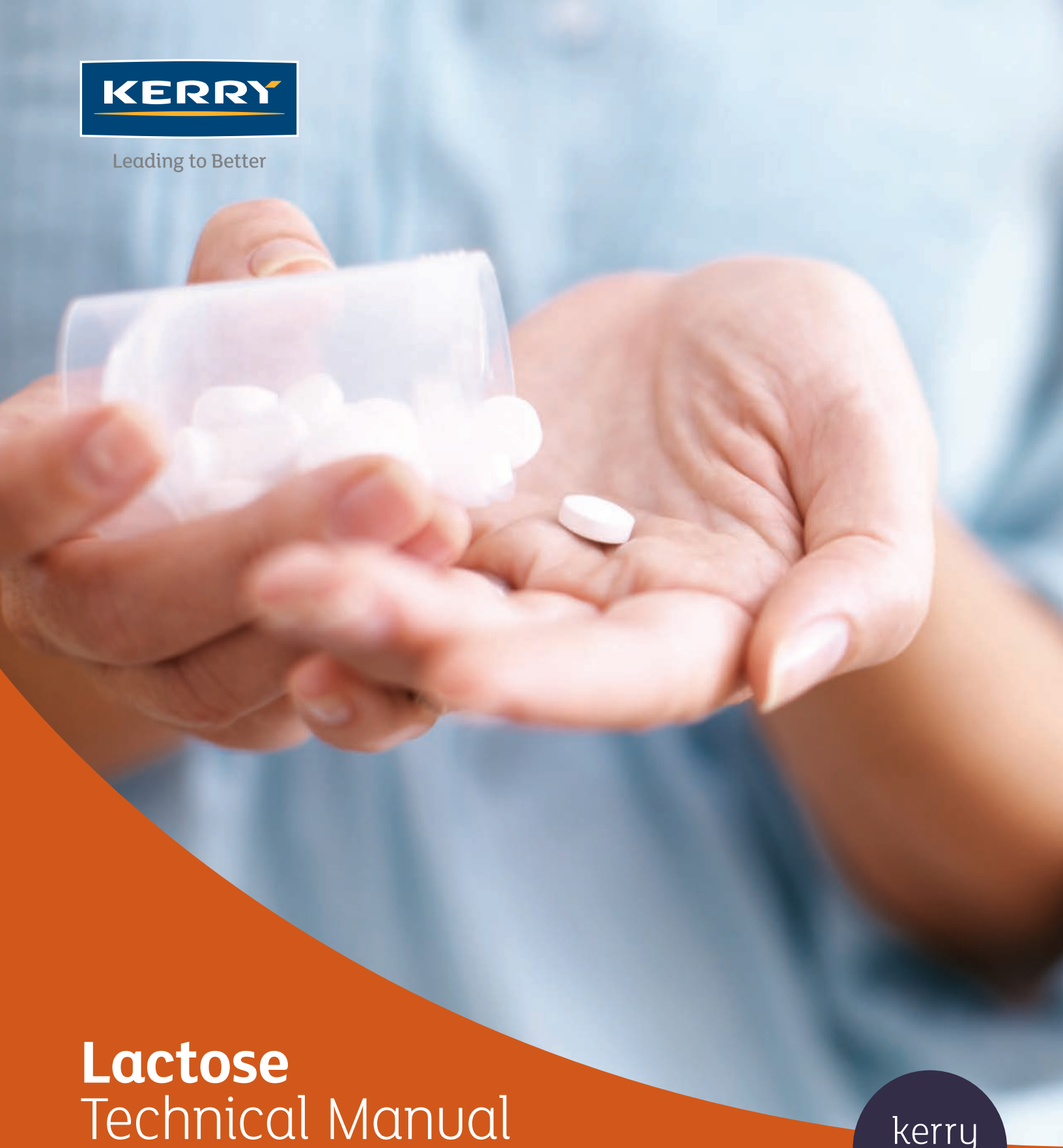
KERRY

Leading to Better



Lactose
Technical Manual

Excipients for direct tabletting, granulation, capsules, sachet filling and inhalation

kerry.com


KERRX
SHEFFIELD

Content

Kerry Pharmaceutical Grade Lactose

Crystalline Monohydrate	Spray Dried Monohydrate	Anhydrous Lactose		Inhalation Lactose	
Sheffield™ Capsulating Grade	Foremost® 315	Sheffield™ DT	Sheffield™ DTHV	Aero Flo™ 65, Monohydrate	Aero Flo™ 85S, Anhydrous
Sheffield™ 80M	Foremost® 316 Fast Flo®	Sheffield™ 60M		Aero Flo™ 55, Monohydrate	
Sheffield™ 200 Mesh		Sheffield™ Impalpable		Aero Flo™ 35, Monohydrate	
Sheffield™ Impalpable				Aero Flo™ 25, Anhydrous	
Foremost® 310					
Foremost® 312					
Foremost® 313					

The Standard of Comparison

For more than 75 years, we have earned our reputation for reliability and excellence in serving the biotech, pharmaceutical and nutrition markets by delivering unsurpassed product value, enhanced opportunities for supply chain consolidation, and new technology innovation. We bring together our superior products with new innovative solutions and market-driving alternatives to help our customers succeed in today's challenging global marketplace.

Customers benefit from our application expertise and vast global resources of a $6 billion global leader. We have the worldwide resources and global technical platform to deliver consistent, high quality products backed by unparalleled service, technical support and formulation customization capabilities.

At Kerry, we make it our business to exceed our customers' expectations every day. We collaborate directly with pharmaceutical formulators in the development of new drugs and delivery systems.

We deliver the Industry's most extensive Lactose product line in the Industry, including anhydrous, spray dried, monohydrate, and inhalation grades of lactose. The Sheffield™ Brand N.F. Anhydrous Direct Tableting (DT) lactose has been recognized since its original patent as the standard of comparison for anhydrous direct compression lactose excipients in the industry. This combined with Foremost Farms and Fast Flo® pharmaceutical-grade lactose product line, helps us provide customers with unsurpassed product value, greater opportunities for supply chain consolidation, and new technology innovation.

We are the leading lactose provider in the world. We prove it every day. Let us prove it to you.

Product Description

Lactose Overview

Lactose is a disaccharide of glucose and galactose obtained from the whey fraction of bovine milk. Depending on the temperatures used to crystallize and dry the lactose solution, it may be produced in either of two crystalline types: monohydrate or anhydrous.

In addition, the lactose disaccharide also has the ability to form two stable isomers known as alpha-lactose and beta-lactose. These two isomers differ in the orientation of the hydroxyl group in the glucose moiety. The monohydrate crystal in primarily the alpha-form, whereas the anhydrous crystal is primarily the beta-form (Zadow, 1984). At equilibrium in water at room temperature, both forms will be present as 62.3% beta-form and 37.7% alpha-form (Whittier, 1944).

Manufacturing Facilities

- FDA inspected facilities that adhere to the USP-NF general chapter 1078 and the IPEC-PQG GMP guidelines
- IPEC Member
- Qualified Contingency Plan
- Validated Processes - complete traceability
- Kosher & Halal certified
- Certified Animal Rennet-free raw materials
- Batch to Batch Consistency
- HEPA Filtered Pack Room & Conveying Air
- Monohydrate and Anhydrous Lines
- Milling and Sieving Capabilities

Pharmaceutical Excipients

Lactose clearly meets the criteria for an ideal excipient. It is chemically and physically inert to other excipients and active ingredients. Widely available worldwide, lactose is well characterized, easy to store, cost-effective and has low lot-to-lot variability (Bolhius and Lerk, 1973; Brittain, 1993). It is also suitable for both wet granulation and direct compression methods of tablet production. Typically, the crystalline grades are used in wet granulation and the spray dried forms are used in direct compression.

Lactose has been used in pharmaceutical preparations since the early 1900s and it is one of the most widely used excipients for capsule and tablet formulations (Shangraw, 1981 and 1993). Large-scale production of lactose in the United States commenced in the 1940s in part as a feedstock for antibiotic fermentation (Weisberg, 1954). In the 1950s, USP grade lactose became available for wet granulation methods of tablet production. Soon after, the direct compression method was developed in the mid-1960s, and the original Anhydrous Direct tableting (DT) Lactose was patented by Sheffield™ Products. The long history of manufacturing Sheffield™ Anhydrous DT products in a registered drug establishment assures our customers of consistent quality and functionality, as well as exceptional purity and corresponding low color.

In the direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. This eliminates the drying steps associated with the wet granulation method. It also reduces the higher costs involved in wet granulation including increased equipment, labor, time, process validation and energy expenditure.

As a result, direct compression is both efficient and economical, well suited to the production of high quality tablets, which exhibit hardness, low friability and excellent dissolution rates. As an added benefit, direct compression can improve the physical and chemical stability of tablets as compared to wet granulation (Bolhius and Lerk, 1973).

Lactose monohydrate is typically used for wet or dry granulation. During wet granulation, liquid binders or adhesives are added to the lactose and active mixture, usually by blending. The mixture is then dried and sized, and compressed into tablets. During dry granulation, the particle size is enhanced by aggregating the particles by roller compaction and then milling to the desired size.

Lactose has many desirable characteristics for use as a pharmaceutical excipient. It is both chemically and physically stable, and highly compatible with other excipients and ingredients. In addition, it is an all-natural product, which is available in a variety of physical forms (Whiteman and Yarwood, 1988). Lactose is especially noted for its low hygroscopicity (Shukla and Price, 1991).

Crystalline Monohydrate

Advantages

- Inert material, high purity, low color
- Moisture stable – 4 year shelf life
- Physically and chemically stable
- Several off-the-shelf grades and custom capabilities
- Milling & Sieving Capabilities (high flow grades available)
- Control of raw material – no supply issues
- High degree of crystallinity, low amorphous content

Products & Recommended Applications

Product	Application
Foremost® Brand Monohydrate 310	Wet or dry granulation (coarse)
Sheffield™ Brand Monohydrate Capsulating Grade	Wet or dry granulation (medium)
Foremost® Brand Monohydrate 312	
Sheffield™ Brand Monohydrate 80M	Wet or dry granulation (medium/fine)
Sheffield™ Brand 200 Mesh	
Sheffield™ Brand Monohydrate Impalpable	Wet or dry granulation (fine)
Foremost® Brand Monohydrate 313	

General Physical and Chemical Characteristics

Product Description

Monohydrate Lactose is a disaccharide obtained from the whey fraction of milk, and consists of one glucose and one galactose moiety. Sheffield™ Brand Monohydrate Lactose, N.F. and Foremost® Brand Monohydrate Lactose, N.F. are crystalline alpha-monohydrate anomers. Both brands meet all requirements of the National Formulary as well as the European and Japanese Pharmacopeias.

Other Physical Characteristics

Free-flowing, non-hygroscopic powder. White to creamy white in color, free of sediment and with excellent stability. A 10% solution (in boiling water) is clear to nearly colorless. Soluble in water at 25°C (77°F) is 20g/100ml.

Packaging and Storage

Store in cool, dry area with container closed when not in use. A minimum shelf life of 48 months is expected for unopened packages.

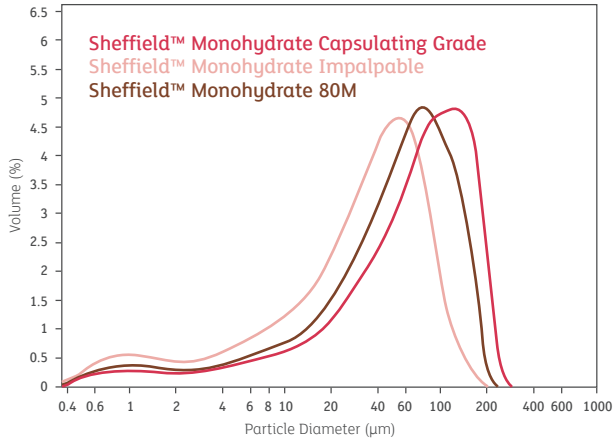
The standard packaging is a polyethylene lined fiber drum with tamper evident seals. The standard net weight for Sheffield™ Brand Monohydrate Lactose, N.F. is 95kg, but Monohydrate Impalpable is 90kg. This product is also available in 100 lb drums or 25kg paper sacks upon request. The standard net weight for Foremost® Brand Monohydrate Lactose,
N.F. 310 is 95kg and 312 and 313 is 90kg. These products are also available in 40kg drums or 25kg paper sacks upon request.

Physical Characteristics		
	Specification	Typical
Color/Clarity (400mm)	0.04 max	0.01 -0.02
Solubility @25°C	N/A	20g/100ml
Chemical Characteristics		
	Specification	Typical
Molecular Weight	N/A	360.3
Water	4.5-5.5% max	4.8-5.2%
Loss on drying	0.5% max	0.10%-0.2%
Residue on ignition	0.1% max	0.03%-0.2%
Acidity/Alkalinity (6g) (0.1N NaOH)	≤0.4ml	0.1ml-0.22ml
Heavy metals (sulfide PPTN)	5ppm max	conforms
Heavy Metals (JP)	5ppm max	conforms
Specific rotation	+54.4 min/ +55.9 max	55.3
Protein/UV absorbing impurities @210-220nm @270-300nm	 0.25 max 0.07 max	 0.04 0.02
Organic volatile impurities	absent	conforms
Microbiological Characteristics		
	Specification	Typical
Total aerobic count	100/g max	conforms
Eschericia coli	negative	conforms
Salmonella	negative	conforms
Enterobacteriacae	negative	conforms
Pseudomonas aeruginosa	negative	conforms
Staphylococcus aureus	negative	conforms
Yeasts and Molds	50/g max	conforms

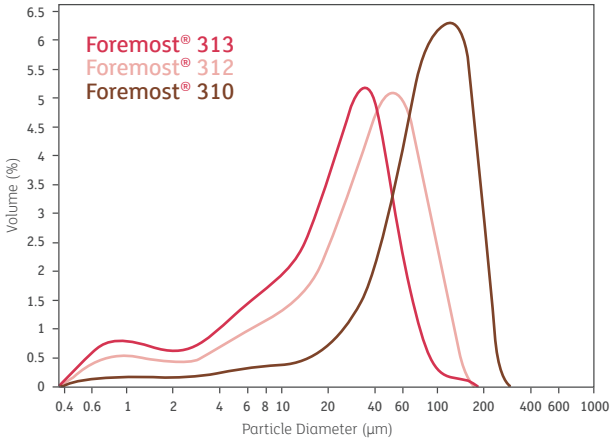
Sheffield™ Brand and Foremost® Brand Lactose, N.F. meets all requirements of the NF, EP and JP.

Particle Size Curves

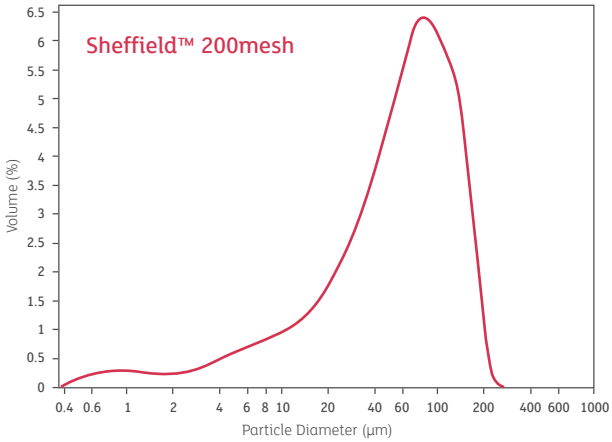
DIFFERENTIAL VOLUME



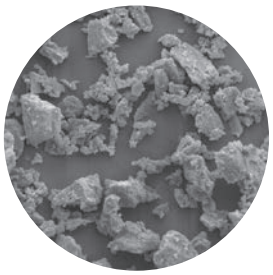
DIFFERENTIAL VOLUME



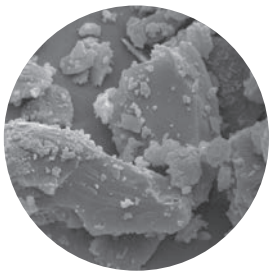
DIFFERENTIAL VOLUME



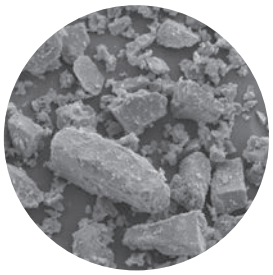
Sheffield™ Brand SEMs (Scanning Electron Microscope Image)



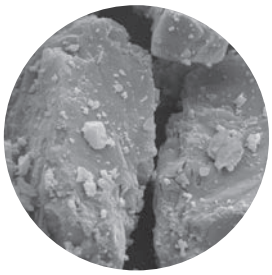
Monohydrate Impalpable
300X



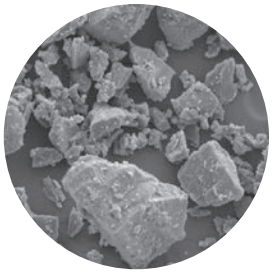
Monohydrate Impalpable
1500X



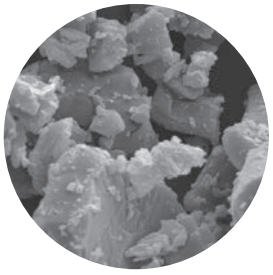
Monohydrate 80M
300X



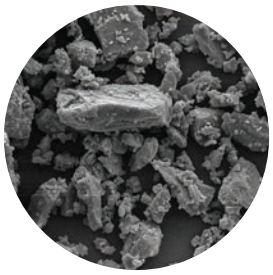
Monohydrate 80M
1500X



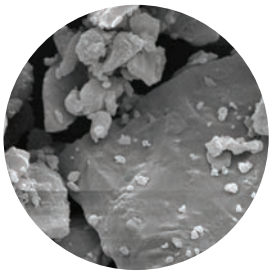
Monohydrate Capsulating
Grade 300X



Monohydrate Capsulating
Grade 1500X

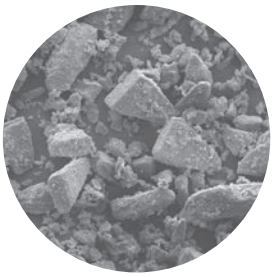


Monohydrate 200 Mesh
300X

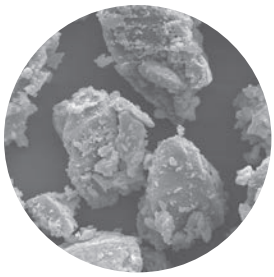


Monohydrate 200 Mesh
1500X

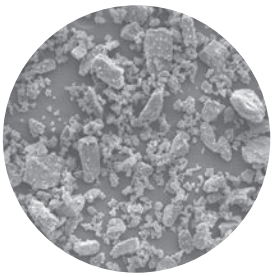
Foremost® SEMs (Scanning Electron Microscope Image)



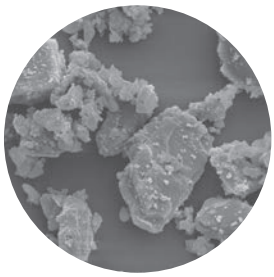
Monohydrate 310
150X



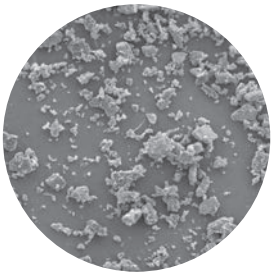
Monohydrate 310
600X



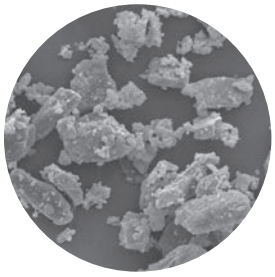
Monohydrate 312
150X



Monohydrate 312
600X



Monohydrate 313
150X



Monohydrate 313
600X

Crystalline Lactose Monohydrate

Crystallinity

Product	% Alpha	% Beta	% Crystalline
Typical Monohydrate	>96	0	99.0

Flowability

Product	Angle of Repose (α)	Compressibility (Carr's Index)	Flowability (g/sec)
Sheffield™ Brand Monohydrate 80M	54.9	33.6	0.91
Foremost® Brand Crystalline 312	54.9	33.6	0.91

Stability Data

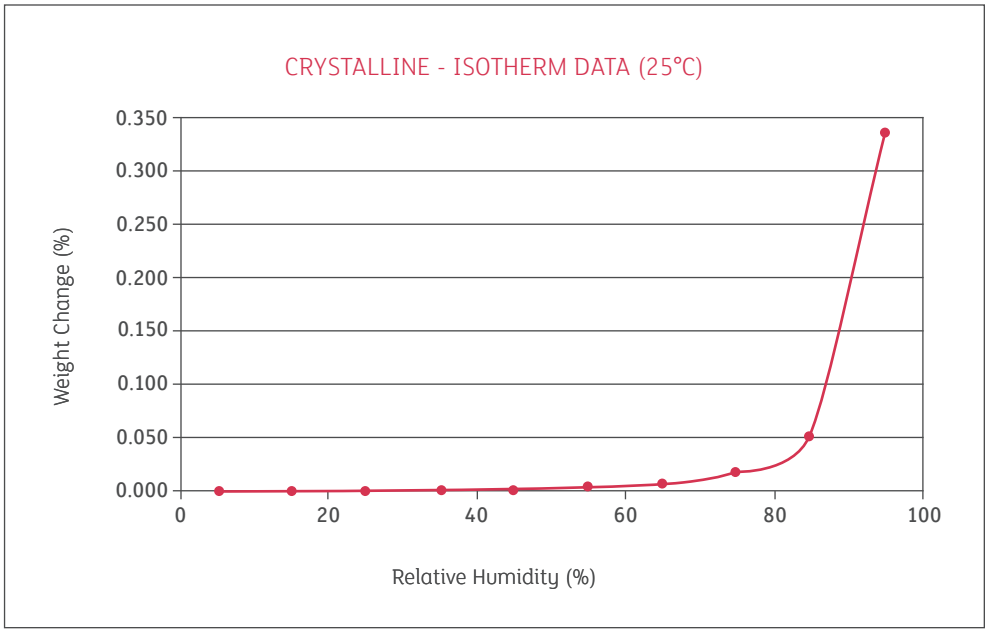
Typical lot of Monohydrate Capsulating Grade

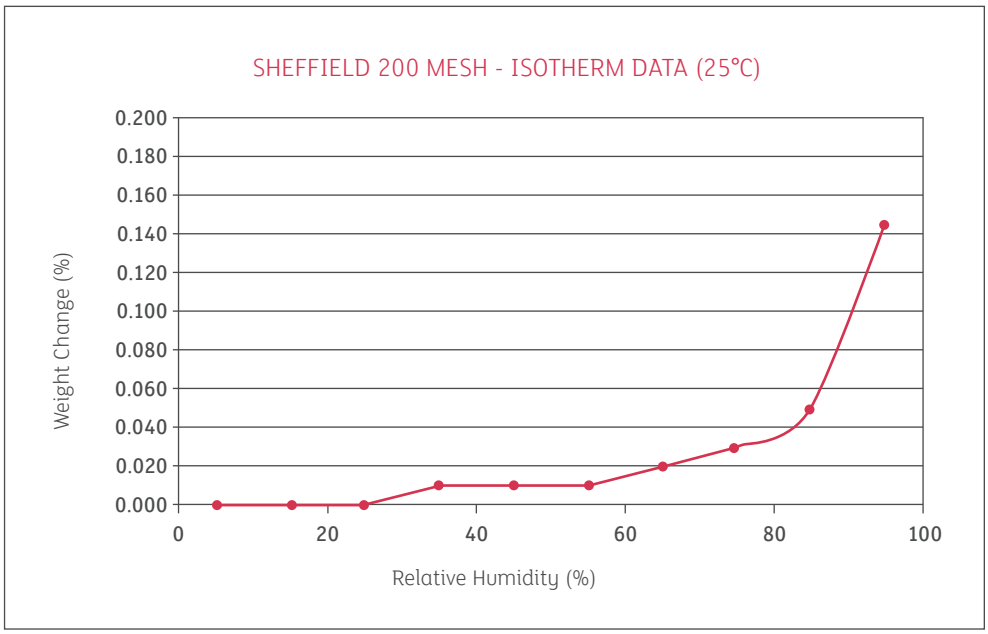
Lot# M021626

Test	Specification	0 months	6 months	12 months	18 months	24 months
ABS 400nm	0.04 max	0.00	0.00	0.01	0.01	0.00
ABS 210-220nm	0.25 max	0.02	0.02	0.02	0.02	0.02
ABS 270-300nm	0.07 max	0.00	0.01	0.01	0.00	0.00
LOD	0.5 max	0.0	0.2	0.0	0.1	0.0
% Water	4.5-5.5	5.3	5.2	5.2	5.1	5.1

Crystalline Lactose Monohydrate

Moisture Uptake Studies





Application Data

Advantages

Lactose monohydrate is typically used for wet or dry granulation. Granulation of crystalline monohydrate lactose is used to optimize particle size (for flowability) and compaction properties. The following study was performed to show an example of crystalline lactose properties before and after granulation.

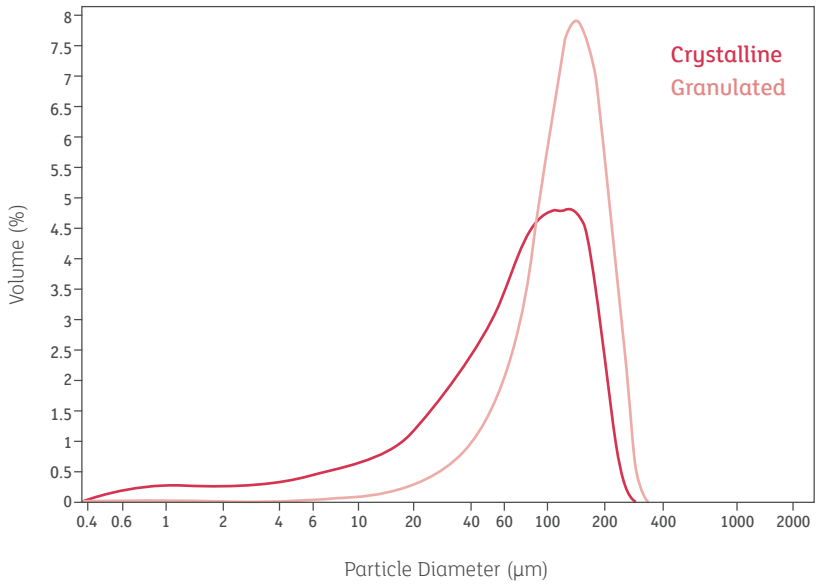
Wet Granulation Formula

Ingredient	Percent
Crystalline Lactose Monohydrate	88
Microcrystalline Cellulose	5
Povidone	5
Crospovidone	2

Flowability

Product	Angle of Repose (α)	Compressibility (Carr's Index)	Flowability (g/sec)
Crystalline	55	34	1.0
Granulation	47	18	4.5

Particle Size and Flowability

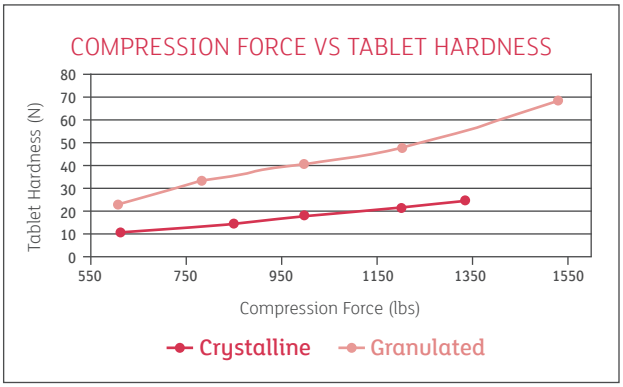


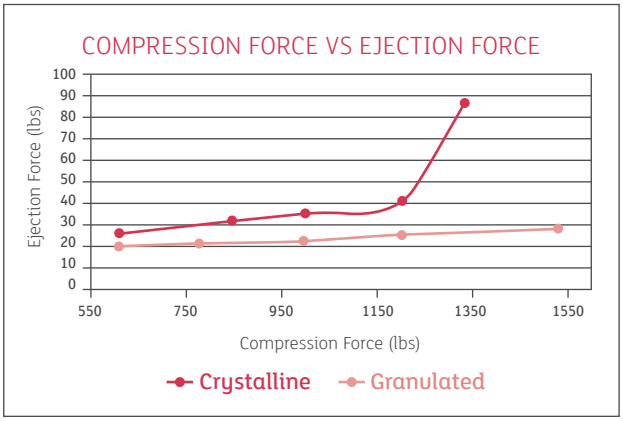
Application Data

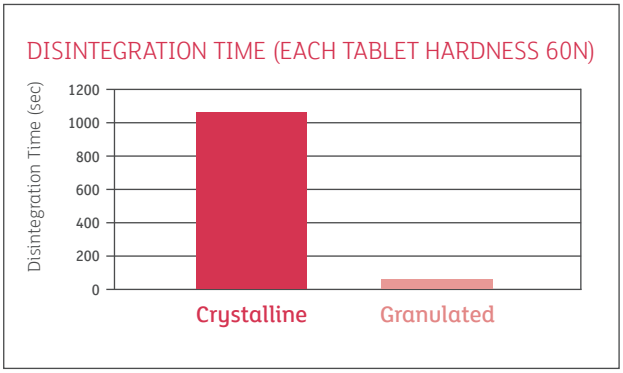
Compaction Properties

Tablet hardness versus compaction force profiles for the crystalline and granulated lactose formulas are given in the below figures. Analysis of the data concluded that granulation forms harder tablets at lower compaction forces relative to the crystalline monohydrate. Lower ejection force profiles are desirable because they not only save energy, but also result in less wear on tablet press dies and less equipment maintenance.

Disintegration profiles for crystalline and granulated lactose formulas is shown in the below figure. Analysis of the data concluded that granulation forms harder tablets that have faster disintegration profiles than the crystalline monohydrate.







Spray Dried Monohydrate

Foremost® Farms USA Products

Spray dried grades include NF Lactose Monohydrate Spray Dried 315 and 316 Fast®. Foremost® 316 Fast Flo® is ideal for direct compression and 315 may be used in direct compression and also used in capsule filling, with 316 Fast Flo® designed for optimal flow through high speed tablet presses.

Advantages

- Excellent tablet hardness at low compression forces
- Eliminate wet granulation technology, reduce equipment and process validation
- Fast dissolution and low friability
- High flowability
- Low color development

Products & Recommended Applications

Product	Application
Foremost® Brand Spray Dried 315	Direct tabletting and capsule filling
Foremost® Brand Spray Dried 316 Fast Flo®	Direct tabletting, high flow

General Physical and Chemical Characteristics

Product Description

Monohydrate Lactose is a disaccharide obtained from the whey fraction of milk and consists of one glucose and one galactose moiety. Foremost® Brand Monohydrate Lactose, N.F. Spray Dried is an optimal mixture of crystalline alpha lactose and amorphous lactose. It meets all requirements of the National Formulary as well as the European and Japanese Pharmacopeias.

Other Physical Characteristics

Free-flowing, non-hygroscopic powder. White to creamy white in color, free of sediment and with excellent stability. A 10% solution (in boiling water) is clear to nearly colorless.

Packaging and Storage

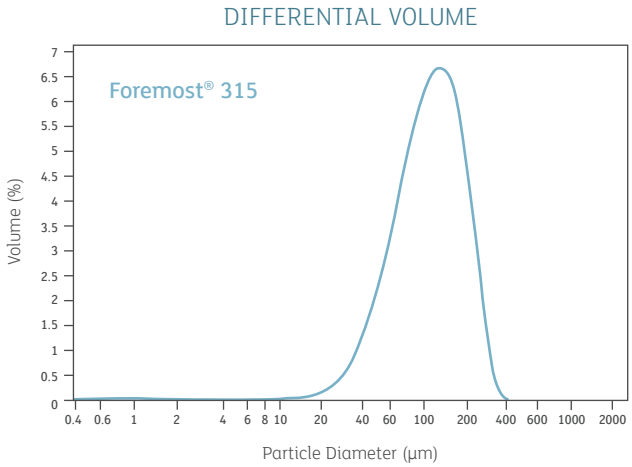
Store in a cool, dry area with container closed when not in use. A minimum shelf life of 18 months for spray dried 315 and 12 months for 316 Fast Flo®.

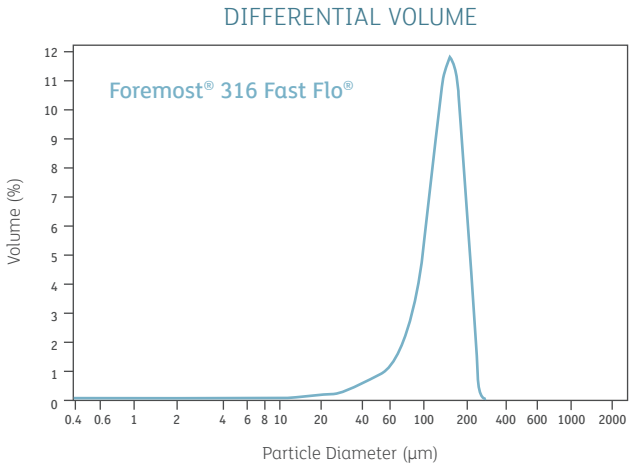
The standard packaging is a polyethylene lined fiber drum with tamper evident seals. The standard net weight for 315 is 95kg and 316 Fast Flo® is 75kg. Products are also available in 40kg drums or 25kg paper sacks upon request.

Physical Characteristics		
	Specification	Typical
Color/Clarity (400mm)	0.04 max	0.01
Chemical Characteristics		
	Specification	Typical
Water	4.5-5.5% max	4.8-5.2%
Loss on drying	1.0% max	0.3%
Residue on ignition	0.1% max	0.02%
Acidity/Alkalinity (6g) (0.1N NaOH)	≤0.4ml	0.1ml
Heavy metals (sulfide PPTN)	5ppm max	conforms
Heavy Metals (JP)	5ppm max	conforms
Specific rotation	+54.4 min/ +55.9 max	+54.8 to +55.2
Protein/UV absorbing impurities @210-220nm @270-300nm	 0.25 max 0.07 max	 0.05 0.01
Organic volatile impurities	absent	conforms
Microbiological Characteristics		
	Specification	Typical
Total aerobic count	100/g max	<10 cfu/g
Eschericia coli	negative	conforms
Salmonella	negative	conforms
Pseudomonas aeruginosa	negative	conforms
Staphylococcus aureus	negative	conforms
Yeasts and Molds	50 cfu/g max	<10 cfu/g

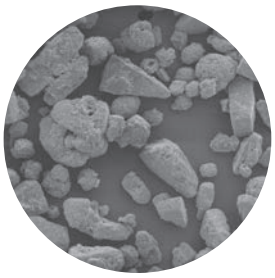
Foremost® Brand Lactose, N.F. meets all requirements of the NF, EP and JP.

Particle Size Curves

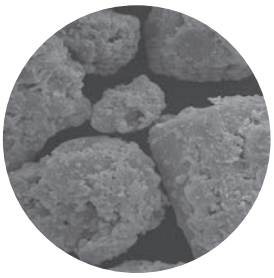




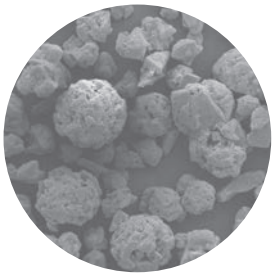
SEMs (Scanning Electron Microscope Image)



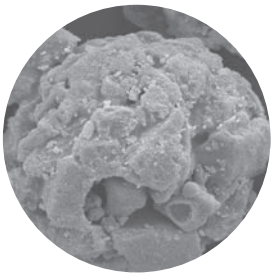
Monohydrate 315
150X



Monohydrate 315
600X



Monohydrate 316 Fast Flo®
150X



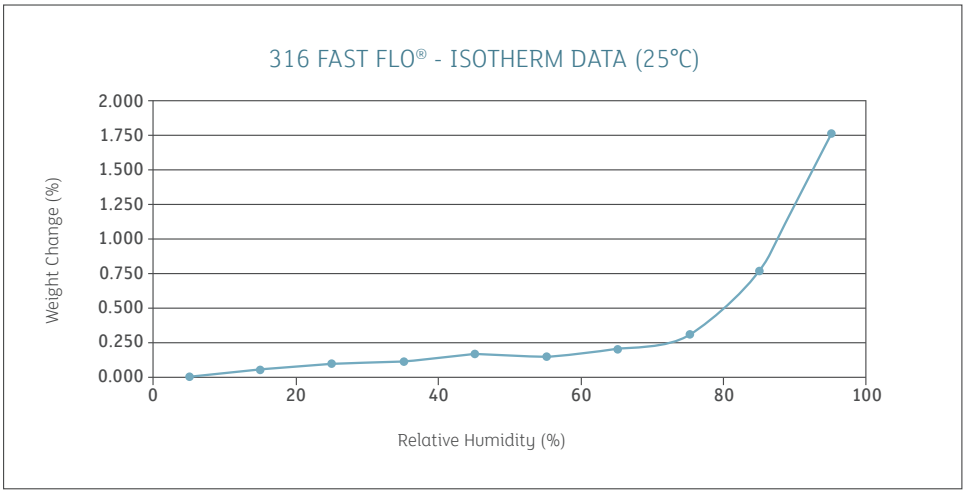
Monohydrate 316 Fast Flo®
600X

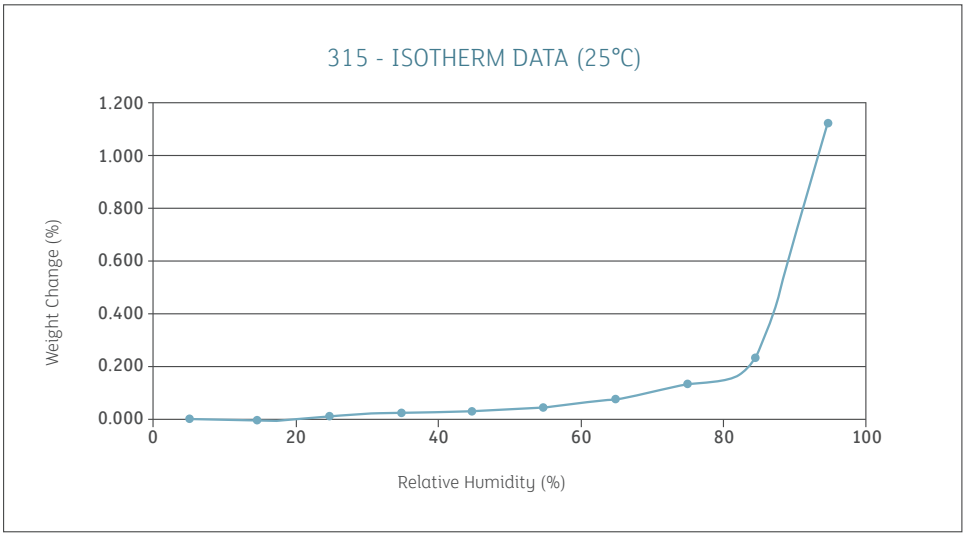
Spray Dried Lactose Monohydrate

Flowability

Product	Angle of Repose (α)	Compressibility (Carr's Index)	Flowability (g/sec)
Spray Dried 316 Fast Flo®	12	10.7	5.86
Spray Dried 315	14	12.24	5.11

Moisture Uptake Studies





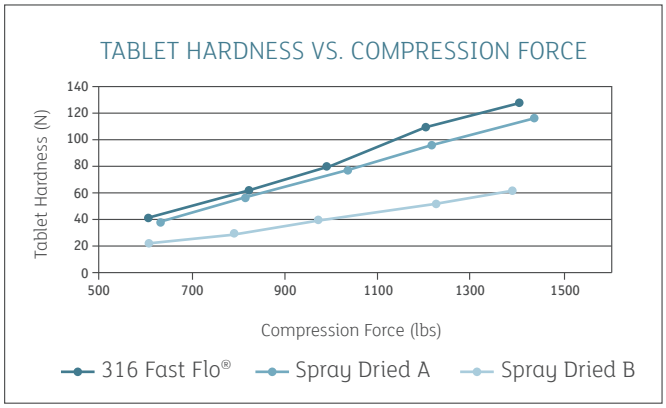
Application Data

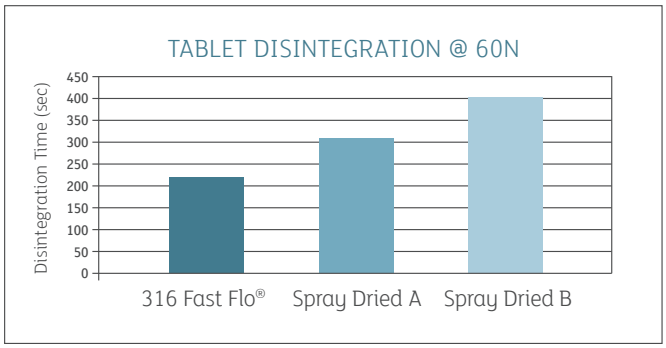
Direct Compression

Lactose Monohydrate spray dried is typically used for direct compression. Foremost® Brand 316 Fast Flo® is a specially processed spray dried product with enhanced flow, compaction, and disintegration properties. The following study was performed to show an example of Foremost® 316 Fast Flo® compared to other spray dried lactose.

Products Tested
(all contain 1% Magnesium Stearate)

- Foremost Brand 316 Fast Flo®
- Spray Dried A
- Spray Dried B





Compaction Properties

Tablet hardness versus compaction force profiles for the Foremost® 316 Fast Flo® and industry spray dried grades are shown in the below figure. Analysis of the data concluded that 316 Fast Flo® forms harder tablets at lower compaction forces relative to the typical spray dried products. Disintegration profiles for the lactose products are shown in the figure below. Analysis of the data concluded that 316 Fast Flo® forms harder tablets that have faster disintegration profiles than the other industry lactose.

Anhydrous Lactose

Advantages

- Eliminate or reduce higher cost or multiple excipients
- Replace wet granulation technology, reduce equipment and process validation
- Excellent tablet hardness at low compression forces
- High purity and no yellowing – pigment free
- Optimal for tableting with unstable active ingredients
- Moisture stable – 4 year shelf life
- Physically and chemically stable
- Low friability & excellent dissolution
- Consistent re-worked tablet properties
- Several grades and custom capabilities
- Certified Kosher and Animal Rennet-Free
- Over 75 years experience – batch to batch consistency

Products & Recommended Applications

Product	Application
Sheffield™ Brand Anhydrous Direct Tableting (DT)	Direct tableting (high flow not required)
Sheffield™ Brand Anhydrous 60M	
Sheffield™ Brand Anhydrous Impalpable	Granulations or Direct tableting (fine)
Sheffield™ Brand Anhydrous DT High Velocity	Direct tableting (high flow required)

General Physical and Chemical Characteristics

Product Description

Anhydrous Lactose is a disaccharide obtained from the whey fraction of milk, and consists of one glucose and one galactose moiety. Sheffield™ Brand Anhydrous Lactose, N.F. is a crystalline mixture of beta and alpha anomers and meets all requirements of the National Formulary.

Other Physical Characteristics

Free-flowing, non-hygroscopic powder. White to creamy white in color, free of sediment and with excellent stability. A 10% solution (in boiling water) is clear to nearly colorless. Soluble in water at 25°C (77°F) is 40g/100ml.

Packaging and Storage

Store in cool, dry area with container closed when not in use. A minimum shelf life of 48 months is expected for unopened packages.

The standard packaging is in 80kg polyethylene lined fiber drums with tamper evident seals. All products are also available in 100lb drums and 25kg paper sacks upon request.

Physical Characteristics		
	Specification	Typical
Color/Clarity (400mm)	0.04 max	0.02
Solubility @25°C	N/A	20g/100ml

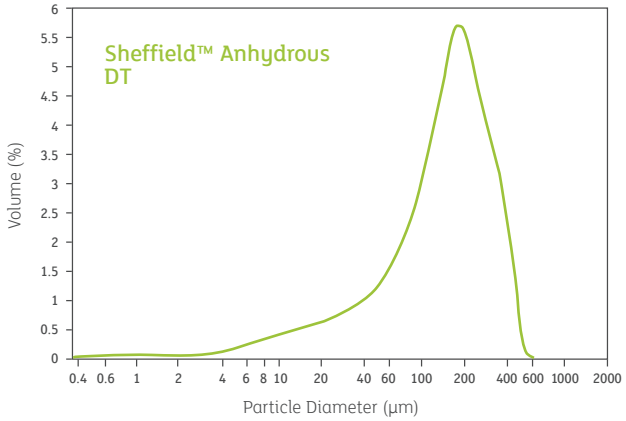
Chemical Characteristics		
	Specification	Typical
Molecular Weight	N/A	342.3
Alpha Anomer	Record	27%
Beta Anomer	Record	73%
Water	1.0% max	0.45%
Loss on drying	0.5% max	0.18%
Residue on ignition	0.1% max	0.03%
Acidity/Alkalinity (6g) (0.1N NaOH)	≤0.4ml	0.22ml
Heavy metals (sulfide PPTN)	5ppm max	conforms
Heavy Metals (JP)	5ppm max	conforms
Specific rotation	+54.4 min/ +55.9 max	55.1
Protein/UV absorbing impurities @210-220nm @270-300nm	 0.25 max 0.07 max	 0.04 0.02
Organic volatile impurities	absent	conforms

Microbiological Characteristics		
	Specification	Typical
Total aerobic count	100/g max	conforms
Eschericia coli	negative	conforms
Salmonella	negative	conforms
Enterobacteriacae	negative	conforms
Pseudomonas aeruginosa	negative	conforms
Staphylococcus aureus	N/A	negative
Yeasts and Molds	50/g max	conforms

Sheffield™ Brand Lactose, N.F. meets all requirements of the NF, EP and JP.

Particle Size Curves

DIFFERENTIAL VOLUME



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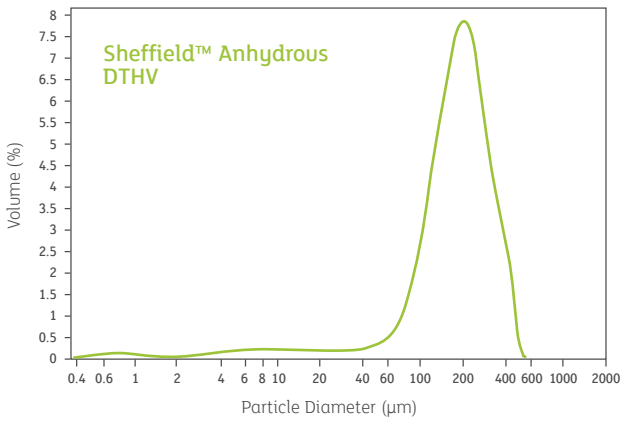

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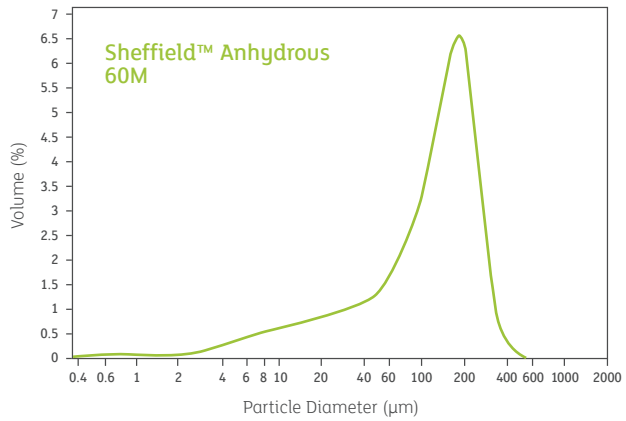

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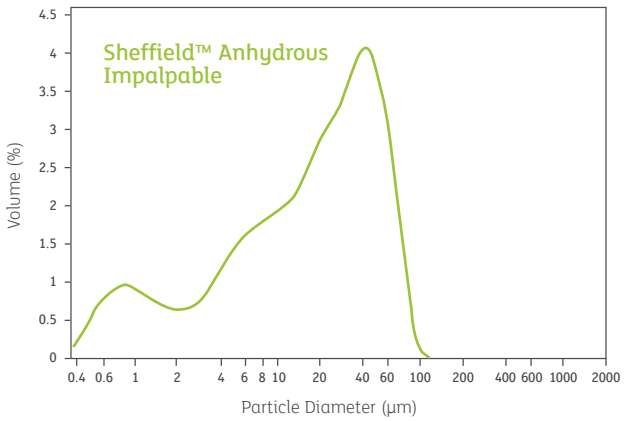
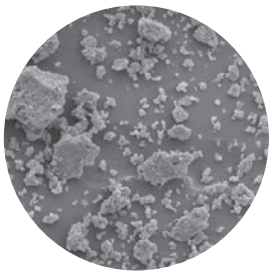
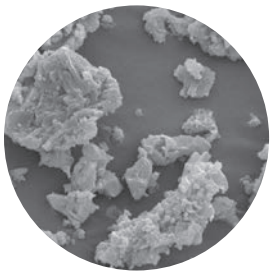


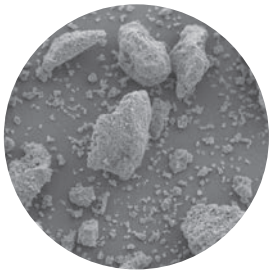
SEMs (Scanning Electron Microscope Image)



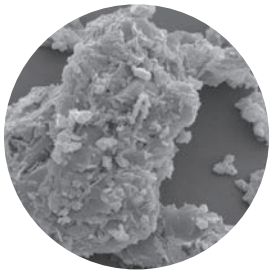
Anhydrous DT
300X



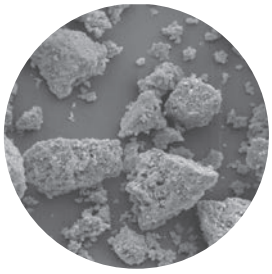
Anhydrous DT
1500X



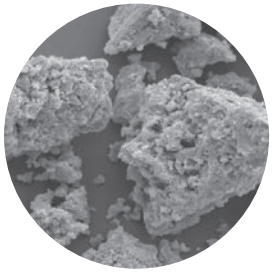
Anhydrous DTHV
300X



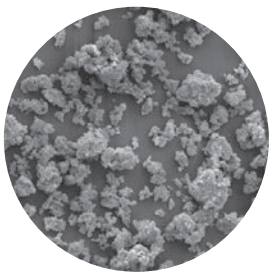
Anhydrous DTHV
1500X



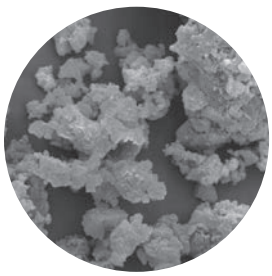
Anhydrous 60M
300X



Anhydrous 60M
1500X



Anhydrous Impalpable
300X



Anhydrous Impalpable
1500X

Anhydrous Lactose

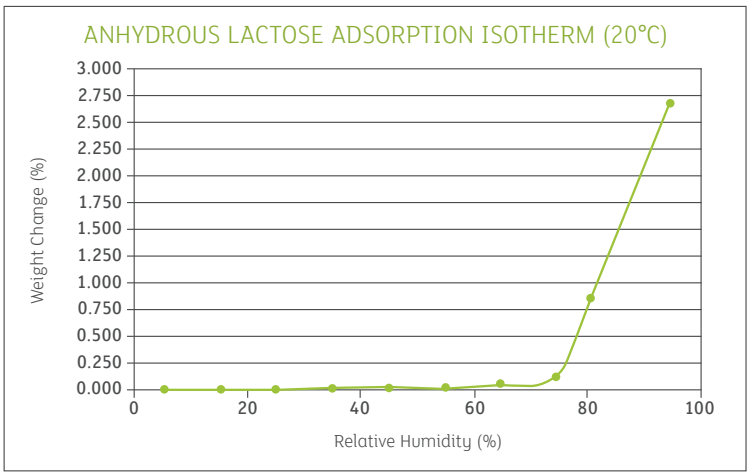
Typical Isomer Ratio

% Alpha	%Beta
27	73

Flowability

Product	Angle of Repose (α)	Compressibility (Carr's Index)	Flowability (g/sec)
Anhydrous Direct Tableting (DT)	50.1	25.3	3.95
Anhydrous DT High Velocity	40.0	17.6	4.24

Moisture Uptake Studies



Stability Data

Typical lot of Anhydrous DT

Lot# M031200

Test	Specification	0 months	6 months	12 months	18 months	24 months
ABS 400nm	0.04 max	0.01	0.02	0.02	0.01	0.02
ABS 210-220nm	0.25 max	0.02	0.02	0.04	0.04	0.04
ABS 270-300nm	0.07 max	0.01	0.01	0.01	0.01	0.02
LOD	0.5% max	0.3	0.1	0.1	0.1	0.1
% Water	1.0% max	0.5	0.5	0.5	0.5	0.5

Application Data Lactose Anhydrous DT

Advantages of Direct Tableting Lactose

Direct compression demands the use of excipients with strictly defined properties. Kerry has created excipients specifically to meet the requirements of the direct compression process: Sheffield™ Brand Anhydrous Lactose, N.F.-Direct tableting, and N.F.-Direct tableting High Velocity.

The originally patented formulation, commonly referred to as Anhydrous DT, is one of the most outstanding and unique direct compression excipients available. Several other grades are now available to optimize tableting performance including Anhydrous DTHV, which has the same superior tableting properties as Anhydrous DT but with exceptional flow. Sheffield™ Brand Anhydrous Lactose offers many distinct advantages over other direct compression products, including; improved tablet hardness at low compaction pressures, low friability, good dissolution, improved moisture stability, reduced color development, and improved reworking ability.

Anhydrous DT and DTHV Lactose consists primarily of beta-lactose existing in crystalline and amorphous forms (US Patent #3,802,914). More specifically, Anhydrous Lactose is composed of aggregates of microcrystals (Brittain, 1991; Shangraw and Bowers, 1981), which in turn provide distinctive compaction characteristics.

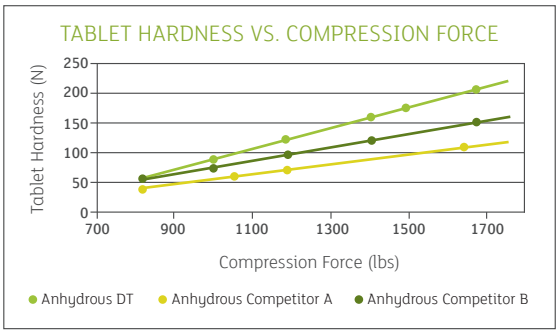
Compaction Properties of Anhydrous DT

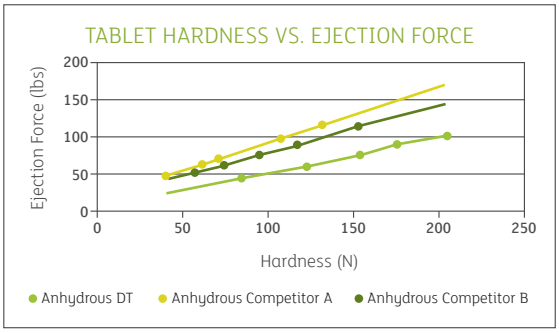
Tablet hardness versus compaction force profiles for lactose formulas are shown in the below figures. Analysis of the data concluded that Sheffield™ Brand Anhydrous DT forms harder tablets at lower compaction forces relative to the other products tested. Sheffield™ Brand Anhydrous DT also exhibited lower ejection forces at similar compaction forces. Lower ejection force profiles are desirable because they not only save energy, but also result in less wear on tablet press dies and less equipment maintenance.

Dissolution profiles for lactose formulas are shown in the below figure. Analysis of the data concluded that Sheffield™ Brand Anhydrous DT forms harder tablets that have similar dissolution profiles as lactose tablets with lower hardness values.

Numerous studies have been performed to examine the physical and chemical characteristics of Anhydrous DT (Brittian, 1991; Shangraw and Bowers, 1981; Whiteman and Yarwood, 1988). In one study, Sheffield™ Brand Anhydrous DT was compared to a different brand of anhydrous lactose, Lactose A, and to a spray dried monohydrate lactose, Lactose B. A variety of properties were compared in both a placebo and acetaminophen (APAP, 4-acetamidophenol, Sigma Chemical, St. Louis, MO) formulation.

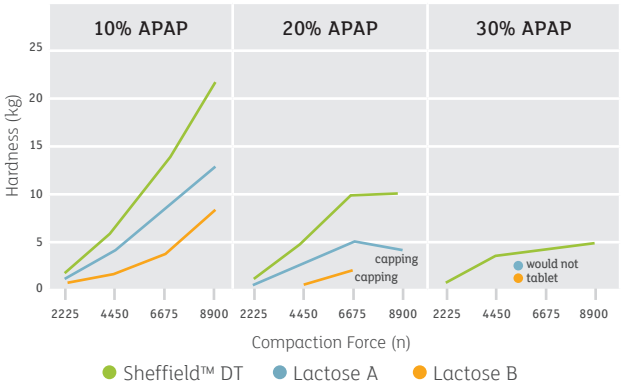
Higher compaction profiles were obtained for Anhydrous DT for three APAP formulations as shown in the below figure. As the APAP concentration increased, tablet hardness decreased for all three products. Only the use of DT Grade resulted in suitable tablets at 20% APAP, where both Lactose A and B began capping. Even more significant is the fact that Anhydrous DT was the product capable of tablet formulation at 30% APAP.



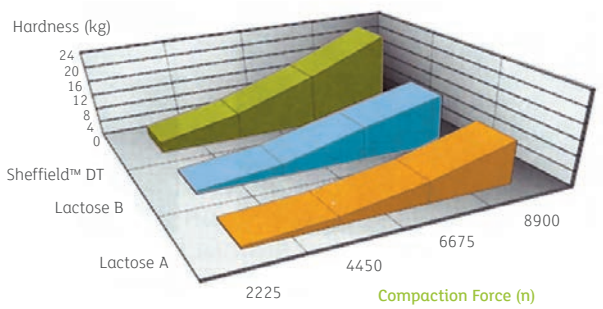


Application Data Lactose Anhydrous DT

Compaction versus tablet hardness profiles for APAP formulations: 0.5% Magnesium stearate, 10-30% APAP, remainder as lactose



Compaction versus tablet hardness profiles of 10% APAP formulations after rework.



Weight Variability

Sheffield™ Brand Anhydrous Lactose has been shown to form compacts with lower weight variation then other direct compression excipients (Whiteman and Yarwood, 1988).

Low Color Development

Sheffield™ Brand Anhydrous Lactose is compatible with actives containing free amines. Free amines are known to react with hydroxymethylfurfural (HMF), resulting in off-colored tablets. Sheffield™ Brand Lactose has reduced HMF levels, virtually eliminating the problem of discoloration.

Reworkability

A major advantage of the direct compression method is the ease with which the product can be reworked if necessary However, some excipients have reduced tableting capabilities when reworked. Sheffield™ Brand Anhydrous Lactose reworks easily and maintains its superior tableting capabilities.

In the figure to the right, tablets from the 10% APAP formulation were evaluated for reworkability by grinding the tablets to a standard mesh and recompressing. The performance of the Anhydrous DT in recompaction remains nearly as high as prior to reworking, providing harder tablets at lower compaction pressure. The below table shows the consistence of DT before and after reworking for tablet hardness, friability, and dissolution time.

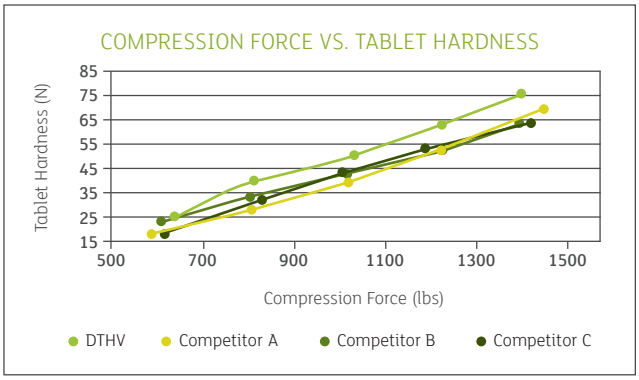
Properties of 10% APAP Tablets before and after rework.

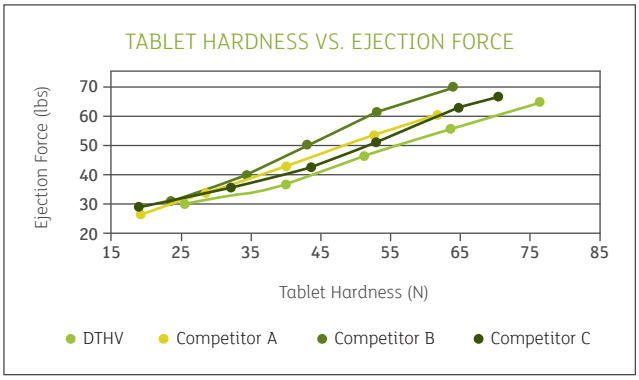
Property	Hardness		Friability		Dissolution	
	Initial	Rework	Initial	Rework	Initial	Rework
Sheffield™ DT	5.2	5.5	0.25	0.25	20	18
Lactose A	5.6	5.8	0.52	0.39	35	30
Lactose B	4.5	4.6	0.66	0.51	18	25

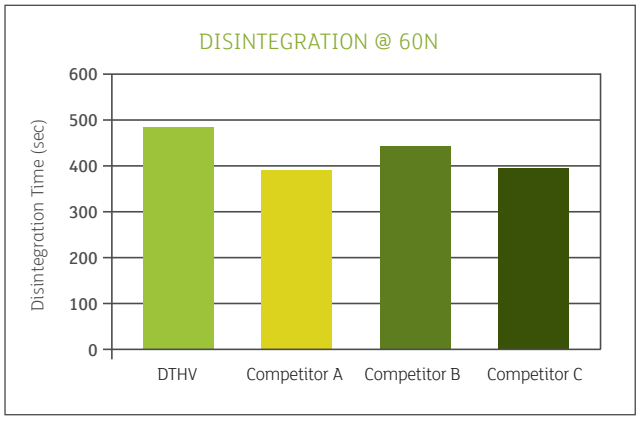
Application Data Lactose Anhydrous DTHV

Compaction Properties of Anhydrous DTHV

Tablet hardness versus compaction force profiles for lactose formulas are shown in the below figures. Relative to other high flowing directly compressible products Analysis of the data concluded that Sheffield™ Brand Anhydrous DTHV forms harder tablets at lower compaction forces relative to other high flowing directly compressible products. Lower ejection force profiles are desirable because they not only save energy, but also result in less wear on tablet press dies and less equipment maintenance.







Inhalation Lactose

Advantages

- Certified Animal Rennet Free Supply
- Inert material, high purity
- Moisture stable – 2 year shelf life
- Physically and chemically stable
- Several off-the-shelf grades and custom capabilities

Recommended Applications

Sheffield™ Brand Inhalation lactose is recommended for use as a carrier/blending agent in dry powder inhalation applications.

Products List

Product
Aero Flo™ 65, Monohydrate
Aero Flo™ 55, Monohydrate
Aero Flo™ 35, Monohydrate
Aero Flo™ 25, Anhydrous
Aero Flo™ 85S, Anhydrous

General Physical and Chemical Characteristics

Product Description

Aero Flo™ was specifically developed for dry powder inhalation (DPI's) applications. Lactose is used as a carrier to ensure even blending, uniform dosing, and because it is inert, there is limited interaction with the active. Kerry's unique processing maintains the crystallinity of the lactose. This results in improved separation of the lactose from the active, compared to spray dried lactose.

Other Physical Characteristics

Free-flowing, non-hygroscopic powder. White to creamy white in color, free of sediment and with excellent stability. A 10% solution (in boiling water) is clear to nearly colorless. Solubility in water at 25°C (77°F) is 20g/100ml.

Packaging and Storage

Store in cool, dry area with container closed when not in use. A minimum shelf life of 24 months is expected for unopened packages.

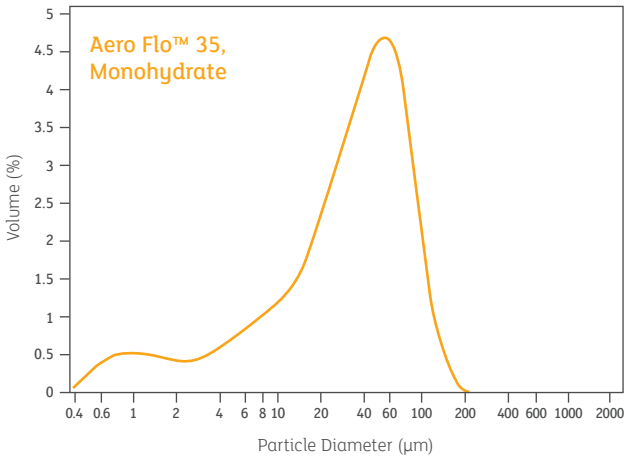
The standard packaging is in 25 kg polyethylene lined HDPE drums with tamper evident seals.

Physical Characteristics				
	Specification(Monohydrate)	Typical (Monohydrate)	Specification (Anhydrous)	Typical (Anhydrous)
Color/Clarity (400mm)	0.04 max	0.002	0.04 max	0.02
Solubility @25°C	N/A	40g/100ml	N/A	20g/100ml
Chemical Characteristics				
	Specification Monohydrate)	Typical (Monohydrate)	Specification (Anhydrous)	Typical (Anhydrous)
Alpha Anomer	Record	>99%	Record	27%
Beta Anomer	Record	N/A	Record	73%
Water	4.5-5.5% max	4.9%	1.0% max	0.45%
Loss on drying	0.5% max	0.10%	0.5% max	0.18%
Residue on ignition	0.1% max	0.03%	0.1% max	0.03%
Acidity/Alkalinity (6g) (0.1N NaOH)	≤0.4ml	0.22ml	≤0.4ml	0.22ml
Heavy metals (sulfide PPTN)	5ppm max	conforms	5ppm max	conforms
Heavy Metals (JP)	5ppm max	conforms	5ppm max	conforms
Specific rotation	+54.4 min/+55.9 max	55.3	+54.4 min/+55.9 max	55.1
Protein/UV absorbing impurities @210-220nm @270-300nm	 0.25 max 0.07 max	 0.03 0.02	 0.25 max 0.07 max	 0.04 0.02
Organic volatile impurities	absent	conforms	absent	conforms
Microbiological Characteristics				
	Specification Monohydrate)	Typical (Monohydrate)	Specification (Anhydrous)	Typical (Anhydrous)
Total aerobic count	10/g max	conforms	10/g max	conforms
Eschericia coli	negative	conforms	negative	conforms
Salmonella	negative	conforms	negative	conforms
Enterobacteriacae	10/g max	conforms	10/g max	conforms
Pseudomonas aeruginosa	negative	conforms	negative	conforms
Staphylococcus aureus	negative	conforms	negative	conforms
Endotoxins	50 Eu/g max	conforms	50 Eu/g max	conforms
Yeasts and Molds	10/g max	conforms	10/g max	conforms

Aero Flo™ meets all requirements of the NF, Ph Eur and JP.

Particle Size Curves

DIFFERENTIAL VOLUME



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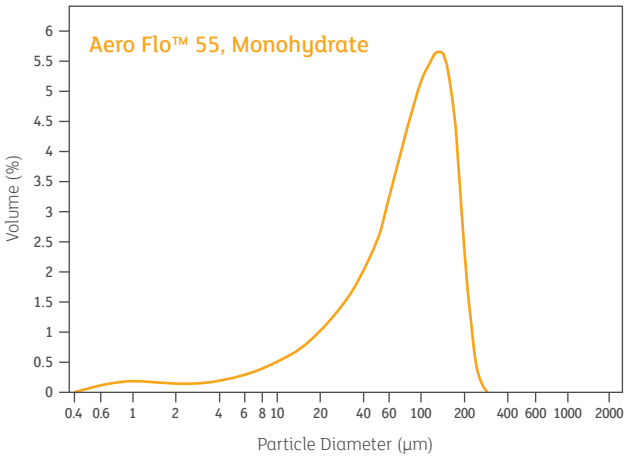

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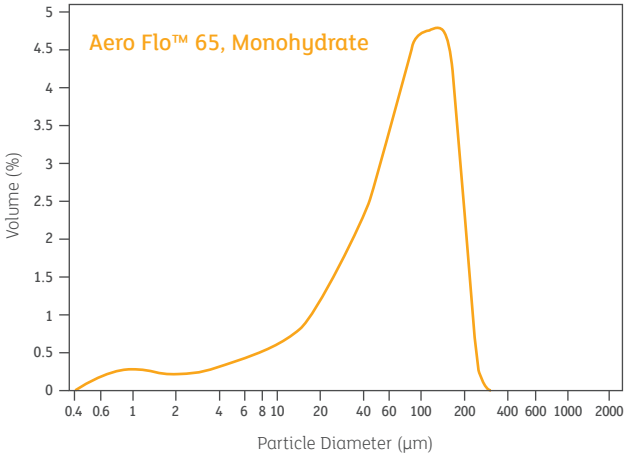

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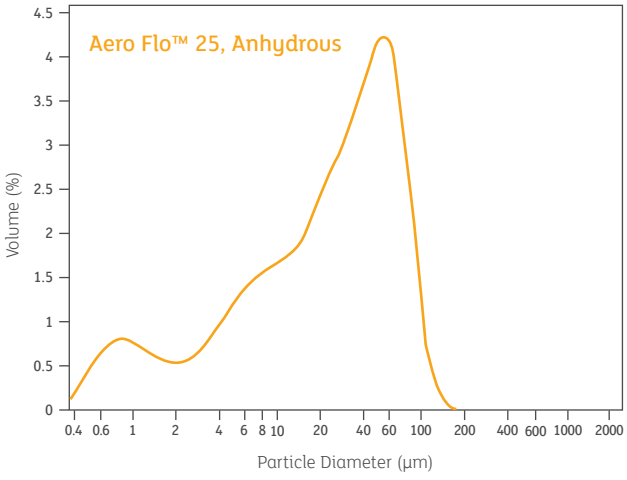

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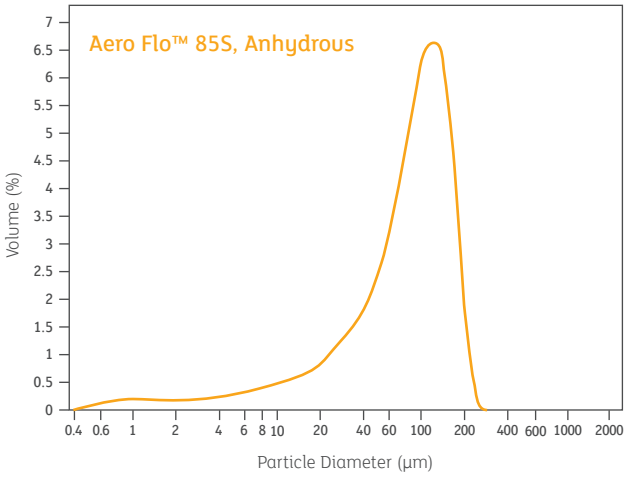
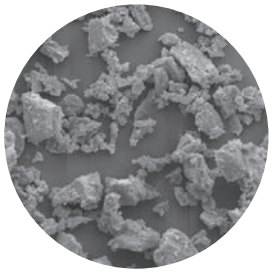
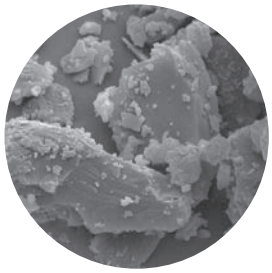


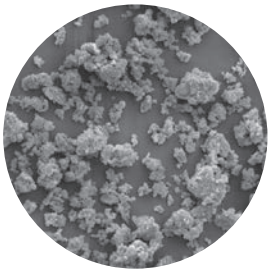
SEMs (Scanning Electron Microscope Image)



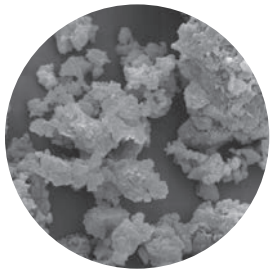
Aero Flo™ 35, Monohydrate
300X



Aero Flo™ 35, Monohydrate
1500X



Aero Flo™ 25, Anhydrous
300X



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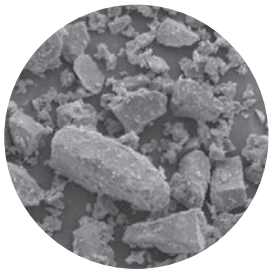
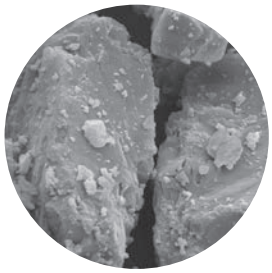


Aero Flo™ 55, Monohydrate
300X



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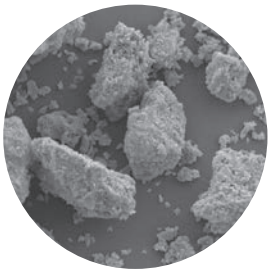
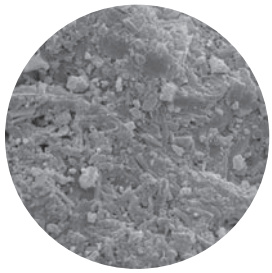


Aero Flo™ 85S, Anhydrous
300X



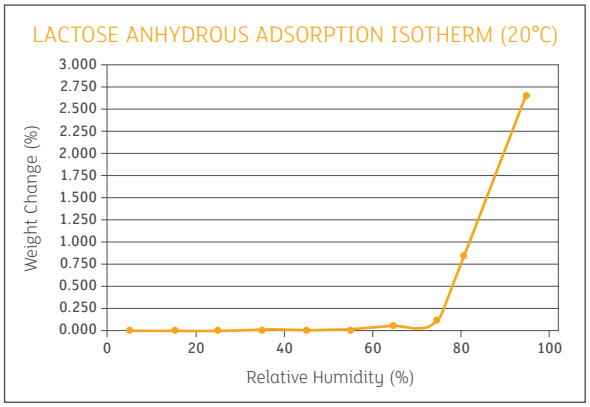
Aero Flo™ 85S, Anhydrous
1500X

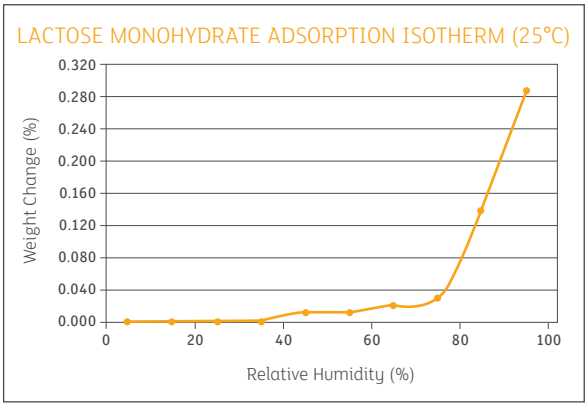
Inhalation Lactose

Typical Isomer Ratio

	% Alpha	%Beta
Monohydrate	>96	0
Anhydrous	27	73

Moisture Uptake Studies





Stability Data

Typical lot of Anhydrous DT

Test	Specification	0 months	6 months	12 months	18 months	24 months
ABS 400nm	0.04 max	0.01	0.02	0.02	0.01	0.02
ABS 210-220nm	0.25 max	0.02	0.02	0.04	0.04	0.04
ABS 270-300nm	0.07 max	0.01	0.01	0.01	0.01	0.02
LOD	0.5% max	0.3	0.1	0.1	0.1	0.1
% Water	1.0% max	0.5	0.5	0.5	0.5	0.5

Typical lot of Monohydrate

Test	Specification	0 months	6 months	12 months	18 months	24 months
ABS 400nm	0.04 max	0.01	0.1	0.1	0.1	0.1
ABS 210-220nm	0.25 max	0.03	0.03	0.02	0.03	0.02
ABS 270-300nm	0.07 max	0.01	0.01	0.01	0.01	0.01
LOD	0.5% max	0.2	0.1	0.1	0.0	0.0
% Water	4.5-5.5% max	5.1	5.1	5.0	4.9	4.8

Application Data

Inhalation Application Study

Using a dry powder inhaler for drug delivery has many advantages over traditional routes including fast delivery of active, no needle use, or no pill swallowing. They also offer advantages over older respiratory delivery methods such as those using nebulizers or pressurized CFC containing aerosols. Dry powder inhalers also offer the potential for delivering a wider range of drugs than these older methods. Typically, with dry powder inhalers, the active ingredient and a carrier are blended and used to fill the inhaler; or with some inhalers, a capsule that includes one dose. During use, the dose delivery is performed by the patient through simply inhaling, or is assisted by a burst of air, depending on the type of inhaler.

Lactose has been used as a carrier in these applications due to its inertness, cost, availability, product options, and patient tolerability. Two of the most important characteristics of the formula are dose uniformity and from a cost standpoint, the amount of active that reaches the patients lungs in relation to the amount in the starting dose. The lactose used as a carrier will most certainly have an effect on both of these characteristics.

In an independent study (Cirrus Pharmaceuticals, 2006), one of the monohydrate and one of the anhydrous products above were compared to industry standard spray dried lactose. The Lactose was blended with micronized albuterol and used to fill an Aerolizer dry powder inhaler. The inhaler was actuated through an Anderson Cascade impactor for all products. The residual active was then measured in the inhaler and parts, and through the stages of the impactor to determine the recovery of the active. The data below shows the recovered dose emitted from the inhaler/parts and the emitted dose of active collected at the end of the impactor.

Blending Results

Blending of albuterol sulfate with three different inhalation lactose products, one from each category (Anhydrous, Monohydrate, and Spray Dried Monohydrate) resulted in good blend uniformity after 35 minutes. The three re-blends were then used in the second half the study.

Anderson Cascade Impaction Results

A variety of parameters were used to characterize the deposition profiles of albuterol sulfate from the blends in ACI studies. The recovered dose (RD) was calculated from the sum of drug collected in the inhaler device, preseparator, throat and mouth pieces, casing and 8 stages of the impactor, whereas the emitted dose (ED) was the amount of drug released from the inhaler device. Percent recovery and percent emission was determined by the ratio of RD and ED to the theoretical dose, respectively, the theoretical does being the dose of albuterol sulfate in the capsules. Fine particle dose (FPD) was the amount of drug collected in stages 1-6 of the impactor (<4.5 (m) Fine particle fraction (FPF) was calculated as a ratio of FPD to RD and also as a ratio of FPD to ED.

Single factor ANOVA demonstrated that there was no significant difference (p-value >0.05) in the percent emissions and FPF as a function of recovered dose between Aero Flo™ 35, Monohydrate and Aero Flo™ 25, Anhydrous. However FPF as a function of emitted dose was higher for Aero Flo™ 35, Monohydrate as compared to Aero Flo™ 25, Anhydrous at 90% confidence interval ($p < 0.1$).

Percent emissions and FPF (both as a function of recovered and emitted dose) was lower for the Competitor Lactose A as compared to both ero Flo™ 35, Monohydrate and Aero Flo™ 25, Anhydrous . There isn't a large difference in particle sizes of these carrier lactose particles; however a difference in their deposition characteristics was recorded.

Application Data

Lactose	Average % albuterol sulfate in unit dose sample after blending for 35 minutes
Aero Flo™ 35, Monohydrate	0.97
Aero Flo™ 25, Anhydrous	1.02
Industry Spray Dried Monohydrate A	0.96

Aero Flo™ 35, Monohydrate as a carrier

Parameter	1st Replicate	2nd Replicate	3rd Replicate	Average
Drug Content in the Capsules (µg)	1206	1159	1200	1188.3
Recovered Dose (RD) (µg)	1191	1127	1158	1158.7
% Recovery	98.9	97.2	96.5	97.5
Emitted Dose (ED) (µg)	1077.2	992.9	1015.3	1028.4
% Emission	89.3	85.7	84.6	86.5
Fine Particle Dose (FPD)	566.3	542.9	566.7	558.7
Fine Particle Fraction as a Function of RD (%)	47.5	48.2	49.0	48.2
Fine Particle Fraction as a function of ED (%)	52.6	54.7	55.8	54.4

Aero Flo™ 25, Anhydrous as a carrier

Parameter	1st Replicate	2nd Replicate	3rd Replicate	Average
Drug Content in the Capsules (µg)	1234	1263	1271	1256
Recovered Dose (RD) (µg)	1170	1270	1223	1121
% Recovery	94.8	100.5	94.6	96.6
Emitted Dose (ED) (µg)	1055.4	1178.1	1116.1	1116.1
% Emission	85.5	93.2	86.4	88.4
Fine Particle Dose (FPD)	513.9	599.6	582.9	565.5
Fine Particle Fraction as a Function of RD (%)	43.9	47.2	47.7	46.3
Fine Particle Fraction as a function of ED (%)	48.7	50.9	52.3	50.6

Industry Spray Dried Monohydrate A as a carrier

Parameter	1st Replicate	2nd Replicate	3rd Replicate	Average
Drug Content in the Capsules (µg)	1164	1221	1197	1194
Recovered Dose (RD) (µg)	1103	1167	1162	1144
% Recovery	94.7	95.6	97.1	95.8
Emitted Dose (ED) (µg)	939	992.1	987.6	972.9
% Emission	80.7	81.3	82.5	81.5
Fine Particle Dose (FPD)	294.9	309.4	312.0	305.5
Fine Particle Fraction as a Function of RD (%)	26.7	26.5	26.9	26.7
Fine Particle Fraction as a function of ED (%)	31.4	31.2	31.6	31.4

Conclusions

ACI studies demonstrated that Aero Flo™ 35, Monohydrate and Aero Flo™ 25, Anhydrous carriers produced fine particle fractions higher than the Competitor inhalation Lactose A.

Appendix

Crystalline Monohydrate Method Used to Determine Data

To expedite the process, the granulations were performed as a wet/dry one step process. The materials were added to a Niro Fluid Bed Top Spray Granulator. Water was then sprayed into the mixture from the top of the chamber to activate the binder and to agglomerate the material. After agglomerating to the desired particle size, the water spray was stopped, and the dryer air remained on to dry the material to the desired moisture content. The material was then ready for compaction.

In the compaction stage, the granulations were blended for five minutes with 1% magnesium stearate and compacted on an instrumented ten-station rotary press (Globe Pharma).

For compression and ejection force measurements, the press was fitted with load cells and software to automatically measure and record force.

For tablet hardness, an automated tablet tester (Pharma-Test PTB 311E 3 in 1 tester) was used to measure the force required to break the tablet.

For the disintegration time, the apparatus was set according to procedure [701] of the U.S. Pharmacopoeia/National Formulary XXIV (2006). Six tablets were added to the basket rack assembly. The emersion fluid contained e-pure water held at 36-37°C. Disintegration time was taken at the time when all tablets were fully dissolved.

A Beckman Coulter laser particle size analyzer was used to measure the product particle size curves.

Spray Dried Monohydrate Method Used to Determine Data

DIRECT COMPRESSION

In the compaction study, the various lactose grades were blended for five minutes with 1% magnesium stearate and compacted on an instrumented ten-station rotary press (Globe Pharma).

For the disintegration time, the apparatus was set according to procedure [701] of the U.S. Pharmacopoeia/National Formulary 27 (2008). Six tablets were added to the basket rack assembly. The emersion fluid contained e-pure water held at 36-37°C. Disintegration time was taken at the time when all tablets were fully dissolved.

GRANULATION

To expedite the process, the granulations were performed as a wet/dry one step process. The materials were added to a Niro Fluid Bed Top Spray Granulator. Water was then sprayed into the mixture from the top of the chamber to activate the binder and to agglomerate the material. After agglomerating to the desired particle size, the water spray was stopped, and the dryer air remained on to dry the material to the desired moisture content. The material was then ready for compaction.

In the compaction stage, the granulations were blended for five minutes with a 1% magnesium stearate and compacted on an instrumented ten-station rotary press (Globe Pharma).

For the disintegration time, the apparatus was set according to procedure [701] of the U.S. Pharmacopoeia/National Formulary 27 (2008). Six tablets were added to the basket rack assembly. The emersion fluid contained e-pure water held at 36-37°C. Disintegration time was taken at the time when all tablets were fully dissolved.

Anhydrous Lactose Method Used to Determine Data

In the first DT compaction study the various lactose grades were blended for five minutes with 1% magnesium stearate and compacted on an instrumented ten-station rotary press (Globe Pharma).

For KI dissolution time, the apparatus was set according to procedure [711] of the U.S. Pharmacopoeia/National Formulary XXIV (2006).

Six tablets were added to the stirred reactor (100 rpm) containing 900ml-distilled water at 36-37°C. A sample was withdrawn after 2 minutes, then every five minutes thereafter. The absorbance at 227nm was measured.

The APAP tablet formula consisted of 10%, 20%, or 30% APAP, 0.5% magnesium stearate (Food Grade D, Witco Chemical), and the balance as lactose.

Mixtures were blended for five minutes in a Patterson-Kelley twin shell blender. Compacts were prepared on a Stokes model RB-2 rotary press instrumented with Kistler load cells to measure compaction and ejection forces. Four of the sixteen stations were used. They were equipped with 3/8 inch flat-faced, beveled edge punches (Elizabeth Carbide Die Co.) The Press was primed by producing 8-10 tablets by hand turning, and then tablets were produced (ca. 120 min.) at pre-determined compaction forces. Tablet weights were maintained at 382mg +/- 1.5%. Tablets were analyzed for hardness, friability, dissolution times and reworkability.

For APAP dissolution time, the apparatus was set according to procedure [711] of the U.S. Pharmacopoeia/National Formulary XVI (1985). Six tablets were added to the stirred reactor (100 rpm) containing 900ml-distilled water at 36-37°C. A sample was withdrawn after 2 minutes, then every five minutes thereafter. After a 1:20 dilution, the absorbance at 240nm was measured. The dissolution time was taken as the time when the absorbance ceased to increase.

In the DTHV compaction study the various lactose grades were blended for five minutes with 1% magnesium stearate and compacted on an instrumented ten-station rotary press (Globe Pharma).

For compression and ejection force measurements, the press was fitted with load cells and software to automatically measure and record force.

For tablet hardness, an automated tablet tester (Pharma-Test PTB 311E 3 in 1 tester) was used to measure the force required to break the tablet.

For the disintegration time, the apparatus was set according to procedure [701] of the U.S. Pharmacopoeia/National Formulary XXIV (2006). Six tablets were added to the basket rack assembly. The emersion fluid contained e-pure water held at 36-37°C. Disintegration time was taken at the time when all tablets were fully dissolved.

For reworkability, a formulation of 10.0% APAP, 05% magnesium stearate and 89.5% lactose was compressed to produce tablets with a hardness of 4.5-5.6Kg. Tablet properties were measured, then the tablets were ground to standard mesh distribution and recompressed. Extra magnesium stearate was not added; tablet weights were adjusted to equal the range of initial tablets, viz. 382mg +/- 1.5%.

A Beckman Coulter laser particle size analyzer was used to measure the product particle size curves.

Inhalation Lactose Method Used to Determine Data

A Beckman Coulter laser particle size analyzer was used to measure the product particle size curves.

For the moisture uptake studies, a temperature/ humidity chamber equipped with a calibrated balance was used.

Albuterol Method Development. Two HPLC methods were developed for the analysis of albuterol sulfate. The method used to analyze the samples from the blending studies is linear from 10-50 (g/ml with no individual standard deviations greater than 3%. The HPLC method that was utilized for the ACI sample analysis is linear from 0.1 to 1 (g/ml with no individual standard deviations greater than 2%.

Micronization of Albuterol. Micronization of albuterol sulfate was preformed using a jet mill with an inlet and opposing pressure of about 1000psi. The albuterol sulfate was characterized (pre- and post-micronization) by laser diffraction particle sizing. Laser diffraction showed a decrease in particle size from X50 of ~9.2 (m and X90 of ~34.66 (m (unmicronized) to a X50 ~1.87 (m and X90 ~4.68 (m (micronized).

Blending Procedure. Micronized albuterol sulfate was mixed separately with the three different grades of lactose in a ratio 1:100 (w/w), which is in close accordance with the ratio employed in the

commercial Ventolin Rotacaps. Albuterol sulfate was mixed with lactose using geometric dilution followed by blending in the Turbula mixer. The blend homogeneity was determined as a function of blending time, six samples were taken post-blend (each 25+/- 5 mg) from different regions of the blend and analyzed by HPLC.

Anderson Cascade Impaction (ACI) Studies. A test method was developed for performing Anderson Cascade Impaction (ACI) testing of the lactose/albuterol dry powder using the current United States Pharmacopoeia convention as a starting point.

The ACI studies were conducted by sampling the aerosol powder from the dry powder inhaler (Aerolizer), at the flow rate determined, through an eight-stage cascade impactor (Anderson Samplers, Inc., Smyrna, GA, non-viable, inertial impactor). The stages will be coated in accordance with the specifications set out in the United States Pharmacopoeia. An Aerolizer will be tested with three collections preformed (n=3).

Five hard gelatin capsules (Size 3) were filled with 25 +/- 2 mg of each blend mixture. The impactor plates (-1 to 6) were coated with silicone oil. A filter paper was place in the last stage of the impactor and 10 ml of 0.01 N HCL was introduced in the preseparator. The impactor was assembled and an Aerolizer containing a filled capsule was fitted into a molded rubber mouthpiece attached to the throat of the impactor and aerolized at 60 +/- L/min for 4 seconds. The deposition test was repeated until four more capsules were actuated in the same manner. After all the 5 capsules had been actuated the impactor was dismantled and the impactor plates, filter paper, inhaler body, mouthpiece, throat, casing and preseparator were washed with 0.01 N HCL. Method development work was preformed to determine the amount of 0.01 n HCL required for washing of the plates so as to be within the working range for HPLC analysis. The concentration of albuterol sulfate in the samples was determined by HPLC. Each blended formulation was tested three times.

A recovery study was also preformed to ensure that the washing solvent was recovering the entire albuterol sulfate on the impactor plates. This was done by adding a known amount of albuterol sulfate solution to the impactor plates, washing the plates with 0.01 n HCL and analyzing the washings by HPLC. A recovery of 98% was obtained.

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