Comparing weight method and float method for pressurised metered dose inhaler as dose counting method.

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Short Report

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Abstract

INTRODUCTION Pressurised metered-dose inhalers (pMDIs) are not equipped with dose counters, so estimating the actuation remaining is difficult. We compared weight method and float method in estimating the actuation remaining in discarded pMDIs.

METHODOLOGY Used non-metered pMDIs were collected from Pharmacy department Hospital Seri Manjung from June to Dec 2018. Each of the returned canister was evaluated using float and weight method to predict the balance actuation in the canister. For the float test, the canister was placed in a container of water. Based on its position in the water, the pMDI was categorised as 1=empty, 2=¼ full, 3=½ full, 4=¾ full, or 5=full. For the weight method, canisters were weighed, and actuation remaining were calculated using a linear regression equation where the general equation is: Actuation remaining = Constant + β*pMDI weight, and further categorised as above. The percentage of empty pMDIs between the two methods were compared.

RESULTS A total of 4517 pMDIs were returned to the pharmacy, of which 2131 (47%) were salbutamol, 1149 (25%) budesonide, 685 (15%) ipratropium/fenoterol, 340 (8%) innovator fluticasone, 182 (4%) generic fluticasone, and 30 (1%) beclomethasone. Overall, the float method classified 75% pMDIs as empty, compared to 71% by the weight method. The percentage of empty salbutamol, generic fluticasone, and beclomethasone pMDIs were similar between both methods. A higher percentage of budesonide pMDIs were classified as empty by the float method compared to the weight method (62% vs 37%). For ipratropium/fenoterol pMDIs, the float method did not identify any empty canisters, but 82% were classified as empty by the weight method.

CONCLUSION This study produced a prediction equation that can be used to estimate remaining actuation in a pMDI based on its weight. There were differences in the identification of empty pMDIs between the float test and the weight method, which varied by drug. The weight method may be a convenience method to be used to measure actuation remaining in pMDIs returned to the pharmacy, 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.

Studies have shown that patients are unable to gauge the amount of actuation remaining in their pMDI. Some of the reported measure by which patient estimate the balance actuation in pMDI are not reliable. Estimation based on patients perception on the weight of the inhaler, force of actuation, sounds, and taste are influenced by the volume of remaining propellants and excipients and does not reflect the actual remaining active ingredients.

In a study by Rubin of paediatric asthma patients, 72% of the children (or their parents) reported using an MDI until they could no longer “hear” the MDI make a sound when it was actuated. In another study by Sander, 25% of patients reported that they consider their inhaler to be empty “when it stopped spraying,” unaware that propellant continues to spray long after the active ingredients has run out. Most patient report that they shake their MDIs to assess the amount of drug remaining in them, also unaware that it might just be propellants. Holt and colleagues asked patients receiving asthma treatment to return their MDIs, when deemed empty, to their physicians. Of 109 returned MDIs, 11% of “empty” MDIs still contained more than 20% (>40 actuation) of the recommended metered actuation. A bronchodilator prescription typically requires refill only a few times a year, yet almost 20% of patients reported refilling
their inhaler at least once a month. The authors speculated that the excessive number of bronchodilator refills might be due, in part, to throwing away partially used inhalers.

The design of metered dose inhaler makes it impossible for an MDI to cease delivering drug actuation at an exact point, and the number of actuations in an MDI need to be more than the recommended actuation. Once the recommended number of medication actuation is expelled, remaining actuations deliver decreasing concentrations of active medication and increasing concentrations of propellants and excipients. Patients who are not tracking medication actuation either discard an MDI that may still contain actuation of drug, or continue to use a product that only contain propellants. The former is costly and the latter will be harmful for patients.

A method that usually taught to patient to determine the remaining amount is by “floats testing” (Figure 1). In float testing, the canister is placed in glass water. If and how the canister floats reflects the relative weight and centre of gravity for the remaining drug solution.

Figure 1: Canister characteristic according to float test.

Table 1: Appearance of canister and estimation of remaining content according to float test.

| No | Description                                      | Float test  |
|----|--------------------------------------------------|-------------|
| 1  | sitting on the bottom of the glass               | full        |
| 2  | floating with nozzle pointing up and out of the water | 3/4 full    |
| 3  | floating with the nozzle point down and under the water, with base near the water surface | 1/2 full    |
| 4  | floating with nozzle down, but at a slight angle to the vertical axis | 1/4 full    |
| 5  | canister on its side, with the nozzle point to the side of the glass | empty       |

However, no universal flotation status accurately reflects when a device has reached the maximum recommended number of actuations. Moreover, this test is not only unreliable since some inhalers will float when they are full, it may damage the MDI by obstructing the metering valve.

A novel method of estimating balance actuation in canister called weight method was recently published by the same team. A linear regression model for each type of active ingredients, where the general equation is: Actuation remaining = Constant + β*pMDI weight. Namely five model are available for the following active ingredients of 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.

This study could be used as a base to determine if patient's pMDI could still be used or exchanged using weighing method. Exchanging pMDI when absolutely necessary could be a cost saving measure as well.

Aim of study

This study aimed to compare between float method and weight method and to determine the balance actuation in canister exchanged by patient.
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 pharmacy department. Hospital Seri Manjung from June to Dec 2018. Weighing scale Sartorius R200D (±0.001g) was used to weigh the canister. Only the metal canister was weighted (the mouth piece was removed).

Among the collected pMDI, canister with illegible batch number or expiry date, canister which expired 1 month before or 1 month after data collection month, Different brand of pMDI other than used to prepare the linear regression and abnormal canister with damage or dent was excluded.

The minimum sample size required for this study was 488/month. This figure was arrived by using Raosoft sample size calculator by setting margin of error at 5%, confidence interval at 99%, population size at 1832 (amount of pMDI dispensed on June 2018) and return rate at 50%. As the study period was for 6 month. 2928 canister need to be collected. To allow rejection rate of 10%, the researcher will collect 3221 canister or the total number of pMDI that during the study period.

The following linear regression equation was used to determine the balance actuation in returned or used canister:

1. Salbutamol : Actuation = 391.0244+ (-13.6 x canister weight).
2. Budesonide: Actuation = 597.477+ (-32.96 x canister weight).
3. Ipratropium/Fenoterol 20/50mg: Actuation = 477.499 +(-18.932 x canister weight).
4. Fluticasone (GSK): Actuation = 260.534+ (-13.892 x canister weight).
5. Fluticasone (Cipla): Actuation = 279.938+ (-13.295 x canister weight).
6. Beclometasone: Actuation = 338.576+ (-12.687 x canister weight).

To determine if the float test corresponds to the weight of canister

All returned pMDI was segregated according to active ingredients and then subjected to inclusion and exclusion criteria. For each canister, the batch number and expiry date was recorded. Next the canister was weighed and the weight was recorded. Finally, the canister was subjected to float test and the category was recorded according to the canister orientation in Figure 1. The float category was than compared to the weight of canister.

To determine the balance actuation in canister exchanged by patient.

The balance actuation in each canister was predicted and categorised according to the weight range using the line of best fit that was built.
Statistical analysis

All descriptive result was presented as number (n) and percentage (%) . A paired t-test was used to compare the difference between classifications of the float methods compared to weight method . For all test Two-tailed p-value <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS for Windows version 22.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 4517 canister was collected and subjected to weight method and float method. Each canister was weighted and subjected to float and weight methods. Table 2 reports distribution of the canister according to balance category,
| Canister                      | n     | Balance scale | Classification (n,%)          |
|------------------------------|-------|---------------|------------------------------|
|                              |       |               | Float method               | Weight method               |
| Salbutamol (GSK)             | 2131  | Empty         | 1708 (80.2)                 | 1746 (81.9)                 |
|                              |       | 1/4full       | 116 (5.4)                   | 116 (5.4)                   |
|                              |       | 1/2full       | 102 (4.8)                   | 100 (4.7)                   |
|                              |       | 3/4full       | 95 (4.5)                    | 76 (3.6)                    |
|                              |       | full          | 110 (5.2)                   | 93 (4.4)                    |
| Budesonide (Glenmark)        | 1149  | Empty         | 716 (62.3)                  | 424 (36.9)                  |
|                              |       | 1/4full       | 144 (12.5)                  | 248 (21.6)                  |
|                              |       | 1/2full       | 289 (25.2)                  | 165 (14.4)                  |
|                              |       | 3/4full       | -                           | 158 (13.8)                  |
|                              |       | full          | -                           | 154 (13.4)                  |
| Ipratropium/Fenoterol (Boehringer) | 685 | Empty         | -                           | 563 (82.2)                  |
|                              |       | 1/4full       | 558 (81.5)                  | 52 (7.6)                    |
|                              |       | 1/2full       | 61 (8.9)                    | 29 (4.2)                    |
|                              |       | 3/4full       | -                           | 15 (2.2)                    |
|                              |       | full          | -                           | 32 (4.7)                    |
| Fluticasone (GSK),           | 340   | Empty         | 261 (76.8)                  | 286 (84.1)                  |
|                              |       | 1/4full       | 30 (8.8)                    | 28 (8.2)                    |
|                              |       | 1/2full       | 39 (11.5)                   | 17 (5)                      |
|                              |       | 3/4full       | 9 (2.6)                     | 6 (1.8)                     |
|                              |       | full          | 1 (0.3)                     | 3 (0.9)                     |
| Fluticasone (Cipla)          | 182   | Empty         | 158 (86.8)                  | 158 (86.8)                  |
|                              |       | 1/4full       | 15 (8.2)                    | 12 (6.6)                    |
|                              |       | 1/2full       | 9 (4.9)                     | 7 (3.8)                     |
|                              |       | 3/4full       | -                           | 4 (2.2)                     |
|                              |       | full          | -                           | 1 (0.5)                     |
| Beclometasone (Ivax)         | 30    | Empty         | 18 (60)                     | 18 (60)                     |
|                              |       | 1/4full       | 7 (23.3)                    | 7 (23.3)                    |
|                              |       | 1/2full       | 3 (10)                      | 3 (10)                      |
|                              |       | 3/4full       | 1 (3.3)                     | 1 (3.3)                     |
|                              |       | full          | 1 (3.3)                     | 1 (3.3)                     |
Generally, there was difference in both method of classification. The amount of canister classified differs between float method and weight method (Table 2). The notable difference is with Budesonide, Ipratropium/Fenoterol and Fluticasone (Cipla) canister. For Budesonide canister there was no canister classified as 3/4full or full with float method but 158 canisters was classified as 3/4full and 154 canisters was classified as full. For ipratropium/fenoterol, no canister was classified as empty with float method but 563 were classified as empty with weight method. Furthermore there was a reduction from 558 from 1/4full in float method to only 52 in 1/4full classification with weight method. The same pattern was noticed with Fluticasone (Cipla) where there was no classification in 3/4full and full category but 4 canisters classified as 3/4full and 1 as full with weight method.

Table 3 reports paired t-test between float methods compared to weight method.

|        | 4517 | Empty     | 3406(75.4) | 3195(70.7) |
|--------|------|-----------|------------|------------|
| 1/4full|      | 325(7.2)  | 463(10.3)  |            |
| 1/2full|      | 503(11.1) | 321(7.1)   |            |
| 3/4full|      | 139(3.1)  | 260(5.8)   |            |
| full   |      | 144(3.2)  | 278(6.2)   |            |
Table 3 Result of Paired Samples Test between weight methods versus float method

| canister       | Mean | Paired Differences | T     | Df  | Sig.(2-tailed) |
|----------------|------|--------------------|-------|-----|----------------|
|                | Mean | Std. Deviation | Std. Error Mean | 95% Confidence interval of the Difference | lower | upper |
|                |      |                  |                | lower | upper          |
| Salbutamol     | Pair Float method | .49 | .061 | .246 | .005 | .050 | .071 | 11.347 | 2130 | .000 |
|                | 1 Weight method | .43 |      |      |     |     |     |       |     |      |
| Budesonide     | Pair Float method | .63 | -.823 | .730 | .022 | -.866 | -.781 | -38.250 | 1148 | .000 |
|                | 1 Weight method | 1.45 |      |      |     |     |     |       |     |      |
| Ipratropium/   | Pair Float method | .53 | .155 | .397 | .015 | .125 | .184 | 10.211 | 684 | .000 |
| Fenoterol      | 1 Weight method | .38 |      |      |     |     |     |       |     |      |
| Fluticasone (GSK) | Pair Float method | .41 | .138 | .362 | .020 | .100 | .177 | 7.035 | 399 | .000 |
|                | 1 Weight method | .27 |      |      |     |     |     |       |     |      |
| Fluticasone (Cipla) | Pair Float method | .18 | -.049 | .241 | .018 | -.085 | -.014 | -2.763 | 181 | .006 |
|                | 1 Weight method | .23 |      |      |     |     |     |       |     |      |
| Beclometasonea | Pair Float method | - | - | - | - | - | - | - | - | - |
|                | 1 Weight method | - |      |      |     |     |     |       |     |      |
| All canister   | Pair Float method | .51 | -.149 | .598 | .009 | -.166 | -.132 | -16.575 | 4516 | .000 |
|                | 1 Weight method | .66 |      |      |     |     |     |       |     |      |
No changes between float method and weight method. Statistical test could not be computed.

On overall Canister was classified higher with weight method (0.66 ± 1.20) as opposed to float method (0.51 ± 1.02); a statistically significant decrease of -0.149 (95% CI, -0.166 to -0.132), t (4516) = -16.757, \( p < 0.000 \). The mean have been increased from 0.51 to 0.66 which indicate that float test method tend to underestimate the classification (content of the canister). The results indicate that Float test classified the canister lower than weight method.

As 1017 canister classification was changed between both the methods, individual paired T-test was done according to each type of canister. Salbutamol canister was classified lower with weight method (0.43 ± 1.03) as opposed to float method (0.49 ± 1.11). A statistically significant decrease of 0.061 (95% CI, 0.05 to 0.071), \( t (2130) = 11.347, p < .0001 \). The Mean between float and weight have been reduced from 0.49 to 0.43 which indicate that float test method tend to overestimate the classification. The results indicate that float test will show the canister to have higher content of solution in the canister. 133 canister was classified higher with float test classification compared with weight method classification.

Budesonide Canister was classified higher with weight method (1.45 ± 1.43) as opposed to float method (0.63 ± 0.85); a statistically significant increase of 0.823 (95% CI, -0.866 to -0.781), \( t (1148) = -38.25, p < .0001 \). The mean between oat method and weight have been increased from 0.49 to 1.45 which indicate that float test method tend to underestimate the classification. 724 canister was classified higher with weight method classification compared with float method classification.

Ipratropium/Fenoterol Canister was classified lower with weight method (0.38 ± 0.95) as opposed to float method (0.53 ± 0.11); a statistically significant decrease of 0.155 (95% CI, -0.125 to 0.184), \( t (648) = 10.211, p < .0001 \). The Mean between float method and weight have been reduced from 0.53 to 0.38 which indicate that float test method tend to overestimate the classification. The results indicate that float test will show the canister to have higher content of solution in the canister.

Fluticasone Canister was classified lower with weight method (0.27 ± 0.71) as opposed to float method (0.41 ± 0.81); a statistically significant decrease of 0.138 (95% CI, 0.1 to 0.177), \( t (339) = 7.035, p < 0.000 \). The mean between float method and weight have been reduced from 0.71 to 0.27 which indicate that float test method tend to overestimate the classification. The results indicate that float test will show the canister to have higher content of solution in the canister.

Fluticasone (generic) Canister was classified higher with weight method (0.23 ± 0.67) as opposed to float method (0.18 ± 0.49); a statistically significant increase of 0.049 (95% CI, -0.085 to -0.014), \( t (181) = -2.763, p = 0.006 \). The results indicate that weight method classified the canister higher than float method. The mean have been increased from 0.18 to 0.23 which indicate that float test method tend to underestimate the classification. The results indicate that Float test classified the canister lower than weight method.

30 Beclometasone canisters were weighed. There was no difference in classification between float method and weight method and hence no statistical significant was found.
Table 4 reports the weight variance between balance category of float and weight method
| Canister               | n   | Category | Classification (%) | Float method mean balance(g) | Variance | Weight method mean balance(g) | Variance |
|-----------------------|-----|----------|--------------------|-----------------------------|----------|------------------------------|----------|
|                       |     |          |                    | mean balance(g)              |          |                              |          |
| Salbutamol (GSK)      | 2131| Empty    | 12.04              | 0.17                        |          | 12.73                        | 0.214    |
|                       |     | 1/4full  | 14.55              | 0.80                        |          | 15.62                        | 1.04     |
|                       |     | 1/2full  | 18.27              | 1.90                        |          | 19.56                        | 1.18     |
|                       |     | 3/4full  | 21.95              | 2.53                        |          | 23.20                        | 1.17     |
|                       |     | full     | 26.32              | 1.67                        |          | 26.72                        | 0.87     |
| Budesonide(Glenmark)  | 1149| Empty    | 9.32               | 0.8                         |          | 8.78                         | 0.04     |
|                       |     | 1/4full  | 12.86              | 0.35                        |          | 9.85                         | 0.48     |
|                       |     | 1/2full  | 15.96              | 1.47                        |          | 12.42                        | 0.40     |
|                       |     | 3/4full  | -                  | -                           |          | 14.69                        | 0.47     |
|                       |     | full     | -                  | -                           |          | 16.93                        | 0.43     |
| Ipratropium/Fenoterol (Boehringer) | 685 | Empty    | 12.50              | 0.06                        |          | 12.55                        | 0.15     |
|                       |     | 1/4full  | 14.44              | 0.23                        |          | 15.95                        | 0.46     |
|                       |     | 1/2full  | 15.94              | 0.78                        |          | 18.42                        | 0.75     |
|                       |     | 3/4full  | 19.04              | 1.38                        |          | 20.89                        | 0.47     |
|                       |     | full     | 23.77              | 1.75                        |          | 24.29                        | 0.64     |
| Fluticasone (GSK)     | 340 | Empty    | 7.92               | 0.05                        |          | 8.059                        | 0.27     |
|                       |     | 1/4full  | 9.71               | 0.23                        |          | 11.28                        | 0.28     |
|                       |     | 1/2full  | 12.08              | 0.84                        |          | 13.04                        | 0.46     |
|                       |     | 3/4full  | 15.66              | 1.56                        |          | 15.42                        | 0.78     |
|                       |     | full     | 18.16              | -                           |          | 17.53                        | 0.62     |
| Fluticasone (Cipla)   | 182 | Empty    | 9.69               | 0.26                        |          | 9.69                         | 0.26     |
|                       |     | 1/4full  | 13.30              | 0.73                        |          | 13.02                        | 0.50     |
|                       |     | 1/2full  | 16.55              | 1.91                        |          | 14.90                        | 0.27     |
|                       |     | 3/4full  | -                  | -                           |          | 17.23                        | 0.31     |
|                       |     | full     | -                  | -                           |          | 18.92                        | -        |
| Beclometasone (Ivax)  | 30  | Empty    | 9.59               | 0.24                        |          | 9.59                         | 0.24     |
|                       |     | 1/4full  | 12.79              | 1.4                         |          | 12.79                        | 1.4      |
|                       |     | 1/2full  | 16.89              | 0.66                        |          | 16.89                        | 0.66     |
The variance between the categories among the canister categorized according to oat method have wide variation indicating external influence such as technique and interpretation could play a role in biasing the observation. On the other hand, the variance between the categories among the canister have small variation. This indicate that weigh method is a better method because the weight categorized among the category are closely spread among the mean value.

**Discussion**

Currently there is no accurate and practical way to gauge the remaining number of effective actuation in a pMDI without the addition of a dose-counting mechanism. pMDIs contain more drug formulation than the labelled number of drug actuation to ensure dosing consistency in each actuation, up to the labelled number.

A study by Talasila\textsuperscript{14} 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. In a study by Holt\textsuperscript{7}, it's reported that patients tend to overestimate the content of canister and 84% of MDIs evaluated in this study had been used well past the recommended number of actuations. This study also came to a similar finding which shows that about 70% of the returned canister was empty. Activating a nearly empty or an altogether empty MDI to deliver orally inhaled asthma medication appears to be a common occurrence when patients use an MDI without a dose counter\textsuperscript{1,2,4}.

The amount of active ingredients in those additional actuations is variable as propellant and excipients form up to 99% of an asthma drug formulation\textsuperscript{11}. Currently available MDI are formulated as suspensions. Suspensions comprise micronized drug substance suspended in propellant and other excipients. If the drug substance adheres to the walls of the container or valve components, dose delivery and particle size distribution could be inconsistent\textsuperscript{11,12}. Actuating beyond the recommended number of actuation will cause the active ingredient delivery per actuation becomes unpredictable, a phenomenon known as “tail-off”\textsuperscript{7}(Figure 4). 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 content\textsuperscript{8}. Advising the patient top use the inhaler until its 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 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 actually inhaling excipients and sub-therapeutic
active ingredients. This is potentially dangerous especially for rescue medication such as Salbutamol.

**Conclusion**

This study concludes that there is statistically significant difference between float method and weight method in which float test method tend to underestimate the content of the canister compared to weight. Weighing pMDI could be used as a dose counter at health care facilities; however it must be noted that the linear regression model may vary with pMDI product.

**Declarations**

**Conflicts of interest**

The authors declared that they have no conflict of interest.

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**Figures**

![Figure 1](image_url)

**Figure 1**

Canister characteristic according to float test3.