KERRY

Leading to Better

Aero Flo®
Inhalation Grade Lactose

kerry.com

Dry Powder Inhalers (DPI) and Lactose

Using a dry powder inhaler (DPI) for drug delivery can provide many advantages over traditional oral delivery of pharmaceuticals. DPI's also offer advantages over older respiratory delivery methods such as those using nebulizers or pressurized CFC containing aerosols. This is due to the fact that dry powder inhalers allow for the potential to deliver a wider range of drugs than these older methods. Typically, with DPI's, the active ingredient and a carrier are blended and used to fill the inhaler; or with some inhalers, a capsule or blister that includes one singular dose. During use, the dose delivery is performed by the patient simply inhaling, or is assisted by a burst of air, depending on the type of inhaler used.

Pharmaceutical Lactose has often been used as a carrier in these applications due to its inertness, low cost, availability, particle size, and patient tolerability. However, two of the most important characteristics of the formula are: dose uniformity, and the efficiency of delivering the drug (i.e. the amount of drug that reaches the patients lungs relative to the amount in the starting dose). The selection of the grade of lactose used as a carrier will most certainly have an effect on both of these characteristics.

Kerry Introduces Aero Flo® Grades of Inhalation Lactose

Aero Flo® Brand Inhalation Grades of lactose are specifically developed for dry powder inhalation (DPI) applications. Kerry's unique processing also maintains the crystallinity of the lactose, which can be a critical factor when formulating DPI's.

Kerry has a long, and well established history of supplying world class lactose, mainly for oral solid dose & capsule filling applications. There is however, a growing demand for lactose that is suitable for developing dry powder inhalers.

In these applications, particle size, and crystal morphology play a critical role in delivering the API to the lungs, without interfering with the absorption of the drug itself.

However, we also recognize that there are important considerations to be factored in to the manufacture of the lactose, based on the API itself, as well as the design of the intended delivery device. The physical properties of the lactose can have a dramatic effect on the pulmonary delivery of the API, if the lactose is not properly paired with consideration to both (API and device) of these.

Kerry's standard grades of lactose designed for pulmonary delivery of drugs are listed below. These grades are specially engineered to have specific particle size ranges, as well as microbiological and endotoxin specifications that are demanded in these DPI applications.

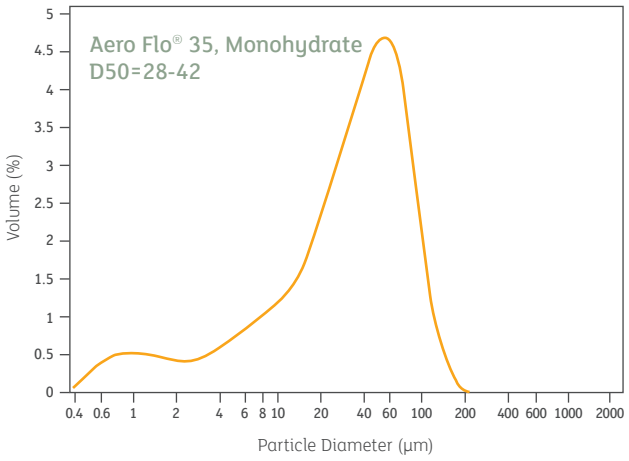
As the particle size is the key differentiator between all of the Aero Flo® grades, the other chemical attributes can be grouped as either derived from Monohydrate Lactose or Anhydrous Lactose, as per the table below. There are four inhalation grades lactose that are monohydrate lactose based (*plus a micronized version); and two inhalation grades that are based on Anhydrous lactose.

Product	Code	Specifications		
		D10	D50	D90
Aero Flo® 35, Monohydrate	5X00064	3-12	28-42	70-95
Aero Flo® 55, Monohydrate	5X00065	6-16	48-62	115-135
Aero Flo® 65, Monohydrate	5X00066	9-18	55-70	135-160
Aero Flo® 60S, Monohydrate	5X00024	19-43	53-66	75-106
Aero Flo® 25, Anhydrous	5X00032	1-6	18-30	60-85
Aero Flo® 85S, Anhydrous	5X00029	15-50	70-105	170-220

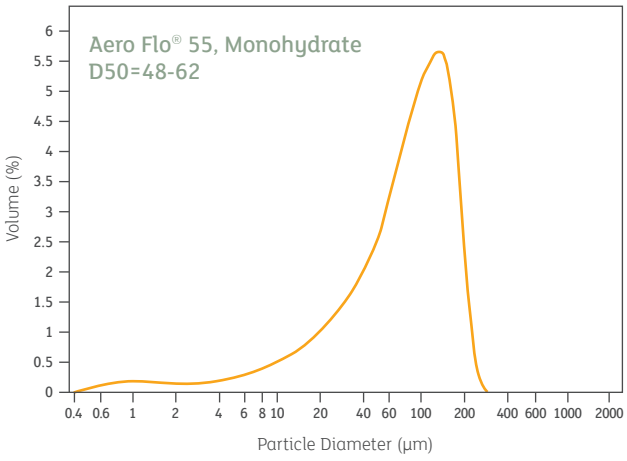
*Micronized inhalation lactose produced with Kerry lactose monohydrate is available from our partner Micro-Sphere SA (median particle size around 3 um, other sizes upon request). If you are interested in this type of product, please contact us for further information.

Particle Size Curves

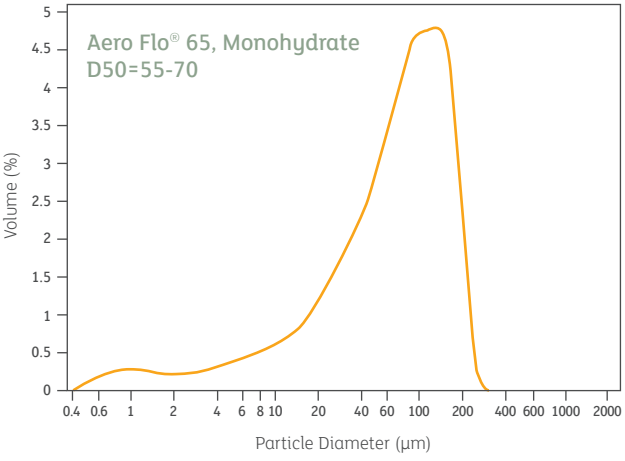
DIFFERENTIAL VOLUME



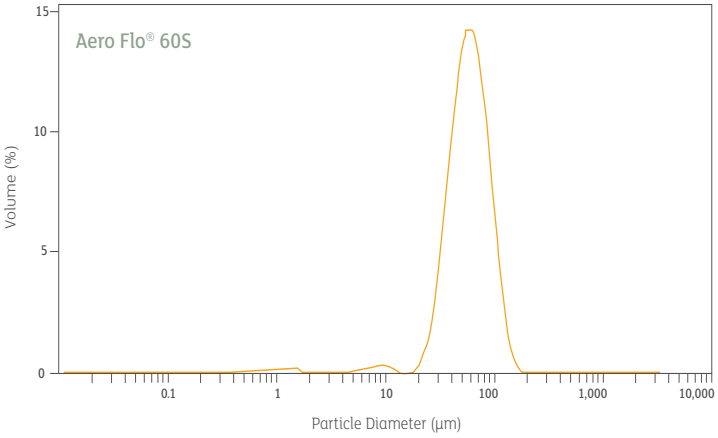
DIFFERENTIAL VOLUME



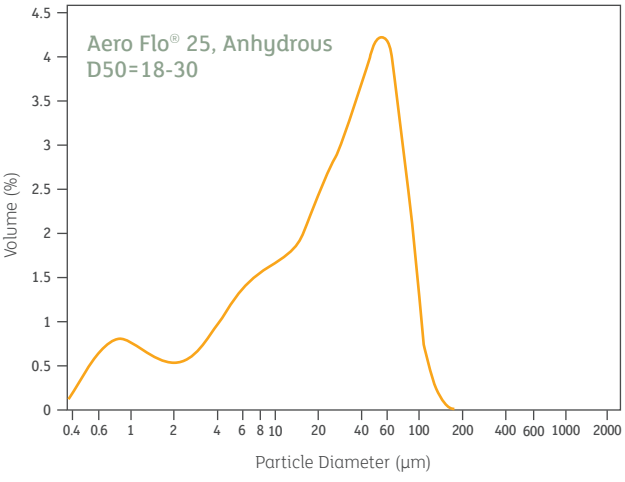
DIFFERENTIAL VOLUME



DIFFERENTIAL VOLUME

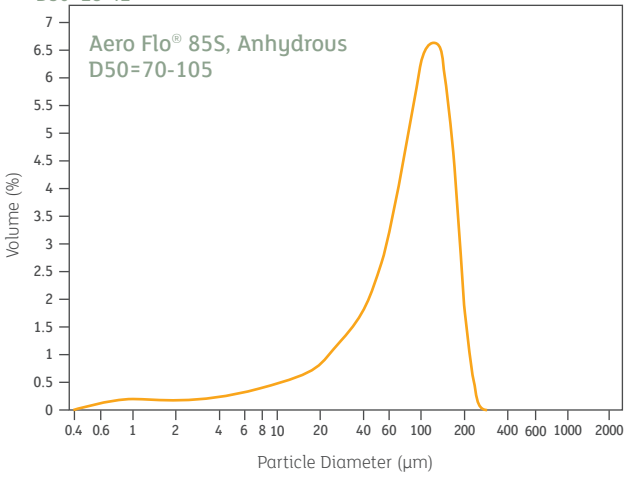


DIFFERENTIAL VOLUME

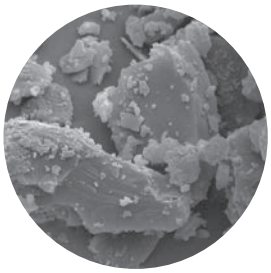


DIFFERENTIAL VOLUME

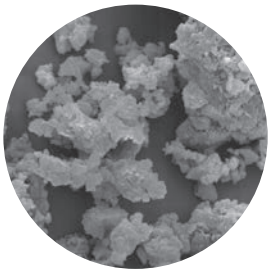
D50=28-42



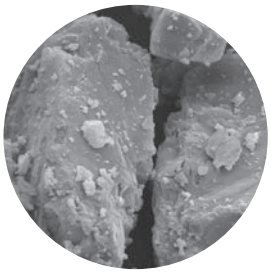
SEMs (Scanning Electron Microscope Image)



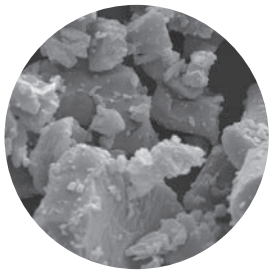
Aero Flo® 35, NF Monohydrate
1500X



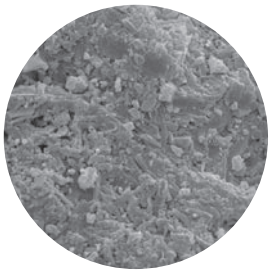
Aero Flo® 25, NF Anhydrous
1500X



Aero Flo® 55, NF Monohydrate
1500X



Aero Flo® 65, NF Monohydrate
1500X



Aero Flo® 85S, NF Anhydrous
1500X

General Physical and Chemical Characteristics

Physical Characteristics		
	Specification(Monohydrate)	Specification (Anhydrous)
Color/Clarity (400mm)	0.04 max	0.04 max
Solubility @25°C	N/A	N/A
Identification		
Appearance of solution		
Chemical Characteristics		
	Specification (Monohydrate)	Specification (Anhydrous)
Alpha Anomer	Record	Record
Beta Anomer	Record	Record
Water	4.5-5.5% max	1.0% max
Loss on drying	0.5% max	0.5% max
Residue on ignition	0.1% max	0.1% max
Sulphated ash		
Acidity/Alkalinity (6g) (0.1N NaOH)	≤0.4ml	≤0.4ml
Heavy metals (sulfide PPTN)	5ppm max	5ppm max
Heavy Metals (JP)	5ppm max	5ppm max
Specific rotation	+54.4 min/+55.9 max	+54.4 min/+55.9 max
Protein/UV absorbing impurities @210-220nm @270-300nm	 0.25 max 0.07 max	 0.25 max 0.07 max
Organic volatile impurities	absent	absent
Microbiological Characteristics		
	Specification (Monohydrate)	Specification (Anhydrous)
Total aerobic count	10/g max	10/g max
Eschericia coli	negative	negative
Salmonella	negative	negative
Enterobacteriacae	10/g max	10/g max
Pseudomonas aeruginosa	negative	negative
Staphylococcus aureus	negative	negative
Endotoxins	5.0 EU/g max	530 EU/g max
Yeasts and Molds	10/g max	10/g max

All of our inhalation grades of lactose are packaged in 25kg, polyethylene lined HDPE drums, and meets the most current requirements of NF, Ph Eur and JP monographs for pharmaceutical lactose.

Aero Flo® Samples

Samples are available in 500g sample packs, and are available upon request.

Application Data

Aero Flo® Case Study

Kerry commissioned an independent case study to investigate the suitability of several different grades of Aero Flo® in combination with two different API's that are commonly delivered using dry powder inhalers, Salbutamol Sulphate (hydrophilic drug) and Fluticasone Propionate (hydrophobic drug). A summary table of that study is below.

Particle Size	Aero Flo® 35	Aero Flo® 25	Aero Flo® 65	Aero Flo® 85S	Aero Flo® 65	Aero Flo® 85S
D10	3-12	1-6	9-8	15-50	9-8	15-50
D50	28-42	18-30	55-70	70-105	55-70	70-105
D90	70-95	60-85	135-160	170-220	135-160	170-220
Cascade Impactor Studies	**Albuterol Sulphate**				**Fluticasone Propionate**	
Drug Content in the Capsules (µg)	1188.3	1256	387	376	373	367
Recovered Dose (RD) (µg)	1158.7	1121	374.4225	353.5904	350.7692	345.1268
% Recovery	97.5	96.6	96.75	94.04	93	92
Emitted Dose (ED) (µg)	1028.4	1116.1	357.61	346.44	350.98	347.93
% Emission	86.5	88.4	92	92	94	95
Fine Particle Dose (FPD)	558.7	565.5	119.92	90.42	81.86	41.75
Fine Particle Fraction as a Function of RD (%)	48.2	46.3	32	26	23	12
Fine Particle Fraction as a Funcion of ED (%)	54.4	50.6	34	26	23	12

As would be expected, the API itself can affect the Fine Particle Dose. FPD is a critical parameter in measuring the efficacy of DPI as this measures the mass of particles that are less than 5 microns in the emitted dose.

In all cases above the Total Emitted Dose (TED) was calculated by summing the amount of drug deposited in the USP throat, preseperator, the various stages of the impactor and the filter.

All formulations produced very good content uniformity of drug in the delivery device, and showed acceptable (>85%) TED. However, FPD results varied depending on whether the lactose was monohydrate or Anhydrous, as well as the particle size distribution of the lactose itself.

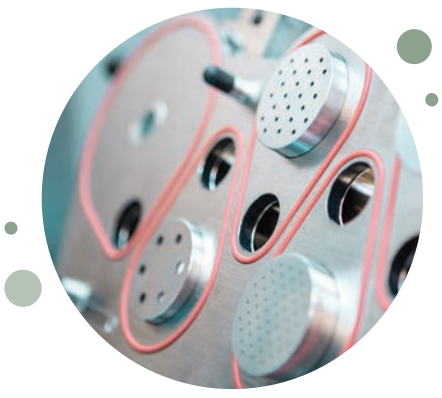
It is therefore very important that you work very closely with your lactose supplier with due consideration for these variables, as well as the API and delivery device itself.

Kerry's Partnership with Micro-Sphere S.A. for DPI Formulations

Kerry has also established a partnership with Micro-Sphere S.A. to assist customers with the development of their DPI formulations. Through this partnership, we are able to provide customers with in depth assessments of a customer's DPI (dry-powder inhaler) formulation to determine critical characteristics such as:

- Particle Size and Morphology:
  - -Laser diffraction
  - -Optical microscope and SEM
- Aerodynamic Particle Size Distribution and API delivery efficiency:
  - -NGI (Next Generation Impactor)
  - -ACI (Andersen Cascade Impactor)
  - -MSLI (Multi Stage Liquid Impinger)
- Delivered Dose and Uniformity of Dosage:
  - -DUSA (Dosage Unit Sample Apparatus)
- Stability studies according to ICH guidelines

Additionally, Micro-Sphere S.A. can assist our customers with DPI analytical method development, formulation optimization, scale-able transfer, as well as validation; all in advance of clinical development. If you are interested in working with us to take advantage of what Micro-Sphere S.A. can do for your formulation, please contact us for further information.



kerry
.com

KERRY