

The linear regression equation for pressurised metered-dose inhaler: Using canister weight to predict balance actuation in asthma inhaler

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Short Report

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Abstract

INTRODUCTION Pressurised metered-dose inhalers (pMDIs) are not equipped with dose counters hence the balance actuation in a canister could not be determined. Each actuation expels a considerable amount of active ingredients and excipients from a canister, thus the balance actuation remaining in a pMDI based on canister weight could be evaluated using a linear regression equation.

METHODOLOGY New pMDIs of 5 active ingredients [salbutamol (GSK) 200 actuation, budesonide (Glenmark) 300 actuation, ipratropium/fenoterol (Boehringer) 200 actuation, fluticasone (GSK/innovator) 120 actuation, fluticasone (Cipla/generic) 120 actuation, and beclometasone (Ivax) 200 actuation] was weighted . using a laboratory scale (Sartorius R200D; 0.01g accuracy). Two of each pMDI were weighed after each actuation, with a 30-second inter-puff interval, and the mean weight was recorded. To minimise variability in measurements, weighing was limited to one operator. The canister was considered empty when there were no changes in weight after repeated actuation. The prediction equation (one for each pMDI) was the line of best fit through data points on the scatter plot of the number of actuations versus weight.

RESULTS AND DISCUSSION There was low variability between pMDIs weights (SD: 0.03g-0.08g)] of the same active ingredients indicating manufacturing uniformity among canisters. Prediction equations were generated for each type of active ingredients, where the general equation is: Actuation remaining = Constant + β *pMDI weight.

CONCLUSION This study produced a prediction equation that can be used to estimate remaining actuation in a pMDI based on its weight. Weighing medication canister could be used to measure actuation remaining in pMDIs, as well as patients' adherence to pMDIs.

Introduction

Pressurized metered-dose inhalers (pMDI) are the basic method of drug delivery of asthma treatment. The pMDI is an economic and portable medication delivery system, but the device does not indicate how much medicine remains in the canister once a patient starts using it.

The design of metered-dose inhaler makes it impossible for a pMDI to cease delivering drug actuation at an exact point, and the number of actuations in a pMDI need to be more than the recommended actuation. Once the recommended number of medication actuation is expelled, the remaining actuations deliver decreasing concentrations of active medication and increasing concentrations of propellants and excipients¹.

This study aims to determine if weighing pMDI will be a viable method to determine the remaining dose in the canister. This study could be used as a base to determine if the patient's pMDI could still be used or exchanged using the weighing method. Exchanging pMDI when necessary could be a cost-saving measure as well.

Aim of the study

This study aimed to prepare a linear regression model of actuation versus weight to determine if weighing pMDI could be used to measure the remaining dose in the canister.

Ethics Approval

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-16-2220-33244)

Methodology

This study was conducted in the pharmacy department. Hospital Seri Manjung. Weighing scale Sartorius R 200 D(± 0.001 g) was used to weigh the canister. New pMDI was used to prepare the linear regression equation. Only the metal canister was weighted (the mouthpiece was removed). The weighing scale was serviced and calibrated by Hospital support service. Data collector was trained to calibrate the weighing machine before each session of data collection.

A data collection form (Form 1: Actuation versus weight monograph) was prepared to collect data on active ingredients, batch number, expiry date, canister weight and actuation. 100 new canisters of each active ingredient from different production batch were weighed to actuation versus weight monograph. Next, 2 new pMDI canisters from each active ingredients were weighed after one actuation, with a 30-second inter-puff interval. To minimise variability in measurements, weighing was limited to one operator. The canister was considered empty when there were no changes in weight after repeated actuation. The prediction equation of one for each pMDI was the line of best fit through data points on the scatter plot of the number of actuations versus weight.

Result And Discussion

50 new canisters from each active ingredient were weighed. There is variation in new canister weight between active ingredient (Table 1) and within active ingredients (Table 2).

Table 1 Mean weight of each actuation according to active ingredients canister						
Canister	Manufacturer	Strength (mcg)	Mean (g)	Std.Dev (g)	Mean weight of actuation (g)	Actuation (Std.Dev)
Salbutamol	GlaxoSmithKline	100	28.65	0.033	0.075	1
Budesonide	Glenmark	200	18.23	0.083	0.03	3
Ipratropium/Fenoterol	Boehringer Ingelheim	20/50	25.34	0.053	0.05	1
Fluticasone (GSK)	GlaxoSmithKline	125	18.8	0.035	0.07	1
Fluticasone (Cipla)	Cipla	125	21.11	0.076	0.075	1
Beclomethasone	Ivax	100	26.78	0.042	0.08	1

The standard deviation of actuation was obtained by dividing the standard deviation of the canister with mean actuation weight. All new canisters have a deviation of 1 actuation except budesonide which have a deviation of 3 actuation. The deviation of actuation was constant (n=1) with each active ingredients except for budesonide which had a deviation of 3-4 actuation according to different batches.

Table 2 Mean weight of each actuation between different batches according to active ingredients canister						
Canister	Batch Num	Num	Mean (g)	Std.dev (g)	Mean weight of actuation (g)	Std.Dev of actuation
Salbutamol	NN0242	30	28.66	0.033	0.075	1
	EX2X	30	28.65	0.037	0.075	1
	NN0241	40	28.64	0.029	0.075	1
Budesonide	12170220	20	18.23	0.065	0.3	3
	12160693	20	18.21	0.100	0.3	4
	12170220	20	18.22	0.100	0.3	4
	12160670	40	18.25	0.069	0.3	3
Ipratropium/Fenoterol	703765	20	25.29	0.037	0.05	1
	701750	80	25.35	0.048	0.05	1
Fluticasone (GSK)	A55X	50	18.79	0.040	0.07	1
	A43Y	50	18.80	0.027	0.07	1
Fluticasone (Cipla)	GB71038	20	21.11	0.061	0.075	1
	GB71037	30	21.05	0.066	0.075	1
	GB71032	60	21.12	0.077	0.075	1
Beclometasone	AES75T	20	26.76	0.044	0.08	1
	AEY36A	80	26.78	0.041	0.08	1

Although there was variation in starting weight among new canister and variation between batched among all the active ingredients, the variation of 1-3 actuation is small. this implies that there is a good uniformity among the starting weight of new canister.

To prepare a linear model of actuation versus weight, the weight of canister was measured after each actuation. The canister is considered empty when there were no weight changes after the last actuation.

Table 3 Description of canister weight and number of actuation according to canister active ingredients							
Canister	Full canister weight ^a	Empty canister weight ^b	content weight	Manufacturer recommended actuation ^c	Total Actuation (%excess)	Hypothetical actuation ^d (%excess)	Mean actuation weight (g) (95%CI)
Salbutamol	28.71	12.13	16.58	200	235(17.5)	221(10.5)	0.075 (0.07-0.078)
Budesonide	18.17	9.015	9.155	300	305((1.7)	305(1.7)	0.03 (0.029-0.031)
Ipra/Fenoterol	25.22	12.55	12.67	200	247(23.5)	253(26.5)	0.05(0.0502-0.0523)
Fluticasone (GSK),	18.81	7.9	10.91	120	152(21.3)	156(30)	0.07(0.0685-0.0718)
Fluticasone (Cipla)	21.04	9.71	11.33	120	152(21.3)	151(25.8)	0.075(0.073-0.076)
Beclometasone	26.75	9.73	17.02	200	218(9)	213(6.5)	0.078(0.0769-0.0794)

- a. The mean weight of new 2 canister
- b. The mean weight of 2 empty canisters from (a)
- c. The manufacture recommended actuation according to the product leaflet
- d. Hypothetical actuation is calculated by canister content divided by mean actuation weight

All canisters could be actuated past the manufacture recommended actuation (Table 3). Budesonide had the least amount of excess actuation (1.7%) and Fluticasone had the most amount of excess actuation (21.3%). Our finding correlates with a study by Brock² which showed that additional actuations were released canister in their study as well. Brock's study compared to our study showed that the excess from Ipratropium/Fenoterol was (27.5% vs 23.5%), Fluticasone (24.2% vs 21.3%), and Salbutamol (9.5% vs 17.5%).

A hypothetical actuation was calculated (Table 3) to compare with manufactures recommended actuation and the total actuation released from the canister .hypothetical actuation was calculated by full canister weight with empty canister weight to get the content weight. The content weight was divided with mean actuation weight to predict the amount of hypothetical actuation in each canister. There was a linear correlation between total actuation, hypothetical actuation and manufacturer recommended actuation.The correlation is strongest between total actuation and hypothetical actuation (r=0.995, p<0.001) compared to manufacturer-recommended actuation and hypothetical actuation(r=0.970, p<0.001). This finding suggests that each canister could be actuated past manufacturer's recommendation similar with a study by Talasila³ to investigate the effect of extra actuation on dose delivery showed that canister should be packaged with extra actuation of 15-30% to deliver the required 200 metered dose as marketed by manufacturer.

Table 4 Comparison on canister weight between 2 studies.			
% medication remaining	No of remaining dose	Paolo ¹⁰	This study
100	200	28.61±0.10	28.71±0.014
75	150	25.16±0.13	25.10±0.014
50	100	21.72±0.17	21.42±0.27
5	10	15.54±0.22	14.79±0.38
0	0	14.84±0.23	14.06±0.41

Table 4 compared the mean weights of the Salbutamol (GSK) obtained from a study done in European country¹⁰ with our finding. There was a linear correlation between the mean weights of both canisters measured on the study ($r = 1, p < 0.0001$). This finding shows that although the canister was acquired from the different region the weight of canister at various actuations is similar.

The amount of active ingredients in those additional actuations is variable as propellant and excipients form up to 99% of an asthma drug formulation⁵. Currently, available MDI are formulated as suspensions. Suspensions comprise micronized drug substance suspended in propellant and other excipients (Figure 1). If the drug substance adheres to the walls of the container or valve components, dose delivery and particle size distribution could be inconsistent^{5,6}. Actuating beyond the recommended number of actuation will cause the active ingredient delivery per actuation becomes unpredictable, a phenomenon is known as "tail-off"⁷ (Figure 2). Tail-off is particularly problematic when the medication delivered by the MDI is formulated as a suspension rather than a solution. Tail-off may be rapid (e.g., within 5 actuations), or erratic, requiring 10–20 actuations before the canister is finally empty of its drug content⁸.

The phenomenon "tail-off" was also observed in this study when the canister was actuated post manufactures recommendation. The 'tail off' could be observed from Salbutamol (Figure 3) at actuation 223 (23 actuation more than recommended), Ipratropium/Fenoterol (Figure 5) from actuation 233 (33 more than manufacturer recommendation), Fluticasone-GSK (Figure 6) from actuation 143 (23 more than recommended), Fluticasone-Cipla (Figure 7) from actuation 147 (27 more than recommended) and Beclometasone (Figure 8) from actuation 202 onwards. 'Tail off' phenomena was not observed for Budesonide canister (Figure 4) as there was no more puff expulsion after 305 actuation (5 more than recommended).

Advising the patient to use the inhaler until it is empty or more than the recommended actuation will not guarantee the accurate actuation of medication will be delivered to the patient. Although there might be some solution in the canister or visible puff could be seen after each actuation, the amount of recommended active ingredients will not be accurate. All manufacturer recommended that the accurate actuation of medication from MDI can only be ensured if the patient uses the recommended number of actuation.

Actuating the canister until its empty might be patient an important contributor to poor asthma control. For example, patients may think they are taking their asthma medication when they inhaling excipients and sub-therapeutic active ingredients. This is potentially dangerous especially for rescue medication such as Salbutamol.

Linear regression model to predict the number of actuation from weight

A linear regression model to predict the number of actuation from weight was created. The model was created by weighing the canister after each actuation.

Table 5: Coefficients of Linear regression								
Canister	model	Unstandardized		Standardized	t	Sig.	95% Confidence interval for B	
		Coefficients		Coefficients			Lower Bound	Upper Bound
		B	Std. Error	Beta				
Salbutamol (GSK)	(Constant)	391.244	.072		5459.897	.000	391.103	391.385
	Canister_weight	-13.603	.003	-1.000	-4000.936	.000	-13.610	-13.596
Budesonide(Glenmark)	(Constant)	597.477	.285		2093.731	.000	596.916	598.039
	Canister_weight	-32.956	.021	-1.000	-1589.752	.000	-32.997	-32.915
Ipratropium/Fenoterol (Boehringer)	(Constant)	477.499	.123		3788.449	.000	477.251	477.747
	Canister_weight	-18.932	.006	-1.000	-2920.816	.000	-18.944	-18.919
Fluticasone (GSK),	(Constant)	260.534	.279		934.067	.000	259.983	261.085
	Canister_weight	-13.892	.020	-1.000	-680.271	.000	-13.932	-13.851
Fluticasone (Cipla)	(Constant)	279.938	.106		2628.820	.000	279.728	280.148
	Canister_weight	-13.295	.007	-1.000	-1959.520	.000	-13.308	-13.281
Beclometasone (Ivax).	(Constant)	388.576	.120		2829.239	.000	338.341	338.812
	Canister_weight	-12.687	.006	-1.000	-2003.407	.000	-12.700	-12.675

Dependent Variable: Actuation

There was a significant linear relationship between actuation and canister weight for the canister measured. The linear relationship for Salbutamol was (b=-13.6, 95%CL [-13.61,-13.596], p<0.0001, r²=1.0). The number of actuation could be predicted from weight by the following formula: Actuation = 391.0244+ (-13.6*canister_weight).

The linear relationship for Budesonide was (b=-32.956, 95%CL [-32.997,-32.915], p<0.0001, r²=1.0). Number of actuation could be predicted from weight by the following formula: Actuation = 597.477+ (-32.96*canister_weight).

The linear relationship for Ipratropium/Fenoterol 20/50mg was (b=-18.932, 95%CL [-18.944,-18.919], p<0.0001, r²=1.0). Number of actuation could be predicted from weight by the following formula: Actuation = 477.499+ (-18.932*canister_weight).

The linear relationship for Fluticasone (GSK) was ($b=-13.892$, 95%CL [-13.932,-13.851], $p<0.0001$, $r^2=1.0$). Number of actuation could be predicted from weight by the following formula: Actuation = $260.534+ (-13.892*\text{canister_weight})$.

The linear relationship for Fluticasone (Cipla) was ($b=-13.295$, 95%CL [-13.308,-13.281], $p<0.0001$, $r^2=1.0$). Number of actuation could be predicted from weight by the following formula: Actuation = $279.938+ (-13.295*\text{canister_weight})$.

The linear relationship for Beclometasone was ($b=-16.687$, 95%CL [-12.7,-12.675], $p<0.0001$, $r^2=1.0$). Number of actuation could be predicted from weight by the following formula: Actuation = $338.576+ (-12.687*\text{canister_weight})$.

Conclusion

There was low variability between pMDIs weights (SD: 0.03g-0.08g)] well as the minimal difference between 1-3 actuation among new canister and difference between 1-4 actuation between batched of each active ingredients indicating manufacturing uniformity among. Each canister could be actuated past manufacturer recommendation with Budesonide had the least amount of excess actuation (1.7%) and Fluticasone had the most amount of excess actuation (21.3%). Prediction equations were generated for each type of active ingredients, where the general equation is: Actuation remaining = Constant + $\beta*\text{pMDI weight}$. Weighing pMDI could be used as a dose counter at health care facilities; however, it must be noted that there will be a unique relationship between each product.

Declarations

Conflicts of interest

The authors declared that they have no conflict of interest.

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Figures



Figure 1

MDI suspension in inside canister5

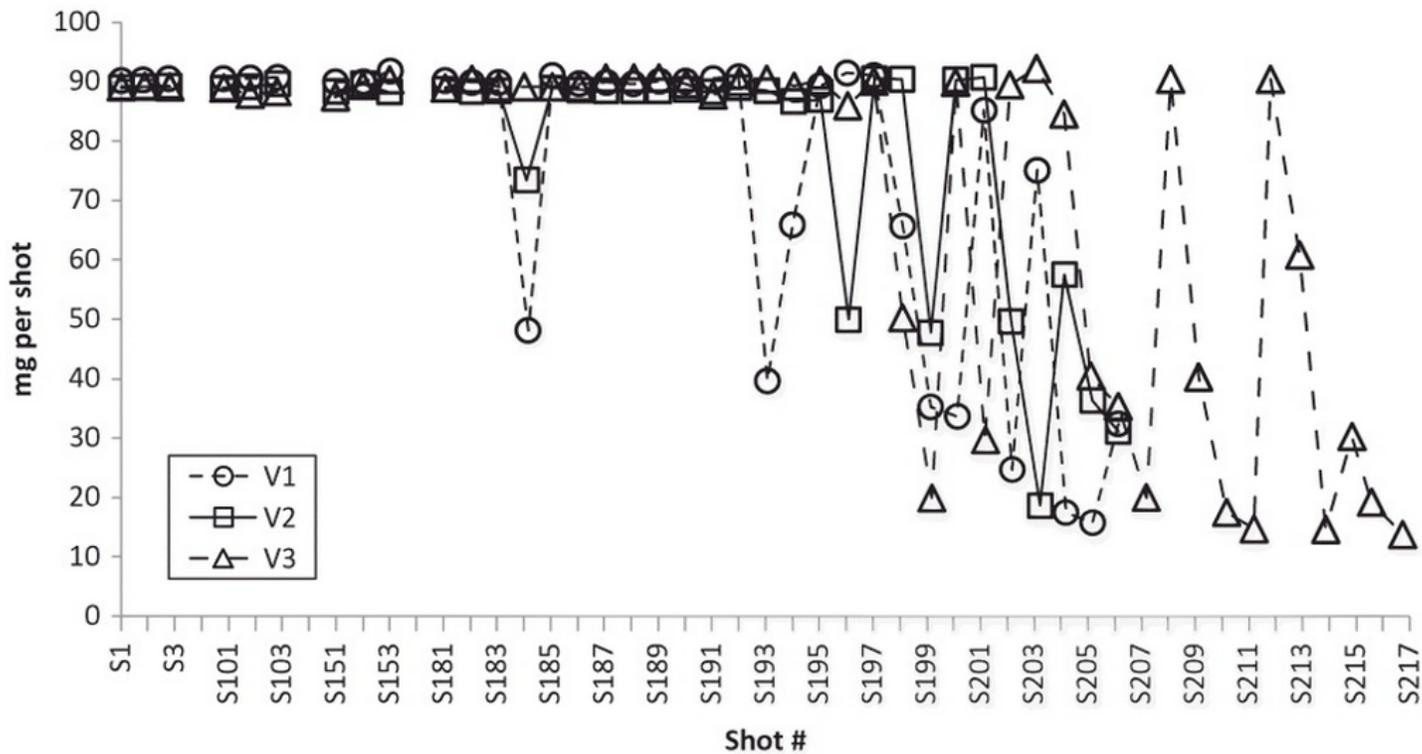


Figure 2

Tail-off characteristics of asthma medications delivered by MDIs 7

Salbutamol 100mcg (GSK). 200 metered actuation

Weight of actuation versus actuation

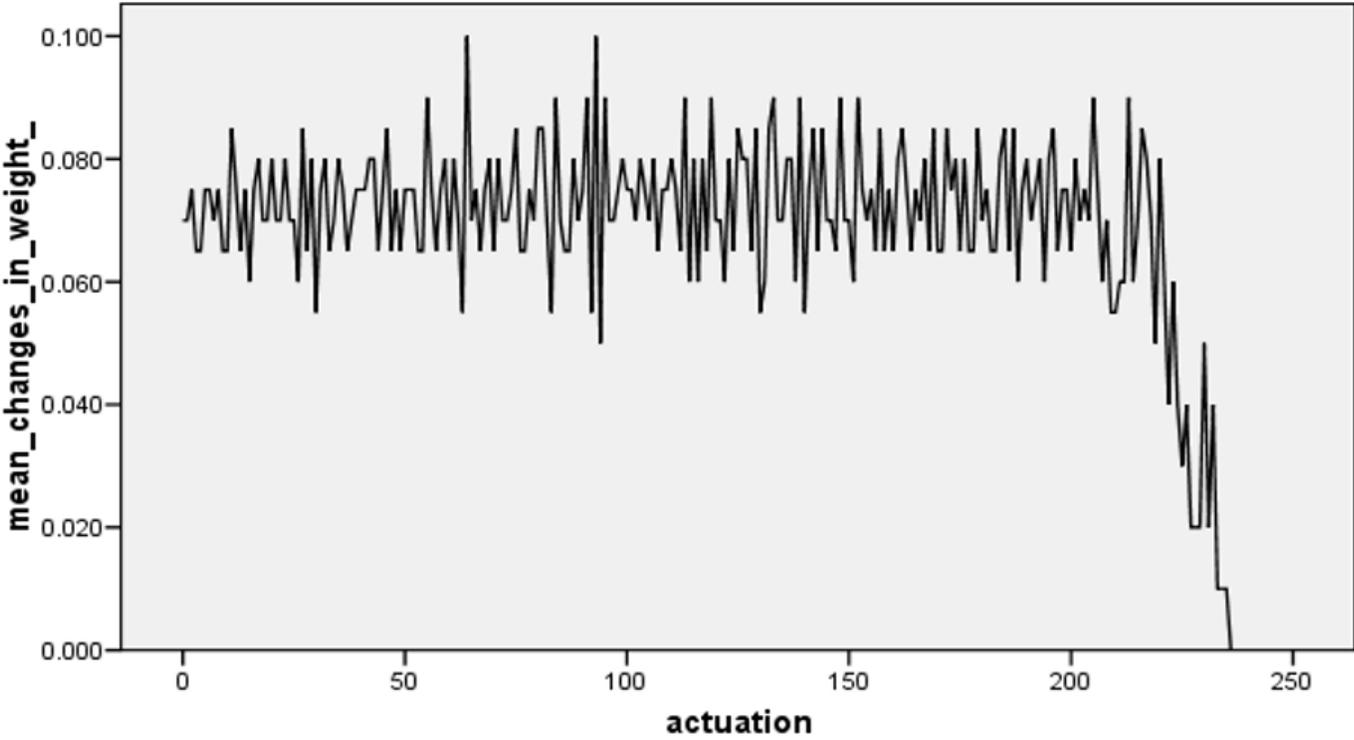


Figure 3

Weight of Salbutamol puff versus actuation.

Budesonide 200mcg (Glenmark) . 300 metered dose

Actuation weight versus actuation

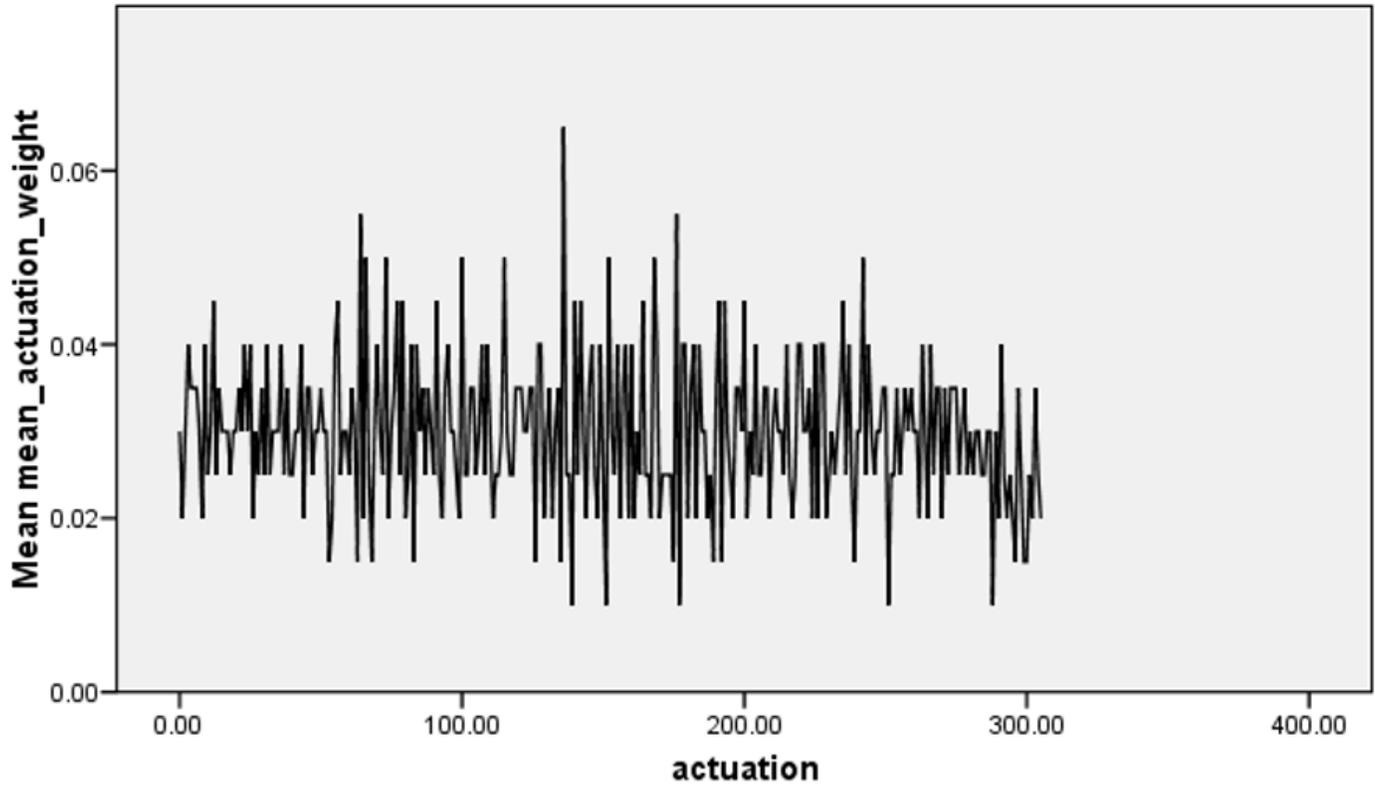


Figure 4

Weight of Budesonide puff versus actuation.

Ipratropium/Fenoterol 20/50mcg (boehringer). 200 metered dose

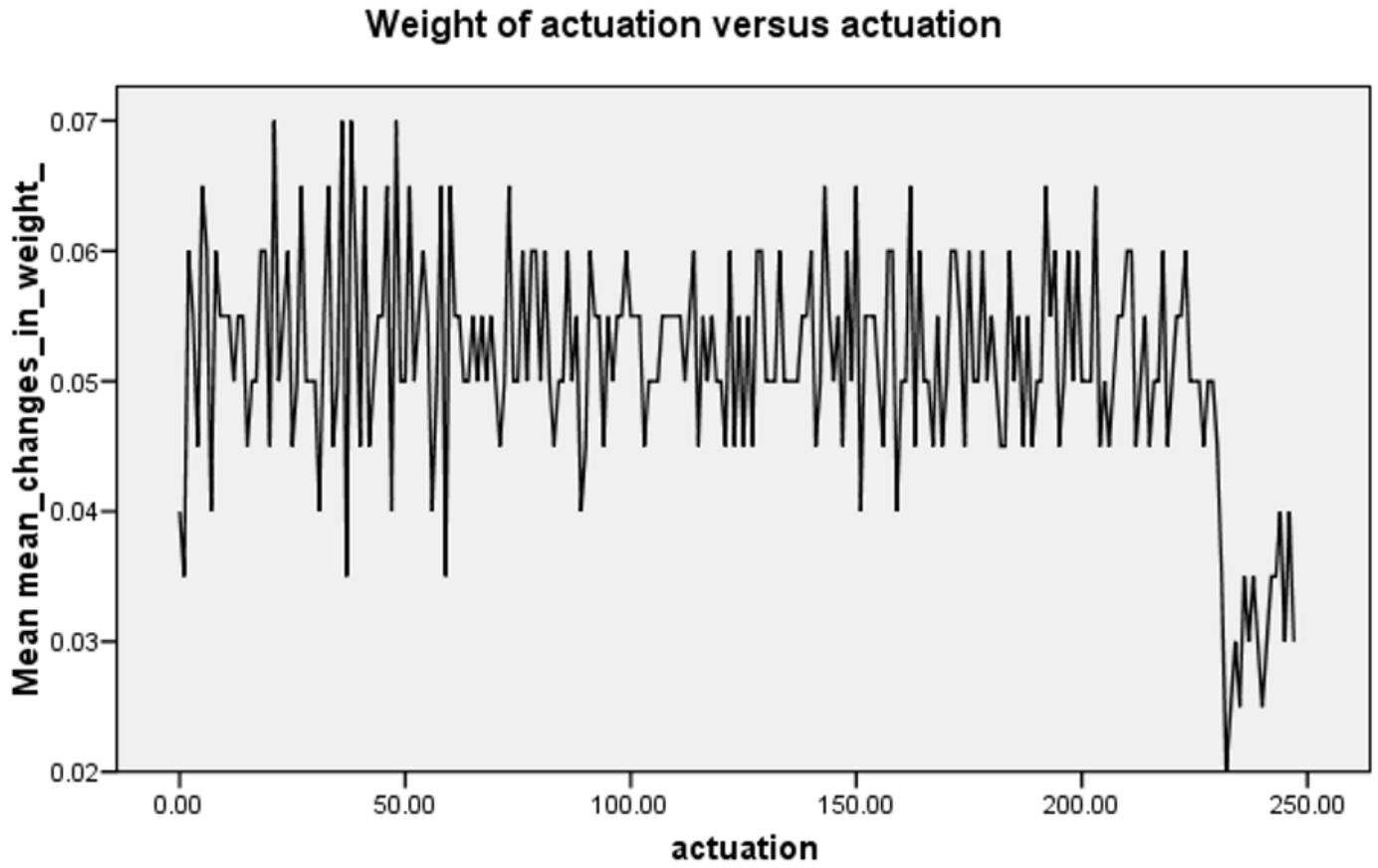


Figure 5

Weight of Ipra/Fenoterol puff versus actuation.

Fluticasone 125mcg (GSK) . 120 metered actuation

Weight of actuatuion versus actuation

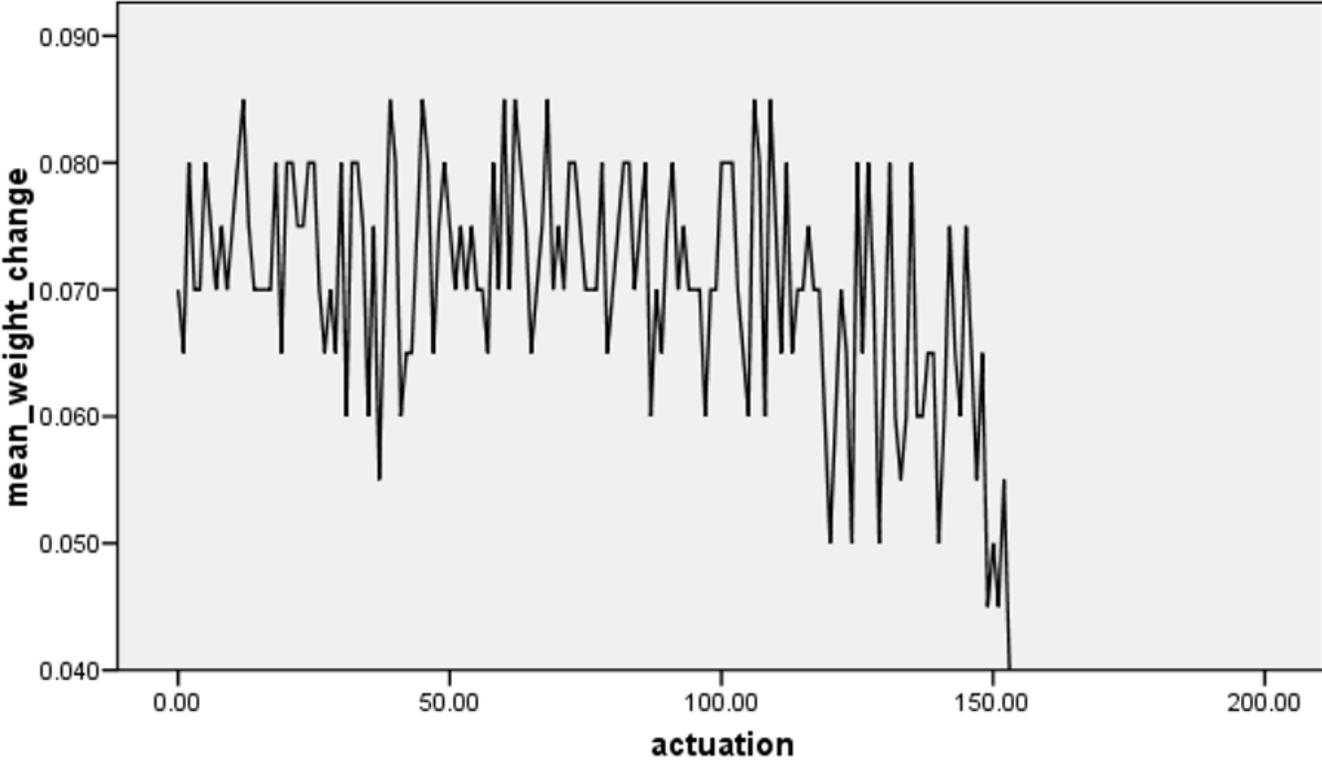


Figure 6

Weight of Fluticasone puff versus actuation.

Fluticasone 125mcg (Cipla) 120 metered dose

actuation weight versus weight

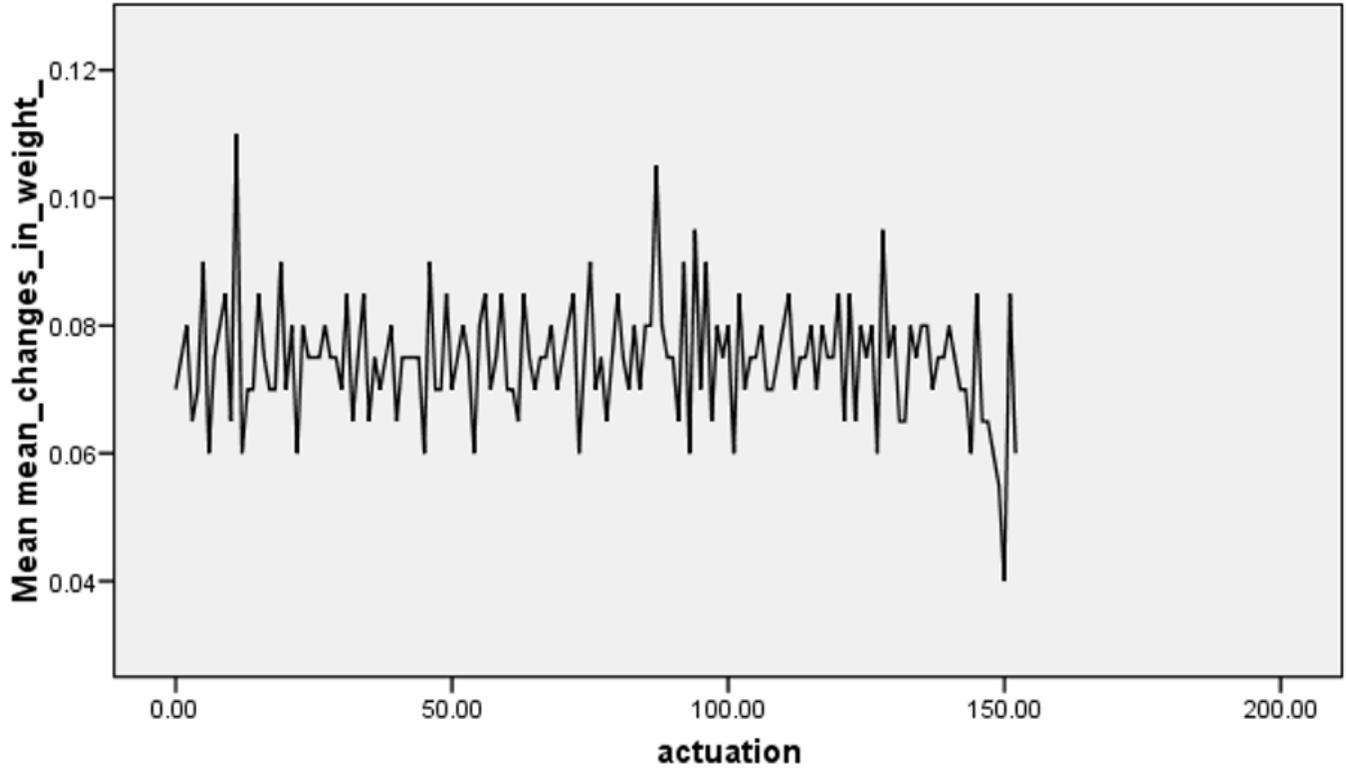


Figure 7

Weight of Fluticasone puff versus actuation.

Beclomethasone 100mcg (Ivax). 200 metered dose

Actuation weight versus weight

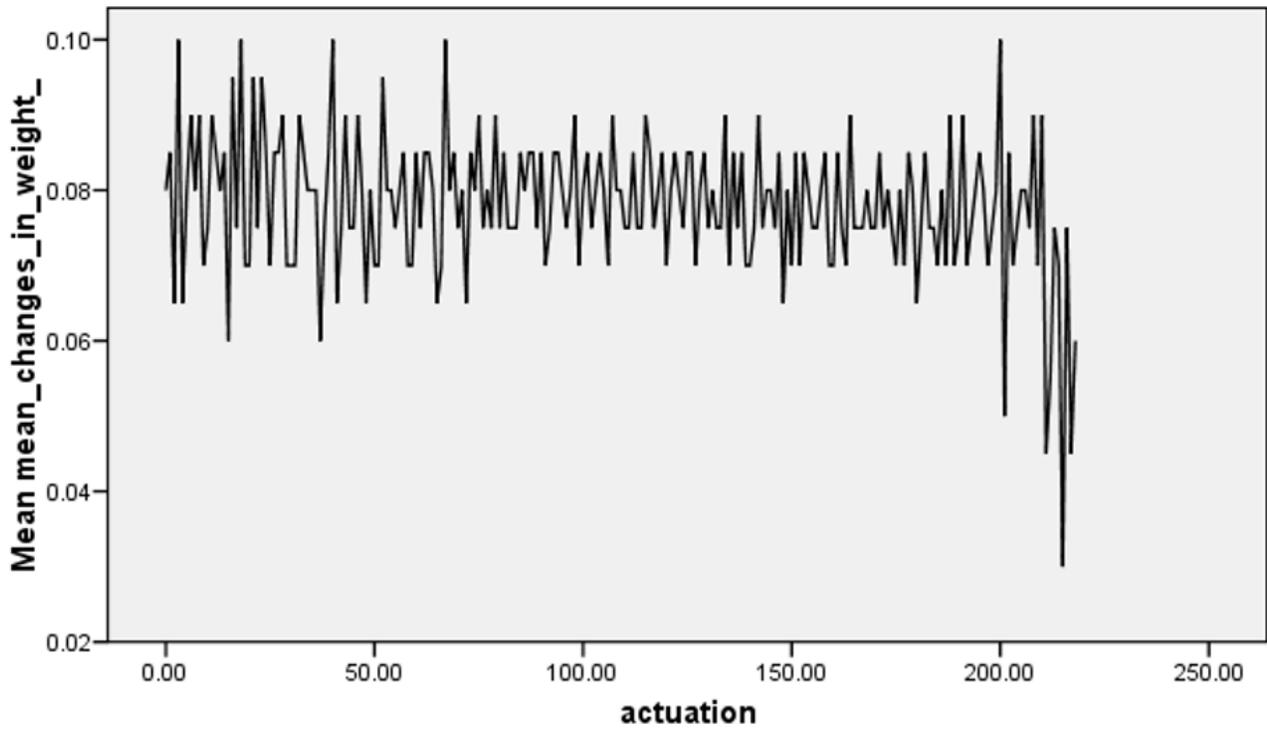


Figure 8

Weight of Beclomethasone puff versus actuation.