Development Sciences
From Science to Medicines

Challenges in Developing High Drug Loaded Redispersible Amorphous Nanoparticle Formulations of BCS IV Compound

23rd Jan 2025, SCPDG
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Purohit et al. JPS 113(2024) 1007-1019

Yu et al. JPS 114(2025) 383-393

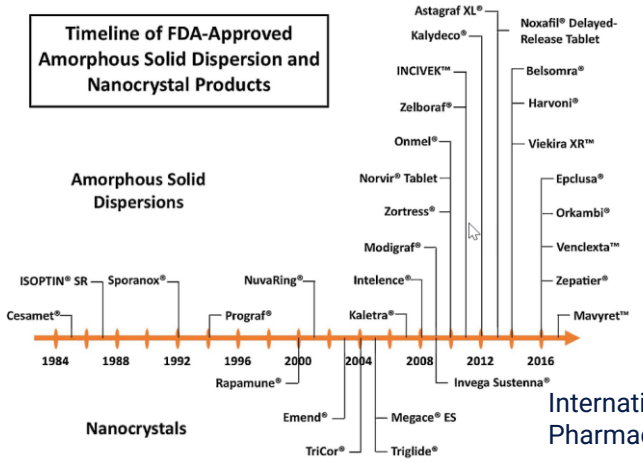
Trend of solubilization challenge for NCE

FROM SCIENCE TO MEDICINES

- There is a growing trend for small molecules that fall in the “poorly soluble/insoluble” category
- About 40% of Marketed products are BCS II/IV and projected to increase to 80%+
- In the last 20 years increasing number of drug products using Amorphous Solid Dispersion (ASD) technology have been approved by FDA

Class I	High solubility, high permeability Marketed 35% - Candidates 5-10%
Class II	Low solubility, high permeability Marketed 30% - Candidates 60-70%
Class III	High solubility, low permeability Marketed 25% - Candidates 5-10%
Class IV	Low solubility, low permeability Marketed 10% - Candidates 10-20%

Pharmaceutics 2017, 9, 50

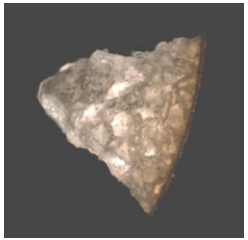


International Journal of Pharmaceutics 535 (2018) 379

Why Amorphous Nanoparticles?

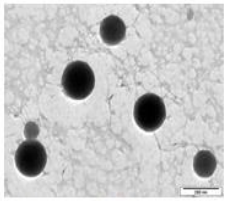
- What's happening during dissolution of ASD?

  Supersaturation → liquid-liquid phase separation (LLPS) or glass-liquid phase separation (GLPS) → drug rich nanoparticles



ASD particle
25 X magnification

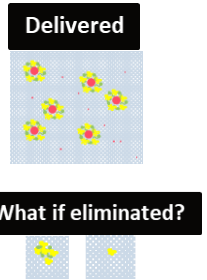
LLPS formation in aqueous media



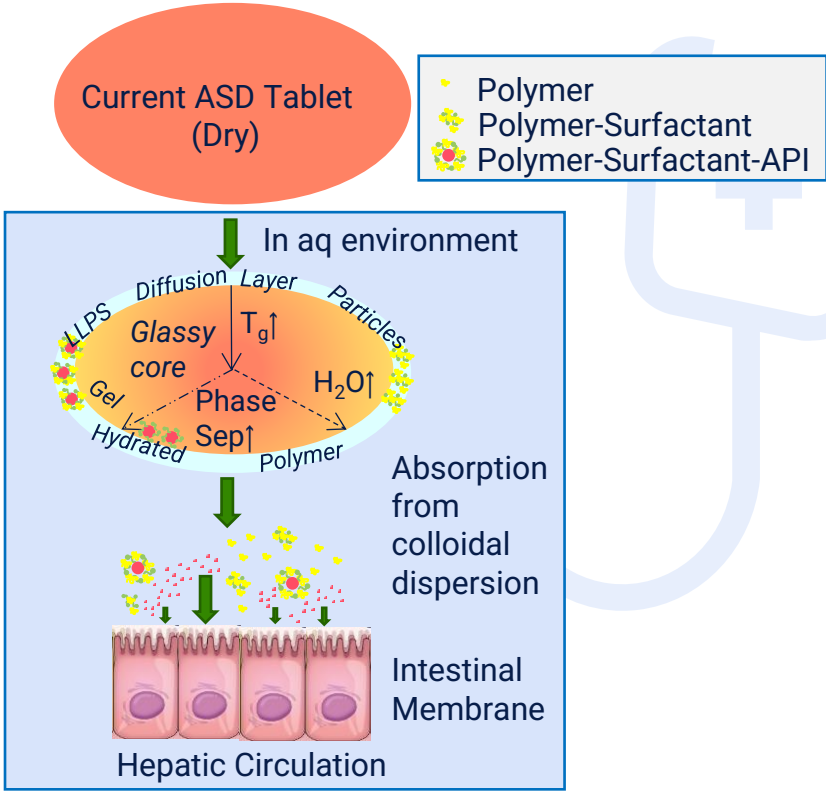
Cryo - TEM

Drug rich nanoparticles

Opportunity: directly engineer nanoparticles
- Similar bioavailability to ASD
- Higher drug load



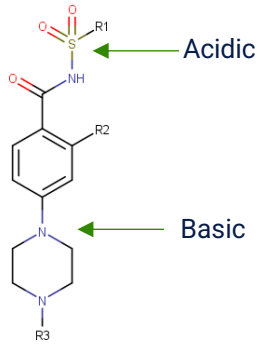
Hypothesis : Release Mechanism

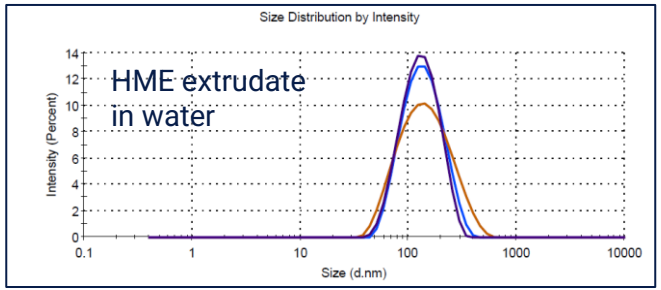


Directly Engineered Nanoparticles: from Bench to Pilot Plant

Model compound
Compound X

BCS IV Compound
Zwitterionic @ pH 6.8
Solid forms: numerous
HME extrudates ~10% API

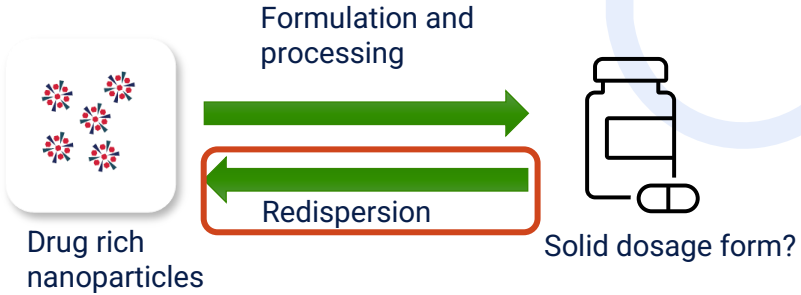




Particle size distribution by dynamic light scattering

Challenges

1. How to generate amorphous nanoparticles (ANP)?
2. How to maintain stability of ANPs?
3. Can these ANPs be processed into a solid dosage form?
4. Can the dosage forms redisperse back to nanoparticles during dissolution?
5. How to scale it up?
6. Would this concept work (clinical performance)?

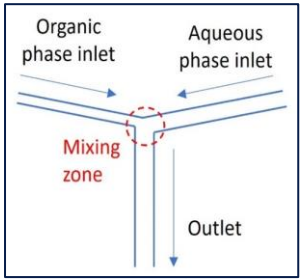


Generating amorphous nanoparticles by solvent anti-solvent precipitation

Solvent anti-solvent precipitation using impinging jet

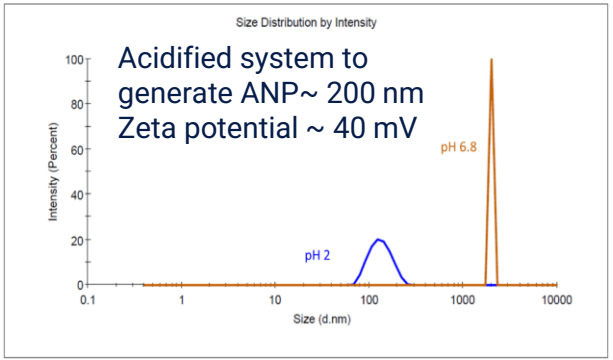
- Supersaturation and mixing at impinging site generated drug rich nanoparticles
- THF selected to solubilize Compound X in organic phase (due to solvate in other solvents)
- Acidified system (API ionized) enabled ANP generation (~200nm) and surface charge
- ANP size was optimized by changing ratio, flow rates, composition

Organic phase	
THF	95%
1M HCl	5%
Compound X	58.5 mg/mL



Aqueous phase	
0.01 N HCl	100%
PVPVA	0.27 mg/mL
Tween 80	0.27 mg/mL

Dilute nanoparticle suspension
API/PVPVA/Tween 80 - 90/5/5
Solid load in suspension ~ 0.5% w/v

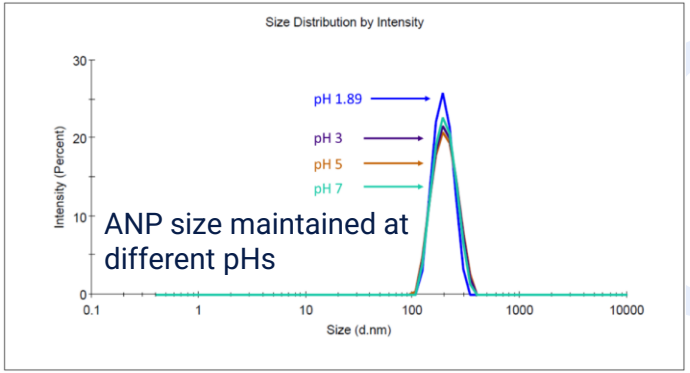


Organic to aqueous ratio	Size (nm)	PDI	Z potential (mV)
1: 6	390	0.029	42.1 ± 6.20
1: 9	180	0.032	43.2 ± 6.00
1: 12	111	0.076	38.2 ± 6.75
1: 14	130	0.110	36.6 ± 6.07

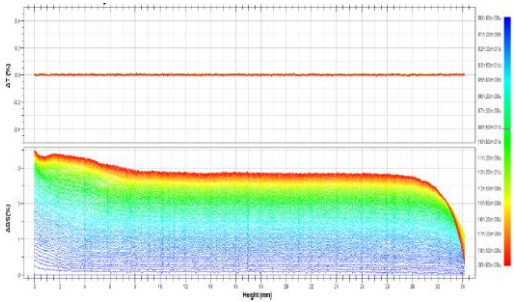
Generating amorphous nanoparticles by solvent anti-solvent precipitation

Stability of ANP in suspension

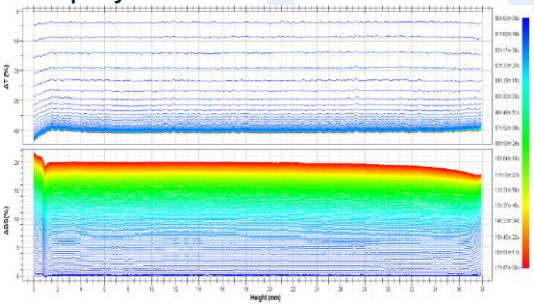
- Acidified system imparts surface charge to stabilize ANPs
- ANP maintained stability after generation when bulk pH was changed to 3, 5, and 7.
- Turbiscan (light scattering index) demonstrates no sedimentation within 20 hrs after generation using polymer and surfactant



Stable for 20 hrs with5% PVPVA 5% Tween 80



Rapid sedimentation without polymer & surfactant



Removal of organic solvent and stabilization of ANP for drying

Solvent removal, washing and up-concentration was performed by tangential flow filtration (TFF)

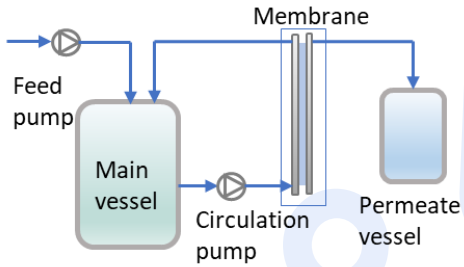
- THF level dropped to 0.13%/almost 100% removed
  pH ≥ 3
- Wet T_g (two T_g)values even in the presence of THF
- These nanoparticles have been shown to exhibit core-shell structures
- Low Tg requires stabilization poses challenges for drying

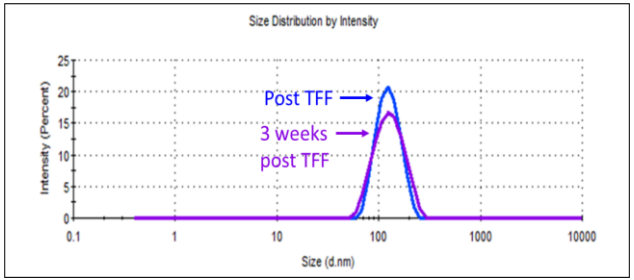
ANP Suspension of Compound X

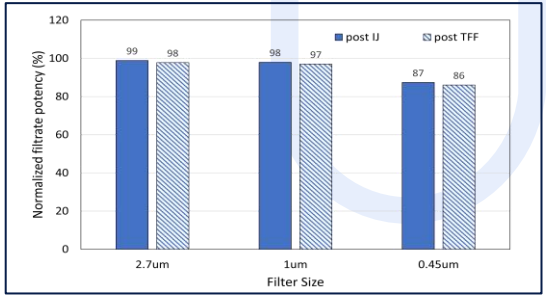
- Suspension had 15% solid content
- 97% were below 1 micron in size
- 86% below 450 nm
- Stable for at least 3 weeks

Wet T_g of the ANPs in the presence and absence of THF

Sample	Tg^1 (°C)	Tg^2 (°C)
Post IJ (THF-water)	48	63
Post TFF (water)	46	79







Filtrate potency data for the nanosuspension before and after TFF

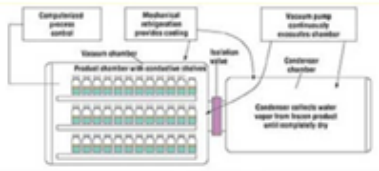
From suspension to solid dosage form

Freeze drying of the 15% solid containing suspension into solid powder with addition of sugar

- Sucrose and Trehalose containing formulations produced
- Cakes have porous structures
- Matrix exhibited embedded nanoparticles
- Added to water resulted in ANP suspension
- ~ 80% of the particles was below 450nm
- Visually trehalose cake re-dispersed faster

ANP Formulation Selected for in vivo studies

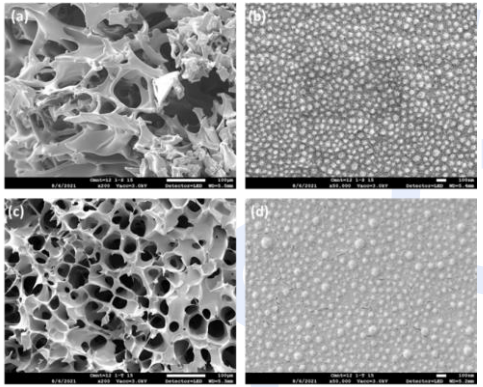
Composition	Function	[%]
Compound X	Active	45
Copovidone	Polymer	2.5
Polysorbate 80	Surfactant	2.5
Trehalose	drying-protectant	50
Total		**100**

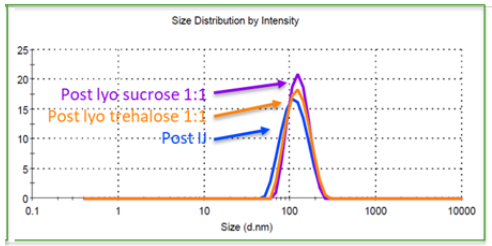


Freeze drying

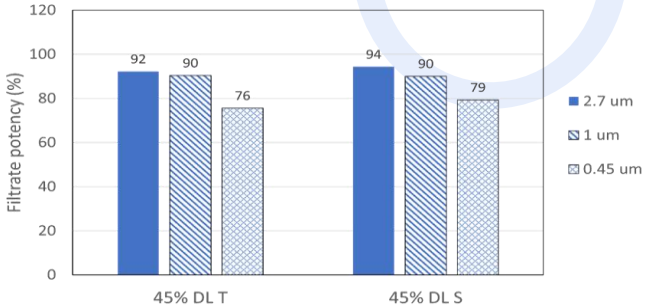
	Sugar	Tot. solid load (%)	ANP/sugar ratio	Final DL(%)
1	Sucrose	15	1:1	45
2	Trehalose	15	1:1	45
3	Mannitol	15	1:1	45
Control	-	15	No sugar	90

Structure of FD cake: top trehalose; bottom sucrose





Dispersibility by DLS



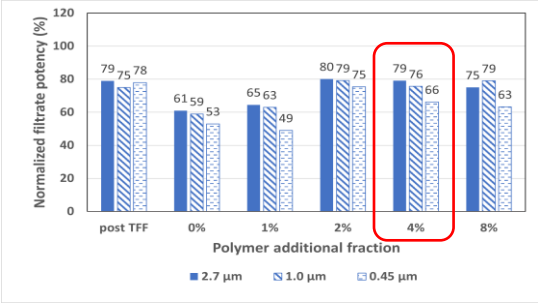
Scale up & In vivo studies in dogs

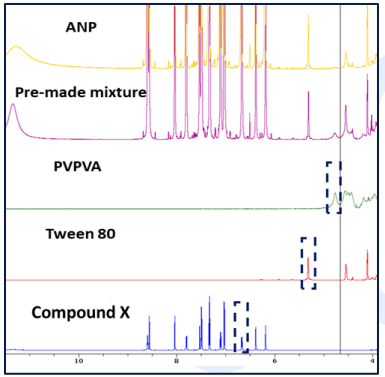
Scale-Up Surprises
- Filter Potency revealed loss of dispersibility: 50% compared to 80% below 450nm
- qNMR studies revealed that the polymer was being lost during TFF
- Screening studies performed with post TFF polymer addition
- 2-8% Polymer when added post TFF exhibited comparable re-dispersion

Final formulation
- 45% Compound X
  Trehalose needed to be slightly reduced

Fed and Fasted Studies in Dogs
- Results compare with ASD tablets
  Comparable in fasted state
  Lower exposure (60% AUC) in fed state
  - With food HME tablets exhibited 4.6 times increase in AUC while ANP was 1.6 times probably because the tablets were retained in the stomach in the presence of food

Filtrate potency of larger batches after freeze drying





1D proton spectral overlay for samples (from bottom to top) of Compound X, Tween-80, copovidone (PVPVA), pre-made mixture, and ANP. The highlighted proton signals were selected for building the standard curve

45% Drug Loaded ANP Formulation

Component	Percent (w/w)
Compound X	45
PVPVA	4.5
Tween 80	2.5
Trehalose	48

Fasted State Dog Study

					Point Estimates	
	$t_{1/2}$	C_{max}	T_{max}	AUC_{inf}	C_{max}	AUC
Tablet	17.1	2.52 (0.43)	4.2 (0.4)	52.4 (7.2)		
ANP Suspension	16.0	2.65 (0.55)	3.8 (0.5)	51.8 (9.2)	0.997	0.967

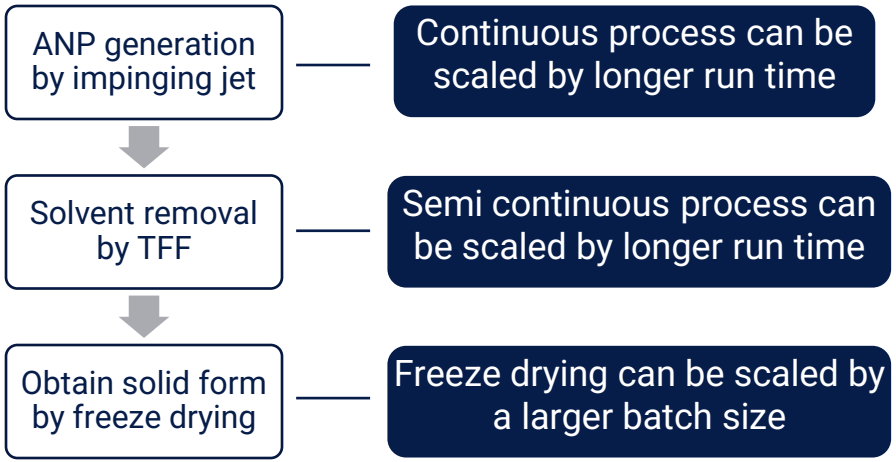
Fed State Dog Study

					Pt. Estimate	
	$t_{1/2}$	C_{max}	T_{max}	AUC_{inf}	C_{max}	AUC
Tablet: reference	21.0	12.5 (1.55)	3.0 (0.8)	241 (19.6)		
ANP Suspension	17.2	6.64 (1.50)	3.4 (0.7)	167 (48.3)	0.48	0.60

t1/2 [hr; harmonic mean]; Cmax [µg/mL]; Tmax [hr]; AUC [µg•hr/mL]

Scale up challenges – pilot scale

Preparation steps



New solid form occurred during engineering run

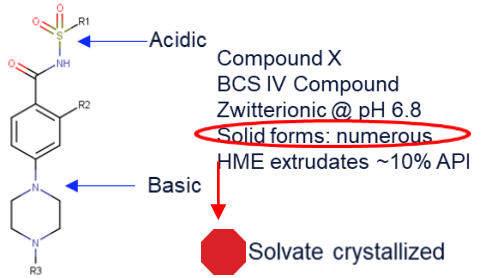
Are ANPs stable during the longer run?

Polymer loss during TFF resulted in decrease in redispersibility

Challenges in scale up – generation of a large batch of ANP

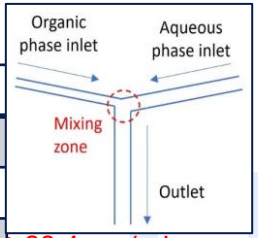
Scale-Up Surprises

- A THF solvate of HCl salt precipitated
- Concentration of API in the Organic was decreased by 2.5x
  - Concentration of organic in suspension increased
  - Batch size changed from 60L to 140L, longer processing time posed stability concerns
  - Rapid particle size increase during engineering run
  - ANP suspension was chilled after generation
  - Lab batch PSD determined by DLS was 141 nm but the cold collection dropped the clinical batch PSD to 75 nm



Removal of organic solvent was critical for suspension stability and redispersibility

Organic phase	
THF	95%
1M HCl	5%
Compound X	~~58.5 mg/mL~~ → 23.4 mg/mL



Dilute nanoparticle suspension
API/PVPVA/Tween 80 - 90/5/5
Solid load in suspension ~ 0.2% w/v

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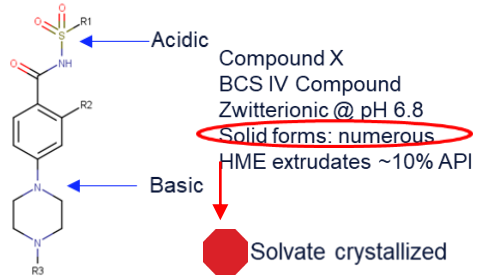

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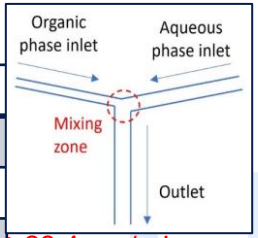

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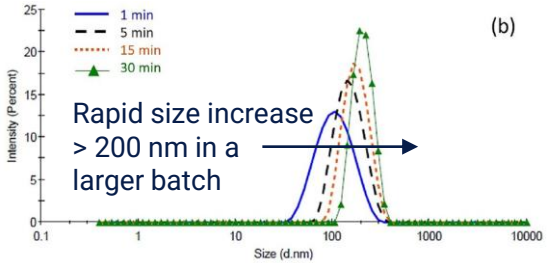

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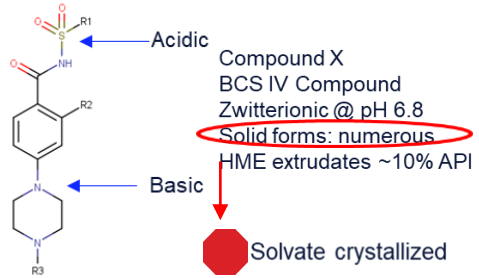

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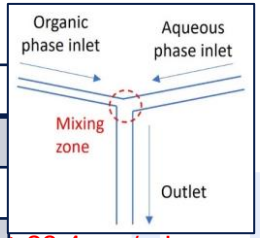

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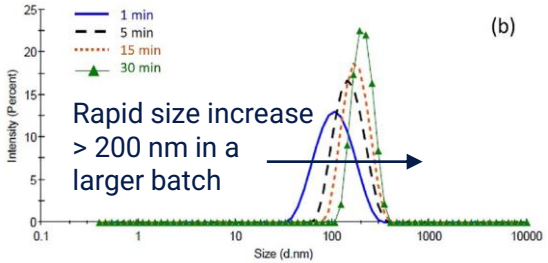
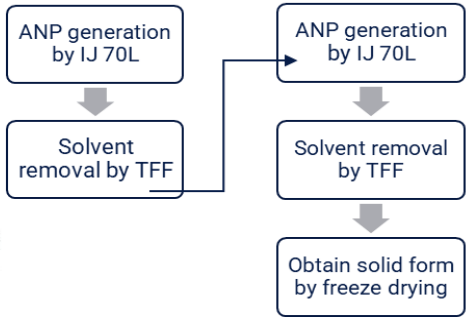


(b)

Clinical manufacturing flow chart



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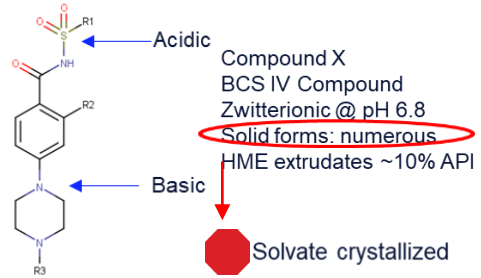

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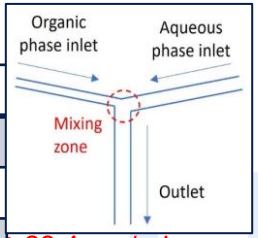

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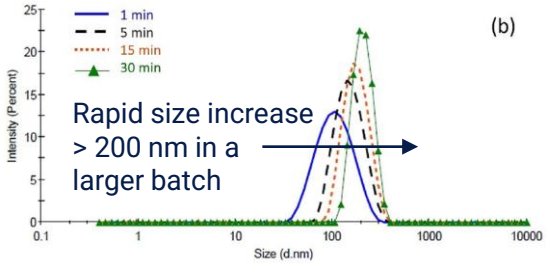

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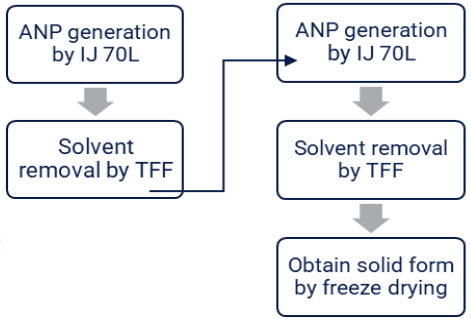

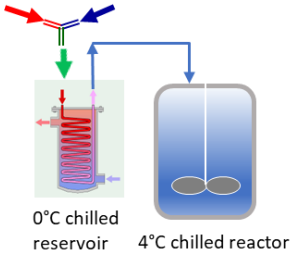

ANP suspension was rapidly cooled

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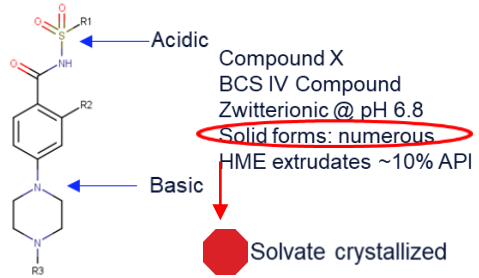
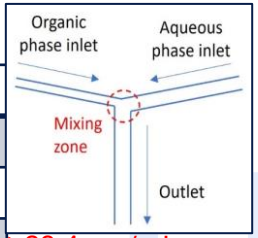
  - ➢ ANP suspension was chilled after generation
  - Lab batch PSD determined by DLS was 141 nm but the cold collection dropped the clinical batch PSD to 75 nm

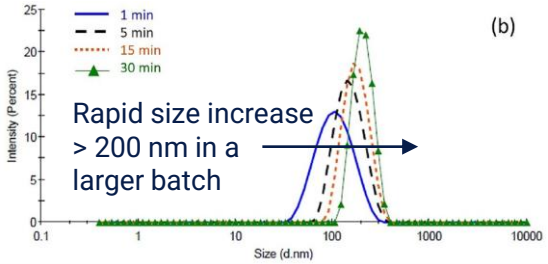


Removal of organic solvent was critical for suspension stability and redispersibility

Organic phase	
THF	95%
1M HCl	5%
Compound X	~~58.5 mg/mL~~ → 23.4 mg/mL

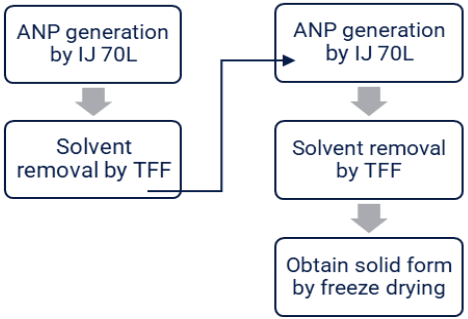


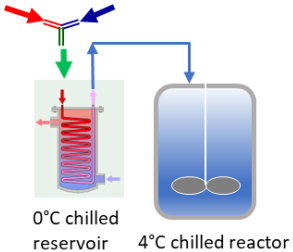
Dilute nanoparticle suspension
API/PVPVA/Tween 80 - 90/5/5
Solid load in suspension ~ 0.2% w/v



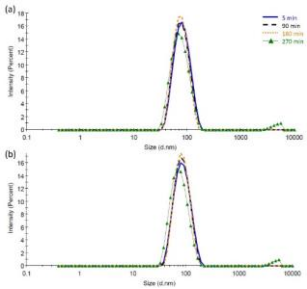
(b)

Clinical manufacturing flow chart





ANP suspension was rapidly cooled



Both batches produced ANP of 75 nm

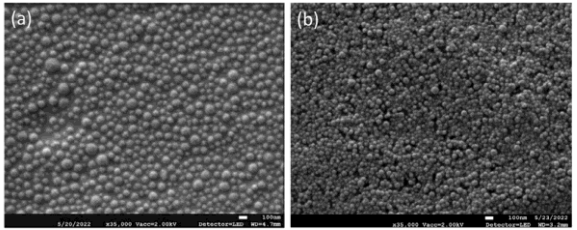
Challenges in obtaining redispersible solid dosage form

Freeze drying of 45% DL suspension into solid powder

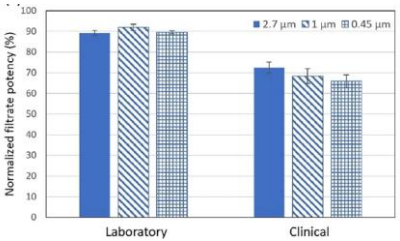
- ANP size of clinical batch smaller than laboratory batch 75 nm vs 140 nm
- Redispersion of clinical batch lower than laboratory
  - Clinical: ~ 65% smaller than 450 nm
  - Lab: ~90% smaller than 450 nm
  - Likely due to smaller particles and larger surface area
- FD powder for oral suspension as final dosage form

%(w/w)	Compound X	PVPVA	Tween 80
Composition	95.20	1.27	3.53
% RSD[a]	0.15	7.23	1.66

Composition by NMR after TFF



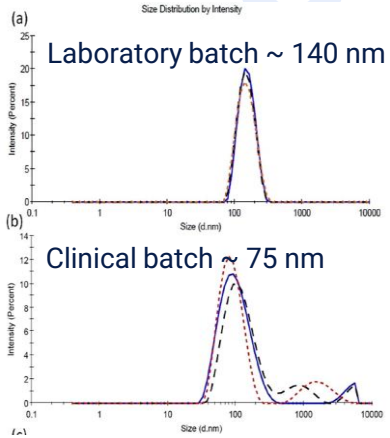
Laboratory batch ANP size > clinical batch



Redispersibility lab scale > clinical scale

%(w/w)	Theoretical	Actual
Compound X	45.0	45.3
PVPVA	2.5	2.6
Tween 80	2.5	1.7
Trehalose	50.0	50.4
Total	100.0	100.0

Compounding before freeze drying



Proof of concept of ANP dosage form of 45% DL

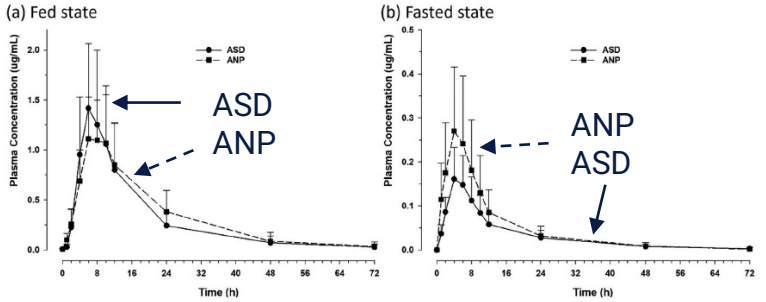
TFF Suspension was FD after polymer and trehalose incorporation

Dosed to humans as reconstituted suspension

Under fed condition, ANP formulation was close to meeting BE for AUC and had 21% lower C_{max}, compared to ASD tablets

Under fasted condition, ANP formulation showed enhanced bioavailabilityand lower food effect compared to ASD tablets

Proof of concept that directly engineered ANP has comparable bioavailability while maintaining a high drug load at 45% DL (vs 10% ASD tablets)



Pharmacokinetic Parameters (units)	ASD Tablets	ANP Formulation
Fed (Cohort 1, *N* = 12)		
C_{max} (μg/mL)	1.54 (1.65, 41)	1.22 (1.31, 35)
T_{max}[a] (h)	6.0 (4.0 – 12.0)	8.0 (6.0 – 12.0)
$t_{1/2}$[b] (h)	13.6 (3.32)	11.9 (2.73)
AUC_t (μg•h/mL)	19.8 (21.8, 50)	22.2 (23.8, 42)
AUC_∞ (μg•h/mL)	20.4(22.5, 53)	22.8 (24.6, 46)
Fasting (Cohort 2, *N* = 12)		
C_{max} (μg/mL)	0.147 (0.162, 44)	0.243 (0.286, 56)[c]
T_{max}[a] (h)	4.0 (4.0 - 8.0)	4.0 (4.0 – 6.0)[c]
$t_{1/2}$[b] (h)	12.9 (2.87)	11.7 (3.63)[c]
AUC_t (μg•h/mL)	2.07 (2.28, 48)	2.91 (3.40, 60)[c]
AUC_∞ (μg•h/mL)	2.14 (2.37, 48)	3.02 (3.50, 59)[c]

Summary

Directly engineered ANP at 45% DL was developed for BCS IV compound from lab to pilot scale

ANP formulation had comparable bioavailability as HME tablets at 10% DL with a lower food effect

Challenges	Mitigation
Generation of IJ by solvent and anti-solvent precipitation	Screened solvent, polymer, surfactant as well as pH adjustement; Optimized IJ process parameters
Stability of ANP after generation	Understanding stabilization mechanism and design organic solvent removal
New solid form occurred during scale up	Lowered concentration of Compound X in solution
Stability of ANP at a larger scale	Control particle size increase by controlling temperature of generated ANP and reducing processing time
Ensure redispersibility after drying	Screened different sugars and identified trehalose

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Jessica Hoskins

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Adam Zaczek

Yan He


abbvie

ANP formulation stability

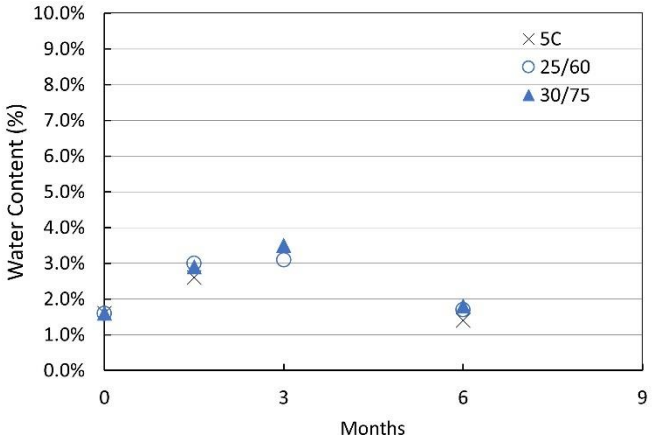
Stability was monitored on crimped FD vials

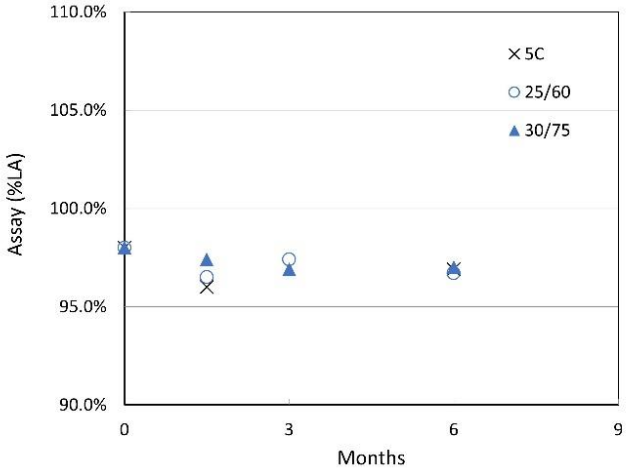
Water content and assay were consistent for 6 months under

- **5 °C**
- **25 °C 60% RH**
- **30 °C 75% RH**

No impurities was increasing

Redispersion time remained at 30s with vortex





Application of ANP formulation

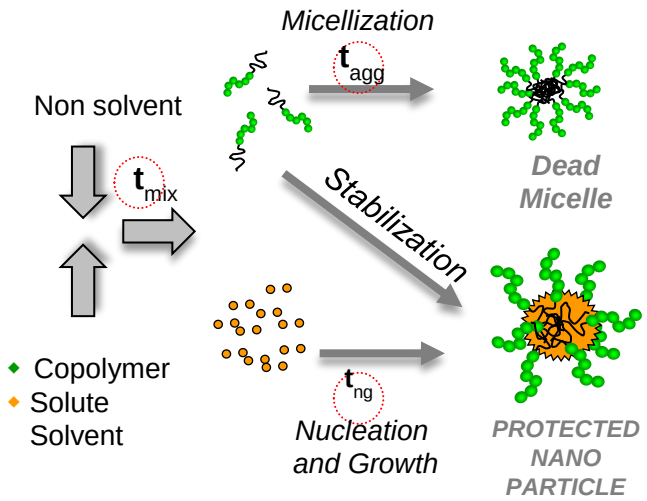
- **Extremely low solubility**
- **High melting point (not suitable for hot melt extrusion)**
- **High pill burden**

Formation of nanoparticles – *solvent anti-solvent precipitation*

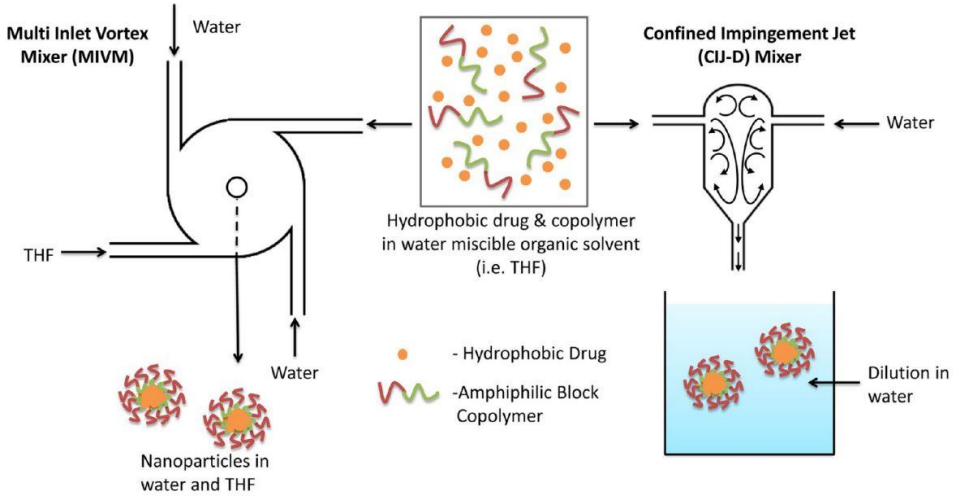
FROM SCIENCE TO MEDICINES

- Controlled mixing of API solution with antisolvent with at high *Reynold's Number*
- Supersaturation leads to precipitation and encapsulation of API in polymer/surfactant

Mechanism of NanoPrecipitation



Design of mixing devices



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Controlling drug nanoparticle formation by rapid precipitation
Suzanne M. D'Addio, Robert K. Prud'homme, *Adv. Drug Deliver. Rev.* 2011, 63 417-426