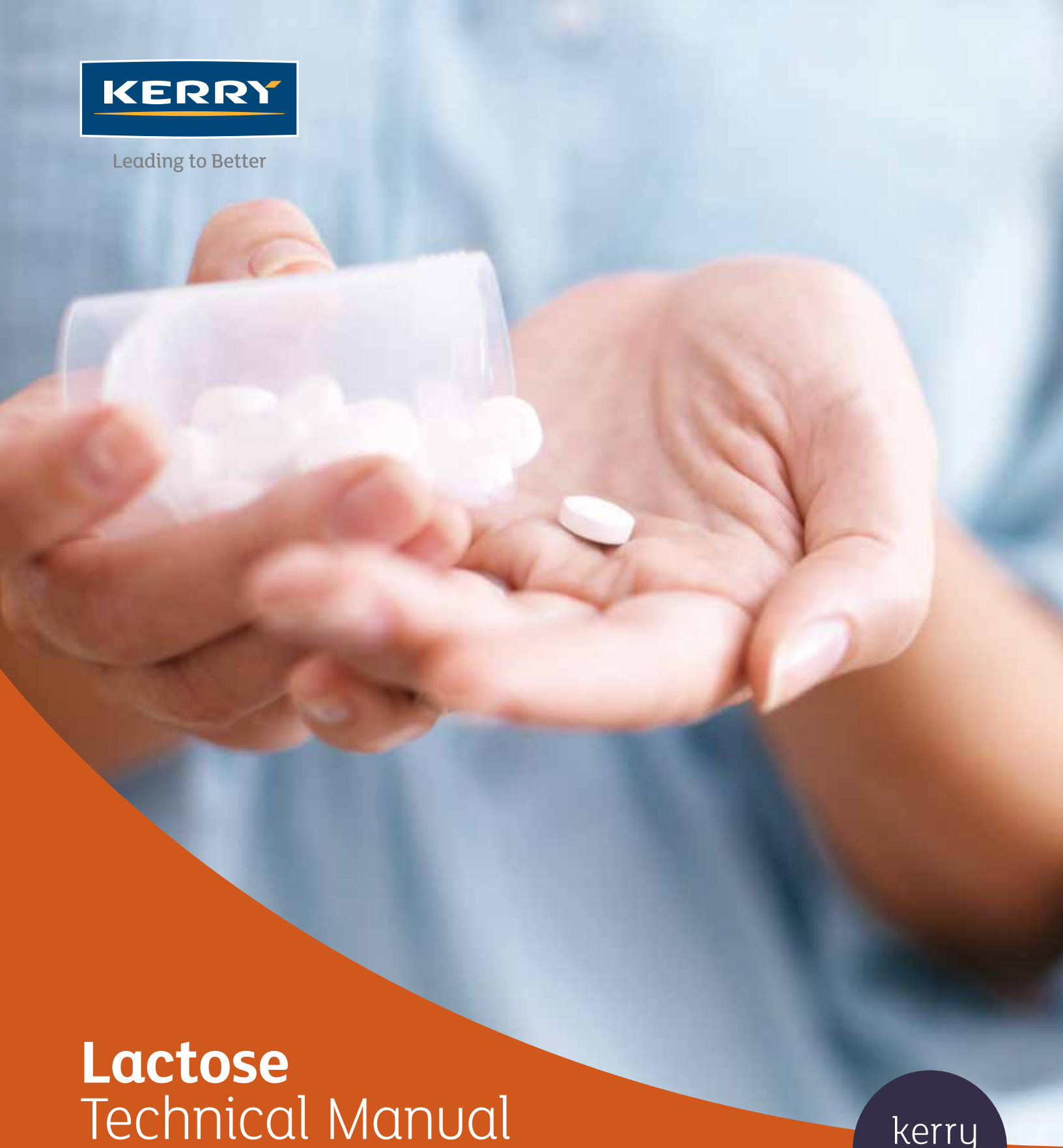
KERRY

Leading to Better



Lactose
Technical Manual

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

kerry.com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Content

Kerry Pharmaceutical Grade Lactose

Crystalline Monohydrate	Spray Dried Monohydrate	Anhydrous Lactose	
Sheffield™ Capsulating Grade	Sheffield™ Spray Dried 315	Sheffield™ Anhydrous DT	Sheffield™ DTHV-I
Sheffield™ 80M	Sheffield™ Spray Dried Fast Flo® 316	Sheffield™ Anhydrous 60M	
Sheffield™ 200 Mesh		Sheffield™ Anhydrous Impalpable	
Sheffield™ Impalpable			
Sheffield™ Monohydrate 310			
Sheffield™ Monohydrate 312			
Sheffield™ Monohydrate 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 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
Sheffield™ Monohydrate 310	Wet or dry granulation (coarse)
Sheffield™ Monohydrate Capsulating Grade	Wet or dry granulation (medium)
Sheffield™ Monohydrate 312	
Sheffield™ Monohydrate 80M	Wet or dry granulation (medium/fine)
Sheffield™ Brand 200 Mesh	
Sheffield™ Monohydrate Impalpable	Wet or dry granulation (fine)
Sheffield™ 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™ Monohydrate Lactose is crystalline alpha-monohydrate anomers. Sheffield™ brand 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.

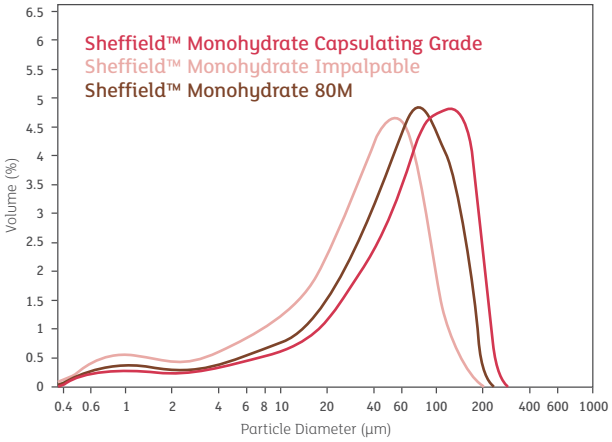
The standard packaging is a polyethylene lined fiber drum with tamper evident seals. The standard net weight for Sheffield™ Monohydrate Lactose is 95kg, but Monohydrate Impalpable is 90kg. This product is also available in 100 lb drums or 25kg paper sacks upon request. The standard net weight for Sheffield™ Monohydrate 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™ Lactose meets all requirements of the NF, Eur.Ph. and JP.

Particle Size Curves

DIFFERENTIAL VOLUME



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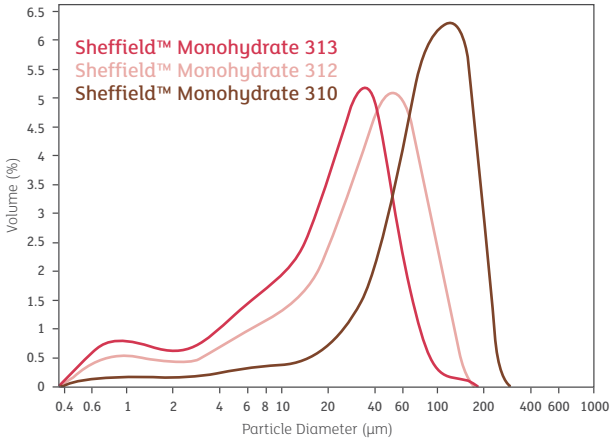
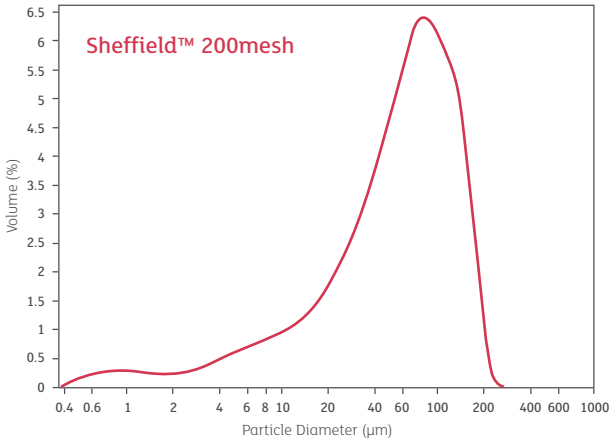
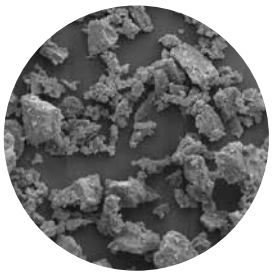


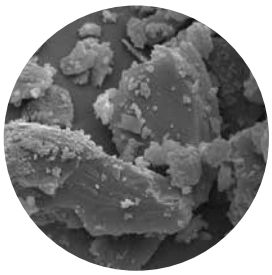
DIFFERENTIAL VOLUME



Sheffield™ Brand SEMs (Scanning Electron Microscope Image)



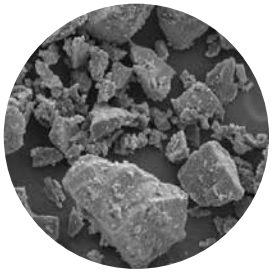
Monohydrate Impalpable
300X



Monohydrate Impalpable
1500X

Monohydrate 80M
300X

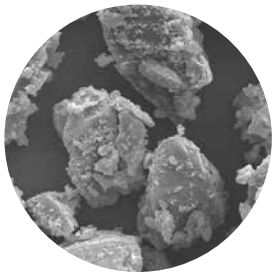
Monohydrate 80M
1500X



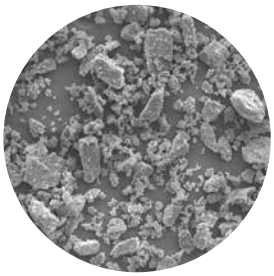
Monohydrate Capsulating
Grade 300X

Monohydrate Capsulating
Grade 1500X

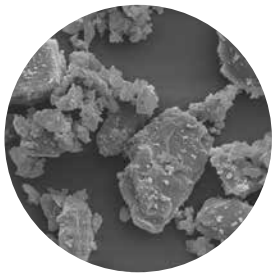
Monohydrate 310
150X



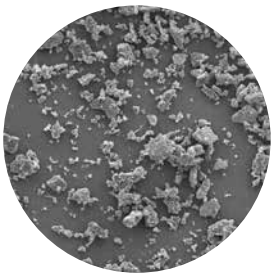
Monohydrate 310
600X



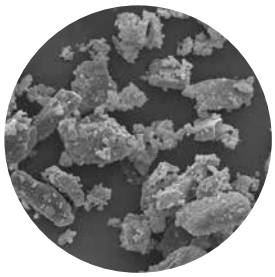
Monohydrate 312
150X



Monohydrate 312
600X



Monohydrate 313
150X



Monohydrate 313
600X

Monohydrate 200 Mesh
300X

Monohydrate 200 Mesh
1500X

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™ Monohydrate 80M	54.9	33.6	0.91
Sheffield™ Monohydrate 312	54.9	33.6	0.91

Stability Data

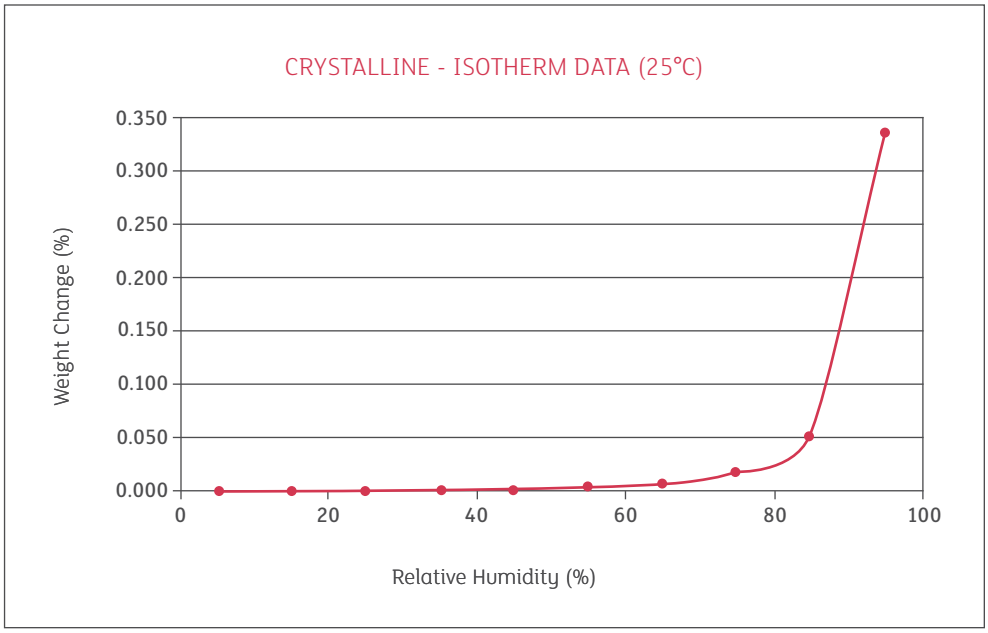
Typical lot of Monohydrate Capsulating Grade

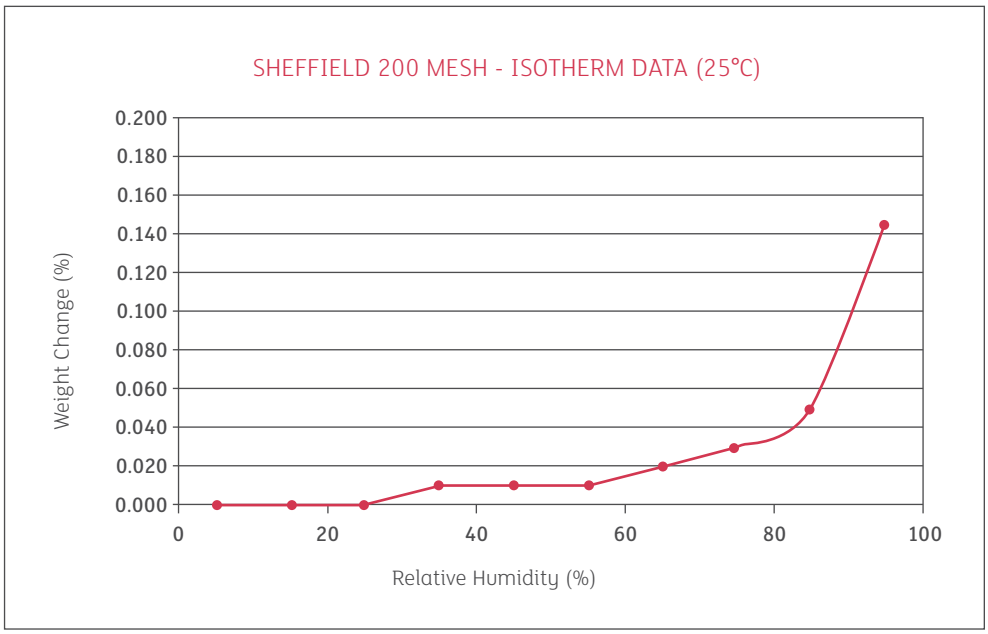
Lot# M021626

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.

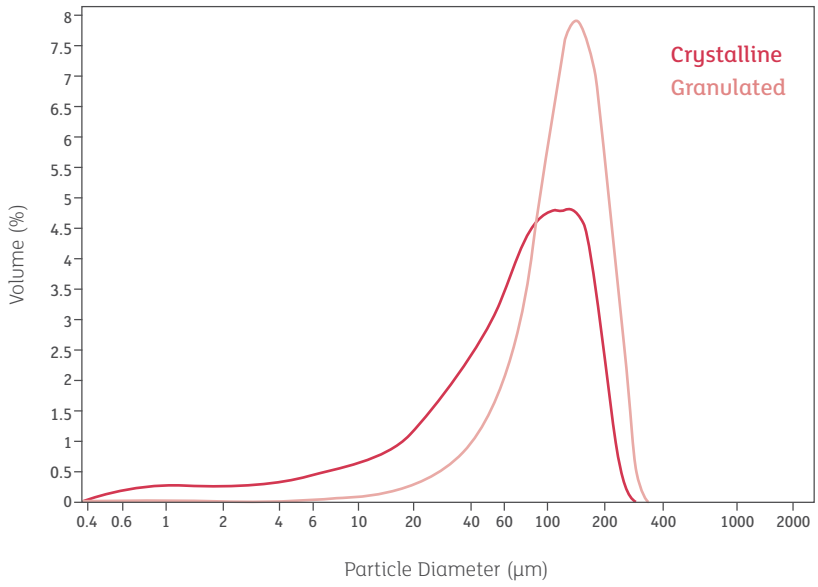
Wet Granulation Formula

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

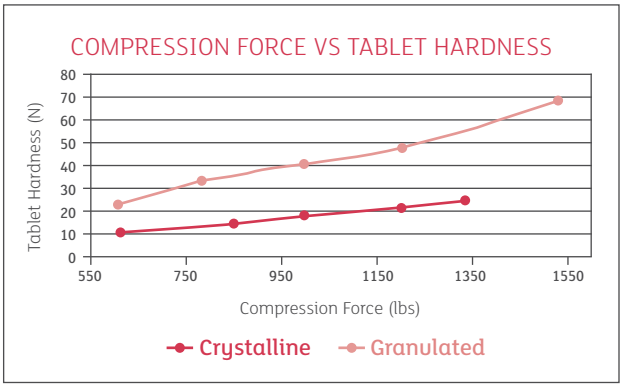


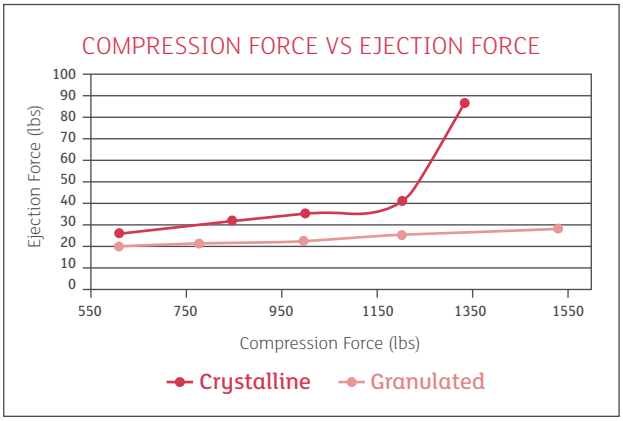
Application Data

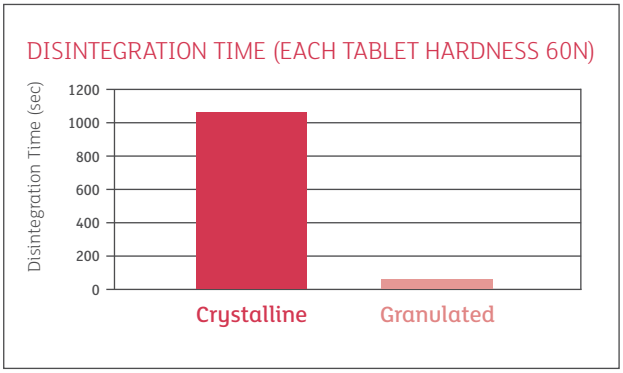
Compaction Properties

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

Spray dried grades include Sheffield Lactose Monohydrate Spray Dried 315 and 316 Fast Flo®. Sheffield™ Spray Dried 316 Fast Flo® is ideal for direct compression and Sheffield™ Spray Dried 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
Sheffield™ Spray Dried 315	Direct tabletting and capsule filling
Sheffield™ 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. Sheffield™ Monohydrate Lactose 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

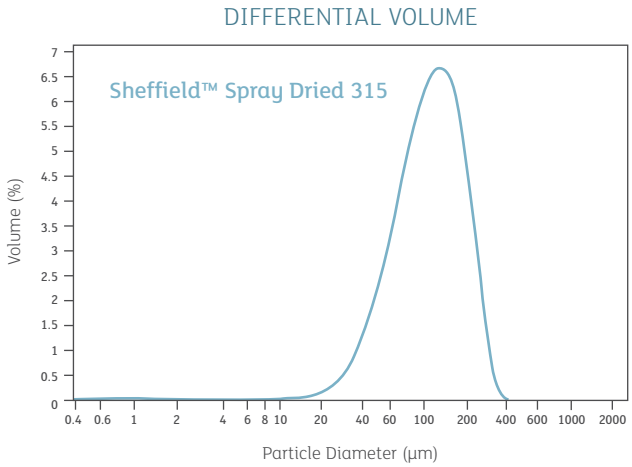
Store in a cool, dry area with container closed when not in use. A minimum shelf life of 18 months for spray dried 315 and 12 months for 316 Fast Flo®.

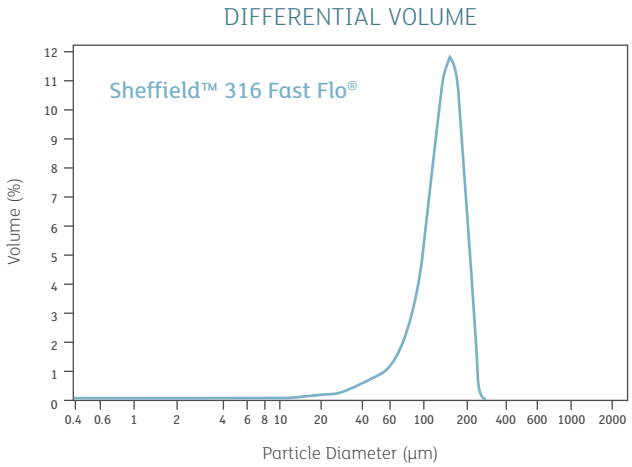
The standard packaging is a polyethylene lined fiber drum with tamper evident seals. The standard net weight for 315 is 95kg and 316 Fast Flo® is 75kg. Products are also available in 40kg drums or 25kg paper sacks upon request.

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

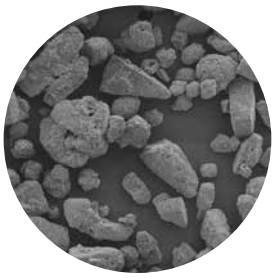
Sheffield™ Lactose meets all requirements of the NF, Eur.Ph. and JP.

Particle Size Curves

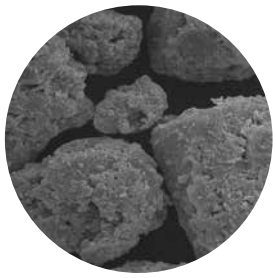




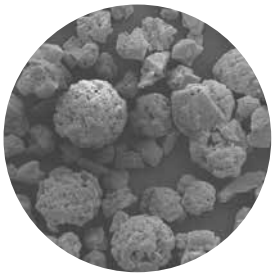
SEMs (Scanning Electron Microscope Image)



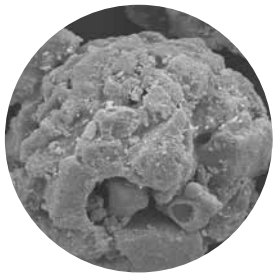
Monohydrate 315
150X



Monohydrate 315
600X



Monohydrate 316 Fast Flo®
150X



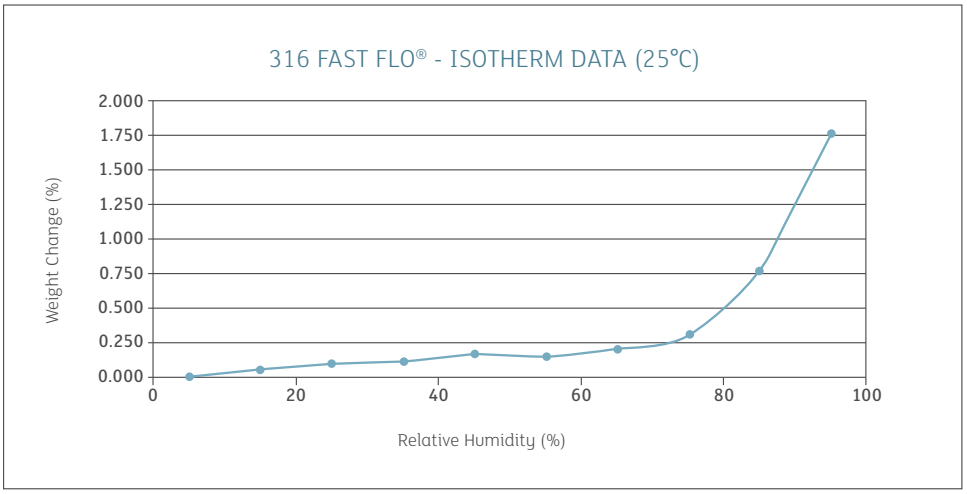
Monohydrate 316 Fast Flo®
600X

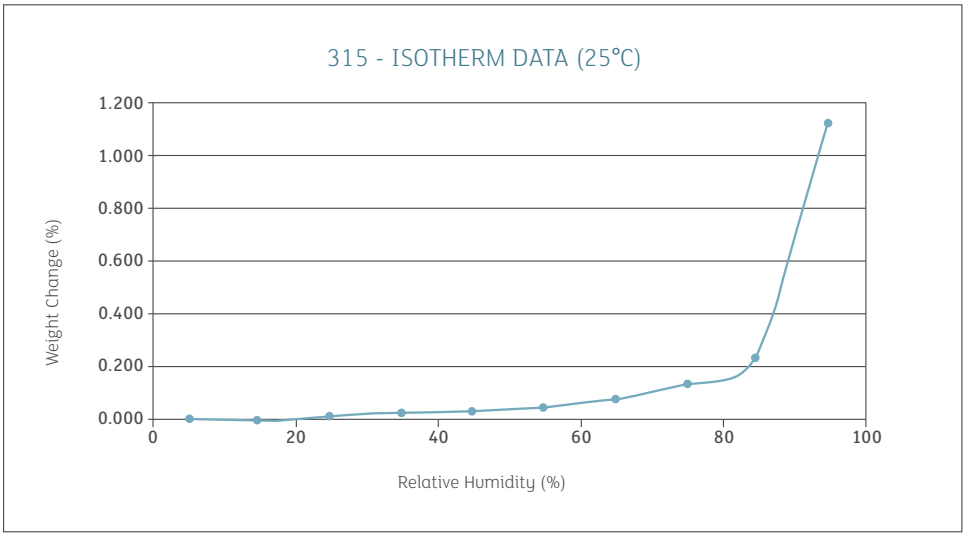
Spray Dried Lactose Monohydrate

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





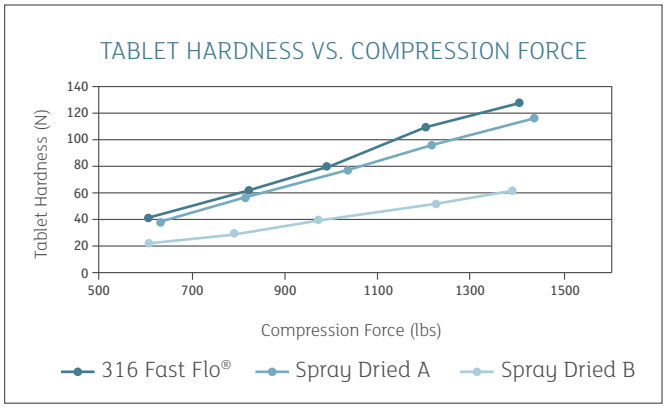
Application Data

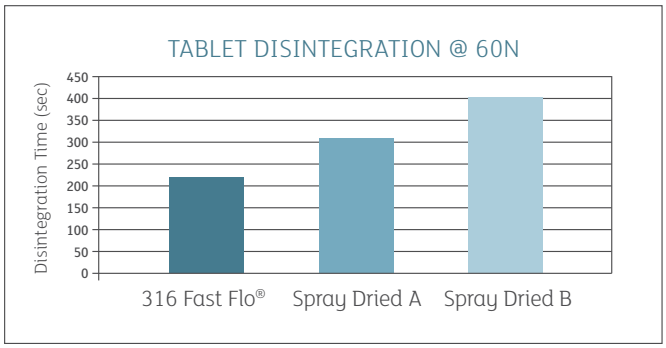
Direct Compression

Lactose Monohydrate spray dried is typically used for direct compression. Sheffield™ 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 Sheffield™ 316 Fast Flo® compared to other spray dried lactose.

Products Tested
(all contain 1% Magnesium Stearate)

- Sheffield Fast Flo® 316
- Spray Dried A
- Spray Dried B





Compaction Properties

Tablet hardness versus compaction force profiles for the Sheffield™ 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™ Anhydrous Direct Tableting (DT)	Direct tableting (high flow not required)
Sheffield™ Anhydrous 60M	
Sheffield™ Anhydrous Impalpable	Granulations or Direct tableting (fine)
Sheffield™ Anhydrous DTHV-I	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™ Anhydrous Lactose 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.

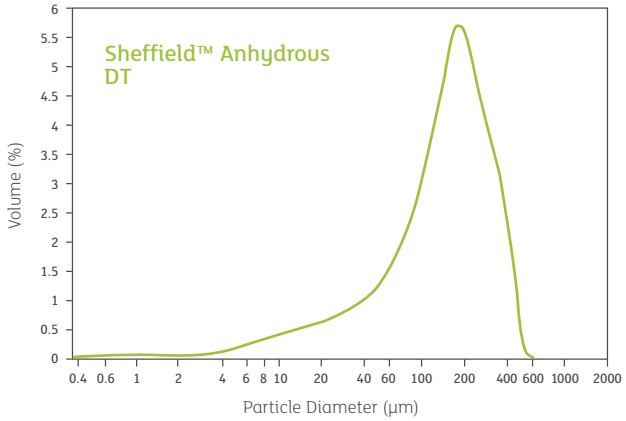
The standard packaging is in 80kg polyethylene lined fiber drums with tamper evident seals. All products are also available in 100lb drums and 25kg paper sacks upon request.

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

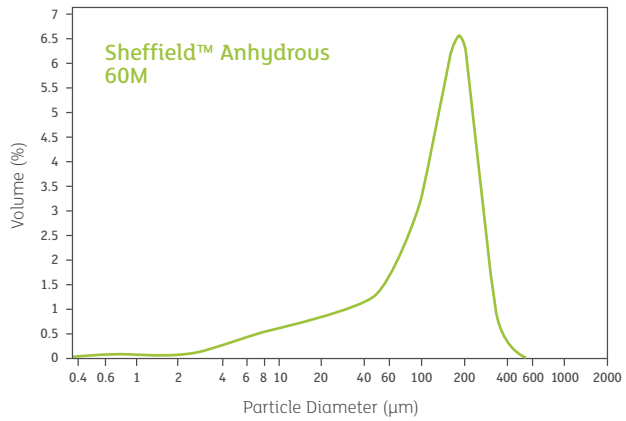
Sheffield™ Lactose meets all requirements of the NF, Eur.Ph. and JP.

Particle Size Curves

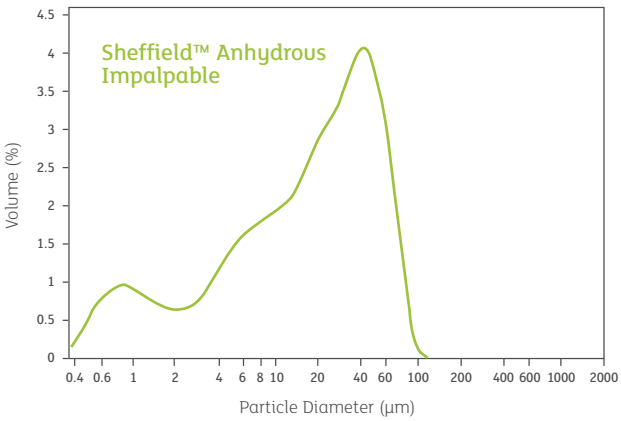
DIFFERENTIAL VOLUME



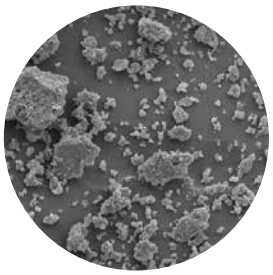
DIFFERENTIAL VOLUME



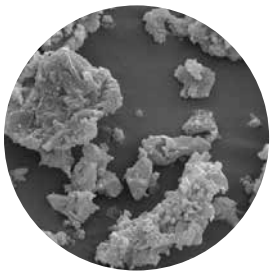
DIFFERENTIAL VOLUME



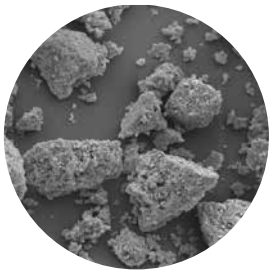
SEMs (Scanning Electron Microscope Image)



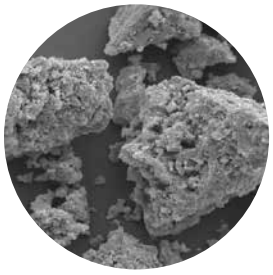
Anhydrous DT
300X



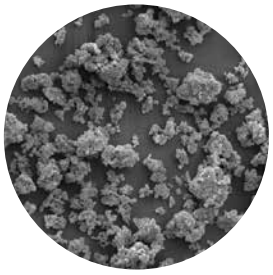
Anhydrous DT
1500X



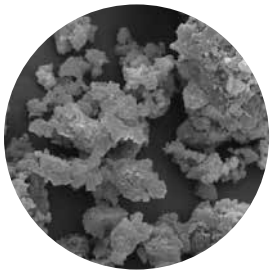
Anhydrous 60M
300X



Anhydrous 60M
1500X



Anhydrous Impalpable
300X



Anhydrous Impalpable
1500X

Anhydrous Lactose

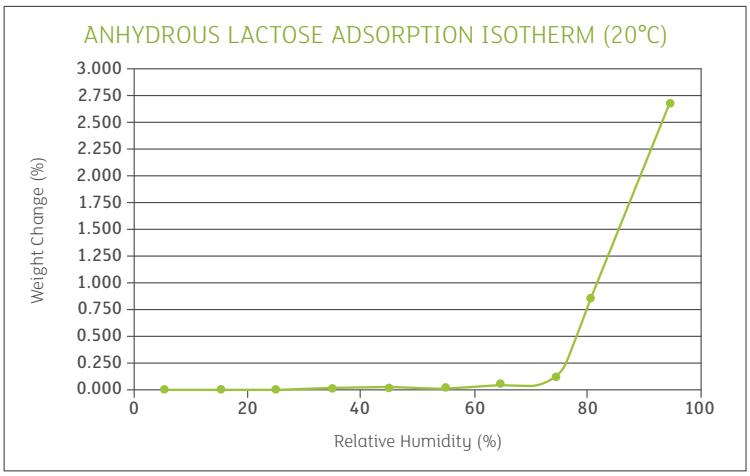
Typical Isomer Ratio

% 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

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-I, which has the same superior tableting properties as Anhydrous DT but with exceptional flow. Sheffield™ 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-I 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.

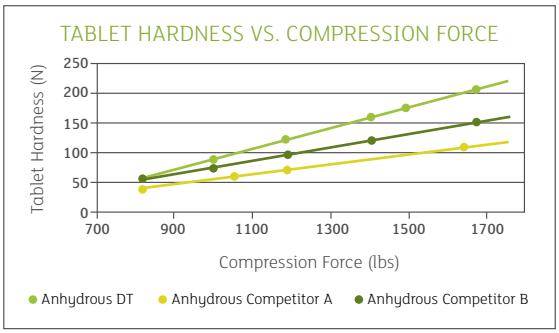
Compaction Properties of Anhydrous DT

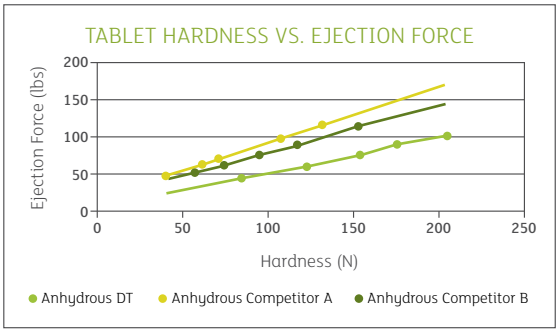
Tablet hardness versus compaction force profiles for lactose formulas are shown in the below figures. Analysis of the data concluded that Sheffield™ Brand Anhydrous DT forms harder tablets at lower compaction forces relative to the other products tested. Sheffield™ Brand Anhydrous DT also exhibited lower 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™ 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.

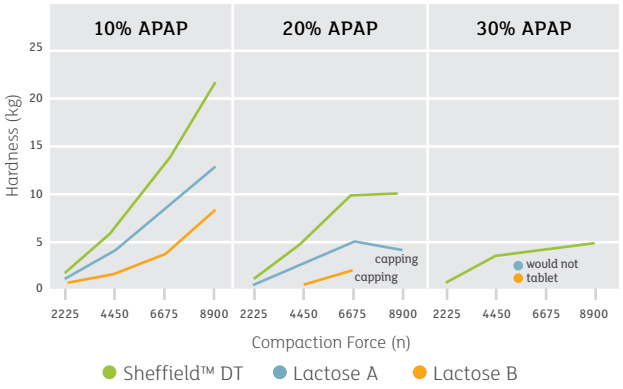
Higher compaction profiles were obtained for Anhydrous DT for three APAP formulations as shown in the below figure. As the APAP concentration increased, tablet hardness decreased for all three products. Only the use of DT Grade resulted in suitable tablets at 20% APAP, where both Lactose A and B began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



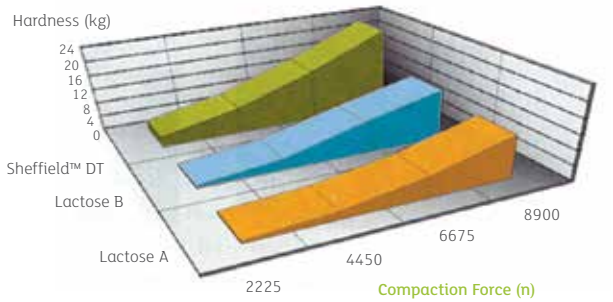


Application Data Lactose Anhydrous DT

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™ 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™ 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.

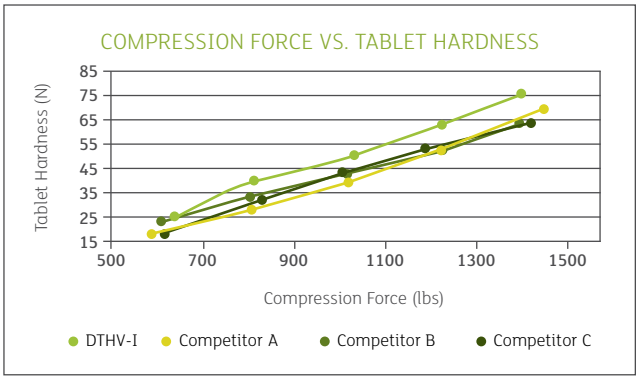
Properties of 10% APAP Tablets before and after rework.

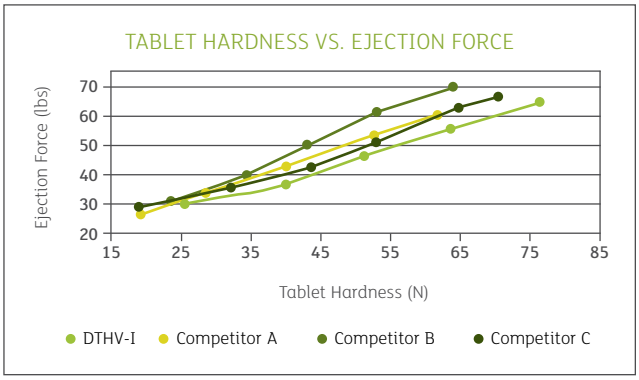
Property	Hardness		Friability		Dissolution	
	Initial	Rework	Initial	Rework	Initial	Rework
Sheffield™ DT	5.2	5.5	0.25	0.25	20	18
Lactose A	5.6	5.8	0.52	0.39	35	30
Lactose B	4.5	4.6	0.66	0.51	18	25

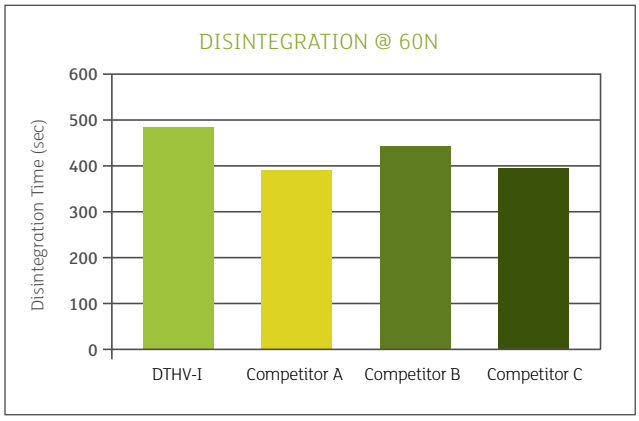
Application Data Lactose Anhydrous DTHV-I

Compaction Properties of Anhydrous DTHV-I

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™ Anhydrous DTHV-I 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.







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-I 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.

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