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PHARMACEUTICS / MANUFACTURING

REDEFINING DRUG-LIKE PROPERTIES WITH KINETISOL®

Dave A. Miller, Ph.D.

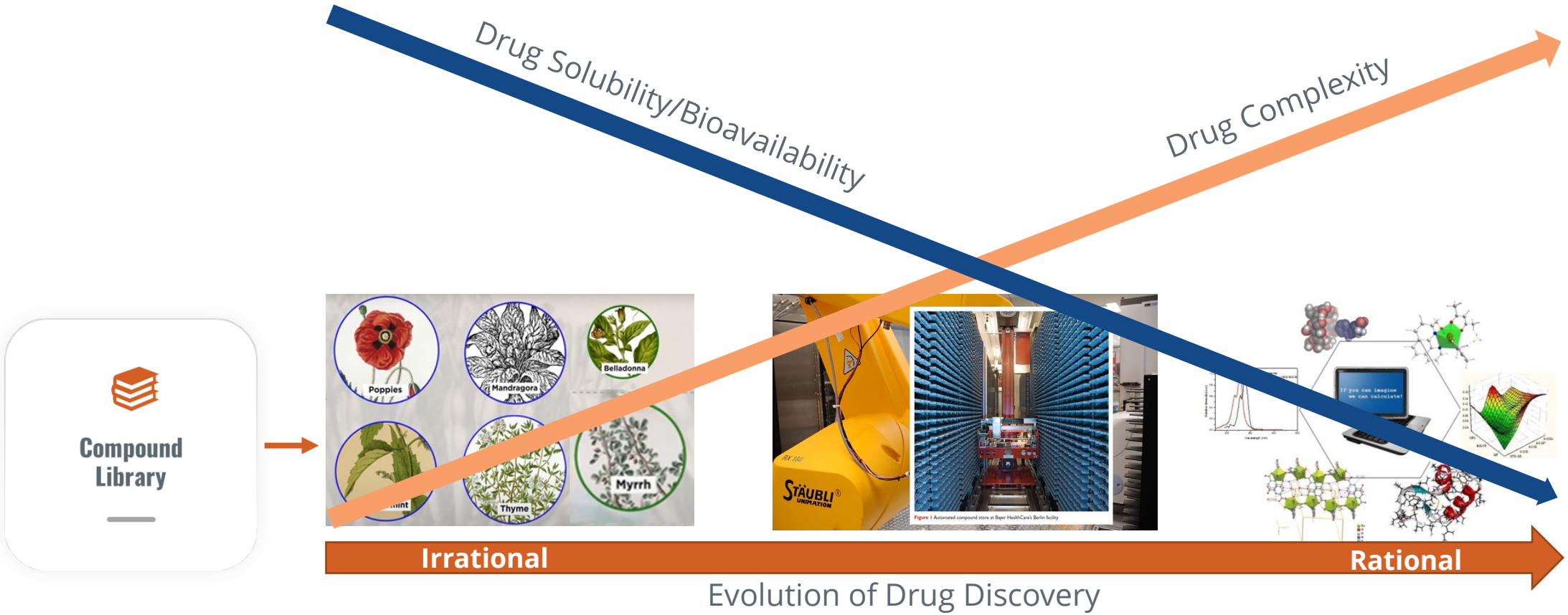
September 17, 2024

Basics of Drug Discovery

Simplified Schematic

The Evolving Solubility Problem

Molecular Complexity vs. Bioavailability



Rules for Compound Developability

Molecular Descriptors vs. Compound Properties

Lipinski's Rule of 5

- Molecular weight < 500 Da
- CLogP < 5
- Hydrogen bond donors ≤ 5
- Hydrogen bond acceptors ≤ 10
- *Rotatable bonds ≤ 10

Developability Limiters

- Aqueous insolubility
- Limited organic solubility
- High melting temperature
- High dose
- Low permeability/high efflux

Commercialized Ro5 Violators

Itraconazole

- X Molecular weight < 500 Da (705.6)
- X CLogP < 5 (5.66)
- ✓ Hydrogen bond donors ≤ 5 (0)
- ✓ Hydrogen bond acceptors ≤ 10 (9)
- X *Rotatable bonds ≤ 10 (11)

Ritonavir

- X Molecular weight < 500 Da (720.9)
- X CLogP < 5 (5.22, Chemaxon)
- ✓ Hydrogen bond donors ≤ 5 (4)
- ✓ Hydrogen bond acceptors ≤ 10 (6)
- X *Rotatable bonds ≤ 10 (18)

Commercialized Ro5 Violators

Venetoclax

- X Molecular weight < 500 Da (868.45)
- X CLogP < 5 (6.76)
- ✓ Hydrogen bond donors ≤ 5 (3)
- ✓ Hydrogen bond acceptors ≤ 10 (10)
- X *Rotatable bonds ≤ 10 (12)

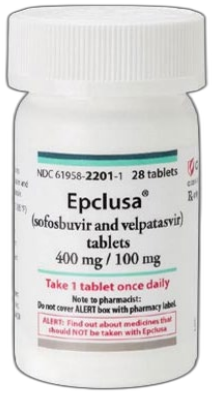
Pibrentasvir

- X Molecular weight < 500 Da (1113.2)
- X CLogP < 5 (5.95)
- ✓ Hydrogen bond donors ≤ 5 (4)
- ✓ Hydrogen bond acceptors ≤ 10 (10)
- X *Rotatable bonds ≤ 10 (17)

Commercialized Ro5 Violators

Valpatasvir

- X Molecular weight < 500 Da (838.02)
- X CLogP < 5 (5.39)
- ✓ Hydrogen bond donors ≤ 5 (4)
- ✓ Hydrogen bond acceptors ≤ 10 (8)
- X *Rotatable bonds ≤ 10 (13)



Ledipasvir

- X Molecular weight < 500 Da (888.99)
- X CLogP < 5 (5.98)
- ✓ Hydrogen bond donors ≤ 5 (4)
- ✓ Hydrogen bond acceptors ≤ 10 (6)
- X *Rotatable bonds ≤ 10 (12)

Approaches to Enhance Drug Solubility

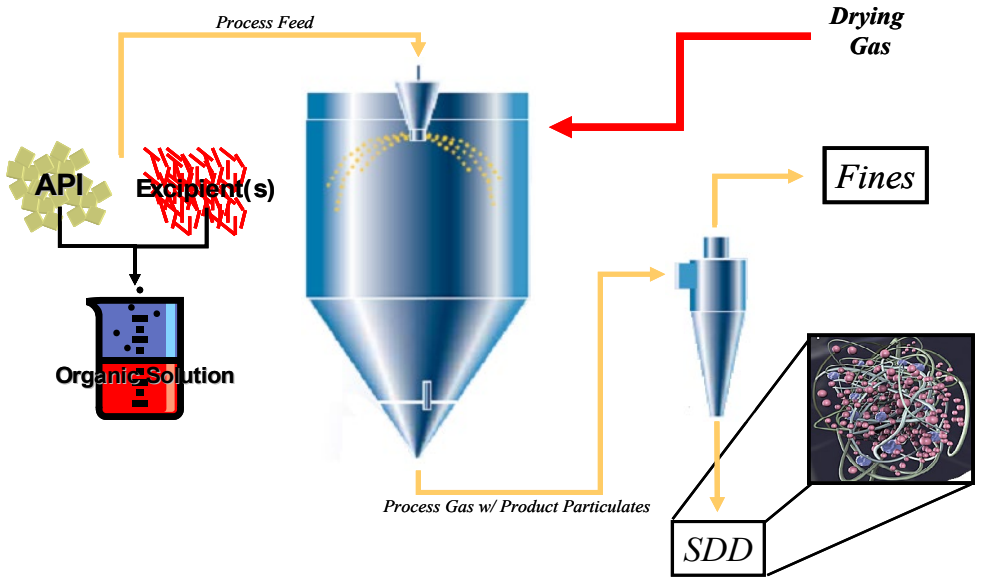
The Rise of ASDs

	TECHNOLOGY	PROBLEMS	RESULT
Liquid Forms	• Solution formulations (Lipids, PEGs, etc.) • Emulsion formulations (SEDDS derivatives)	**Limited by drug's solubility in vehicle**	**Not powerful enough for insoluble drugs**
Solid Forms	• Crystalline salts • Co-crystals	**Molecular properties not amenable or insufficient solubility improvement**	**Rarely the solution for insoluble drugs**
	• High energy polymorphs	**Instable or insufficient solubility improvement**	
	• Nanoparticles • Microcrystalline solid dispersions	**Addresses dissolution rate, not solubility**	
Amorphous Solid Dispersions (ASDs)	Spray Drying, Hot Melt Extrusion KinetiSol	**Most Broadly Applicable Solution for the Most Difficult Solubility Limitations**	

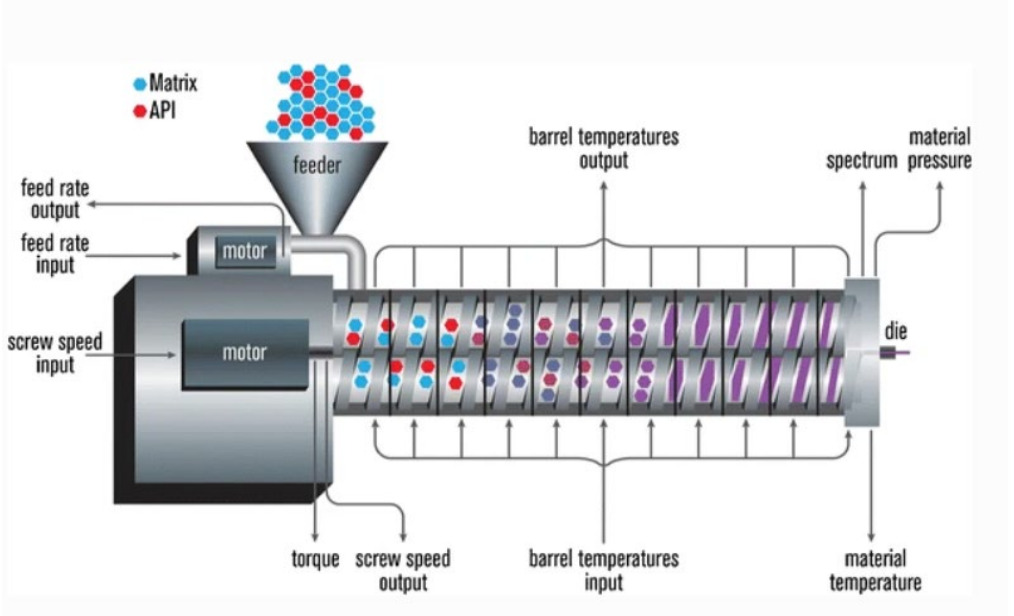
Spray Drying and HME Emerge

Leading ASD Technologies

Spray Drying

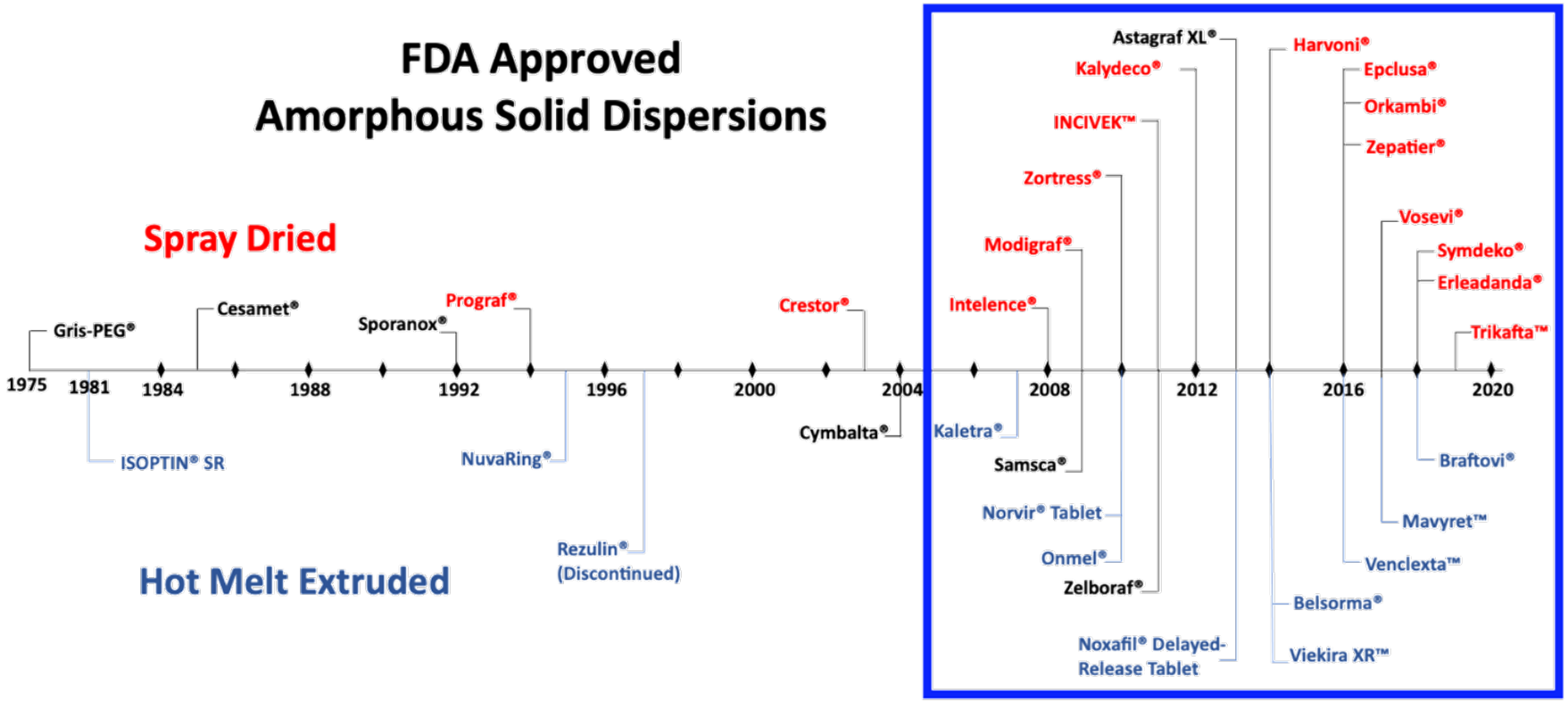


Hot Melt Extrusion



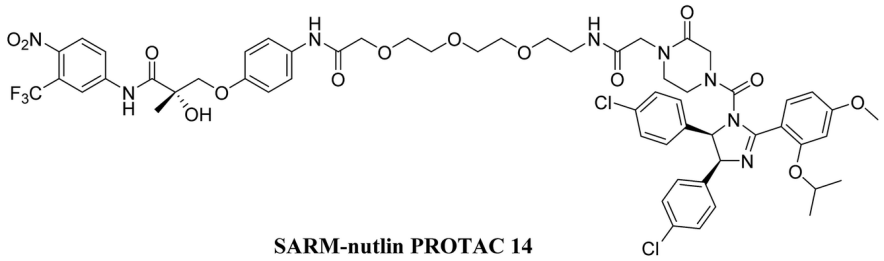
Surge of ASD Products

2008 - 2020



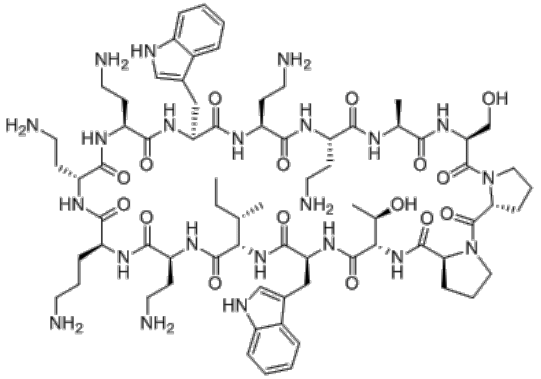
Current Expansion of the Druggable Space

Heterobifunctional

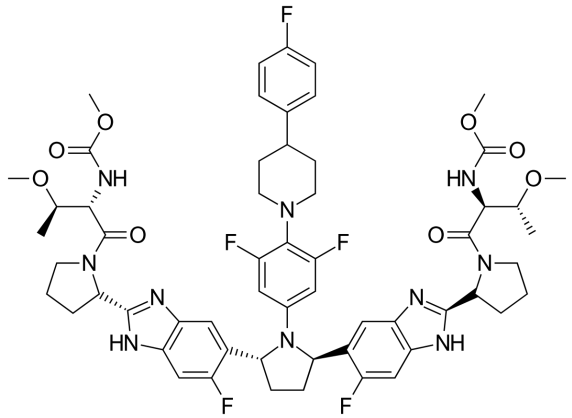


SARM-nutlin PROTAC 14

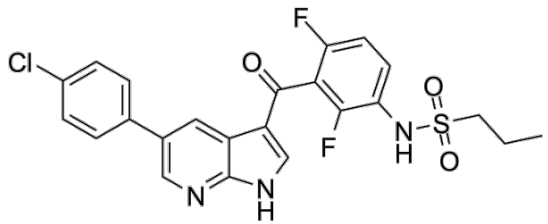
Macrocyclic



Peptidomimetic



Bick Dust



Vemurafenib/Zelboraf

Rule of 5 vs. Key Drug Properties

Rule of 5

- ✓ Molecular weight < 500 Da (489.9)
- ✓ CLogP < 5 (4.62)
- ✓ Hydrogen bond donors ≤ 5 (2)
- ✓ Hydrogen bond acceptors ≤ 10 (4)
- ✓ Rotatable bonds ≤ 10 (6)

Developability Properties

- X Aqueous insolubility (< 2 µg/ml FaSSIF)
- X Limited organic solubility (< 6 mg/ml)
- X High melting temperature (272 °C)
- X High dose (960 mg BID)
- X Low permeability/high efflux (2.9E-6)

Client Compound

Rule of 5 vs. Key Drug Properties

Rule of 5

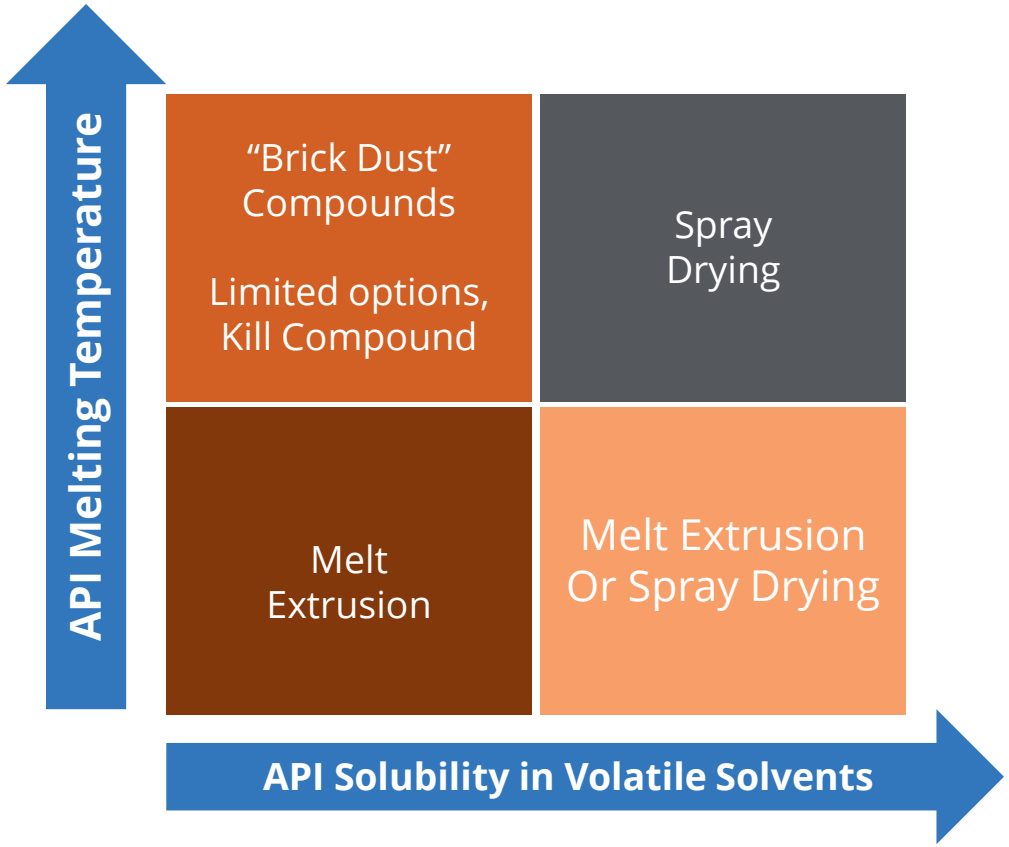
- ✓ Molecular weight < 500 Da (<400)
- ✓ CLogP < 5 (~3)
- ✓ Hydrogen bond donors ≤ 5 (3)
- ✓ Hydrogen bond acceptors ≤ 10 (3)
- ✓ Rotatable bonds ≤ 10 (<5)

Developability Properties

- X Aqueous insolubility (~ 1 µg/ml FaSSIF)
- X Limited organic solubility (< 3 mg/ml)
- X High melting temperature (>350 °C)
- X High dose (>600 mg BID)
- X Low permeability/high efflux (~1E-6)

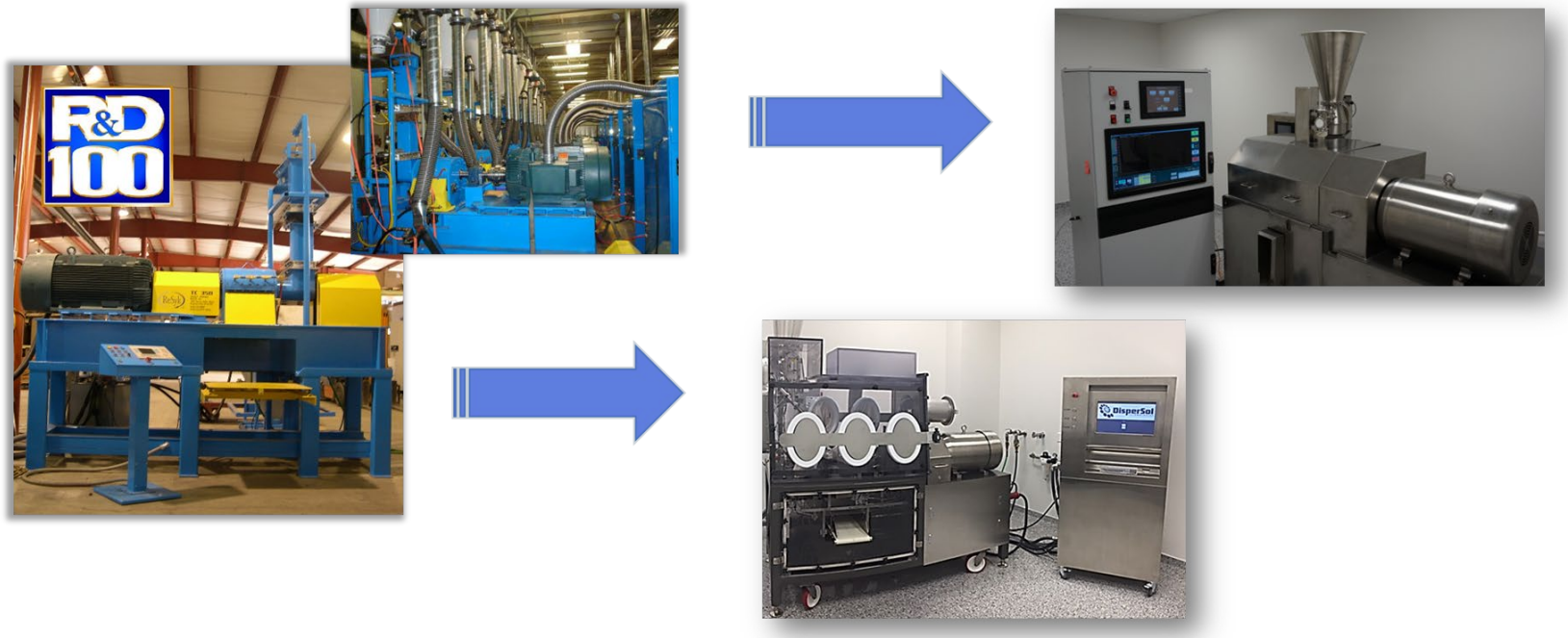
Rational Discovery into Undevelopable Chemical Space

Gaps in ASD formulation coverage



Origin of The KinetiSol® Technology

Plastic recycling and pharmaceutics collide



1997: Innovative processing technology commercialized to solve plastic recycling challenges

2007: KinetiSol is born when plastics processing technology is applied to polymeric drug delivery challenges

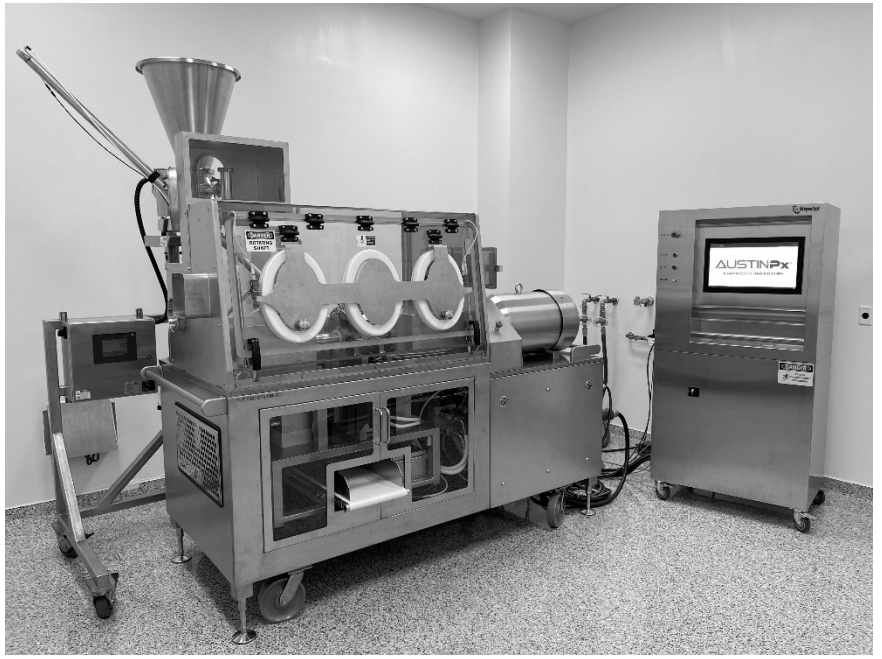
2008 – present: World-class engineering and pharmaceutical science applied to perfect the technology and formulation platform

KinetiSol Equipment: Research to Commercial Scale

Small Footprint Translates to Lower Operational Cost

Lab-scale KinetiSol Processing Equipment

- **Feasibility and rapid formulation screening**
- **Preclinical to small scale GMP** (7g - 200g/hr)



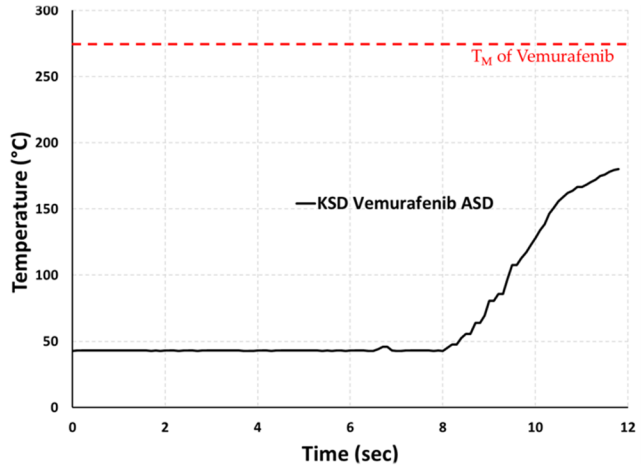
Manufacturing Scale KinetiSol Equipment

- **GMP manufacturing from FIH to Commercial**
- **1kg up to 40kg/hr**
- **PAT integration**

KinetiSol Process

Process

- Ultra high-speed mixing
- 10 – 20 seconds
- T_{max} < 200 °C
- No solvents
- Up to 40 kg/hr



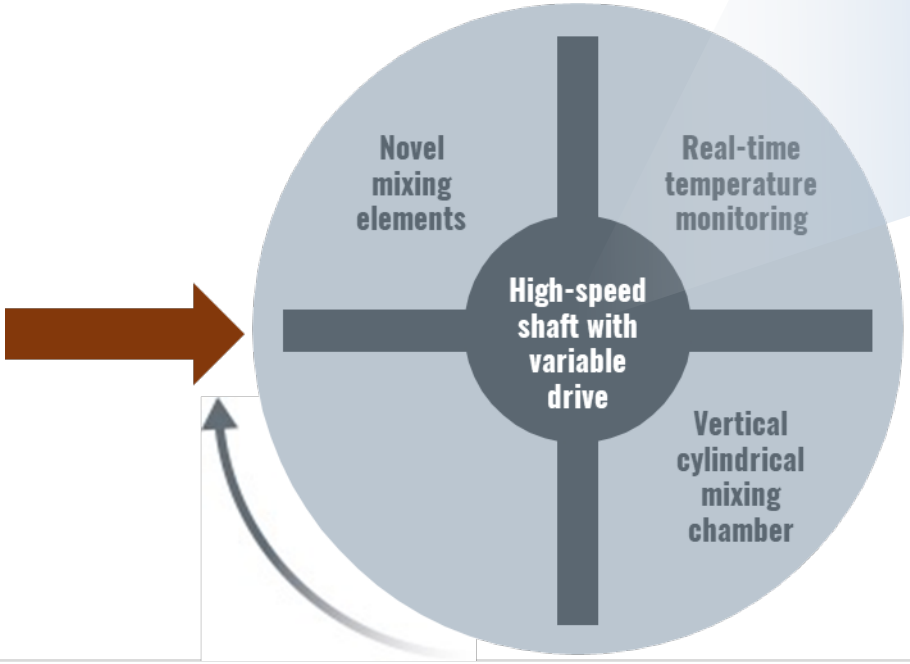
Input

Drug substance (API)

- Crystalline
- Insoluble
- Poorly bioavailable

Excipients

- Polymers
- Surfactants
- Stabilizers
- Solubilizers
- Innovative mixtures



Output

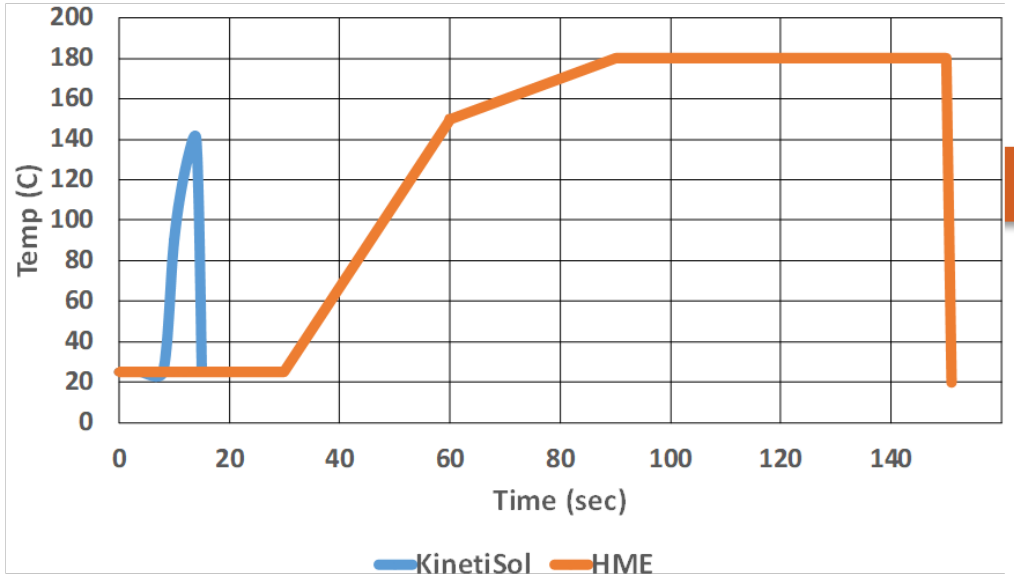
Amorphous Solid Dispersion Powder

- Soluble
- Bioavailable
- Stable
- Directly compressible
- Patentable

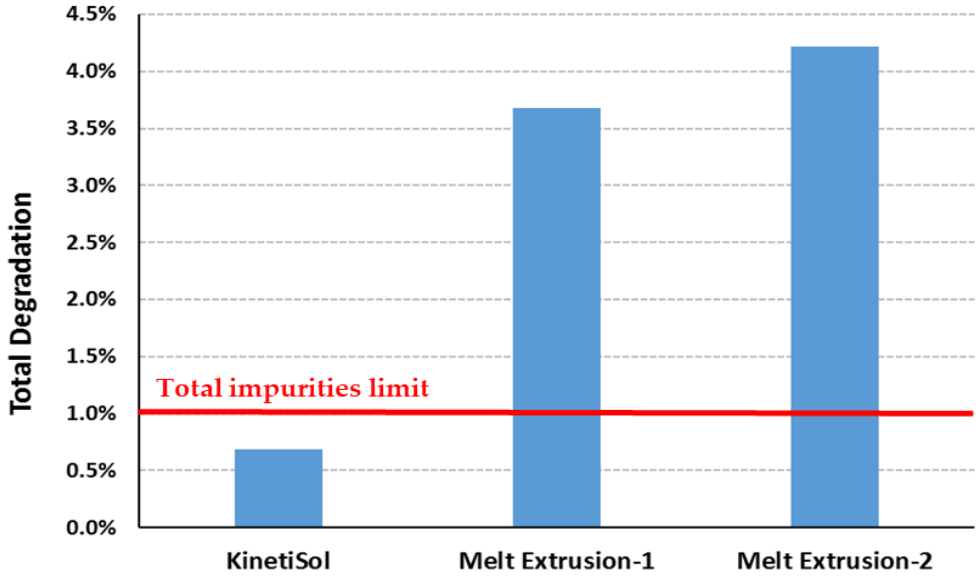
KinetiSol: Superiority to Hot Melt Extrusion

Reduced Time at Temperature = Lower Impurities

Temp vs. Time Processing Profiles



Total Impurities Comparison



KinetiSol's rapid processing time reduces time that the API is subjected to high temperatures and HME tailing residence time issues, therefore leading to lower total degradation and applicability to thermally labile drugs

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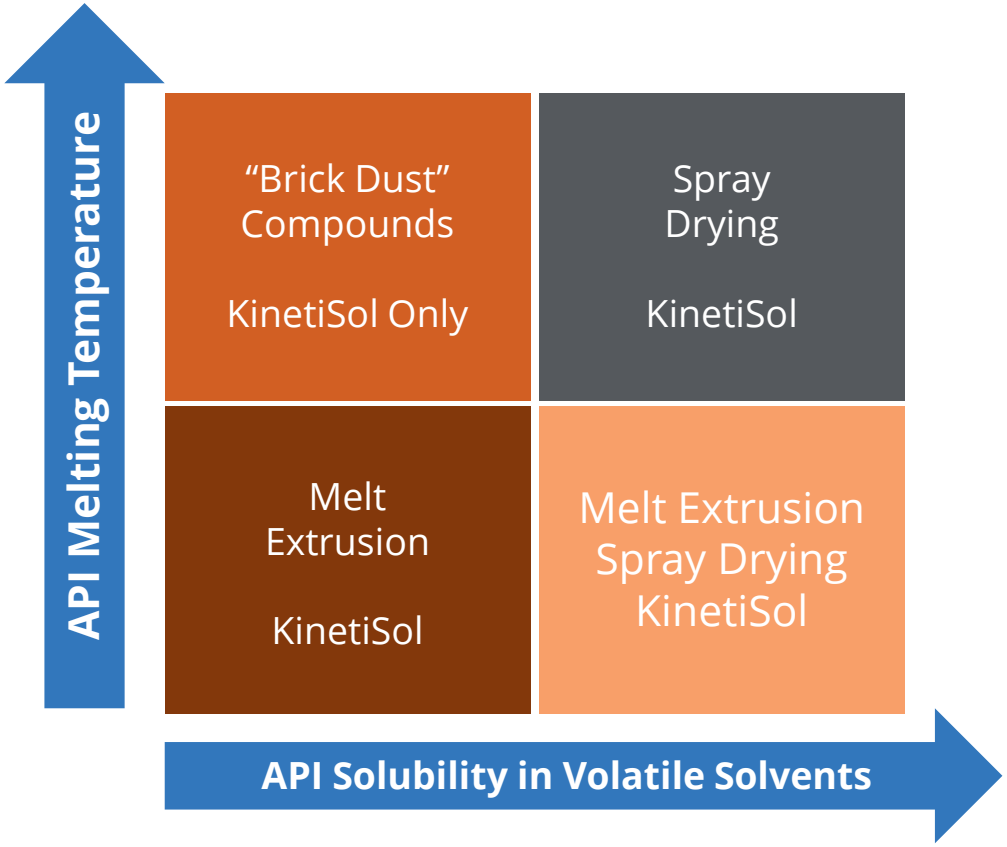
KinetiSol Fills in ASD Coverage Gaps

Emerges as the Technologically Superior ASD Process



Leading technology for brick dust

Thermal process w/ minimal heat

Non-solvent, low environmental impact

Largest formulation design space

KinetiSol Shifted the ASD Boundaries

No solvents

- Cost, toxicity, environment
- No common solvent requirement

Minimizes temperature + time

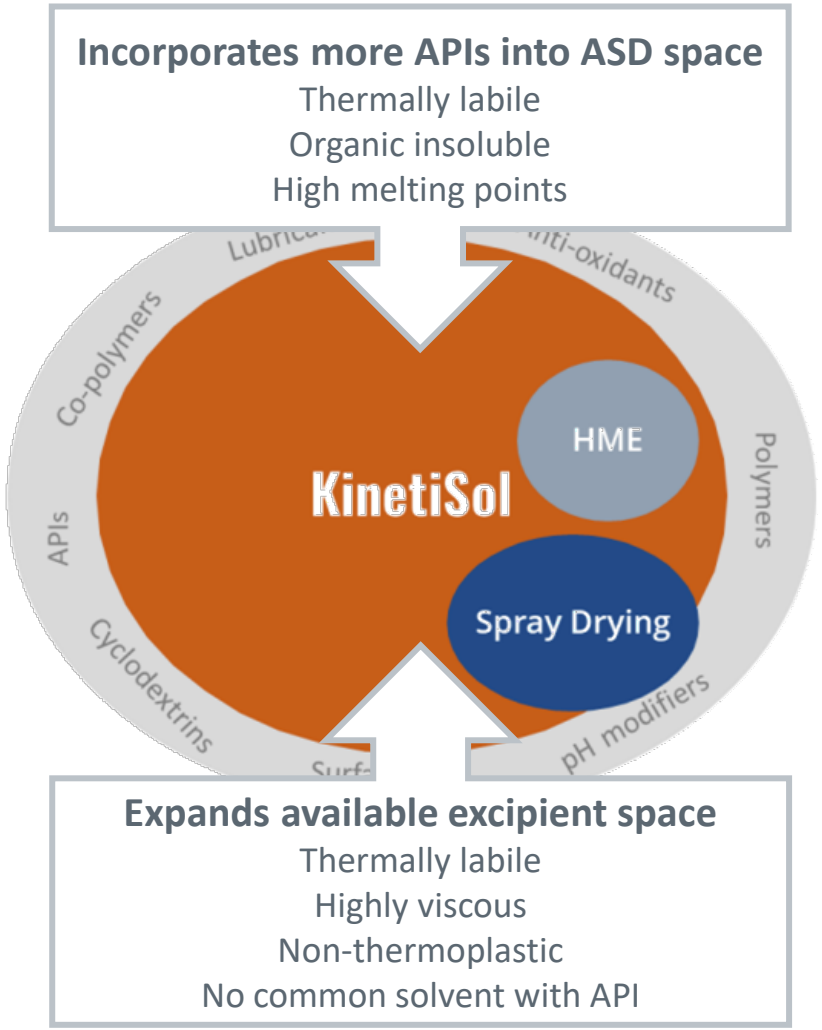
- Mitigates thermal degradation
- ASDs independent of drug melt temp

Much wider formulation space

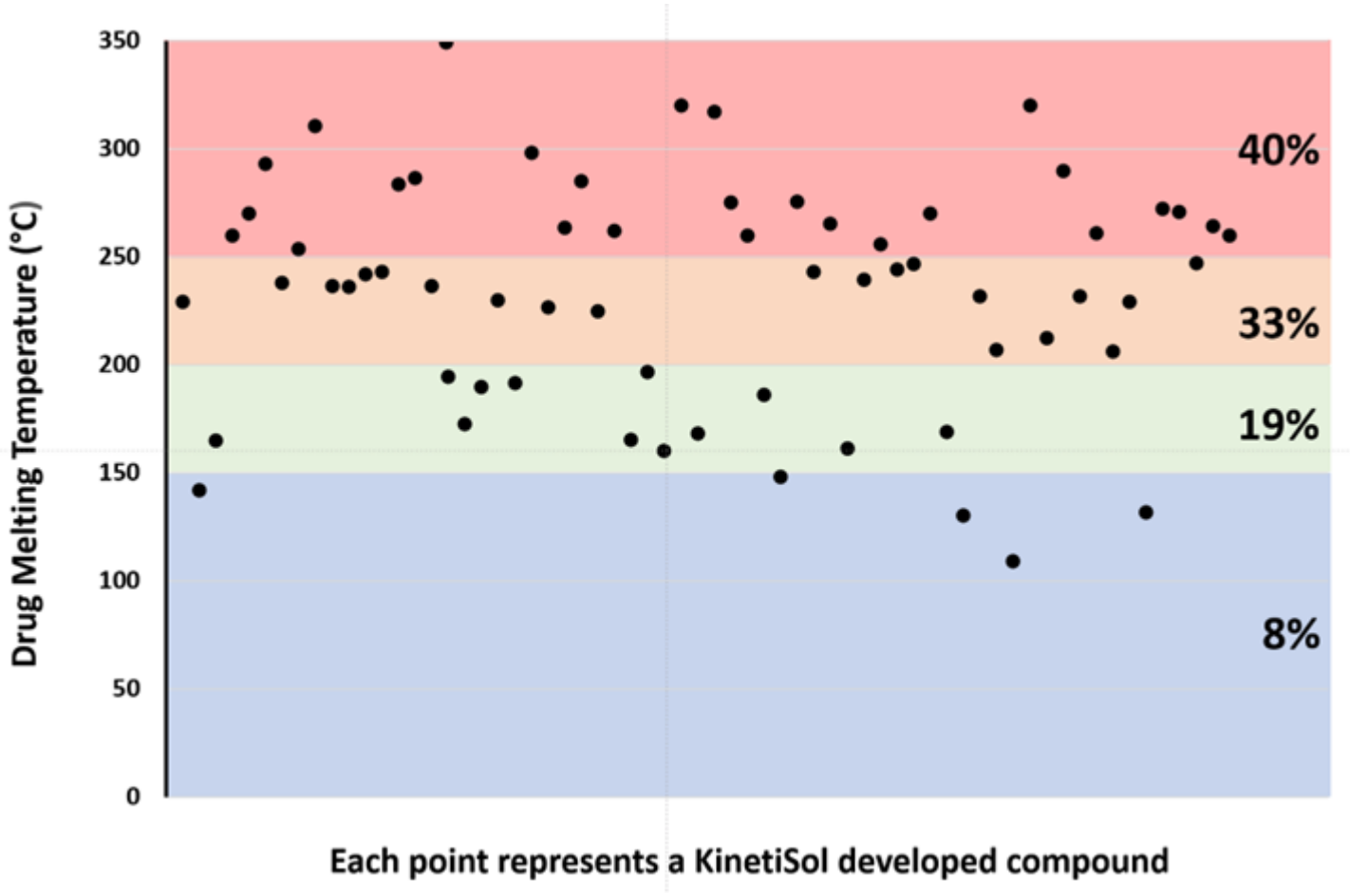
- Improved performance and product design
- Exclusivity generating IP

Complete molecular mixing

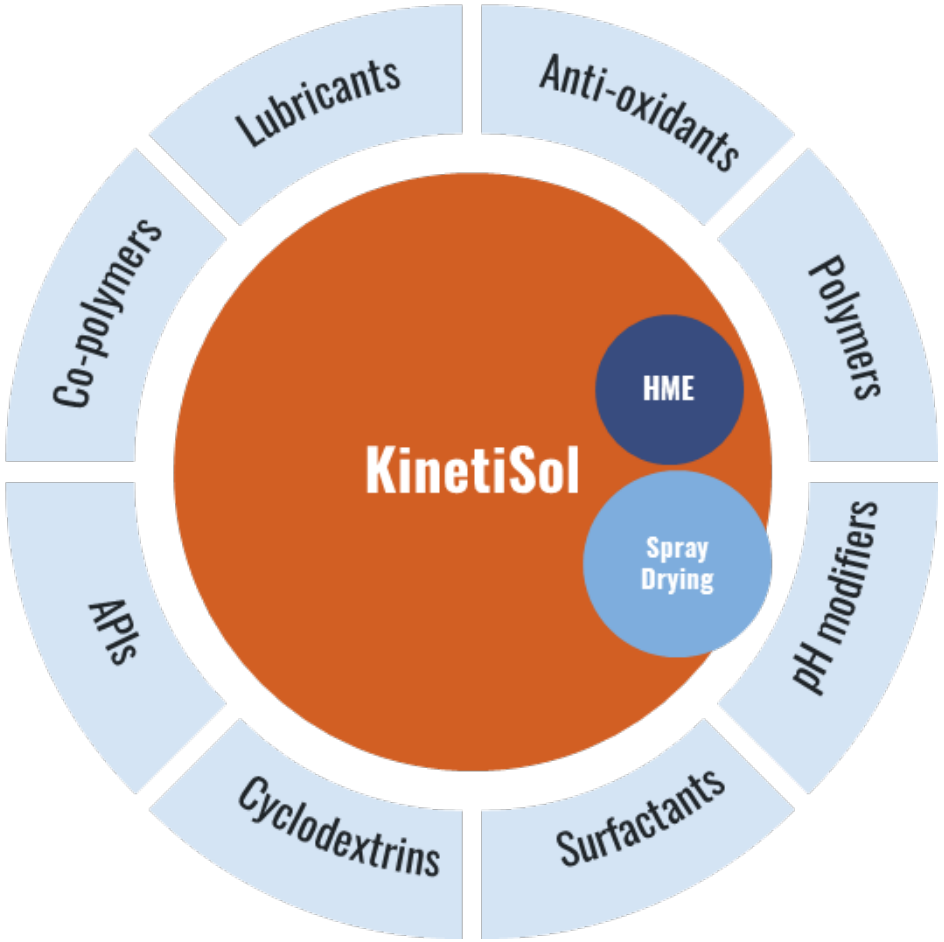
- Superior performance and stability



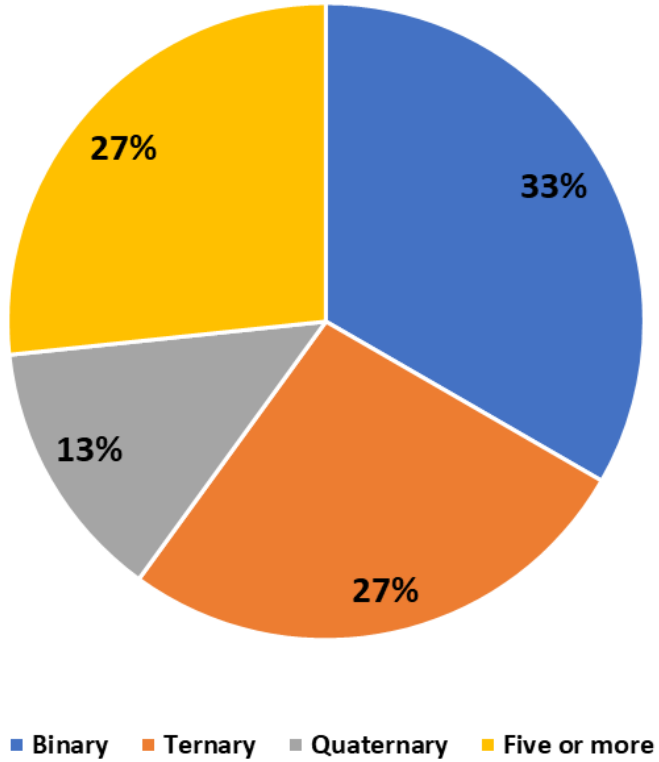
KinetiSol Development History by Melting Temperature



Greater Formulation Options = Better ASD Products



Analysis of clinical stage KinetiSol drug products by ASD components (n = 15)



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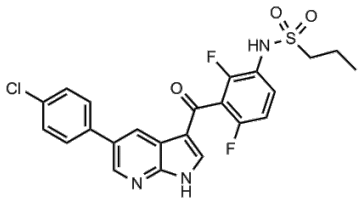
MOLECULE ENABLEMENT CASE STUDIES



KinetiSol Processing of Vemurafenib

A Comparative Evaluation to Solvent Controlled Precipitation

AAPS PharmSciTech (© 2018)
DOI: 10.1208/s12249-018-0988-1

CrossMark

Research Article

Theme: Applications of KinetiSol Dispersing for Advanced Amorphous Solid Dispersions
Guest Editor: Dave A. Miller

Improved Vemurafenib Dissolution and Pharmacokinetics as an Amorphous Solid Dispersion Produced by KinetiSol® Processing

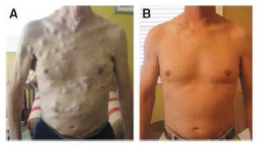
Daniel J. Ellenberger,[1,2,3] Dave A. Miller,[1] Sandra U. Kucera,[1] and Robert O. Williams III[2]

Zelboraf® vemurafenib

Roche

Genentech
A Member of the Roche Group

Vemurafenib (BRAF)
Approved in 2011 for Metastatic Melanoma



Before Therapy Week 15

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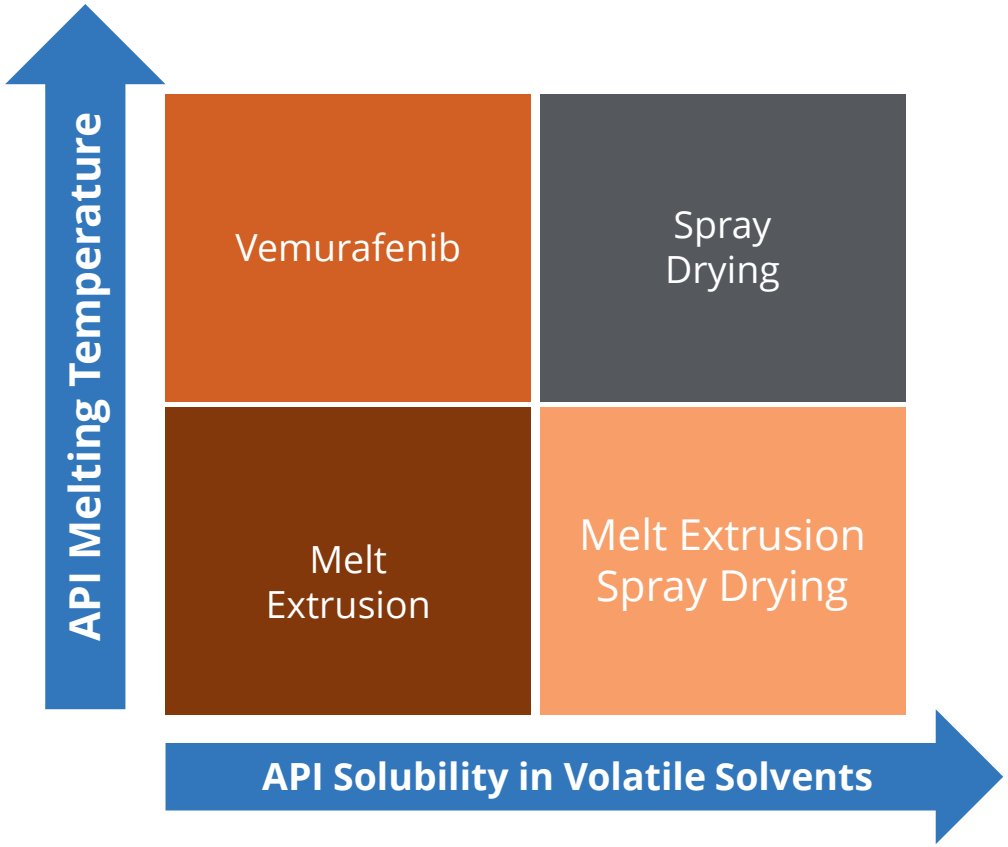
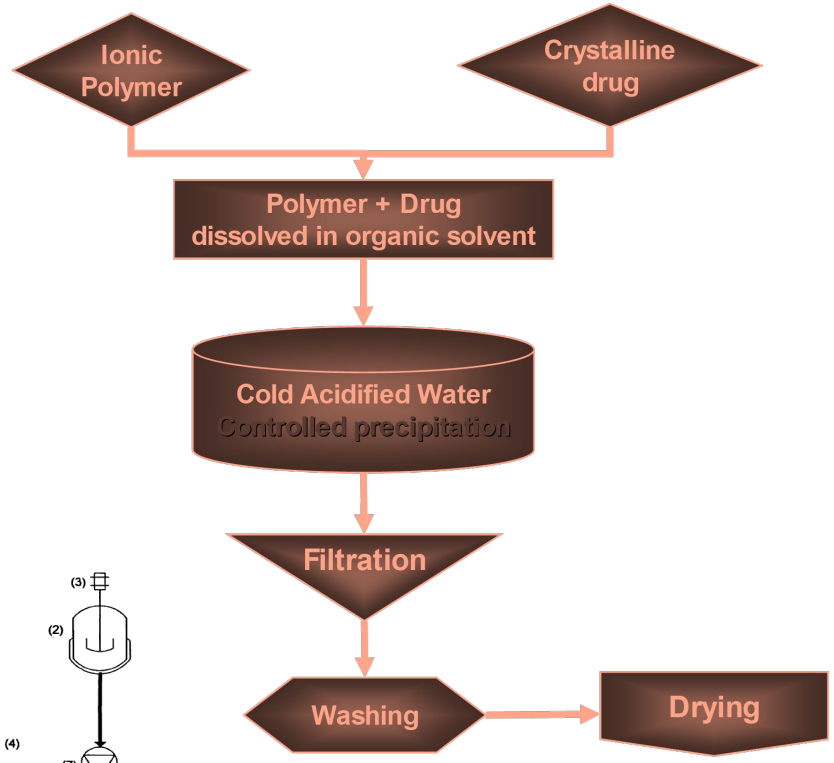
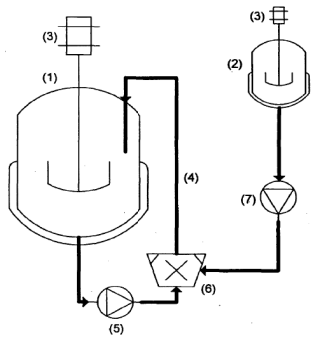
2007: The Vemurafenib Conundrum



Denotations	Vemurafenib, RO5185426, PLX4032
Mol. Wt.	489.93 g/mol
T_M	272 °C
T_g	106 °C
LogP	3
pKa	7.9, 11.1
Solubility	1 µg/mL FaSSIF
Organic solubility (volatiles)	< 6 µg/mL (best solvent)
Dose	960 BID

Zelboraf: Vemurafenib ASD by Precipitation Technology





Micro-precipitated bulk powder (MBP)

- A.K.A. Solvent/anti-solvent precipitation
- Complex, multi-step process
- Mixed solvent waste streams
- Narrow formulations space

Zelboraf™ Drug Product Manufacturing
1. API manufacture
2. MBP: Amorphous API in HPMCAS (3:7)
3. Roller compaction
4. Tablet compression
5. Tablet coating

KinetiSol Processing of Vemurafenib

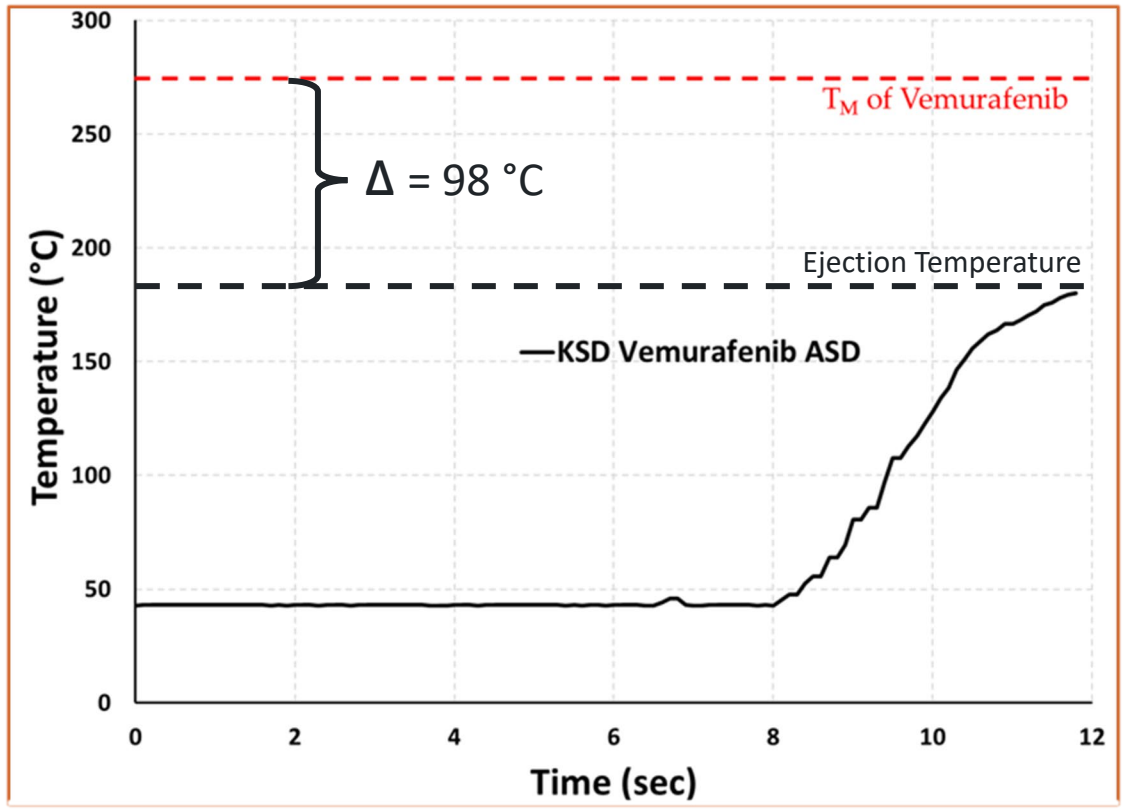
Commercial Formulation

Component	Percent (w/w)
Vemurafenib	30%
Aqoat-LMP	70%

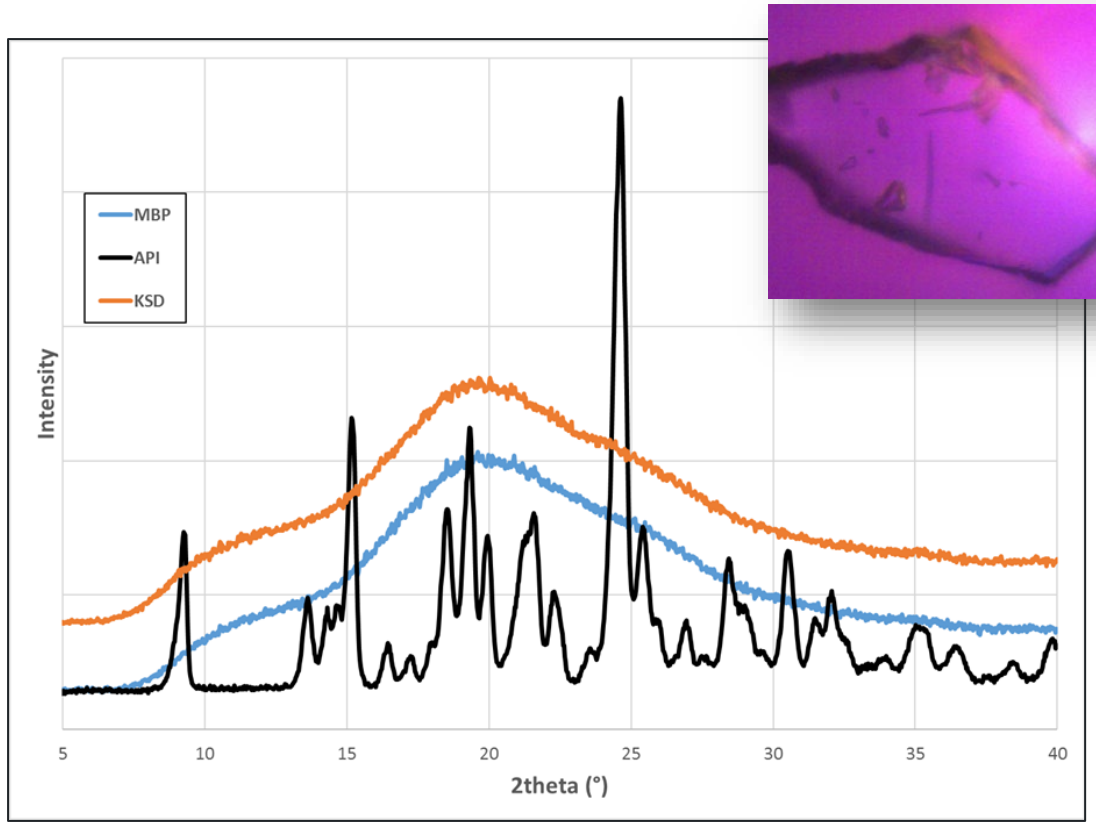
Product Milling

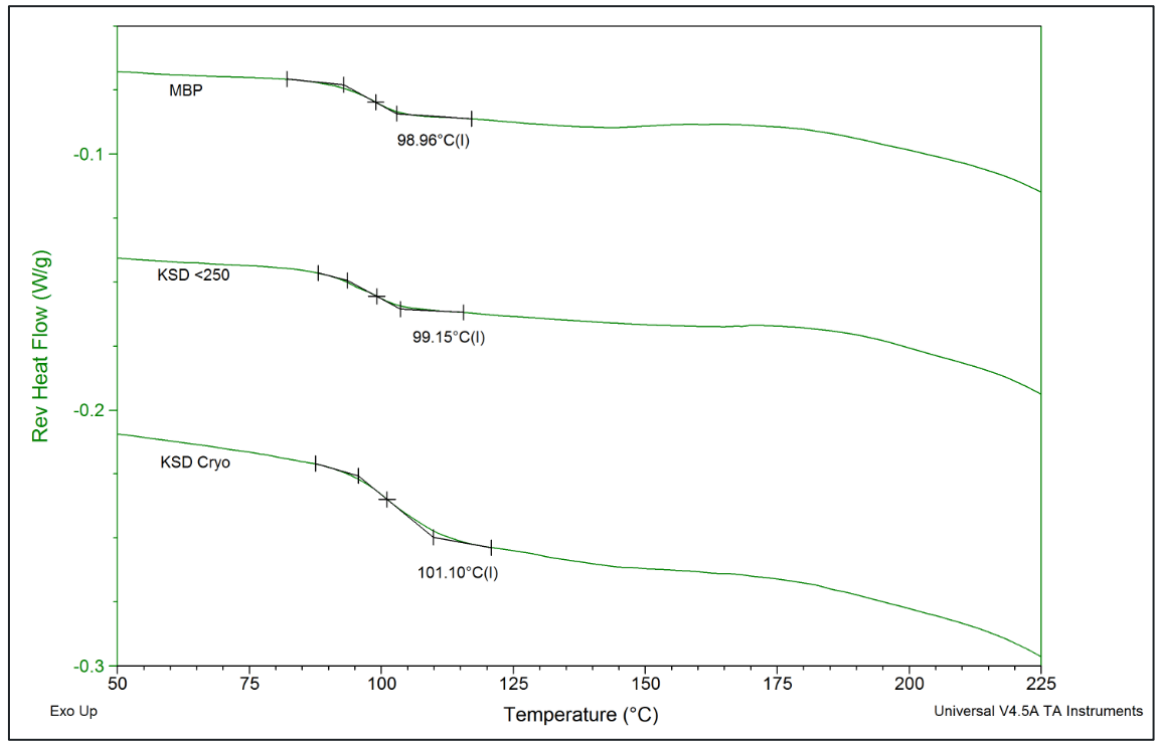
- Hammer milling = **$KSD_{<250\mu m}$**
- Cryogenic piston milling = **KSD_{cryo}**
- To evaluate the effect of PSD on performance

KinetiSol Temperature Profile



Solid-State Analysis

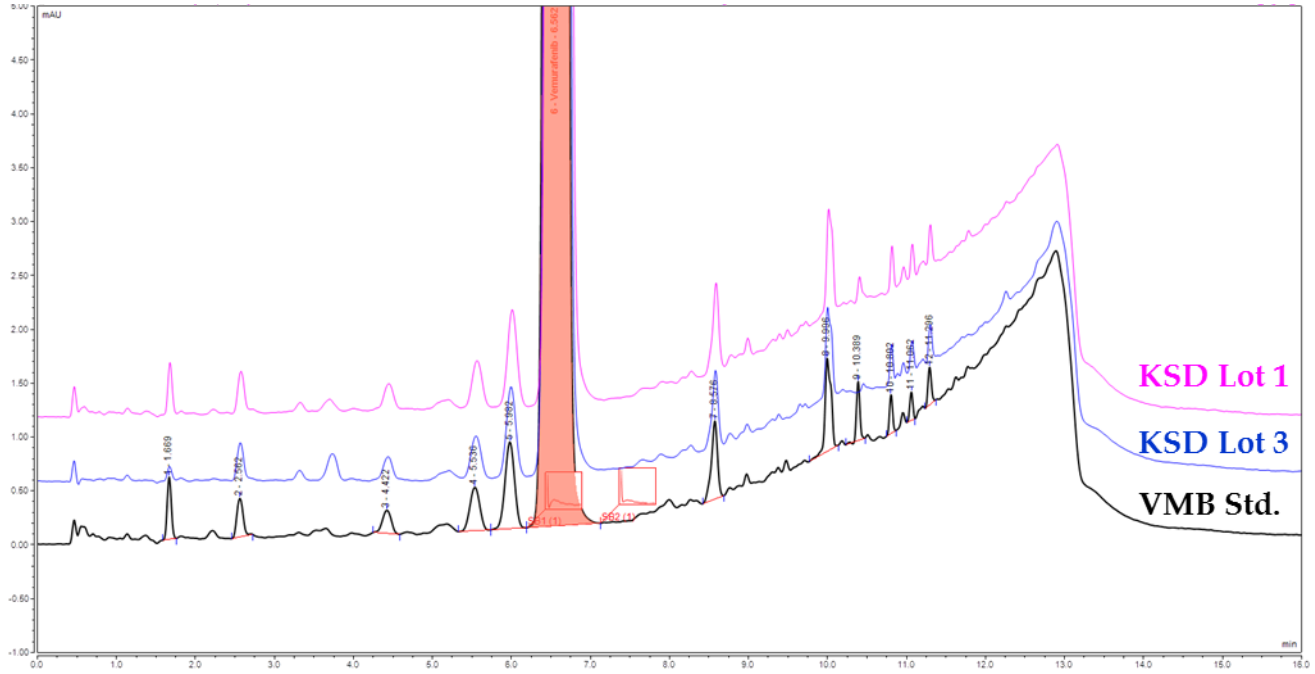




Absence of crystalline VEM confirmed by XRD and PLM

Single T_g matching MBP

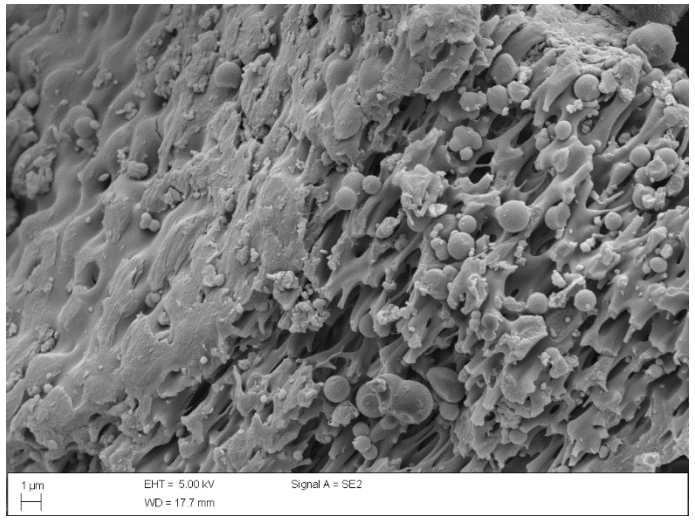
No Process Related Degradation



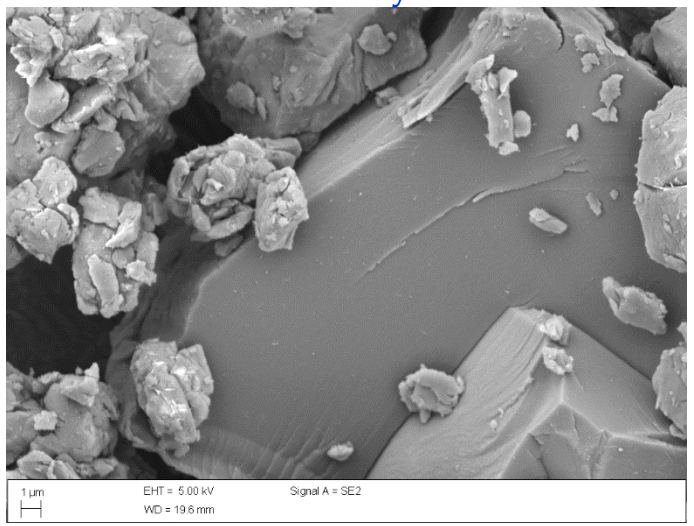
Sample	Purity (%RA)
VMB Standard (bulk API)	98.63
KSD Lot 20141022.01	98.64
KSD Lot 20141022.03	98.68

Particle Properties

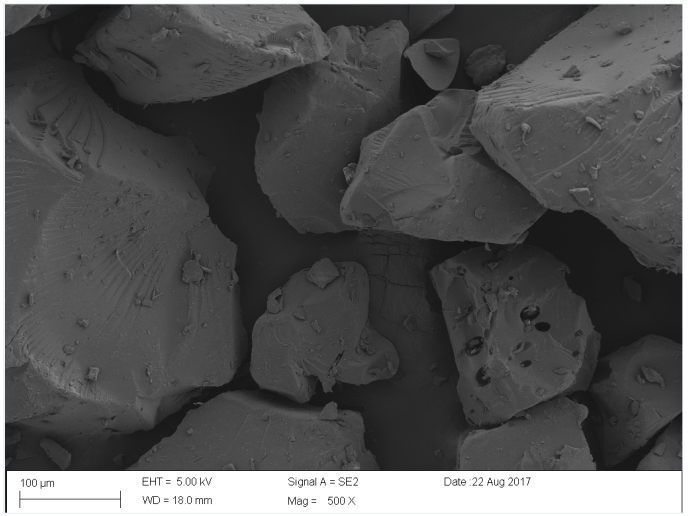
MPB



KSD_{cryo}

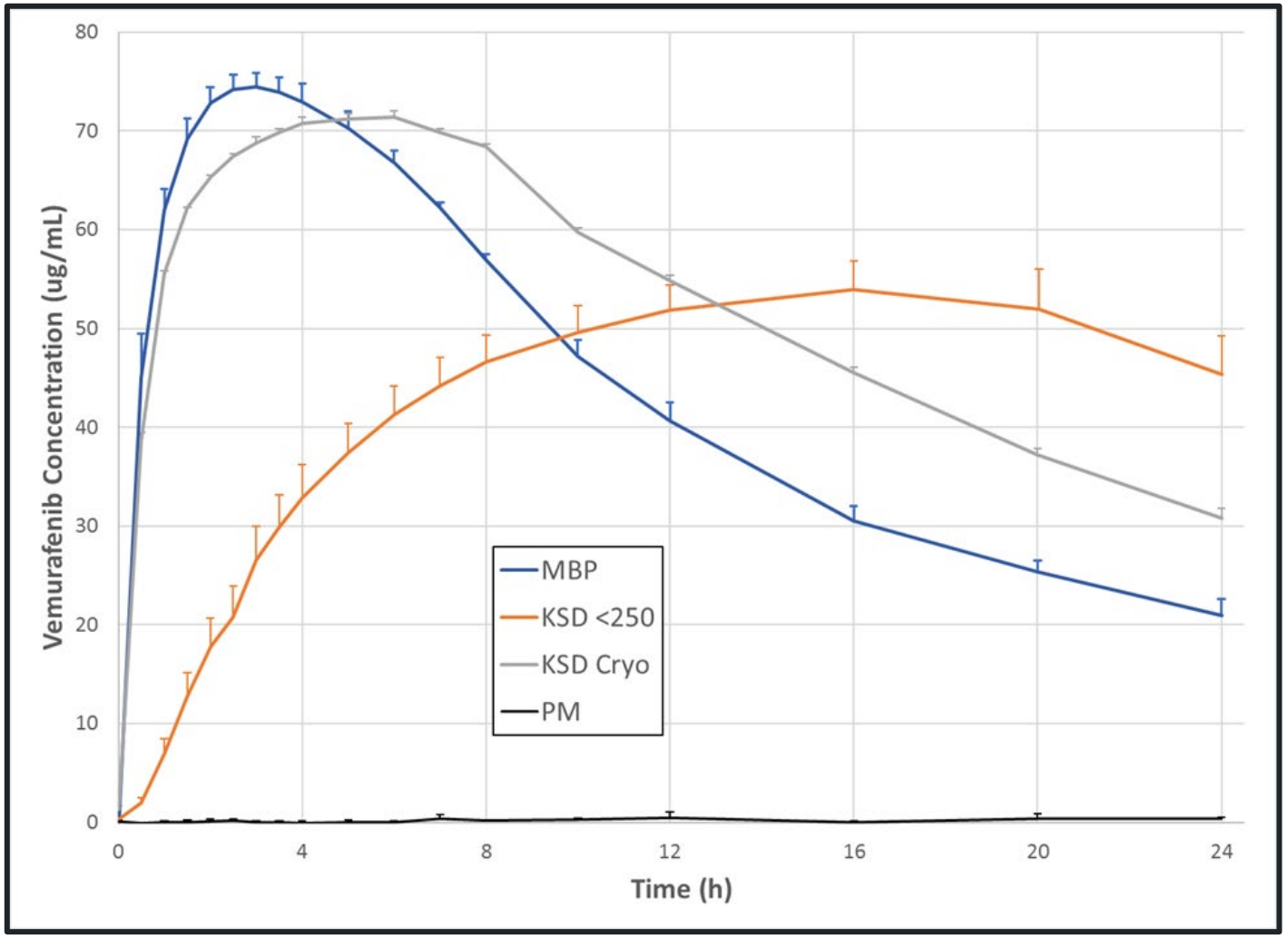


$KSD_{<250µm}$

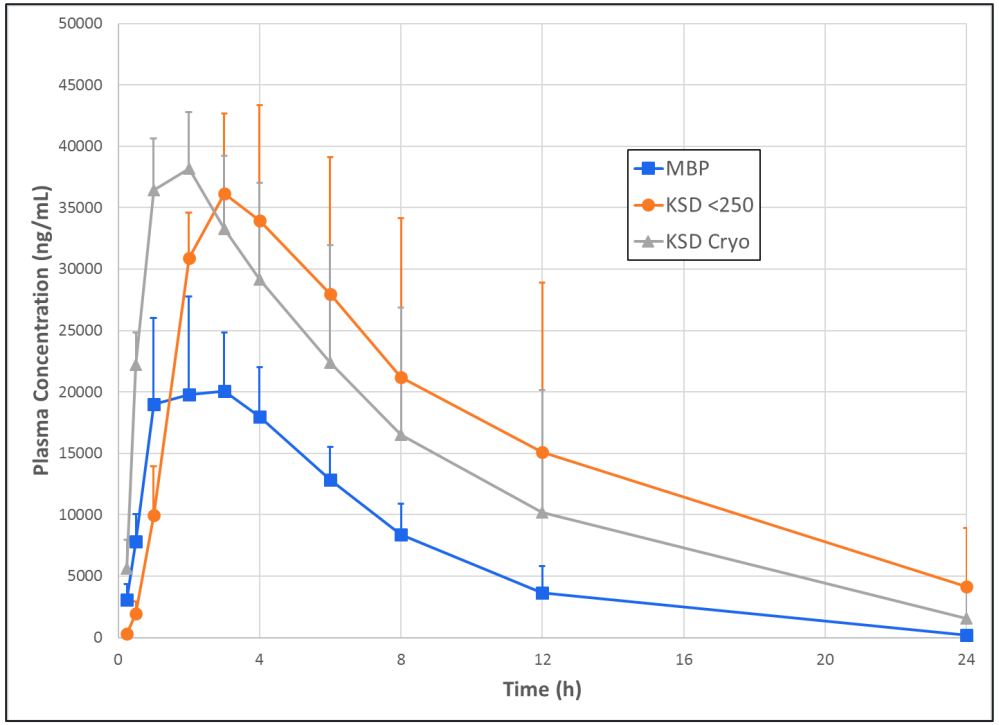


Sample	D10 (µm)	D50 (µm)	D90 (µm)	Specific Surface Area (m2/g)
MBP	2.39 ± 0.13	74.14 ± 1.68	220.90 ± 5.65	6.13 ± 0.05
$KSD_{<250\ µm}$	14.02 ± 0.84	132.74 ± 3.43	300.79 ± 2.62	0.20 ± 0.02
KSD_{cryo}	2.14 ± 0.23	12.94 ± 1.42	78.96 ± 3.43	1.21 ± 0.06

Non-Sink Dissolution in pH 6.5 FaSSIF



KSD vs. MBP: Rodent PK Study



Sample	MBP	$KSD_{<250\ \mu m}$	KSD_{Cryo}
t_{max} (h)	2.0 ± 0.8	3.5 ± 0.6	1.8 ± 0.5
C_{max} (ng/mL)	21,750 ± 5,171	37,250 ± 7,556	38,375 ± 4,492
$AUC_{0\rightarrow\infty}$ (hr·kg·ng/mL/mg)	6,661 ± 1,910	17,607 ± 11,060	16,738 ± 9,340
F-value	**1**	**2.6**	**2.5**

- t_{max} in agreement with in-vitro dissolution data: MBP ≅ KSD_{cryo} < $KSD_{<250\ \mu m}$
- Both KSDs exhibit about 70% greater C_{max} and 2.5-fold greater mean AUC
- **Limiting precipitation (controlling porosity) critical to maximizing oral absorption?**

BOEHRINGER INGELHEIM – COMPOUND D

KinetiSol® Processed ASDs: Performance *in vivo* and in non-clinical safety studies

Keith Horspool Ph.D., Chen-Ming Lee Ph.D.,
Vice President, Material & Analytical Sciences
Boehringer Ingelheim, CT, USA

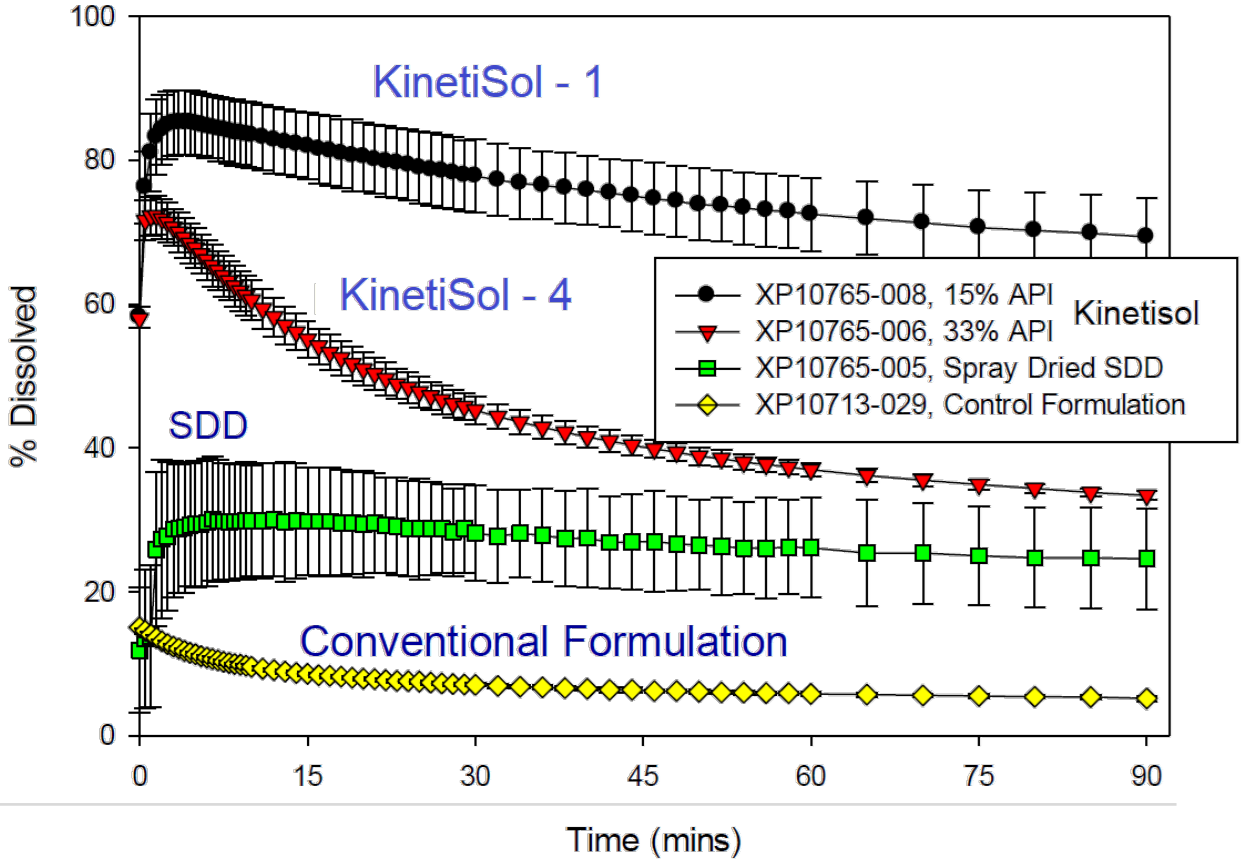
AAPS Partner Presentation Session, November 14th, 2017

Boehringer Ingelheim – Compound D

Mwt = ~ 450, Mpt ~300°C
Solubility SIFF=1.44mcg/ml, low in organics
Do (top human dose)= >200

Compound D Challenges

- Water insoluble
- 300 ºC Melting Point
- Poor organic solubility
- High human dose
- Non-viable SDD process



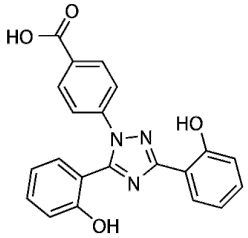
Boehringer Ingelheim – Compound D

Pharmacokinetic Comparison in Rodents

Formulation	T_{max} (hr)	C_{max} ± SD(nM)	AUC ± SD (nM × h)	Relative BA to IFF (%)
IFF Formulation	5.50	22,100 ± 6,070	276,000 ± 65,900	--
In-house SDD	6.50	35,000 ± 10,100	455,000 ± 166,000	165
Kinetisol-4 (High API load)	5.00	44,100 ± 16,000	593,000 ± 77,800	215
Kinetisol-1 (Low API load)	4.00	46,600 ± 8,320	615,000 ± 34,800	223

- KinetiSol generated a 30% increase in BA over an SDD at 2x drug load
- KinetiSol manufacturing was viable, Spray drying was not

JADENU®
(deferasirox)



Expanding Patient Reach for Deferasirox

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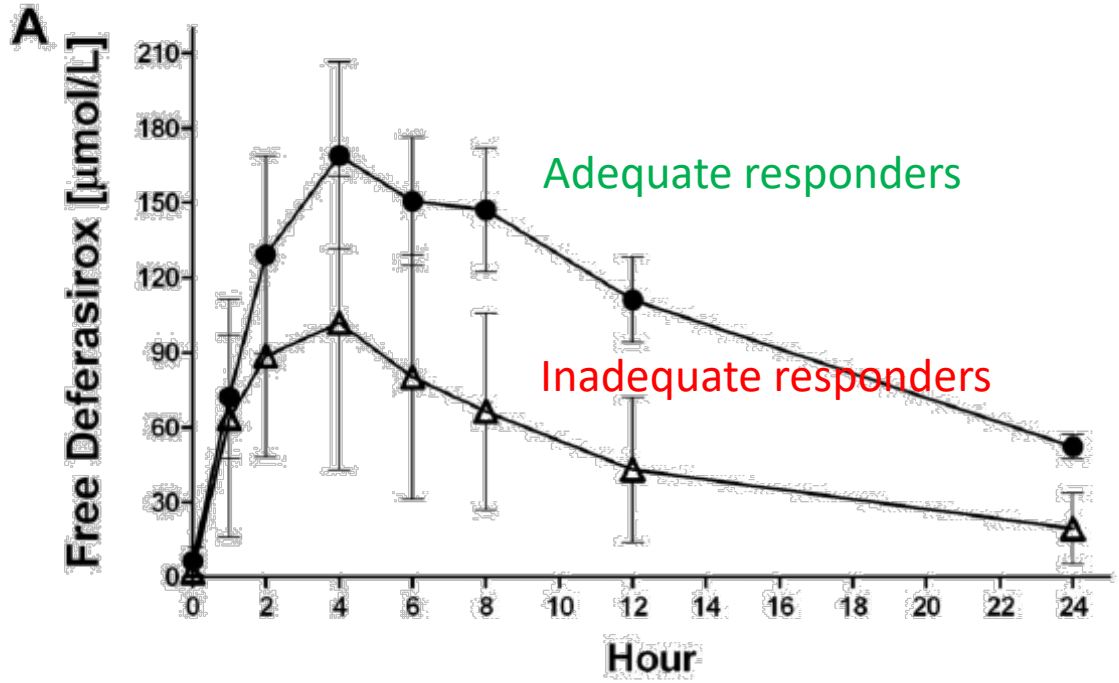
Deferasirox: Unmet Clinical Need

- 30% of patients are inadequate responders due to low BA
- Poor BA due to:
  - pH dependence and poor solubility
  - High oral doses, up to 40mg/kg
- Improved formulation needed to extend DFX therapy to inadequate responders

DFX Pharmacokinetic Analysis in Patients



From: Chirnomas et al. Blood, 5 Nov. 2009, Vol. 114, No. 19

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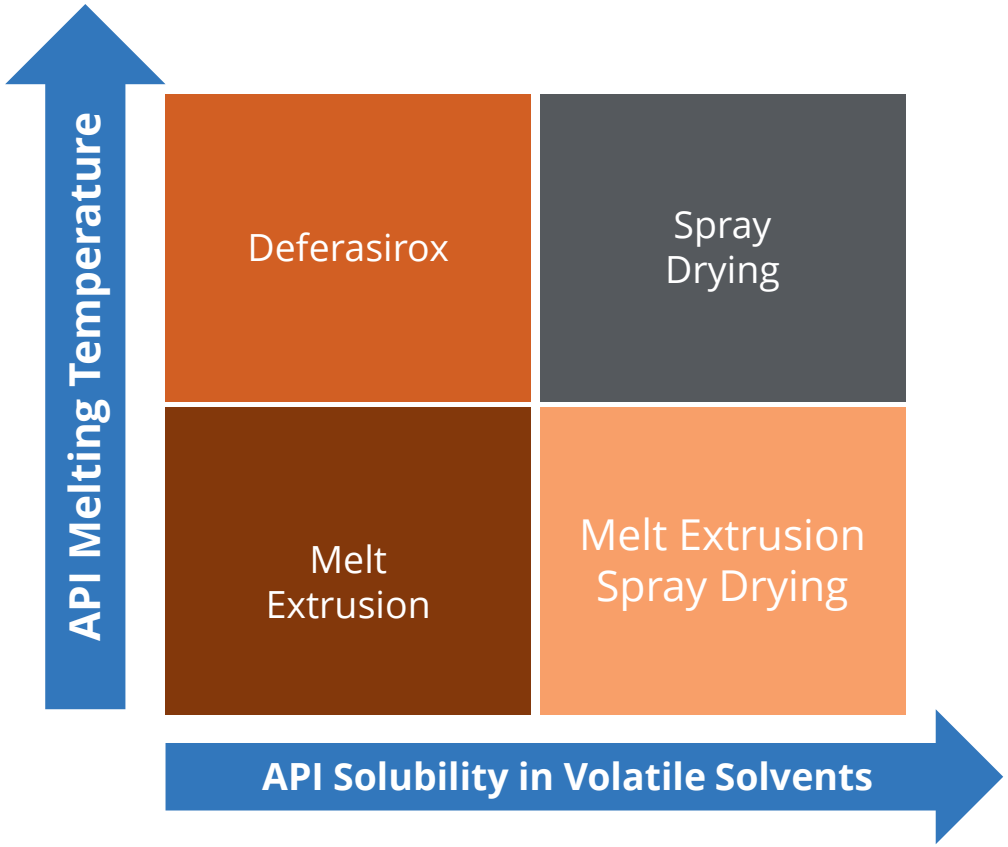
37

Deferasirox's Therapy Limiting Properties

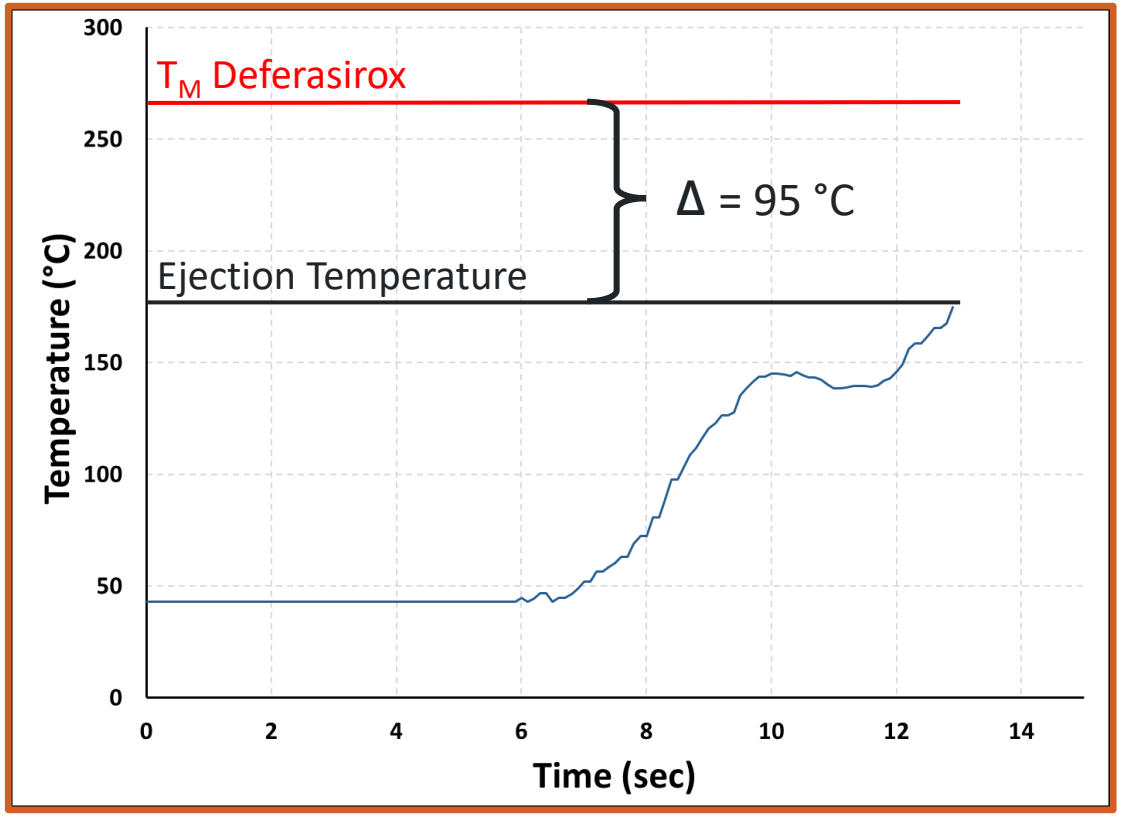


Denotations	Deferasirox, ICL670A
Mol. Wt.	373.4 g/mol
T_M	265 °C
T_g	105 °C
LogP	6.3
pKa	4.61, 10.12, 12.08
Solubility @ pH 1.2	< 1 µg/mL
Solubility @ pH 7.0	300 µg/mL
Organic solubility (volatiles)	< 2 µg/mL (best solvent)
Dose	14 – 40 mg/kg QD

KinetiSol Enables ASDs of Deferasirox

Lead KDFX Formulation

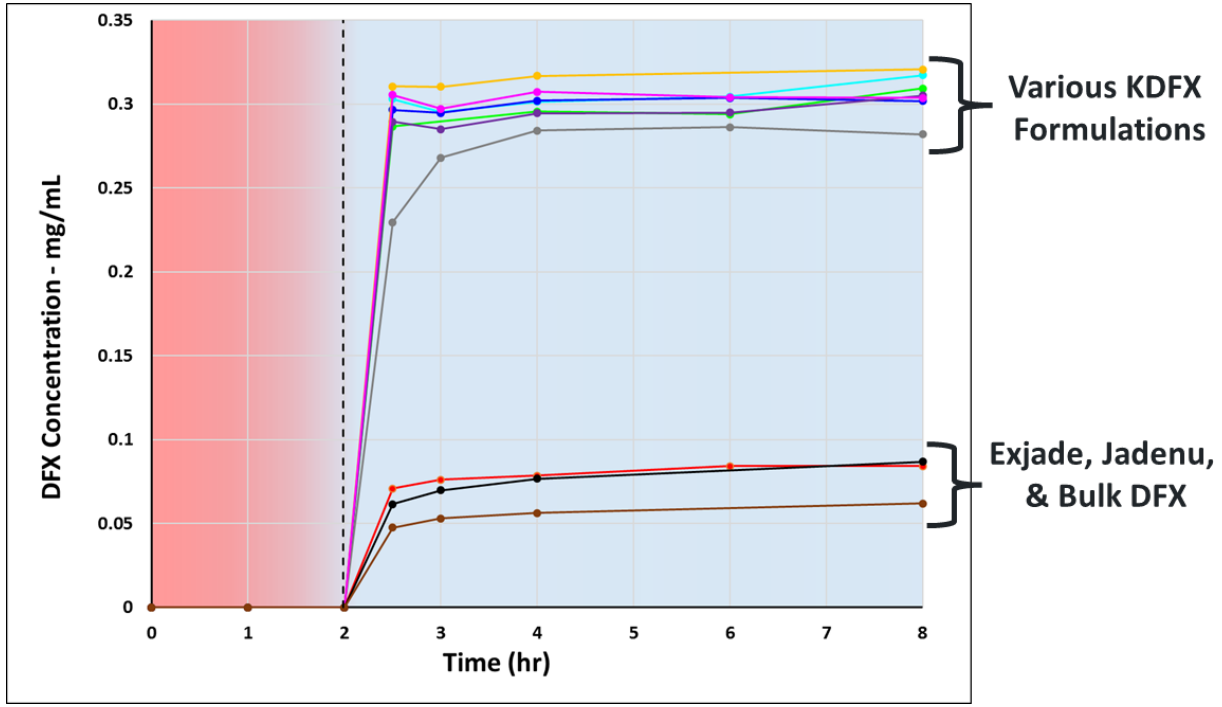
Component	Percent (w/w)
Deferasirox	50.0
Copovidone	24.75
Eudragit L100-55	24.75
Magnesium Stearate	0.5



KinetiSol Reformulation

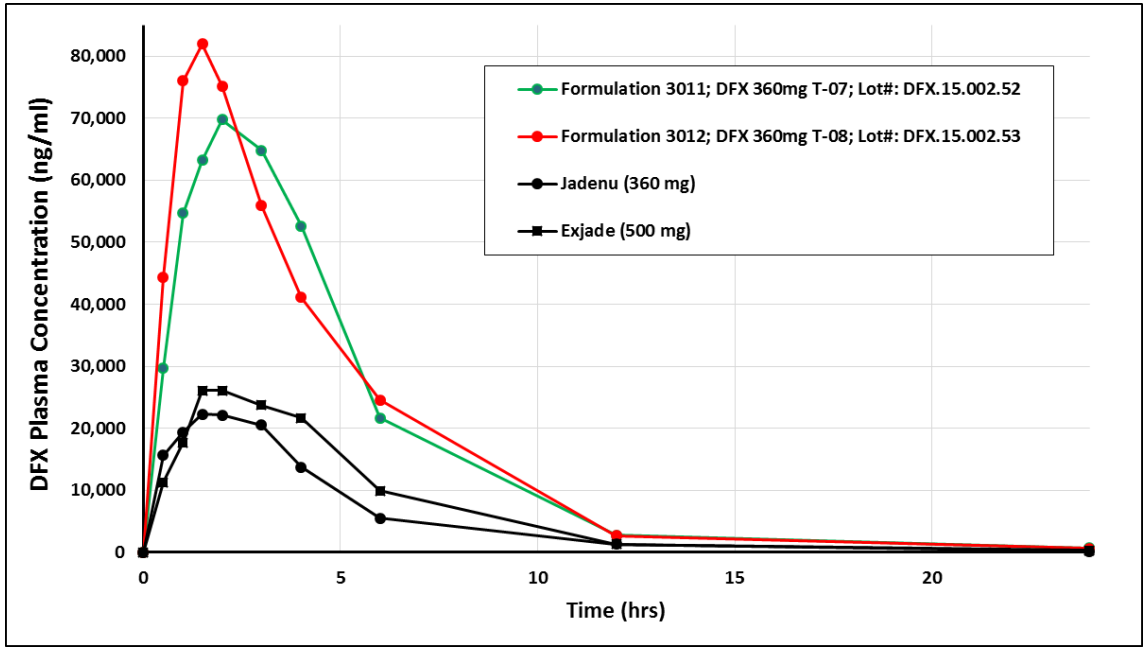
Improved Biopharmaceutical Performance

Bio-relevant Dissolution Analysis



KinetiSol formulations at 50% DFX loading produce substantial dissolution rate enhancement within the intestinal tract

Pharmacokinetic Analysis In Dog Model



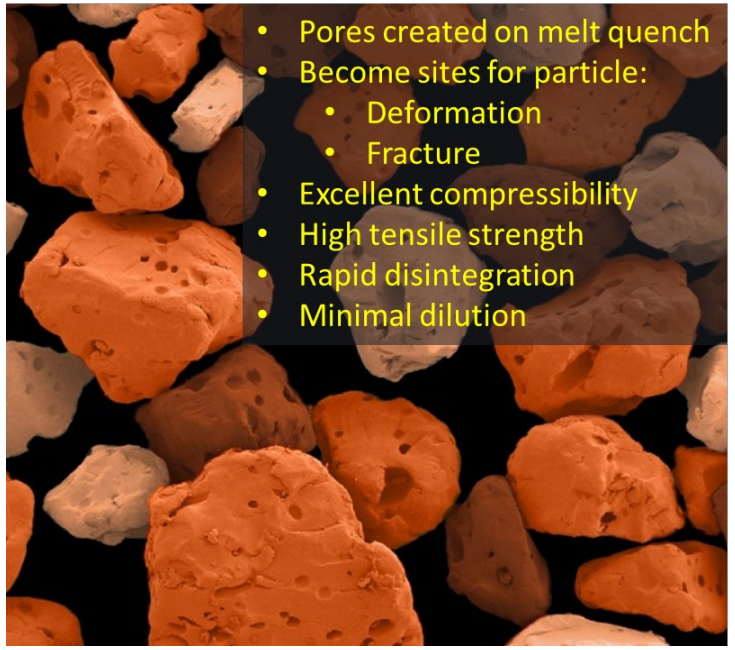
KinetiSol formulations exhibit 300% increase in oral absorption at high dose (36 mg/kg) in beagle dogs

High-Dose Tablet Enablement

Minimizing Pill Burden

KDFX Tablet: P3/Com. Formulation

Component	KDFX IR Phase 2/3 Tablet	
	% w/w	mg/tablet
Internal Phase		
Deferasirox	40.0	360.0
Eudragit L100-55	19.8	178.2
Kollidon VA 64	19.8	178.2
Magnesium Stearate	0.4	3.6
External Phase		
Microcrystalline cellulose	13.0	117.0
Croscarmellose sodium	6.0	54.0
Colloidal silicon dioxide	0.5	4.5
Magnesium stearate	0.5	4.5
Total	**100.0**	**900.0**



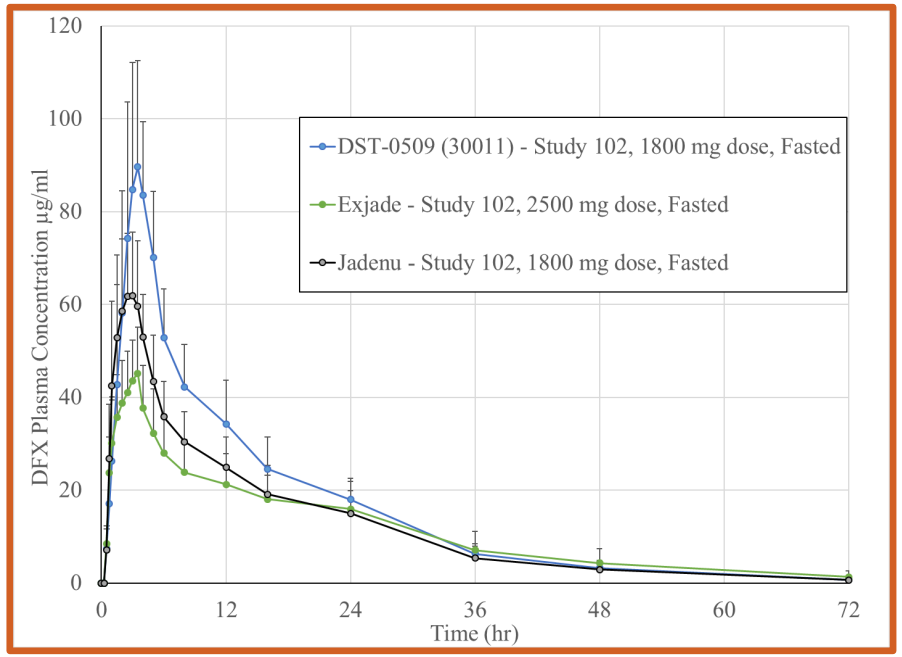
Tableting Parameters/Results

Parameter	Units	30011
Bulk density of internal phase	g/ml	0.549
Tablet shape	--	Modified capsule
Cup depth	mm	1.47
Major axis	mm	19
Minor axis	mm	9.28
Avg. compression force	kN	17
Avg. tablet thickness	mm	6.76
Avg. fracture force	N	160.8
Tensile strength	MPa	1.31
Disintegration time	Min	< 5

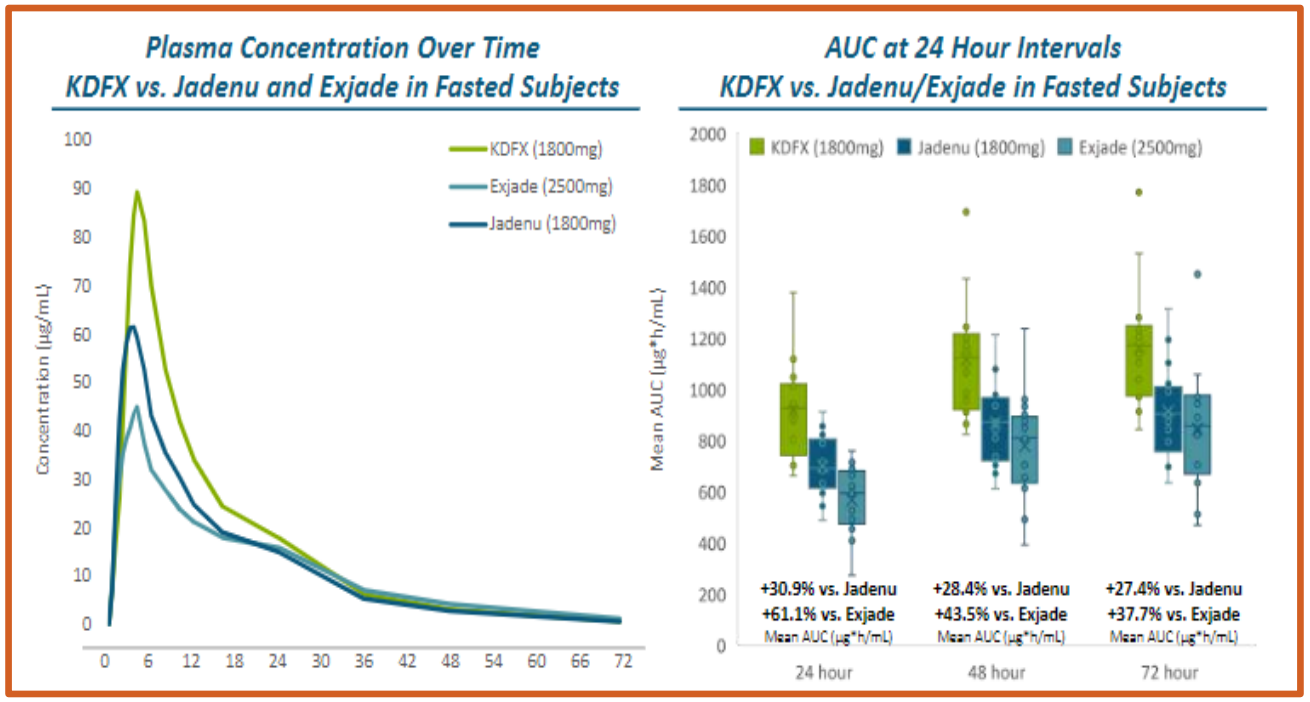
- 360mg DFX per tablet, 40% of the tablet's total weight
- Good fracture force and tensile strength at typical compression forces
- Disintegration time < 5 minutes

KDFX: Proof in Patients

Phase I



Phase II



- Phase I signaled superior bioavailability in healthy subjects
- Phase II indicates conversion of non-responders to responders

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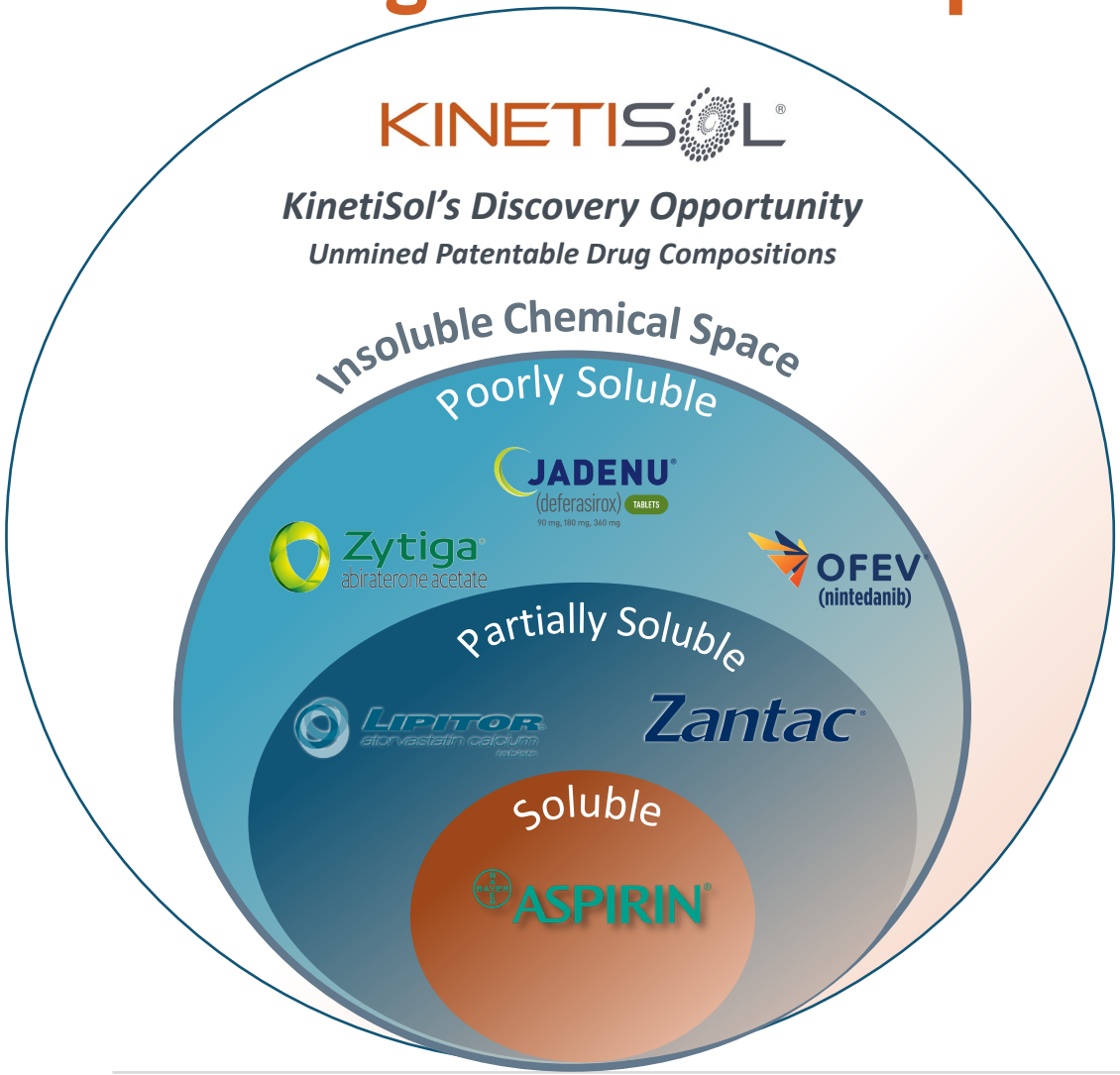
Great Drugs Go Undeveloped in Insoluble Chemical Space



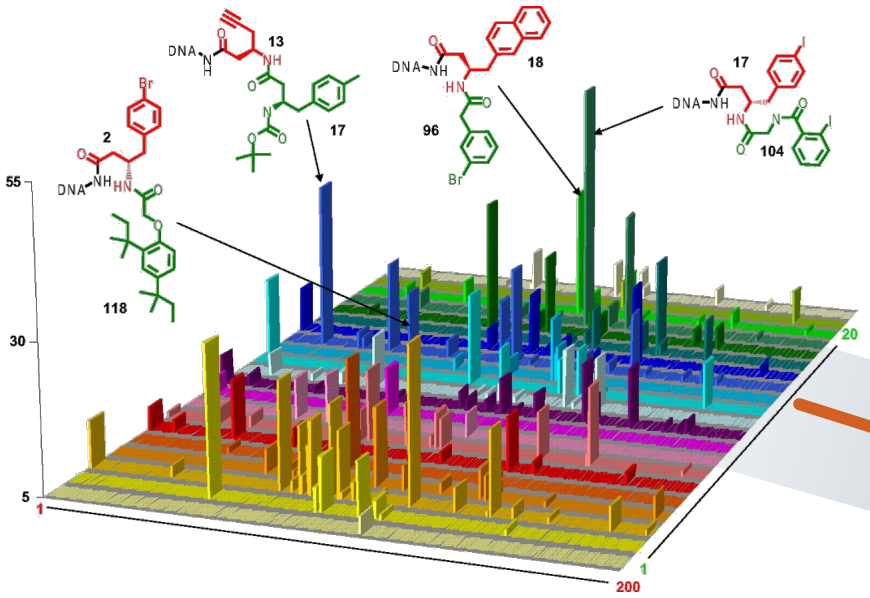
Redefine the Rules, Reveal the Undiscovered

Insoluble chemical space is richest source of high potency drugs

- Proven through empirical drug discovery
- Commonly seen in rational drug design
- Space deliberately avoided for inability to deliver therapeutic drug concentrations
- Greatly expands the boundaries of developability
- Kinases and many other validated targets can only be drugged by insoluble chemical scaffolds

Unlocking the Potential; Reducing Risk in Drug Discovery

All Target Specific Drug Generation Leads (Both Soluble and Insoluble)



- **Solubility No Longer a Limitation**
- **KinetiSol *Targets* Poor Solubility**
- **Expands Developability Rules (KinetiSol's Rules)**

KINETISOL®

Unfettered access to the vast majority of undiscovered insoluble NCEs with high potency and validated target affinity

Predictive chemistry, AI, and machine learning filters out for poor water solubility and druggability concerns

Current Discovery Efforts:

Few Soluble NCEs with reasonable affinity (>40% of NCEs)

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PHARMACEUTICS / MANUFACTURING

KinetiSol: Publication History

2023

Stephen A. Thompson, Urvi Gala, Daniel A. Davis, Jr., Dave A. Miller, Sandra U. Kucera, and Robert O. Williams III. Can the Oral Bioavailability of the Discontinued Prostate Cancer Drug Galeterone be Improved by Processing Method? KinetiSol® Outperforms Spray Drying in a Head-to-head Comparison. AAPS PharmSciTech. 2023, 24:137.

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AustinPx
111 W. Cooperative Way, Bldg. 3
Georgetown, TX 78626

512.686.4740
info@austinpx.com
www.austinpx.com