ISSN: 0976-4607
Research Article

International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

Formulation and Evaluation of Dry Powder Inhaler for Tiotropium Bromide

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Abstract

Dry powder inhalers (DPIs) for Triotropium Bromide were developed with a view to treat bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema effectively. 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, Moisture content, Assay ,and Locking length. The influence of composition of DPI and overages on performance of DPI was studied. The better fine particle fraction was obtained from the DPIs formulated with 10:90 ratio of fine lactose (Lactohale 300): coarsey lactose (Respitose SV003) and having 20% w/w overages.

Key words: Dry powder inhalers, Tiotropium bromide, Fine particle fraction, Emitted dose and Overages.

INTRODUCTION

Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant. A combination of the physicochemical properties, particle size, shape, surface area and morphology affects the forces of interaction and aerodynamic properties, which in turn determine the fluidization, dispersion, delivery to the lungs and deposition in the peripheral airways. (Williams III RO, 2008).

Tiotropium bromide is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic (Sweetman SC, 2009 & Merck index).

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Tiotropium bromide 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. The amount of overages required to emit the desired dose was also investigated and presented here.

Materials and Methods

Materials

Tiotropium Bromide, Various grades of Lactose monohydrate like Lactohale 300, Sorbolac400, Inhalac 230, Respitose SV003, DCL11 and Flowlac100.

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 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.1.

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

Tiotropium DPI 18 mcg 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.

Manufacturing process

An accurately weighed amount of Tiotropium bromiode 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 inhalers with different proportions of fine lactose.

Tiotropium DPI 18 mcg formulations were prepared with 0%, 5%, 10%, 15%, 20% and 30% fine lactose (Sorbolac 400) with 25 mg fill weight and Inhalac 230 as coarse lactose as per composition given in Table.3.

Manufacturing process

An accurately weighed amount of Tiotropium bromiode was mixed separately in each case with fine coarse lactose blend in geometric progress and passed through 60# mesh, 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 grades of fine lactose

Tiotropium DPI 18 mcg formulations were prepared with 10% fine lactose (sorbolac 400/ lactohale 300) and 90% of inhalac 230 with 25 mg fill weight as per composition given in Table.4 to select the fine lactose grade by evaluating the DPI performance.

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

Tiotropium DPI 18 mcg 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.

Evaluation of dry powder inhaler formulations

Physical appearance

The capsules were visually observed.

Averages fill weight per capsule

Open the 20 capsule with out losing any part of the shell and remove the contents as completely as possible. Weighed the 20 capsules content and determine the average of fill weight with the following formulae

$$\text{Average fill weight (mg)} = \frac{\text{20 Capsules content in mg}}{20}$$

Moisture content

Transfer 35 to 40 ml of a mixture of methanol to the titration vessel and titrate with Karl Fischer reagent to detect any moisture that may be present. Quickly 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

$$SF \times 100/W$$

Where

W = Weight of the Sample, in mg.

S = Volume of the KF reagent, in ml.

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

Assay (drug content determination)

Transferred 10 capsules into a 100 ml volumetric flask and added 10ml of water sonicate to dissolve the capsule and added the suitable volume of diluent, sonicate 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.

Locking length

Checked the locking length with vernier calipers and recorded the reading (Steckel H, 1997).

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. 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).

The influence of overages in dry powder was carried out on Tiotropium 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). 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 and Figure.2. 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%).

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 Tiotropium on DPI performance. All the formulations showed good content uniformity and the results are showed in Table.9 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).

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. 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. 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). Respitose SV003 showed better fine particle fraction than other coarse lactose grades (Inhalac230, DCL11 and Flowlac100). Tiotropium 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 Tiotropium is given in Table.15 and Fine particle fraction and emitted dose were better with 20 capsules sample size whem compared with 10 and 15 samples size (Table.16), and drug distribution pattern observed.

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

CONCLUSION

The performance of Dry powder inhaler is found to be dependent 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 Tiotropium bromide 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.

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	0.614	0.720	1.19	15%	250 µ
Sorbolac 400	0.360	0.780	2.16	54%	30 µ
Inhalac 230	0.640	0.760	1.19	16%	230 µ
Respitose SV003	0.635	0. 780	1.22	19%	100 µ
Lactohale 300	0.350	0.770	2.20	55%	10 µ
Flowlac 100	0.600	0.730	1.21	18%	220 µ

Table.2 Formulated dry powder inhalers with overages

Formulation	Active ingredient	Dose (mcg)	Overages %w/w	Active ingredient	Lactose monohydrate
				mcg/capsules	mg/capsules
DPI_1	Tiotropium bromide monohydrate	18^b	0	22.5	Upto 25mg
DPI_2			5	23.625	Upto 25mg
DPI_3			10	24.75	Upto 25mg
DPI_4			20	27.0	Upto 25mg

22.5mcg of Tiotropium bromide monohydrate equivalent to 18mcg of tiotropium

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

Formulation	Active ingredient	Dose (mcg/ capsule)#	Fine lactose portion in w/w	Sorbolac 400	Inhalac 230
				mg/capsules	mg/capsules
DPI_5	Tiotropium bromide monohydrate	27^b	0	0	Upto 25mg
DPI_6			5	1.25	Upto 25mg
DPI_7			10	2.5	Upto 25mg
DPI_8			15	3.75	Upto 25mg
DPI_9			20	5.0	Upto 25mg
DPI_{10}			30	7.5	Upto 25mg

 # including 20%w/w overages

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

Formulation	Active ingredient	Dose (mcg/ capsule)#	Fine lactose grade	Fine lactose	Inhalac 230
				mg/capsules	mg/capsules
DPI_{11}	Tiotropium bromide monohydrate	27^b	Sorbolac 400	2.5	Upto 25mg
DPI_{12}			Lactohale 300	2.5	Upto 25mg

 # including overages

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

Formulation	Active ingredient	Dose (mcg/ capsule)#	Coarse lactose grade	Sorbolac 400	Coarse lactose
				mg/capsules	mg/capsules
DPI_{13}	Tiotropium bromide monohydrate	27^b	Inhalac 230	2.5	Upto 25mg
DPI_{14}			DCL11	2.5	Upto 25mg
DPI_{15}			Flowlac100	2.5	Upto 25mg
DPI_{16}			Respitose SV003	2.5	Upto 25mg

 # including overages

Table.6 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	0.614	0.720	1.19	15%	250 µ
Sorbolac 400	0.360	0.780	2.16	54%	30 µ
Inhalac 230	0.640	0.760	1.19	16%	230 µ
Respitose SV003	0.635	0. 780	1.22	19%	100 µ
Lactohale 300	0.350	0.770	2.20	55%	10 µ
Flowlac 100	0.600	0.730	1.21	18%	220 µ

Table.7 Characterization of DPI formulated with different overages

Formulation	Parameters		
	Content uniformity (% based on average)	**Weight variation in mg**	**Assay (%)**
DPI_1	87.6-110.6	72.9-83.4	97.6
DPI_2	90.4-112.9	70.4-80.6	106.9
DPI_3	87.6-108.8	71.7-79.4	114.7
DPI_4	89.4-115.4	76.9-82.7	118.9

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

n=3	**mcg of Tiotropium per dose**				**% 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 capsules	1.2 ± 0.2	1.3 ± 0.1	1.5 ± 0.2	1.6 ± 0.2	6.7	6.9	7.1	7.2
drug collected in device	1.5 ± 0.3	1.8 ± 0.4	2.1 ± 0.3	2.4 ± 0.4	8.4	9.5	9.9	10.8
Emitted dose	15.2 ± 1.1	15.8 ± 1.5	17.6 ± 1.4	18.2 ± 1.3	84.9	83.6	83.0	82.0
Total dose	17.9 ± 1.2	18.9 ± 1.7	21.2 ± 1.9	22.2 ± 1.8	100%			

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 (%)**
DPI_5	93.0-105.4	75.0-79.4.	116.1
DPI_6	96.1-107.6	70.4-76.4	120.0
DPI_7	94.2-108.4	75.3-78.0	118.2.
DPI_8	93.3-107.4	72.3-76.0	116.2
DPI_9	88.4-109.0	76.4-81.0	111.4
DPI_{10}	84.6-106.0	74.3-79.6	109.0

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

Tiotropium DPI 18 mcg						
	DPI_5	DPI_6	DPI_7	DPI_8	DPI_9	DPI_{10}
% 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

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

Formulation	Parameters		
	Content uniformity (% based on average)	Weight variation in mg	Assay (%)
DPI_{11}	87.4-113.3	73.1-82.7	122.0
DPI_{12}	86.9-112.4	74.3-79.9	109.5

Table.12 Drug distribution data from Tiotropium DPI formulated with different grades of fin lactose

Parameter	Tiotropium bromide dihydrate Equivalent to Tiotropium	
	mcg per Capsules	
	DPI_{11}	DPI_{12}
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

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 (%)
DPI_{13}	93.3-110.6	75.6-79.6	104.4
DPI_{14}	94.1-108.4	76.4-79.1	100.9
DPI_{15}	82.2-109.6	71.4-76.3	106.8
DPI_{16}	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
DPI_{13}	108.9 ± 4.9	22.6 ± 2.1
DPI_{14}	104.6 ± 6.7	12.9 ± 2.3
DPI_{15}	106.7 ± 8.7	13.4 ± 2.4
DPI_{16}	108.9 ± 6.7	29.4 ± 2.0

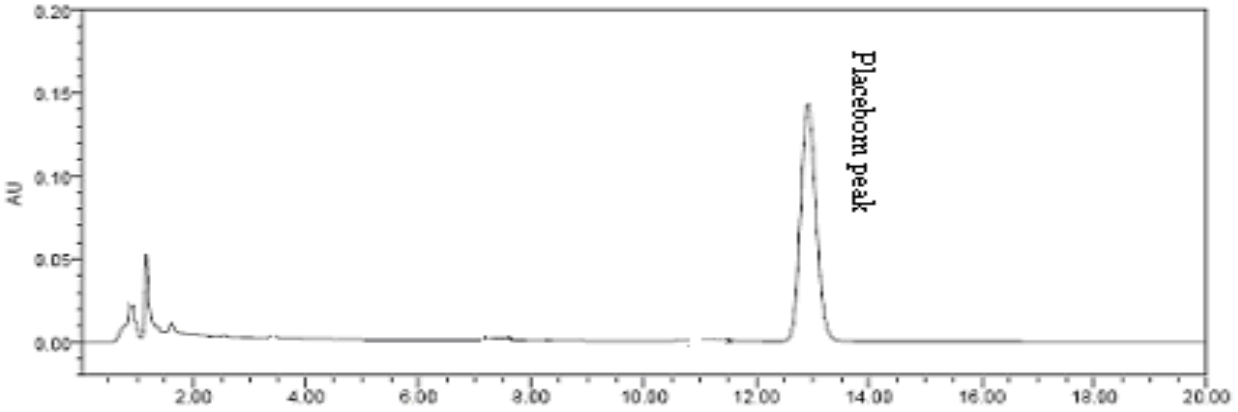
Table.15 Anderson cascade distribution with various sampling sizes of Tiotropium DPI 18mcg

	mcg/capsule (n=3)		
Sample size	**10 capsules**	**15 capsules**	**20 capsules**
Device	3.00 ± 1.2	3.13 ± 1.1	2.76 ± 0.8
Capsules shells	0.87 ± 0.2	0.74 ± 0.2	0.88 ± 0.3
Induction port	1.92 ± 0.2	1.90 ± 0.3	2.01 ±0.1
Pre-separator	8.20 ± 1.2	8.80 ± 0.8	8.60 ± 1.1
Stage 0	0.51 ± 0.08	0.45 ± 0.02	0.52 ± 0.04
Stage 1	0.68 ± 0.02	0.67 ± 0.04	0.74 ± 0.08
Stage 2	0.40 ± 0.01	0.34 ± 0.01	0.48 ± 0.02
Stage 3	1.01 ± 0.01	0.76 ± 0.01	1.09 ± 0.02
Stage 4	0.68 ± 0.09	0.70 ± 0.02	0.86 ± 0.01
Stage 5	0.21 ± 0.01	0.20 ± 0.01	0.30 ± 0.01
Stage 6	0.00 ± 0	0.00 ± 0	0.00 ± 0
Stage 7	0.00 ± 0	0.00 ± 0	0.00 ± 0
Filler	0.00 ± 0	0.00 ± 0	0.00 ± 0
Capsules shells + device	3.87 ± 0.2	3.87 ± 0.2	3.64 ± 0.3

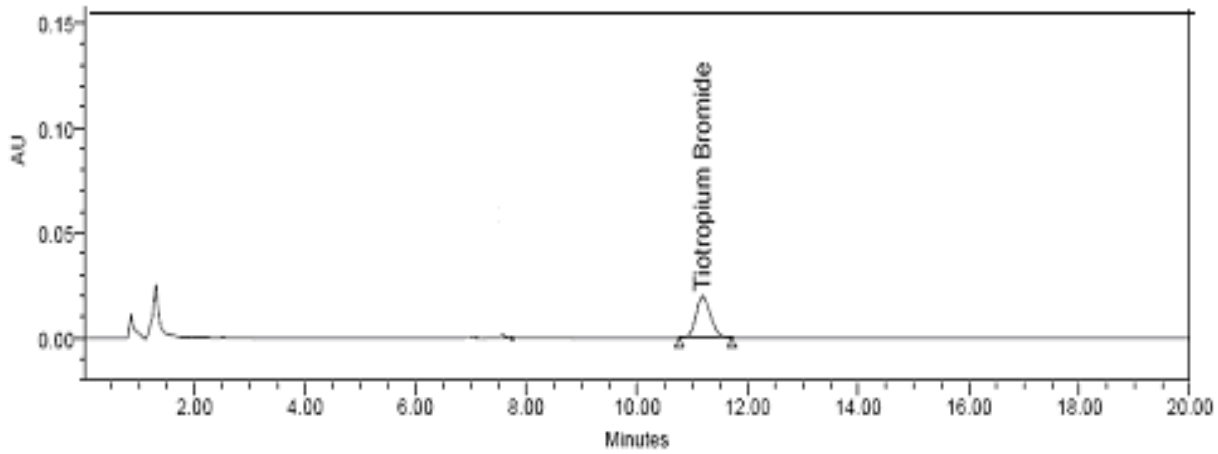
Table.16 Effect of sample size on cascade impactor testing of Tiotropium DPI

Product	**Tiotropium DPI 18mcg(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

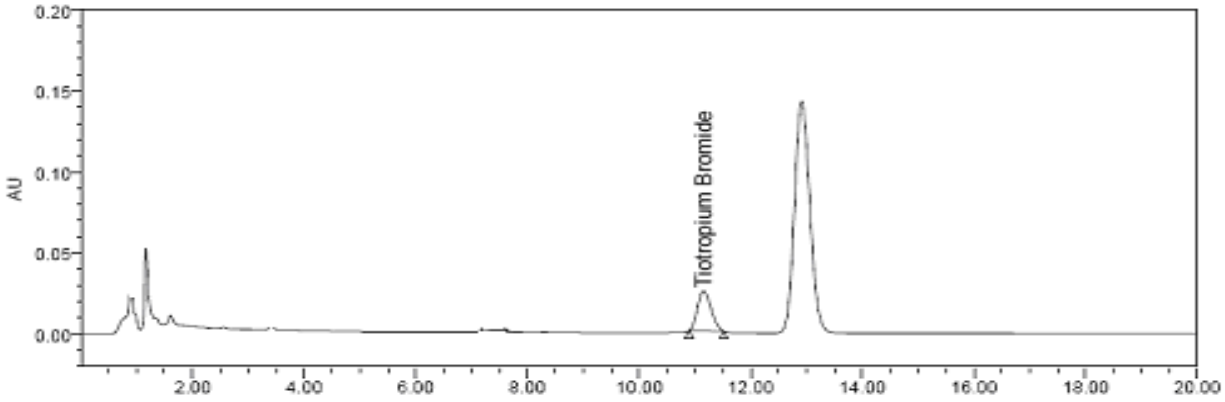
Figure.1 Compatibility chromatograms of Tiotropium DPI



Tiotropium placebo chromatogram



Tiotropium standard chromatogram



Tiotropium sample chromatogram

Figure.2 Histograms correlating emitted dose and overages of Tiotropium DPI 18 mcg

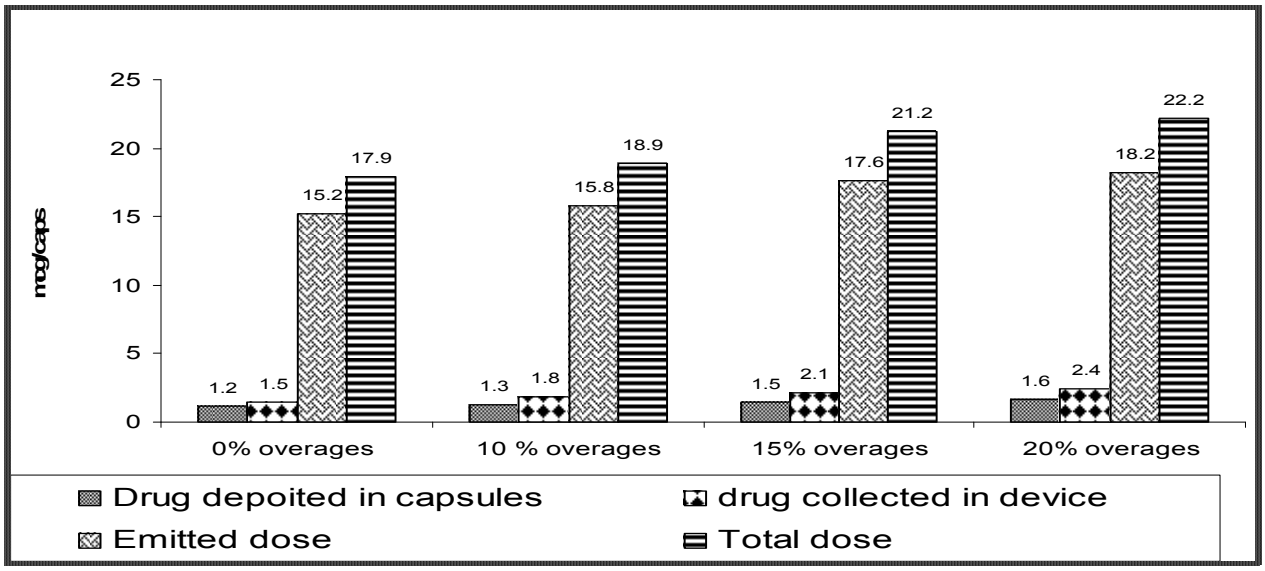
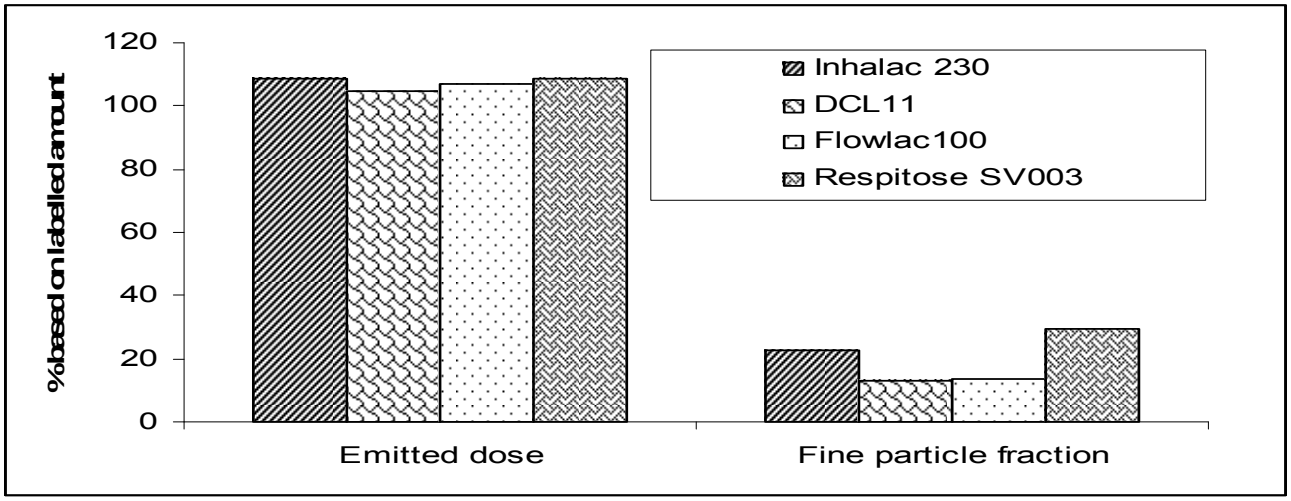


Figure.3 Effect of coarse lactose grade on Tiotropium DPI performance



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