Fumaric Acid Microenvironment Tablet Formulation and Process Development for Crystalline Cenicriviroc Mesylate, a BCS IV Compound

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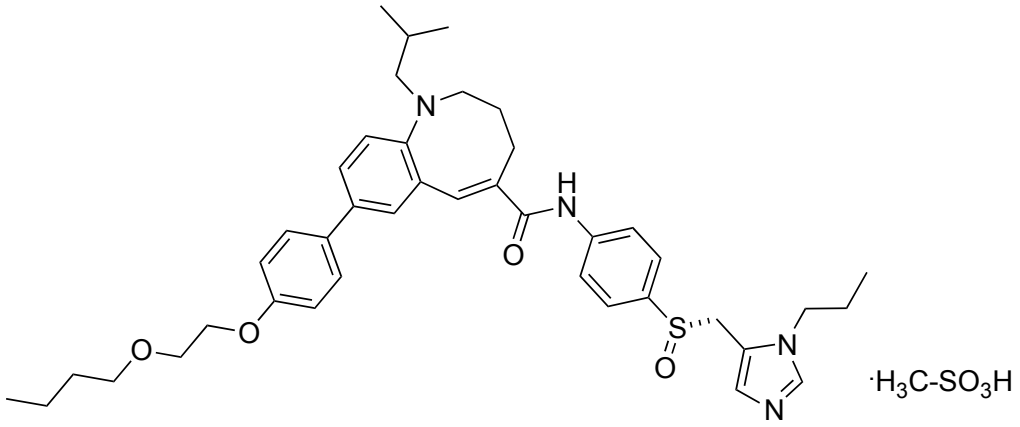
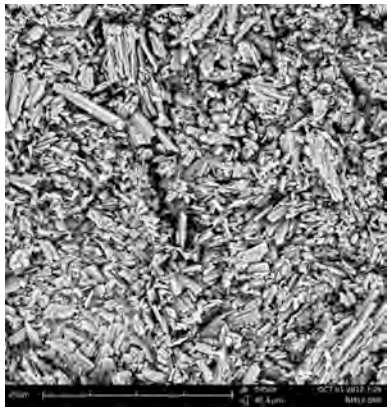
Presentation Outline

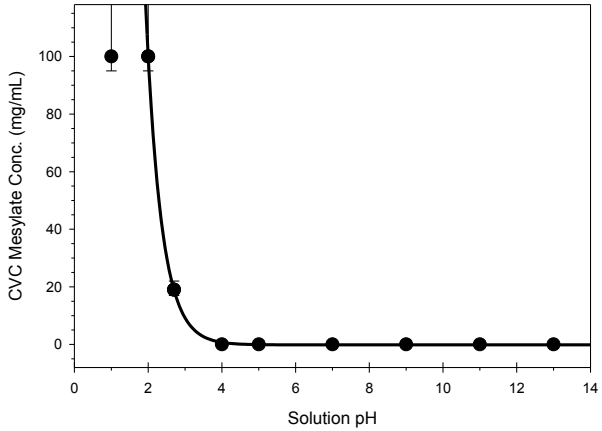
- Properties of Cenicriviroc Mesylate (CVC)
- Formulation and Process Background
- Challenges and Objectives
- Microenvironment pH Modification
- Formulation Screening Study
- Dog PK Evaluation
- FBRM Application in Formulation Selection
- Characterization of Scale-up Batches

Physicochemical Properties of CVC

- CCR5 and CCR2 dual chemokine receptor antagonist
- BCS IV
- Solubility
  - Intrinsic (pH 6.3): <0.002 mg/mL
  - 0.01 N HCl (pH 2): >100 mg/mL
- Papp: < 1 × 10^{-6} cm/sec
- Non-hygroscopic
- pKa_1: 4.3 pKa_2: 6.2
- log P: >3
- Melting point: 153°C
- Milled API







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CVC as CCR5 Antagonist in HIV Infection Treatment

- CCR5 chemokine receptor is a validated HIV target (entry inhibitors)
- CCR5 and CCR2 receptor antagonist
  - IC_{50} CCR2 = 3.1 nM
  - IC_{50} CCR5 = 5.9 nM
- Once-daily dosing
  - Plasma $T_{½}$ = 30-40 hours

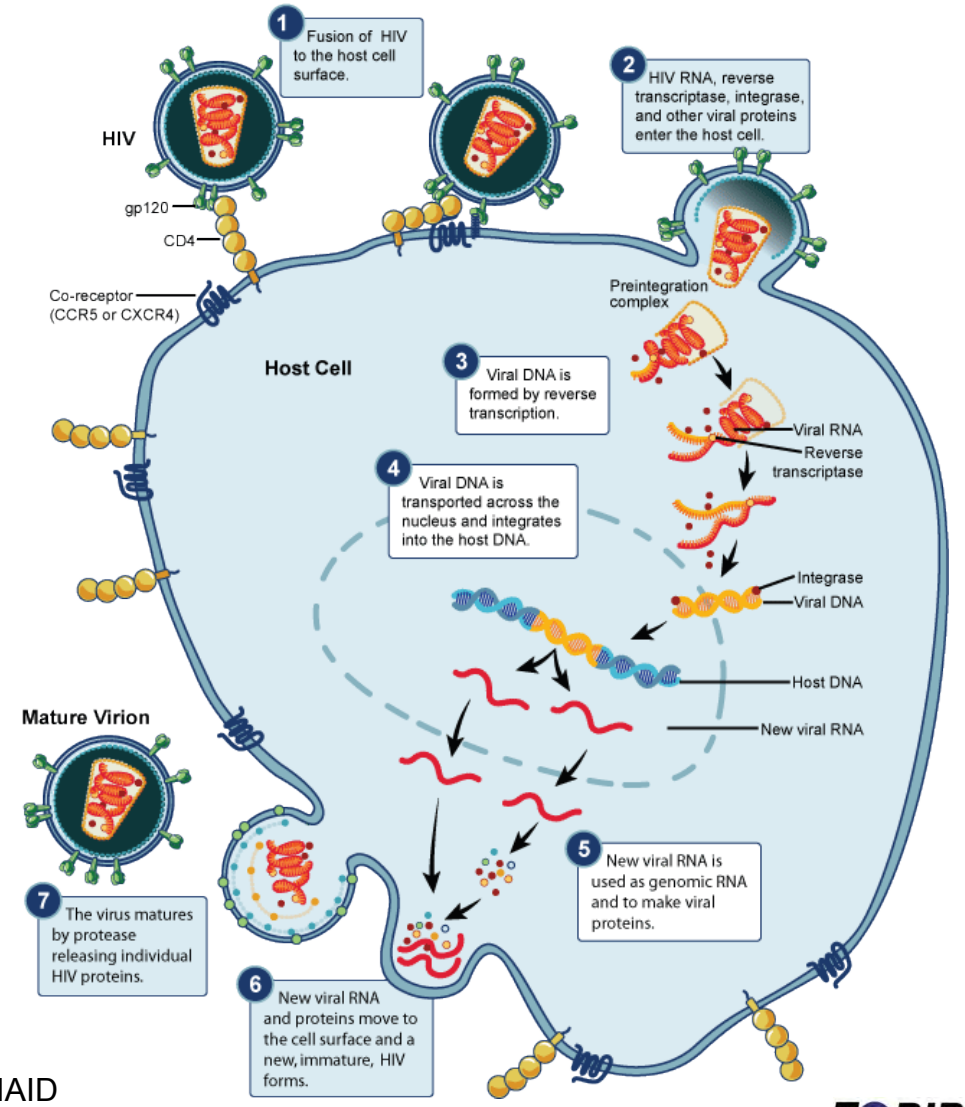

Photo source: NIAID

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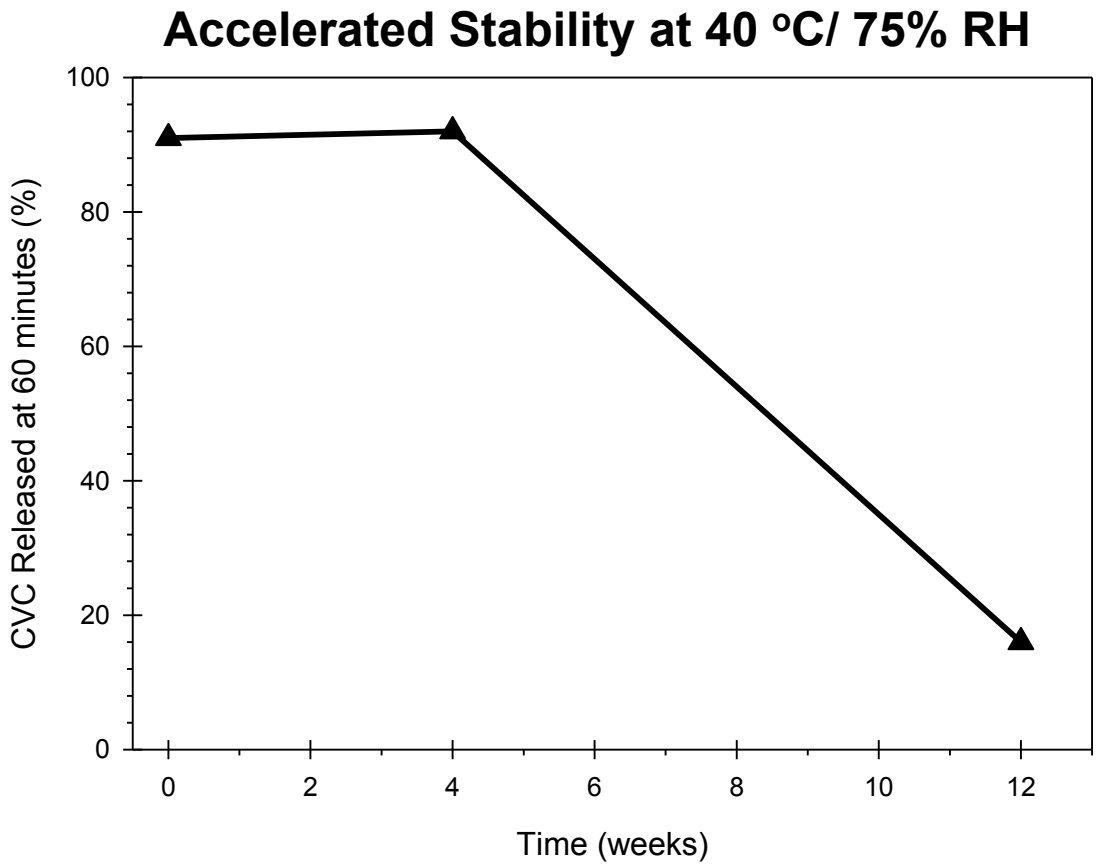
Historical Drug Product:
Phase 1 and Phase 2a, pH Modified Tablet Formulation

Components	Conc. (% w/w)	Unit Formula (mg/unit)
Cenicriviroc Mesylate	4.74	28.45
Mannitol	56.93	341.55
Microcrystalline Cellulose	13.33	80.00
Silicon Dioxide	2.00	12.00
Citric Acid	**12.50**	**75.00**
Croscarmellose Sodium	5.00	30.00
Hydroxypropyl Cellulose	2.00	12.00
Talc	2.00	12.00
Magnesium Stearate	1.50	9.00
Total	100.0%	600.0 mg

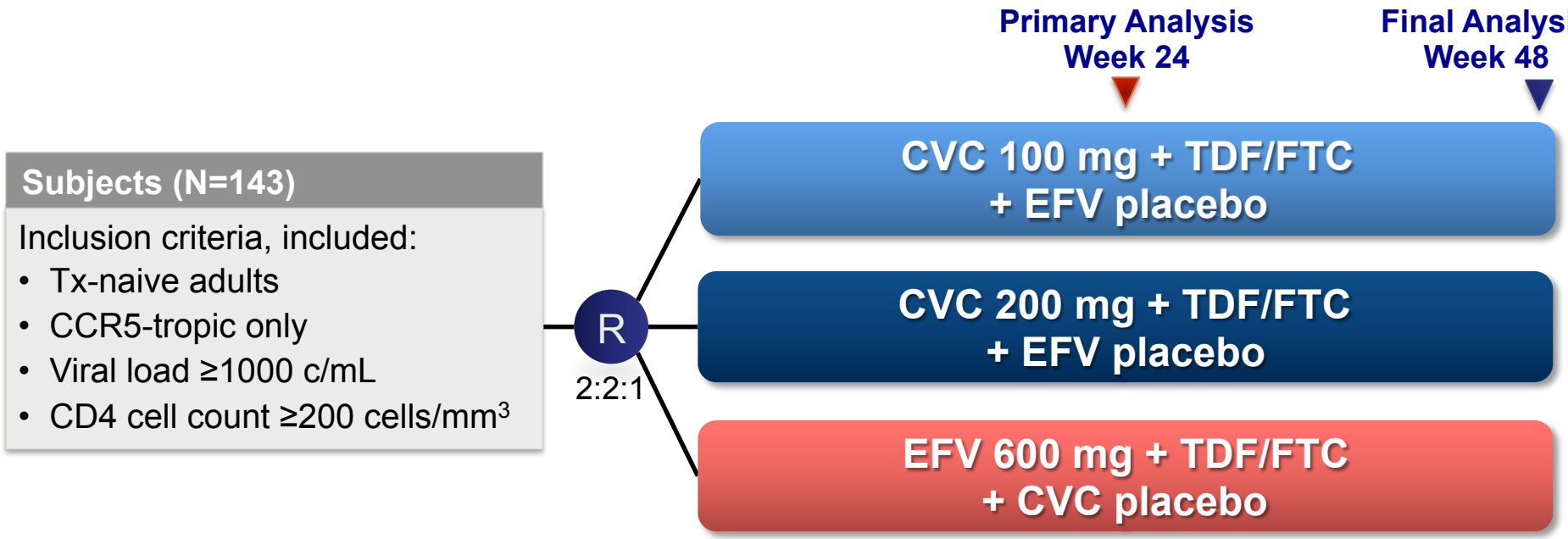
Dissolution Decrease of Phase 1 and 2a Citric Acid Formulation



Historical Drug Product:
Phase 2b, Spray-Dried Dispersion Tablet Formulation

Components	Conc. (% w/w)	Unit Formula (mg/unit)
Cenicriviroc Mesylate	8.33	50.00
Hypromellose Acetate Succinate	**25.00**	**150.00**
Sodium Lauryl Sulfate	2.00	12.00
Croscarmellose Sodium	6.00	36.00
Microcrystalline Cellulose	27.83	167.00
Mannitol	27.83	167.00
Silicon Dioxide	1.00	6.00
Magnesium Stearate	2.00	12.00
Total	100.0%	600.0 mg

CVC Phase 2b Clinical Trial Design (Study 202)



Primary endpoint: Subjects (%) with HIV RNA <50 copies/mL at Week 24 (Snapshot)

Study regimen: **6 tablets daily with split dosing schedule**

- CVC/placebo (4 tablets) taken with breakfast
- EFV/placebo (1 tablets) taken at bedtime, plus
- Truvada® (1 tablets)

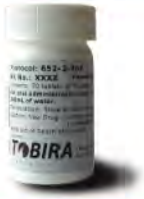
- Tropism determined by both Quest genotypic and Monogram Trofile® phenotypic tropism assays
- Stratified by baseline viral load (< or ≥100,000 c/mL)

Study Regimen – Drug Administration

A total of 6 tablets/day with split dosing schedule

STUDY 202

DOSING INSTRUCTIONS

CENICRIVIROC/ PLACEBO			Take 2 tablets from each bottle in the morning with breakfast and 8 oz. (240 mL) of water.
TRUVADA			Take 1 tablet with 8 oz. of water, with or without food and at any time.
EFAVIRENZ/ PLACEBO			Take 1 capsule on an empty stomach with 8 oz. of water, at bedtime.

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Historical Drug Product Formulation Challenges for CVC

- Poor Chemical Stability
  - Lipid formulation
  - Wet granulation formulations
- Poor Physical Stability
  - Citric acid-containing formulation
  - Wet granulation formulations
  - Increase in moisture content
- Tablet Size/API Concentration
  - Phase 2b formulation 8.3% CVC
  - Multiple tablet burden for 100 mg and 200 mg dose
  - Requires formulation with higher API load and/or bioavailability to enable combination with other antiretroviral agents in a single tablet

Tablet Reformulation Objectives

- Develop a single, once daily, oral tablet formulation suitable for CVC dose adjustment up to 200 mg
- Maximize CVC concentration to maintain core tablet weight below 900 mg
- Use as a common formulation for various fixed-dose combination products
- Demonstrate acceptable chemical and physical stability
- Bioavailability comparable to or exceeding the spray-dried dispersion formulation
- Reduce sensitivity to gastric pH variability
- Develop a robust and scalable manufacturing process

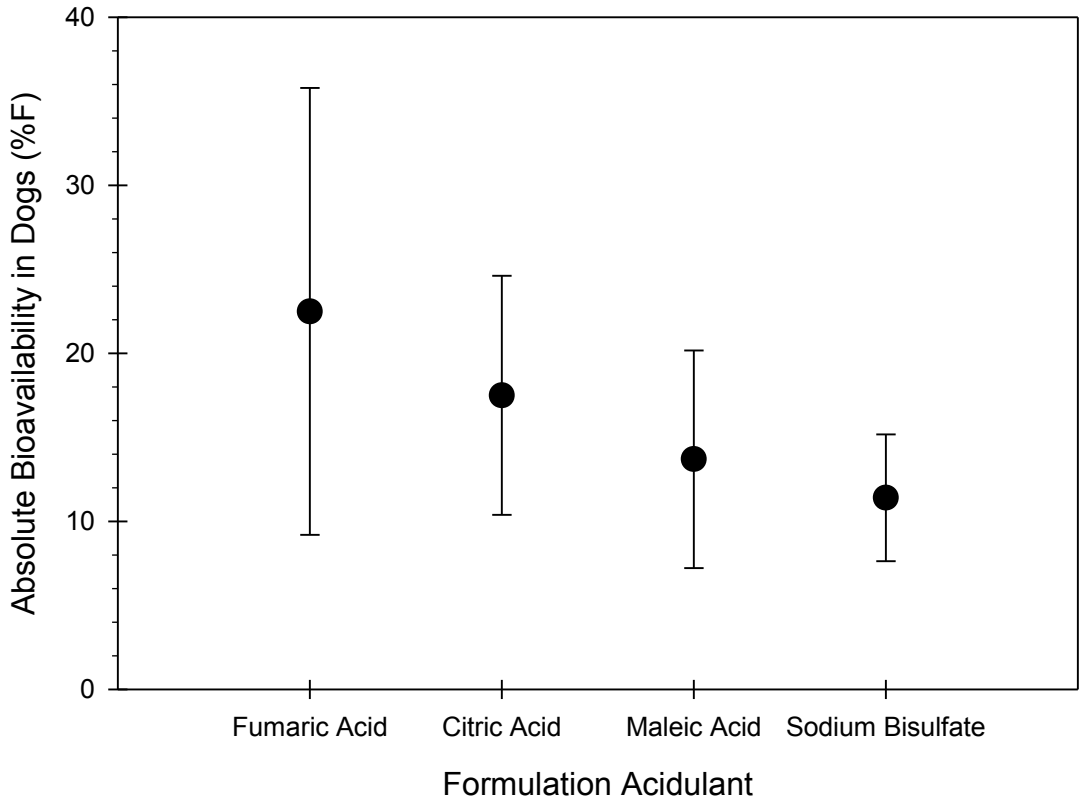
Screening Study with Pharmaceutically Acceptable Acids

Components	Unit Formula (mg/unit)			
	Citric Acid	Fumaric Acid	Maleic Acid	Sodium Bisulfate
Cenicriviroc Mesylate	28.45[a]	28.45[a]	28.45[a]	28.45[a]
Mannitol	7.88	7.88	7.88	7.88
Hydroxypropyl Cellulose	2.62	2.62	2.62	2.62
Croscarmellose Sodium	3.50	3.50	3.50	3.50
Citric Acid	**43.75**	-	-	-
Fumaric Acid	-	**43.75**	-	-
Maleic Acid	-	-	**43.75**	-
Sodium Bisulfate	-	-	-	**43.75**
Silicon Dioxide	0.43	0.43	0.43	0.43
Magnesium Stearate	0.88	0.88	0.88	0.88
Total	87.5	87.5	87.5	87.5

[a] equivalent to 25 mg cenicriviroc

Dog PK Results of Acid Screening Study

N=5 dogs, fasted, no pretreatment



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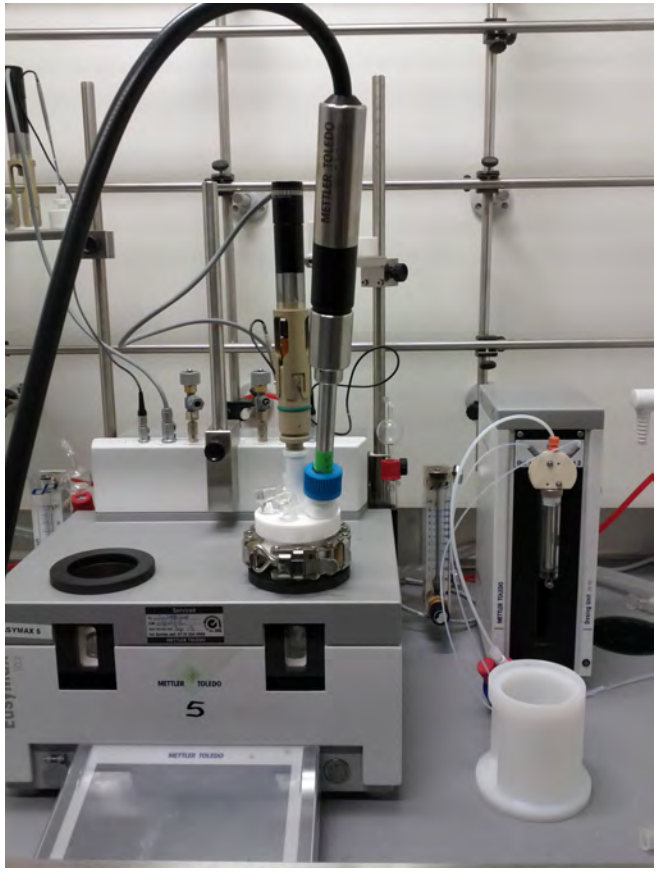
Lab Equipment Setup

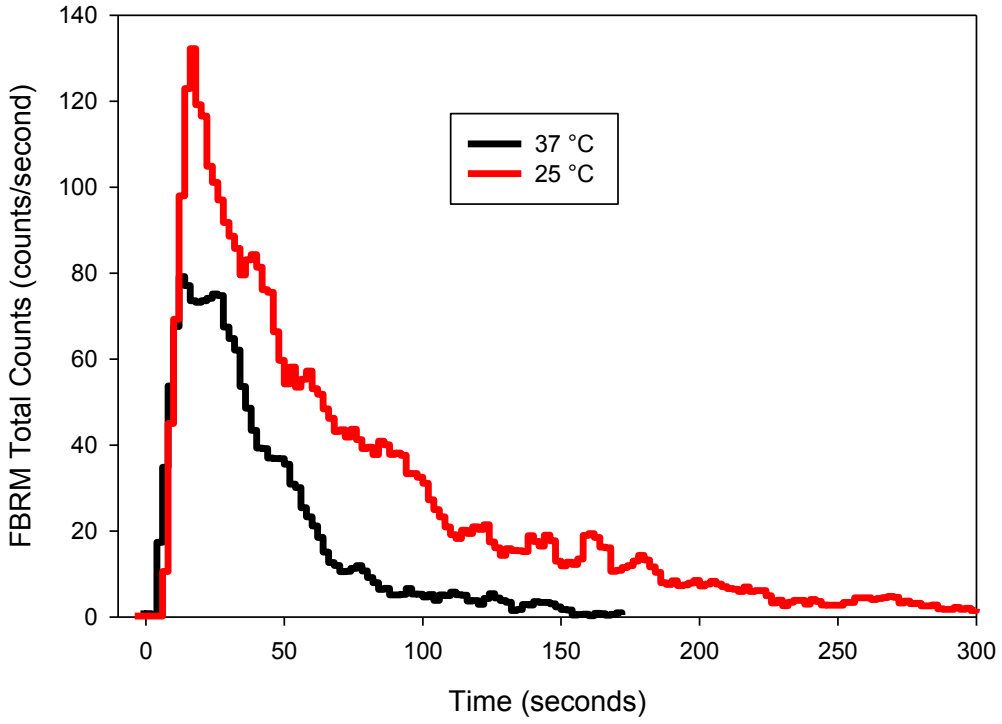
- Mettler Toledo EasyMax
- G400 FBRM probe
- 2 m/s scan speed
- 90 mL purified water
- 250 rpm impeller speed
- Upward pumping, 4 blade impeller
- Macro mode
- Length weighting for granular systems



FBRM Application:
Dissolution Kinetics of Acidic Excipients

Method
- 200 mg acid
- 90 mL purified water
- 200 rpm impeller speed
- Upward pumping, 4 blade impeller

Results
- Fumaric acid had slowest dissolution rate
- Increased contact time during dissolution
- Other acids dissolve too rapidly (regardless of pKa)
  - Correlates with increased absorption in dog pK study



Acid	Dissolution time (sec) 25 °C	37 °C
Adipic	68	32
Citric	6	<2
Fumaric	**312**	**152**
Maleic	4	<2
Sodium Bisulfate	26	<2
Succinic	46	8
Tartaric	6	<2

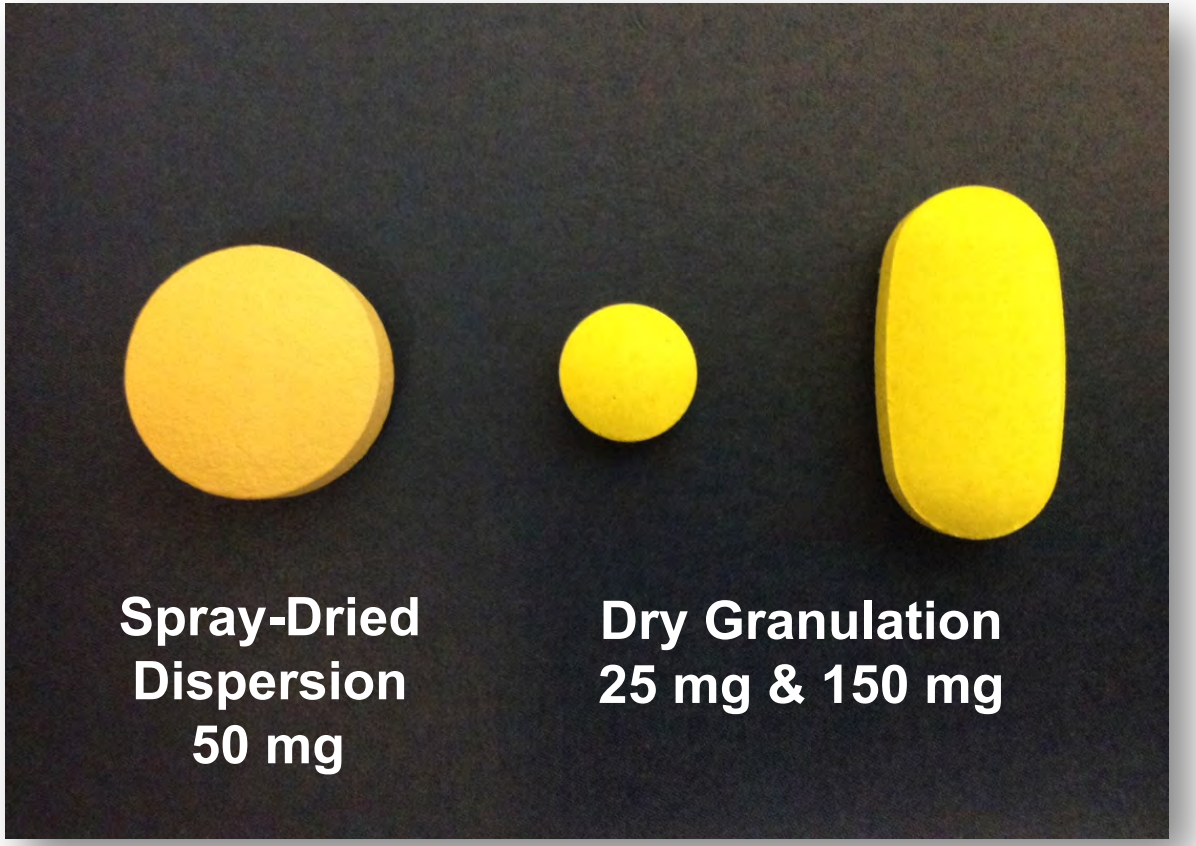
Formulation Optimization

- Dry Granulation Process (Vector TFC-Lab Micro)
- 500 psi roll pressure
- 400 g batch size

	Unit Formula (mg/unit)			
Components	**DG1**	**DG2**	**DG3**	**DG4**
Cenicriviroc Mesylate	170.69[a]	170.69[a]	170.69[a]	170.69[a]
Fumaric Acid	160.00	160.00	**160.00[b]**	160.00
Microcrystalline Cellulose	252.68	272.18	272.18	272.18
Crospovidone	-	-	-	**19.50**
Croscarmellose Sodium	**58.50**	**39.00**	**39.00**	**19.50**
Magnesium Stearate	8.13	8.13	8.13	8.13
Total	650.0	650.0	650.0	650.0

[a] equivalent to 150 mg cenicriviroc
[b] added extragranularly

CVC Tablet Prototypes



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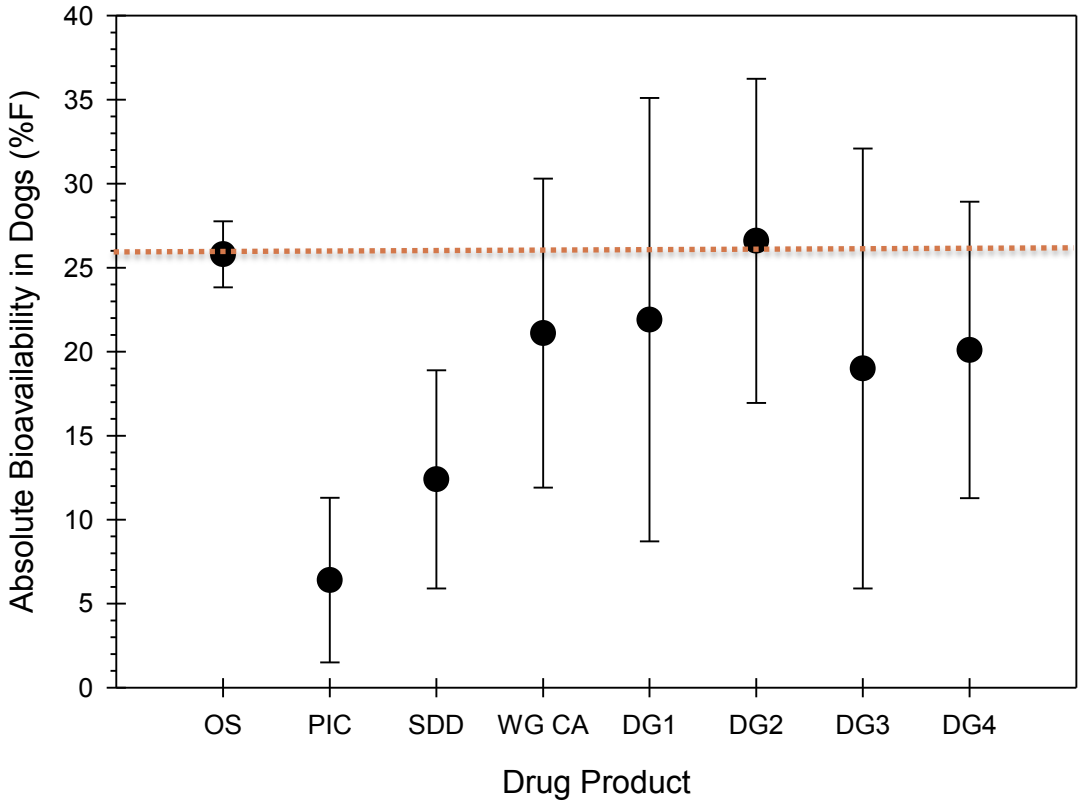
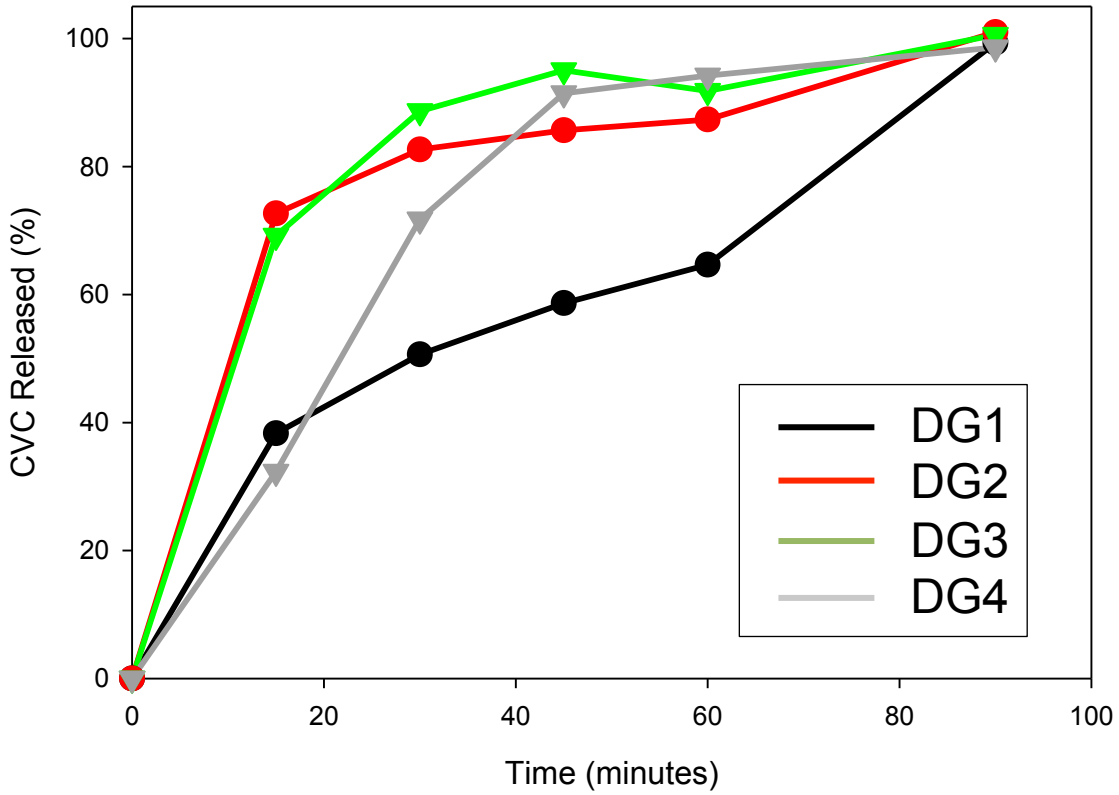
Dog PK of Fumaric Acid Prototype Formulations

- DG2 formulation had similar exposure as an oral solution
- Fumaric acid prototypes had increased bioavailability as compared to the SDD or PIC prototypes
- N=5 dogs, fasted, no pretreatment



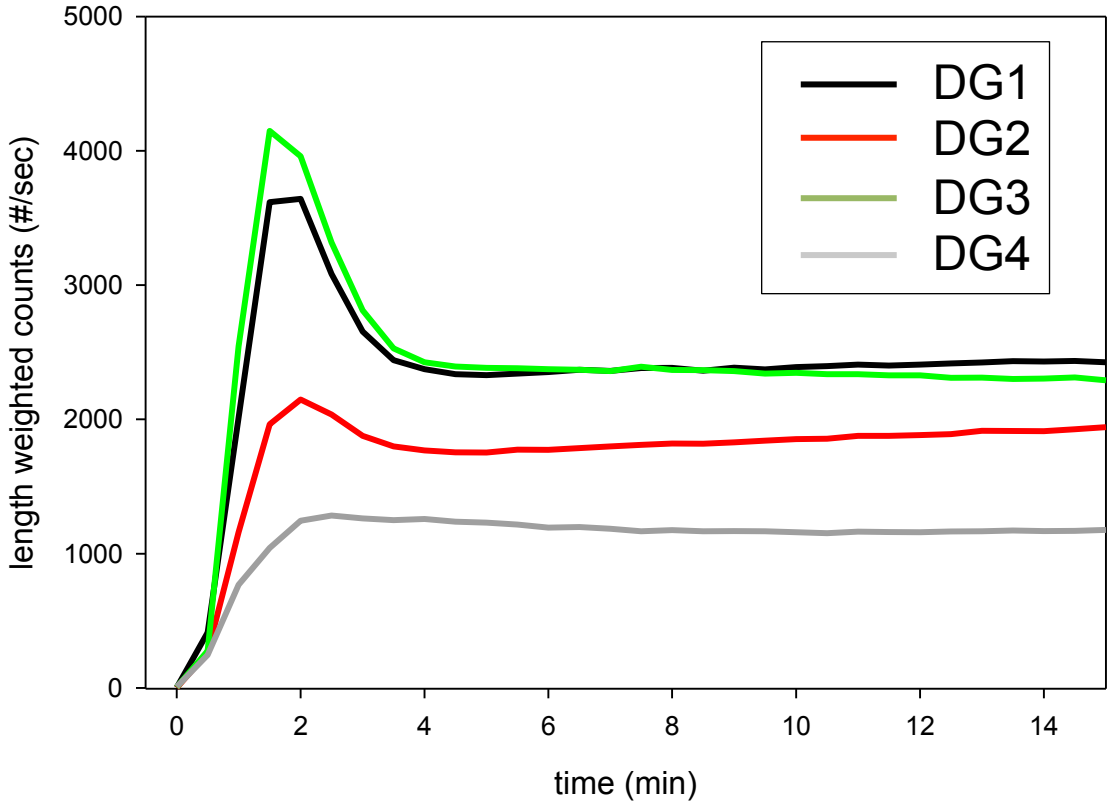
In vitro Dissolution

- USP Type II, 0.1 N HCl + 0.1% CTAB
- 50 rpm paddle speed
- N=3
- No correlation between dissolution and dog PK



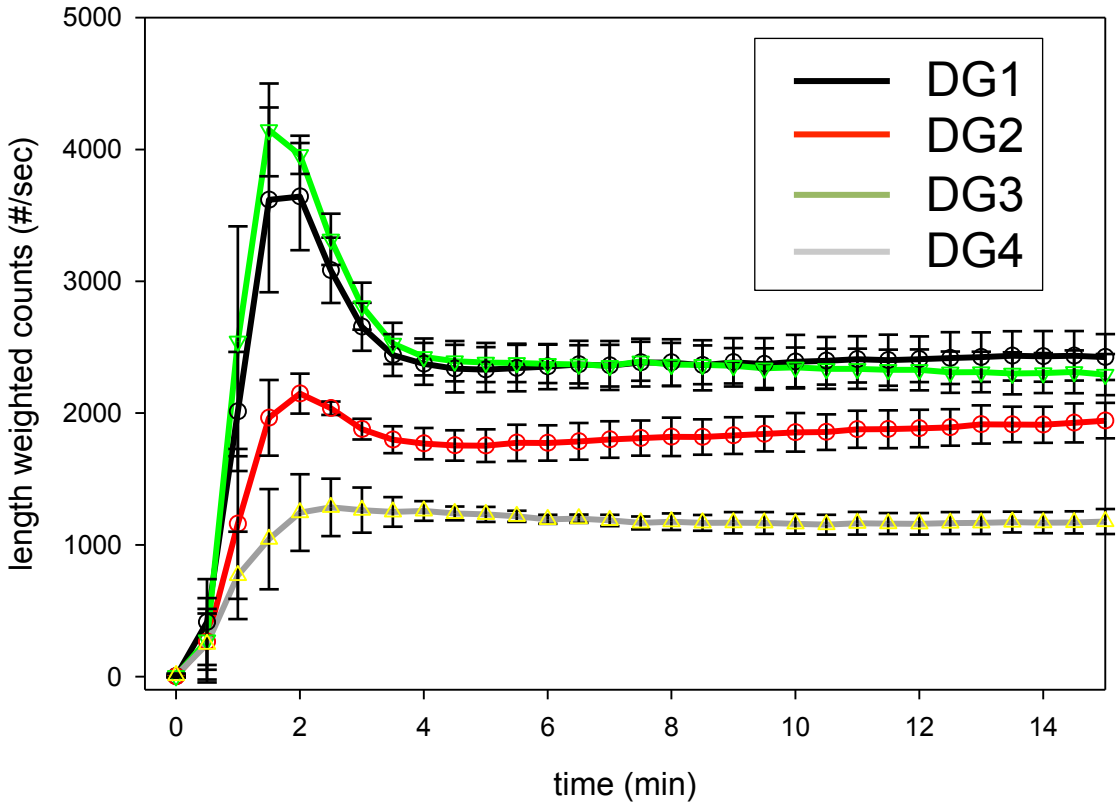
Total Length Weighted Counts, 1-1000 micron

- DG1 high disintegrant and DG3 extragranular fumaric acid had high counts upon disintegration
- DG2 disintegrated rapidly but had lower counts
- DG4 disintegrated by slow erosion



Total Length Weighted Counts, 1-1000 micron

- Average of 5 samples
- Demonstrates good method reproducibility



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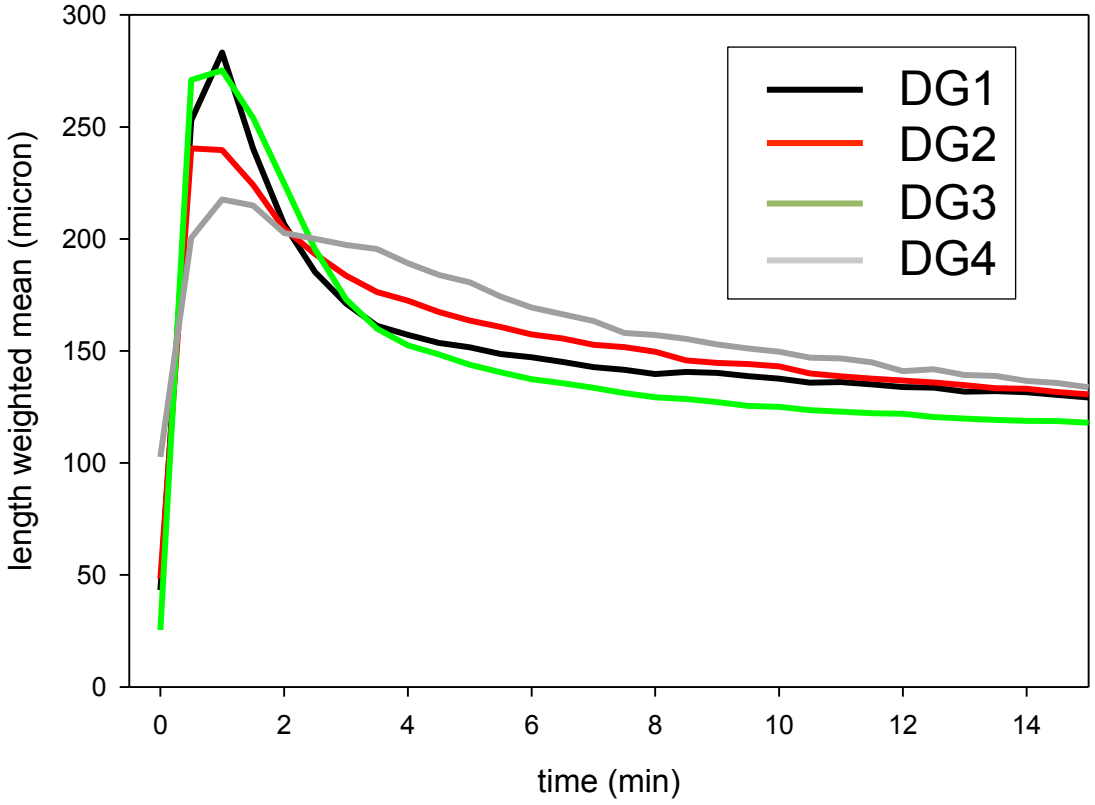
Length Weighted Mean

- Length weighted means show a similar trend and converge to a similar mean chord length corresponding to the insoluble excipients



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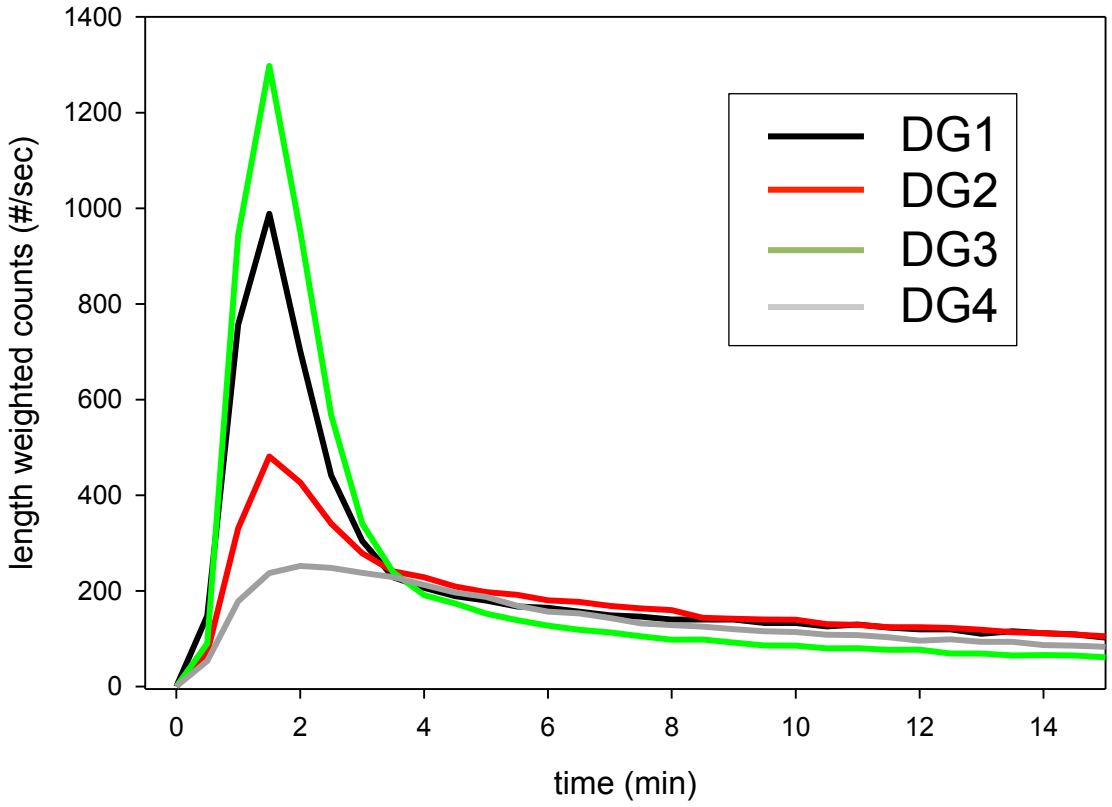
Length Weighted Counts, 300-1000 micron

Rank order of particle counts are consistent over the binned size ranges



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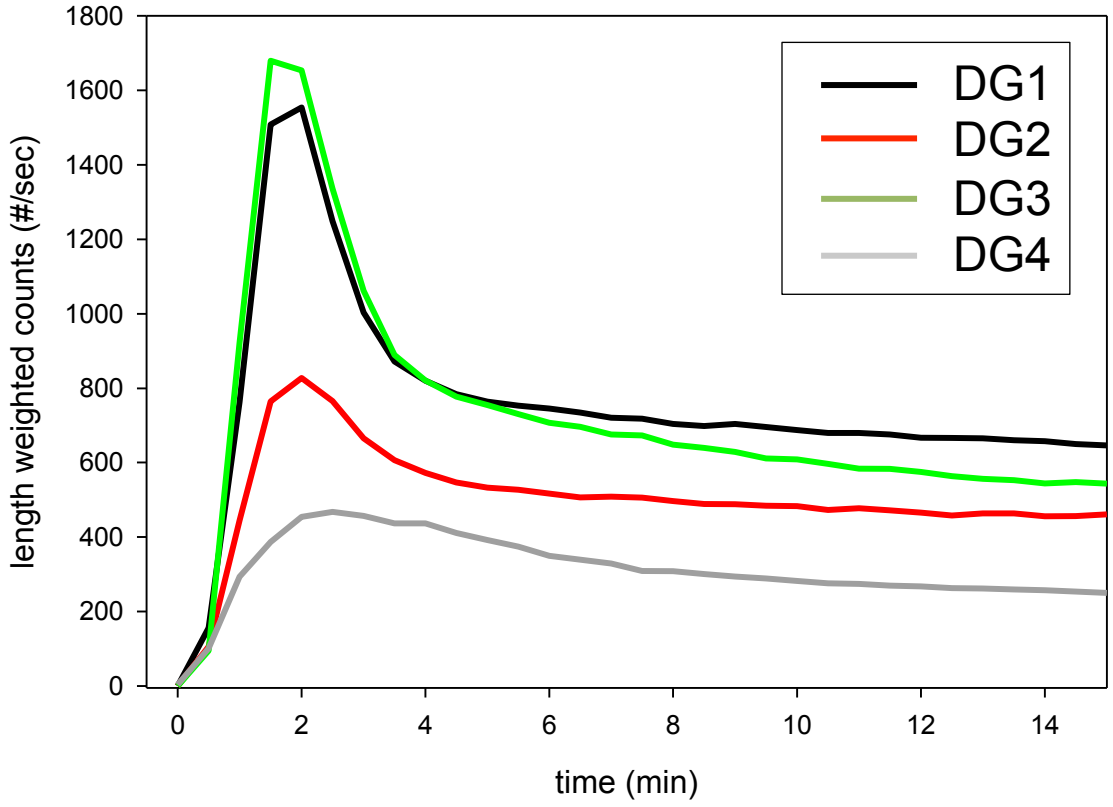
Length Weighted Counts, 150-300 micron



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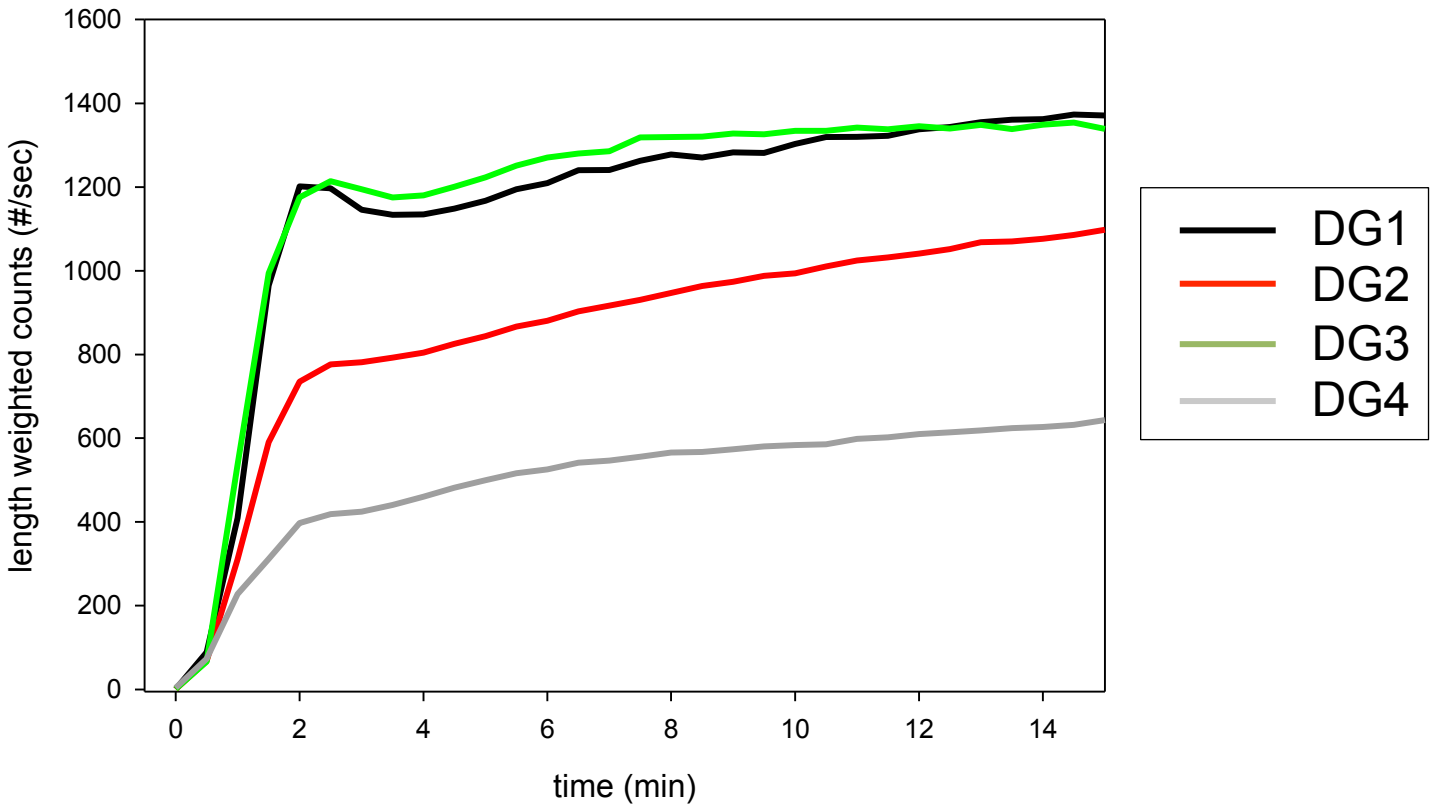
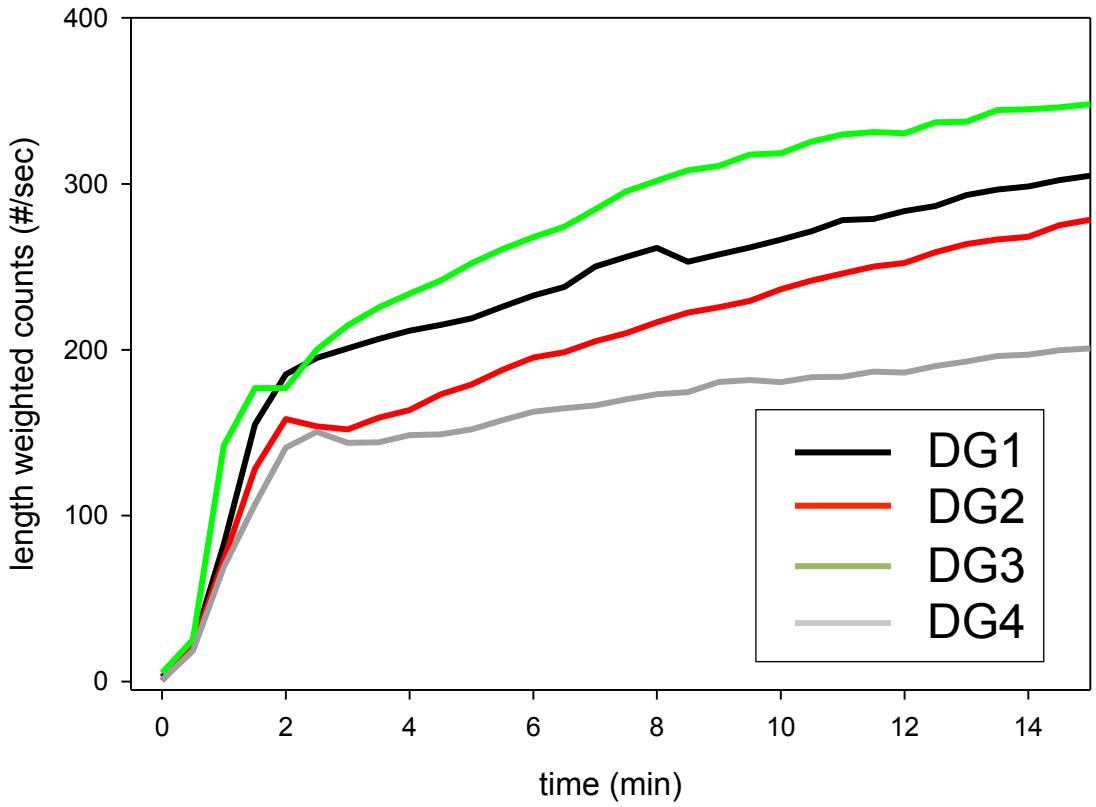
Length Weighted Counts, 50-150 micron



Length Weighted Counts, <50 micron



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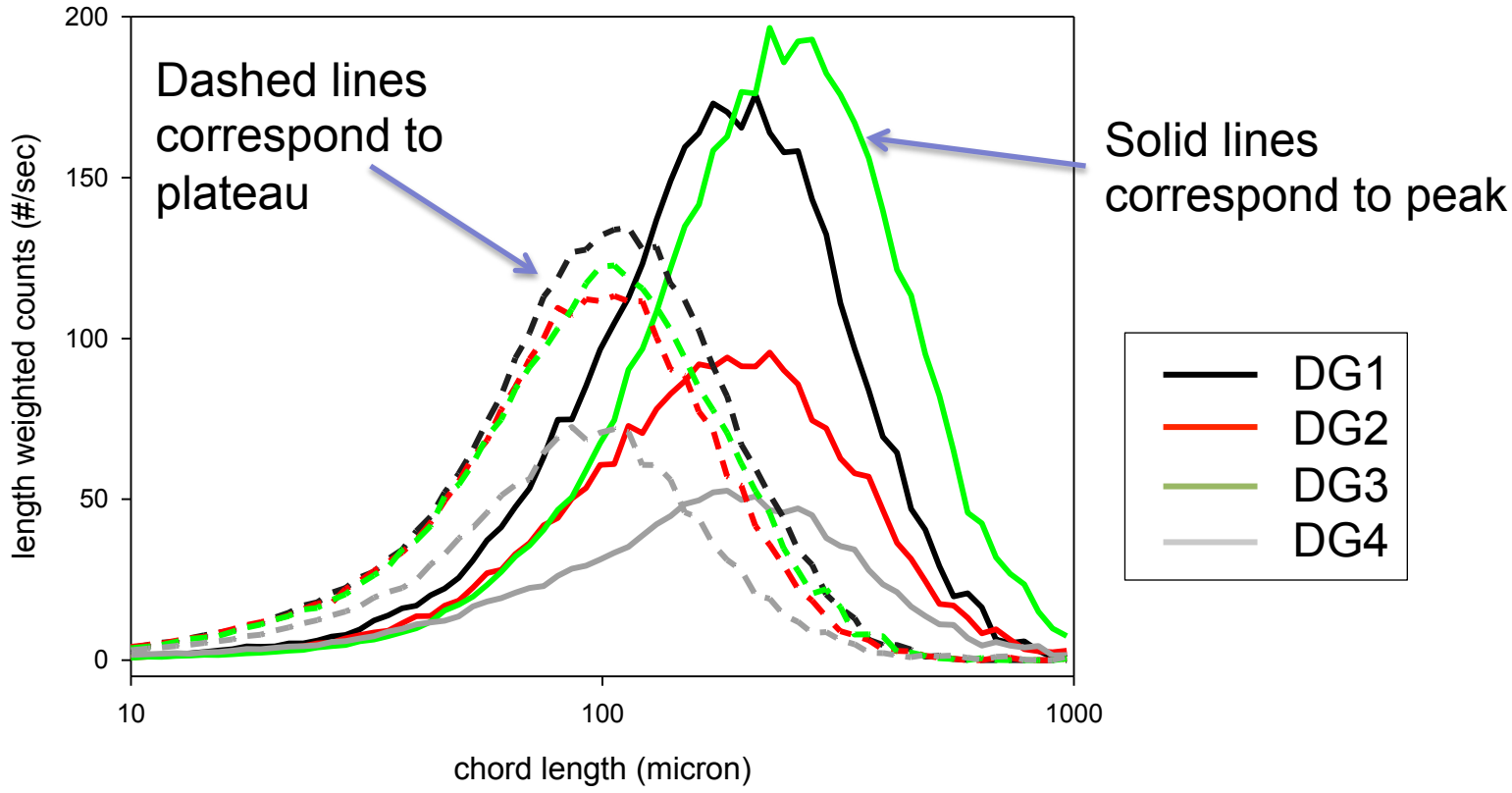
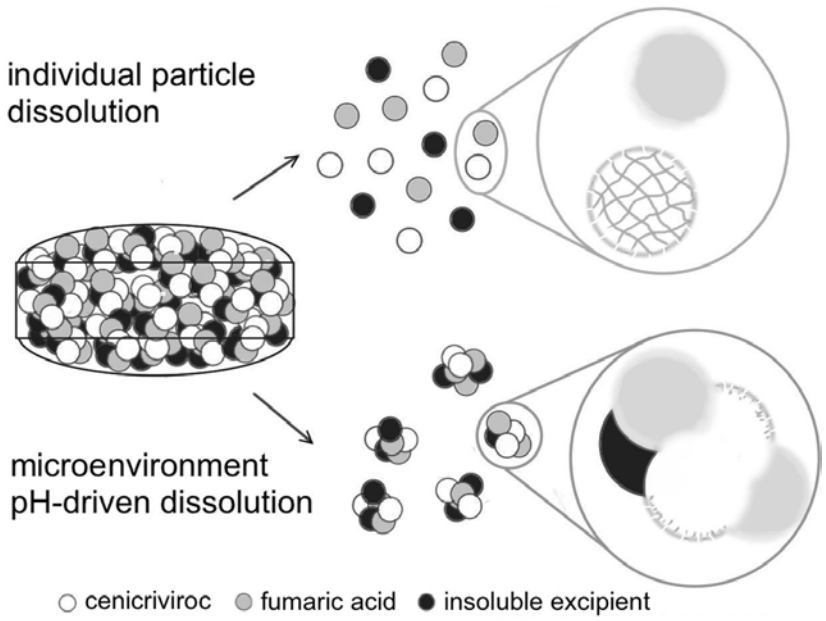
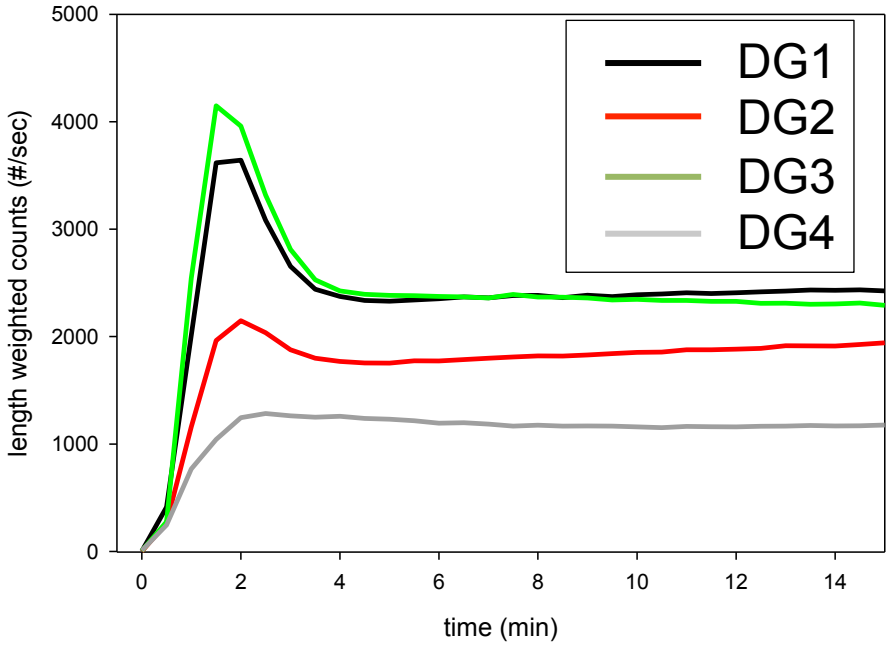
Peak and Final Distributions



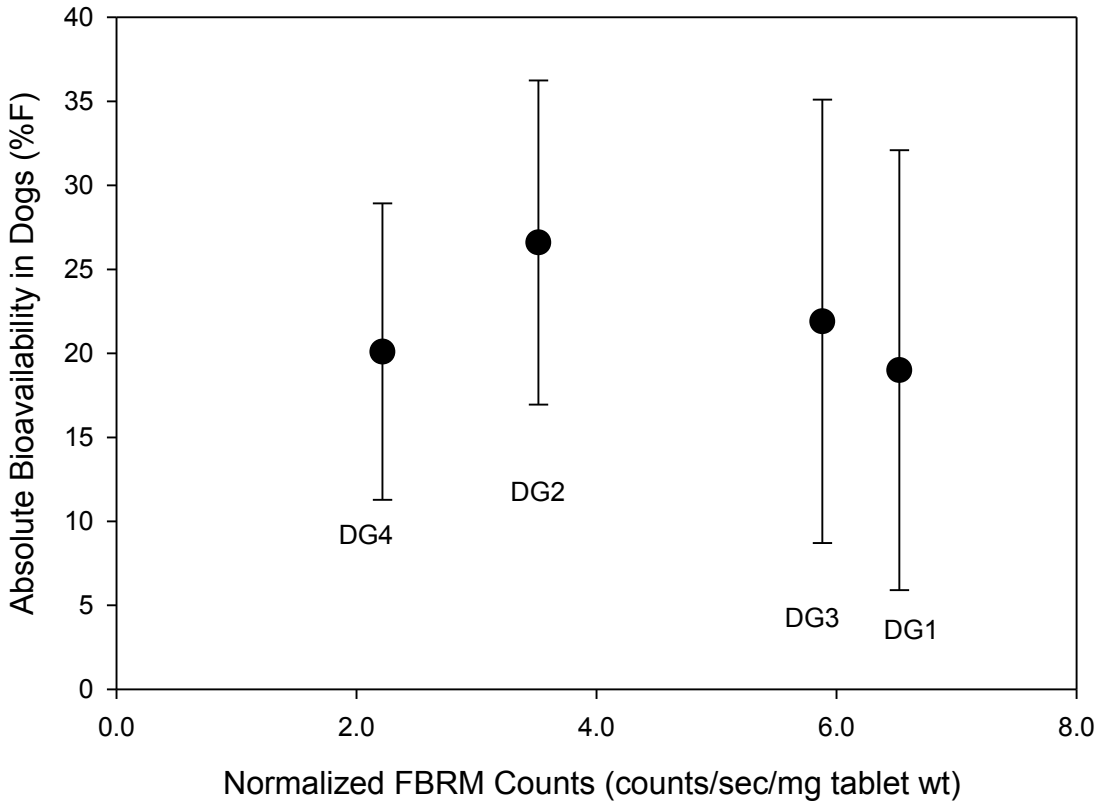
Total Length Weighted Counts

- Low counts (at peak) correlate with granules remaining intact and prolonged low microenvironment pH via slow dissolving fumaric acid
- DG1 and DG3 fast disintegration circumvented optimal interaction with fumaric acid

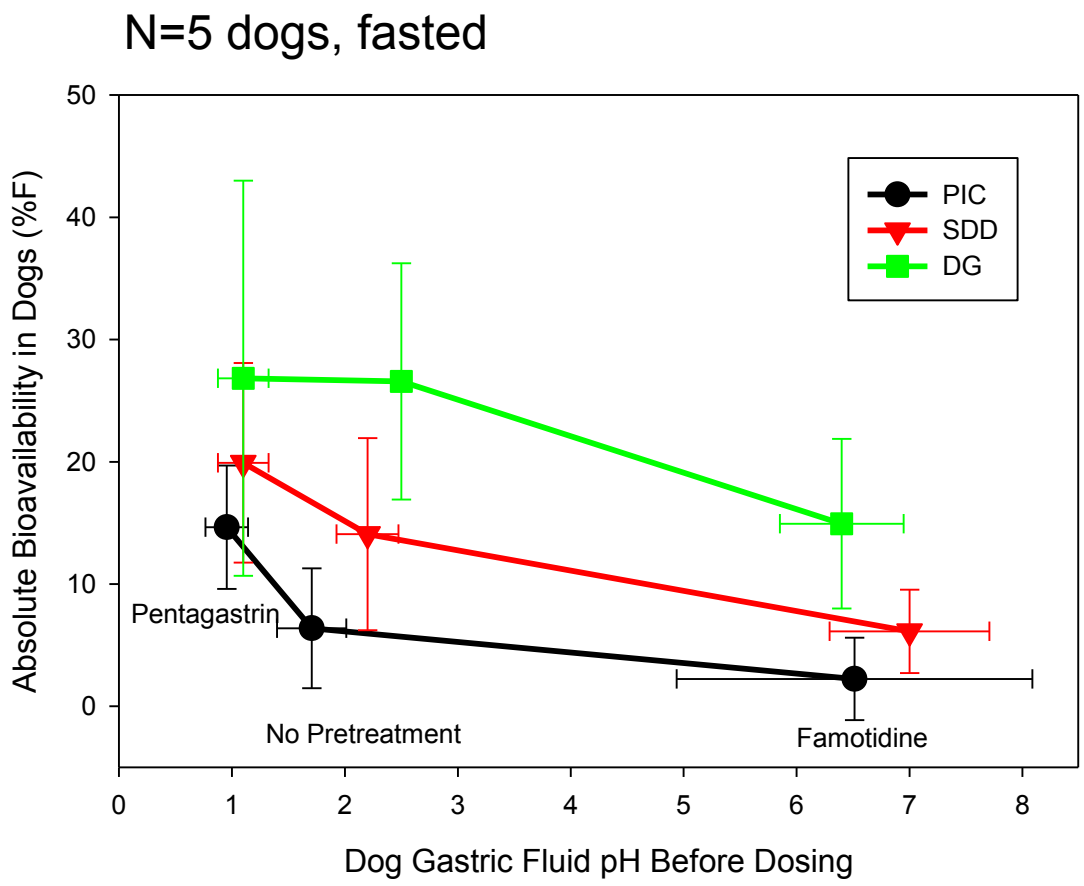




Dog PK Normalized by Maximum Counts and Tablet Weight



Effect of Gastric pH on Dog PK



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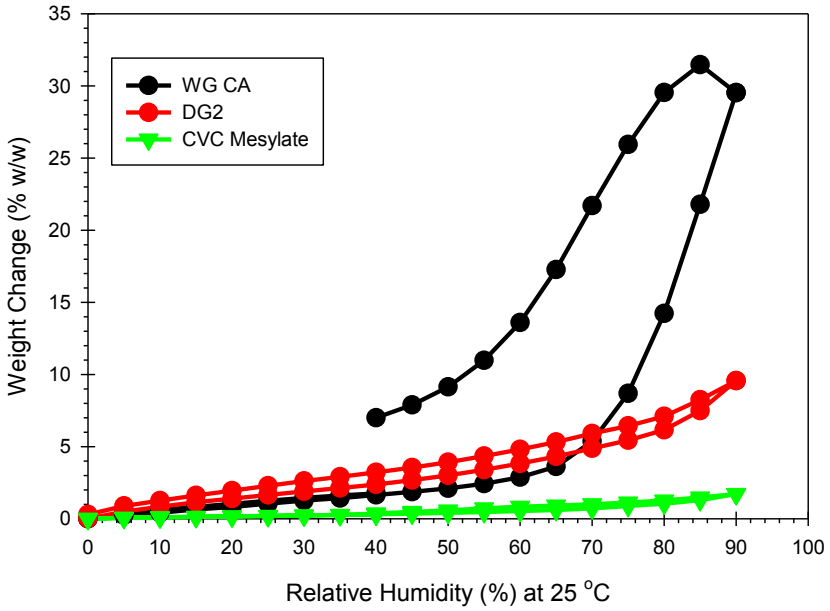
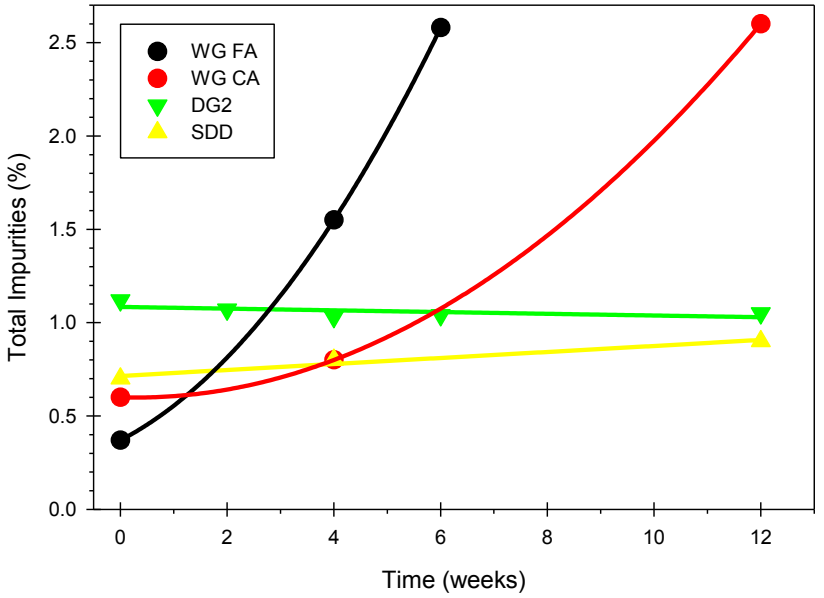
Physical and Chemical Stability





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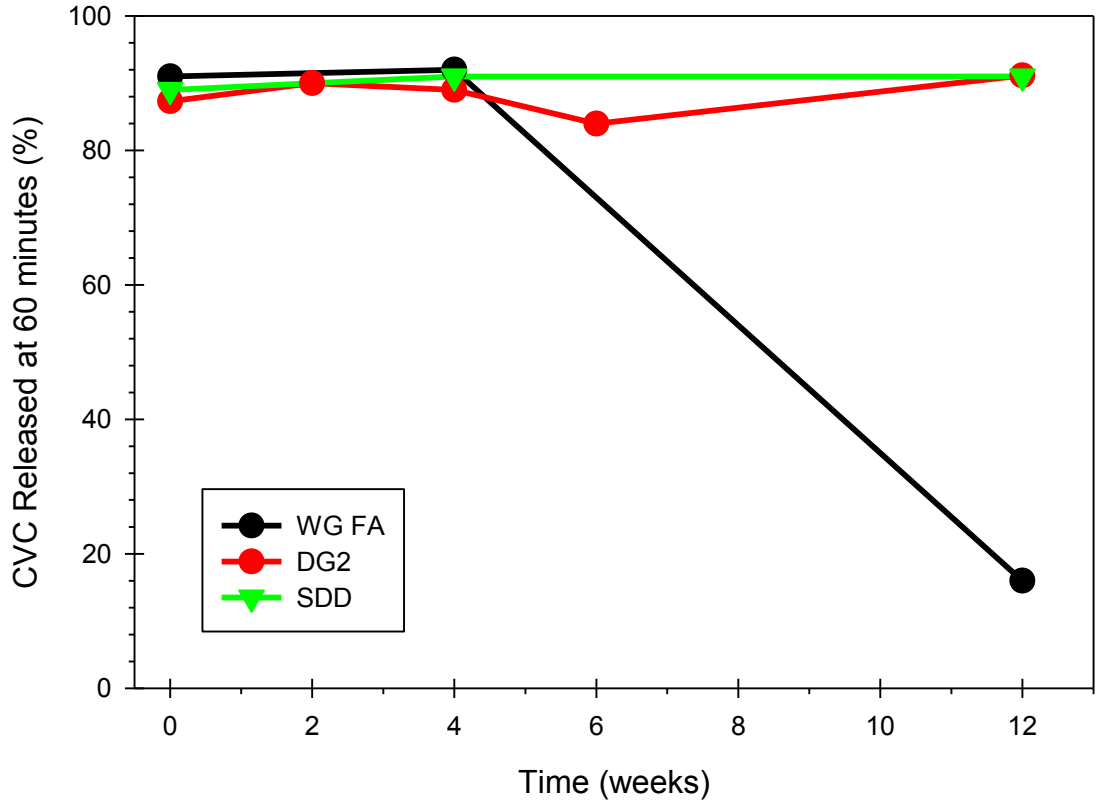
Dissolution Stability



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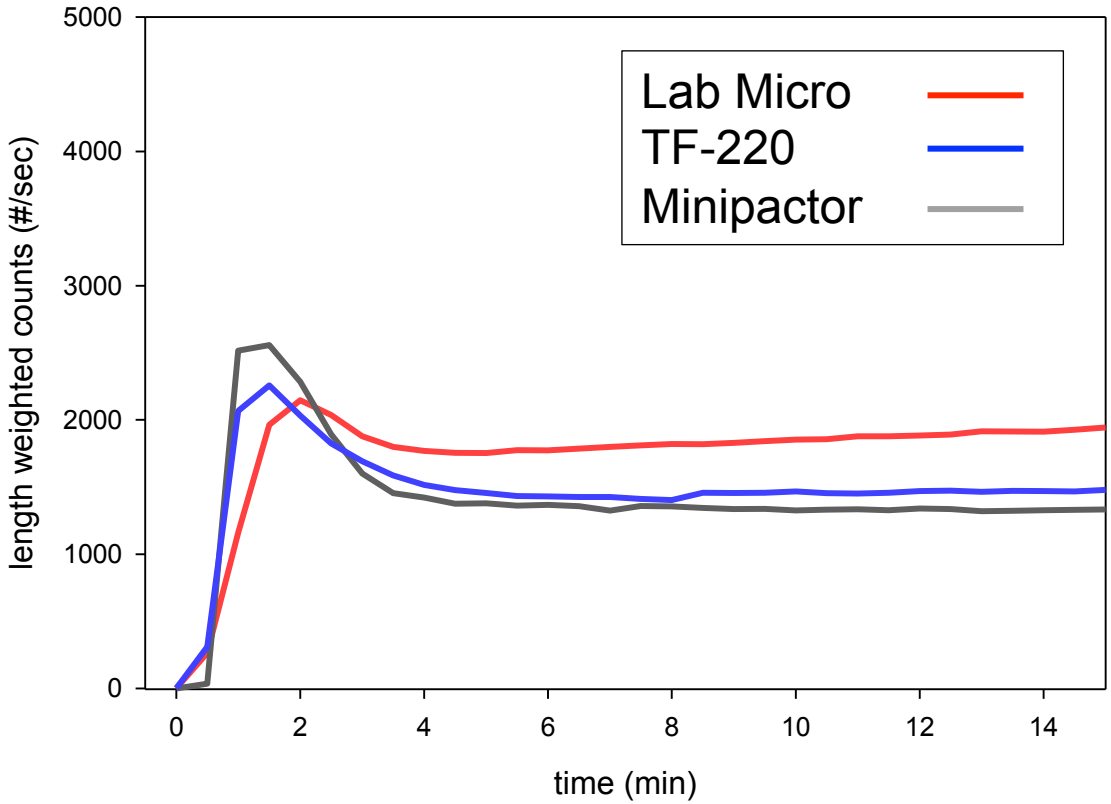
Scale-up and Transfer of Process

- Process scale-up to approximately 5 kg batch size
- Qualify 2 different models of roller compactors

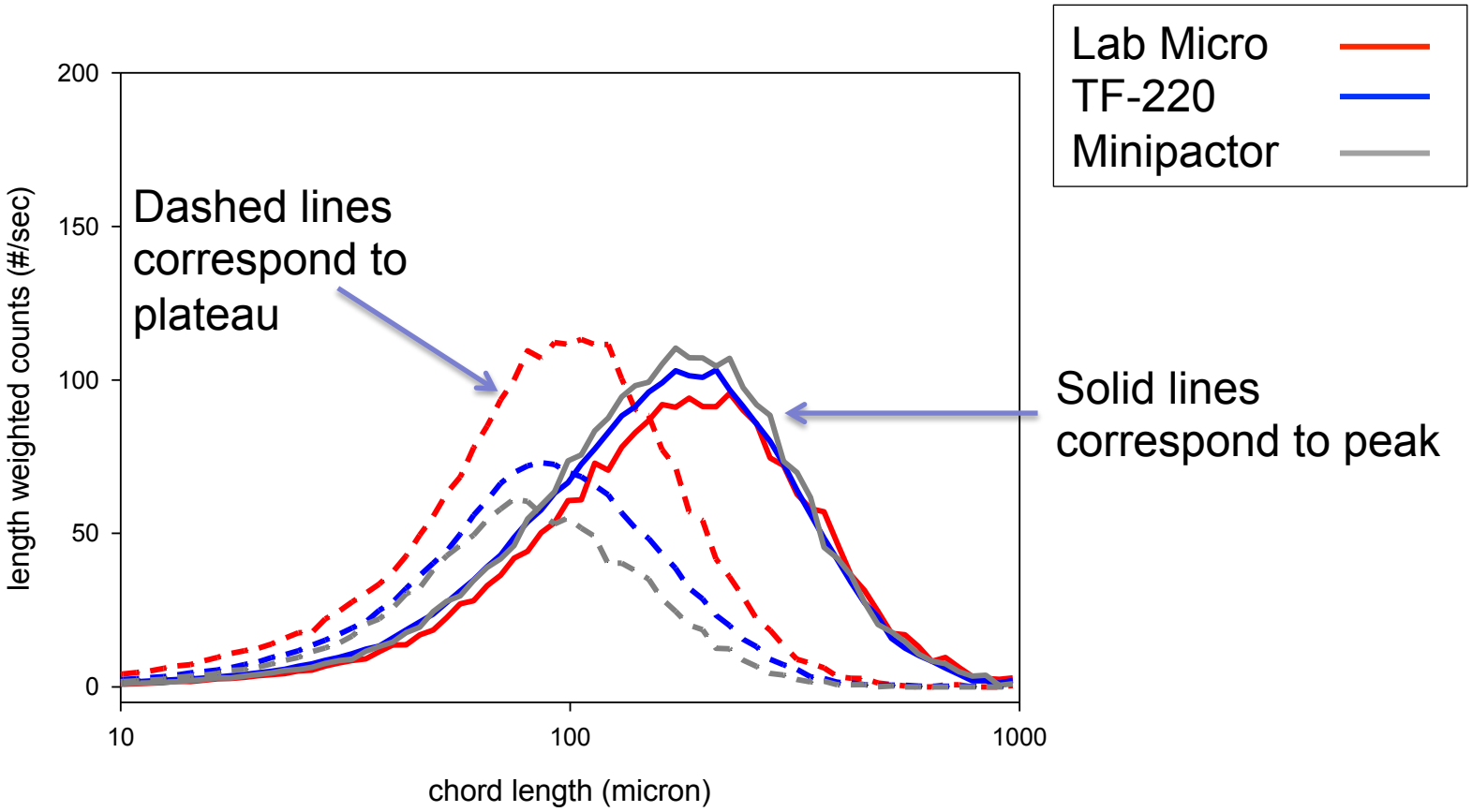
Vector TF-220

Gerteis Minipactor

Tablet Disintegration Total Length Weighted Counts



Peak and Final Distributions



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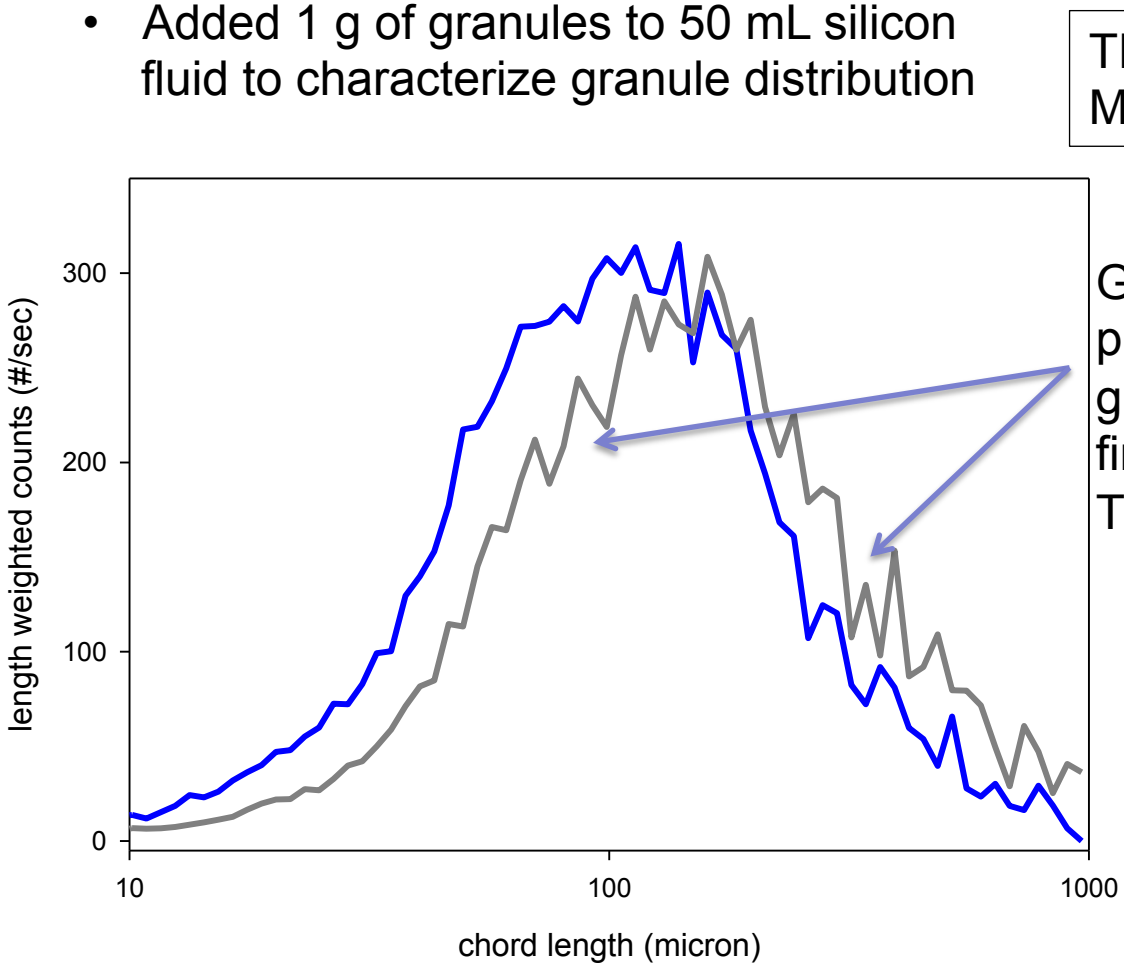
Granule Distribution in Silicon Oil

- Added 1 g of granules to 50 mL silicon fluid to characterize granule distribution



Gerteis Minipactor produces coarser granules with less fines than the TF-220

Conclusions

- New single tablet formulation at 150 mg CVC (650 mg total weight) performed as well as 4 x 50 mg CVC (2,520mg total weight) spray-dried dispersion formulation
- Tablet disintegration characterization by FBRM supported formulation selection
- FBRM detected and quantified distinct disintegration regimes between the formulations
- Formulation disintegration characteristics were maintained during scale-up and between 2 roller compactor designs
- FBRM is a useful drug product performance characterization tool applicable for formulation screening, process optimization, scale-up, equipment and site transfers

Acknowledgments

- Mettler-Toledo AutoChem
- WuXi AppTech
- APC Ltd