Aquestive®

Advancing medicines.
Solving problems.
Improving lives.

Case Study
Overcoming solubility and permeability challenges

OUR QUEST

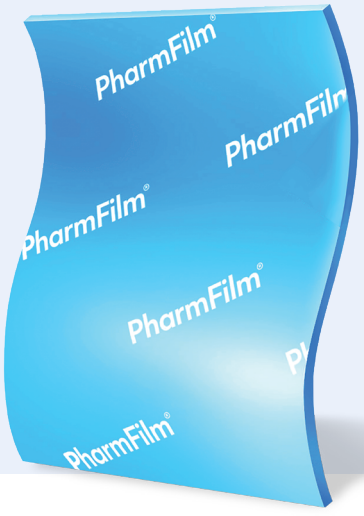
To provide meaningful clinical and therapeutic advances for patients with seizure clusters and their caregivers

The Background

In the United States, 1.2 million epilepsy patients suffer from uncontrolled breakthrough seizures.[1]

Diazepam is a benzodiazepine rescue treatment prescribed to patients to help interrupt a pattern of increased seizure activity, known as seizure clusters.[2]

Aquestive® Therapeutics recognizes the need for an oral formulation of diazepam and is leveraging its proprietary PharmFilm® technology to develop a potential oral treatment with convenient and comfortable dosing.



THE CHALLENGE

Given its Biopharmaceutics Classification System (BCS) class II status, the physical and chemical characteristics of the diazepam API presents some significant challenges to formulating a rescue therapy

Lingual film, pill, or tablet

While diazepam is highly permeable in the gastrointestinal tract, the slower rate of enteral absorption would not provide the rapid onset of action required.[3]

Sublingual delivery

The sublingual mucosa of the oral cavity is thin and permeable, allowing for rapid absorption and high bioavailability.[4] But placement under the tongue may be problematic for patients and caregivers due to the clenched teeth that may occur during seizures.[3]

Buccal delivery

The smooth, relatively immobile, and large surface area of the buccal mucosa provides a stable microenvironment for safe and easy administration and optimal mucoadhesion.[4] However, the thick nature of the buccal mucosa makes it less permeable than the sublingual mucosa.[4] To achieve the target product profile, Aquestive saw an opportunity to create a unique formulation leveraging PharmFilm® technology. The product in development has the potential to provide the rate of absorption, bioavailability, and onset of action necessary to treat acute episodes of seizure clusters.

TARGETED SITE OF ACTION

Aquestive's formulation experts selected the buccal mucosa as the targeted site of application to allow for proper administration and caregiver safety.

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SOLUTION

Aquestive developed a novel solvent system intended to enhance the solubility and permeability of the diazepam API that is currently under development

STEP 01 ▸ Formulation and Prototype Development

Aquestive's analytics and formulation specialists explored an extensive range of permeation enhancers and co-solvents, and conducted excipient compatibility and solubility testing to identify the most effective solvent system.

STEP 02 ▸ Ex-vivo Permeation Screening

≈8 weeks of ex-vivo permeation testing using excised porcine tissue was initiated to determine the ideal mix of ingredients to optimize solubility, permeability, and absorption and achieve the desired onset of action.

STEP 03 ▸ In-vivo Pharmacokinetic Testing

The solvent system was incorporated directly into the PharmFilm® technology polymer matrix. In-vivo testing with porcine colonies was conducted to optimize the matrix and achieve the target product profile necessary for clinical development and future commercialization.

STEP 04 ▸ Phase 2 Clinical Trial

Aquestive executed full scale up and tech transfer. A Phase 2 clinical trial, led by Dr. Allen Heller et al, was conducted in which diazepam buccal film was evaluated for safety, tolerability, and usability profile.[5,6]

"During acute seizure episodes, medications that are simple to administer, quickly absorbed, and fast-acting can make a meaningful difference in preventing clusters, preventing status epilepticus, improving safety, and allowing patients to return to normal activities more quickly. That's why, as an epileptologist, I believe a convenient and effective rescue treatment option, such as this buccal film formulation of diazepam, represents an important innovation with the potential to improve care and outcomes for many patients with refractory seizures."

– **Dr. Lawrence J Hirsch, MD**
Professor of Neurology
Chief, Division of Epilepsy and EEG
Yale Medicine

Scientific Expertise and Versatile Drug Delivery Technology

The expert analysts and formulation scientists at Aquestive take a drug-by-drug approach to determine how PharmFilm® drug delivery technology can be optimized to achieve a desired product profile and help improve the treatment experience.

Through the use of proprietary, FDA-approved permeation enhancers and a wide array of patented solvent systems, PharmFilm® technology can be customized to enhance bioavailability, absorption, and onset of action, which may improve the delivery of molecules with poor solubility, poor lipophilicity, and poor permeability.

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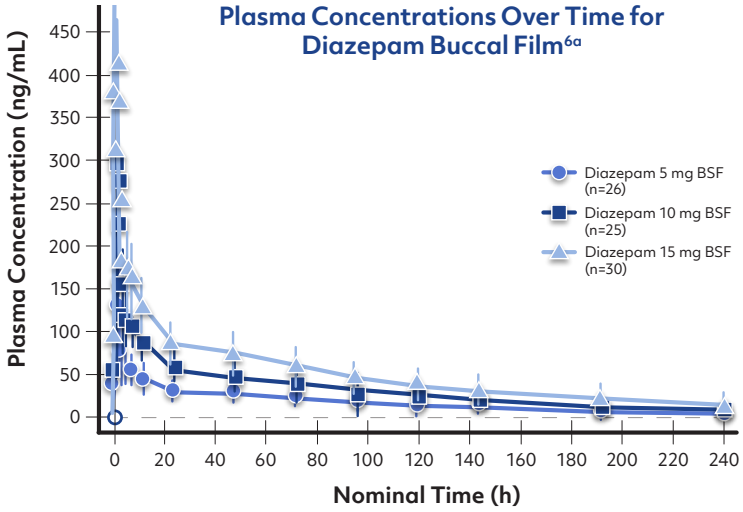
THE RESULTS

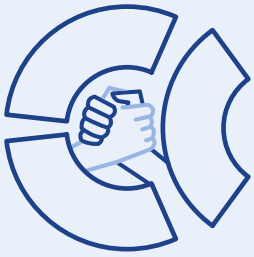
Pharmacokinetic Results of Diazepam Buccal Film Clinical Study[6,7]



- Diazepam buccal film contains diazepam in a dissolvable polymer-based matrix designed to maximize transport across the buccal mucosa[6]
- Successful absorption and achievement of therapeutic blood levels[7]
- There were no serious adverse events for this case study. Somnolence (5.7% overall) and dizziness (2.9% overall) were the most common adverse events classified as probably related to study drug[7]

"Overcoming the challenging properties of the drug and potentially creating the first transmucosal application is a result of our commitment to advancing medicines through novel drug delivery technology and scientific expertise."

– Stephanie Varjan
Sr. Formulation Scientist, Aquestive Therapeutics



How can we partner with you?

As worldwide leaders in oral film technology, we look to develop strategic partnerships that support our quest to advance medicines, solve problems, and improve lives. Reach out to discuss how we can put our scientific expertise and innovative drug delivery technology to work for you.

Joseph Crusco
Director, Business Development
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Libervant™ (diazepam buccal film) is an investigational drug being evaluated for use in children and adults with refractory seizures, who remain on stable regimens of antiepileptic drugs, to control bouts of increased seizure activity. The product profile, data from our trials, and related statements have not been approved by the FDA. Aquestive has received conditional acceptance of the use of this trade name, which is subject to final FDA review and acceptance.

[a]Performed under fasted conditions; N=29-33, Subjects 7 and 9 are non-responders to Diastat. Trial #162021. Single-dose, randomized, 4-period, 4-sequence, open-label crossover, single-site study comparing the pharmacokinetics of diazepam following single doses of the rectal gel and buccal soluble film formulations. All PK parameters values were dose-normalized to the 10 mg dose [7]

References: 1. Laxer KD, et al. *Epilepsy Behav.* 2014;37:59-70. **2.** Holsti M, et al. *Arch Pediatr Adolesc Med.* 2010;164:747-53. **3.** Cereghino JJ. Curr *Treat Options Neurol.* 2007;9:249-55. **4.** Mitul P, et al. *IRJP.* 2011;2:4-11. **5.** Jung C, et al. AES Poster. 2018. **6.** Heller AH, et al. American Academy of Neurology. 2018. **7.** Rogaswski MA, et al. AES Poster. 2018.