Effect of Rise in Simulated Inspiratory Flow Rate and Carrier Particle Size on Powder Emptying From Dry Powder Inhalers

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ABSTRACT The purpose of this study was to evaluate the effect of carrier particle size and simulated inspiratory flow increase rate on emptying from dry powder inhalers (DPIs). Several flow rate ramps were created using a computer-generated voltage signal linked to an electronic proportioning valve with a fast response time. Different linear ramps were programmed to reach 30, 60, 90, and 120 L/minute over 1, 2, or 3 seconds. At the lower flow rates, 100-ms and 500-ms ramps were also investigated. Three DPIs, Spinhaler, Rotahaler, and Turbuhaler, were used to test the effect of flow rate ramp on powder emptying. To test the effect of carrier particle size, anhydrous lactose was sieved into 3 particle sizes, and 20 mg of each was introduced into #2 and #3 hard gelatin capsules for Spinhaler and Rotahaler, respectively. Emptying tests were also carried out using the on/off solenoid valve described in the United States Pharmacopeia (USP) (resulting in no ramp generation). Powder emptying increased from 9% to 46% for Rotahaler and 69% to 86% for Spinhaler from the shallowest (3 seconds to reach peak flow) to the 100-ms ramp for the 53- to 75- μ m lactose size range at 30 L/minute. Similar trends were observed for larger particle size fractions at the same flow rate. However, at higher airflow rates (60, 90, and 120 L/minute), there was no significant increase in percentage of emptying within the ramps for a particular particle size range. Trends observed were similar for placebo-filled Turbuhaler and commercially available Rotacaps used with Rotahaler, with the steepest ramp demonstrating more complete emptying. Percentage of powder emptying determined by the USP solenoid valve

overestimated the emitted dose compared with the ramp method at 30 L/minute for all 3 devices. Results indicate that there is a significant difference in powder emptying at 30 L/minute from the shallowest to the steepest ramp within a particular size range. Within a particular particle size range, the USP method produced more complete emptying than even the steepest ramp, especially at the lower flow rates. Thus, when the USP device is used to estimate DPI emptying at lower flow rates, the results are likely to overestimate DPI performance significantly.

INTRODUCTION

Diseases in the conducting and respiratory airways can be treated by local administration of drug by inhalation (1,2). This method requires precise dose delivery to the lung during normal patient use of their inhalation delivery system. Dry powder inhalers (DPIs) are one of several inhalation aerosol delivery systems that have been investigated for this role (3-6). The majority of commercially available DPIs consist of micronized drug powder mixed with an inert carrier, usually lactose or pure drug processed to improve its bulk flow properties. Hard gelatin capsules or blister packages containing individual doses of drug formulation are placed into the device, or doses are metered from a bulk reservoir. The device is manually manipulated to rupture the capsule or blister or to initiate dose metering. Subsequently, the patient's inspiratory airflow causes aerosolization then deaggregation of the powder. Such systems are called passive inhalers because they contain no energy source independent of the patient to aerosolize the drug they contain.

The extent of dose delivery to the lung can change because of the variability in inhalation characteristics between patients (7,8). As airflow increases through the inhaler with increasing inspiratory effort,

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increased emptying and fine particle generation probably results from increased pneumatic entrainment and deaggregation of particle agglomerates (9,10). Higher inspiratory flow rates, however, increase deposition by impaction in the oropharynx and at airway bifurcations, whereas they reduce deposition by sedimentation and diffusion because of the reduction of particle residence times. Hence, the deposition pattern of drug in the lung and the resulting efficacy depend in a complex manner on inspiratory flow rate.

Test methods originally developed for metered dose inhalers (MDIs) have been adapted to permit meaningful in vitro evaluation of DPIs. Because the resistance to airflow in DPIs is highly variable among different device designs, testing must be performed at a flow rate typical of those generated by patients inhaling through a specific device (11-13). In addition, a fixed volume of air, roughly equivalent to a full inhalation, is used to generate and test aerosol from a DPI.

Although in vitro test methods for DPIs were no doubt developed by pharmaceutical manufacturers selling DPIs as early as the early 1960s, and such methods obviously garnered the approval of regulatory agencies, there were initially no publicly available testing methods and specifications for DPIs (14). To remedy this, the United States Pharmacopeia (USP) developed a standardized method and suggested testing DPIs at a constant pressure drop (4.0 kPa), resulting in a specific test flow rate (15) for each inhaler. In addition, controls were put in place to ensure that the appropriate flow rate was instantaneously achieved through the DPI by diverting air through the inhaler using a solenoid valve and an electronic timer. The same system ensured that whatever the test flow rate, the total volume of air pulled through the inhaler was 4 liters. Current in vitro testing therefore replicates both the peak rate at which a patient might be expected to inhale through a DPI and the patient's volume of inhalation. However, this method does not take into account how this peak flow rate is achieved during patient use.

In reality, there are differences in the ways in which each patient approaches a particular flow rate, as shown in Figure 1.

Figure 1. Inhalation profiles of 5 healthy volunteers using a high-resistance DPI.

Differences can also be noted within the same patient on separate occasions. The flow profiles may affect powder emptying and deaggregation from DPI devices and might also explain why in vitro and in vivo device performance frequently differs when the same flow rate is achieved in both cases.

The purpose of this research is to evaluate the effect of the rate of increase in airflow approaching a fixed plateau airflow rate on powder emptying from DPIs. The intent is to develop a simple and robust system that more closely predicts in vivo DPI performance and could ultimately be capable of simulating actual patient inhalation profiles. While investigating these specific aims, the following hypotheses will be tested:

Steeper rises in flow rate (“steep ramps”) cause more complete device emptying compared with shallower ramps that approach the same flow rate and total inhaled volume. For a particular inspiratory flow rate ramp, larger particles are more efficiently emptied from DPIs compared with smaller sized particles.

MATERIALS AND METHODS

Because the USP device for in vitro DPI testing causes instantaneous generation of a specific peak flow rate, modifications had to be made to the system to make it capable of generating variable inspiratory

flow profiles using an electronic proportioning valve in place of the “on/off” solenoid valve.

Several flow rate ramps were created using a computer-generated 0- to 10-volt signal to control a fast-responding electronic proportioning valve (model # R59211NP221; Teknocrat Inc., Melbourne, FL), which controlled the airflow rate through test inhalers (Figure 2).

Figure 2. Schematic diagram of the testing apparatus.

No signal completely closed the valve, preventing airflow through the inhaler. As the voltage was increased, the valve opened, and it was fully opened at 10 V. Because there is a nonlinear relationship between valve opening and flow rate, a calibration curve of “volts” versus “flow” was developed. Ramps were then created by programming the computer to output escalating voltage signals over finite time periods (100 ms and 500 ms or 1, 2, or 3 seconds). In all cases, a constant air volume of 4.0 was drawn through the inhaler by 1 or more vacuum pumps connected via a manifold (model # 0323-V3; Gast Manufacturing Corporation, Benton Harbor, MI). The trapezoidal rule was employed to calculate the volume of air inhaled over each 10-ms interval. The time corresponding to 4.0 L was determined, and the vacuum pump was shut off at the specified time. Rather than relying on the voltage versus flow rate calibration only, we monitored the actual airflow rates through the system in real time by a calibrated pressure transducer (model # PX 653; Omega Engineering, Stamford, CT) and a separate channel on the data acquisition system. The simulated inhalations were programmed to reach peak flow

rates of 30, 60, 90, and 120 L/minute over 1-, 2-, or 3-second periods. These profiles can be considered stylized flow profiles that are somewhat representative of the “ramp steepness” observed when patients inhaled through a typical DPI device. The 100-ms and 500-ms ramps were investigated at 30 and 60 L/minute only.

The USP emitted-dose sampling apparatus consisted of a glass fiber filter in a support housing connected to the test DPI mouthpiece at one end and the flow control valve and vacuum pumps at the other. Rotahaler (GlaxoWellcome, Research Triangle Park, NC), Spinhaler (Rhone-Poulenc Rorer Pharmaceuticals, Collegeville, PA), and Turbuhaler (Astra Draco Pharmaceuticals, Lund, Sweden) were chosen for testing because they are representative of low-, medium-, and high-resistance DPIs, respectively (16). Turbuhaler placebo inhalers were used as donated by the manufacturer. Rotacaps were purchased commercially (lot #8ZPO942; GlaxoWellcome), but Spincaps were unavailable in the United States. The Spinhaler and Rotahaler were used to evaluate the effect of carrier particle size on device emptying. Lactose (lot # M 016695; Quest International, Hoffman Estates, IL) was sieved into 3 particle size ranges; 53 to 75 μm , 105 to 125 μm , and 125 to 150 μm . Approximately 20 mg of each lactose size fraction was manually filled into #2 (lot # 63271; Eli Lilly, Indianapolis, IN) and #3 capsules (lot # 11633; Eli Lilly) for Spinhaler and Rotahaler, respectively. Uniformity of capsule fill weight was checked by sampling 20 random capsules. The weight of each DPI unit was recorded before following the patient instructions to load the dose. The USP procedure for emitted dose determination from a mouthpiece of a DPI was followed, except for the use of flow rate ramps rather than the use of a constant instantaneous flow rate. The DPI unit was reweighed after the run, and the difference in the weight was recorded ($n = 5$). To assess possible weight changes from moisture uptake or release, 5 blank tests were carried out in which DPIs were reweighed without dispensing the dose.

Emptying tests were also carried out using the unmodified USP apparatus. Although the USP recommends testing at a constant pressure drop (4.0

kPa), resulting in a test flow rate of 60 L/minute for Turbuhaler and 100 L/minute for Rotahaler as well as Spinhaler, testing was carried out over an entire range of flow rates: 30, 60, 90, and 120 L/minute to account for different patient breath profiles.

RESULTS AND DISCUSSION

Two-way analysis of variance was used to analyze the data at a significance level of $p < 0.05$. Percentage of capsule emptying increased from 9% to 46% for Rotahaler when the 3-second ramp was compared with the 100-ms ramp within the 53- to 75- μm lactose size range at 30 L/minute, as shown in Figure 3.

Figure 3. Percentage powder emptying versus particle size for 5 different ramps and the USP apparatus. Device: Rotahaler; Flow Rate: 30 L/minute.

The USP (no ramp) determination at the same flow rate and particle size range showed 48% powder emptying, which was considerably higher. Similar trends were observed for higher particle size ranges at the same flow rate. At 60 L/minute, there was no significant increase in percentage of emptying within the ramps for a particular size range. Similar trends were observed for 90 and 120 L/minute. For example, at 120 L/minute, Rotahaler demonstrated an increase from 97% to 100% from the 3-second to the 1-second ramp within the 53- to 75- μm size range, presumably because the capsule was ostensibly empty and therefore incapable of releasing more powder. Percentage of powder emptying employing

the USP device closely matched the ramp method at this flow rate for all the particle size ranges. Table 1 summarizes the percentage powder emptying from Rotahaler for the different flow rate ramps, particle sizes and flow rates.

Table 1. Percentage powder emptying data from Rotahaler for different flow rate ramps, particle sizes, and flow rates

PARTICLE SIZE	Percent Powder Emptying			
	30 l/min	60 l/min	90 l/min	120 l/min
3 SECONDS RAMP				
53-75 μm	9.7 $\pm$ 1.03	70.7 $\pm$ 3.32	84.2 $\pm$ 2.58	96.5 $\pm$ 2.31
105-125 μm	21.9 $\pm$ 5.07	70.2 $\pm$ 4.43	85.3 $\pm$ 4.04	98.9 $\pm$ 0.89
125-150 μm	11.7 $\pm$ 1.92	78.2 $\pm$ 2.63	91.3 $\pm$ 2.13	100.0 $\pm$ 1.6
Rotacaps	11.9 $\pm$ 3.19	23.2 $\pm$ 1.45	75.6 $\pm$ 1.81	97.6 $\pm$ 1.11
2 SECONDS RAMP				
53-75 μm	20.5 $\pm$ 4.13	73.4 $\pm$ 6.99	86.8 $\pm$ 3.05	96.6 $\pm$ 2.94
105-125 μm	21.5 $\pm$ 1.91	74.6 $\pm$ 4.57	91.2 $\pm$ 2.99	98.2 $\pm$ 1.56
125-150 μm	18.2 $\pm$ 2.75	75.0 $\pm$ 5.35	89.7 $\pm$ 3.65	98.0 $\pm$ 2.15
Rotacaps	18.2 $\pm$ 5.17	34.7 $\pm$ 1.09	82.8 $\pm$ 1.09	99.3 $\pm$ 3.96
1 SECOND RAMP				
53-75 μm	27.3 $\pm$ 4.31	77.5 $\pm$ 6.40	91.3 $\pm$ 4.48	100.2 $\pm$ 1.5
105-125 μm	20.3 $\pm$ 2.13	79.6 $\pm$ 3.84	92.1 $\pm$ 2.81	98.6 $\pm$ 0.96
125-150 μm	29.5 $\pm$ 2.71	82.4 $\pm$ 5.42	95.9 $\pm$ 3.66	98.9 $\pm$ 1.47
Rotacaps	25.3 $\pm$ 4.33	40.4 $\pm$ 1.30	86.2 $\pm$ 1.60	99.0 $\pm$ 4.11
500 MILLISECOND RAMP				
53-75 μm	32.7 $\pm$ 7.03	75.4 $\pm$ 7.92	NT	NT
105-125 μm	32.1 $\pm$ 4.44	73.9 $\pm$ 5.09	NT	NT
125-150 μm	40.9 $\pm$ 7.85	75.1 $\pm$ 3.81	NT	NT
Rotacaps	21.4 $\pm$ 3.32	68.7 $\pm$ 6.34	NT	NT
100 MILLISECOND RAMP				
53-75 μm	46.0 $\pm$ 5.51	73.1 $\pm$ 8.19	NT	NT
105-125 μm	48.1 $\pm$ 5.58	81.1 $\pm$ 7.16	NT	NT
125-150 μm	46.6 $\pm$ 6.12	80.9 $\pm$ 6.57	NT	NT
Rotacaps	52.4 $\pm$ 7.02	85.1 $\pm$ 5.44	NT	NT
USP (NO RAMP)				
53-75 μm	47.9 $\pm$ 3.89	75.9 $\pm$ 5.26	100.0 $\pm$ 1.21	100.4 $\pm$ 0.7
105-125 μm	45.7 $\pm$ 3.15	78.2 $\pm$ 4.59	99.4 $\pm$ 1.78	100.5 $\pm$ 0.6
125-150 μm	50.3 $\pm$ 7.37	79.5 $\pm$ 3.48	99.4 $\pm$ 1.29	101.3 $\pm$ 0.5
Rotacaps	46.4 $\pm$ 4.83	79.9 $\pm$ 8.73	99.7 $\pm$ 2.07	100.7 $\pm$ 4.3

NT: Not Tested

Percentage of emptying increased from 69% to 86% for Spinhaler from the shallowest to the 100-ms ramp within the 53- to 75- μm size range at 30 L/minute, as shown in Figure 4.

Figure 4. Percentage powder emptying versus particle size for 5 different ramps and the USP apparatus. Device: Spinhaler; Flow Rate: 30 L/minute.

The USP apparatus determination at the same flow rate and particle size range showed 83% powder emptying. At higher flow rates (60, 90, and 120 L/minute), there was no significant increase in percentage of emptying within the ramps for a particular size range. Also, there was no significant difference between the ramp method and the USP method at these flow rates. For example, at 120 L/minute, percentage of emptying from Spinhaler was not significantly different from the shallowest (99.5%) to the 1-second (99.6%) ramp within the 53 to 75- μm size range. This result was attributed to almost complete powder emptying in both cases before the final flow rate of 120 L/minute was attained. Table 2 shows the percentage powder emptying from Spinhaler under all test conditions.

Turbuhaler (Figure 5) showed that percentage of powder emptying increased from 63.2% to 88.0% when the 3-second ramp was compared with the 100-ms ramp at 30 L/minute (83% powder emptying was estimated using the USP apparatus at the same flow rate).

Table 2. Percentage powder emptying data from Spinhaler for different flow rate ramps, particle sizes, and flow rates

Particle Size	Percent Powder Emptying			
	30 l/min	60 l/min	90 l/min	120 l/min
3 SECONDS RAMP				
53-75 μm	69.1 $\pm$ 6.54	87.5 $\pm$ 2.20	99 $\pm$ 0.93	99.5 $\pm$ 1.45
105-125 μm	72.5 $\pm$ 2.36	98.0 $\pm$ 3.57	99.2 $\pm$ 0.75	98.6 $\pm$ 3.24
125-150 μm	82.4 $\pm$ 1.98	98.1 $\pm$ 2.67	98.3 $\pm$ 2.53	99.7 $\pm$ 1.15
2 SECONDS RAMP				
53-75 μm	74.8 $\pm$ 5.08	95.3 $\pm$ 1.39	97.8 $\pm$ 2.13	100.1 $\pm$ 1.5
105-125 μm	74.9 $\pm$ 1.27	98.6 $\pm$ 1.67	99.6 $\pm$ 1.19	99.6 $\pm$ 0.96
125-150 μm	88.1 $\pm$ 3.92	98.4 $\pm$ 1.29	100.1 $\pm$ 1.39	99.5 $\pm$ 0.93
1 SECOND RAMP				
53-75 μm	78.3 $\pm$ 2.51	97.6 $\pm$ 2.90	99.2 $\pm$ 1.75	99.6 $\pm$ 0.93
105-125 μm	74.8 $\pm$ 3.97	98.5 $\pm$ 1.54	99.1 $\pm$ 1.51	100.2 $\pm$ 0.9
125-150 μm	87.9 $\pm$ 1.55	97.4 $\pm$ 2.55	99.3 $\pm$ 1.44	99.2 $\pm$ 1.95
500 MILLISECOND RAMP				
53-75 μm	86.8 $\pm$ 2.41	91.7 $\pm$ 2.16	NT	NT
105-125 μm	87.9 $\pm$ 6.01	92.8 $\pm$ 1.03	NT	NT
125-150 μm	90.2 $\pm$ 6.49	94.6 $\pm$ 4.11	NT	NT
100 MILLISECOND RAMP				
53-75 μm	86.4 $\pm$ 5.49	95.8 $\pm$ 3.39	NT	NT
105-125 μm	88.5 $\pm$ 5.56	93.9 $\pm$ 2.89	NT	NT
125-150 μm	88.5 $\pm$ 6.54	96.2 $\pm$ 1.31	NT	NT
USP (NO RAMP)				
53-75 μm	83.4 $\pm$ 3.45	95.4 $\pm$ 4.11	100.1 $\pm$ 1.3	100.1 $\pm$ 1.2
105-125 μm	83.0 $\pm$ 4.37	96.1 $\pm$ 3.15	98.7 $\pm$ 0.57	100.8 $\pm$ 0.9
125-150 μm	86.3 $\pm$ 1.89	95.5 $\pm$ 4.22	99.4 $\pm$ 1.55	100.5 $\pm$ 0.5
NT: Not Tested

Figure 5. Percentage powder emptying versus flow rate for 5 different ramps and the USP apparatus. Device: Turbuhaler; Flow Rate: 30 L/minute.

However, the trend was not as prominent at the higher flow rates (60 and 90 L/minute). In this case, testing was not carried out at 120 L/minute because it would be almost impossible for a patient to achieve such a high flow rate through a high-resistance device such as the Turbuhaler. Table 3 shows the percentage powder emptying from Turbuhaler for the different flow rate ramps and flow rates.

Table 3. Percentage powder emptying data from Turbuhaler for different flow rate ramps and flow rates

Ramp	Percent Powder Emptying		
	30 l/min	60 l/min	90 l/min
3 SECOND	63.2±3.03	66.4±5.12	92.0±3.80
2 SECOND	66.4±2.88	91.6±3.57	93.3±2.87
1 SECOND	89.0±1.87	91.3±5.60	91.8±3.56
100 MILLISECOND	85.0±4.47	92.0±8.36	NT
500 MILLISECOND	88.0±8.36	90.0±7.07	NT
USP(NO RAMP)	83.0±3.46	95.0±4.12	98.6±1.14

NT: Not Tested

In order to validate the effect of ramps on a commercially available formulation, Ventolin Rotacaps were tested with the Rotahaler device. For the 30-L/minute flow rate condition in Rotahaler, percentage of emptying was the highest (52.4%) with the 100-ms ramp compared with 18.2% and 11.9% with the 2-second and the 3-second ramps, respectively. For the 60- L/minute flow rate condition, 85.1% was released with the 100-ms ramp, as compared with 34.7% and 23.2% with the 2-second and the 3-second ramps, respectively. In case of the 90 L/minute flow rate condition, the percentage released was about 86.2% with the 1-second ramp, as compared with 82.8% and 75.6% with the 2-second and 3-second ramps, respectively. Overall, there was a significant difference between the different flow rate ramps approaching 30, 60, and 90 L/minute at the 0.05 significance level.

Collectively, these results indicated that, as expected, there was an increase in the percentage of lactose released with increasing flow rates. In general, at each flow rate, a slight increase in device emptying was noted going from the shallowest to the steepest

ramp, which was most evident at the lower flow rates. This increase may be because at lower flow rates (at the beginning of shallow ramp) an initial movement of bulk powder (without entrainment) might allow it to accumulate in crevices or on inaccessible surfaces (and even become compacted) within the DPI. It is also possible that a steeper ramp would exert a greater air impact, causing more particle deaggregation and entrainment compared with a shallower ramp, thus enhancing powder emptying. At higher flow rates, the percentage released was not significantly different among the different ramps. This result might be because aggregates experience a high flow rate shortly after beginning to move but before they escape out of the most turbulent regions of fast-moving air within the device. The trends observed were similar for all 3 devices.

The results also showed that carrier particle size had a significant effect on percentage emptying from DPI systems. In general, as particle size increased from ~50 to 150 μm , the percentage emptying increased as the ramp became steeper or as the flow rate increased.

Hence, in vitro DPI emptying tests at a fixed, instantaneously achieved flow rate may not be representative of what occurs under conditions that more closely mimic the inhalation patterns of patients who generate low flow rates.

CONCLUSIONS

Powder emptying from the 3 devices using flow rates greater than or equal to those recommended by USP (based on device resistance) was approximately the same using the USP or ramp-generating methods. Only at lower flow rates than those recommended by USP do differences in emptying become apparent between the 2 methods.

It appears that flow rate, the rate at which that flow rate is achieved, and particle size have a statistically significant effect on percentage of emptying from a broad range of passive DPI systems, especially at lower flow rates. Percentage of powder emptying determined by the USP method was statistically

higher compared with the ramp method at 30 L/minute for all 3 devices, with the same trend at higher peak flow rates. Although we have presented no data to evaluate emitted drug dose, emitted particle size, in vivo deposition, or biological effect, it should be recognized that complete DPI emptying is a precursor of all these events. These data suggest that the existing USP method appears appropriate at higher flow rates but should be viewed skeptically at lower flow rates. They also suggest that patients capable of achieving only low inspiratory flow rates will be more likely to receive erratic doses than might otherwise be expected.

This observation calls into question the practice of using the USP apparatus over a wide range of flow rates to suggest that passive DPI performance is independent of flow rate.

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REFERENCES

1. Rees J, Price J. Asthma in children: treatment. *BMJ*. 1995; 310:1522-1527.
2. Cutie A, Sciarra J. Therapeutic inhalation aerosols in the treatment of asthma. *Am J of Hosp Pharm*. 1989;46:1845-1855.
3. Prime D, Atkins P, Slater A, Sumby B. Review of dry powder inhalers. *Advanced Drug Delivery Reviews*. 1997;26:51-58.
4. Bell J, Treneman B. Design and engineering of dry powder inhalers. *Respiratory Drug Delivery IV*. Buffalo Grove, IL: Interpharm Press; 1994:93-99.
5. Nantel N, Newhouse M. Inspiratory flow rates through a novel dry powder inhaler (Clickhaler) in pediatric patients with asthma. *J Aerosol Med*. 1999;12:55-58.
6. Lucas P, Andersen K, Staniforth J. Protein deposition from dry powder inhalers: fine particle multiplets as performance modifiers. *Pharm Res*. 1998;15:562-568.
7. Hindle M, Byron P. Dose emissions from marketed dry powder inhalers. *Int J Pharm*. 1995;169-176.
8. Clark A, Bailey R. Inspiratory flow profiles in disease and their effects on the delivery characteristics of dry powder inhalers. *Respiratory Drug Delivery IV*. Buffalo Grove, IL: Interpharm Press; 1996:221-228.
9. Hickey J, Concessio N, Platz R. Factors influencing the dispersion of dry powders as aerosols. *PharmTech*. 1994;18:58-64.
10. Srichana T, Martin G, Marriott C. The relationship between drug and carrier deposition from dry powder inhalers *in vitro*. *Int J Pharm*. 1998;167:13-23.
11. DeBoer A, Winter H, Lerk C. Part 1. Inhalation characteristics, work of breathing and volunteer's preferences in dependence of the inhaler resistance. *Int J Pharm*. 1996;130:231-244.
12. DeBoer A, Gjaltema D, Hagedoorn P. Inhalation characteristics and their effects on in vitro drug delivery from dry powder inhalers. Part 2. Effect of peak flow rate (PIFR) and inspiration time on the *in vitro* drug release from three different types of commercial dry powder inhalers. *Int J Pharm*. 1996;138:45-46.
13. Steckel H, Muller B. *In vitro* evaluation of Dry Powder Inhalers. Part 2. Influence of carrier particle size and concentration on *in vitro* deposition. *Int J Pharm*. 1997;154:31-37.
14. Byron P. Compendial dry powder testing: USP perspectives. *Respiratory Drug Delivery IV*. Buffalo Grove, IL: Interpharm Press; 1994:153-162.
15. Stimuli to the revision process. *Pharmacopeial Forum* 23. 1997;6:5216
16. Clark A, Hollingworth A. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers. Implications for *in vitro* testing. *J Aerosol Med*. 1993;6:99-110.