ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and Evaluation of Dry Powder Inhaler of Ciclesonide

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ABSTRACT

Dry powder inhalers (DPIs) for Ciclesonide were developed with a prospect for the maintenance treatment of asthma as prophylactic therapy in adult and adolescent patients 12 years of age and older. The formulations were prepared with different grades of Lactose monohydrate like Lactohale 200, Respitose SV010, Inhalac 200, Respitose ML006, Sorbolac 400 and Lactohale 300, which differ in their properties like particle size, surface morphology, moisture uptake which affect the fluidization, dispersion and drug deposition into respiratory portion of lungs and are evaluated for physical appearance, Locking length, Average fill weight per capsule, content uniformity, Emitted dose, fine particle dose, Moisture content and Assay. The DPIs formulated with 15:85 ratio of fine lactose (Lactohale 300) coarsey lactose (Respitose SV010) and having 10% w/w overages showed the better fine particle fraction.

Keywords: Ciclesonide, Dry powder inhalers, Emitted dose, Fine particle dose, Twin stage liquid Impinger (TSLI).

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ISSN: 0975-8585

INTRODUCTION

Dry powder inhalers (DPIs) are devices through which a active drug containing dry powder formulation is delivered for local or systemic effect via the pulmonary route. This type of drug delivery has several advantages such as rapid drug absorption since most of the surface area resides in the alveolated regions of the deep lung which contain a rich capillary network to facilitate rapid gas exchange. Avoids first pass metabolism. Ciclesonide is a glucocorticoid used to treat obstructive airway diseases. It is marketed under the brand name Alvesco(metered dose inhaler) for asthma and Omnaris/Omniair(nasal spray) for hayfever in the US & Canada. It is used by inhalation in the management of asthma in adults and adolescents aged 12 years and older. The usual dose is 160 micrograms once daily from a metered-dose aerosol; the dose may be reduced to 80 micrograms once daily for maintenance. It is preferably given in the evening. Ciclesonide is given intranasally for the treatment of seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older; children 6 years of age and older may be treated for seasonal allergic rhinitis. A dose of 200 micrograms once daily is given as 2 sprays of 50 micrograms into each nostril. Ciclesonide is a corticosteroid it prevents the release of substance in the body that cause inflammation [1]. The various physicochemical properties such as particle size, surface area, shape and morphology affects the forces of interaction and aerodynamic properties, which determine the fluidization, dispersion, delivery to the lungs and deposition in the peripheral airways [2]. The aerodynamic particle size influences drug deposition in the respiratory tract. Particles with an aerodynamic diameter (dae) larger than 6 µm deposit mainly in the oropharyngeal region, particles with a dae between 4 and 6 µm deposit in the conducting airways (e.g. bronchioles), while particles with dae less than 2 µm deposit in the peripheral regions of the lung (e.g. alveoli). The aerodynamic diameter of drug particles should ideally be between 1 and 5 mm for deep lung penetration [3] but they are characteristically cohesive having poor flow. However, the fraction of deeply inspirable drug particles from most carrier-based DPI formulations at present is considered relatively low since only 10 % total dose can be delivered to the lower airways, the site of action for most aerosolised drugs. several attempts to improve the delivery efficiency of drug particles to the lung have been made including: the design of novel inhaler devices, the production of smooth carrier particles [4], the use of lactose particles of different surface morphologies , the mixing of different grades of lactose carriers [5, 6]. The “active sites” hypothesis suggests the presence of different adhesive sites in which one is more adhesive than others. It has been proposed that fine excipient particles preferentially bind to areas on the surface of the coarse carrier with the strongest binding characteristics, thus forcing drug particles to bind to areas with weaker binding characteristics. It has been described that the fine particles are likely to fill up carrier surface irregularities. They may accumulate in a cavity or crevice of a carrier particle, allowing the passivation of the strongest binding site, and they are then no longer available for aerosolisation. In addition, when a high proportion of fine particles is added, the formation of multiple, complete layers of fines covering the surface of the coarse lactose particles may occur, thereby hindering direct contact between drug and carrier and promoting drug particle detachment from the carrier surface during aerosolisation. This phenomenon may also decrease the cohesion of the powder by improving the slip between particles. During inspiration, drug particles are more easily liberated from the surface of the carrier particles, increasing the generation of aerosol and the proportion of drug available for inhalation [7]. Ciclesonide dry powder inhalers were formulated with various

proportions and different grades of fine and coarse lactose. The effect of these parameters on efficiency of dry powder inhalers was studied and results are reported here.

MATERIALS AND METHODS

Materials

Ciclesonide was a kind gift sample from Arch pharma labs, Mumbai. Various grades of Lactose monohydrate like Lactohale 200, Lactohale 300 and Sorbolac 400 obtained from Domo Friesland. Respitose SV010 , Respitose ML006 obtained from DMV-Fonterra excipients, Inhalac 200 obtained from Molkerei Meggle wassenburg, and all other reagents used were of analytical grade .

Equipment

Twin stage liquid impinger (TSLI), High performance liquid chromatography (HPLC), Vacuum pump, Flow meter and Capsules partial filling machine.

Preparation of DPI

For inhalation formulations 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 and bulk and tapped density were measured. Results of tapped and bulk densities were given in Table.4 and Table.5. An accurately weighed amount of Ciclesonide was mixed separately in each case with Lactose monohydrate in geometric progress 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.

Preparation of the dry powder inhaler with different percentages of fine lactose

Ciclesonide DPI 200 mcg (220 mcg including 10% overages) formulations were prepared with changing the percentage of fine lactose (Respitose ML006) shown in the Table.1

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

Ciclesonide DPI 200 mcg (220 mcg including 10 % overages) formulations were prepared with 15 % fine lactose (Respitose ML006/sorbolac400/lactohale300) and 85 % of lactohale 200 with 25 mg fill weight as per composition given in Table.2 to select the fine lactose grade by evaluating the DPI performance.

Formulation of the dry powder inhalers with different coarse lactose grade.

Ciclesonide DPI 200 mcg (220 mcg including 10 % overages) formulations were prepared with various grades of coarse lactose such as lactohale 200,Respitose SV010 and

ISSN: 0975-8585

Inhalac 200 along with 15 % lactohale 300 with 25 mg fill weight as per composition given in Table.3.

Table.1 Formulation of dry powder inhaler with various percentages of fine lactose

Formulation	Active ingredient	Dose (mcg/capsule)#	Fine lactose portion in formulation(%)	Respitose ML006	Lactohale 200
				mg/capsules	mg/capsules
F1	Ciclesonide	220	0	0	Upto 25mg
F2	Ciclesonide	220	5	1.25	Upto 25mg
F3	Ciclesonide	220	10	2.5	Upto 25mg
F4	Ciclesonide	220	15	3.75	Upto 25mg
F5	Ciclesonide	220	20	5.0	Upto 25mg
F6	Ciclesonide	220	30	7.5	Upto 25mg

 # includes 10% overages

Table.2 Formulation of dry powder inhaler with various grades of fine lactose

Formulation	Active ingredient	Dose (mcg/capsule)#	Fine grade lactose	Fine grade lactose	Lactohale 200
				mg/capsules	mg/capsules
F7	Ciclesonide	220	Respitose ML006	3.75	Upto 25mg
F8	Ciclesonide	220	Sorbolac 400	3.75	Upto 25mg
F9	Ciclesonide	220	Lactohale 300	3.75	Upto 25mg

 # includes 10% overages

Table.3 Formulation of dry powder inhaler with various grades of coarse lactose

Formulation	Active ingredient	Dose (mcg/capsule)#	coarse grade lactose	Lactohale 300	Coarse lactose
				mg/capsules	mg/capsules
F10	Ciclesonide	220	Lactohale 200	3.75	Upto 25mg
F11	Ciclesonide	220	Respitose SV010	3.75	Upto 25mg
F12	Ciclesonide	220	Inhalac 200	3.75	Upto 25mg

 # includes 10 % overages

Evaluation

Non-Compendial test

Physical appearance

The capsules were visually observed of the particulate matter and for sticky nature of blend inside the capsule shell .

Locking length

Checked the locking length with vernier callipers and recorded the reading.

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Uniformity of weight

Weighed accurately 20 capsules individually taking care to preserve the identify of each capsules. removed the contents of each capsule as completely as possible . weighed capsule as completely as possible . weighed accurately the emptied shells individually and calculate for each capsule the net weight of shell from the respective gross weight and calculate the net content of each individual capsule

Net content of the individual unit (W_I)=(W_T-W_E)

W_T=weight of the individual filled capsules(mg)
W_E=weight of the empty capsules in mg

Moisture content

Transfer 50 ml of a mixture of methanol to the titration vessel and titrate with Karl Fischer reagent to detect any moisture that may present in the formulation. Quickly add about 100 mg of powder, mix and again titrate with the Karl Fischer reagent. Calculate the water content of the specimen, in %, taken by the formula

% Moisture content = BF x 100/W

Where,
W = Weight of the Sample, in mg.
B = (Burette reading)Volume of the KF reagent, in ml.
F = the water equivalence factor of KF reagent, in mg.

Compendial Test

Uniformity of Content

10 capsules were randomly selected and transferred accurately the content of one capsule to 10 ml volumetric flask each time . washed the inner walls of the emptied capsules to remove any adherent with diluent and transferred the washing to the same volumetric flask. 5 ml of the diluent was added and sonicated for about 10 min ,equilibrated to room temperature and diluted to volume with diluent , mix , estimated the drug content by HPLC. calculate the % deviation of content of each unit from the average content per capsule.

Assay (drug content determination)

Transferred the content of 10 capsules to 100 ml volumetric flask. Added about 50 ml of diluent and sonicate for 10 min ,allow to equilibrate to room temperature and dilute to volume with diluent mix . Filtered through a 0.45 µ membrane and estimated the drug content with HPLC.

Deposition of the Emitted Dose (with TSLI)

Prepare the inhaler for use and connect it to the inlet of the apparatus using a mouthpiece adapter to ensure an airtight seal. Use a mouthpiece adapter which ensures that the front face of the inhaler mouthpiece fits with the front face of the sample collection tube. Draw air through the inhaler using the predetermined conditions. The flow rate was 60L/min for 4 sec Repeat the procedure until the number of deliveries which constitute the minimum recommended dose have been sampled. Collect the sample from stage 1 and stage 2 separately and analysed for drug content by HPLC. Repeat the procedure for a further 9 doses. Emitted dose is the amount of drug deposited in both stage 1 and stage 2 of the TSLI, and Fine particle dose is the amount of drug deposited in the stage 2.

Deposition studies in cascade Impactor

Cascade impactors measure aerodynamic particle size which is a function of properties such as density and viscosity as well as the physical dimensions of the particles concerned. Cascade impactors operate on the principle of inertial impaction. The inhaler is connected to the induction port by means of the mouthpiece adaptor which provides an airtight seal between the induction port and the delivery device concerned. Each stage of the impactor comprises a single or series of nozzles or jets through which the sample laden air stream is drawn directing any airborne particles towards the surface of the collection plate for that particular stage. The flow rate was 28.3 l/min and at the end of the test, the particle mass relating to each stage collection plate is recovered using a suitable solvent and then analysed usually using HPLC to determine the amount of active drug actually present. By analysing the amount of drug deposited on the various stages in this manner, it is then possible to calculate the Fine Particle Dose (FPD)

***In vivo* deposition studies**

The fasted rats were anesthetized by intraperitoneal injection of sodium pentobarbital. The rat was placed in a holder with the body positioned face up and its upper incisors hooked onto the frame. The middle of the fifth and sixth tracheal cartilages from the glandula thyroidea was cut, and a polyethylene tube (2 mm diameter× 3 cm) was inserted 1.5 cm into the trachea for cannulation. The ciclesonide dry powder inhalation formulation was introduced by intratracheal administration using a veterinary dry powder insufflator equipped with a three-way cock. Compressed air for releasing the particles was generated by depressing the plunger from 2 to 0.5 mL on the syringe scale. The delivery tube of the insufflator was inserted into the tracheal cannula and the rat's breathing was stopped for 2 s. Next, an air pulse was released through the three-way cock to deliver the particles, and the positionwas held for 5 s. The delivery tube was then removed from the cannula .*In vivo* fluorescent images of lungs of rats after administration were observed. Indocyanine green (ICG) was used as a fluorescent marker. Fluorescent images of lungs taken from the back side of rats after administration of dry powder inhaler . Fluorescent images of lungs taken from the back side of rats were recorded using a Maestro G NIR (FL 500) (Kurabo, Tokyo, Japan). The exposure time was 300 ms, the excitation wavelength was 615–665 nm, and the measurement wavelength was 700 nm.

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RESULTS AND DISCUSSION

Micromeritic properties

Physical properties such as bulk density, tapped density and particle size of various lactose grades were evaluated and showed in Table.4 and 5. Based on the flow properties lactose grades can be as ***Lactohale 300 < Sorbolac 400 < Respitose ML006 < lactohalec 200 < Inhalac 200 <Repitose SV010.*** Lactohale 300 , Sorbolac 400 and repitose ML006 alone are not suitable as carriers for dry powder inhalers; hence they are blended with coarse lactose to improve the flow properties.

Table 4: Physical properties of Lactose monohydrate of coarse 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)
Lactohale 200	0.60	0.90	1.50	33.30	150 µ
Respitose SV010	0.72	0.86	1.19	16.27	170 µ
Inhalac 200	0.68	0.80	1.33	25.00	195 µ

Table 5: Physical properties of Lactose monohydrate of fine 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)
Respitose ML006	0.48	0.78	1.62	38.46	48 µ
Sorbolac 400	0.34	0.70	2.05	51.44	30 µ
Lactohale 300	0.36	0.76	2.11	52.63	10 µ

Compendial and Non compendial test for dry powder inhaler with different percentages of fine lactose

The capsules were visually observed and were found to be free of particle matter and there was no sticking of blend inside the capsule of the prepared formulations. Studies are carried out to evaluate the effect of fine lactose Respitose ML006 percentage (0-30 %) and coarse lactose Lactohale 200 on performance of DPIs containing Ciclesonide on DPI performance. The values of locking length, weight variation, Moisture content formulations from F1 -F6 were found to be within the limit and showed good content uniformity and the assay values were found to be within the limit, results are showed in Table.6. 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.7) and the fine particle deposition was increased with the incorporation of fine lactose (Table.7). The emitted dose (delivered dose) was within the ICH limits (80-120 %). Thus the ratio of fine and coarse lactose influences the performance of dry powder inhalers. Finally it is concluded that 15 % of fine lactose and 85 % coarse lactose is suitable as carrier for development of dry powder inhaler.

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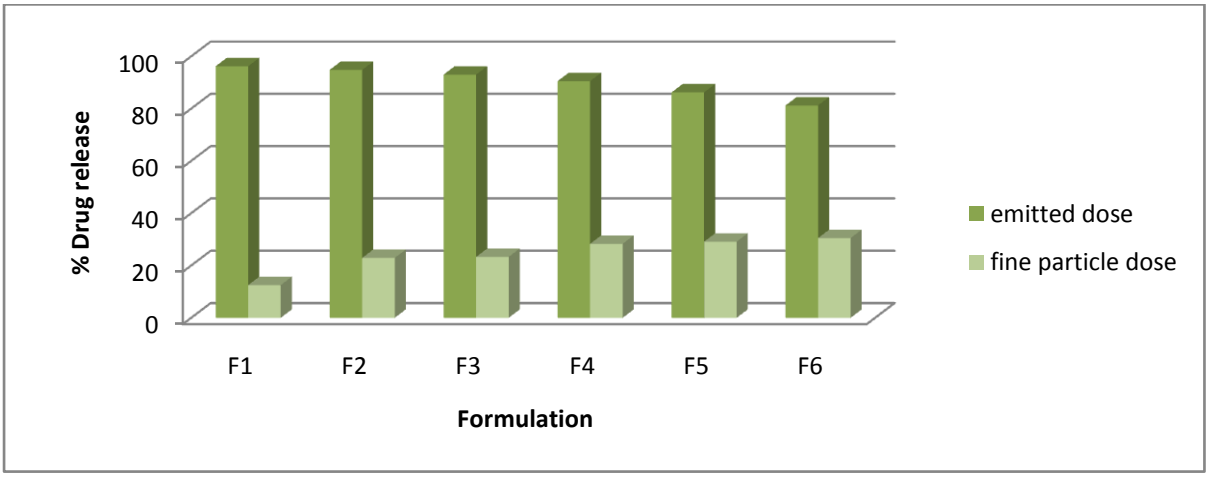
Table.6 Physical tests of DPI formulation with various portions of fine lactose

Formulation	Parameters				
	Locking length	Content uniformity (% based on average)	Weight variation in mg	Moisture content of blend	Assay(%)
F1	15.43	97.6-107.6	23.5-28.2.	4.7	105.34
F2	15.60	93.8-105.4	22.8-26.8	4.9	103.62
F3	15.48	92.2-106.3	24.7-27.9	5.3	106.24
F4	15.68	93.1-105.4	24.3-28.2	4.5	104.70
F5	15.63	90.2-106.4	22.7-28.0	4.9	105.25
F6	15.56	85.2-105.3	23.4-28.2	5.3	105.30

Table.7 Effect of fine lactose percentage on Fine particle fraction

Formulation	% Of fine lactose	Emitted dose (%)	Fine particle Dose (%)
F1	0	96.2	12.5
F2	5	94.8	22.9
F3	10	93.0	23.3
F4	15	90.5	28.3
F5	20	86.2	29.1
F6	30	81.2	30.5

Fig.1: Histogram showing the %drug deposition in TSLI of the formulation containing different percentage of fine lactose.



Compendial and Non compendial test for dry powder inhaler with different fine grade lactose

The capsules were visually observed and were found to be free of particle matter and there was no sticking of blend inside the capsule of the prepared formulations. Effect of various fine lactose grades (Respitose ML006, Sorbolac 400 and Lactohale 300) on performance of dry powder formulation was evaluated. They were tested for the desired Compendial and non compendial tests. The values of locking length , weight variation , Moisture content formulations from F7 -F9 were found to be within the limit and showed good content uniformity and the assay values were found to be within the limit . They were also tested for

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emitted dose, fine particle fraction (Lung deposition) and the results are showed in Table.9 .Emitted dose and fine particle fraction was tested with twin impinger apparatus**.** All the samples were analyzed with HPLC**.** The formulation F9 showed the better emitted dose and fine particle dose which consists of lactohale 300 which is more cohesive and prevent the sticking of the formulation blend to the capsules or inhaler devices and also adhere to the active sites of the coarse lactose which leads to the drug to bind to the lesser active in coarse lactose leading to the deagglomeration of drug and carrier hence higher deposition so, lactohale 300 was selected as fine grade lactose to formulate the Ciclesonide dry powder inhaler.

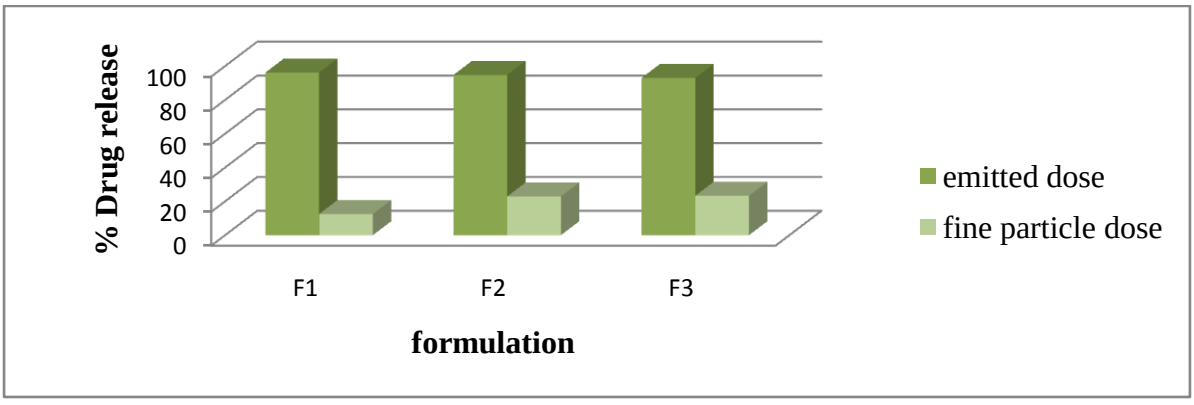
Table 8: Physical tests on DPI formulated with different grades of fine lactose

Formulation	Parameters				
	Locking length	Content uniformity (% based on average)	Weight variation in mg	Moisture content of blend(%)	Assay(%)
F7	15.52 ± 0.09	94.6-106.2	23.9-27.8	4.9	104.44
F8	15.43	95.2-105.6	22.8-26.8	5.3	103.74
F9	15.45	93.2-104.9	24.6-27.2	5.2	105.28

Table 9: Effect of different fine grade lactose on Fine particle fraction

Formulation	Fine grade lactose	Emitted dose (%)	Fine particle Dose (%)
F7	Respitose ML006	90.5	28.3
F8	Sorbolac 400	93.0	30.6
F9	Lactohale 300	94.5	33.3

Fig 2: Histogram showing the %drug deposition in TSLI of the formulation containing different grade of fine lactose.



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Compendial and non compendial test for dry powder inhaler with different coarse lactose

The capsules were visually observed and were found to be free of particle matter and there was no sticking of blend inside the capsule of the prepared formulations. Effect of various coarse lactose grades (Lactohale 200, Respitose SV010 and Inhalac 200) on performance of dry powder formulation was evaluated. They were tested for the desired compendial and non compendial tests. The values of locking length , weight variation, Moisture content formulations from F10 -F12 were found to be within the limit and showed good content uniformity and the assay values were found to be within the limit (Table 10). Emitted dose and fine particle fraction was tested with twin impinger apparatus**.** All the samples were analyzed with HPLC and the results were shown in the table 11**.** The formulation F11 showed the better fine particle dose which consist of Respitose SV010 compared to the other coarse grade lactose used.

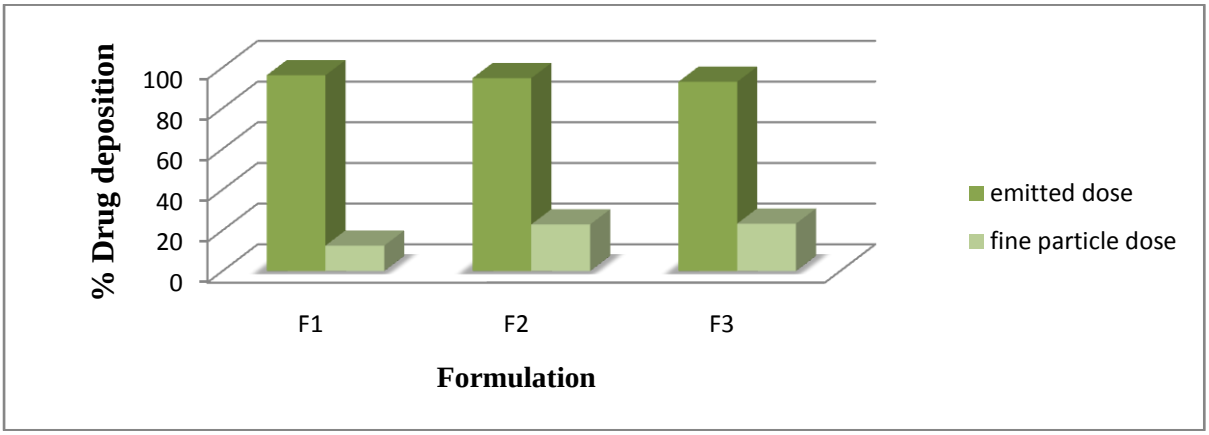
Table.10 Physical tests on DPI formulated with different grades of coarse lactose

Formulation	Parameters				
	Locking length	Content uniformity (% based on average)	Weight variation in mg	Moisture content of blend	Assay(%)
F10	15.45	95.6-104.2	22.9-28.2	5.1	105.24
F11	15.51	96.2-106.6	23.4-27.8	4.8	105.72
F12	15.60	94.7-107.9	22.2-28.5	5.3	106.25

Table.11 Effect of different coarse grade lactose on Fine particle fraction

Formulation	coarse grade lactose	Emitted dose (%)	Fine particle Dose (%)
F10	Lactohale 200	94.5	33.3
F11	Respitose SV010	95.4	34.6
F12	Inhalac 200	93.2	31.3

Fig 3: Histogram showing the % drug deposition in TSLI of formulation containing different grade of coarse lactose.



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The dry powder inhaler device play an important role in the drug deposition so the drug deposition studies were performed by using two inhaler devices having varying resistance. The results were shown in the (Table 12).

Table.12 Comparison Of Drug Deposition In TSLI By Rheohaler And Evohaler of the optimised formulation.

Formulation number	Formulation composition	Rheohaler		Evohaler	
		Emitted dose (%)	Fine particle Dose(%)	Emitted dose (%)	Fine particle Dose(%)
F11	Respitose SV010:lactohale 300(85%:15%)	95.4	34.6	97.3	37.2

The deposition of the drug increases with increase in the resistance of the dry powder inhaler. The results of the deposition studies shown in the table 12 which were compared between the Rheohaler and Evohaler , as Evohaler having the higher resistance showed the higher depoistion

Fig 4: Histogram showing the % drug deposition in TSLI by using Rheohaler and Evohaler.

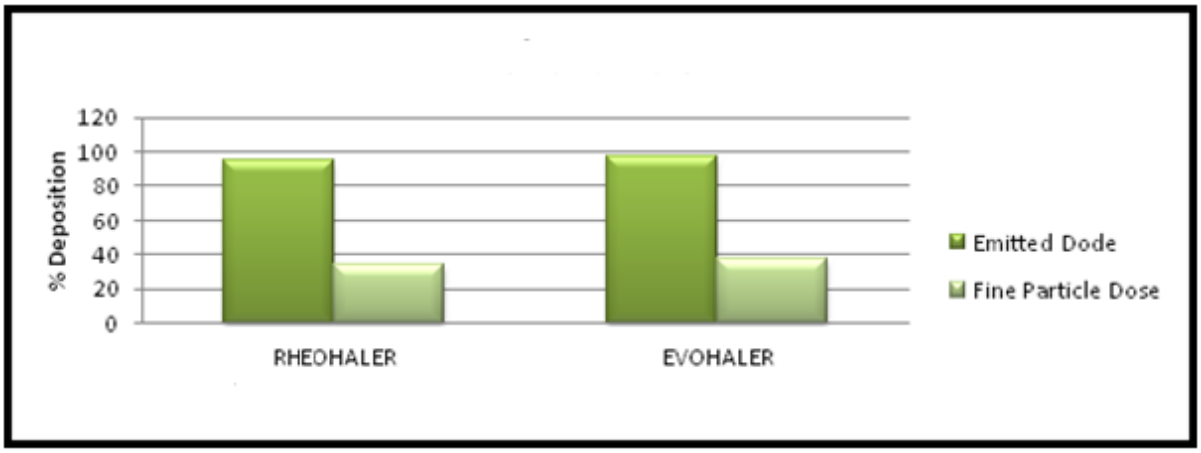

Table.13 Drug deposition studies of optimised formulation in Andresen cascade Impactor by using Rheohaler and Evohaler.

Formulation number	Formulation composition	Rheohaler	Evohaler
		Fine particle Dose(%)	Fine particle Dose(%)
F11	Respitose SV010:lactohale 300(85%:15%)	24.32	26.02

The increase in the fine particle dose in Andresen cascade impactor by Evohaler compared to that of Rheohaler due to high turbulance created in the Evohaler hence deagglomeration of the drug and carrier and hence higher deposition.

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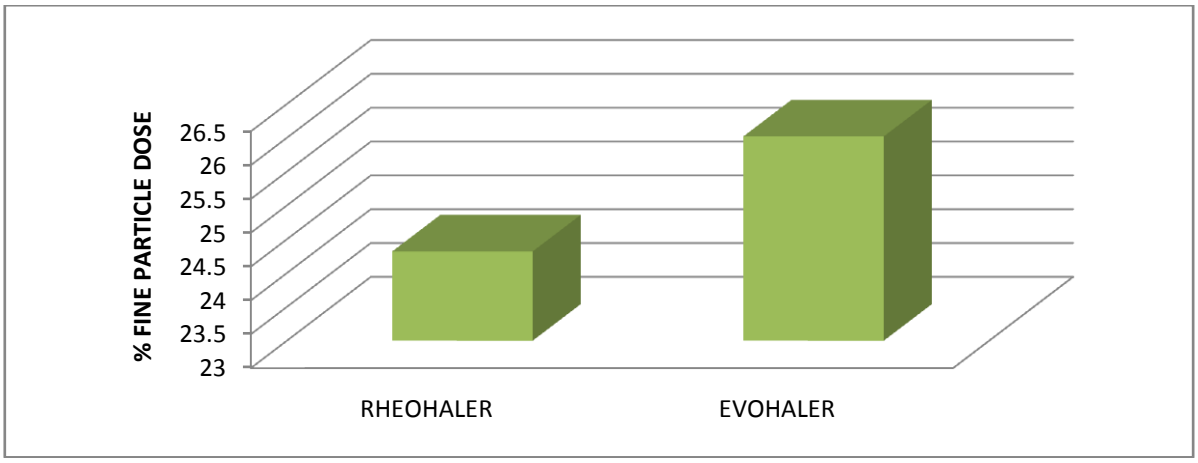
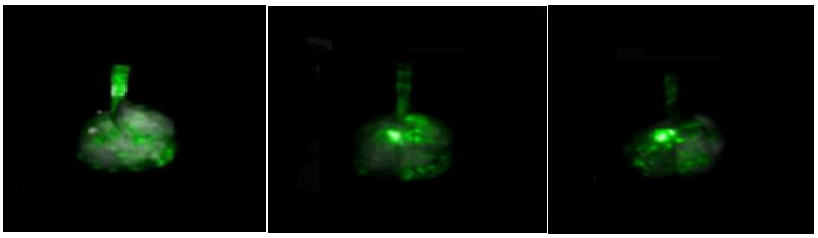
Fig 5: Histogram showing the % drug deposition of optimised formulation in Andresen cascade Impactor by using Rheohaler and Evohaler.



In vivo deposition studies

The *In vivo* deposition studies showed the deposition of Ciclesonide in the respiratory portions of the lungs of the rat Fig.6

Fig .6: *In vitro* deposition of Ciclesonide in rat



5min **1hr** **2hr**

CONCLUSION

The performance of Dry powder inhaler is found to be dependent on 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 ciclesonide was found to be optimum when it is formulated with 15:85 ratio of fine lactose (Lactohale 300): coarsey lactose (Respitose SV010) and having 10% w/w overages.

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