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Research Article

Effect of fine lactose fraction on in vitro deposition of Mometasone furoate dry powder inhaler

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Abstract: Dry powder inhaler (DPIs) has attained considerable attention due to their propellant-free formulation and the patient's inherent coordination with actuation. Dry powder inhaler consist of micronized (<5um) drug alone or mixed with carrier particles. Lactose is the more widely used carrier in dry powder inhalers (DPIs).This study was carried out to investigate the effect of weight fraction of fine lactose as a carriers on aeroionisation behaviour of Mometasone furoate dry powder inhaler.Lactohale 200 and Lactohale 210 two commercial lactose monohydrate were belened in different ratios with fixed amount Mometasone furoate .A low resistance Rotahaler and medium resistance Cyclohaler were used to evaluate the effect of inhaler design on the deposition profiles of Mometasone furoate.Average fill weight per capsule, content uniformity, Uniformity of delivered dose by DUSA, invitro depositon, Moisture content, Assay .Twin stage liquid impinger was used to determine the invitro deposition of Mometasone furoate.Better invitro depositon was observed formulation having lactose ratio (70:30),that is 70% coarse lactose and 30% lactose fine .
Keywords: Dry powder inaler, lactose monohydrate, DUSA, Twin stage impinger, Device resistance

INTRODUCTION

Aerosolized administration of drugs to the lung has become an important and effective method for treatment pulmonary been employed for many years to treatment of pulmonary diseases, such as asthma, bronchitis and emphysema. [1] Dry powder inhaler consist of powder formulation is composed of micronized drug (<5µm) powder either alone or mixed with coarser and combination of coarser and fine carrier. [2] Lactose monohydrate (LMH) is the excipient of choice for the use as carrier for adhesive mixtures for dry powder inhalation. Recent research has revealed that the type and quality of LMH significantly alters the efficiency of dry powder inhaler performance. [3,4] Although lactose monohydrate is a well known and well characterized excipient, the quality of lactose—sieved or milled quality, source of lactose—used for the formulation of an inhalation powder is of utmost importance and significantly influences the efficiency of the product. It has also been reported that the particle size and the size distribution of lactose in a DPI formulation affects the aerosolization properties of the powder [5]

Mometasone furoate dry powder inhaler has an excellent safety and efficacy profile. For patients with persistent asthma who require treatment with an inhaled corticosteroid, Mometasone furoate is an excellent therapeutic choice.[6] For the treatment of persistent asthma in patients aged >or= 12 years. Mometasone furoate -DPI has low systemic bioavailability and high glucocorticoid receptor affinity compared with most other ICSs.. Studies show that Mometasone furoate -DPI 200 or 400 µg Q.D PM treatment significantly improves lung function and symptom control in patients with mild, moderate or severe asthma. Mometasone furoate -DPI 400 µg Q.D PM is reported to be equivalent to fluticasone propionate 250 µg b.i.d. and beclometasone dipropionate 168 microg b.i.d. and more efficacious than budesonide 400 µg, b.i.d. or Q.D. Mometasone furoate -DPI is generally well tolerated, with minimal effects on the hypothalamic-pituitary-adrenal axis.[7] Objective of this study to evaluate the effect of fine and coarse lactose weight fraction and device resistance on invitro deposition of Mometasone Furoate DPI. Five formulation of Mometasone furoat and lactose monohydrate were prepared in order to determine the effects of weight fraction of carrier on in vitro deposition of the drug. To investigate the deposition profile of aerosolised Mometasone Furoate. Two inhaler devices with different internal resistance Rotahaler and Cyclohaler were taken for study the effect of inhaler device resistance on in vitro deposition of Mometasone furoate.

Rotahaler device is a mouthpiece inhaler instrument. It is a two-piece device made up of plastic. It is a breath-activated device that can be used by patients suffering from asthma. It has a pre-metered single medication dose provision that helps in taking inhalations for relieving attacks of asthma. This device is very simple to use and also very cost effective. [8].Cyclohaler also single dose system with piercing type device.

MATERIALS AND METHODS

Materials

Micronized Mometasone Furoate was supplied by Anuh pharma; Commercial grades of lactose Lactohale 200 and Lactohale 210 were obtained as α

lactose monohydrate from DFE Pharma .The device Rothaler and Cyclohaler were available commercially. Capsules size 3 obtained from Natural capsules Pvt. Limited.

Equipment

Manual Capsules filling machine , Dose uniformity sampling apparatus (DUSA), Twin stage liquid impinger (TSLI), High performance liquid chromatography (HPLC), Vacuum pump, Flow meter .

Particle Size measurement

A small amount (about 10 mg) of mometasone furoate and lactose powder were dispersed separately in 10 ml of water and sonicated for 3 min to avoid agglomeration. Particle sizes of powder were measured by laser diffraction (Mastersizer 2000).Sample measurement time was 10 second. The particle size distribution was calculated and represented as a volume distribution, and was also characterized by the 10th, 50th and 90th percentile of the cumulative particle undersize frequency distribution.

Preparation dry powder inhaler

An accurately weighed amount of each lactose monohydrate that is coarse and fine dried at 60^0c for 1 hour ,Passed dried lactose separately through sieve no 60# mesh and mix both lactose for five minute again passed through same sieve for three times. Accurate amount Mometaone furoat was mixed with Lactose monohydrate mixture as shown in table .1, in geometric process, and passed through 60# mesh for three times and blended in polybag for 15 minute and filled in to size "3" hard gelatine capsules with partial filling manual capsule filling machine with fill weight of 25 mg per capsules.

Table.1: Formulation trail with different of Corase (Lactohale 200) and fine lactose (Lactohale210) with Mometasone Furoate

SL NO	Mometasone furoate (µg)	Lactohale200: Lactohale210	Lactohale210 (mg)/ Capsules	Lactohale200 (mg)/ Capsules
F1	400	90:10	2.5	Q.S. to 25
F2	400	80:20	5	Q.S. to 25
F3	400	70:30	7.5	Q.S. to 25
F4	400	60:40	10	Q.S. to 25
F5	400	50:50	12.5	Q.S. to 25

Evaluation of Dry Powder Inhaler of Mometasone Furoate

Formulations of Mometasone furoate dry powder inhaler prepared were evaluated for the following parameters-

Physical appearance: The capsules were visually observed after formulation for sticking and any lump formulation inside the capsule shell.

Micromeritic properties: Physical properties such as bulk density, tapped density, was measured to saw the flow property of each formulation.

Averages fill weight per capsule: Randomly 20 capsules were selected without losing any part of the shell and removed the content from each capsule completely and weighed together and weighed of empty shell was taken. Calculated the average content for each capsules by using following formula.

Calculations

Average net content (mg) = $(W_t-W_e/20)$

Where, wt= Totale weight of 20 filled Blend in capsules in mg

We= weight of 20 empty capsules Shell in mg.

Moisture content: Transfered 30 to 40 ml of methanol to the titration vessel and titrated with Karl Fischer reagent to detect any moisture that may be present. Add about 200 mg of powder, mix and again titrate with the Karl Fischer reagent. Calculate the water content of the specimen, in mg, taken by the formula.

BF x 100/W

Where

W = Weight of the Sample, in mg.

B = Volume of the KF reagent, in ml.

F = the water equivalence factor of KF reagent, in mg.

Measurement of content uniformity: Drug content uniformity was performed to ensure that the Mometasone furoate was blended uniformly with the lactose upon powder mixing. Content uniformity measurements were undertaking by randomly sampling of ten samples of approximately 25 ± 2 mg from the powder blend of each batch produced, and the amount of Mometasone furoate was determined by HPLC .The uniformity of drug content was performed for 10 capsules in each formulation (F1-F5). The results of percentage of drug content per capsule are summarized in table 4.

Uniformity of delivered dose. By DUSA

Uniformity of delivered dose was measured by DUSA (Dose uniformity sampling apparatus, Colony specific). The apparatus consists of a filter support base with an open-mesh filter-support, a collection tube that

is screwed to the filter-support base and a mouthpiece adapter to ensure an airtight seal between the collection tube and the mouthpiece. Inhaler for use was connected it to the inlet of the apparatus using a mouthpiece adapter to ensure an airtight seal. One port of a differential pressure meter was connected to the pressure reading point P1, and the other was open to the atmosphere. Pump was switched on, 2-way solenoid valve was opened and flow control valve was adjusted until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H_2O) as indicated by the differential pressure meter and the apparatus was operated at an air flow rate of 100 l/min for 2.4 s. The content of the apparatus was quantitatively collected and the amount of Mometasone furoate was determined by HPLC method. The procedure was careied out for 10 capsules for each batch.

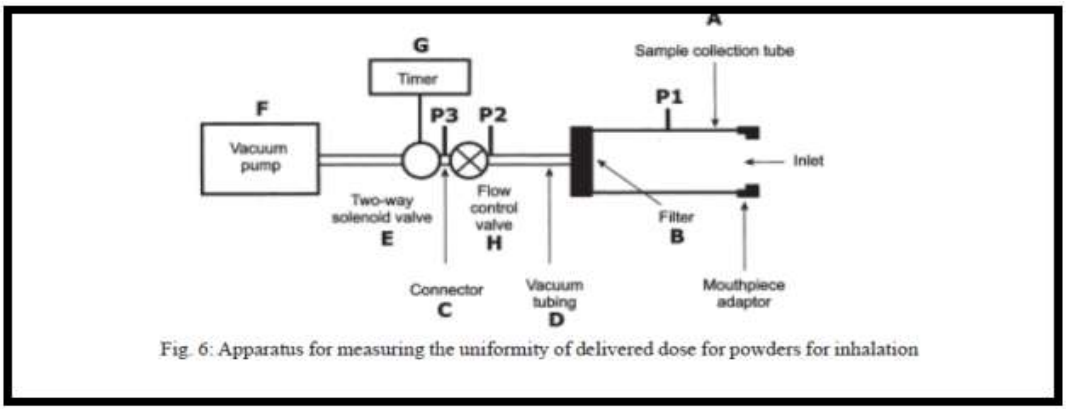

Figure 2 : Apparatus for measuring the uniformity of delivered dose for inhalation

In vitro deposition

In the TSLI test, 7ml of methanol was introduced in stage 1 and 30 of the same solvent was placed in stage 2 of the apparatus .The capsule to be tested was placed in Rotahaler and Cyclohaler were attached to the throat piece of the impinger. The assemble was checked and when found to be airtight and vertical; the vacuum pump was switched on .After the pump had run for 5seconds at 60ml/min, the dose was released. The pump was allowed to run for another 5 seconds at 60ml/min following the release of the dose. The deposition test was repeated until ten capsules had been actuated in the same manner. The inhaler body, capsule shell and mouthpiece were washed with the same solvent. The sample thus obtained was used to measure the amount of drug retained in the each inhaler device, the upper stage (Stage 1) that is the non-respirable fraction and lower stage (Stage 2) that is the respirable fraction of the impinger. The entire samples were analyzed for the content of Mometasone furoate using HPLC method.

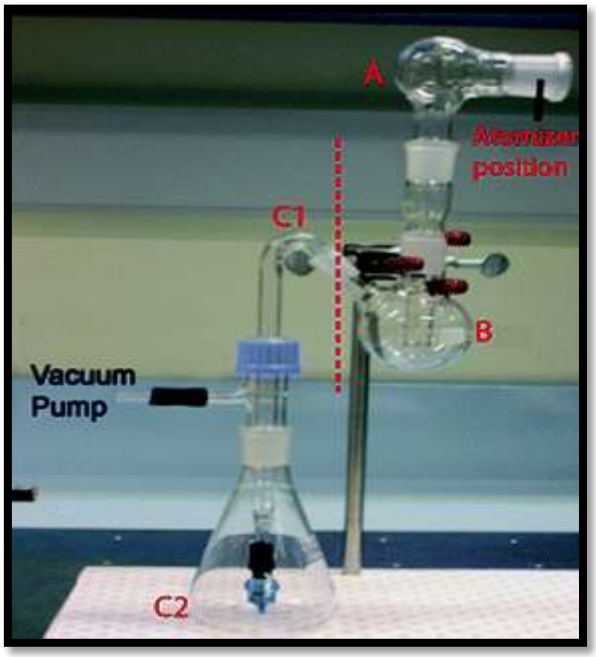

Figure 3: Twin stage liquid impinger for invitro deposition

RESULT AND DISCUSSION:

Table 2.Particle size distributions of the materials

Material	Cumulative percent (Under size)		
	$d_{10\%(\mu m)}$	$d_{50\%(\mu m)}$	$D_{90\%(\mu m)}$
Mometasone Furoate	0.86	1.95	3.92
Lactohale 200	13	62	132
Lactohale 210	2.7	16	46

Table 3. Result of micromeritic properties of all the formulations

Sl no	Formulations	Micromeritic properties			
		Bulk density	**Tapped desity**	**Hausner Ratio**	**Car's index**
1	F1	0.549	0.742	1.35	26.00
2	F2	0.585	0.783	1.33	27.28
3	F3	0.546	0.786	1.43	30.50
4	F4	0.587	0.893	1.32	34.21
5	F5	0.648	1.044	1.20	37.03

Table 4. Result of Average net content, Moisture content and content uniformity

Sl no	Formulations	Average net content mg	Moisture content (%)	Drug content based on average
1	F1	24.85	4.4	97.5±1.5
2	F2	25.82	4.3	98.8±2.6
3	F3	26.70	4.1	99.7±2.5
4	F4	22.89	4.9	95.7±1.6
5	F5	23.05	4.6	96.9±2.1

Table 5. Result of uniformity of delivered dose by DUSA

1. Parameter	2. Formulation				
	3. F1	4. F2	5. F3	6. F4	7. F5
8. %delivered dose	85.7	89.2	88.1	88.5	92.1
	89.1	85.1	94.5	94.1	87.7
	88.5	90.2	88.2	96.4	91.4
	84.9	91.2	90.6	89	89.9
	88.9	86.3	89.5	90.8	94.7
	96.2	89.2	93.8	94.7	97.4
	88.1	91.3	95.2	88.4	88.6
	86	96.2	89.9	88.6	91.5
	88.2	93.5	89.4	95.4	93.6
	86.4	90.1	91.5	94.2	89.4
9. Average	88.2	90.2	91.0	92.01	91.6

Table 5: Results of deposition of formulations (F1-F5) with different concentrations of coarse and fine grade lactose operated by Rotahaler and Cyclohaler

Sl no	**Formulation**	**%In vitro deposition from Rotahaler**			**%In vitro deposition from Cyclohaler**		
		D	S1	S2	D	S1	S2
1	F1	13.25	52.23	24.64	12.70	53.72	26.51
2	F2	15.61	50.56	26.71	11.55	54.31	28.64
3	F3	14.46	53.07	27.94	12.40	53.43	32.98
4	F4	16.75	52.72	23.58	15.64	50.42	27.71
5	F5	17.90	52.53	21.71	17.11	49.13	25.94

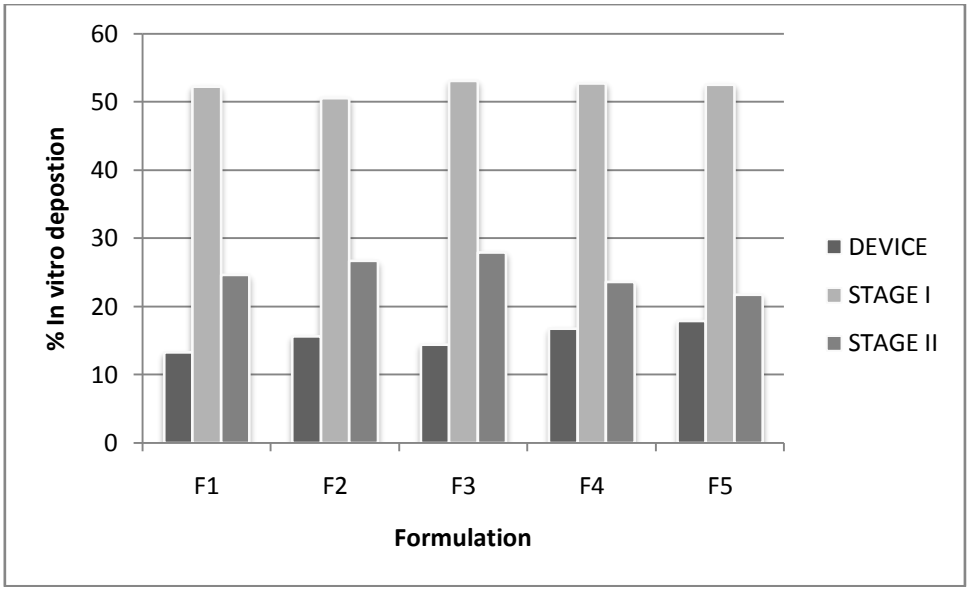

Figure 4. In vitro deposition data of Rotahaler

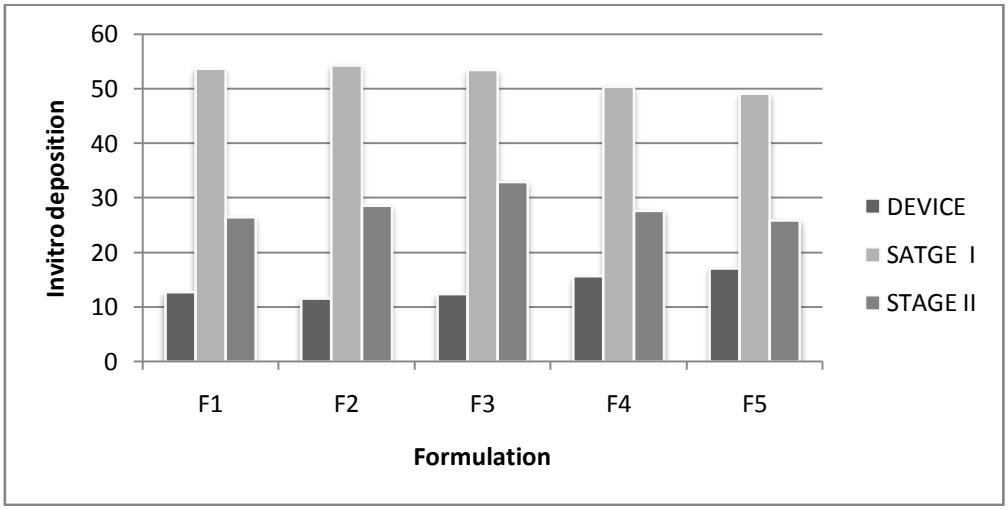

Figure.5. In vitro deposition data of Cyclohaler

Table .6. % of RD, ED, FPF in TSLI by using Rotahaler and Cycohaler

Formulation	Rotahaler			Cyclohaler		
	RD (%)	ED (%)	FPF (%)	RD (%)	ED (%)	FPF (%)
F1	90.12	76.87	24.64	92.98	80.23	26.51
F2	92.88	77.27	26.71	93.50	82.95	28.64
F3	95.47	81.01	27.94	98.81	86.41	32.98
F4	93.08	76.30	23.58	93.77	78.14	27.71
F5	92.11	74.24	21.71	92.18	75.07	25.94

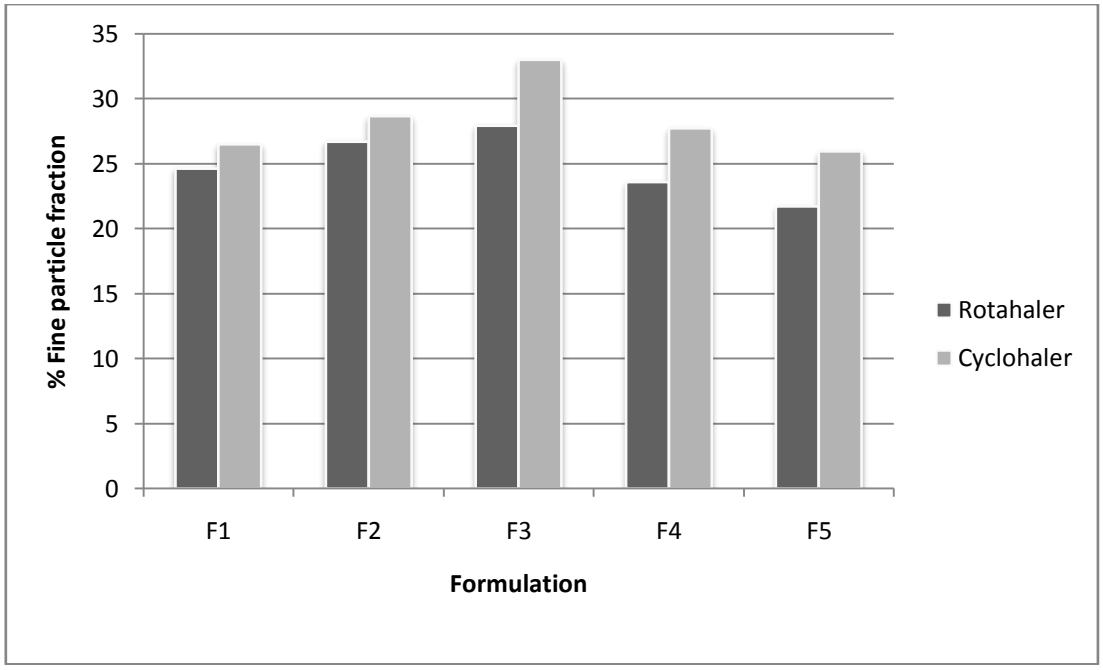

Figure .3. Histogram showing the % fine particle fraction (FPF) in TSLI by using Rotahaler and Cyclohaler

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. Table 2 shows the particle size distribution data of the materials employed in this study. The Mometasone Furoate powder had a $d_{50\%}$ of 1.96 µm and $d_{90\%}$ of 3.91 µm. The commercial of Mometasone furoate sample with a particle size $d_{90\%}$ smaller than 3.91 µm exhibited a suitable particle size range for DPI formulation..Physical properties such as bulk density, tapped density evaluated showed in Table.3 Flow property generally increases with increasing weight fraction of fine lactose. Average net content, Moisture content for all formulations were found to be within the limit and showed good content uniformity. The uniformity of delivered dose was carried out for 10 capsules in each formulation (F1-F5). The results of percentage drug delivered from each capsule are given in table 5.Emitted dose and fine particle fraction was tested with twin impinger apparatus. The type of inhalation device and weight fraction of carrier have significant influences on the FPF of the drug . The highest FPF was obtained for formulations containing 30% lacohale 210 (Fig. 4). The FPF of the drug aerosolised from this formulation using Rotahaler and Cyclohaler were found to be about 27.94 and 32.68%, respectively. Compared to Rotahaler all formulations which were aerosolised by the use of Cyclohaler yielded significantly higher FPF.So 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 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 Rotahaler and Cyclohaler , as Cycohaler having the higher resistance, showed the higher deposition.

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 Mometasone Furoate was found to be optimum when it is formulated with 30:70 ratio of fine lactose (Lactohale 210): coarse lactose (Lactohale 200). FPF and dispersibility of the drug were depended on weigh fraction of the carriers used in the formulation as well as the type of inhalation device. The deposition of the drug increases with increase in the resistance of the dry powder inhaler. The results of the deposition studies were compared between the Rotahaler and Cyclohaler, as Cyclohaler having the higher resistance compared to Spinhaler showed the higher deposition.

References

1. Suarez S, Hickey AJ. Drug properties affecting aerosol behaviour. Respiratory Care, 2000; 45: 652-666.
2. Prime D, Atkins PJ, Slater A, Sumby B. Review of dry powder inhalers. Adv Drug Deliv Rev 1997; 26: 51-58.
3. Zoey MD, Razia S, Stewart PJ, Influence of physico-chemical carrier properties on the in vitro aerosol deposition from interactive mixtures. Int.J.Pharm. 2003; 252:87-98
4. Zeng XM, Martin GP, Marriott C, Pritchard C. Lactose as a Carrier in Dry Powder

Formulations: The Influence of Surface Characteristics on Drug Delivery. J.Pharm.Sci. 2001; 90:1424-1434

1. 5.H. Steckel, P. Markefka, H. teWierik, R. Kammelar, Functionality testing of inhalation grade lactose, European Journal of Pharmaceutics and Biopharmaceutics, 2004; 57:495–505.
5. Tracy B Fausnight ,Timothy J Craig , Mometasone furoate dry powder inhaler for the treatment of asthma
2. Expert Opinion on Pharmacotherapy , 2011, 12(17):2707-2712.
6. Urzo A A, Mometasone furoate dry-powder inhaler for the control of persistent asthma, Expert Opinion on Pharmacotherapy 2007; 8(16):2871-84.
7. http://www.verticalpharmacy.net/asthma-medicines/rotahaler-344.html