AUSTINPx™

PHARMACEUTICS / MANUFACTURING

Case Study

Using KinetiSol™ Technology to Improve an Abandoned Prostate Cancer Medication

Introduction

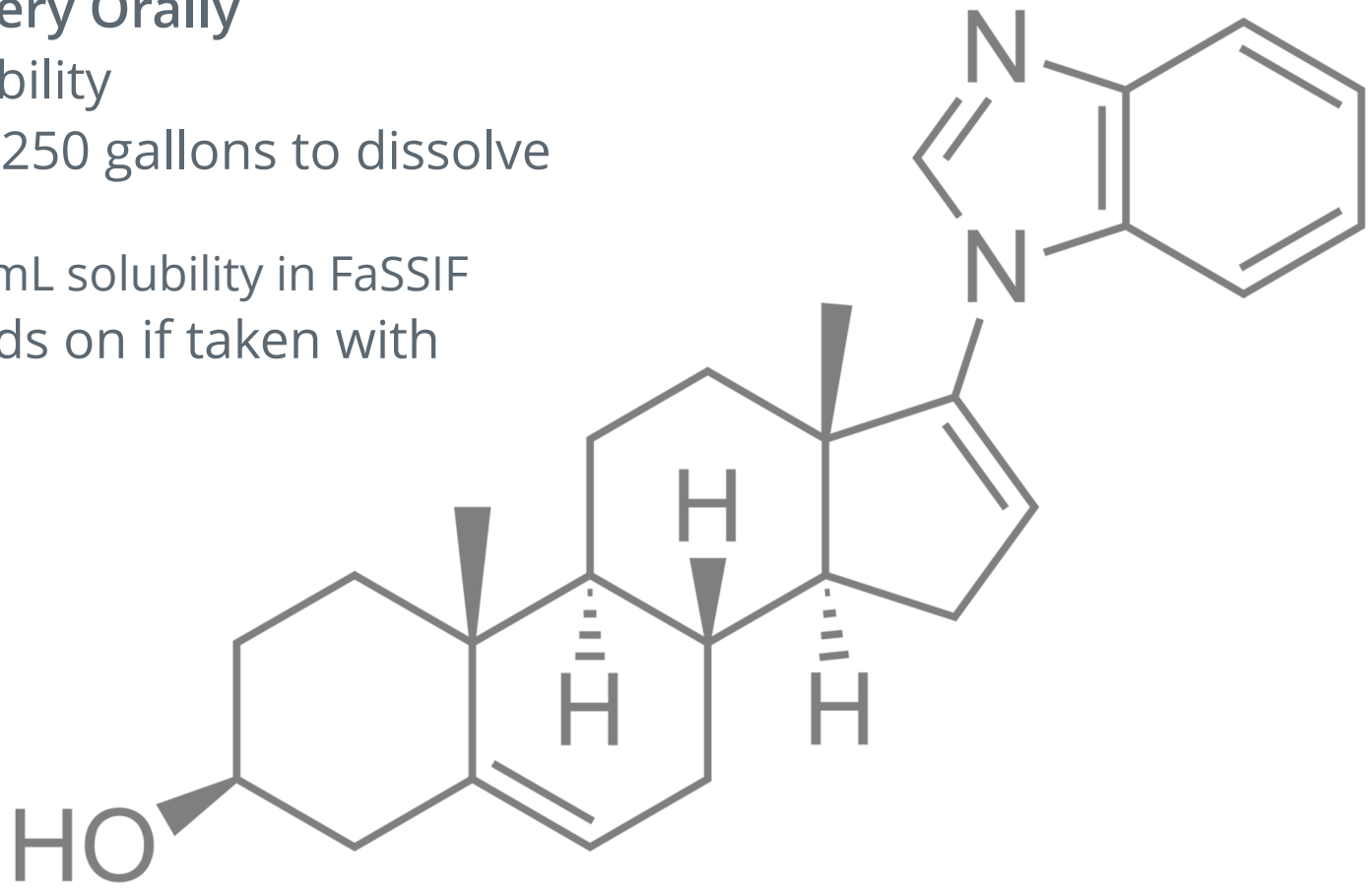
Galeterone, a novel prostate cancer candidate treatment, was discontinued after a Phase III clinical trial due to lack of efficacy

- Formulated as a Spray Dried Dispersion (SDD)
- Large dose of 2550 mg (6 capsules daily)
- Despite increased bioavailability of SDD formulation Galeterone failed in Phase 3 Clinical Trial due to poor efficacy
- AustinPx reformulated as a KinetiSol Solid Dispersion (KSD) and increased in vivo exposure by 2x

Galeterone Specific Challenges

Challenging Chemical to Delivery Orally

- Low and variable bioavailability
- Very low water solubility (>250 gallons to dissolve daily dose)
  - 2550 mg dose with 2 mcg/mL solubility in FaSSIF
- Oral drug exposure depends on if taken with food (food effect)



Prostate Cancer Background

In 2019, there were approximately 175,000 new cases of prostate cancer, contributing to 10% of male cancer-related fatalities.

The initial strategy for treating prostate cancer primarily focused on starving the cancer cells of testosterone and androgens, the substances that drive their growth. Treatment options included castration through either chemical or surgical methods, anti-androgen medications, and chemotherapy.

Despite a variety of medication choices, achieving a definitive cure for prostate cancer remained a challenging task. This challenge was compounded by the rapid development of drug resistance, complicating the effective management of the disease. Furthermore, numerous promising new drugs encountered significant obstacles related to their chemical properties, hindering their development and application in clinical settings.

Galeterone Clinical Trial Background

PHASE 1

Simple formulation – "Powder-in-Capsule" (PIC)

Large dose of 2600 mg (8 capsules daily)

Substantial food effect (meal increases exposure)

No major safety concerns

Successful Trial
Led to improved formulation

PHASE 2

Amorphous Solid Dispersion (Spray dried)

Large dose of 1700-3400 mg (4-8 capsules daily)

Minimal/no food effect

Signs of improved efficacy

Successful Trial
Promising efficacy

PHASE 3

Amorphous Solid Dispersion (Spray dried)

Large dose of 2550 mg (6 capsules daily)

Patient population had aggressive cancer

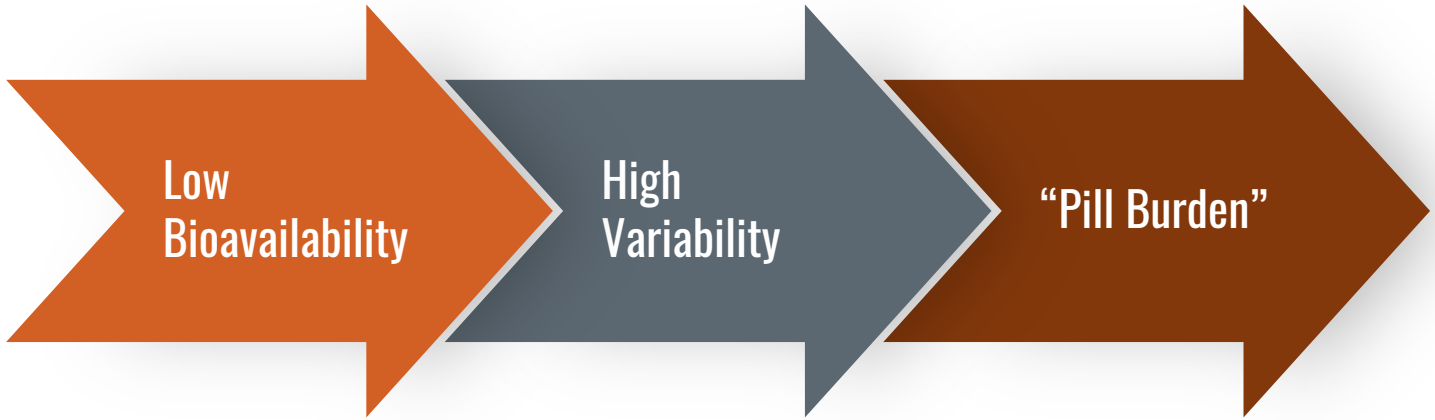
Low efficacy caused early trial end. Why?

Unsuccessful Trial
Ended early due to low efficacy

Challenges

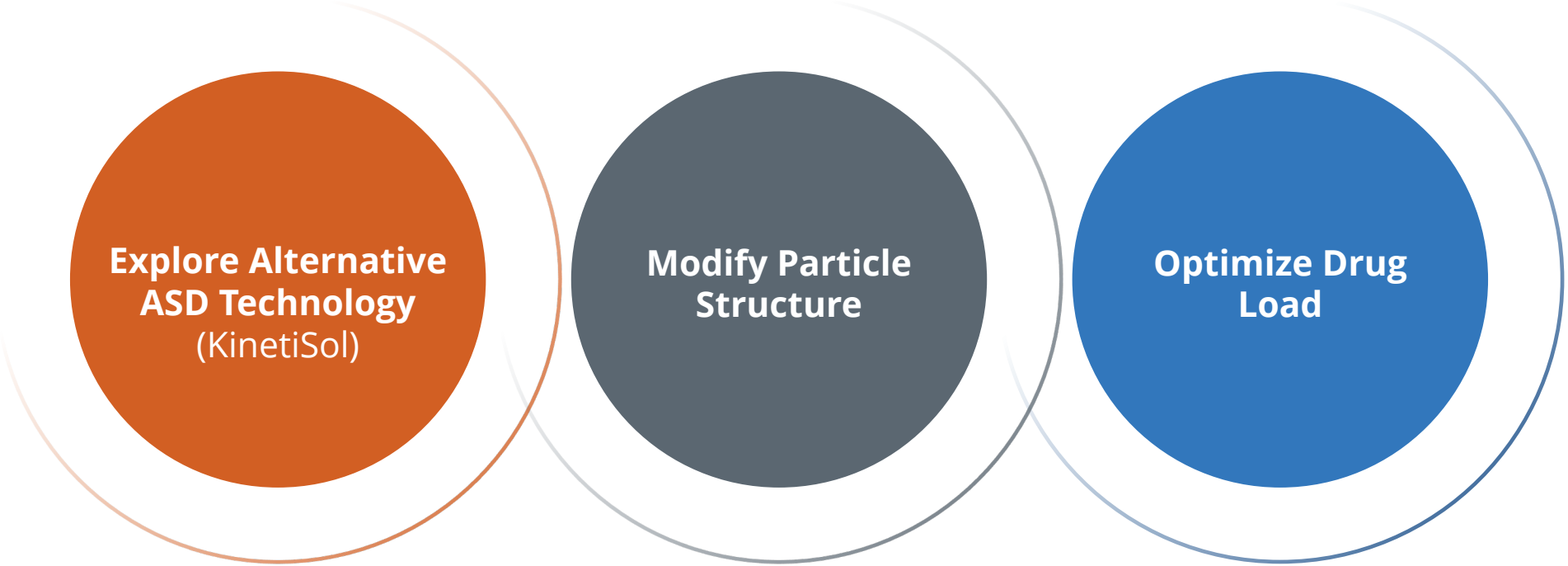
The majority of treatment candidate molecules have low bioavailability as a result of low solubility.

- Low bioavailability may diminish therapeutic effect
- Some patients do not achieve required exposure even with high dose
- High doses and frequent dosing intervals
- “Pill burden”: reduces patient compliance & worsens patient outcomes due to rigid or complex dosing regimens



Research Objective: Galeterone Reformulation

Would changing the ASD particle structure and lowering drug load improve clinical outcomes?



Solution

Improve Particle Structure

Optimized Particle Size and Density

Spray Drying makes small particles (~1-25 micrometers); often aids in dissolution but not always

- For this drug (dissolves in stomach) and polymer (only dissolves in intestines), larger particles are better
- SDDs have high surface area
- High apparent surface area

KinetiSol creates larger ASD particles, with higher density

- Maximize dissolved drug in the intestines (where absorption occurs)

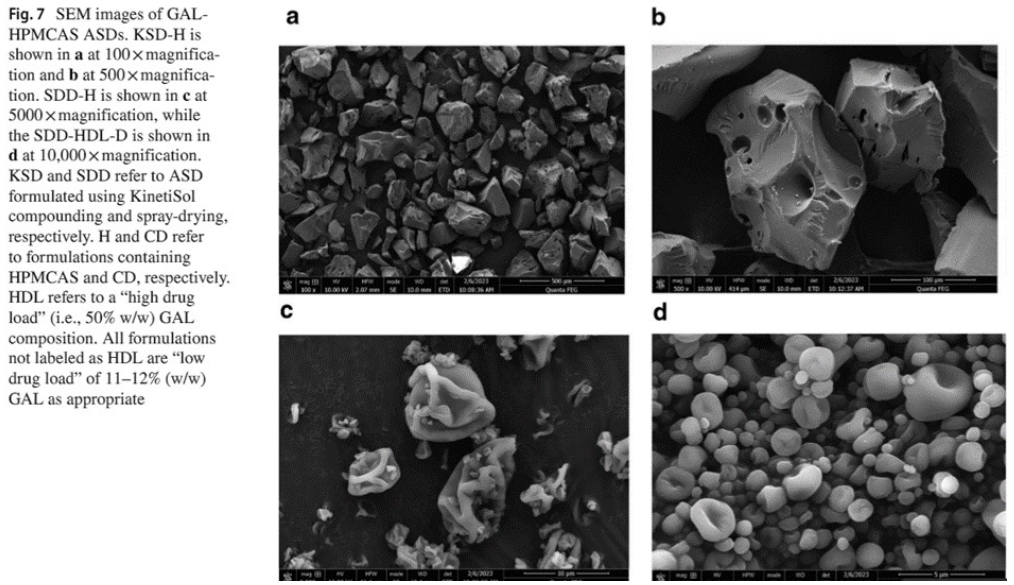


Fig. 7 SEM images of GAL-HPMCAS ASDs. KSD-H is shown in **a** at 100× magnification and **b** at 500× magnification. SDD-H is shown in **c** at 5000× magnification, while the SDD-HDL-D is shown in **d** at 10,000× magnification. KSD and SDD refer to ASD formulated using KinetiSol compounding and spray-drying, respectively. H and CD refer to formulations containing HPMCAS and CD, respectively. HDL refers to a "high drug load" (i.e., 50% w/w) GAL composition. All formulations not labeled as HDL are "low drug load" of 11–12% (w/w) GAL as appropriate

Spray Drying
(Small Particles)

KINETISOL®
(Larger Particles)

Solution

Optimize drug loading for higher performance

Optimized Particle Size and Density

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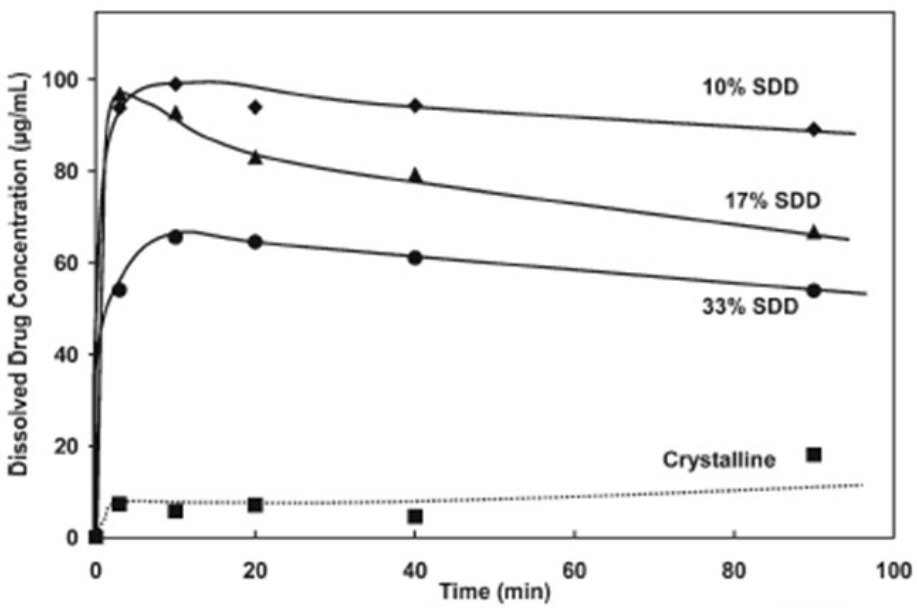
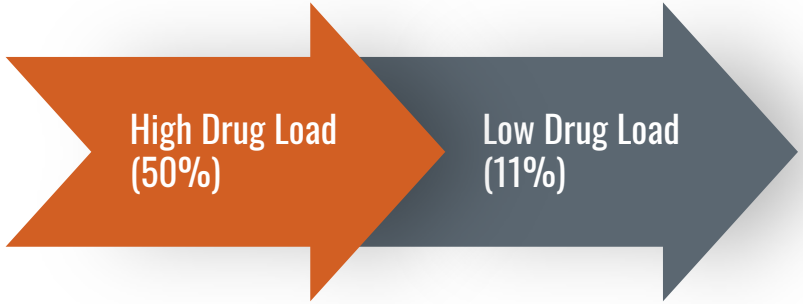
Curatolo et al. Pharm Res 26(6) 1419 - 1431





Dissolution Results: KinetiSol Outperforms Spray Dried ASD

Spray Dried High Drug Load (Clinical Formulation) - Poorest Dissolution

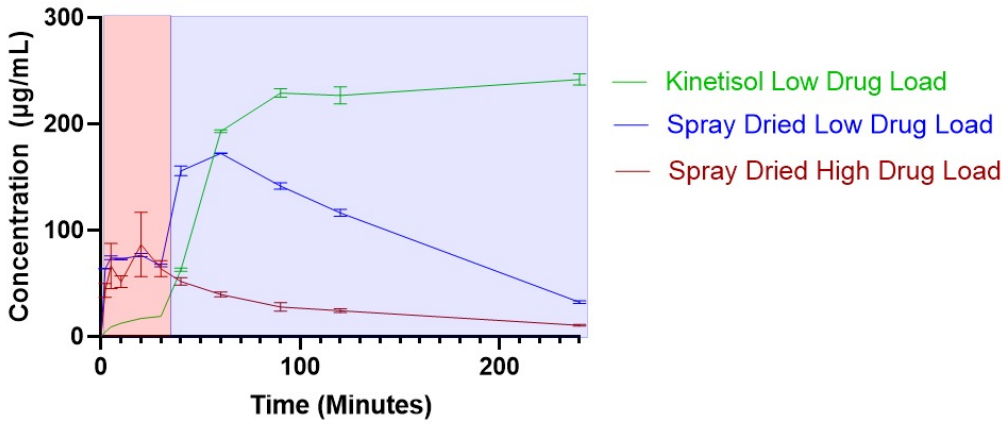
- Poor "Spring" and Poor "Parachute"

Spray Dried Low Drug Load – Intermediate Dissolution

- Good "Spring" but Poor "Parachute"

Kinetisol Low Drug Load – Best Dissolution

- Good "Spring" and Good "Parachute"
- Limits release in stomach to maximize intestinal concentrations



Lowering Drug Load (Spray Dried) has 3.7x dissolution area under the curve (AUC)

- Modest bioavailability increase, but no pill burden benefit

Lower Drug Load (Kinetisol) has 7.2x dissolution AUC

- Expected overall benefit in pill burden and bioavailability

Formulation	Relative Dissolution vs. Clin. Form.	Reduction in Drug Loading vs. Clin. Form. (i.e., amount of drug per unit ASD)	ASD Efficiency** vs. Clin. Form.
Kinetisol Low Drug Load	7.2x	4.5x	1.6
Spray Dried Low Drug Load	3.7x	4.5x	0.82
Spray Dried High Drug Load (Clin. Form.)	1	N/A	1

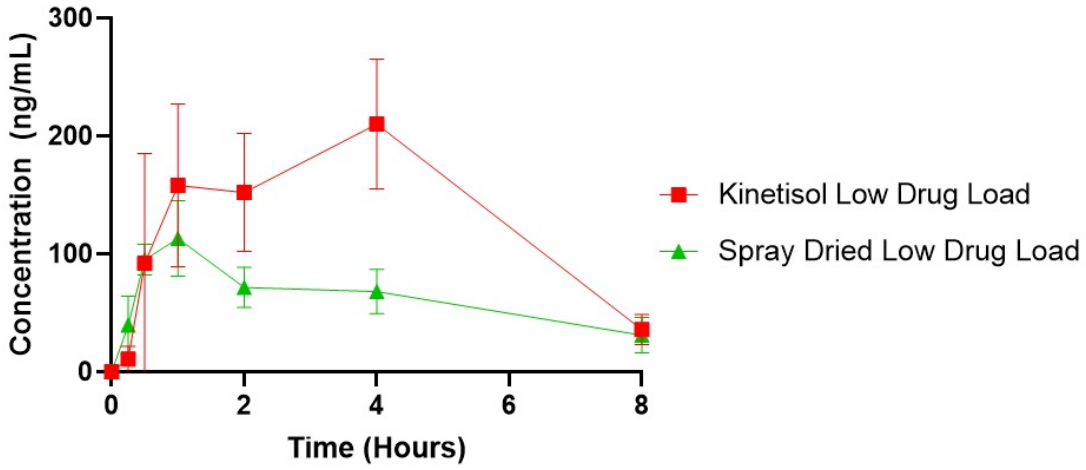
***ASD Efficiency – Drug exposure per unit weight of ASD*

PK Results

- **Dosed 50 mg/kg suspensions in 0.5% methylcellulose (pH 2) to rats (n=3)**
- **Lower drug load SD selected to make fair comparison**
- **KinetiSol outperformed equivalent SD (2.15x)**
- **KinetiSol's dense particles delayed drug release (Tmax) but doubled maximum concentration**

In vivo data 0.25-24 hours

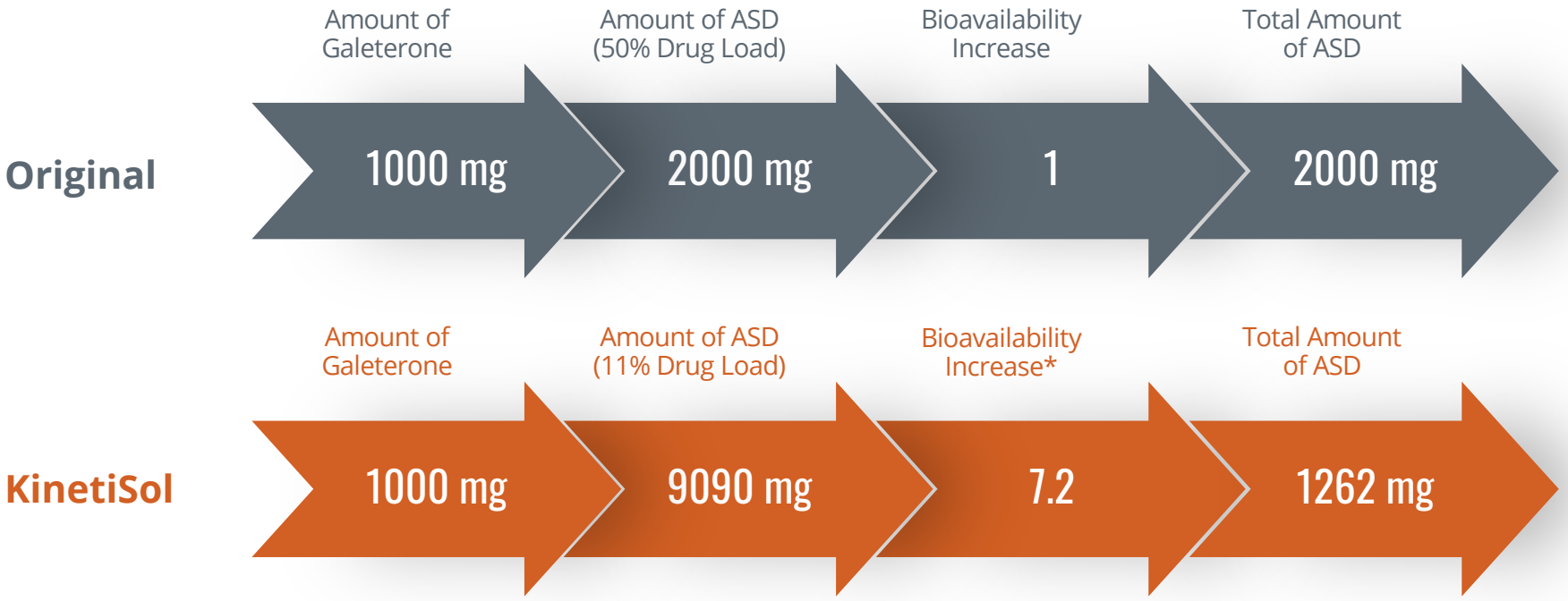
Formulation	Time at Maximum Concentration (hours)	Maximum Concentration (ng/mL)	Relative Bioavailability (versus 11-89 SDD)
Kinetisol Low Drug Load	4.00 +/- 0	210 +/- 55	**2.15**
Spray Dried Low Drug Load	0.83 +/- 0.29	113 +/- 31	1.00



Results: Reducing Pill Burden

Bioavailability and dissolution results suggest that by decreasing drug loading in ASDs, that pill burden can be decreased

Imagine we want the equivalent of 1000 mg of Galeterone Clinical Formulation but as Kinetisol Low Drug Load



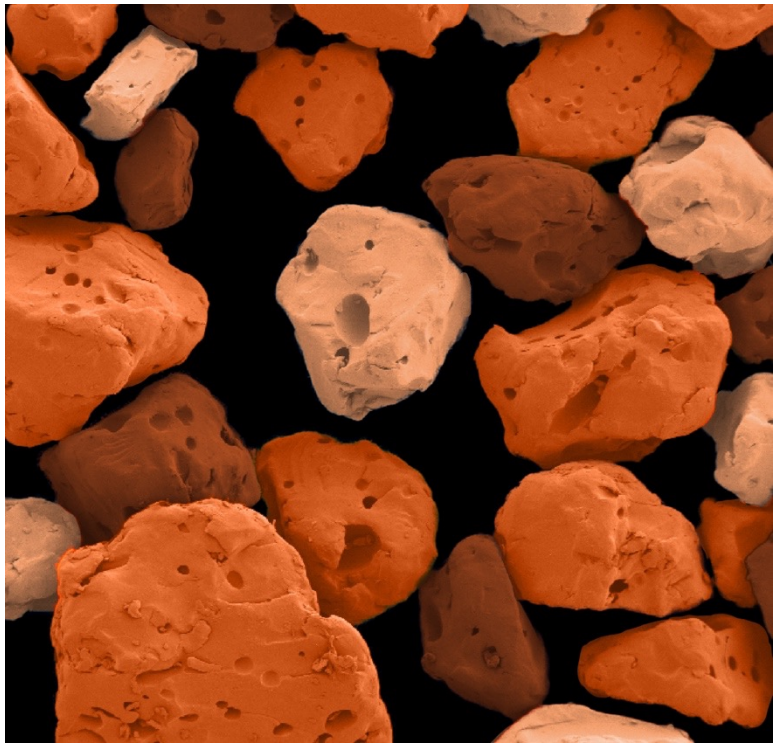
Same Exposure with 63% of Pill Mass

**Extrapolated from rat bioavailability and dissolution studies*

Conclusion

Galeterone Reformulation

1) **Lowering ASD drug load increases dissolution performance**
2) **KinetiSol Low Drug Load ASD had ~7x dissolution performance vs. Clinical Formulation**
3) **Optimized particle morphology through KinetiSol formulations improved "parachute" vs. Spray Dried**
4) **2x exposure in an in vivo rat study**
5) **Despite lower drug loading, KinetiSol formulation would be expected to have greater exposure per quantity of ASD given to patient → lower pill burden**



It is estimated that with improved exposure, those patients not achieving adequate exposure at higher doses would have demonstrated improved therapeutic response.

About AustinPx

AustinPx was founded to help developers realize the full potential of their drug candidates.

There are many obstacles to bringing a drug to market, including poor bioavailability and accelerated timelines. That's where we come in. Our client-centric approach is designed to simplify the complexity of outsourcing and our team of formulation, analytical and manufacturing experts work with you to overcome challenges and identify opportunities to do more, faster.

As the inventors of the KinetiSol™ Technology - a next generation amorphous solid dispersion (ASD) technology for poorly soluble APIs - we look to disrupt the ASD industry with its smaller footprint, broader design space, and greener processing solution.

AUSTINPx™

PHARMACEUTICS / MANUFACTURING

THANK YOU

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