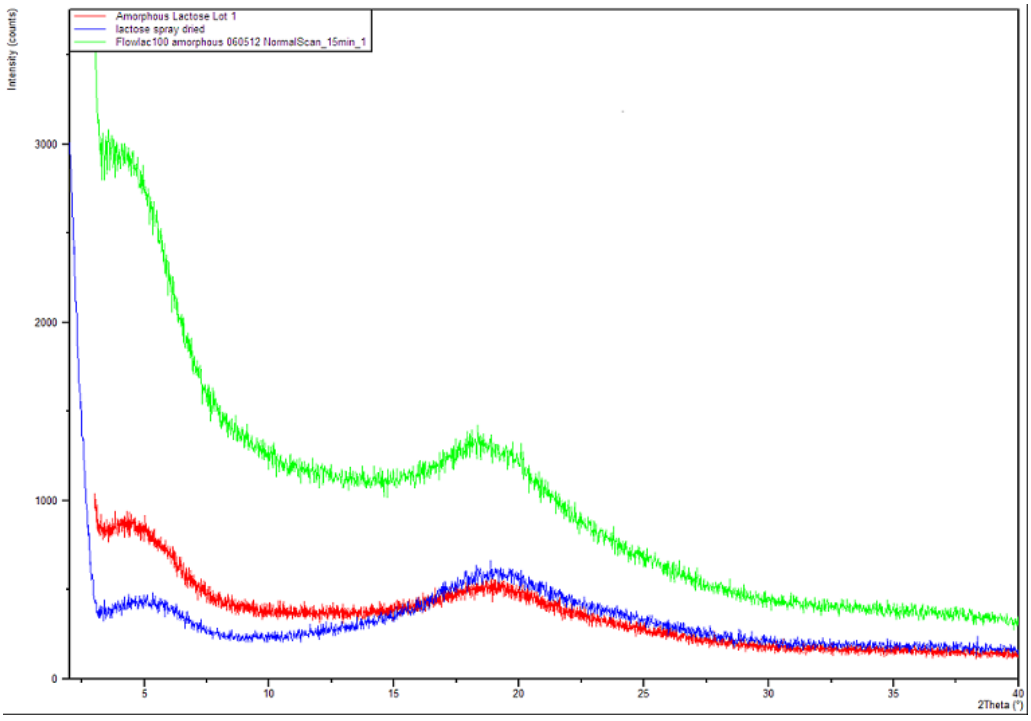


Figure 8. XRPD Scan of amorphous Flowlac 100 and spray dried lactose. Flowlac 100 amorphous plotted against spray dried lactose manufactured in house from crystalline lactose, confirms that Flowlac 100 amorphous contains very high amorphous concentration.

DSC

DSC was used to determine melting points for crystalline and amorphous lactose. It was used to confirm monohydrate as dehydration was observed at 140°C. The crystalline material showed a melt at 141.68°C (Figure 9). The amorphous material showed a recrystallization to lactose Anhydrous at a temperature around 160°C and a Tg at 55.77°C.

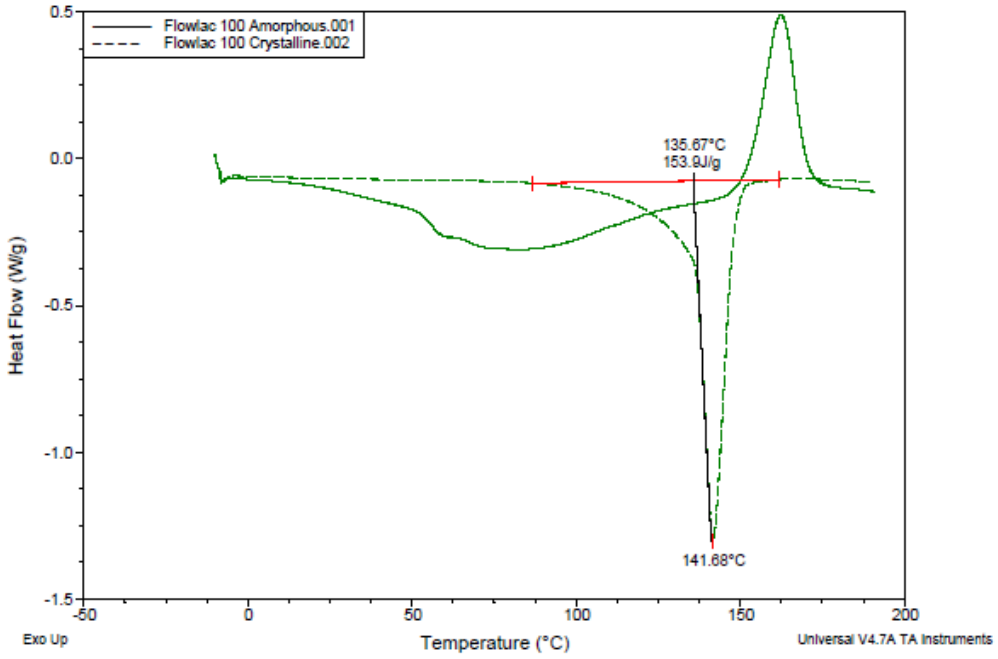


Figure 9. DSC Overlay Flowlac 100 crystalline and Flowlac 100 amorphous.

Moisture Sorption

Amorphous lactose is known to convert back to its crystalline form with exposure to moisture. The moisture isotherm of Flowlac 100 amorphous was determined using a VTI-SA+ Vapor Sorption Analyzer by TA Instruments-Waters. The moisture adsorption/desorption isotherm shows a 3% by weight moisture pick-up by the sample from 10-40%RH. The rate of moisture pick-up increases from 40-50%RH as the sample weight increased by another 4.5% within about 500mins. Samples were kept with silica gel desiccants to protect from humidity.

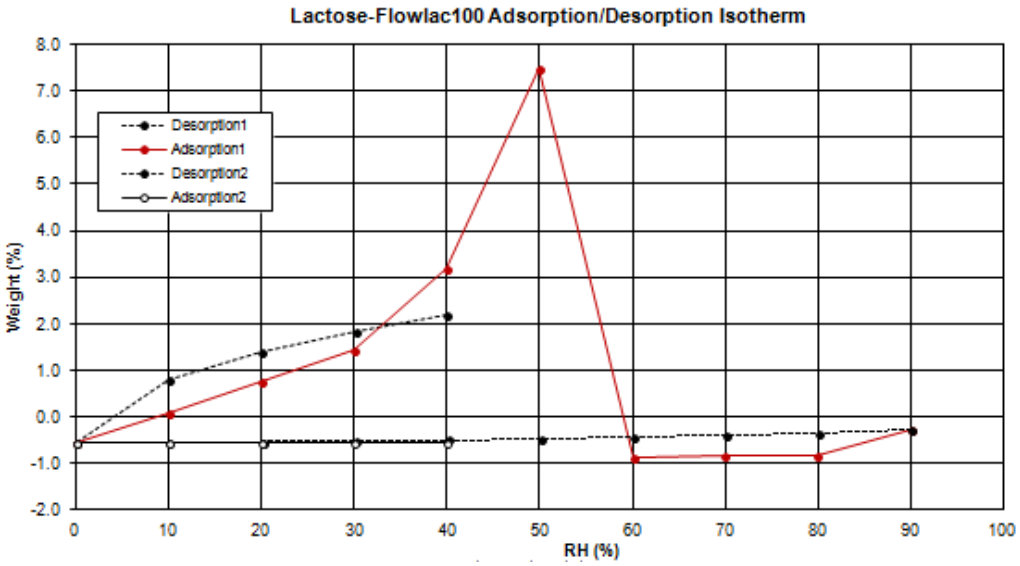


Figure 10. Flowlac 100 amorphous Adsorption/Desorption Isotherm

Microscopy: Polarized Light Images

Flowlac crystalline exhibited bifringence under polarization, whereas Flowlac amorphous did not. Images of other grades of lactose were captured for reference. Flowlac 90 (c) is the same material as Flowlac 100 but with a different particle size distribution. Flowlac 100 crystalline (b) is composed of large spherical particles, while Flowlac 100 amorphous (a) consist of very small spherical particles. Tablettose 80 (d) an agglomerated type of lactose and lactose impalpable (f) both exhibit irregular shaped particles. Different manufacturing processes create lactoses of very different morphologies, crystalline content and particle size distribution. This in turn affects their surface area, processability and compaction behavior.

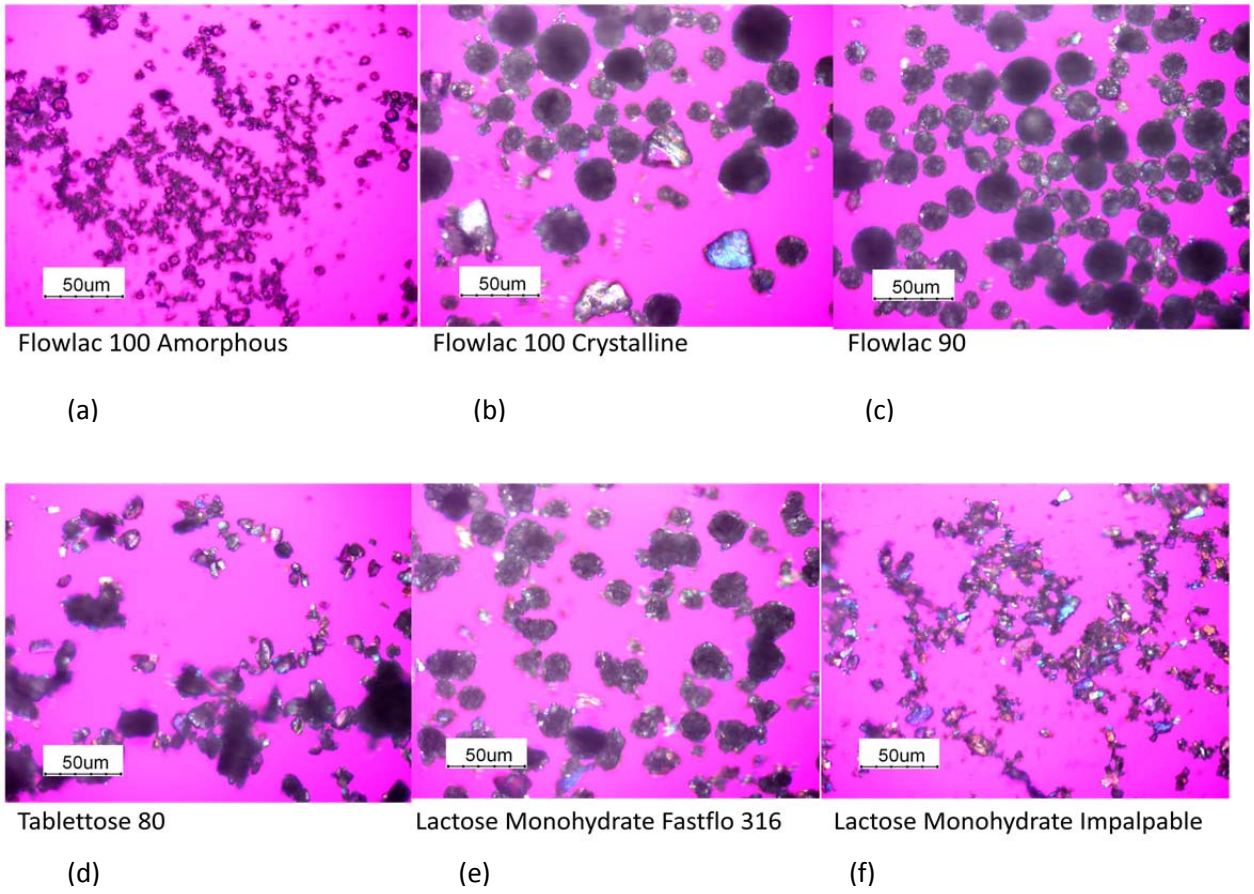


Figure 11. Types of Lactose under Polarized Light Microscopy

Microscopy: SEM

Scanning electron microscopy was utilized to evaluate the microscopic differences between Flowlac 100 crystalline, Flowlac amorphous and microcrystalline cellulose, Avicel PH102. SEM images illustrate that microcrystalline cellulose is made of irregular shaped particles containing a large surface area. Flowlac 100 crystalline is composed of round spherical particles with rough surfaces. In contrast, Flowlac 100 amorphous is composed of very small particles.

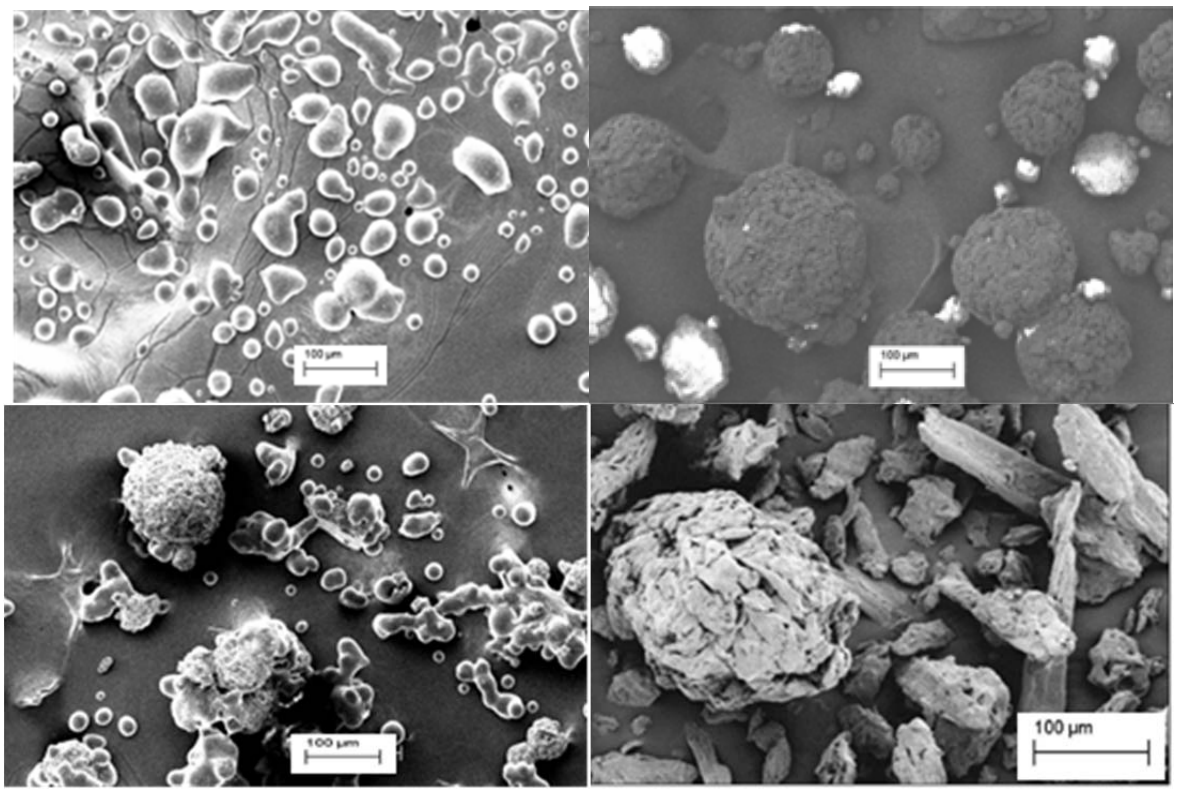


Figure 12. SEM Images. Above from left to right: amorphous Flowlac 100; crystalline Flowlac 100; Below from left to right: Mixture of amorphous and crystalline Flowlac 100; microcrystalline cellulose, Avicel PH102.

Bulk, Tapped and True Density, Particle Size, Surface Area and Flow Function

Table 3. Summary of Bulk, Tapped and True Density Results; Carr's Index, Hausner's Ratio, Particle Size (d10, d50, d90), FFc and Surface Area Values

	lactose monohydrate Flowlac 100 crystalline	lactose monohydrate Flowlac 100 amorphous	microcrystalline cellulose, Avicel PH102
Bulk Density (g/cm³)	0.60	0.60	0.37
Tapped Density(g/cm³)	0.73	0.82	0.49
Carr's Index	18 Fair	28 Poor	25 Passable
Hausner's Ratio	1.22 Fair	1.38 Poor	1.33 Passable
True Density(g/cm³)	1.5534 (±0.0013)	1.4560 (±0.0015)	1.5771 (±0.0021)
Particle size d10 (µm)	50.27 (±0.58)	8.61 (±0.10)	35.16 (±0.43)
Particle size d50 (µm)	126.16 (±1.79)	20.74 (±0.21)	113.54 (±0.05)
Particle size d90 (µm)	209.41 (±2.56)	60.25 (±1.14)	234.76 (±0.66)
FFc (@2kpa)	22.0 Free flowing	1.9 Very cohesive	6.5 Easy flowing
Surface Area (m²/g)	0.1840 *	0.2391 (± 0.0073)	

* (Raut et al., 2011)

With regards to bulk density, blends with bulk densities of ~0.6g/ml are generally regarded as directly compressible. Both types of lactose studied fall under this category. Tapped Density is a good indication of the way particles rearrange itself in a space. Large changes between bulk and a tapped density of a material is an indication of the materials compressibility. Amorphous lactose exhibits a greater difference between its bulk and tapped densities indicating better

compressibility compared to crystalline lactose. Bulk and Tapped densities were used to calculate the Carr's Index. Carr's measures compressibility and also gives an indication of flowability. The bulk and tapped density results illustrate that microcrystalline cellulose, Avicel PH102 show passable Carr's Index and Hausner's Ratio values. Flowlac crystalline shows fair values- which translates to fair flow and compressibility. In comparison, Flowlac amorphous have poor to very poor flow.

According to FFc Values at 2kPa Flowlac 100 crystalline is considered a free flowing material. Pure Avicel PH102 is considered easy flowing, while Flowlac 100 amorphous is considered a very cohesive poor flowing material. Flowlac 100 crystalline's excellent flow can be attributed to its larger particle size and spherical shape. The amorphous form exists as smaller particles that have an increase surface area with increased particle contact. Increased particle contact lends towards particle cohesion and poor flow, illustrated by a small FFc value of 1.9 (Table 3, Figure 13). The flowability ratings from Carr's Index (calculated from Bulk and Tap Density) and Hausner's Ratio displayed in Table 3 has a similar rank order.

Particle Size d50 follows the same trend as their FFc values (Table 3). Flowlac 100 crystalline with the largest d50 particle size, exhibits the best flow. On the other hand, Flowlac 100 amorphous with the smallest particle size d50, has the lowest FFc value indicating poor flow and a very cohesive material.

Amorphous lactose has a larger surface area compared to its crystalline counterpart. This is attributed to its smaller particle size as well as inherent properties of amorphous solid materials. Amorphous solids have decreased order and more degrees of freedom. It inherently contains

large amounts of free or void volume. Amorphous materials typically have more inter-particle contact areas wherein bond formation can occur and when compressed, can act as a 'binder'[16.17].

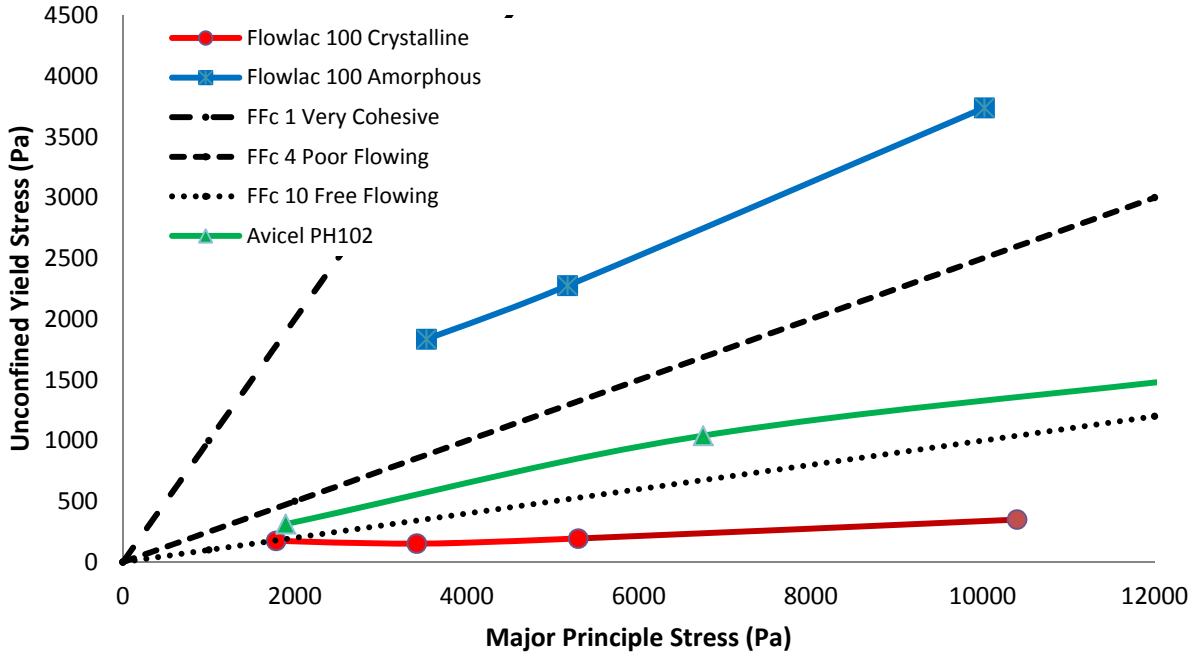


Figure 13. Shear Cell Flow Function Graph Results. A bulk powder with a value of FFc≥10 is considered a free flowing powder, while a material with an FFc value of ≤1 is considered non-flowing.

Table 4. Results from Powder Rheometer Measurements

	Flowlac 100 crystalline	Flowlac 100 amorphous	microcrystalline cellulose, Avicel PH102
BFE (mJ)	157	57.3	278
SI	1.05	0.828	1.38
SE (mJ/g)	3.74	60.1	5.22

The FT4 powder rheometer is capable of a variety of tests that measures a number of flow behavior measurements. Flowlac 100 amorphous has the lowest Basic Flowability Energy

(BFE) value indicating that it is the most cohesive material tested. This is likely due to its smaller particle size. Avicel PH102 has the highest BFE value which corresponds well to its characteristic as a free-flowing material.

Microcrystalline cellulose, Avicel PH102 has a Stability Index (SI) value of 1.38. The most likely mechanism to affect the stability of this material is moisture uptake as Avicel is known to pick up moisture. Avicel PH102 can also sometimes be very statically charged depending on conditions in the lab.

Specific Energy (SE) values indicated moderate cohesion for most powders. Flowlac 100 crystalline had an SE of 3.74 indicating low cohesion in the material. In comparision, amorphous material had a value of 60.1 indicating very high cohesion.

Compressibility Results

Figure 14 illustrates the compressibility test results from the powder Rheometer. Flowlac 100 amorphous exhibits a five-fold increase in compressibility compared to its crystalline counterpart at 15kPa applied normal stress. Percent change in compressibility of Flowlac amorphous increased with increased applied stress, while compressibility of Flowlac crystalline plateaued at higher stresses. This is can be attributed to smaller particle size, more efficient particle packing and arrangement; and the inherent mechanical characteristics of the amorphous material itself.

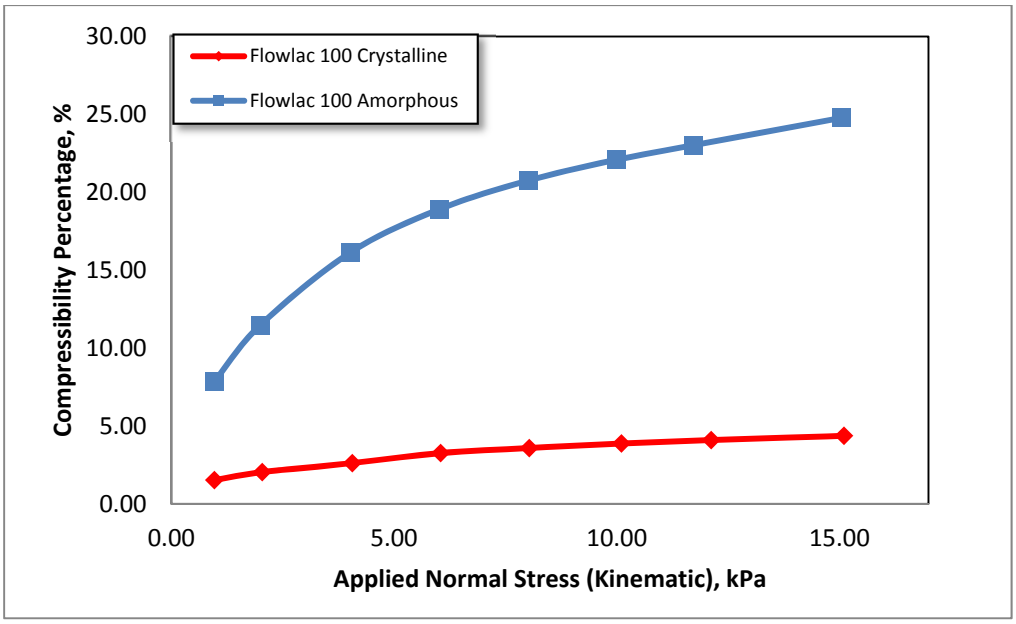


Figure 14. Compressibility of Blends. Shown as Change in Compressibility (%) with Increasing Applied Normal Stress (kPa). Flowlac 100 amorphous exhibits a five-fold increase in compressibility compared to its crystalline counterpart at 15kPa.

Permeability Results

Air permeability through a material was measured by recording the pressure drop across the powder bed under applied normal stress. Results indicate that a larger amount of air pressure is required to pass through the amorphous blend compared to others, indicating a material that is more cohesive. This corresponds to the results from the compressibility test, is attributed to the amorphous material's small particle size.

Placebo Roller Compaction Studies

During the initial RC emulation of Flowlac 100, material sticking to the die cavity wall was observed. Ribbons had defects on surfaces and corners; and increased ejection forces were displayed by the Presster. To alleviate this, a 5%w/w suspension of Magnesium stearate and Ethanol was swabbed onto the tooling surfaces and die cavity and allowed to dry before each

compression. Blends were hand filled into the die for each sample prep, carefully pouring material to ensure that the die was filled evenly, preventing air pockets and major void spaces that produce inconsistent ribbons to occur. Resulting ribbons had consistent dimensions and quality, measured compression forces and 3-point bend test break force values.

Texture Analyzer

Pure amorphous lactose ribbons showed larger average AUC values compared to crystalline ribbons (1.471kg.sec versus 1.041 kg.sec) when manufactured using the same ribbon compaction conditions. Area under the stress-strain curve is the strain energy per unit volume absorbed by the material. Conversely, the area under the unloading curve is the energy release by the material. The area under the curve can simply be explained as the quantity of energy a material can absorb without suffering damage. A ductile material will have a larger area under the curve as it can absorb more strain energy before 'breaking'. A brittle material will break more easily with increasing stress. As the induced strain increases, the material first deforms in the straining direction. As the strain increases further, the material breaks apart. A material with stronger bonds will exhibit greater strength and stiffness, and the material will require a much higher strain energy for breakage[30] . The test indicated that amorphous lactose is more ductile than crystalline lactose. In addition, it indicated that amorphous lactose ribbons have stronger bonds with a larger measured AUC.

Table 5. Texture Analyzer Area Under the Curve Results

Area (kg.sec) AUC	100% crystalline	100% amorphous
Average (SD)	1.041 (±0.025)	1.471 (±0.164)

Solid Fraction and Tensile Strength of Placebo Ribbons Manufactured Via Roller Compaction

The relationship between measured ribbon solid fraction and tensile strength is illustrated in Figure 15. Higher tensile strengths at a narrow range of SF can be achieved by amorphous lactose compared to crystalline lactose. At a SF value of 0.85, amorphous lactose achieves TS of around 4.5, compared to about 1.5 for crystalline. This indicates that at similar ribbon densities, amorphous lactose forms stronger compacts and overall better bonds.

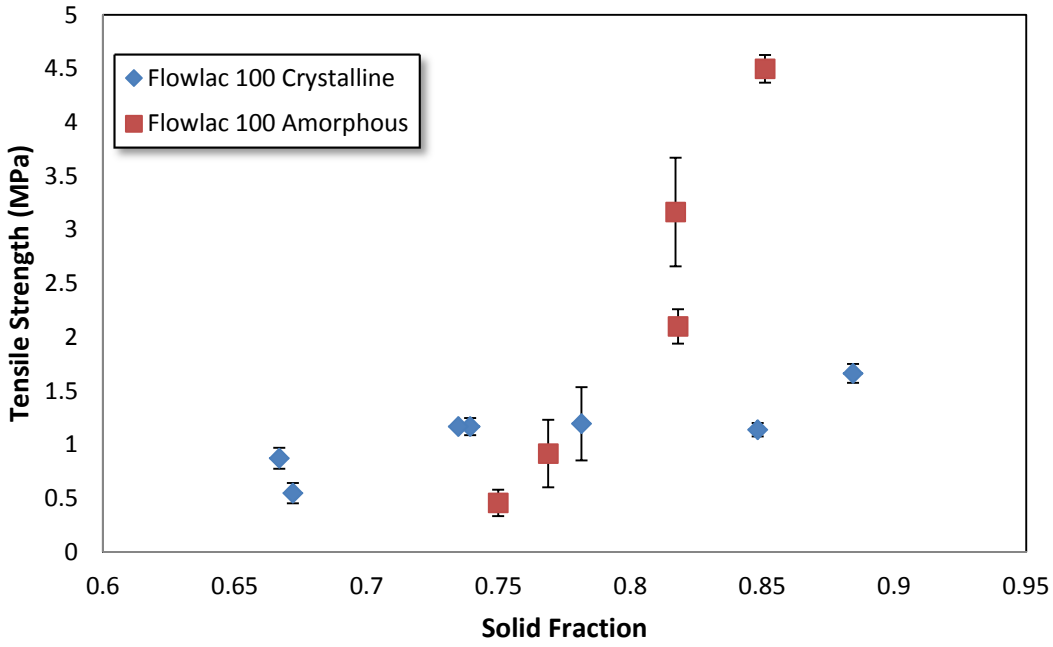


Figure 15. Tensile Strength and Solid Fraction of Flowlac 100 Crystalline and Flowlac 100 Amorphous Ribbons

Compression force is the force required to make the ribbon compact. Lower compression forces are preferred during ribbon and tablet manufacture because it means that lower pressures are required to manufacture them, and that less energy is imparted onto the system. Compression forces required to successfully manufacture good ribbons and tablets differ for each material and

depend on the materials innate physicochemical properties. SF is also affected by the nature of the materials and the unit operation parameters used to process them.

An indicator of the bond strength of a material is its tensile strength. In Figure 16, for compression values greater than 20kN, higher TS values were achieved byFlowlac100 amorphous ribbons. As compression force is increased, tensile strengths of the ribbons increase proportionally compared to crystalline lactose. This indicates that the amorphous material has superior compactibility because stronger bonds were formed using lower forces.

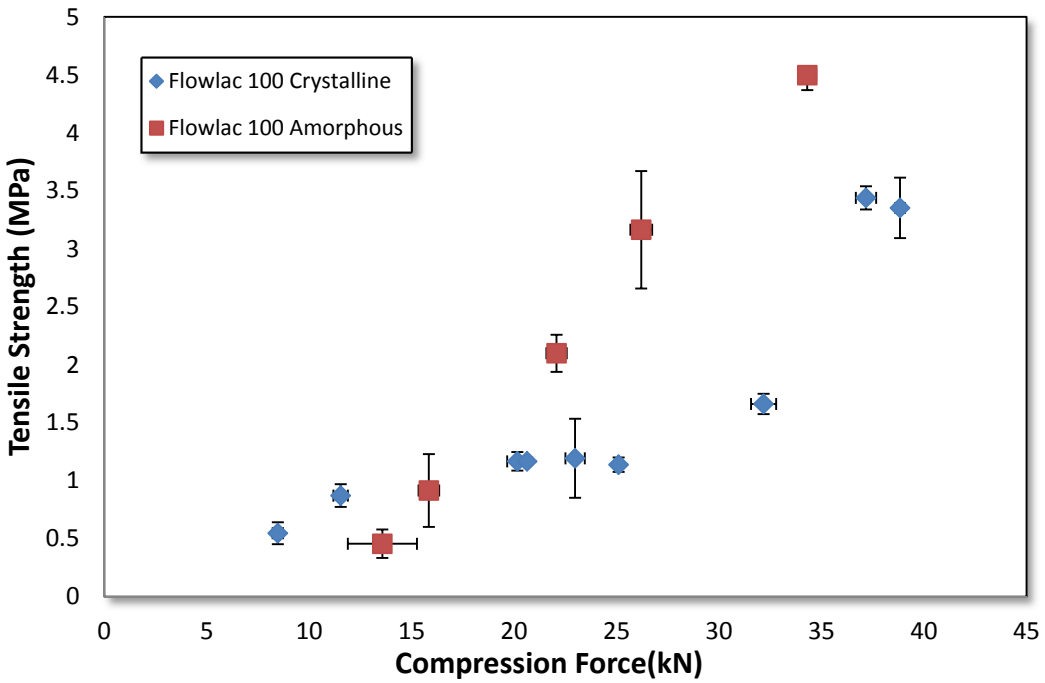


Figure 16. Ribbon Tensile Strength (MPa) vs. Upper Compression Force (kN)

Mixtures of crystalline and amorphous lactose with microcrystalline cellulose, Avicel PH102 show improved compactability compared to pure amorphous or crystalline lactose; with ribbon tensile strengths reaching the desired 1.2- 2.0 Mpa target values at lower compression forces

(Figure 17). This is expected because microcrystalline cellulose is a very compressible material, more ductile and undergoes plastic deformation. Binary formulations containing Flowlac amorphous and Avicel show a compactibility profile behaving more similar to pure Avicel compacts.

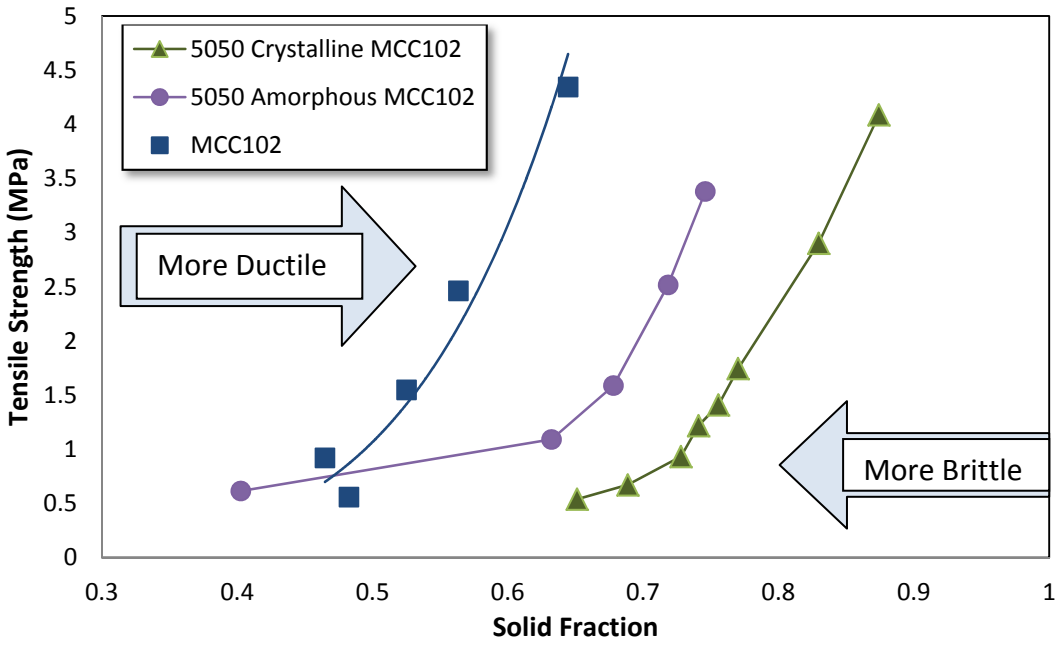


Figure 17. Ribbon Tensile Strength (MPa) vs. Ribbon Solid Fraction. Microcrystalline cellulose (MCC) is a ductile material, whereas lactose more brittle.

It may be that amorphous lactose has a higher bonding capacity over a unit area. When Sebhatu and Alderborn (1999) measured the effective contact area of amorphous spray dried lactose, it correlated reasonably well with the measured tablet strength. Tensile strength is mainly controlled by the degree to which the particles are deformed during compression. The contact process between adjacent particles is affected by the way particles fragment and form bonds. Particle deformation induces fragmentation, and these fragmentation events create contact sites to which more bonding can occur. In general, larger particles result in reduced tablet strengths at a given effective contact area compared to smaller particles. The steeper slope of amorphous

lactose (Figure 16) compared to crystalline lactose suggests that amorphous lactose forms form stronger interparticulate bonds than crystalline lactose. These strong interparticulate bonds are likely due to its smaller particle size, which offer more effective contact areas, and a smoother surface for a higher deformability. In a 1999 paper, Sebhantu and Alderborn concludes that "The tensile strength of lactose tablets is controlled mainly by the degree of deformation of the particles, rather than their degree of fragmentation which occurs during compaction, and that the different compactabilities of amorphous and crystalline lactose are to some degree due to differences in particle deformability but also to differences in interparticulate bonding capacity"[1].

25%Drug Load Model Drug Roller Compaction Simulation Studies

Roller Compaction Emulator "The Presster" Results: Ribbon Solid Fraction and Tensile Strength: Compactibility / Tablettability

When crystalline lactose and amorphous lactose ribbons were prepared at the same TS target of approximately 1.2Mpa and then compacted into tablets, crystalline lactose exhibited better Tablettability compared to its amorphous counterpart (Figure 19). This was counterintuitive to the hypothesis that amorphous lactose being more compressible than its 'brittle' crystalline form. An observation during ribbon compaction was that when manufactured to the same TS conditions, amorphous lactose ribbons were visually denser, harder and almost 'plastic' like in appearance compared to crystalline lactose. Previous texture analyzer test results on pure material ribbons showed greater AUC values for amorphous lactose indicating that these ribbons had higher bond strength. It was postulated that although amorphous lactose showed better ribbon compactibility compared to crystalline lactose at the same compression forces, granules manufactured from the same TS ribbons exhibited poorer tablettability due to loss of re-compactibility. With the amorphous formulation, more bonding sites were formed during the

first densification step resulting in less available surface for bond formation to occur during the tableting step. The amorphous ribbons may have been over-compacted. Previous compaction studies on tablets have shown that formulations containing amorphous lactose are more compactible than crystalline counterparts. In roller compaction, materials experience compaction in two steps, the roller compaction and the tablet compaction step. Since amorphous lactose is inherently more compressible and compactable than crystalline lactose, amorphous lactose ribbons can be compacted at with lower forces, lower TS and still achieve acceptable Tablettability (Figure19).

Twenty five percent drug load paracetamol formulations manufactured with amorphous lactose were further investigated. Ribbons were manufactured to three different ribbon tensile strength targets: 0.25Mpa, 0.5Mpa and 1.2Mpa. Ribbons were subsequently milled and compacted under the same conditions. Amorphous lactose ribbons manufactured with lower tensile strength values- producing 'softer ribbons', resulted in granules that kept their re-compressibility (Figure 18). A larger reduction in tablet volume is observed with increasing compression force when 'softer ribbons' are manufactured. This also corresponds to increased tensile strength in tablets.

In Figure 19, stronger amorphous tablets- illustrated by higher TS values can be obtained with ribbons manufactured at 0.5TS. Amorphous tablets manufactured from 'softer' 0.5TS ribbons produced compacts/tablets with better compressibility and improved tablettability over ribbons manufactured at 1.2TS. Between 200-250MPa, Tablets manufactured from 0.5TS ribbons produced tablets that had 50% higher TS values. Crystalline lactose failed to make acceptable ribbons at 0.5TS, and required at least 1.2TS to form adequate ribbons for further processing. Amorphous lactose tablets manufactured from 0.5TS ribbons displayed higher TS values

compared to crystalline lactose tablets (Figure 19). This indicates that the amorphous lactose formulation showed better tablettability over its crystalline counterpart when ribbons were appropriately processed. Although similar tablettability profiles can be achieved with both types of lactoses, it can be argued that amorphous lactose compacts have better overall bonding as illustrated by friability results.

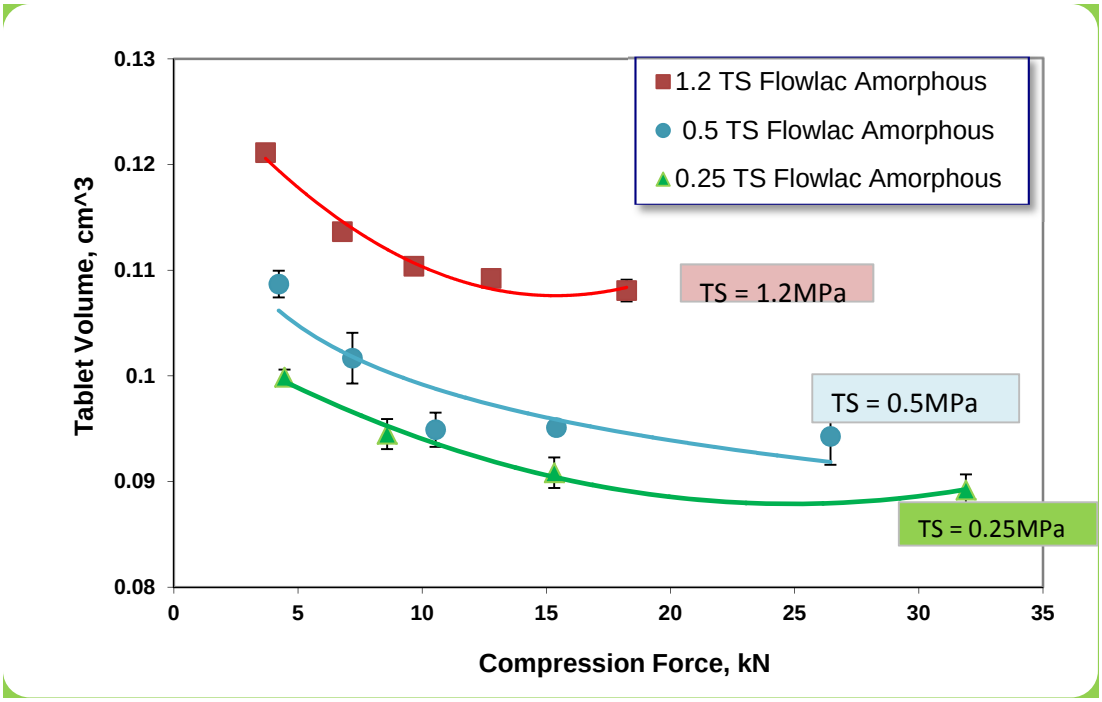


Figure 18. Compressibility Profile of 25%DL Paracetamol with Amorphous Lactose Tablets Manufactured from Ribbons of Varying Tensile Strengths

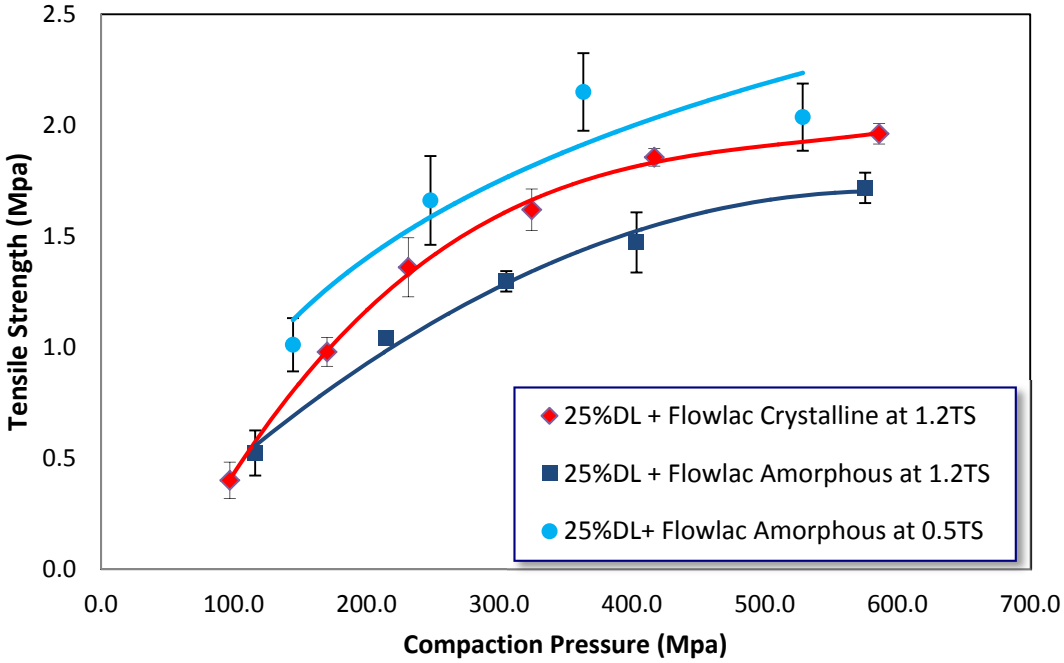


Figure 19. Tablettability Profile of 25%DL Paracetamol and Amorphous Lactose Tablets Manufactured from Ribbons of Varying Tensile Strengths

Friability

Friability test indicates that although tensile strength of Flowlac 100 crystalline tablets seemed comparable to Flowlac 100 amorphous with increased compaction pressure, (when both ribbons manufactured at 1.2MPa TS targets, Figure 20) friability of Flowlac crystalline tablets were poor. Tablets crumbled on the edges, considered to be the weakest parts of the tablet, and failed the friability test (1.80%). Flowlac amorphous tablets manufactured at both 0.5 and 1.2TS retained low friability (0.83% and 0.82% respectively), produced tablets with stronger bonds overall and acceptable physical appearance.

Figure 20. Friability Results. As per USP, tablets pass the friability test when percent weight loss is below 1%. Crystalline tablets had higher percent weight loss in contrast to amorphous tablets.

(A) Flowlac crystalline (B) Flowlac amorphous (C) Flowlac amorphous

25%DL Tablets @ 1.5TS	**Flowlac 100 crystalline**	**Flowlac 100 amorphous**	**Flowlac 100 amorphous**
Image	A	B	C
Ribbon TS (MPa)	1.2	1.2	0.5
Friability (%)	1.80	0.82	0.83

CONCLUSION

This study investigated the fundamental differences in physical characteristics and mechanical properties of crystalline and amorphous lactose. Differences in mechanical properties of tablets manufactured by roller compaction were also evaluated. Crystalline and amorphous lactose possess very different material characteristics. Amorphous lactose exists as smaller particles that offer better compressibility, while crystalline lactose offer processing advantages such as better flow.

The strength of a compact, albeit a ribbon compact or compressed tablet depends on a number of factors. The most important are particle size and compression force. Particle size is an inherent material property that is related to its surface area. Larger particles have smaller surface areas, while smaller particles have larger surface areas- areas wherein potential bonds can form. In addition, materials with smaller particle size distributions tend to be more compressible than those with larger particle distributions. Compression behavior of a material is dictated by the inherent properties of the material itself- whether a material is more ductile or brittle. This will determine a materials bonding properties which can be measured by compactibility and tablettability experiments.

Amorphous lactose offers better compressibility than its crystalline counterpart. This can be attributed to its small particle size, large surface area and bonding properties. Inherent properties of amorphous materials itself, disordered with higher degrees of freedom and containing large amounts of free volume (void volume) allow it to be more compressible. Amorphous lactose ribbons manufactured via roller compaction process exhibited better compactibility than crystalline lactose. Higher tensile strengths and bond strengths can be achieved at lower compression forces. Amorphous lactose formed stronger interparticulate bonds because of its small particle size which offer more effective contact areas, a smoother surface, and higher deformability because of its ductile property.

In the feasibility study, crystalline and amorphous lactose formulations with a poorly compressible model drug at 25% DL were successfully manufactured via a roller compaction emulator. Although the tablettability profiles of both lactose formulations were relatively

similar, friability results indicated that amorphous lactose formulations produced tablets with better bonds within the compact, as illustrated by its improved friability.

Results from this research suggests that using lactose with a high concentration of amorphous content offers advantages over its crystalline counterpart, such as increased ribbon tensile strength under lower compression forcesand higher tensile strengths at similar solid fractions. Amorphous lactose exhibit properties that make it more amenable to a roller compaction process, however, careful consideration must be taken to ensure that the amorphous ribbons and granules does not lose its re-compressibility before tablet compression. A mixture of both crystalline and amorphous lactose would offer the best of both worlds. Physical attributes of a material can have a great impact on the quality attributes of a product. A deep understanding of the physical characteristics of lactose and how the material behaves as the brittle component of a formulation is key to the development of tablets with proper physical attributes.

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APPENDIX

Principles of Roller Compaction

Dry granulation (DG) via roller compaction (RC) is a pharmaceutical manufacturing process whereby particles are consolidated by exerting a mechanical pressure on two compacting rolls to produce a densified sheet or 'ribbon' of product. The resulting ribbon is then milled to form granules of a particular particle size distribution, which can be filled into capsules or compressed into tablets.

Dry granulation via roller compaction provides a major advantage over wet granulation because no water or organic solvent addition is required, and therefore a preferred method for manufacturing moisture sensitive drugs. This process is commonly used to increase material density and to improve flow without the application of heat and is the preferred manufacturing process for heat sensitive drugs. This is a useful, environmentally friendly process requiring less material, energy, processing steps and equipment footprint. It also offers a simpler manufacturing procedure, provides a readily scaleable process with a higher production throughput . It is an efficient technique employed to increase material density, creating granules with good powder-flow and material characteristics.

Roller Compactors of various sizes and models are available in the industry. A bench top roller compactor, for example, a Vector TF Micro can be utilized for early feasibility studies and have a throughput of a few kilograms per hour. A pilot/manufacturing scale roller compactor such as a Gerteis Minipactor (Figure 1) on the other hand have a throughput up to 100kg/hr, and production scale roller compactors 400kg/hr.

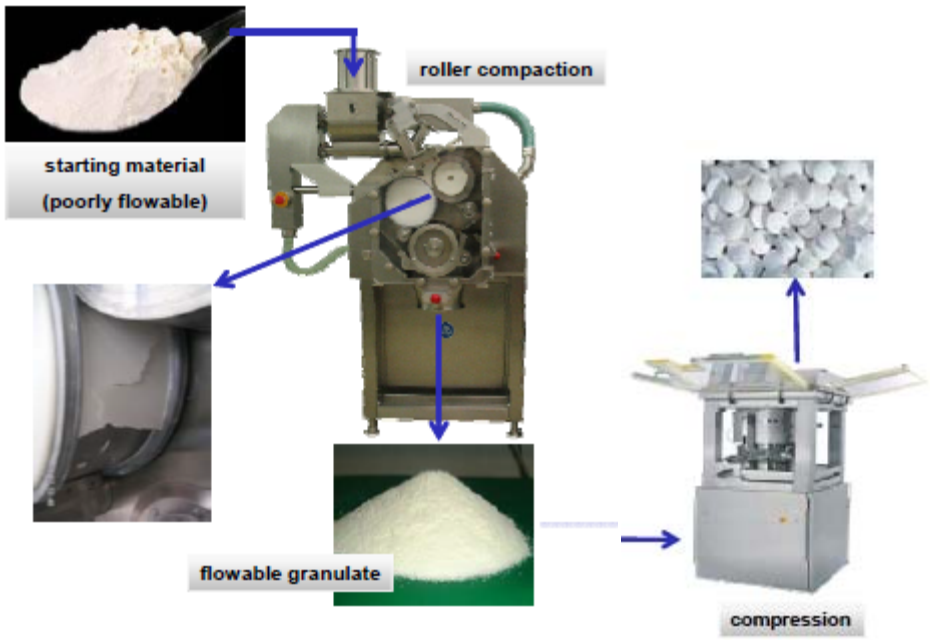


Figure 1.Gerteis MiniPactor Roller Compactor. Fine powder is forced through two counter rotating rolls. As the volume decreases through the region of maximum pressure, the material is densified and formed into a solid compact or 'ribbon'. The compact is then milled into a particular particle size distribution. The blend is lubricated to create a final blend. The final blend can be filled into capsules or compressed into tablets.

Powder is compressed into ribbons and then milled into granules

In summary, The pharmaceutical industryemploys roller compaction for several reasons:

- To improve flow of materials by densifying the material and producing blends with a particular particle size range
- Ensures final blend uniformity though controlling particle density and size

- Reduce dust and handling risks
- Scalable process
- Cost reduction
- Decrease waste and product loss during processing
- More environmentally friendly process requiring less material, energy, processing steps, footprint, and does not require solvent use.

Key critical parameters in roller compaction are: Screw speed and configuration, Roll Force (kN), Roll Gap (mm), Roll Speed (rpm), Roll Diameter , Roll Surface and the type of Mill. Roll Force is the most important parameter in roller compaction. This is the force the rolls are imparting on materials. Roll force and roll gap are inter-related- to maintain a particular force a certain roll gap must be maintained. These two parameters are material dependent and are set in order to reach key ribbon attribute targets of tensile strength and solid fraction.

Simulating Roller Compaction: Roller Compaction Emulator

The roller compaction portion of this research will be performed using Metropolitan Computing Corporation's (MCC) The Presster. The Presster is a linear tablet press emulator that has been modified to run simulations of various roller compactors. In this study, the roller compactor emulation was based on the Gerteis Minipactor. Surrogate ribbons were manufactured using rectangular D-tooling.

The Presster enables a prediction of 'ideal' ribbons by simulating critical parameters such as roll force, roll pressure, roll speed, and roll radius- allowing a representative measurement of its effects on ribbon properties using only a small fraction of material. This technique can be seen

as a material sparing alternative at bench top scale. It cannot however emulate certain roller compaction aspects such as non-homogenous ribbon density, the powder feeding mechanism, and other shear forces the powder experiences as it travels through a conventional roller compactor.

In a study by Zinchuk and Mullarney using an equivalent RC emulator, the mechanical and physical properties of real ribbons were found to be equivalent when normal variations in the solid fraction and tensile strength determinations are considered. When compacted to the same SF, the simulated ribbons were found to exhibit similar compression behavior and equivalent mechanical properties (tensile strength) as those manufactured using a roller compactor. The simulation can be used for process specific predictive and scale up studies and requires only a fraction of material to conduct roller compaction feasibility studies compared to conventional roller compaction equipment. The simulation enables more relevant feasibility studies by addressing the effects of roller compaction specific process variables such as roll pressure, speed and size on ribbon properties. (Zinchuk)

Ribbon solid fraction (SF) and tensile strength (TS) were evaluated as key ribbon properties. For ribbons, material densification is a function of multiple factors: powder properties such as flow, bulk and tapped density, processing parameters such as roll pressure and speed, as well as instrument geometry factors such as roll and feed screw size (Zinchuk). Tensile strength and solid fraction will be considered the primary indicators of ribbon behavior during roller compaction processing.

Table 1. Compressibility Index, Hausner's Ratio and Flow Characterization Guide

Compressibility Index (%)	Flow Character	Hausner Ratio
<10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

Flow Functions using Ring Shear Tester

Flow was measured using a Ring Shear tester. In a shear cell measurement, the unconfined yield stress (FC, σ_c) is the maximum stress on a powder plane. It is the stress causing the failure. This value measures the compressive strength of a bulk solid. The Major Principle Stress (SIGMA1, σ_1) is the consolidation stress- the stress imparted onto the bulk powder. The FFc value is the ratio of the consolidation stress to the unconfined yield strength.

$$\mathbf{FFc} = \boldsymbol{\sigma_1 / \sigma_c} \qquad \text{(eqn1)}$$

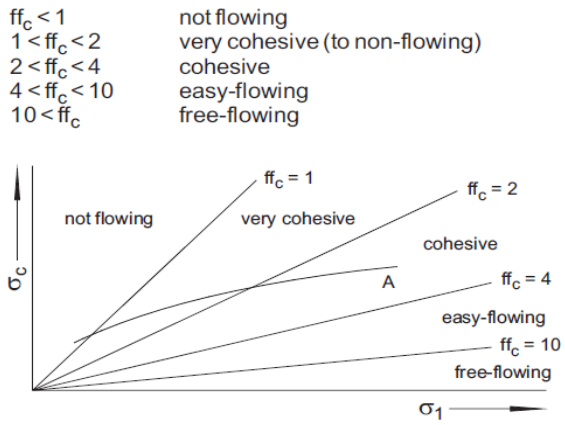


Figure 2. The standard classification of powder flowability measured as Flow Functions (FFc) is as follows. A bulk powder with a value of FFc=10 is considered a free flowing powder, while a material with an FFc value of <1 is considered non-flowing.

Powder Flow Behavior from Powder Flow Rheometer

FT4 Powder Rheometer is another instrument that measures the bulk, flowability and processability characteristics of powders. Powder Rheometers can provide fast, repeatable, sensitive measurements. This instrument measures the bulk powder's response to aeration, consolidation, flow rate; and measures bulk properties of density, compressibility and permeability. The dynamic testing methods use a 48mm diameter blade and a 25mm split vessel. All samples for each test are first pre-conditioned using the instruments set conditioning methodology. The conditioning blade action gently disturbs the powder bed and creates a uniform, lightly packed test that is reproducible and free of operation sampling and preparation errors. (Freeman Technology)

Using the Freeman Technology FT4 Powder Flow Rheometer the following tests were performed:

Stability and Variable Flow Rate (REP+VFR) - Measures Basic Flowability Energy(BFE), Stability Index (SI) and Specific Energy(SE) as flowability parameters.

BFE is the energy required to establish a particular flow pattern in a conditioned, precise volume of powder. It is calculated from the work done in moving the blade through the powder from the top of the vessel to the bottom. BFE can be dependent on many physical and environmental properties such as size and distribution, shape, moisture content, texture, cohesivity, porosity, density, surface additives, electrostatic charge etc. and is used to measure effects of flow additives, moisture content, attrition/segregation, physical properties and electro static charging. Cohesive powders have low BFE values, while powders that flow freely under gravity have high BFE as maximum flow energy is demanded by non-cohesive powders which should have lower shear strength.[8]

Basic Flowability Energy (BFE) = Value in Energy Test 7 (mJ)

Small changes of $0.9 < SI < 1.1$ are normal values for most powders. A robust material should have an SI value of ~1 and would not be greatly affected by external pressures that make it flow. $SI > 1$ indicates that the powder is affected by a number of reasons, including de-aeration, agglomeration, segregation, moisture uptake or electrostatic charge. SI values < 1 means that the powders stability is being affected by attrition, de-agglomeration or over blending of an additive. **Stability Index, SI = Energy Test 7/ Energy Test1**

Specific Energy is a dynamic measurement that measures how powder will flow in an unconfined or low stress environment. It is calculated from the work done in moving the test blade through the powder bed from the bottom to top of the vessel, and normalized against mass.

It mostly relates to cohesion and particle size, shape and texture. It is particularly useful in correlating flow performance of a powder in gravimetric feeding, die filling.[8]

Specific Energy, SE (mJ/g) = [(Up Energy Cycle 6 + Up Energy Cycle 7) / 2] / Split Mass

As a rule, the higher the SE the more cohesive the powder. Freeman technology uses a rough guide:

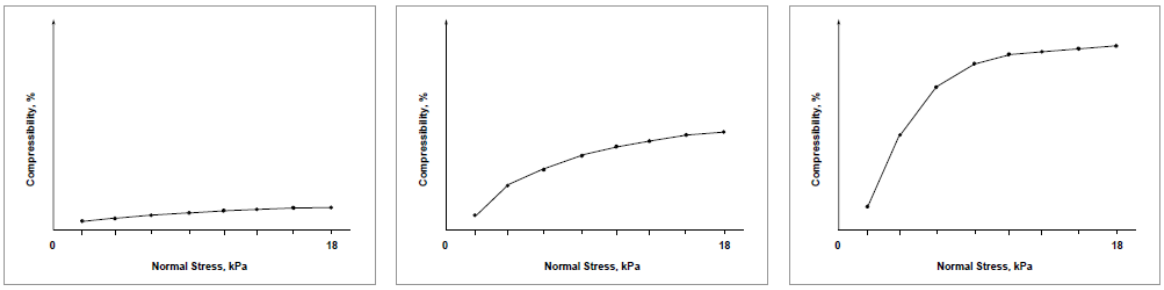
SE < 5 = Low Cohesion

5 < SE < 10 = Moderate Cohesion

SE > 10 = High Cohesion

Compressibility Test - Compressibility is determined by how density changed as a function of applied normal stress. This factor is important for transportation, and most importantly for processing i.e. Direct compression, roller compaction and screw feeding. A cohesive powder will have a higher compressibility index. The instrument measures compressibility as the percentage change in volume after compression (%).[8]

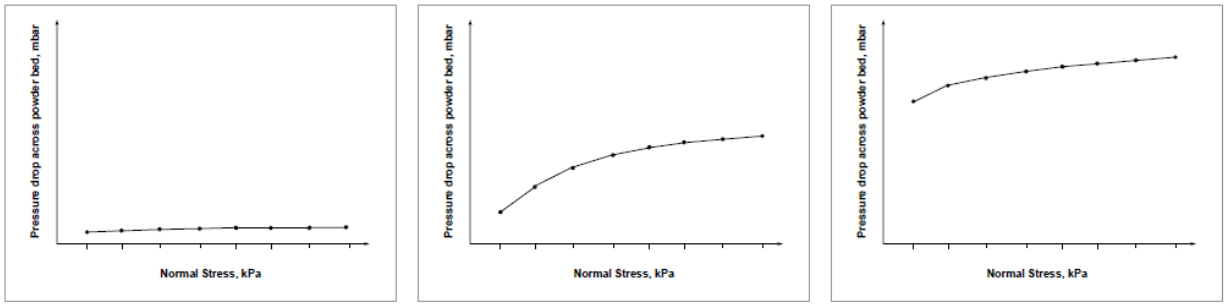
Compressibility Index = Density after Compression / Conditioned Bulk Density



Low compressibility	Moderate compressibility	High compressibility
Little change in volume even at high normal stress. Minimal excess air in bulk and efficient particle packing. Usually non-cohesive, large particle size or granular materials.	Average sensitivity to compression. Likely to have some cohesive properties. Typical of most powders.	High sensitivity to compression. Large amounts of entrained air. Likely to be very cohesive powder with small particle size.

Figure 3. Typical Compressibility Test Results (Freeman)[8]

Permeability Test- The test is represented as a pressure drop across the powder bed versus the normal stress for a constant air velocity. The greater the pressure drop, the less permeable the sample. It is affected by porosity as well as particle properties like shape and texture. This is an important aspect of powder behavior especially during hopper flow, direct compression, pneumatic transfer and aerosolisation. Pressure drop through powder bed was measured at a constant 2mm/s air velocity as a function of applied normal stress.



High permeability	Moderate permeability	Low permeability
Minimal pressure drop across powder bed. Compression has little or no affect on the permeability. Usually non-cohesive, large particle size or granular materials.	Pressure drop increases with increased compression, suggestion porosity is reducing. Available channels for air to pass are reducing in size and number. Typical of powders with some cohesion and/or a wide particle size distribution.	High pressure required to establish air flow through powder. Either very small or limited number of channels between particles. Irregular particle shape could also contribute to permeability. Likely to be very cohesive powder with small particle size.

Figure 4. Typical Test Results for Permeability Test (Freeman Technology)[8]