Micronized Benzodiazepines for Sublingual Applications Produced by Using Advanced Focused Ultrasound
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ABSTRACT SUMMARY
Novel formulations of the benzodiazepine drug Lorazepam that may be useful for nasal or sublingual applications have been developed using a micronized form of the API produced by applying a non-contact, isothermal, Advanced Focused Acoustics (AFA) sonication approach. We envision new formulations can outperform the ATIVAN sublingual tablets and after further optimization to display high bioavailability and rapid onset of action.

INTRODUCTION
Following a market introduction of the blockbuster drug Valium (diazepam) half-a-century ago, benzodiazepines (BZD) continue to maintain a strong status in psychopharmacology and are widely used clinically for the managements of conditions such as anxiety, insomnia, seizures, and alcohol withdrawal, with multiple BZD scaffolds of various potency approved by FDA over the years. They act selectively on the gamma-aminobutyric acid-A (GABA-A) receptors in the brain. It enhances a response to the inhibitory neurotransmitter GABA by opening GABA-activated chloride channels and allowing chloride ions to enter the neurons thus rendering them negatively charged and resistant to excitation.

The typical administration route for the BZD drugs is oral but they are also given IV, IM, and rectally. This is where Covaris AFA can play important role as cavitations itself are proven to sterilize the formulations i.e., self-sterilization is a possible mechanism. Lorazepam, one of the “classical” BZDs, is often used for treating acute anxiety. It is poorly soluble in water (solubility of ca. 0.1 mg/ml) and the typical time to reach a peak drug concentration in human plasma ranges from 90 to 120 min. Although the onset of action is faster, it requires a significant amount of time for a full effect of the drug to take place if IV or IM administration to be avoided. A slightly better outcome is demonstrated by the ATIVAN Sublingual Tablets, a commercial sublingual form of Lorazepam formulated with lactose, magnesium stearate, microcrystalline cellulose and corn starch.1 A liquid oral form of the drug is marketed as Lorazepam Intensol and formulated with propylene glycol and PEG but has a limited acceptance due to safety concerns. There is a clear need to generate broader range of Lorazepam formulations for better management of multiple patient disease condition, especially in the area of epilepsy.2 We used Covaris AFA technology (Figure 1) to successfully micronize Lorazepam.

EXPERIMENTAL METHODS
Micronization of the (RS)-9-chloro-6-(2-chlorophenyl)-4-hydroxy-2,5-diazabicyclo[5.4.0]undeca-5,8,10,12-tetraen-3-one (Lorazepam) has been conducted using a Covaris S220x focused ultrasonicator. In a typical experiment in optimized conditions, 20 mg of the Lorazepam has been dispersed in 2 ml of DI water with 0.5 % lecithin, placed in a thick walled 12x24 mm round-bottom tube and sonicated at 5°C over a period of 15 min at the maximum energy output (80 W nominal). The particle size distribution has been measured on a Malvern Mastersizer Model S particle size analyzer equipped with a small sample attachment. The suspension has been lyophilized
on a VirTis lyophilizer. Stability of the drug has been confirmed by HPLC. The resulting powder has been also formulated in a tablet form (50 mg weight tablets containing 1 mg dose of Lorazepam) using an ingredient matrix similar to the ATIVAN Sublingual Tablet formulation.

RESULTS AND DISCUSSION

As a result of Lorazepam milling, the particle size has been reduced to D(v, 0.5) of 0.96 microns (Figure 2). The milling can also be conducted using a multi-pass and single-pass flow integrated Covaris systems (Figures 3, 4) to allow for the process scale-up and manufacturing of the larger batches of the material.

In order to verify stability of the drug, we assayed the material before and after processing by HPLC and confirmed an absence of the degradation products. Microscopic studies as well as thermal analysis by TGA and DSC revealed no apparent phase transitions of Lorazepam, too. We successfully incorporated micronized material into a tablet form with lactose, microcrystalline cellulose, corn starch, and magnesium stearate. The advanced formulations to include solubility enhancers and bioadhesive ingredients to facilitate intranasal and sublingual delivery are under investigation.

CONCLUSION

Novel formulations of the sublingual micronized forms of Lorazepam may be attractive for future development. They hold promise to show improved PK profile in animal models with shortened time to reach the peak concentration in plasma and early onset of action. It will be clinically relevant for treatment of acute anxiety, insomnia, muscle spasms and other conditions. Advanced Focused Acoustics could potentially be applied to develop poorly water-soluble benzodiazepines into new products.

REFERENCES