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Review of the TAIFUN® Multidose Dry Powder Inhaler Technology

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Although pressurized metered dose inhalers (pMDIs) currently constitute a majority of the market share in the inhalation market, dry powder inhaler (DPI) products have become increasingly popular due to their reliability and product performance. One such DPI is the TAIFUN® inhaler that is a reservoir-based DPI system with the ability to produce consistent and uniform doses in vitro. Originally developed for the pulmonary delivery of salbutamol, the TAIFUN® inhaler platform has since been used to develop a product for breakthrough cancer pain management using fentanyl citrate as the active drug. In vivo results show the TAIFUN® inhaler is able to deliver a rapid onset of action and increased relative bioavailability compared with other fentanyl products currently on the market.

Keywords dry powder inhaler; pulmonary; inhalation; fentanyl; breakthrough cancer pain

INTRODUCTION

Over the last 50 years, the most popular device for delivering drug to the lungs constituting over 80% of the global market has been the pressurized metered dose inhaler (pMDI) (O'Connor, 2004). Up until the last decade, pMDIs used chlorofluorocarbons or CFCs as a propellant, which have recently been shown to contribute to the depletion of the ozone layer. As a result, CFCs are being phased out of all aerosols including pMDIs. Reformulation of propellant-driven aerosols includes other propellant systems such as hydrofluoroalkanes (HFAs). These HFAs, although more environmentally friendly and possessing the necessary properties of a good propellant, have slightly different physical properties to the original CFCs, leading to changes in product performance. Consequently, reformulation of the existing pMDI products with the goal of obtaining bioequivalent product performance to the original CFC-based products has been challenging. (Cripps Schelze, Woodhouse, 2000) Additionally, precise coordination between the actuation of traditional pMDIs and patient inspiration must exist to obtain uniform dosing (Smith & Parry-Billings, 2003). Owing to the high velocity of the emitted particles, the dose can potentially become impacted on the back of the patient's throat leading to lower absorption levels in the lungs. Stability problems during development can also occur because many formulations require either complete dissolution of the drug within the propellant (potential for chemical instability, e.g., active degradation) or suspended within the propellant (physical instability, e.g., Ostwald ripening).

Alternatively, scientists have developed the dry powder inhaler (DPI) as a means to deliver precise amounts active drugs to the lungs. DPIs generally comprise active drug and excipients contained within an apparatus designed to accurately meter and aerosolize the drug into inhalable particles. Although there are many technologies and formulations available in the literature, traditional DPI formulations comprise micronized active drug blended with lactose-based carrier particles. DPI designs can be divided into two distinct groups: premetered and reservoir-based systems. Premetered DPIs provide a single unit dose typically stored in a capsule or aluminum blister pack, which protects the product from potential moisture ingress. Premetered DPIs are further subdivided into single dose systems that require the patient to reload the inhaler after each use and multidose systems in which many doses can be taken before the patient must reload or dispose of the inhaler. Reservoir-based DPIs contain a free flowing inhalation powder providing multiple doses contained within a depot inside the inhaler, and generally protected from moisture via a desiccant system. Reservoir-based DPIs must also have a system for metering precise doses of powder during each actuation of the inhaler.

Because DPI systems do not contain a propellant system to aerosolize the powder, the patient must inhale with sufficient power to accelerate the air flow and create the turbulence needed to aerosolize the dry powder. This critical air flow rate along with careful design of the inhaler flow path, create the necessary shear forces to break apart the powder into smaller inhalable particles. Therefore, a mutual partnership must exist between the powder formulation and its associated physical properties and the inhaler design to create the precise shear forces required to obtain particles that can be delivered to the lungs. Because aerosolization of the powder is a result of

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patient inspiration, proper timing between actuation and inspiration as in traditional pMDIs is not required.

At a minimum, an effective DPI must be able to repeatedly dose precise aliquots of powder (this is especially important for reservoir-based inhalers) and uniformly aerosolize the dry powder into repeatable particle sizes measured by its mass median aerodynamic diameter (MMAD) and fine particle dose (FPD). If an inhaler cannot repeatedly meter accurate and precise doses of powder, dose content uniformity cannot be achieved and product reliability is compromised. Similarly, if the inhaler cannot uniformly aerosolize the powder at a given flow rate (or pressure drop) leading to a variable FPD and dose-to-dose variability in vivo. Premetered inhalers rely on accurately metered doses into the capsule or blister pack, whereas reservoir systems typically rely on volumetric dosing of the powder in situ to obtain a uniform metered dose.

DISEASE STATES UTILIZING DPIs AS A TREATMENT

Disease states traditionally treated by pMDIs, DPIs, and nebulizers include asthma and chronic obstructive pulmonary disease (COPD) (Virchow et al., 2008). By treating these disease states directly, less active drug is required to achieve a therapeutic effect. Additionally, when treating systemically through pulmonary administration, smaller dosages relative to oral administration are required. This is due to rapid absorption into the lung and bloodstream and bypassing first hepatic pass metabolism (when applicable). The rapid onset of action is critically important in disease states such as asthma when asthma attacks can become life threatening. Owing to these advantages, the pulmonary delivery route is currently being investigated to treat other nontraditional disease states, including diabetes (Arnolds & Heise, 2007), cancer (Sharma et al., 2001), prevention of fungal infections (Hoeben et al., 2006; McConville et al., 2006; Vaughn et al., 2005), and breakthrough pain management (BPM) (Farr & Otulana, 2006).

Although the asthma and COPD markets overshadow these other emerging inhalation areas, there is considerable industry activity and opportunity in these newer therapeutic fields. For example, the current market for the management of breakthrough cancer pain is estimated to be around US$2–3 billion worldwide (Datamonitor, 2006). Breakthrough cancer pain is characterized by rapid onset reaching peak intensity within a few seconds or minutes and can last for many minutes to a few hours. Currently, fentanyl citrate is the drug of choice to treat breakthrough pain. Fentanyl citrate branded products include Duragesic®, Actiq®, and Fentora®, which are delivered by the transdermal or transmucosal routes. Duragesic® is a transdermal patch and has a slower onset of action compared with Actiq® and Fentora®, which are available in a lollipop and buccal tablet, respectively. The majority of the dosage forms currently used to treat breakthrough cancer pain have a relatively slow onset of action. There is an unmet medical need for a dosage form with a very rapid onset of action to treat these breakthrough episodes.

THE TAIFUN® INHALER

The TAIFUN® inhaler (Figure 1A) is a reservoir-based DPI originally developed and approved for use in 10 territories within the European Union to administer salbutamol for the treatment of asthma. The salbutamol TAIFUN® inhaler is able to precisely and accurately meter as many as 200 individual doses. However, as fentanyl citrate is a highly potent class II substance, the label claim of the product has been reduced to 30 individual doses through a reduction in the volume of the reservoir. After the patient actuates the inhaler by rotating the cap and mouthpiece (Figure 1B), a unit of powder is volumetrically filled into a slot in the dose pin (Figure 2A) using a patented method (Lankinen, 1997). As the patient inhales, air passes through a one-way valve forcing the inhalation powder tangentially into the vortex chamber, where turbulent forces shear the micron-sized fentanyl citrate particles from their larger lactose carriers (Figure 2B) (Lankinen, 1995). The increase in air velocity within the chamber can reach up to 17.7 m/s at a flow rate of 30 L/min and have an acceleration of approximately 52,000 m/s^2

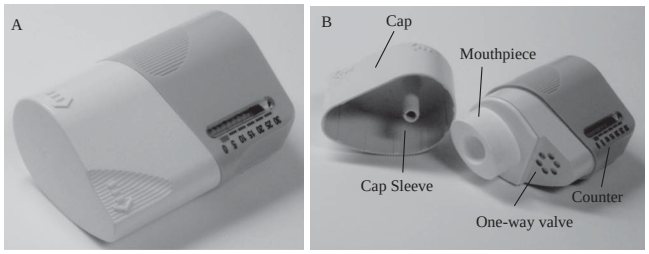

FIGURE 1. TAIFUN® inhaler (A) and inhaler with cap off (B).

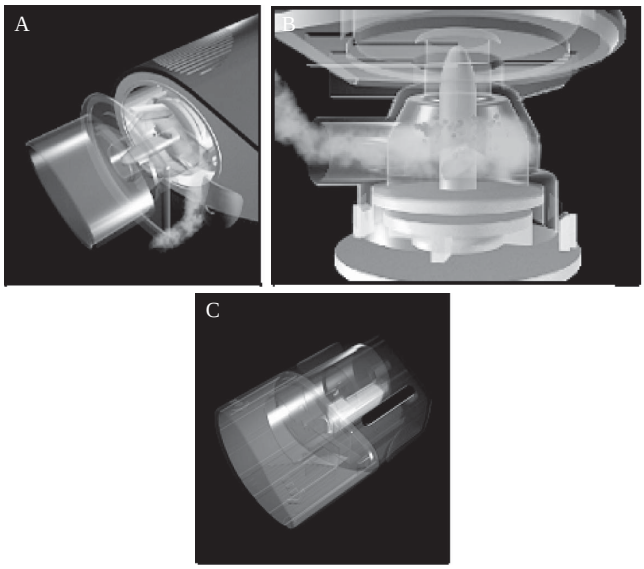

FIGURE 2. Entrainment of air into the vortex chamber and dose pin (A) causing turbulent air flow to break up the powder by shear forces (B). Desiccant capsule situated within the powder reservoir (C).

(more than ~5,300 times gravitational acceleration of gravity). Such forces are more than adequate to aerosolize the powder into a size distribution that is suitable for inhalation.

Prior to actuation, the powder is stored in a reservoir located in the center of the inhaler and is protected by a patented desiccant system (Figure 2C). The number of doses remaining in the TAIFUN® inhaler is indicated by means of a dose indicating system that counts down in unit doses. The desiccant system within the reservoir is designed to maintain a constant moisture or humidity level within the inhaler (Lankinen, 2000). The desiccant, silica gel, having a predetermined level of moisture is encased in a material consisting of polycarbonate and acrylonitrile butadiene styrene (ABS) resin. This plastic resin is semipermeable to water vapor therefore allowing for both adsorption and desorption of water vapor on the silica gel leading to a constant humidity level within the reservoir.

Lastly, the cap contains a cap sleeve that fits around the dose pin when in the resting position. By incorporating the sleeve into the design, it is possible to prevent an accidental double dosing of powder into the slot of the dose pin. This is critical when using potent compounds such as fentanyl citrate where overdosing could lead to tragic results.

POWDER MANUFACTURING PROCESS

Inhalation powders used in the TAIFUN® inhaler are manufactured through a wet suspension method (Lankinen, 2003; Lankinen & Salonen, 2006) known as the LURUX® method that enables micronized active drug to adhere onto the surface of a carrier such as lactose. The wet suspension method is preferred to traditional high-shear blending methods for low-potency blends because it increases homogeneity and minimizes drug losses from adherence to the sides of mixing vessel walls through static forces. The wet suspension method is able to consistently achieve homogeneous dry powders containing fentanyl citrate (at a unit dose scale) with potencies as low as 21.0 mcg/mg as static forces are dissipated in the liquid environment. Following filtration, drying, and sieving, an inhalation powder is formed whereby fentanyl particles are distributed across the surface of the lactose carrier particles.

After the manufacturing process, the bulk inhalation powder is filled into a TAIFUN® inhaler subassembly and the remaining components of the inhaler are assembled. The final step before sealing the inhaler in a protective aluminum foil pouch is to prime the inhaler. The priming of the inhaler through actuation and discharge of the inhaler ensures an even coating of powder on the interior surfaces of the inhaler thereby preventing low first doses due to static interactions between the micronized fentanyl citrate and the plastic surfaces.

IN VITRO CHARACTERIZATION OF THE TAIFUN® INHALER

Model batches of the LURUX® process at two different target concentrations were previously manufactured, filled into the TAIFUN® inhaler, and tested to illustrate the in vitro properties of the fentanyl TAIFUN® product. The bulk inhalation powders had actual potencies of 20.7 and 45.8 mcg/mg (target 21.0 and 45.7 mcg/mg), which are required to achieve a target delivered dose of 100 and 200 mcg/dose of fentanyl to the patient (Table 1). Additionally, blend uniformity (n=10) of the bulk powder was measured and determined to be within acceptable industry standards for both the 100 and 200 mcg/dose powders.

Uniformity of dose content throughout the life of the container (beginning, middle, and end of life) revealed consistent results both intra-and interinhaler as seen in Figures 3 and 4 for both the 100 and 200 mcg/dose strengths. For the 100 mcg/dose strength, individual inhaler %RSDs (relative standard deviations) (n=10) ranged from 4.5 to 8.8% whereas individual inhaler %RSDs (n=10) for the 200 mcg/dose strength ranged from 3.3 to 7.7%. The mean of the beginning (♦), middle (■), end (▲), and mean delivered dose (line) are presented in Figures 3A and 4A. In almost all cases, the mean of the beginning doses is slightly lower than the middle and end doses due to the priming method. For both strengths, the mean delivered dose is very close to the target delivered dose (100 and 200 mcg/dose), all of which are within the USP and EP specifications of ±15% of the target delivered dose indicating good repeatability throughout inhaler life. Additionally, no individual doses were outside ±25% of the target delivered dose. Across the individual doses (Figures 3B and 4B), variability ranged between 3.3 and 9.9% and 3.2 and 6.2% for the 100 and 200 mcg/dose strengths, respectively.

Additional inhaler performance properties are presented in Table 1. Fine particle fraction (FPF) was calculated to be 27.6 ± 2.4% and 30.6 ± 1.3% for the 100 and 200 mcg/dose, respectively. The FPD for both the 100 and 200 mcg/dose strengths was determined to be 26.4 ± 2.7 and 61.4 ± 3.2 mcg, respectively. These values are significantly higher than literature values reported by other DPIs currently on the market; however,

TABLE 1
Bulk Inhalation Powder an Inhaler Performance Properties for 100 and 200 mcg/dose Strength Powder

	100 mcg/dose	200 mcg/dose
Bulk powder properties		
Potency (mcg/mg)	20.7	45.8
Blend uniformity (%RSD)	1.9	1.0
Inhaler performance properties		
FPD (mcg)	26.4 ± 2.7	61.4 ± 3.2
FPF (%)	27.6 ± 2.4	30.6 ± 1.3
MMAD (μm)	2.8 ± 0.1	3.0 ± 0.1
GSD	1.6	1.6

FPD, fine particle dose; FPF, fine particle fraction; MMAD, mass median aerodynamic diameter; GSD, geometric standard devision.

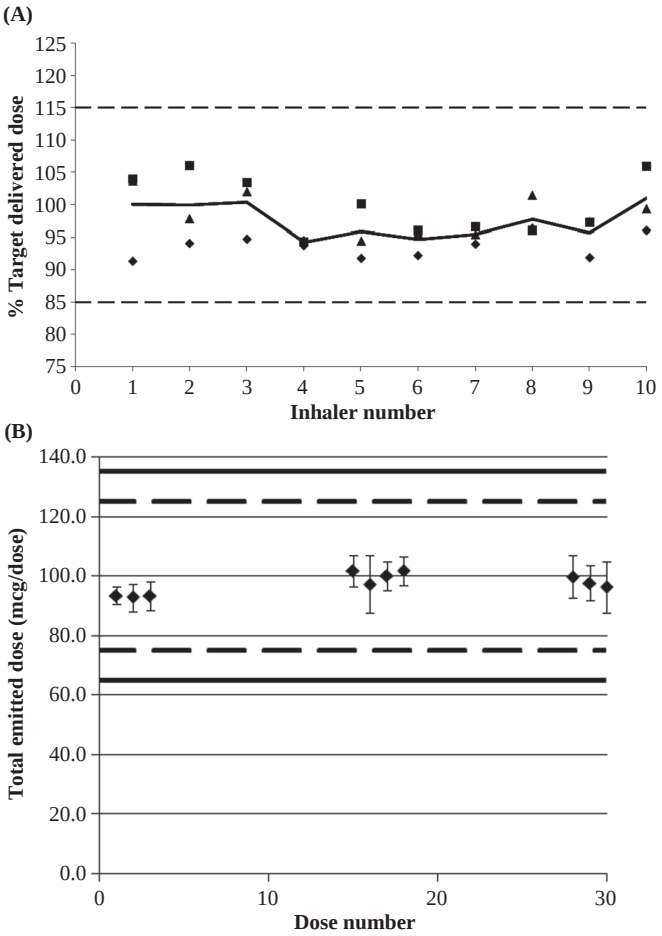

FIGURE 3. (A) Dose content uniformity through life of container (n=10) of 100 mcg/dose strength represented by mean beginning (doses 1–3, ♦), mean middle (doses 15–18, ■), mean end (doses 28–30, ▲), and overall mean (line). (B) Average total emitted dose (n=10) as function of dose number for 100 mcg/dose fentanyl TAIFUN® inhaler. TED_{avg} (mcg/dose) (♦), ±25% (dashed), and ±35% (solid).

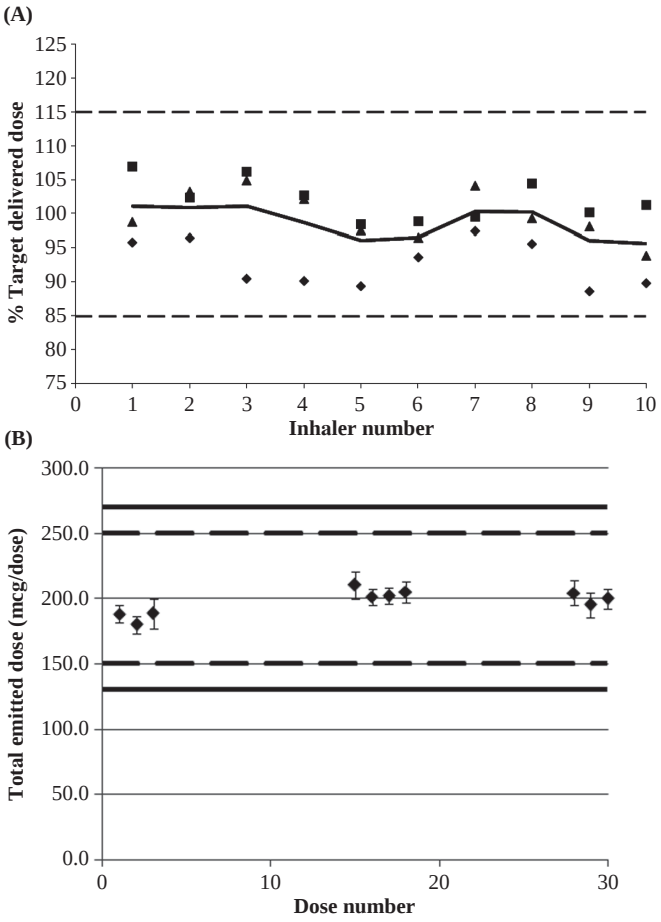

FIGURE 4. (A) Dose content uniformity through life of container (n=10) of 200 mcg/dose strength represented by mean beginning (doses 1–3, ♦), mean middle (dose 15–18, ■), mean end (doses 28–30, ▲), and mean delivered dose (solid line). (B) Average total emitted dose (n=10) as function of dose number for 200 mcg/dose fentanyl TAIFUN® inhaler. TED_{avg} (mcg/dose) (♦), ±25% (dashed), and ±35% (solid).

in depth comparisons are difficult because results can vary based on the method, testing parameters, and equipment, in addition to being product specific. Both product strengths produced aerosolized powders with a MMAD of 2.8–3.0 µm as measured by Andersen cascade impaction according to USP guidelines. Typically, particles with a MMAD less than 5.0 µm will deposit within the respiratory tract and thus are available for absorption in the bloodstream.

A separate study was conducted with three different batches of 200 mcg/dose strength inhalers to determine the repeatability of the metering system. The mouthpiece was removed and a plastic tube connected to a dose collection tube was used to capture all powder metered into the dose pin after each actuation. Batch 7F09W (♦), 7F10W (■), and 7D15W (▲) had bulk powder blend uniformities of 3.7, 4.7, and 3.3% RSD, respectively (Table 2). The %RSD of 30 doses for the three inhalers

TABLE 2
Relationship Between Blend Uniformity of 200 mcg/dose Bulk Inhalation Powder and Dose-to-Dose Variability from TAIFUN®

Batch	Blend Uniformity (n=10) (%)	Dose-to-Dose Variability (n=90) (%)
7F09W	3.7	4.9
7F10W	4.7	4.5
7D15W	3.3	6.4

(Figure 5) for each batch revealed %RSDs of 4.9, 4.4, and 6.4%, for 7F09W, 7F10W, and 7D15W, respectively. It was observed that the metered dose variability was only slightly higher than the variability observed within the powder itself. Because the method to determine the metered dose variability was based on a concentration, the metered dose variability also

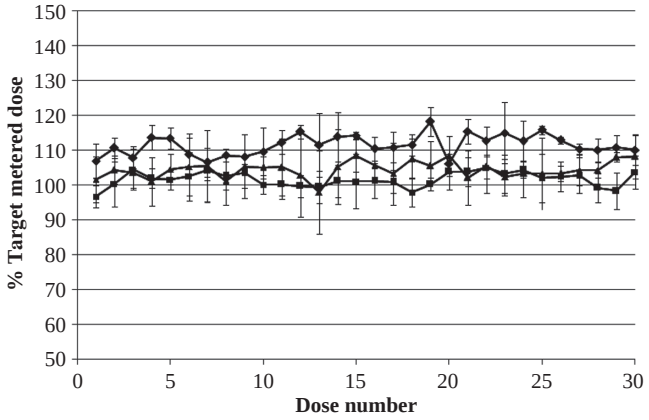

FIGURE 5. Dose to dose variability for 200 mcg/dose batches 7F09W (♦), 7F10W (■), and 7D15W (▲).

includes the variability associated with the powder. Therefore, it was concluded that the metering system is highly reproducible.

IN VIVO CHARACTERIZATION OF THE TAIFUN® INHALER

During a Phase I trial of the fentanyl TAIFUN® product in 32 healthy volunteers, the dose proportionality of fentanyl pharmacokinetics using dosage strengths ranging from 100 to 800 mcg/dose was examined. As shown in Figure 6A, the T_{max} for all strengths was less than 2 min and the C_{max} and $AUC_{0–0.5\ h}$ was proportional with increasing fentanyl dosage strength. In the same study, pulmonary administration using a 200 mcg fentanyl TAIFUN® dose was compared with a 200 mcg oral dose using Actiq® (Figure 6B). Fentanyl TAIFUN® exhibited a significantly more rapid onset of action with a T_{max} of 1 min whereas the oral 200 mcg Actiq® peaked near 60 min. It is also notable that the relative bioavailability of 200 mcg fentanyl TAFIUN® by pulmonary administration is 2.5 times greater than the 200 mcg Actiq® dosed orally. These in vivo studies confirm pulmonary delivery of fentanyl achieves a rapid onset of action with significantly improved bioavailability compared with oral delivery.

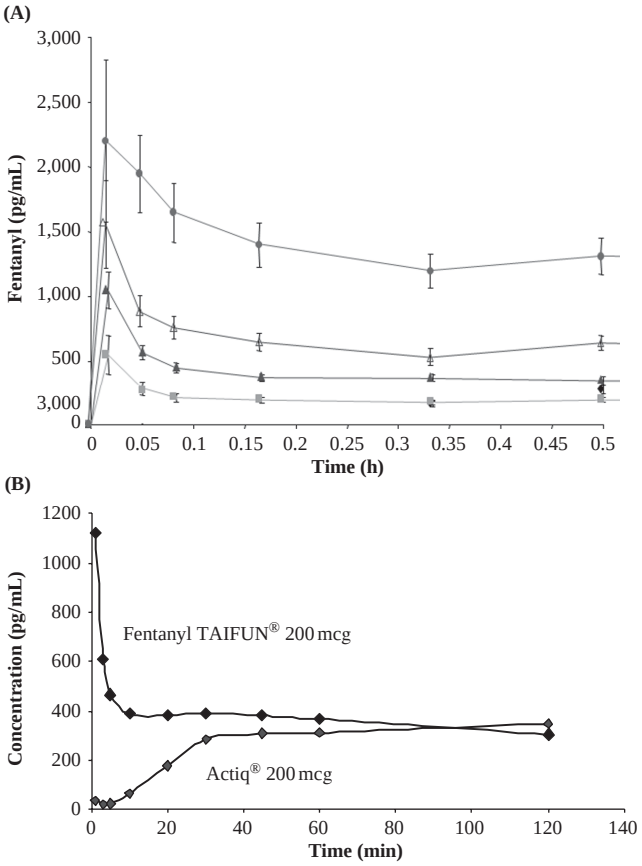

FIGURE 6. (A) Dose proportionality pharmacokinetic results from fentanyl TAIFUN® inhaler; 100 mcg (■), 200 mcg (▲), 400 mcg (Δ), and 800 mcg (•). (B) Comparison of the pharmacokinetic profiles for pulmonary delivery using fentanyl TAIFUN® 200 mcg and orally delivered Actiq® 200 mcg.

CONCLUSIONS

DPIs overcome many limitations of pMDIs, which has contributed to the rise in their popularity over the last few decades. However, there is a relationship between the powder formulation and the inhaler design making development of a DPI product expensive and time consuming. It is these formulation and design challenges that have limited the number of DPIs currently on the market. For the treatment of breakthrough cancer pain, the inhaler is an ideal drug delivery system that can provide a noninvasive route of administration and still maintain rapid drug delivery. The TAIFUN® DPI is a reservoir-based system that produces reproducible metered doses and uniform emitted doses with high respirable fractions. In vivo studies have demonstrated a rapid onset of action (T_{max}=1 min) and high bioavailability can be achieved indicating pulmonary delivery of fentanyl citrate is ideal for breakthrough cancer pain management therapy.

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