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INFLUENCE OF CARRIERS ON PERFORMANCE OF SALBUTAMOL SULPHATE DRY POWDER INHALER

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ABSTRACT

Dry powder inhaler(DPIs) for Salbutamol Sulphate is indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and acute prophylaxis against exercise induced asthma. To prevent the retentive losses from DPI, an excess amount in the form of overages is more often incorporated in to the DPI's.The flow properties of the medicament is influenced by the nature and proportion of excipient employed in the preparation of DPI. The formulations were prepared with different grades of Lactose monohydrate like Lactohale 300, Sorbolac400, Inhalac 230, Respitose SV003, DCL11 and Flowlac100 and evaluated for physical appearance, average fill weight per capsule, content uniformity, uniformity of delivered dose, emitted dose and assay. The influence of composition of DPI and overages on performance of DPI was studied. The DPI formulated with 10:90 ratio of fine lactose (Lactohale 300): coarse lactose (Respitose SV003) and having 20% w/w overages offered the desired fine particle fraction, emitted dose and satisfied the Compendial and non compendial requirements.

KEYWORDS : *DPI, inhalation, lactose monohydrate, overages, SalbutamolSulphate.*

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INTRODUCTION

The DPI device presents medication to the patient as a dry powder in a form that can be inhaled orally for delivery to the target lung tissues.[1] DPI's contain active ingredient(s) alone or with a suitable excipient(s).The final product performance of powder blend in DPI'S ultimately depends on the drug and carrier morphology.The most important factors to be considered in designing and manufacturing of DPI include particle size, shape, surface area, and aerodynamic properties of powder which in turn determine the fluidization, dispersion, delivery to the lungs and deposition in the peripheral airways. Salbutamol Sulphate is indicated for the long-term, once-daily maintenance, treatment of bronchospasm

.Salbutamol is a non catecholamine, not metabolized by Carboxy o methyl transferase (COMT) and thus exhibit long duration of action than Isoprinalin which is often referred to as an anti cholinergic.[2,3,4] Inhaled salbutamol sulfate has a rapid onset of action, providing relief within 5-15 minutes of administration and cost effective in the form of DPI.

MATERIALS AND METHODS:

Salbutamol Sulphate, Various grades of Lactose monohydrate like Lactohale 300, Sorbolac400, Inhalac 230, Respitose SV003, DCL11 and Flowlac100, Acetonitrile of HPLC grade were collected from Natco Pharma Limited, Kothur**.**

EQUIPMENT:

Dosage unit sampling apparatus (DUSA), Anderson cascade impactor (ACI), Twin stage impinge(TSI), High performance liquid chromatography (HPLC),Vacuum pump, Flow meter, Pamasol filling crimping machine,and Capsules partial filling machine.

PREPARATION OF DRY POWDER INHALER:[5,6,7]

An accurately weighed amount of Salbutamol Sulphate was mixed separately in each case with Lactose monohydrate in geometric progression and passed through 60# mesh and blended in polybag and filled in to size "3" hard gelatin capsules with partial filling manual capsule filling machine with fill weight of 25 mg per capsules. Other formulations were also prepared in the same way. The particle size of active drug should be less than 5µ and hence the drug selected for the research was within this limit. Particle size was determined for different lactose grades, bulk and tapped density were measured. Results of tapped and bulk densities were given below.

Table.1 Physical properties of Lactose grades used in DPI formulations

Lactose grade	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Carr's index	Particle size (90% particles less than)
DCL11	0.613	0.730	1.18	14%	240µ
Sorbolac 400	0.350	0.770	2.06	52%	29µ
Inhalac 230	0.650	0.750	1.17	15%	220µ
Respitose SV003	0.625	0.790	1.23	18%	110µ
Lactohale 300	0.340	0.760	2.23	53%	12µ
Flowlac 100	0.620	0.720	1.21	17%	220µ

Preparation of the dry powder inhaler for evaluation of overages importance in dry powder inhaler formulation:

Salbutamol Sulphate DPI 200 µg formulations were prepared with 0%, 5%, 10% and 20% of overages with 25 mg fill weight and Lactose monohydrate as diluent as per composition given in Table.2.

Table.2 Formulated Salbutamol Sulphate dry powder inhalers with overages

Formulation	Active ingredient	Dose (µg/capsule)	Overages %w/w	Active ingredient	Lactose monohydrate
				µg/ capsules	mg/ capsules
DPI1	Salbutamol sulphate	200	0	21.5	Upto 25mg
DPI2			5	22.625	Upto 25mg
DPI3			10	23.75	Upto 25mg
DPI4			20	26.0	Upto 25mg

Preparation of the dry powder inhalers with different proportions of fine lactose:

Salbutamol Sulphate DPI 200 µg formulations were prepared with 0%, 5%, 10%, 15%,20% and 30% fine lactose (Sorbolac 400) and Inhalac 230 as coarse lactose as per composition given in Table.3.

Table.3 Formulation of Salbutamol Sulphate dry powder inhaler with various percentages of fine lactose

Formulation	Active ingredient	Dose (µg/capsule) #	Fine lactose portion in w/w	Sorbolac 400	Inhalac 230
				mg/capsules	mg/ capsules
DPI5	Salbutamol sulphate	200	0	0	Upto 25mg
DPI6			5	1.35	Upto 25mg
DPI7			10	2.5	Upto 25mg
DPI8			15	3.75	Upto 25mg
DPI9			20	4.0	Upto 25mg
DPI10			30	8.5	Upto 25mg

 # including 20% w/w overages

Preparation of the dry powder inhaler with different grades of fine lactose:

Salbutamol Sulphate DPI 200 µg formulations were prepared with two different grades of 10% fine lactose (Sorbolac 400/ Lactohale 300) and 90% of Inhalac 230 with 25mg fill weight as per composition given in Table.4 to select the fine lactose grade by evaluating the DPI performance.

Table.4 Formulation of dry powder inhaler with various grades of fine lactose

Formulation	Active ingredient	Dose (µg/capsule) #	Fine lactose grade	Fine lactose	Inhalac 230
				mg/capsules	mg/capsules
DPI11	Salbutamol sulphate	200	Sorbolac 400	2.5	Upto 25mg
DPI12			Lactohale 300	2.5	Upto 25mg

 # including overages

Formulation of the dry powder inhalers with different grades of coarse lactose:

Salbutamol Sulphate DPI 200 µg formulations were prepared with various grades of coarse lactose such as Inhalac 230, DCL11, Flowlac100 and Respitose SV003 along with 10% Sorbolac 400 with 25 mg fill weight as per composition given in Table.5.

Table.5 Formulation of Salbutamol Sulphate dry powder inhaler with various grades of coarse lactose

Formulation	Active ingredient	Dose (µg/capsule) #	Coarse lactose grade	Sorbolac 400	Coarse lactse
				mg/capsules	mg/capsules
DPI13	Salbutamol sulphate	200	Inhalac 230	2.5	Upto 25mg
DPI14			DCL11	2.5	Upto 25mg
DPI15			Flowlax 100	2.5	Upto 25mg
DPI16			Respitose SV003	2.5	Upto 25mg

EVALUATION OF DRY POWDER INHALER FORMULATIONS [8]

Physical appearance: The capsules were visually observed.

Average fills weight per capsule: 20 capsules with out losing of drug to any part of the shell were opened and the contents were removed as completely as possible. Weighed the 20 capsules content and determined the average of fill weight.

Assay (drug content determination): Transferred contents of 10 capsules into a 100 ml volumetric flask and added 10ml of water sonicated to dissolve the capsule and added the suitable volume of diluent acetonitrile and water(60:40) ,sonicated to dissolve for about 10 minutes with intermittent shaking (for complete dispersion), made the volume with diluent. Filtered through a 0.45µ membrane and estimated the drug content with suitable analytical method HPLC.

Compendial tests on DPI: Content uniformity, Uniformity of delivered dose (DUSA for DPI and Critical flow controller), Deposition of emitted dose (With Twin impinger and Critical flow controller) and Particle size distribution by Anderson cascade impactor were conducted as per I.P, 2007.

Results and discussion: Physical properties such as bulk density, tapped density and particle size of various lactose grades were evaluated and showed in Table.6.

Table.6 Physical properties of Lactose grades used in Salbutamol Sulphate DPI formulations

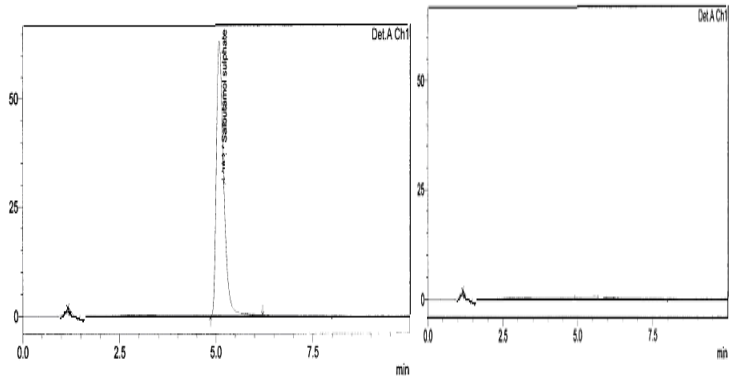
Lactose grade	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Carr's index	Particle size (90% particles less than)
DCL11	0.514	0.710	1.20	15%	240 µ
Sorbolac 400	0.350	0.790	2.15	52%	35 µ
Inhalac 230	0.630	0.750	1.18	17%	220 µ
Respitose SV003	0.625	0.790	1.24	18%	110 µ
Lactohale 300	0.340	0.760	2.22	54%	10 µ
Flowlac 100	0.610	0.740	1.24	17%	210µ

Based on the flow properties lactose grades can be as ***Lactohale 300 < Sorbolac 400 < Respitose SV003 < Flowlac 100 < Inhalac 230 <DCL11***

Lactohale 300 and Sorbolac 400 alone are not suitable as carriers for dry powder inhalers; hence they are blended with coarse lactose to improve the flow properties.

The compatability of the drug with the carrier was investigated with HPLC technique and they were found to be compatible (Figure.1).

Fig.1:Compatibility chromatograms of Salbutamol Sulphate standard (a) and DPI form (b)



(a) (b)

The influence of overages in dry powder inhaler was carried out on salbutamol sulphate DPI. All the formulations were formulated with range of 0-20% extra quantity of active ingredient and evaluated for official tests and they satisfied the compendial requirements (Table.7).

Table.7 Characterization of Salbutamol Sulphate DPI formulated with different overages

Formulation	Parameters		
	Content uniformity (% based on average)	Weight variation in mg	Assay (%)
DPI1	88.6-100.6	73.9-82.4	98.6
DPI2	92.4-114.9	71.4-82.6	105.9
DPI3	88.6-110.8	72.7-78.4	113.7
DPI4	88.4-117.4	77.9-81.7	119.9

The drug collection pattern by using dosage unit sampling apparatus at flow rate of 30 lpm for 8 sec. Samples were analyzed by HPLC method. Results showed that 7-11% of drug retention in capsule shells and 4-8% of drug deposition in device. Only 82-88% of the dose was emitted from the device and the results are showed in Table.8.

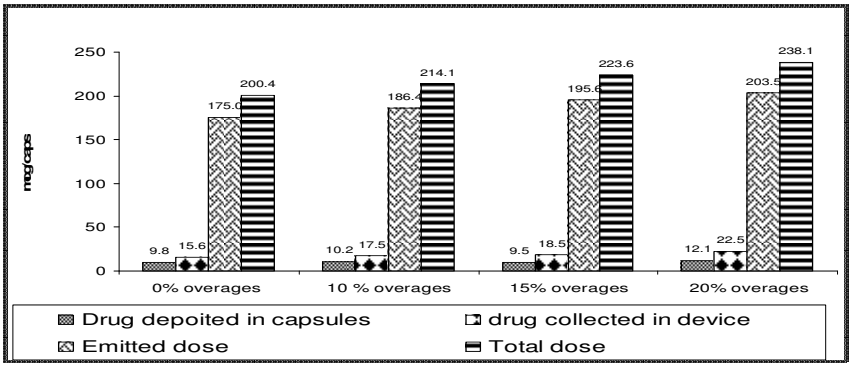
Table.8 In vitro performance parameters of Salbutamol Sulphate DPI formulated with overages

	µg of salbutamol Sulphate per dose±S.D (n=3)				% based on total dose			
Formulation	*DPI_1*	*DPI_2*	*DPI_3*	*DPI_4*	*DPI_1*	*DPI_2*	*DPI_3*	*DPI_4*
Overages	0%	10%	15%	20%	0%	10%	15%	20%
Drug deposited in 10 capsules	9.8 ± 0.6	10.2 ± 0.7	9.5 ± 1.1	12.1 ± 0.9	4.9	4.8	4.2	5.1
drug collected in device	15.6 ± 0.8	17.5 ± 0.9	18.5 ± 0.8	22.5 ± 1.1	7.8	8.2	8.3	9.4
Emitted dose	175.0 ± 5.2	186.4 ± 6.8	195.6 ± 4.6	203.5 ± 5.1	87.3	87.1	87.5	85.5
Total dose	200.4 ± 6.1	214.1 ± 7.5	223.6 ± 5.6	238.1 ± 6.4	100%			

The observed data indicated that around 15-20% active ingredient deposited either in capsule shell or dry powder inhaler device. To overcome these problem 20% overages is recommended in dry powder inhaler formulations to deliver 100% of active ingredient from the dry powder inhaler device to the patient.

The influence of the retained drug in the device on the drug delivered from the subsequent applications of the same device for the drug delivery was also studied. The results are showed in Figure.2. The emitted dose (delivered dose) was with in the ICH limits (80-120%).

Fig.2: Histograms correlating emitted dose and overages of Salbutamol Sulphate DPI 200 µg



Studies are carried out to evaluate the effect of fine lactose sorbolac S400 percentage (0-30%) and coarse lactose Inhalac 230 on performance of DPIs containing salbutamol on DPI performance. All the formulations showed good content uniformity and the results are showed in Table.9

Table.9 Compendial test data of DPI formulation with various portions of fine lactose

Formulation	Parameters		
	Content uniformity (% based on average)	Weight variation in mg	Assay (%)
DPI5	93.0-105.4	75.0-79.4	116.1
DPI6	96.1-107.6	70.4-76.4	120.0
DPI7	94.2-108.4	75.3-78.0	118.2
DPI8	93.3-107.4	72.3-76.0	116.2
DPI9	88.4-109.0	76.4-81.0	111.4
DPI10	84.6-106.0	74.3-79.6	109.0

Emitted dose and fine particle fraction are determined with twin impinger apparatus and samples were analysed by HPLC. A significant difference was noticed in the emitted dose and fine particle deposition with respect to composition of the formulation. The emitted dose was found to be decreased with increasing concentration of fine lactose (Table.10) and the fine particle deposition was increased with the incorporation of fine lactose (Table.10).

Table.10 Effect of fine lactose percentage on Fine particle fraction

Salbutamol sulphate DPI 200µg						
	DPI5	DPI6	DPI7	DPI8	DPI9	DPI10
% of fine lactose	0	5	10	15	20	30
Emitted dose (%)	94.5 ± 3.6	91.6 ±6.4	91. 5 ± 6.3	87.3 ± 5.4	83.1 ± 3.9	76.4 ± 8.6
Fine particle Dose (%)	8.6 ± 0.4	10.2 ± 0.6	13. 5 ± 0.6	13.8 ± 0.8	14.1 ± 1.2	15.2 ± 1.6

Thus the ratio of fine and coarse lactose influences the performance of dry powder inhalers. Finally it is concluded that 10% of fine lactose and 90% coarse lactose is suitable as carrier for development of dry powder inhaler.

Effect of various fine lactose grades (lactohale 300 and sorbolac 400) on performance of dry powder formulation was evaluated. They were tested for the desired compendial and non compendial tests. Content uniformity and uniformity of delivered dose were tested by dosage unit sampling apparatus at 30 lpm flow rate. Emitted dose and fine particle fraction was tested with twin impinger apparatus**.** All the samples were analyzed with HPLC**.** All the formulations were tested for emitted dose, uniformity of delivered dose, content uniformity of dose; fine particle fraction (Lung deposition) and the results are showed in Table.11&12.

Table.11 Physical tests on Salbutamol Sulphate DPI formulated with different grades of fine lactose

Formulation	Parameters		
	Content uniformity (% based on average)	Weight variation in mg	Assay (%)
DPI1	87.4-113.3	73.1-82.7	122.0
DPI2	86.9-112.4	74.3-79.9	109.5

Table.12 Drug distribution data from salbutamol sulphate DPI formulated with different grades of fine lactose

Parameter	Salbutamol sulphate in µg per capsules	
	DPI11	DPI12
Upper chamber	16.12 ± 2.5	11.23 ± 3.1
Lower chamber	2.65 ± 0.1	5.12 ± 0.2
Capsule	1.57 ± 0.02	2.64 ± 0.03
Device	0.5 ± 0.01	1.12 ± 0.01
Total dose	20.84 ± 3.1	20.11 ± 3.4
Emitted dose	18.77 ± 2.9	16.35 ± 3.1

All the formulations complied content uniformity of emitted dose and content of active ingredient, how ever significant difference in fine particle fraction were observed with respect to lactose grades. Lactohale 300 showed better fine particle fraction than sorbolac 400.

Effect of various coarse lactose grades (inhalac 230, DCL11, Flowlac 100 and respitose SV003) on performance of dry powder formulation was studied. They were subjected to the desired compendial and non compendial tests. Content uniformity this tested with the general methods and uniformity of delivered dose was tested by using dosage unit sampling apparatus at 30 lpm flow. Emitted dose and fine particle fraction were determined (Table.13 & 14) with twin impinger apparatus.

Table.13 Compendial tests data from the capsules filled with DPI containing different grades of coarse lactose

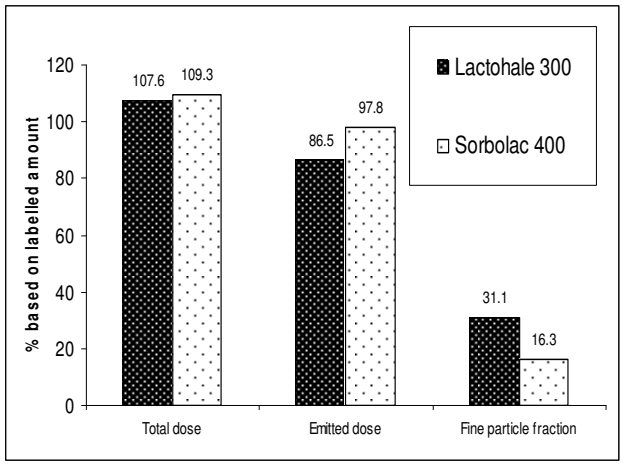
Formulation	Parameters		
	Content uniformity (% based on average)	Weight variation in mg	Assay (%)
DPI3	93.3-110.6	75.6-79.6	104.4
DPI4	94.1-108.4	76.4-79.1	100.9
DPI5	82.2-109.6	71.4-76.3	106.8
DPI6	90.0-115.4	70.6-78.0	107.9

Table.14 Data correlating coarse lactose grade and emitted dose, fine particle fraction

Formulation	Emitted dose (%)	% of fine particle fraction
DPI3	108.9 ± 4.9	22.6 ± 2.1
DPI4	104.6 ± 6.7	12.9 ± 2.3
DPI5	106.7 ± 8.7	13.4 ± 2.4
DPI6	108.9 ± 6.7	29.4 ± 2.0

All the formulations complied content uniformity of emitted dose and content of active ingredient, how ever significant difference in fine particle fraction were observed with respect to lactose grades (Figure.3).

Fig .3 :Effect of coarse lactose grade on Salbutamol Sulphate DPI performance.



Respitose SV003 showed better fine particle fraction than other coarse lactose grades (Inhalac230, DCL11 and Flowlac100). Salbutamol sulphate DPI, formulation was tested for drug recovery by employing 10, 15 and 20 capsules at a flow rate of 30 lpm.

Drug distribution in various stages was observed with 10, 15 and 20 capsules in Aderson cascade impactor testing of salbutamol sulphate is given in Table.15.

Table.15 Anderson cascade distribution with various sampling sizes of Salbutmol Sulphate DPI 200µg

	µg/capsule (Average of three trials)		
Sample size	**10 capsules**	**15 capsules**	**20 capsules**
Device	18.23 ± 2.1	16.50 ± 3.1	17.90 ± 1.8
Capsules shells	12.41 ± 2.1	13.40 ± 1.9	11.59 ± 2.5
Induction port	57.73 ± 6.8	53.20 ± 6.8	60.94 ± 7.2
Pre-separator	117.73 ± 9.1	106.50 ± 10.5	103.54 ± 9.4
Stage 0	13.58 ± 1.6	15.40 ± 4.6	12.65 ± 1.2
Stage 1	10.43 ± 0.9	9.26 ± 2.9	8.95 ± 0.9
Stage 2	4.13 ± 0.2	3.94 ± 1.4	4.26 ± 0.5
Stage 3	7.72 ± 0.2	8.10 ± 0.9	8.65 ± 1.1
Stage 4	5.8 ±0.3	5.64 ± 0.9	5.20 ± 0.6
Stage 5	3.24 ± 0.1	4.12 ± 0.1	4.69 ± 0.2
Stage 6	0.24 ± 0.02	0.33 ± 0.04	0.56 ± 0.01
Stage 7	0.08 ± 0	0.15 ± 0	0.10 ± 0
Filler	0.27 ± 0.05	0.34 ± 0.05	0.10 ± 0
Capsules shells + device	30.64 ± 3.4	29.90 ± 5.4	29.49 ± 4.2

Fine particle fraction and emitted dose were better with 20 capsules sample size when compared with 10 and 15 samples size (Table.16), and drug distribution pattern observed.

Table.16 Effect of sample size on cascade impactor testing of salbutamol Sulphate DPI

Product	**Salbutamol Sulphate DPI (n=3)**		
Sample size (capsules)	**10**	**15**	**20**
% FPF	12.78 ± 2.1	11.11 ± 2.0	15.17 ± 2.1
% of Emitted dose	75.61 ± 5.1	76.78 ± 4.8	81.11 ± 4.3

% of Total Dose	97.11 ± 5.6	98.28 ± 6.1	101.33 ± 5.1
MMAD	4.90 ± 0.5	4.74 ± 0.2	4.74 ± 0.2
GSD	1.64 ± 0.1	1.73 ± 0.1	1.65 ± 0.1

There is no correlation observed in between sample size and Anderson cascade data. Good recovery observed for low dose drug like salbutamol sulphate with sample size 20.

CONCLUSION:

The above cited research concludes that theperformance of Dry powder inhaler depends on overages, proportion of fine and coarsey lactose and the lactose grade employed in the preparation of Dry powder inhalers. The performance of Dry powder inhalers containing salbutamol hydrochloride was found to be optimum when it is formulated with 10:90 ratio of fine lactose (Lactohale 300): coarsey lactose (Respitose SV003) and having 20% w/w overages.

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