

# DELIVERY PERFORMANCE OF DIHYDROERGOTAMINE MESYLATE (DHE) USING THE BREATH SYNCHRONIZED, PLUME CONTROLLED TEMPO™ INHALER (BSPCI)

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## INTRODUCTION

There are approximately 35 million migraine sufferers in the United States, with an incidence of 18% female and 6% of the male population<sup>1,2</sup>. There are similar rates of incidence in Europe<sup>3</sup>.

**Dihydroergotamine Mesylate (DHE)** is a well known migraine treatment that is currently administered orally (poor bioavailability), nasally (variable absorption, long time to peak plasma levels) or by injection (usually involves urgent attendance at ER or doctor's office).

The **Tempo™ BSPCI** (Figure 1) confers the following benefits to pulmonary drug delivery compared to existing pMDIs:

- ↑ **Emitted Dose (ED)**
- ↓ **Throat Deposition**
- ↑ **Fine Particle Dose**
- ↑ **Fine Particle Fraction (FPF)**
- ↑ **Dose to Dose Consistency**
- ↑ **Fast Speed of Action**



Figure 1: Tempo BSPCI

## TEMPO™ BSPCI BACKGROUND

**Tempo** is designed to significantly enhance drug delivery compared to pressurized metered dose inhalers (pMDIs), and consists of two lead differentiating features:

### •Flow Control Chamber (Figure 2)

The *flow control chamber* manipulates flow of discharged plume to decrease droplet momentum and size, to allow propellant to evaporate, and to match plume velocity with the patient's inspiratory breath.

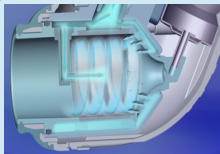


Figure 2: Air flow at start of inhalation

### •Synchronous Trigger (Figure 3)

The *synchronous trigger* automatically discharges drug at a set point in the patient's breath to reproducibly target the appropriate bio-space at the same point in the patient's inspiration cycle.

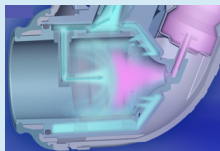


Figure 3: Plume control during canister discharge (immediately following synchronous trigger)

## MATERIALS AND METHODS

### (a) Product Development

•Particle engineered DHE microcrystals (Figure 4, volume median diameter, 2.9 μm) were formulated into aluminum canisters on a Pamasol filling line which was subsequently used for all development.

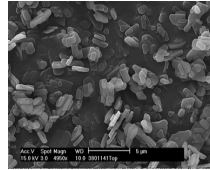


Figure 4: Engineered DHE microcrystals



Figure 5: **Left:** DHE formulation immediately post shaking and **Right:** 5 minutes post shaking (suspension remains loosely flocculated)

•Formulations were visually observed in pressure resistant glass bottles for suspension stability and canisters were gravimetrically tested for shot weight variation.

•Modular parts of the Tempo BSPCI were rationally optimized for the following parameters:

- Clogging Tendency:** orifice diameters: 0.008 to 0.012"
- Plume Shape:** high-speed photography
- Particle Size:** Malvern Spraytec; 200 ms data collection in flash mode, with USP induction port attached
- Particle Size Distribution:** 8-stage Andersen Cascade Impactor, operating at 28.3 Lmin<sup>-1</sup>
- Emitted Dose:** Dosing Unit Sampling Apparatus

•For *in vitro* testing, DHE was assayed using a validated HPLC method with detection at 210 nm in an acetonitrile/ phosphate buffer mobile phase.

### (b) Clinical Performance

•Clinical performance of DHE delivery from Tempo was tested in healthy human volunteers.

•An arm of the study (n=6) was designed to include a comparison of the standard 1 mg DHE IV slow bolus dose (3 min) vs. four DHE inhalations from Tempo (FPD, <4.7 μm = 0.22 mg/inhalation) in the same subjects (12 day washout between doses).

•Plasma samples were taken at 5, 10, 15, 30, 60, 90, 120, 180, 240 and 360 minutes.

•DHE was assayed from plasma with a fully validated liquid chromatography – tandem mass spectrometry (LC-MS/MS) analytical method.

## RESULTS

### (1) Formulation Development

Formulations of DHE in HFA propellant were **highly dispersible** and showed no tendency to agglomerate (Figure 5). Thermal cycling (14 d) and accelerated temperature storage (3 mo) resulted in no change to **physical suspension stability** or **chemical stability**.

### (2) Aerosol Performance

Aerosol performance was improved by manipulating several device variables. Performance was studied in a variety of Tempo configurations by Cascade Impaction. Results are presented in Figure 6 which highlights the following key results:

- Throat deposition** was modifiable and reduced 78% relative to a reference actuator
- FPF was maximized** >1.8x in all Tempo configurations investigated

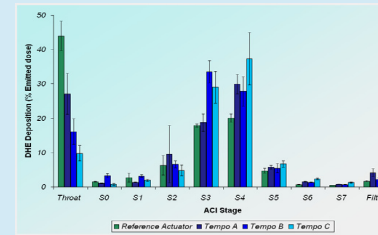


Figure 6: Aerosol Performance of the DHE formulation with a reference actuator and 3 Tempo device configurations. (Throat deposition was minimized in Tempo from 44.0% to 9.6% and FPF (<4.7 μm) was maximized from 45.4% to 83.1%, relative to the reference actuator.)

### (3) Device Consistency

Tempo devices were found to be consistent and met pharmacopoeial standards. Figure 7 displays ED consistency from shots 5-8 across 39 individual Tempo BSPCI devices. ED performance was found to be tightly distributed about the mean, highlighting consistency of performance.

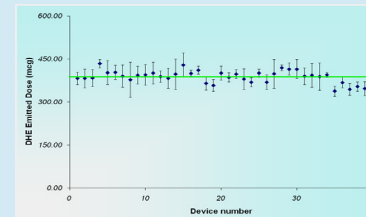


Figure 7: DHE emitted dose vs. device; Emitted dose shows a high level of consistency across 39 devices (n=4 actuations per device).

## RESULTS CONTINUED

### (4) Clinical Performance

DHE clearly displayed rapid absorption with a  $t_{max}$  of 0.2 hr following pulmonary administration. This compares favorably when evaluated against IV administration (Figure 8) as well as commercial intranasal DHE preparations that typically yield slower  $t_{max}$  values of 45 min, with clinical onsets of activity beginning ~30 min post-administration.

The  $t_{max}$  for the IV DHE dose was rapid (<5 min, first sampling timepoint, ~2 min after end of infusion) with similar  $t_{max}$  for pulmonary DHE when delivered by Tempo (4 puffs were inhaled with 20-40 seconds between puffs).

The  $C_{max}$  was significantly reduced with pulmonary DHE which may alter the side effect profile [reduction in dizziness, lightheadedness, and nausea (62.5% IV subjects vs. 16.7% inhaled)].

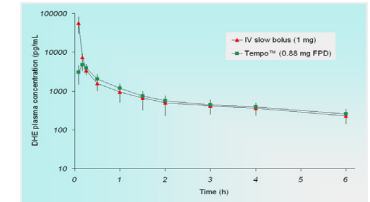


Figure 8: Intravenous (IV) and Inhaled (Tempo) plasma profile of DHE in healthy human volunteers (n=6, cross over).

Area Under the Curves (AUCs) for IV and inhaled were essentially equivalent after 0.2 hr, with the only difference being due to the plasma spike from the IV administration.

## CONCLUSION

The Tempo BSPCI provides a means of improving aerosol performance, which is highly relevant when delivering drugs for systemic administration where precise and consistent dosing and titration is often necessary. Tempo consistently improves dose to dose consistency within and between patients, reduces throat deposition, increases emitted dose, and increases both fine particle dose and fine particle fraction.



## REFERENCES

1. Stewart WF, Lipton RB, Celentano DD, et al. Prevalence of migraine headache in the United States: relation to age, income, race, and other socioeconomic factors. JAMA 1992; 267:64-69.
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3. Stewart WF, Shechter A, Rasmussen BK. Neurology 1994 Jun;44(6 Suppl 4):S17-23.