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CHARACTERIZATION OF POWDER FLOW PROPERTIES USING POWDER RHEOMETRY

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ABSTRACT

Surface morphology of powder formulations can affect their flow properties. In this study, the powder flow characteristics of a high drug payload powder formulation manufactured as a ternary mixture and a co-spray dried formulation was studied. The bulk powder properties, dynamic flow properties and shear properties were studied using the FT4 Rheometer. The ternary mixture consisting of irregularly shaped particles exhibited higher conditioned bulk density, specific energy, aeration energy, pressure drop, compressibility values and low flow function values, indicating it is more cohesive than the spray-dried formulation. The spray-dried formulation consisting of smoother rounded particles exhibited improved powder flow properties compared to the ternary mixture. The powder rheometry study data provided insight into powder properties and correlated well with the influences of surface morphology of the two formulations in this study.

KEYWORDS: Ternary Mixture, Spray drying, Powder Rheometry.

1. INTRODUCTION

Powder formulations are complex systems consisting of solids, gases, and liquids, with the particles (solid) suspended in air (gas), and often, there is adsorbed moisture (liquid) on the particles [Freeman 2014]. A large number of factors affect the flow behaviour of powder formulations e.g., van der Waals forces (Zhou, 2010; Donovan, 2011), intermolecular attractive forces collectively called cohesive forces, adhesives forces which are attractive forces between different molecules (Donovan, 2011), i.e., drug and excipients. Powder flow is sensitive to particle shape (Schulze, 2014; Mukherjee, 2012) and surface roughness (Donovan, 2011). Powder-processing operations like milling, sieving, and blending can generate vast quantities of electrostatic charge due to the movement of powders, i.e., triboelectrification (le, 2012), which can result in segregation and problems with powder flow in process equipment. The influence of multiple parameters makes it challenging to predict the behaviour of powder formulations. Powder rheometry studies give insight into the powder behaviour so that the powder handling processes like blending, capsule filling, tablet compression, product stability and storage can be defined.

In this study, a powder for inhalation formulation consisting of salbutamol sulphate (SS), a bronchodilator, Ciprofloxacin HCl, an antibiotic, and Mannitol, a mucolytic, was developed as a potential combination therapy for chronic lung diseases with mucus hyper-secretion and with Pseudomonas aeruginosa infection. The formulation was prepared as a ternary mixture using the physical blending process and spray drying process. The powder for inhalation formulation contained a high percentage of fine drug particles, making it cohesive, and this could lead to handling and processing challenges. Spray-drying the formulation is an alternate option, and this process is commercially scalable, e.g., the marketed product TOBI Podhaler is based on the spray-drying technology (Miller, 2015) platform PulmoSphere^{TM}.

The formulations were studied for the effect of particle morphology on powder flow properties. Traditionally, bulk powder properties were estimated by measuring the poured and tapped bulk density, Hausner ratio, and Carr's Index (Schulze, 2014). In this study, the FT4 Rheometer Freeman Technology, Worcestershire, UK., was used to study the two formulations as it enables the comprehensive measurement of different powder properties, e.g., Bulk properties, dynamic flow properties, and shear properties.

2. MATERIAL AND METHODS

The raw materials Ciprofloxacin HCl (Aarti Industries, India), Salbutamol sulphate (Cipla Ltd, India), and Mannitol (donated by Indeus Life Sciences Pvt. Ltd, India) were used to prepare test formulations.

2.1 Preparation of test formulations

The ternary mixture containing micronized Salbutamol as sulphate and Ciprofloxacin as hydrochloride with Mannitol in the ratio 0.2: 32.5: 80 was prepared by sieving to remove any agglomerates and tumble blended in a stainless-steel jar for 15 mins. The mixture was allowed to equilibrate for a minimum of 24 hours before commencing testing.

The spray-dried formulation was manufactured using LabUltima Spray dryer, India. The particles were prepared by spraying a 2 % aqueous solution of Salbutamol as sulphate, Ciprofloxacin as hydrochloride and Mannitol in the same ratio as the ternary mixture using a two-fluid spray nozzle. The feed rate was 2 ml/min, and the atomizing pressure was set between1.3-1.5 bar. The Inlet temperature was set between 100-130 °C to obtain an outlet temperature of 85 ±10°C.

2.2 Scanning electron microscopy (SEM)

The morphology of both formulations was determined using a scanning electron microscope (Model Supra 5; Carl Zeiss, Germany) operated at 10 kV. The samples were mounted on a metal stub with double-sided adhesive tape and were gold-coated under a vacuum before imaging.

2.3 Particle size by laser

The measurement of the particle size distribution of the powders has been done by a Mastersizer 3000 laser particle size analyzer (Malvern Instruments Ltd., Worcestershire, UK) supplied with an Aero S dry dispersion unit. Dispersion conditions were 3.5 bar, 30 % feed rate and a hopper gap of 2 mm. Measurement parameters were obscuration of 0.1–15, particle refractive index and absorption of 1.620 and 0.1, respectively, and the dispersant refractive index for air was 1.000. Calculations were performed using Mastersizer software.

2.4 Powder rheometry

Powder rheometry tests were conducted using FT4 Rheometer – Freeman Technology, Worcestershire, UK. The samples were tumbled before testing to put them into a homogeneous state with respect to segregation. Conditioning of the blend was done by rotating the 23.5 mm blade (*a* 5° helix) in a clockwise direction, with a tip speed of 100 mm/s, using the set-up of a 25 mm split vessel with a built-in balance. Sample conditioning cycle was performed to remove any pockets of air, local compaction, and variability due to the operator handling the powder (Freeman; Freeman 2006).

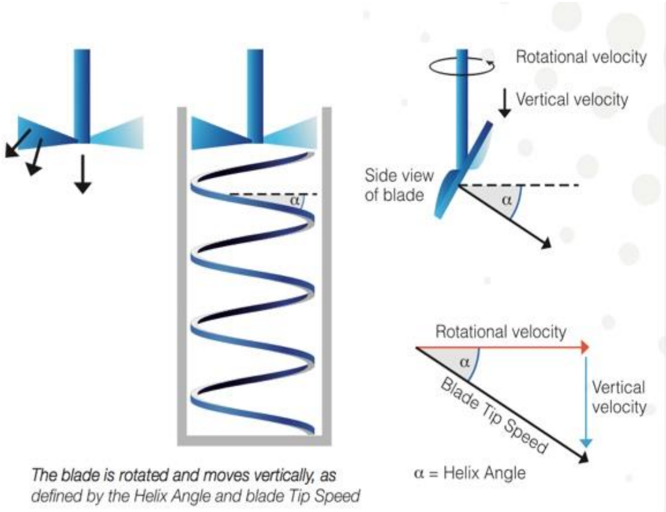

Fig. 1: Dynamic flow measurements (© Freeman Technology).

2.4.1 Dynamic flow properties

Dynamic flow properties were studied by rotating the blade with a tip speed of 100 mm/s in the conditioned precise volume of powder and measuring the torque and the axial force acting on the blade (Fig. 1). The resistance to the flow is calculated and expressed as flow energy. For the test of *Stability Index (SI),* seven consecutive conditioning, and test cycles were performed, and energy measurements were recorded. *Basic flowability energy (BFE, mJ)* was the 7th energy measurement during the test for SI. *Specific energy (SE, mJ/g)* was measured during the upwards-clockwise movement of the blade with the powder in an unconfined state.[9 - 12] The *Flow rate index (FRI)* was measured as the response of the powder to changing flow rates.

2.4.2 Aeration

Aeration was the measure of the changes in flow properties due to the introduction of air into the sample. Aeration measurements were conducted using a 25 mm dia. x 35 ml non-split vessel with a porous base. The test was conducted at variable air velocities and measuring the Aerated energy, AE at those velocities.[13]

2.4.3 Bulk powder properties

Conditioned Bulk Density (CBD) was studied using a 25 ml split vessel with a built-in scale after the conditioning cycle was performed, the test vessel was split, and CBD was calculated by dividing the weight of split mass after conditioning by the volume after splitting.[14]

Compressibility was measured by compressing conditioned powder using a vented piston and subjecting it to a range of stress between 1-15 kPa, and the change in powder bed height was measured.[15]

Permeability Test was conducted at a constant air velocity of 2mm/s while the normal stress applied by the vented piston was increased from 1 kPa to 15 kPa in eight steps.[16]

2.4.4 Shear properties

Shear properties were measured using a 23.5 ml shear cell kit. The Flow Function coefficient (FF or ffc) was used to grade the flowability of the powder and is calculated from the ratio of MPS to UYS.[15,26]

3. RESULTS AND DISCUSSION

3.1 Scanning electron microscopy

The difference in particle shape and surface morphology of the formulations was seen in the SEM images. The ternary formulation consisted of irregularly shaped particles with rough surfaces (Fig. 2), whereas the spray-dried formulation consisted of all three components in a matrix state and had a smooth, rounded surface (Fig. 3); this was in line with the expectation from the spray method used for the manufacturing process. Surface morphology also plays a role in the processing and handling of powders during manufacturing. The smooth spray dried particles are expected to have better flow properties, which was further studied in the powder rheometry section.

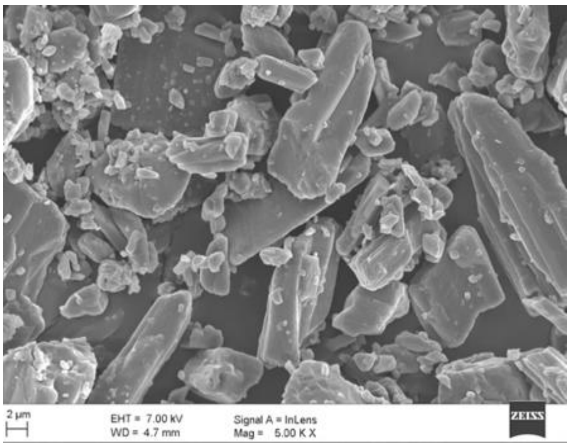

Fig. 2: SEM Ternary Mix Formulation.

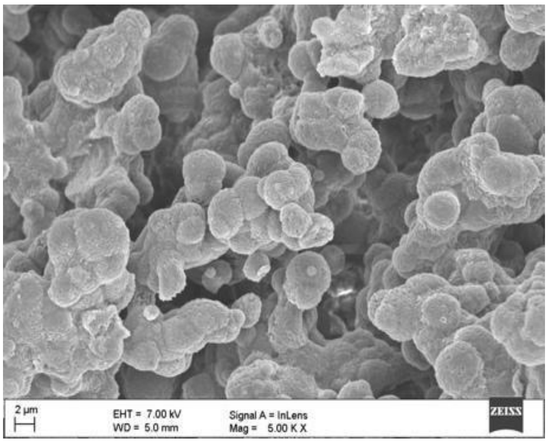

Fig. 3: SEM Spray-dried Formulation.

3.2 Laser diffraction

Particle size distributions were characterized by the median diameter D50 and the span. The span represents the width of the particle size distribution and is calculated by the following formula:

Span = (D90 − D10)/D50

The PSD of the ternary mixture and the Spray dried sample are similar (Table 1). However, from the SEM images, the Spray dried particles appear porous and less dense; hence, the particle size may be similar, but the bulk density may differ.

Table 1.0: Particle size distribution by laser.

Sr. no.	Formulation	D_{10}	D_{50}	D_{90}	Span
1	Physical mixture	2.60	11.03	39.08	3.30
2	Spray dried	5.89	16.41	37.96	1.95

3.3 Powder rheometry

In similar experiments conducted earlier, S. Enferad (2019) studied flowability in glass beads vs. agglomerated lactose and found that agglomerated lactose exhibited the lowest flowability. M Ghadiri (2020) mentioned particle shape affected the flow due to particle interlocking. In this experiment, the impact of the difference in the particle shape and surface morphology of the particles on powder flow was studied using the FT4 Rheometer.

3.3.1 Dynamic flow properties

The test for the *Stability Index* investigates changes in the energy measurements that result after repeated testing and to understand the mechanical stability of the powder due to the changes like interlocking, caking, agglomeration, or fluidization that can occur in the powder on repeated handling and processing. SI of 0.9 to 1.1 indicates a stable material not easily affected by stirring. Spray-dried material had an SI of 0.9, which is closer to unity, indicating it is a more stable and robust formulation as compared to the ternary mixture, which has a SI 0f 0.6, indicating it was affected by repeated stirring movement, resulting in changes probably due to interlocking and agglomeration. The *Basic Flowability Energy* was the energy required to displace powder during a non-gravitational forced flow. Higher BFE indicates higher resistance to flow in a constraint environment BFE is sensitive to particle shape (Nan, 2017). The ternary mixture exhibits a higher BFE value of 173 *mJ* vs. the spray-dried material 117 *mJ*, indicating that it is more resistant to flow in a constrained environment and is more cohesive than the spray-dried formulation. *Specific energy* is the energy required under gravity-induced flow, i.e. resistance to flow in an unconstraint environment. SE < 5 ~ indicates low cohesion, SE between 5 and 10 ~ indicates moderate cohesion and SE > 10 ~ highly cohesive powders. SE of the ternary mixture was 8.2 *mJ/g*, and that of the spray-dried formulation was 5.5 *mJ/g*. *The higher* SE value of the ternary mixture can be attributed to higher frictional forces and mechanical interlocking between the irregularly shaped particles. In contrast, the spray-dried material consists of smoother rounded particles, hence reduced contact with the surrounding particles, resulting in less friction. A powder formulation can be exposed to processes with different flow rates in its manufacturing process cycle. The effect of variable flow rate can be understood from the *FRI value***.** FRI ~1 indicates insensitive to change in flow (Free flowing powder). FRI 1.5 to 3.0 indicates average sensitivity to powder flow (Easy flowing powder). FRI > 3.0 indicates high sensitivity to flow (cohesive powder).[21] The FRI value of the ternary mixture was 1.7, and that of spray-dried was 1.5, indicating that both the powders are relatively insensitive to change the flow rate.

3.3.2 Aeration

The presence of air in a powder can significantly affect its flow properties. The Aeration energy of the ternary mixture and spray-dried material was 38.7 mJ and 8.3 mJ, respectively, and the Aeration ratio was 3.5 and 13.7 resp. Higher aeration energy and lower aeration ratio values seen with the ternary mixture, indicated it was a cohesive powder having low sensitivity to the application of air as compared to the spray-dried formulation, which, due to its spherical shape, allowed air to pass around it, exhibiting a high reduction in aeration energy thereby indicated it was a less cohesive powder.

3.3.3 Bulk powder properties

Bulk Density values are used to determine the volume a powder will occupy and is essential information for processes like blending and blister/capsule filling for powder formulation applications. The rough surface of the ternary mixture lead to interlocking and a more cohesive and compact blend, and hence resulted in a higher *Conditioned Bulk Density* of 0.47 g/ml. The smooth and probably porous spray-dried particles, had lesser contact points lead to a freer flowing, less cohesive powder and thus a lower *Conditioned Bulk Density* of 0.36 g/ml.

Compressibility is a measure of the ability of the powder to become compacted when subjected to normal stress, and in real life, is related to powder behaviour during storage in bins or hoppers and processes like roller compaction. A higher compressibility percentage at all stresses (Fig. 4) indicates that the ternary mixture may exhibit more void gaps or air pockets in between the bulk, has a more cohesive nature and is sensitive to applied stress. The spray-dried formulation is relatively unaffected by increasing stress after an initial increase perhaps due to its smooth rounded shape.

Permeability is a measure of the ease with which the powder bed will release air under stress conditions. It gives insight into powder behaviour during the filling process, handling, transfer, or during the performance in powder for inhalation applications. It can be seen from the graphs for Permeability (Fig. 5) that the ternary mixture exhibited a higher pressure drop value, with increasing stress indicating that the ternary mixture is less permeable due to its cohesive nature. The spherical spray-dried formulation with minimum contact point had interspaces, making it more permeable.

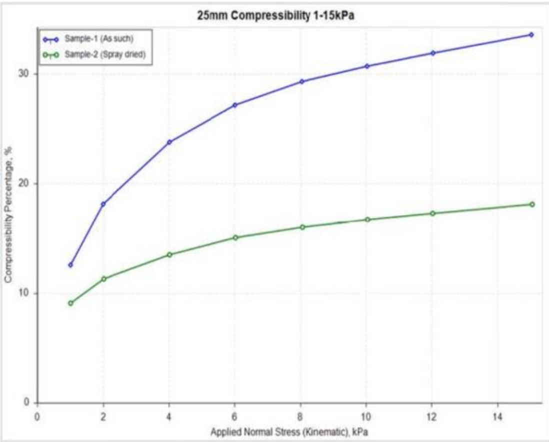

Fig. 4: Compressibility graph.

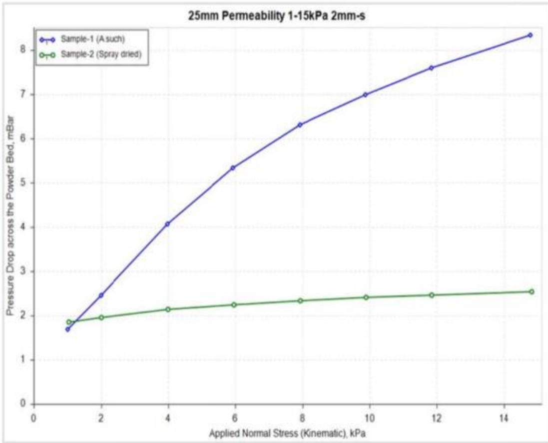

Fig. 5: Permeability graph.

3.3.4 Shear properties

Shear stress measures the stress required to initiate flow in a consolidated powder. It helps understand the behaviour of the powder movement from a static state to a dynamic state, e.g. will the powder flow in hopper and silos, or will it exhibit blockages, ratholing etc. ffc < 4 ~ cohesive powder, ffc 4-10 ~ easy flowing powder & ffc >10 ~ free flowing powder. The ternary mixture's low flow function value of 1.6 indicates poor flow properties post consolidation. This can be attributed to the friction of the irregularly shaped particles. This friction is less in the smooth rounded spray-dried particles; hence, they exhibit high flow function values of 7.0, i.e. they exhibit improved powder flow properties.

4. CONCLUSION

Particle shape and surface morphology affect bulk powder properties and powder flow properties. Higher values of BFE, SE, % Compressibility, and low Flow Function values were seen for the ternary mixture consisting of irregularly shaped particles which are subject to higher frictional forces and mechanical interlocking, resulting in a cohesive blend vs the spray-dried formulation consisting of spherical and smoother particles. Lower pressure drop values in the test for permeability and lower aeration energy indicate that under similar conditions, the spray-dried formulation will fluidize to a greater extent than the ternary formulation. The study suggests that the spray-dried formulation will have fewer challenges during processing. The FT4 Rheometer comprehensively tests multiple parameters important in understanding powder behaviour. It can allow informed decisions to be made for designing and validating, handling, and manufacturing processes, and manufacturing equipment. Further studies need to be conducted to co-relate particle size data in combination with the powder rheometry data to get better insights into the porosity of the spray dried formulation.

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