Unlocking Strength Scaling for Extended-Release Tablet Development: Research Gaps and Opportunities

FY2025 GDUFA Public Workshop

Silver Spring, MD

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Outline

- Overview of oral extended-release (ER) drug products and release mechanisms
- Brief introduction on hydrophilic HPMC (hydroxylmethylcellulose) matrix ER tablets
- Regulatory guidance on demonstrating bioequivalence (BE) for additional strengths
- Case studies
- Summary & key research gaps

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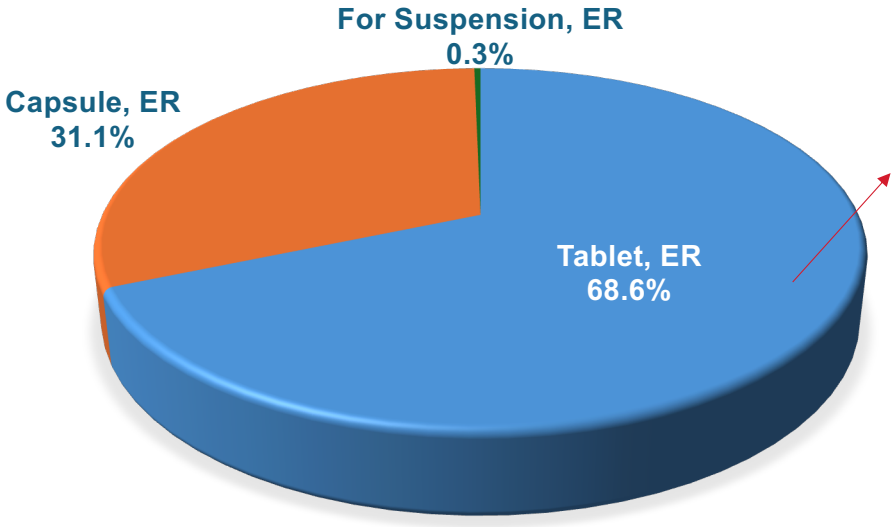
Oral ER Product Overview



FDA APPROVED ORAL ER PRODUCTS

78 out of 105 (~75%) products based on same API(s) have multiple strengths

Total: 2259 oral ER drug products (accessed in May 2025)

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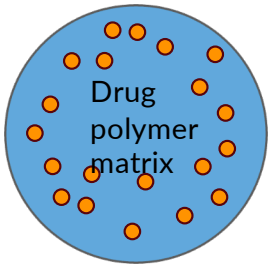
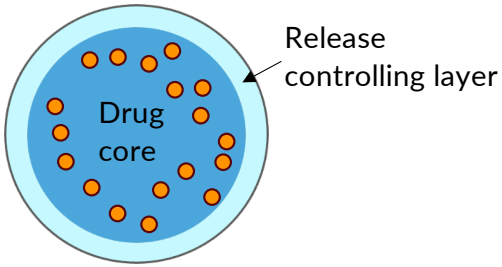
Drug Release Mechanisms of Oral ER Tablets

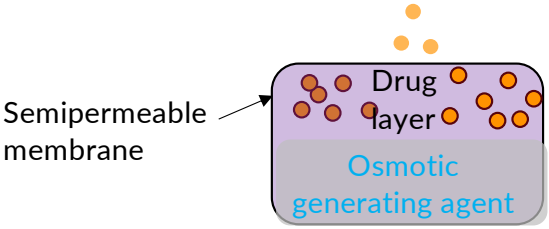
Matrix-Type



Reservoir-Type

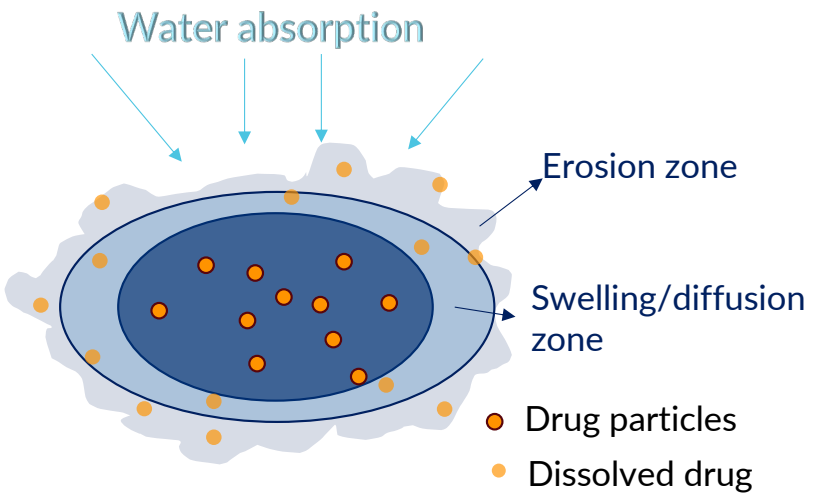


Osmotic-Type



Release mechanisms: diffusion, erosion, dissolution, reservoir, osmotic, or combination of these.

HPMC Matrix Tablets



Drug release controlled by swelling, diffusion and/or erosion

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Examples of Hydrophilic HPMC Matrix Tablets

API	Products	Indication	Strengths	PSG's on additional strengths
Alprazolam	Xanax® XR	Anxiety disorder	0.5, 1, 2, 3 mg	0.5, 1, and 2 mg based on: 1) Acceptable BE on the 3 mg; 2) Formulation proportional similarity across all strengths; 3) Acceptable in vitro dissolution of all strengths (2007)
Carbamazepine	Tegretol® XR	Anticonvulsant	100, 200, 400 mg	100 and 200 mg based on: 1) Acceptable BE for the 400 mg; 2) Acceptable in vitro dissolution of all strengths; 3) Formulation proportional similarity across all strengths (revised 2015)
Guanfacine HCl	Intuniv®	ADHD, hypertension	1, 2, 3, 4 mg	1, 2, and 3 mg based on: 1) Acceptable BE for the 4 mg; 2) Acceptable in vitro dissolution of all strengths; 3) Formulation proportional similarity across all strengths (revised 2016)
Metformin HCl	Metformin HCl	Antihyperglycemic	500, 750, 1000 mg	500 mg based on: 1) Acceptable BE for the 750 mg and 1000 mg; 2) Acceptable dissolution testing across all strengths; 3) Formulation proportional similarity across all strengths (finalized 2008 for 750 mg, revised 2010 for 1000 mg)
Quetiapine fumarate	Seroquel® XR	Schizophrenia, bipolar	50, 150, 200, 300, 400 mg	Based on most recent FDA guidance for industry on BE studies (revised 2024)
Zolpidem	Ambien® CR	Sedative	6.25, 12.5 mg	6.25 mg based on: 1) Acceptable BE on the 12.5 mg; 2) Formulation proportional similarity across all strengths; 3) Acceptable in vitro dissolution of all strengths (finalized 2011)

Orange Book (https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm); Product-Specific Guidances for Generic Drug Development. https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development, accessed in May 2025.

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Demonstrating BE for Additional Strengths

FDA Guidance (2021)

- The reference product (R) demonstrates dosage form equivalence and similar dissolution performance across different strengths.
- The test product (T) includes the same excipients and drug and excipients of different strengths can be either proportional or not proportional in quantity.
- The additional strength of T has the same drug release mechanism as the strength of the test product that underwent an acceptable in vivo BE study compared to the R.
- Similar dissolution profiles between the strength on which the BE testing was conducted and other strengths, based on the similarity factor (f_2) test or other appropriate statistical approaches in at least three dissolution media (e.g., a pH of 1.2, 4.5, and 6.8).

EMA Guidance (2010)

- Same excipients across different strengths.
- Quantitatively proportional composition, i.e. the ratio between the amount of each excipient to the amount of API is the same for all strengths. If deviates, fulfill the following:
  i. The amount API is less than 5 % of the tablet core weight, the weight of the capsule content.
  ii. Same amounts of core excipients and only the amount of API is changed.
  iii. The amount of a filler is changed to account for the change in amount of API.
- Appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo BE testing.

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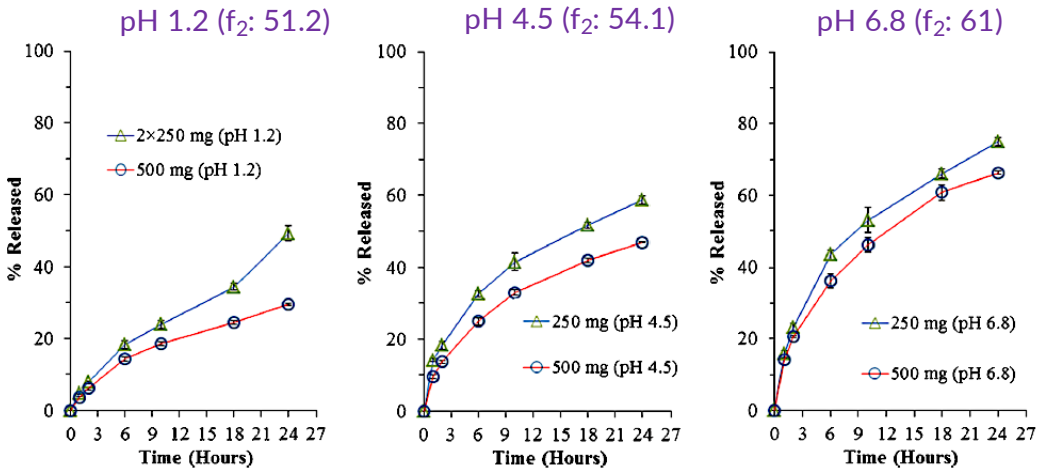
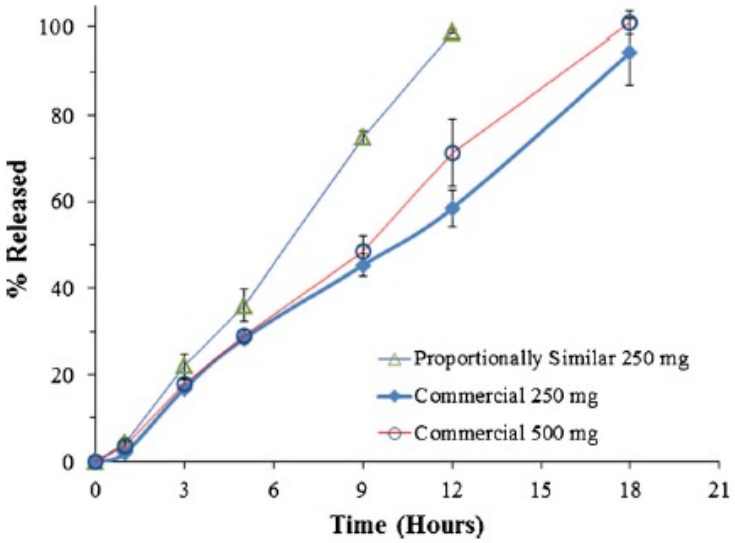
Case Study I

Drug A (pKa 4.8) oval ER tablets with high viscosity HPMC
Strengths: 250 mg & 500 mg



Proportionally similar lower strength 250 mg pass f_2 but not bioequivalent using an IVIVC-based test.



Proportionally dissimilar (50% higher HPMC and 25% decrease in surface/volume) lower strength 250 mg (commercial 250 mg) using the IVIVC-based test.

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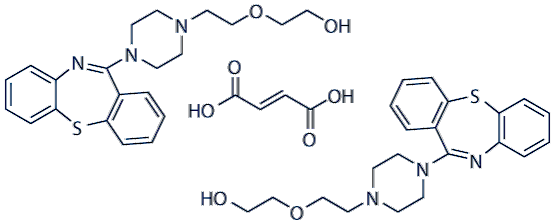
Lin. ZY, The AAPS Journal, 2016, 18(2): 333-345.

Case Study II

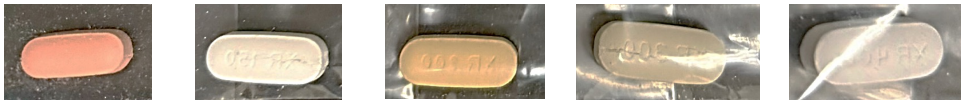
Quetiapine fumarate (QF)



BCS Class II
(pKa 3.31 and 6.97, log P 2.97)

Seroquel® XR indicated for schizophrenia, bipolar, and adjunctive therapy with antidepressants

50 mg *150 mg* *200 mg* *300 mg* *400 mg*



Dose–unit proportionality (50, 200, 300, and 400 mg)

Parameter (units)	*n*	Estimated slope*	95% CI
AUC_{ss} (ng · h/mL)	10	0.92	0.79 to 1.1
$C_{max,ss}$ (ng/mL)	10	1.00	0.91 to 1.09

AUCss, area under the plasma concentration–time curve at steady state; CI, confidence interval; Cmax,ss, maximum plasma concentration at steady state

Linear PK in the dose range o.f 100 to 800 mg

Parameter (units)	Estimate of slope	Standard error	95% CI	*p*-value of H_0: slope = 1	Estimate of intercept α*
AUC^t (ng·h/mL)	0.90	0.08	0.76 to 1.06	0.21	13.61
C^{max} (ng/mL)	0.85	0.08	0.68 to 1.01	0.07	1.16

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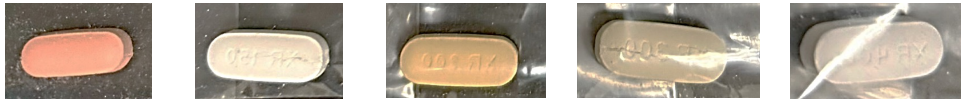
Pharmacokinetic profile of quetiapine XR Bui et al. Current Medical Research & Opinion, 2013, 29(7): 813-825.

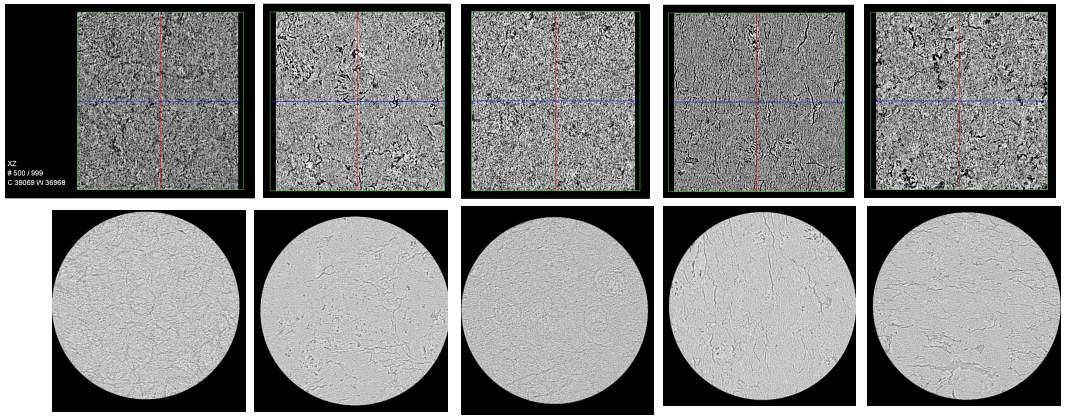
Case Study II_QF ER HPMC matrix Tablets

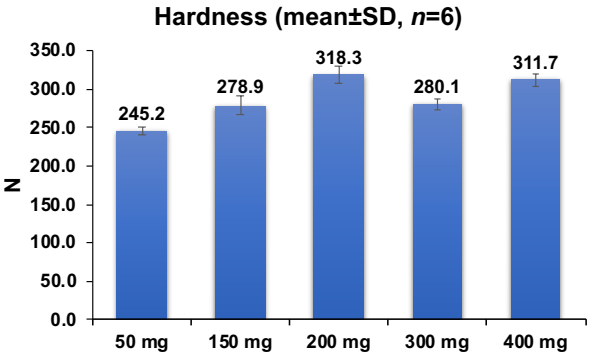
Seroquel® XR



Thickness (mm, n=10)	5.2	5.6	5.8	6.1	6.6
Width (mm, n=6)	6.7	6.8	6.8	7.8	7.8
Length (mm, n=6)	16.4	17.4	17.4	19.2	19.2
Weight (mg, n=10)	513.91±3.45	587.55±2.81	620.58±3.95	825.81±4.73	866.86±6.30

Resolution:
0.55 μm/voxel





Matrix structure similarity in the dry state.

Unpublished data_Shen Lab

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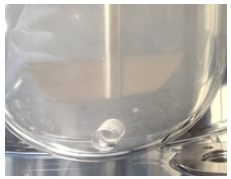
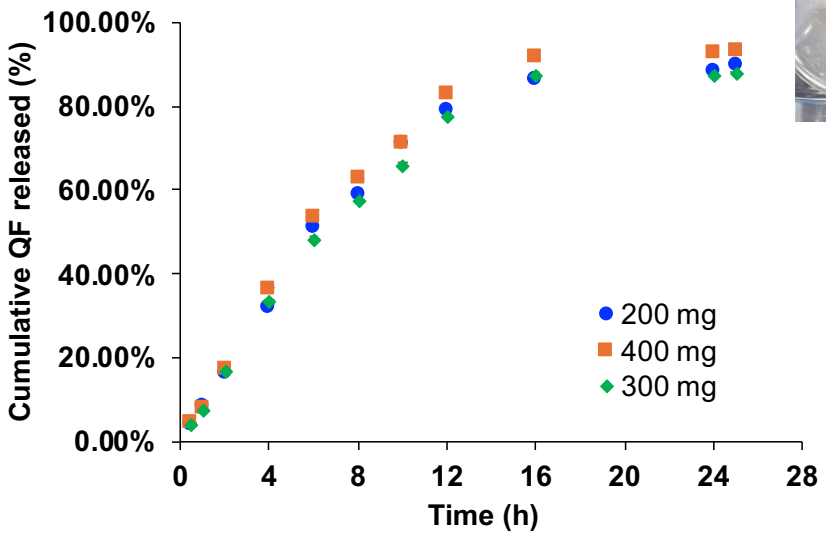
Case Study II_In Vitro Dissolution of QF ER Tablets

Method 1 (USP/FDA recommended method)

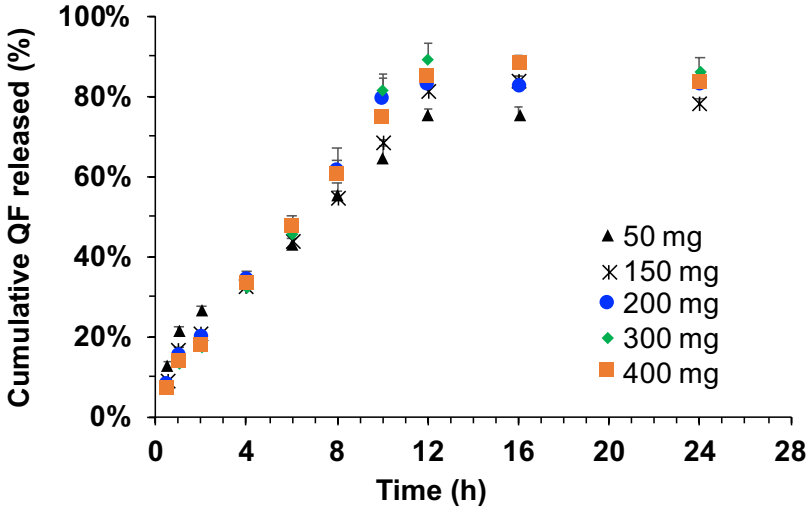
Apparatus: USP 1 with 20 mesh
Rotation peed: 200 rpm (250 rpm at 24 hours)
Temperature: 37°C
Media: 900 mL of 0.05 M citric acid and 0.09 N NaOH (pH 4.8) for 5 hours followed by adjusting pH to 6.6 by addition of 100 mL of 0.05 M dibasic sodium phosphate and 0.46 N NaOH.





Method 2 (in biorelevant media)

Apparatus: USP 2 with sinkers
Paddle speed: 125 rpm (200 rpm at 24 hours)
Temperature: 37°C
Media: 900 mL of FaSSGF (pH 1.6) for 1 hour and FaSSIF (pH 6.5) for 24 hours



Similar dissolution performance across different strengths in different pH media (Mean±SD, *n*=3).

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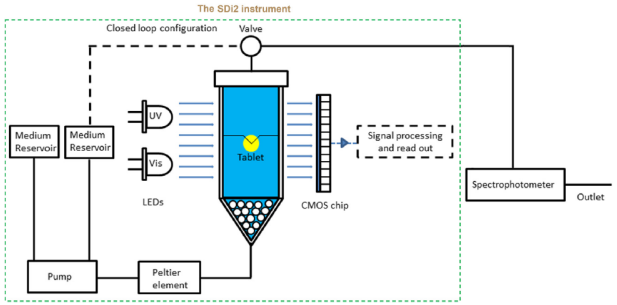
Unpublished data_Shen Lab

Case Study II_In Vitro Dissolution of QF ER Tablets

Matrix changes during dissolution

SDi2 imaging in the USP/FDA biphasic media

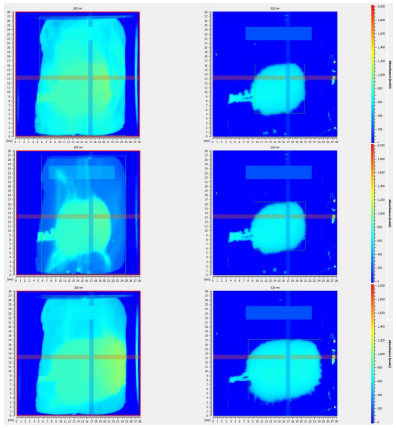


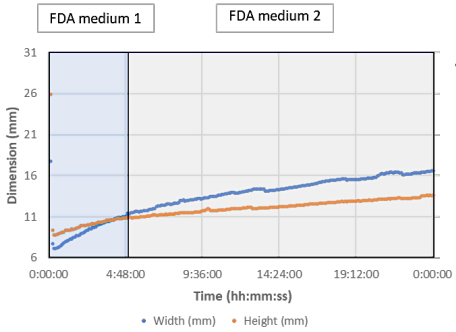
200 mg

04:55:00
ΔH: 0.26 mm
ΔW: 2.14 mm

05:10:00
ΔH: 0.25 mm
ΔW: 2.23 mm

24 hours
ΔH: 2.97 mm
ΔW: 7.34 mm

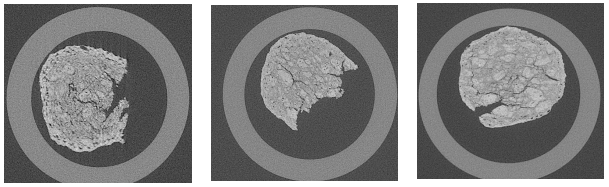




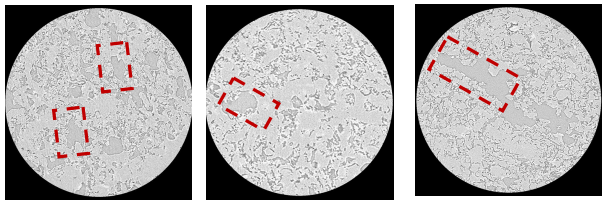
XRM imaging of 3-hour dissolution data in biphasic fasted biorelevant media

50 mg *200 mg* *400 mg*

4X, 20 µm



4X, 1.5 µm



Matrix changes (e.g., swelling, erosion, porosity) were observed during dissolution.

Unpublished data_Shen Lab

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Case Study II

Estimated formulation compositions based on public resources

Seroquel® XR

	Mass (mg)	Weight %	Mass (mg)	Weight %	Mass (mg)	Weight %	Mass (mg)	Weight %	Mass (mg)	Weight %
QF	57.56	11.5	172.69	30.0	230.26	38.4	345.38	43.2	460.50	52.9
Hypromellose	150	30.0	172.5	30.0	180	30.0	240*	30.0	261	30.0
lactose monohydrate	125.72	25.1	74.65	13.0	52.87	8.8	49.31	6.2	15.50	1.8
cellulose, microcrystalline	125.72	25.1	74.65	13.0	52.87	8.8	49.31	6.2	15.60	1.8
magnesium stearate	5	1.0	8.63	1.5	9.0	1.5	16	2.0	17.40	2.0
sodium citrate, dihydrate	36	7.2	71.88	12.5	75	12.5	100	12.5	100	11.5
Coating materials#										
Total (mg/tablet) / Percentage of weight without coating	500	100	575	100	600	100	800	100	870	100

coating materials contain polyethylene glycol 400, titanium dioxide, ferric oxide yellow, ferric oxide red

Formulation similarity across strengths in terms of hypromellose concentration (~30%)

* US Patent 5,948,437, METHOCEL® 2208: METHOCEL® K100LV/K4M Premium CR (5/1, w/w)

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Case Study II

UPS/PhEur/JP designation	% Methoxyl	% Hydroxypropoxyl	Viscosity grade	Nominal viscosity (cP)
METHOCEL® 2208	19-24	4-12	K100 Premium LV	100
			K4M Premium CR	4,000

f_2	F1	F2	F3
RLD	36.7	64.4	81.72

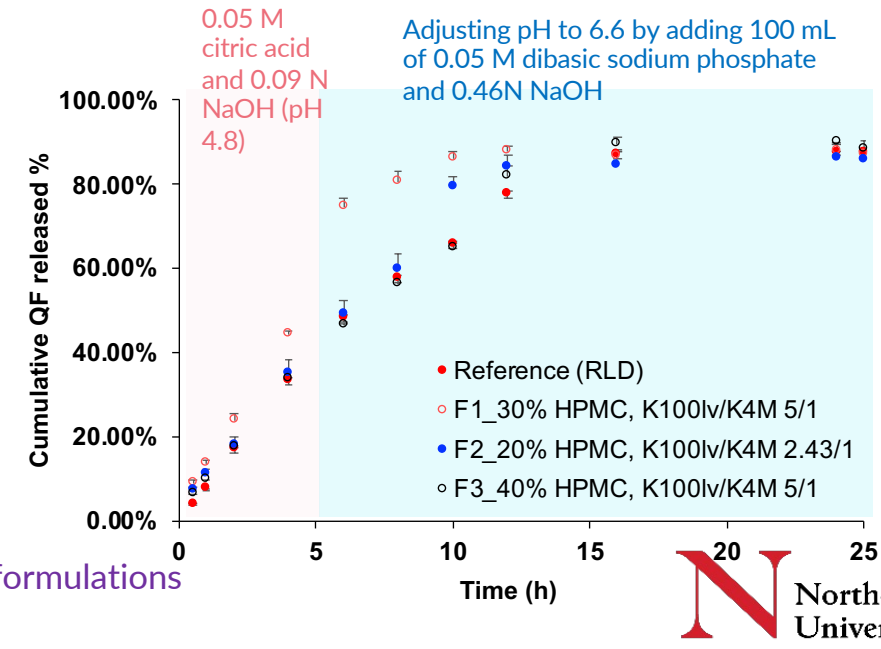
	Reference* (300 mg)	F1	F2	F3
HPMC %	30%	30%	30%	40%
K100/K4M ratio (w/w)	5/1	5/1	2.75/1	5/1

*US Patent 5,948,437; F1 similar composition vs. F2 & F3 different compositions

RLD 300 mg

LM 300 mg

biphasic dissolution (USP method)



Dissolution performance was similar for 300 mg QF ER tablet formulations with varying compositions (Mean±SD, *n*=3).

Unpublished data_Shen Lab

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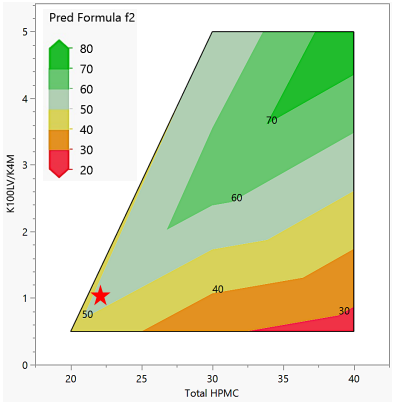
Case Study II

DOE studies to define formulation "safe" space across strengths (200 mg and 300 mg)

300 mg (response surface model)

Block/Run	Factors		Response	
Day	Total HPMC (%)	K100/K4M	Exp. f2	Pred. f2 (excluding rapid-release formulations)
1	40	5	81.72	77.47
1	30	2.75	64.39	65.43
2	40	5	73.22	77.47
2	20	2.75	18.43	66.34
3	30	0.5	32.51	31.29
3	20	5	23.16	34.79
4	30	5	50.27	50.27
4	30	0.5	30.07	31.29
5	40	0.5	25.7	25.70
5	20	0.5	48.6	48.60
6	30	2.75	67.06	65.43
6	30	2.75	64.83	65.43



	RLD 300 mg	F1	F2	F3	F4	F5 ★
HPMC %	30%	30%	30%	40%	40%	22.5%
K100/K4M ratio (w/w)	5/1	5/1	2.75/1	5/1	2.75/1	1/1
f_2	/	36.7	64.4	81.72	74.75	71.39

Compositionally dissimilar 300 mg QF ER tablet formulations demonstrated similar dissolution performance (Mean±SD, *n*=3).

Unpublished data_Shen Lab

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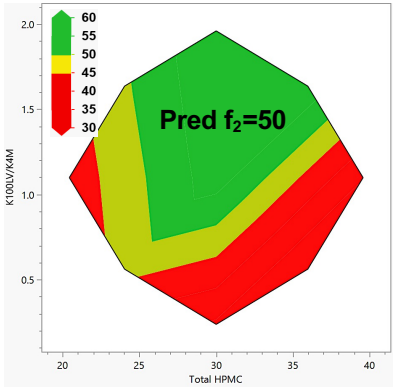
Case Study II

DOE studies to define formulation "safe" space across strengths (200 mg and 300 mg)

200 mg (central composite design, orthogonal blocks)

Run	Design	Total HPMC	K100lv/K4M	f2	Pred f2
1	0, 0	30	1.1	58.1	57.59
2	+1, +1	36	1.6	53.7	58.51
3	+1, −1	36	0.6	29.6	29.50
4	−1, +1	24	1.6	47.3	49.27
5	−1, −1	24	0.6	49.7	46.76
6	0, 0	30	1.1	60.9	57.59
7	0, 0	30	1.1	51.1	57.59
8	+α, 0	40	1.1	37.8	35.31
9	0, 0	30	1.1	65.0	57.59
10	0, 0	30	1.1	56.3	57.59
11	0, 0	30	1.1	55.0	57.59
12	-α, 0	20	1.1	40.7	41.74
13	0, -α	30	0.2	31.9	34.24
14	0, +α	30	2.0	63.3	59.51



	RLD 200 mg	F2 (300 mg)	F1 ' (200 mg)	F2' (200 mg)	F3' (200 mg)
HPMC %	30%	30%	30%	30%	36%
K100/K4M ratio (w/w)	/	2.75/1	2.75/1	1.1/1	1.6/1
f_2	/	64.4	36.7	56.3	53.7

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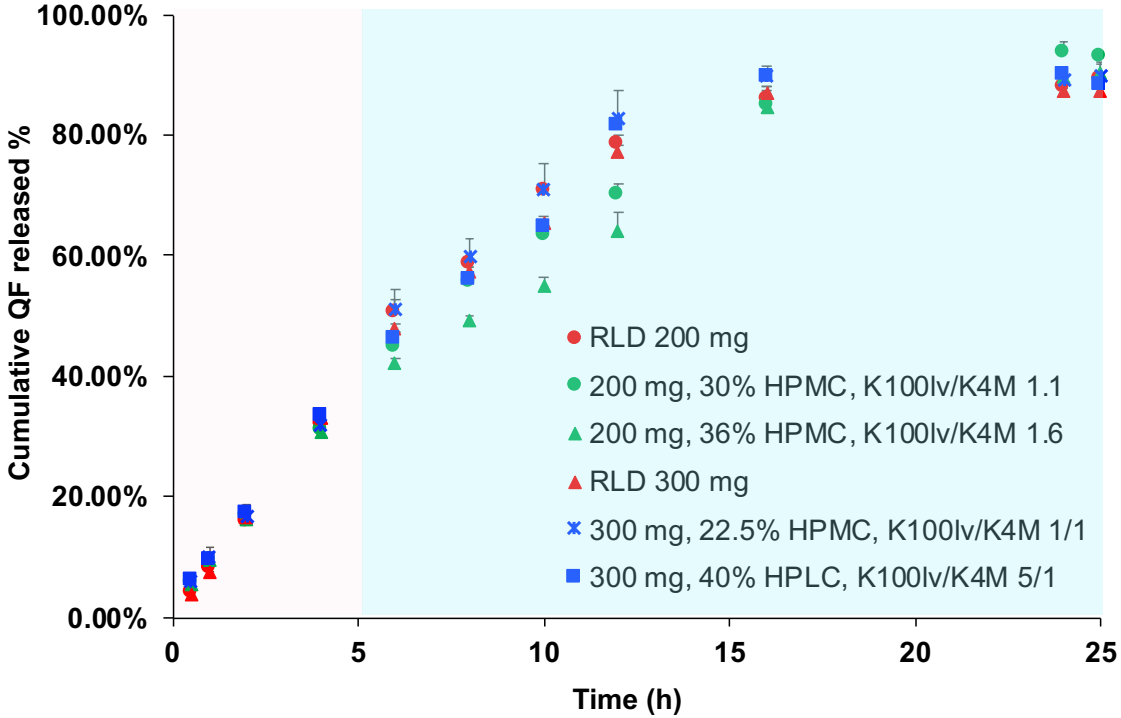
Unpublished data_Shen Lab

Case Study II

Comparison of 200 mg vs 300 mg QF ER tablet formulations



f_2>50

Compositionally dissimilar 200 mg QF ER tablet formulations showed similar dissolution performance to 300 mg formulations (Mean±SD, *n*=3).

Unpublished data_Shen Lab

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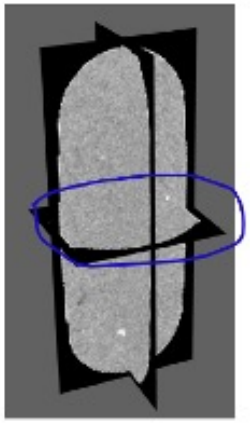
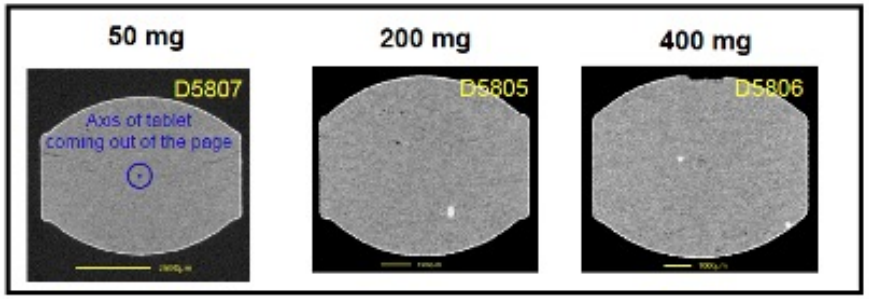
AI-enabled Imaging Assessment of 3D microstructure

Relationship between strength scaling and 3D microstructure

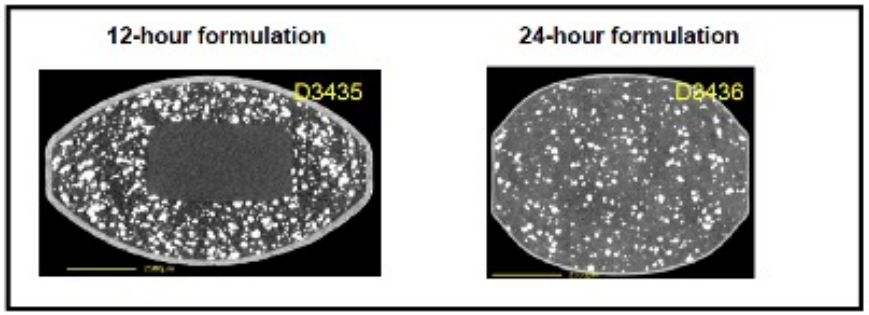


Representative cross-section of full field of view micro-CT (13 um resolution)

Seroquel XR: Different tablet strengths have **identical** microstructure and release profiles



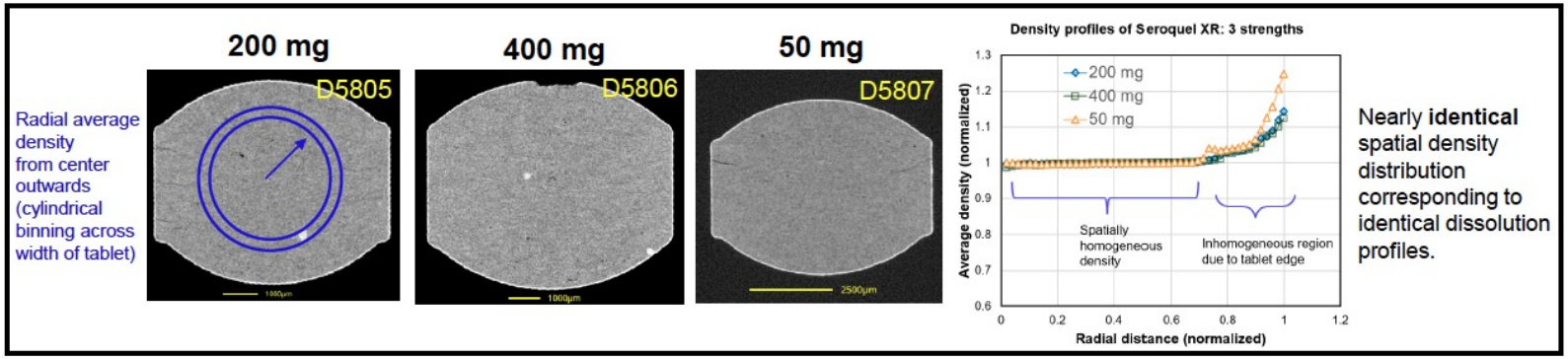
Claritin-D: Different tablet strengths have **different** microstructure and release profiles



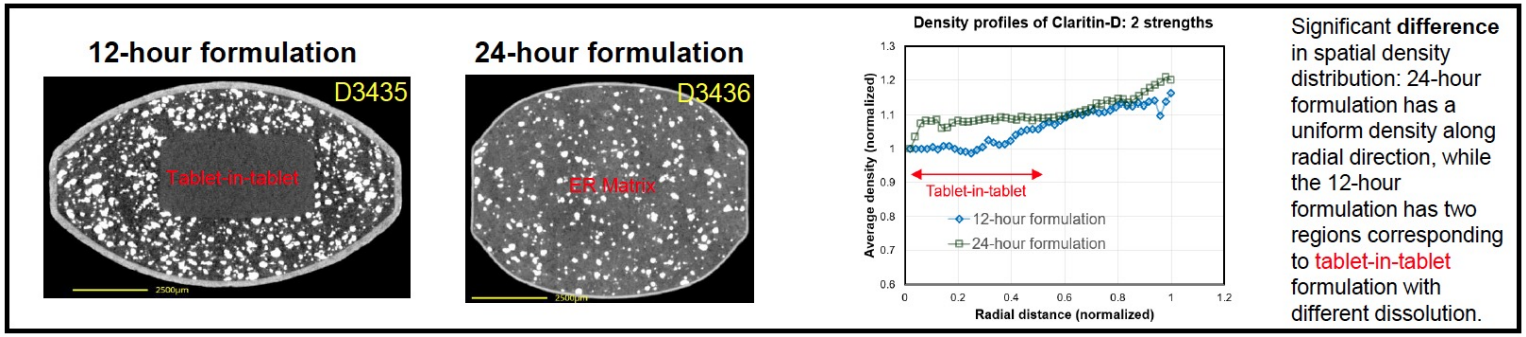
Credited to Drew Jyoti, Shawn Zhang, digiM

AI-enabled Imaging Assessment of 3D microstructure

Seroquel® XR has similar/identical microstructure (based on true density distribution*) under the dry state and in vitro dissolution profiles across strengths



Claritin-D has different microstructure and release profiles across strengths



**True Density Measurement via micro-CT Imaging, digiM Patent Pending 63/367,532, 2022 Andrew Clark, et. al.*

Credited to Drew Jyoti, Shawn Zhang, digiM

Key Takeaways

- Compositionally dissimilar QF ER tablet formulations demonstrated equivalent dissolution performance both within individual strengths and across multiple strengths.

- The amount and ratio of different grades of HPMC within the same excipient designation can impact significantly impact the performance of QF ER tablets across various strengths.

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Research Gaps

- **Identify critical quality attributes (CQAs) for strength scaling**: Additional research is needed to understand and identify the key CQAs that influence strength scaling. Define the appropriate factors and formulation strategies required to enable reliable strength scaling.

- **Understand structure similarity/dissimilarity and its impact:** Further investigation is needed to assess the capability of imaging and image analysis tools to support strength scaling and to demonstrate bioequivalence (BE) across different strengths.

- **Develop biorelevant/biopredictive in vitro dissolution methods:** Additional effort is needed to develop and validate biorelevant/biopredictive in vitro dissolution methods that effectively support strength scaling under relevant physiological conditions (e.g., including potential food effects).

- **Improve understanding Strength Scaling Across MR Product Types:** Additional studies are required to expand our understanding of strength scaling strategies for various types of modified-release (MR) oral products, including both matrix-based and coated systems.

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Thank you for your attention!

Questions?

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