A Novel, Modified-Release Drug Delivery Technology Containing Amphetamine and Methylphenidate Ion-Exchange Complexes

Lori Dansie, PhD, MBA, Thomas R. King, MS, MPH, Judith C. Kando, PharmD, BCPP, Antonio Pardo, MD
Tris Pharma, Inc., Monmouth Junction, NJ

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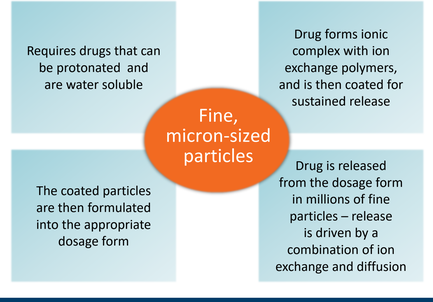
LD, JCK, TRK, and AP are all employees of Tris Pharma, Inc., the developer of LiquiXR®, Dyanavel® XR, Quililvant XR®, and QuilliChew ER®

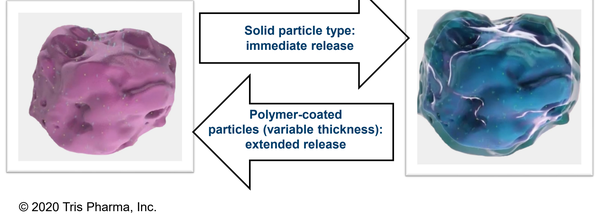
Rationale

- ADHD guidelines recommend treatment with a psychostimulant (typically, amphetamine or methylphenidate).
- Ideal stimulant coverage for most patients provides an immediate effect within 1 hour of dose followed by an extended duration of efficacy (up to 12-14 hours post-dose). To facilitate this need, the LiquiXR drug delivery technology was developed.
- LiquiXR complexes any protonated, water-soluble active drug product to an ion-exchange resin particle. A portion of these particles is then coated with an aqueous, pH-independent polymer designed to provide sustained release of drug product.
- The polymer coating applied to the ion-exchange resin particles is of varying thickness, allowing for extended release of active drug product while uncoated particles provide for immediate release of active drug product. The resulting release characteristics allow for customized, sustained release of active drug for up to 24 hours post-dose.
- The LiquiXR drug delivery technology has already been successfully utilized in the development of treatment options (liquid suspension and chewable tablet) that offer rapid absorption and sustained plasma levels after once-daily dosing: Dyanavel XR (amphetamine extended-release oral suspension; AMPH EROS), MEROS (methylphenidate for extended-release oral suspension, MEROS), and MPH ERCT (methylphenidate extended-release chewable tablets; MRCT). The studies and data supporting these products are summarized here.

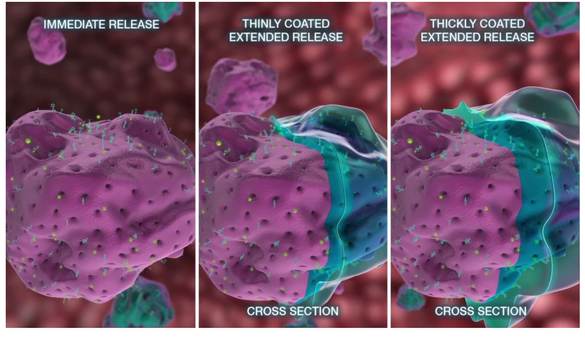
Scientific Basis for the LiquiXR® Drug Delivery Technology



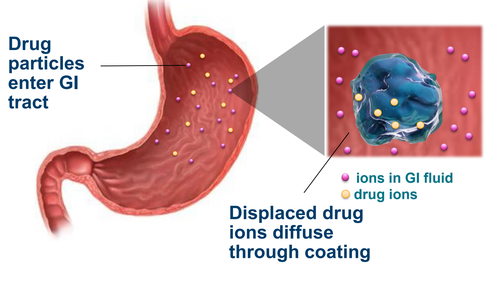
Particle Types



Mechanism of Release (MOR) of the LiquiXR Drug Delivery Technology

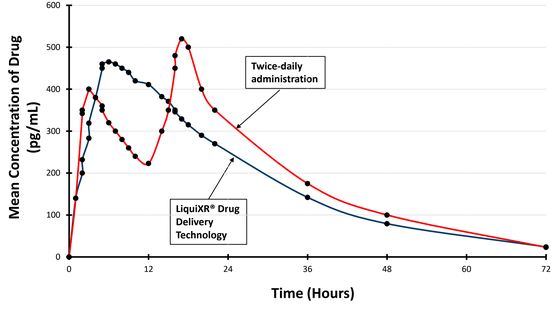


- The delivery system utilizes an ion-exchange resin that complexes with the drug through ionic binding.
- The combination of free drug, resin-bound uncoated drug, and resin-bound coated drug with variable thickness coating results in immediate-release and extended-release components
- A specific ratio of immediate-release and extended-release components gives each product its specific pharmacokinetic profile
- After drug release, the ion-exchange resin is excreted in the feces



- Active drug product is released from the dosage form in millions of particles, with the release driven by a combination of ion exchange and diffusion.
- The release of the drug from the drug-resin complexes occurs by a combination of **ion-exchange and diffusion.**
- The extended-release **coating of variable thicknesses slows the diffusion** of ions entering and exiting the complexes.

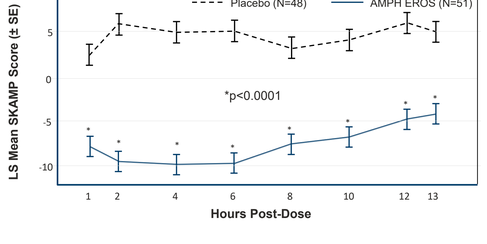
Resulting Pharmacokinetic Profile



Pharmacokinetic (time x concentration) profile comparing LiquiXR technology (blue curve) compared with twice-daily administration (shown in grey). The LiquiXR drug delivery system allows for customization of the release of a drug to obtain its desired sustained release profile.

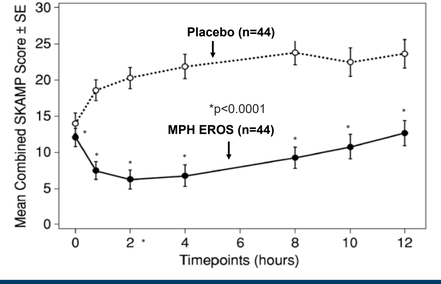
Amphetamine-Extended Release Oral Suspension (AMPH EROS)

- The efficacy of AMPH EROS was established in a Phase 3, placebo-controlled laboratory classroom study. In that study, attention-deficit/hyperactivity disorder (ADHD) symptoms in children on an optimized dose of amphetamine (range 10-20 mg/day) were statistically significantly improved compared with symptoms in children treated with placebo
- For children treated with AMPH EROS, onset of effect was demonstrated by statistically significant decreases in SKAMP Total Score compared with placebo at 1 hour after dosing (see Figure below), and efficacy was observed through 13 hours post-dose. The effect size was comparable to effect sizes demonstrated for other psychostimulants tested in studies using a similar design.
- The efficacy data reported for AMPH EROS provides an excellent example of the potential utility and clinical application of the LiquiXR® drug delivery technology for other active drug products requiring an immediate-release and extended-release profile.



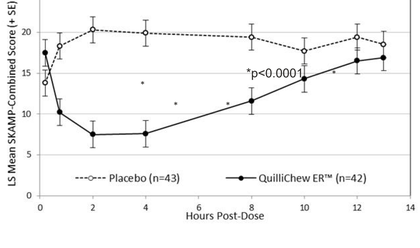
Methylphenidate-Extended Release Oral Suspension (MEROS)

- The efficacy of MPH EROS was investigated in a randomized, double-blind, placebo-controlled, crossover design in a laboratory classroom setting in which 45 subjects aged 6-12 years with ADHD were treated for 4-6 weeks with MPH EROS to optimize dose, then randomized to 2 weeks of double-blind crossover treatment.
- Efficacy was established using the SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) rating scale. Efficacy was assessed at multiple time points post dose (0.75, 2, 4, 8, 10, and 12 hours).
- SKAMP-C scores were found to be statistically significantly improved at all time points measured.



Methlphenidate Extended-Release Chewable Tablets (MPH ERCT)

- The efficacy of MPH ERCT was evaluated in a laboratory classroom study conducted in 90 pediatric subjects (ages 6 to 12 years) with ADHD. The study began with a 6-week open-label dose optimization period followed by a double-blind treatment. The dose could be titrated weekly in increments of 10 to 20 mg until a therapeutic dose or the maximum dose of 60 mg/day was reached.
- At the end of the double-blind treatment period, attention and behavior was measured using the SKAMP.
- The SKAMP-Combined score, measured at 0.75, 2, 4, 8, 10, 12, and 13 hours post-dose during the laboratory classroom day at the end of the double-blind treatment period, was used to assess the primary and the key secondary efficacy parameters. The primary efficacy endpoint was the average of treatment effects across all the time points as specified above during the classroom day. QuilliChew ER also showed improvement over placebo at 0.75, 2, 4, and 8 hours post-dosing.



Summary

When utilized in the delivery of psychostimulant medications for ADHD, the LiquiXR drug delivery technology provides for an immediate release followed by extended-release profile that demonstrated efficacy in treatment of ADHD for these patient populations, with an acceptable safety profile.