RESEARCH ARTICLE

Effect of Magnesium Stearate and Fines on Delivery of Dry Powder for Inhalation using Sucrose as a Carrier

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ABSTRACT

Typically, lactose is utilised as carrier in Dry Powder Inhaler commercially. However, with the widening scope of DPI in therapeutic categories other than COPD and asthma, a need for the alternate carrier is arising. In this study, we used sucrose, a non-reducing sugar, as an alternate carrier. Effect of addition of fines and magnesium stearate was studied on powder flow properties and aerosolization performance. The air jet milling technique was used to generate sucrose fines. DSC and XRD studies showed no change in sucrose polymorph upon micronization. Levosalbutamol sulphate was used as a model drug, powder blends were prepared by low shear tumbling type blender. Powder formulations were studied for PSD, blend homogeneity, and flow properties. The percentage of particles smaller than 5 microns rose when fines were added as indicated by PSD data. SEM study revealed that the added fines get adsorbs on the coarse carrier, thus minimizing the adhesive interactions between drug and coarse carrier. *In-vitro* deposition was studied using low and high resistance devices on glass Twin Stage Impinger (TSI). Addition of fines and the magnesium stearate improves aerosolization performance showing higher Fine Particle Fraction (FPF) by almost 2 folds than the formulation containing coarse carrier alone.

Keywords: Dry powder for inhalation, Sucrose, Magnesium stearate, Particle size, Fines.

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INTRODUCTION

With its high blood vessel mass, thin epithelial membrane barrier, large surface area of the lungs, limited enzyme activity, evasion of the degradation system, and efflux transporter activity, as well as its decreased adverse effects due to smaller dose requirements, the pulmonary route offers an attractive gateway for non-invasive drug delivery by inhalation. The dry powder inhalers (DPIs) are more commonly used than nebulizers, pressurised metered-dose inhalers (PMDs), and nebulizers because they are easy to use, cheap, and don't require propellant. Additionally, APIs in their dry form are more stable and provide the opportunity to deliver medications with an extensive choice of physicochemical properties. For systemic absorption, DPI is also broadening its utility domain beyond management of local airway diseases like asthma, infections, cystic fibrosis, COPD, etc., to systemic diseases such as diabetes, neurological disorders, etc.[1]

The DPI product is a powder formulation filled into hard capsules or blisters or suitable receptacles that are provided along with an inhaler device designed to release the contents, and deliver the API(s) to the respiratory tract. DPI formulation basically comprises micronized drug/s (1–5 μm) either with or without a carrier. Since micronized drug particles, with increased surface area and energy, are frequently very cohesive, tending to form agglomerates with inferior flow characteristics and pose difficulties in handling as well as metering the dose.[2] The cohesive forces are generally more than the dispersion force created during aerosolization by inspiration which limits fluidization and dispersion so that emissive and dispersive performance, dose accuracy, and consistency are not uniform. These difficulties can be overcome by the inclusion of carrier material in the formulation that assists drug aerosol formation, augments the respirable fraction, increases the bulk, and improves the powder flowability for uniform filling. The small medication particles are freed from the carrier and introduced into the respiratory tree as the coarse carrier particles cling to the surface of the sticky binary combination. As this is happening, the carrier particles hit the area of the throat and go down the throat.

Most of the commercially available DPI formulations contain API in a small proportion (0.05–10%) blended with carrier particles (particle size 50-200 μm).[3] The contribution

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of carrier to DPI is more than 99 % w/w hence performance of DPI depends mostly on carrier. In addition to being inexpensive and easily accessible, the carrier particles should not only be inert but also biocompatible, biodegradable, non-toxic, and physicochemically stable. One of the most popular ways for drug delivery in DPIs is through lactose.[4,5] However, it presents problems of incompatibility of Maillard reaction with APIs bearing primary amino groups including peptides and proteins; and change in particle properties with change in manufacturing methods.[6] Moreover, these formulations cannot be administered in patients with lactose intolerance or patients avoiding products of bovine origin.[7] The range of drugs to be incorporated in DPI is also widening and may require carrier with higher loading capacity.[8] Hence alternative carriers are being searched for the DPI formulations.[9] Many of the sugars and a few polysaccharides as dextrose, sorbitol, mannitol, maltitol, erythritol, xylitol, trehalose, cellobiose, raffinose, cyclodextrins, inulin, stachyose and verbascose or a combination of two or more of them have been studied as DPI carrier.[10] Use of carrageenan, gelatin, chitosan etc polymers as a carrier for inhalable formulations has also been reported.[11,12]

Sucrose, an established food component and pharmaceutical excipient of plant origin, is a non-reducing sugar so does not experience Maillard reaction.[13,14] The patents have disclosed its use as a DPI carrier.[15,16] It was used as an excipient for co-spray drying an API to formulate high-dose powder dry inhalation formulations.[17] In pulmonary deposition via impaction experiments by quantifying the saccharide DPI carriers deposited in pulmonary route, Babenako et al reported deposition of spray freeze dried sucrose in the oropharynx region to be 66.62% with respect to the applied dose.[18] The flowability of sucrose was independent of the moisture content since the spray freeze-dried sucrose with extraordinary moisture content (7.5%) had better deposition than spray dried sucrose with lower moisture content (3%). The spray freeze-dried sucrose would be porous and fluffy particles with reduced inter-particulate forces resulting in improved fluidization.[19] Interest generates here about the applicability of sucrose as a carrier for DPI albeit employing a simpler technique of maneuvering the carrier particle characteristics.

With lactose, mannitol, a simple way adopted for DPI performance improvement is to add extrinsic carrier fines to coarse carrier particles or to generate fines during the processing.[20] Lactose carriers with a higher proportion of intrinsic fines improved DPI performance positively and the removal of the intrinsic fines affected the performance negatively.[21] The improvement in DPI dispersion performance of this single excipient platform is explained with different hypotheses based on active sites mechanism, agglomeration, effective deagglomeration, buffering mechanism, fluidization enforcement and case-dependent mechanism.[22] However, there are studies with contradictory results too. Steckel et al. reported that occurrence of fines in a lactose carrier decreased FPF[23] and According to another study, adding sorbitol fines to a sorbitol carrier reduced the FPF, whereas adding mannitol fines to a mannitol carrier had no effect on product performance.[24] The fine carrier to be employed is suggested to be slightly larger than drug particles or of the similar to API particle size while the proportion of fine with respect to coarse particles are employed in a wide range.[25] Proportion of fines to coarse particles appears to be influenced by the carrier materials themselves and methods of incorporation of fines. Hence, adopting the method of carrier fine inclusion for using sucrose as a carrier demands the evaluation of such parameters.

The drug-carrier adhesion, which usually is strong, prevents complete drug detachment from the carrier. A second excipient material as magnesium stearate, leucine is frequently added to the carrier-drug blend (with or without carrier fines) to modulate and improve the detachment and formulation performance.[26,27] Such dual excipient platform based DPI are accepted for clinical use.[28] Functions of magnesium stearate in DPI are described as a lubricant (antiadherent or antifriction), force control agent, performance enhancer, water barrier and stabilizer. The quantity to be used in the formulation is found to be dependent on factors such as API, particle size, etc. The optimum amount of magnesium stearate falls in the range needed to cover all carrier particles with a perfect film. If the quantity of magnesium stearate utilized exceeds the optimum, it overwhelms the carrier particles and the thickness of the film increases causing a considerable decrease in flowability.[29]

In response, commercial sucrose (Biohale® Sucrose) offered for inhalation application was used in study as a carrier for DPI for a model drug, levosalbutamol sulphate. To enhance the performance, carrier fines and the second accepted pulmonary excipient, magnesium stearate was included in the formulation. More specifically, the effect of carrier fines and magnesium stearate alone and in combination was studied to see any supplementary effect of the combination on aerodynamic performance. To this end, the carrier fines, flow properties, particle size distribution and morphology of formulations were correlated with the FPF determined using two inhalation devices with varying device resistance.

MATERIALS AND METHODS:

Materials

Micronized levosalbutamol sulphate (Vamsi Labs, Solapur, India), Magnesium stearate (Ligamed MF-2-V Premium, Peter Greven, Bad Münstereifel, Germany), Sucrose (Biohale® Sucrose, DFE Pharma, Nordrhein-Westfalen, Germany), Hydroxypropyl methylcellulose capsule(Capsugel, New Jersey, USA) were received as a gift sample from Glenmark Pharmaceuticals Ltd. Inhalation devices used; Lupihaler® (Lupin Limited, India) Revolizer® (Cipla Limited, India).

Micronisation of sucrose

The micronization was carried out using Spiral Air Jet Mill 75RPS (Ruchapharma, India). A milling pressure of 3.5-4 kg/cm^2 and an injection pressure of 7 kg/cm^2 were found suitable for the process. Sucrose was fed manually to air jet mill, one micronization cycle was found adequate to get desired micronized material particle size. Micronisation was carried out at room temperature (20 ^{o}C to 25 ^{o}C) and 30-40 % relative

humidity. Micronized sucrose (hereafter called fine sucrose or fines) was stored in a tightly closed glass bottle to prevent moisture ingress and particle agglomeration.

Preparation of formulation blends

Formulation blends of API, carrier and magnesium stearate were prepared on low shear tumbler mixer, Alphie^{TM} (Hexagon Product Development, India). This works by the kinematic inversion principle and gives good blend homogeneity in a relatively shorter mixing time. Biohale® Sucrose was passed through a mesh size of 250µm, the fraction collected below 250µm sieve is used as a 'coarse sucrose'. Four different formulations containing 0.4% w/w of levosalbutamol sulphate (D_{90} -3.67µm) were prepared with either coarse sucrose or mixture of coarse and fine sucrose, in combination with or without 0.8% of magnesium stearate (D_{90} -17µm) as stated in Table 1.

Mixing process for formulation without magnesium stearate (D-C and D-CF)

The drug was added to sucrose (coarse or mixture of coarse and fine) geometrically, and then passed through 250 µm sieve. Powder blending was done with two mixing cycles of 10 minutes each at a blender speed of 42-44 rpm and a sieving step (through 250µm sieve) in between two mixings.

Mixing process for formulation with magnesium stearate (D-CM and D-CFM)

Sucrose (coarse or mixture of coarse and fine) was pre-blended with magnesium stearate for 20 min at 42-44 rpm and then the drug was added geometrically. The blend was passed through 250 µm sieve and then blending was done with two mixing cycles of 10 minutes each at a blender speed of 42-44 rpm and a sieving step (through 250 µm sieve) in between two mixings.

Blending was carried out in stainless steel container assembled on Alphie mixer. Blends were rested in a stainless steel container for at least 12 hours.

Particle size distribution

Using the Scirocco 2000 dry powder feeder in conjunction with the Mastersizer 2000 (Malvern Instruments, United Kingdom), the particle size distribution of formulation blends and sucrose (fine and coarse) was ascertained through the application of the laser light diffraction method. D_{10}, D_{50}, $D_{90,}$ specific surface area and fraction below 5µm were recorded.

Bulk Powder Characterization

Bulk density, tap density, Carr's index, and Hausner ratio were used to evaluate the powder bulk properties of formulation blends in conjunction with coarse and fine sucrose. A graduated glass measuring cylinder was filled with each powder blend using a funnel. After recording bulk volume, tapped volume was determined by using Tap Density Apparatus (ETD-1020x ELECTROLAB, India). For the determination of tapped volume, the measuring cylinder was dropped from height 3 ± 0.2 mm at a nominal rate of 300 taps per minute. Initially, 500 and then 750 taps were found sufficient as there was no difference in tapped volume. Each sample was measured three times.

Blend uniformity

Six 25 mg samples were taken from various parts of the mixing vessel to ensure that medicine was homogeneous throughout the blends before the capsules were filled. The concentration of drug in samples was analyzed using UV spectrophotometer (UV- 2450, Shimadzu, Japan) at the wavelength of 276 nm in distilled water.[30] 5% of RSD was considered as a uniform powder mixing.

Scanning electron microscopy

Using scanning electron microscopy, we examined the powder blends' morphology and surface properties. Using double-sided sticky tape, the powder sample was secured to the SEM-stub. Under vacuum, a tinny layer of gold was applied to sample. A 10 kV working voltage was used for the analysis of samples using the Supra 55 (Carl Zeiss, Germany). Various magnifications of images were recorded.

DSC

The thermal characteristics were measured using STARe software on a DSC (Model DSC 3, METTLER TOLEDO, Switzerland). Five milligrams of the material was put into a non-hermetically sealed 40 microliter aluminium DSC pan and crimped. Scan rates of 10 °C/min in a N2 gas atmosphere with 50 ml/min were applied to each sample as they were subjected to temperatures ranging from 30 to 300 °C.

XRD

By employing the D2 Phaser (Bruker, USA), XRD patterns of samples were acquired. Operational voltage was 30 kilovolts and the current was 10 milliamperes. A sample holder made of aluminium was used for each specimen. Every sample was examined within 2θ angle range of 5° to 50°, with a precision of 0.02° increment.

In-vitro aerosolization study

Every powder was hand-filled into a size 3 hydroxypropyl methylcellulose capsule with a fill weight of 25 mg after the blends had rested for at least 12 hours to neutralise the static charge. Using a glass Twin Stage Impinger(TSI, Copley Scientific, Nottingham, UK), apparatus A in European Pharmacopoeia) and a low resistance device (Lupihaler®) or a high resistance device (Revolizer®) we measured in-vitro drug distribution of each formulation. (Figure 1).

Distilled water was added in volumes of 7 mL and 30 mL in stage 1 and 2 of TSI assembly respectively. Side button/s were pressed to pierce the capsule. As per the recommendations of the European Pharmacopoeia (apparatus A), a flow rate of 60 ± 5 L/min was maintained while the device was attached to the TSI assembly for 5 seconds. Ten capsules were used for each test. Rinsing the stage one by one allowed to collect the drug that had been collected in each stage. The drug concentration was determined using a UV spectrophotometer (UV-2450, Shimadzu, Japan) operated at 276 nm in distilled water. Percentage FPF and the emitted dose (ED) were calculated.

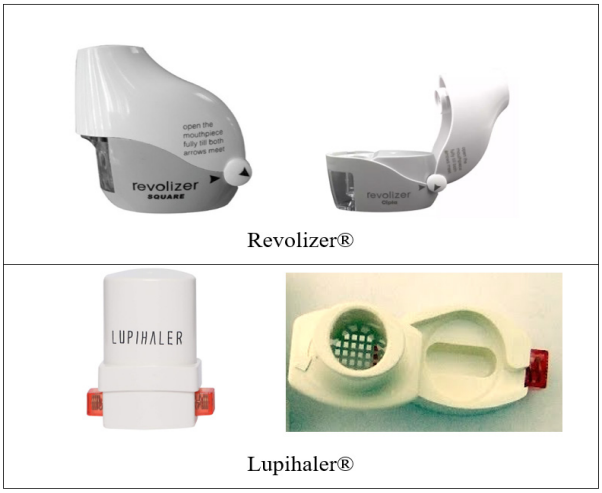

Figure 1: Revolizer® and Lupihaler® (Closed and open view)

Table 1: Composition of formulations with model drug levosalbutamol sulphate

Ingredients	*Formulation ID*			
	D-C	*D-CM*	*D-CF*	*D-CFM*
Levosalbutamol sulphate (D)	0.4%	0.4%	0.4%	0.4%
Magnesium stearate (M)	-	0.8%	-	0.8%
Fine sucrose (F)	-	-	25%	25%
Coarse sucrose (C)	qs	qs	qs	qs

RESULTS AND DISCUSSION

Particle Size Distribution

According to the results of the laser diffraction examination, the formulations had a very different distribution of particle sizes (Table 2). D_{10} values were lower in the formulations that contained fine sucrose, and hence the particle size distribution was wider. With addition of fine sucrose, the fraction below 5µm was increased by about 10 folds (from 1.56, 0.92% to 15.28, 13.48%). However, the presence of magnesium stearate showed very less impact on size distribution. As indicated by Grasmeijer et al., the fine carrier should have particle size similar to the drug or slightly larger than drug.[25] The micronized material had particle size distribution within inhalable range (mean particle size 2.4µm), with the increase in specific surface area by almost 50 folds (4.19 m^2/g) as compared to coarse sucrose (0.09 m^2/g). Hence, the spiral air jet milling method was found suitable for the micronization of sucrose particles.

Powder Densities and Flow Properties

The fine sucrose produced by air jet milling had significantly lower bulk(0.17 g/cm^3 versus 0.74 g/cm^3) and tapped densities(0.38 g/cm^3 versus 0.90 g/cm^3) than coarse sucrose indicating the formation of smaller, low density particles as supported by particle size distribution data also. The increase in fines and the low density particles could be a reason for higher FPF in the formulations containing fine sucrose due to easier fluidization. The addition of magnesium stearate has resulted in increased powder densities. Additionally, Hausner's Ratio and Carr's Index indicate that the formulation containing magnesium stearate along with fine sucrose had improved flow properties compared to its counterpart formulation without magnesium stearate. These effects of increased powder densities and improved flow could be attributed to decrease in inter-particle forces due to the addition of magnesium stearate.[31] The comparative powder densities are accessible in Table 3.

Blend Uniformity

In DPI formulations, sometimes a high variability of drug concentration in a blend could be more worrisome than the drug delivery to the lungs. The selected blending process was found suitable as all the formulations had drug concentrations within the 90-110% and RSD < 5% (Figure 2).

Morphology

SEM images (Figure 3) show the coarse sucrose particles having a nearly rounded shape with surface irregularities and indentation causing higher surface roughness. Formulations with the addition of fine sucrose (D-CF and D-CFM) resulted in the adsorption of smaller particles on the coarse carrier. This has led to decreased surface dents of coarse carrier and relatively smoother surface. Based on these SEM images one can accept that formulation with fine sucrose can have a higher surface area owing to occurrence of a large number of smaller particles, and this has been substantiated by specific surface area data obtained by laser diffraction analysis (Table 2). Addition of magnesium stearate alone(D-CM) showed no noteworthy change in surface morphology compared to coarse sucrose(D-C). The saturation of active sites of coarse carrier due to addition of fine sucrose is confirmed by SEM images. The fine sucrose filled the indentations and partially covered surface of the coarse carrier. in-vitro deposition study results are also in alignment with SEM images showing higher FPF owing to saturation of active sites by addition of fines which allows easier drug detachment upon inhalation due to reduced drug and coarse sucrose interaction; thus helps in better drug dispersion.[32]

Solid State Properties

The main objective of performing DSC and XRD analysis was to evaluate effect of micronization process on polymorphic form of sucrose. The crystalline thermodynamically stable polymorph of sucrose shows a melting endotherm at around 185°C, whereas the metastable polymorph does so at a lower temperature around 150°C.[33] The coarse sucrose exists in crystalline form with traces of metastable form as evident from the DSC thermogram (Figure 4) which shows an endothermic peak at 181°C and a small peak at 145°C. The micronized sucrose shows a relatively sharp and intense endothermic peak at 187°C and without the appearance of a peak at around 145-150°C. This indicates the absence of a metastable form of sucrose since the energy imparted during the micronization process may have been utilized in the transition of traces of

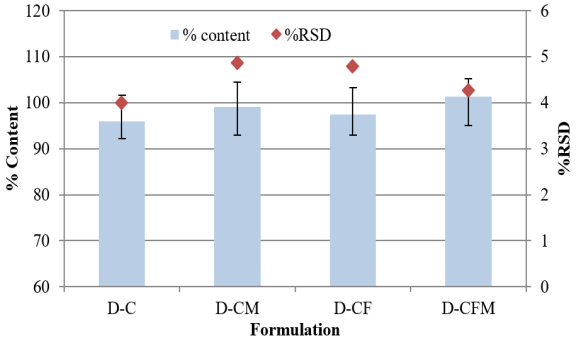

Figure 2: Blend uniformity (n = 6, min and max shown by error bar and %RSD on secondary vertical axis)

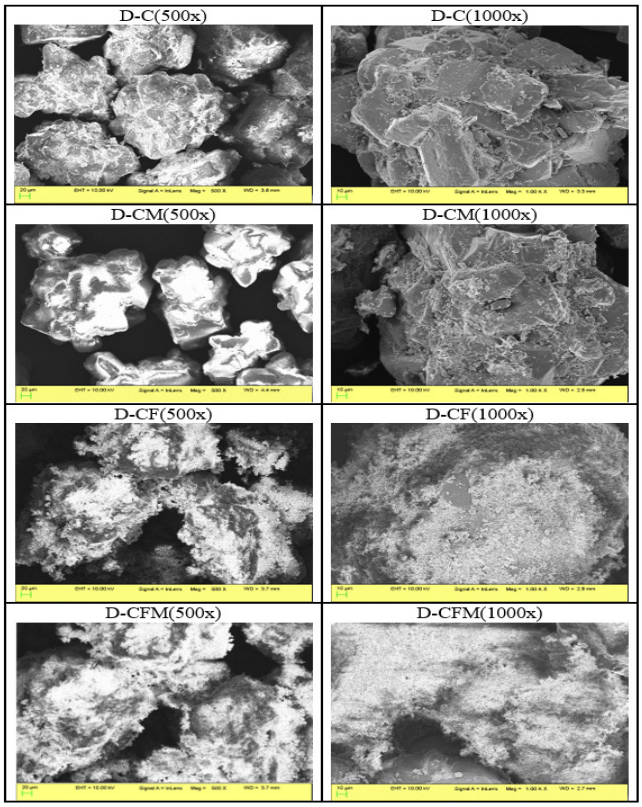

Figure 3: SEM Images with different magnification as 500 and 1000X

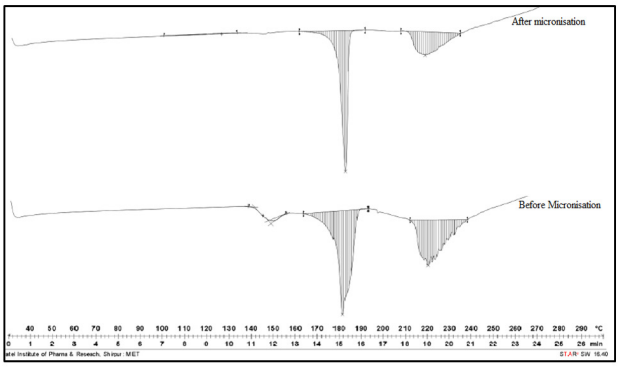

Figure 4: DSC thermograms of sucrose before and after micronisation

Table 2: Particle size distribution of sucrose and formulation powders

S. No	*Material/ Formulation ID*	*PSD, in µm*			*%Below 5 µm*	*SSA m²/g*
		D10	*D50*	*D90*		
1	Fine sucrose (F)	0.6	2.4	6.1	83.14	4.19
2	Coarse sucrose (C)	48.0	193.4	333.6	1.64	0.09
3	D-C	46.1	204.6	346.7	1.56	0.09
4	D-CM	58.6	207.9	349.9	0.92	0.07
5	D-CF	3.0	175.8	335.3	15.28	0.52
6	D-CFM	3.2	170.7	323.7	13.48	0.46

Table 3: Powder densities and flow properties (n = 3)

Physicoc hemical properties	*Coarse sucrose*	*Fine sucrose*	*D-C*	*D-CM*	*D-CF*	*D-CFM*
Bulk density (g/cm^3)	0.74 ± 0.01	0.17 ± 0.01	0.73 ± 0.01	0.75 ± 0.01	0.49 ± 0.01	0.60 ± 0.03
Hausner's ratio	1.21 ± 0.01	2.27 ± 0.07	1.2 ± 0.04	1.24 ± 0.02	1.42 ± 0.02	1.25 ± 0.02
Tapped density (g/cm^3)	0.90 ± 0.01	0.38 ± 0.01	0.88 ± 0.02	0.93 ± 0.01	0.70 ± 0.01	0.75 ± 0.03
Carr's index	17.09 ± 0.69	55.94 ± 1.31	16.39 ± 2.73	19.35 ± 0.99	29.73 ± 0.83	20.14 ± 1.28
Flow (Based on CI)	Fair	Very poor	Fair	Fair	Poor	Fair

metastable form to a high melting thermodynamically stable form.[34]

X-ray diffractograms (Figure 5) of micronized and native sucrose show characteristic sharp peaks at 2θ values of 11.7, 13.1,18.8,19.6, and 24.7, and absence of broad halo amorphous peak indicating crystallinity. XRD peaks are matching with the previously reported 2θ values.[35] The presence of characteristic peaks along with completely superimposed X-ray diffractograms for before and after the micronization process indicates no change in polymorphs of sucrose.

Overall, DSC and XRD studies show that the micronisation process didn't affect the crystallinity as compared to the 'as supplied' sucrose carrier.

In-vitro Aerosolization Study

In addition to the formulation aspects, inhalation device correspondingly plays a major role in performance of DPI. In order to achieve sufficient turbulence forces for efficient aerosolization of drug particles, inhalation devices with high resistance require a lower inspiratory flow rate whereas those with lower resistance may require a higher inspiratory flow rate.[36] In this study, two inhalation devices were employed, one with low resistance (Lupihaler, 0.017 $KPa^{1/2}$/L/min) and the other with high resistance (Revoliser, 0.047 $KPa^{1/2}$/L/min).

The in-vitro deposition parameters of all formulations summarizing, device and capsule retention, FPF and ED are displayed in Table 4.

Table 4: *In-vitro* deposition: FPF and ED (n = 3)

Formulation ID	*Inhalation device*	*Device and Capsule retention (%)*	*FPF(%)*	*ED (%)*
D-C	Low resistance	6.05 ± 0.58	12.94 ± 1.83	93.40 ± 3.66
D-CM		9.19 ± 3.57	20.79 ± 1.48	91.58 ± 4.90
D-CF		9.57 ± 0.79	29.41 ± 1.55	91.14 ± 2.08
D-CFM		10.20 ± 1.15	30.21 ± 3.28	89.94 ± 1.33
D-C	High Resistance	14.86 ± 1.53	7.10 ± 1.24	85.47 ± 1.53
D-CM		11.71 ± 1.15	15.36 ± 2.31	83.62 ± 1.48
D-CF		14.60 ± 1.36	21.02 ± 2.44	83.46 ± 1.47
D-CFM		14.98 ± 0.65	22.56 ± 1.09	86.14 ± 3.81

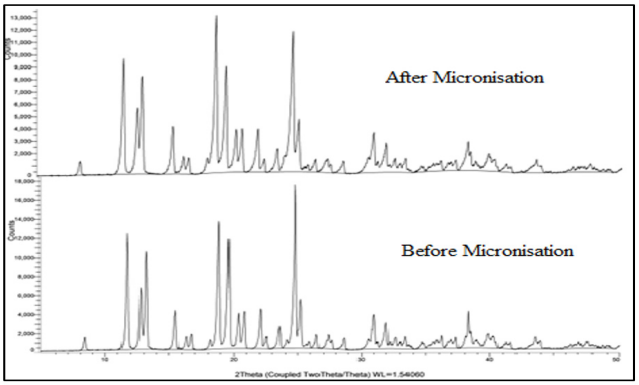

Figure 5: XRD of before and after micronisation of sucrose

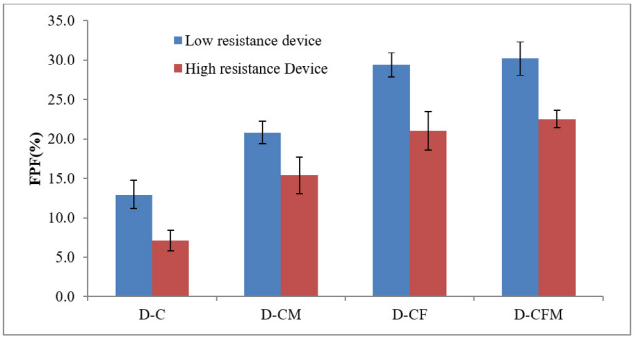

Figure 6: %FPF tested with low and high resistance device

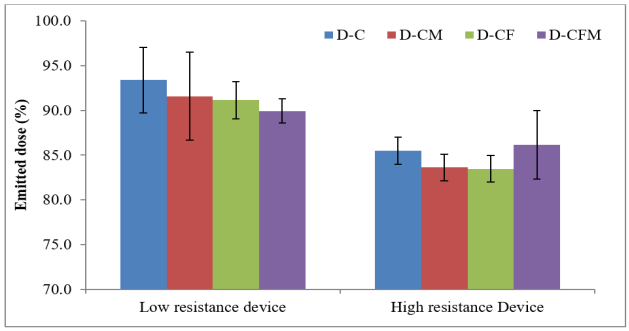

Figure 7: Emitted dose tested with low and high resistance device

The FPF data indicates that the addition of fines and magnesium stearate resulted in higher in-vitro lung deposition. The reduced drug and coarse carrier adhesive forces due addition of magnesium stearate; formation of smaller agglomerates and surface smoothing of coarse carrier by addition of fines could be the reason for improved performance. Formed agglomerates can act as a cushioning agent and avoid press-on forces getting exerted on drug particles, thus eventually reducing the stronger drug-carrier interactions.[37] However, addition of both, i.e fines and magnesium stearate, did not show any synergistic increase in FPF. Both low and high resistance devices showed similar FPF trends with respect to fines and magnesium stearate addition (Figure 6). However, the FPF with low resistance device was considerably higher than the high resistance device. Similar observations were reported earlier by Steckel *et al.*[38] One of the reasons for this lower FPF with high resistance device could be the large amount of drug retained in capsule and device (about 14%) hence not available for stage 2 deposition.

The emitted dose calculated by summation of stage 1 and stage 2 deposition shows that the low resistance device has higher emitted dose than the high resistance device (Figure 7). This can again be attributed to the high capsule and device retention. The formulations with fine sucrose (D-CF and D-CFM) showed more than two fold rise in FPF than the formulation with coarse sucrose alone(D-C). The possible explanation for this could be an increased fraction of particles with a size less than 5 microns as seen from PSD measurements[39] (Table 2). The effect of the addition of magnesium stearate was less pronounced than the addition of fines on aerosolization behavior, this could be due to the use of low shear blender which imparts relatively less mixing energy.[40]

Overall, considering the lower device and capsule retention, higher FPF and ED, the low resistance inhalation device seems to be better in aerosolization performance for the studied formulations.

CONCLUSION

For sucrose as a carrier in DPI, the addition of fines and force control agent could be beneficial. The addition of fines, as a result of blocking active sites on coarse carrier or by avoiding press-on forces, has been shown to increase the aerosolization efficiency of powders. The air jet milling process can be effectively used to generate sucrose fines with desired particle size distribution while retaining its polymorphic form. Although the addition of magnesium stearate along with fines did not show any further improvement in FPF, use of magnesium stearate can be helpful in improving the powder flow characteristics and thus ease of powder handling during the manufacturing process which is always a concern with microfine API and fine carrier in DPI. The choice of inhalation device can be done suitably based on the intended amount of drug deposition in the airways. Hence, it can be concluded that sucrose fines and magnesium stearate can be effectively used for fine tuning and improving the performance of DPI.

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