Generic Oral Modified Release Drug Products: Establishing Bioequivalence for Additional Strengths

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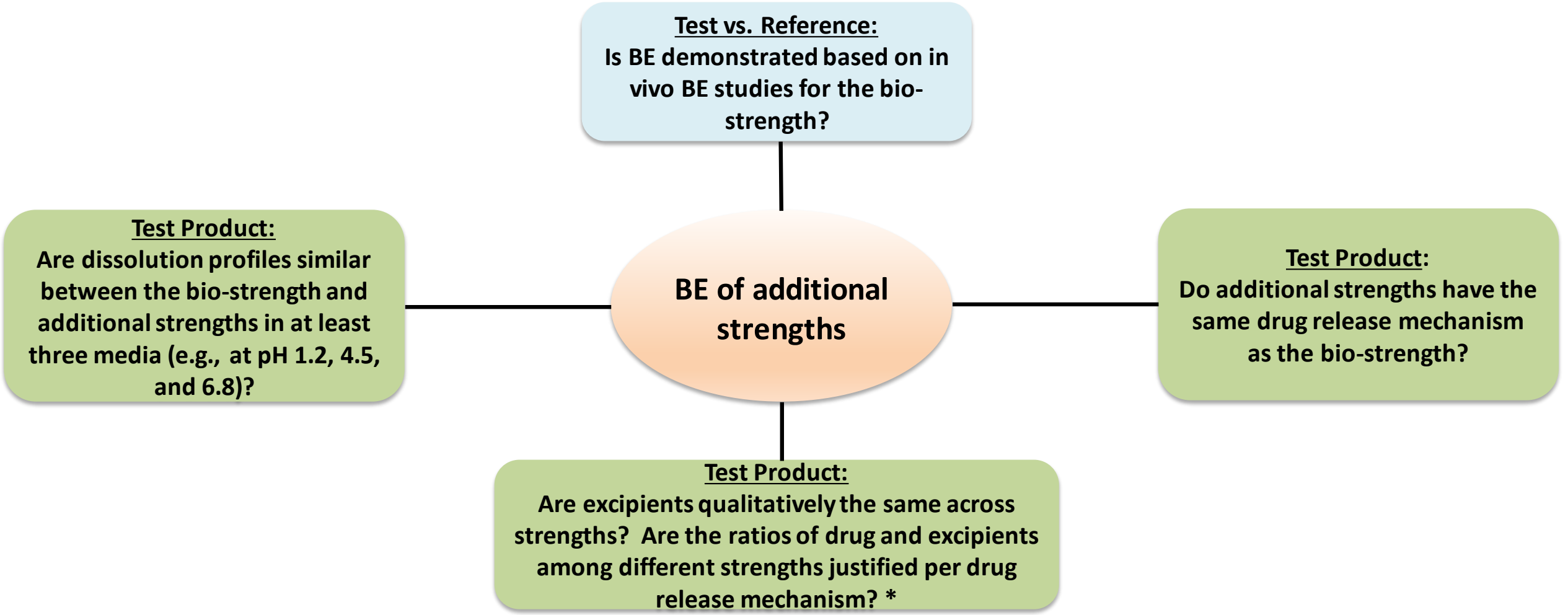
Outline

- Background
- Considerations in bioequivalence (BE) demonstration for additional strengths of generic oral modified release (MR) drug products
  - ✓ Bio-strength: bioequivalence (Test vs. Reference)
  - ✓ Dissolution profile similarities across strengths of test product
  - ✓ Formulation assessment across strengths of test product
- Case studies
  - ✓ Identification and exploration of release-controlling excipients (RCE)
  - ✓ Demonstrating BE for additional strengths
- Conclusions

Background

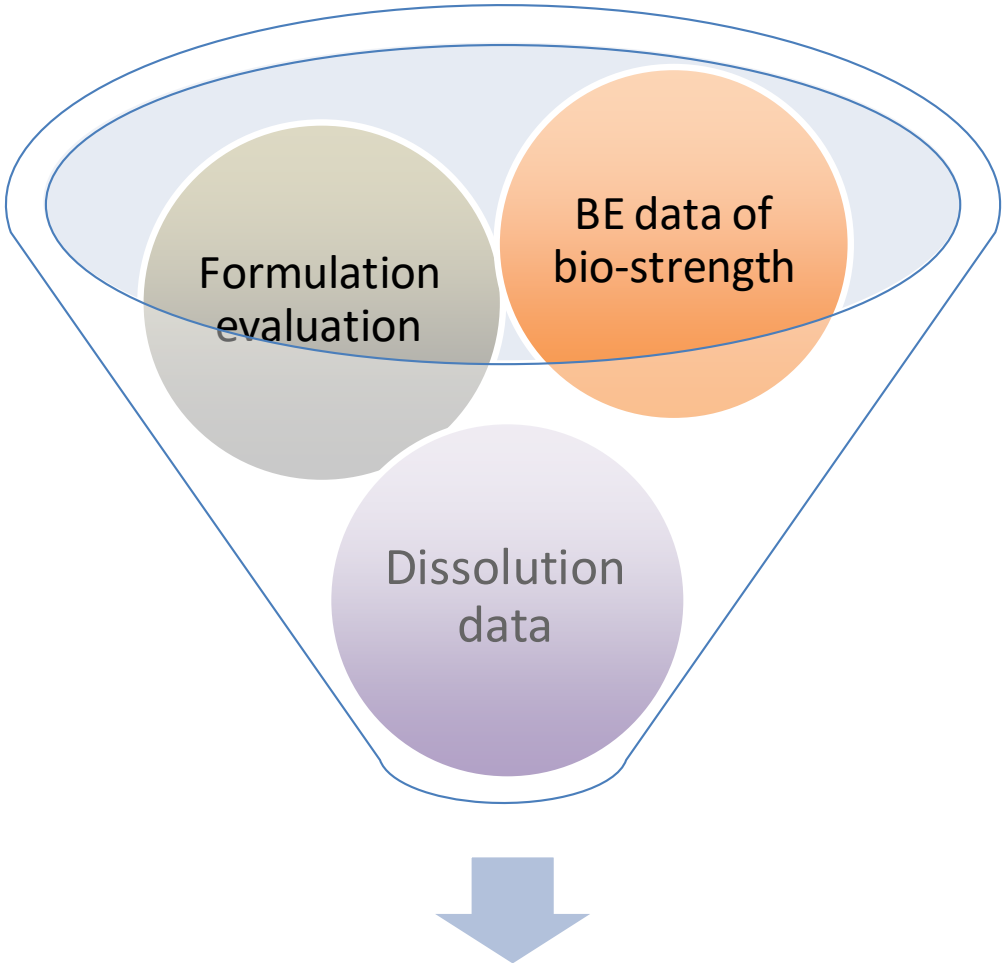
- For an oral MR drug product with multiple strengths
  - Generic applicants may conduct in vivo BE studies on one strength ("**bio-strength**"; usually the highest strength)
  - Alternative methods may be used to demonstrate BE for **additional strengths** in lieu of additional in vivo BE studies on those strengths when certain criteria are met:
    - *Reference listed drug (RLD):* Generally if the RLD exhibits similar bioavailability across different strengths given at the same dose
    - *Test product*: detailed in subsequent slides

Considerations in BE Demonstration for Additional Strengths of Oral MR Products



***Note**: Formulation composition proportionality may not be the only factor to determine the need for an in vivo BE study to demonstrate BE.

BE Demonstration of Additional Strengths -Totality-of-Evidence



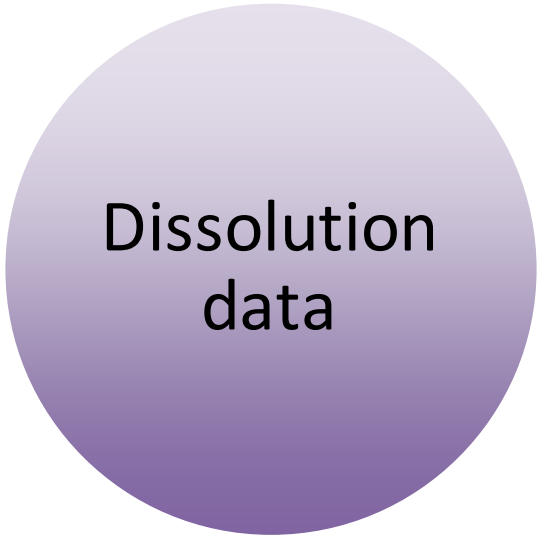
BE Demonstration of additional strengths

BE Data of Bio-strength

BE data of bio-strength

- Study conduct: Fasting and fed
- Pharmacokinetic parameters:
  I. AUC_{0-t}, AUC_{0-inf}, AUC truncated or partial AUCs if applicable, and C_{max}
  II. Supportive information: T_{max}, K_{el} and $t_{1/2}$
- Confidence interval values: 80.00% – 125.00%

Dissolution Testing

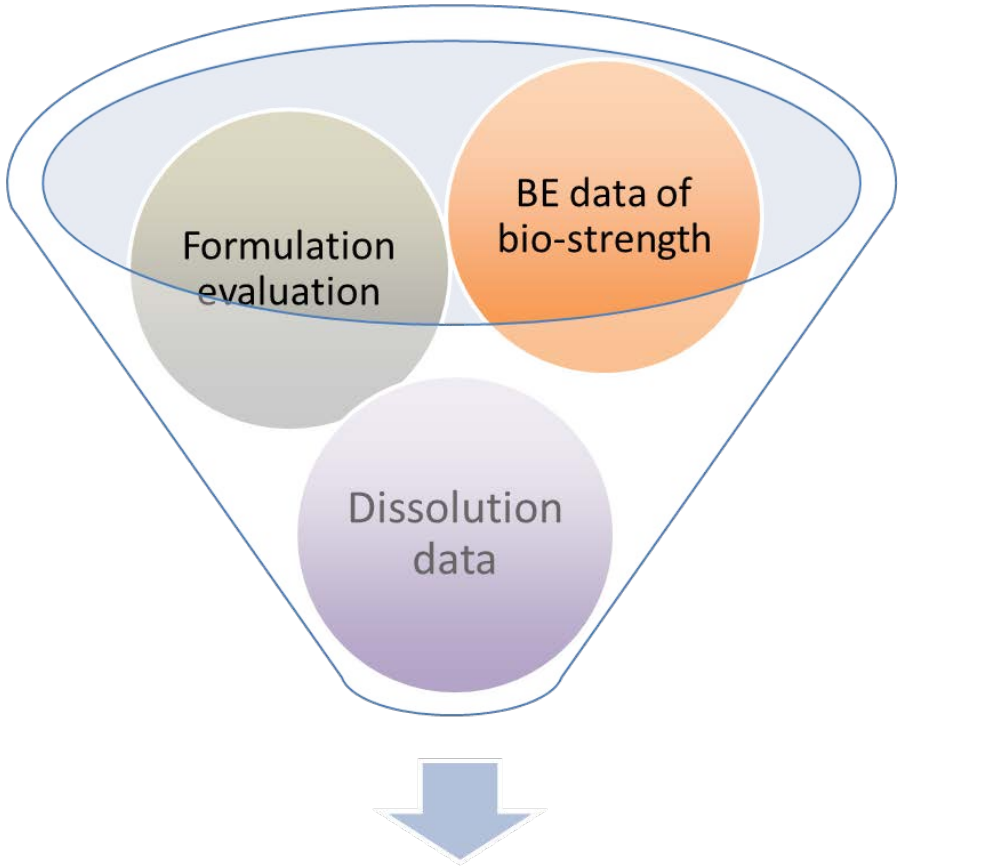


- Dissolution testing of all strengths is acceptable
- The drug products should exhibit similar dissolution profiles between the bio-strength and additional strengths based on the similarity factor (f_2) test or other appropriate statistical approaches in at least three dissolution media (e.g., at pH 1.2, 4.5, and 6.8)
- We recommend that applicants generate dissolution profiles on the test and reference products of all strengths

Formulation Evaluation

1. Identify RCE and non-release controlling excipients (NRCE) in the formulation (Case A1 - A2)
2. Assess formulation composition across strengths (Case B1 – B5)
   - Evaluate % difference in each RCE and NRCE between the bio-strength and additional strengths separately

BE Demonstration of Additional Strengths -Totality-of-Evidence



The decision on the BE demonstration of additional strengths is the result of considering all three pieces of information.

Function of Excipients

- A specific excipient may be an RCE or NRCE depending on API properties, formulation design, and location in formulation as illustrated below.

  a) Sodium citrate (in matrix tablet)
     - pH-dependent API: could be an RCE
     - pH-independent API: may be an NRCE

  b) HPMC E5LV (tablets with a release controlling film)
     - In film: could be an RCE
     - In core tablet: may be an NRCE

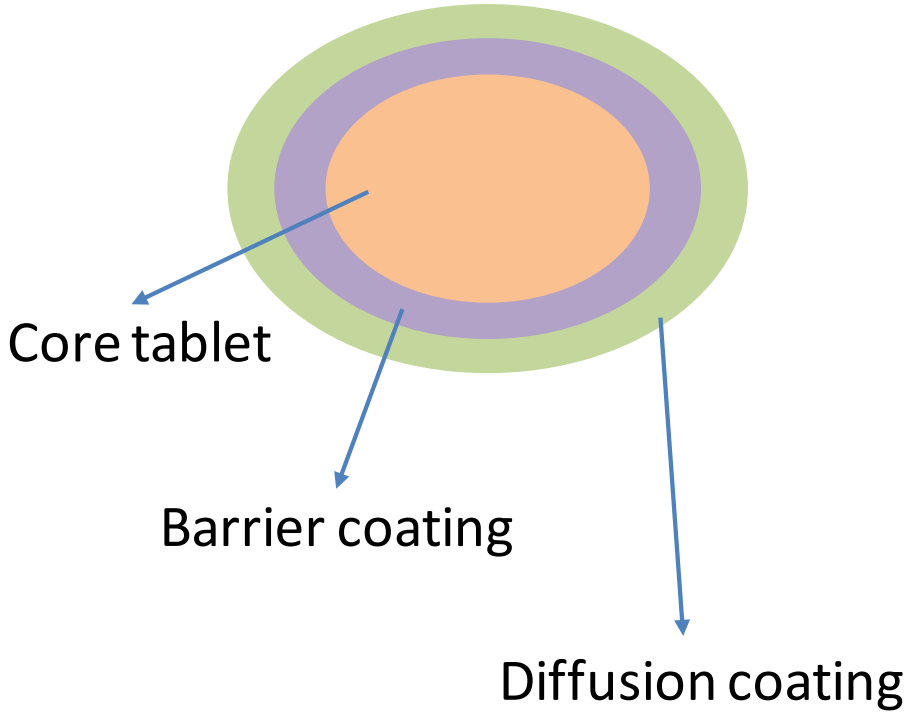
  c) Mannitol: (matrix tablet vs osmotic pump tablet)
     - In osmotic pump system: may or may not be an RCE
     - In matrix system : may be an NRCE

API: active pharmaceutical ingredient; HPMC: hydroxypropyl methylcellulose

Case A1 _Formulation and RCE Assessment

	mg/tablet	% w/w
Core tablet		
HPMC K100M	140	21.3
MCC	212	32.2
Alginic Acid	40	6.1
Magnesium Stearate	8	1.2
Barrier coating		
Ethylcellulose	69	10.5
Talc	28	4.2
Diffusion coating		
API	100	15.2
Ethylcellulose	55	8.4
Polysorbate 80	3	0.5
Talc	3	0.5
Total	*658*	*100*

MCC: microcrystalline cellulose



Case A1 _Assessment of RCE

Assessment of the formulation components

	Core tablet	Barrier coating	Diffusion coating
Effect on dissolution	Low	Medium	High

Assessment of barrier coating formulation variables

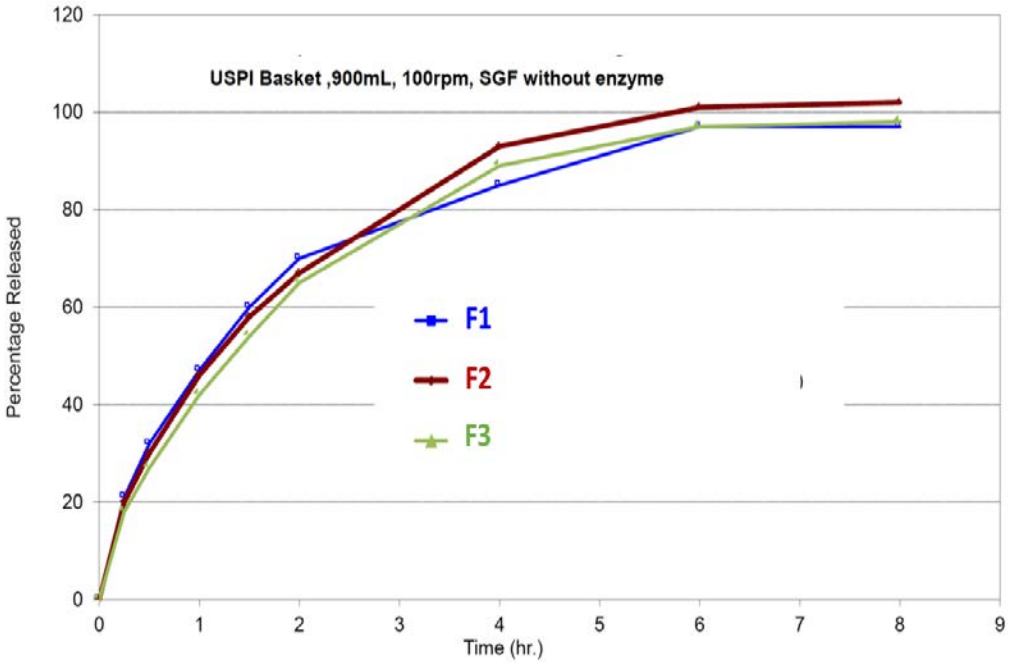
	Ethylcellulose level	Talc level
Effect on dissolution	High	Low

Assessment of diffusion coating formulation variables

	Ethylcellulose level	Polysorbate 80 level	Talc level
Effect on dissolution	High	High	Low

Case A1 _RCE Determination in Barrier Coating

	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)
Core tablet			
HPMC K100M	140	140	140
MCC	212	212	212
Alginic Acid	40	40	40
Magnesium Stearate	8	8	8
Barrier coating			
Ethylcellulose	**53**	**61**	**69**
Talc	28	28	28
Diffusion coating			
API	100	100	100
Ethylcellulose	55	55	55
Polysorbate 80	3	3	3
Talc	3	3	3
Total	*642*	*650*	*658*



- Change of ethylcellulose amount on the barrier coating doesn't affect drug release rate

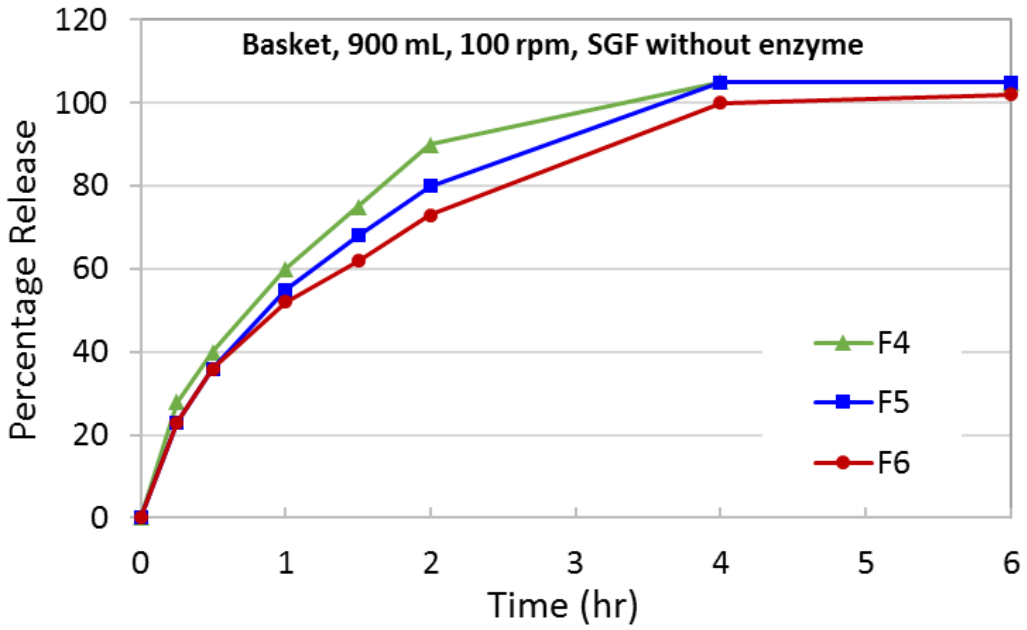
USP: United States Pharmacopeia; SGF: Simulated gastric fluid

Case A1 _Diffusion Coating Evaluation

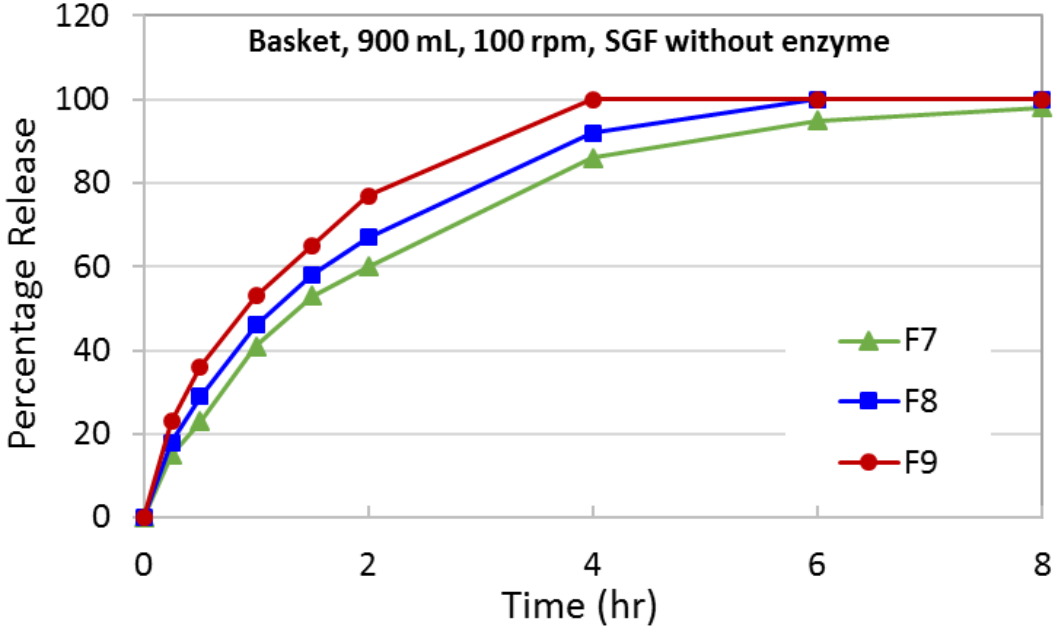
	Ethylcellulose Level			Polysorbate 80 Level		
	F4 (mg/tab)	F5 (mg/tab)	F6 (mg/tab)	F7 (mg/tab)	F8 (mg/tab)	F9 (mg/tab)
Core tablet						
HPMC K100M	140	140	140	140	140	140
MCC	212	212	212	212	212	212
Alginic Acid	40	40	40	40	40	40
Magnesium Stearate	8	8	8	8	8	8
Barrier coating						
Ethylcellulose	69	69	69	69	69	69
Talc	28	28	28	28	28	28
Diffusion coating						
API	100	100	100	100	100	100
Ethylcellulose	**50**	**58**	**66**	55	55	55
Polysorbate 80	3	3	3	**2**	**4**	**6**
Talc	3	3	3	3	3	3
Total	*653*	*661*	*669*	*657*	*659*	*661*

Case A1 _Diffusion Coating Evaluation

Ethylcellulose Level



Polysorbate 80 Level



SGF: Simulated gastric fluid

- Change of ethylcellulose amount and polysorbate 80 amount on diffusion coating affects drug dissolution rate

Case A2 _Formulation and RCE Assessment

	mg/tablet	% w/w
API	200	41.6
Ethylcellulose 10	40	8.3
Ethylcellulose 100	75	15.6
Lactose	50	10.4
MCC	50	10.4
Sodium citrate	55	11.4
Silicon dioxide	6	1.2
Magnesium Stearate	5	1.0
Total	*481*	*100*

matrix tablet

API: solubility is pH-dependent

Case A2 _Understanding the RCE through Design of Experiments (DOE) Study

- DOE study

Factors	% w/w per a tablet		
	Low level	Intermediate level	High level
Ethylcellulose 10	7	8	9
Ethylcellulose 100	15	16	17
Sodium citrate	10	11	12

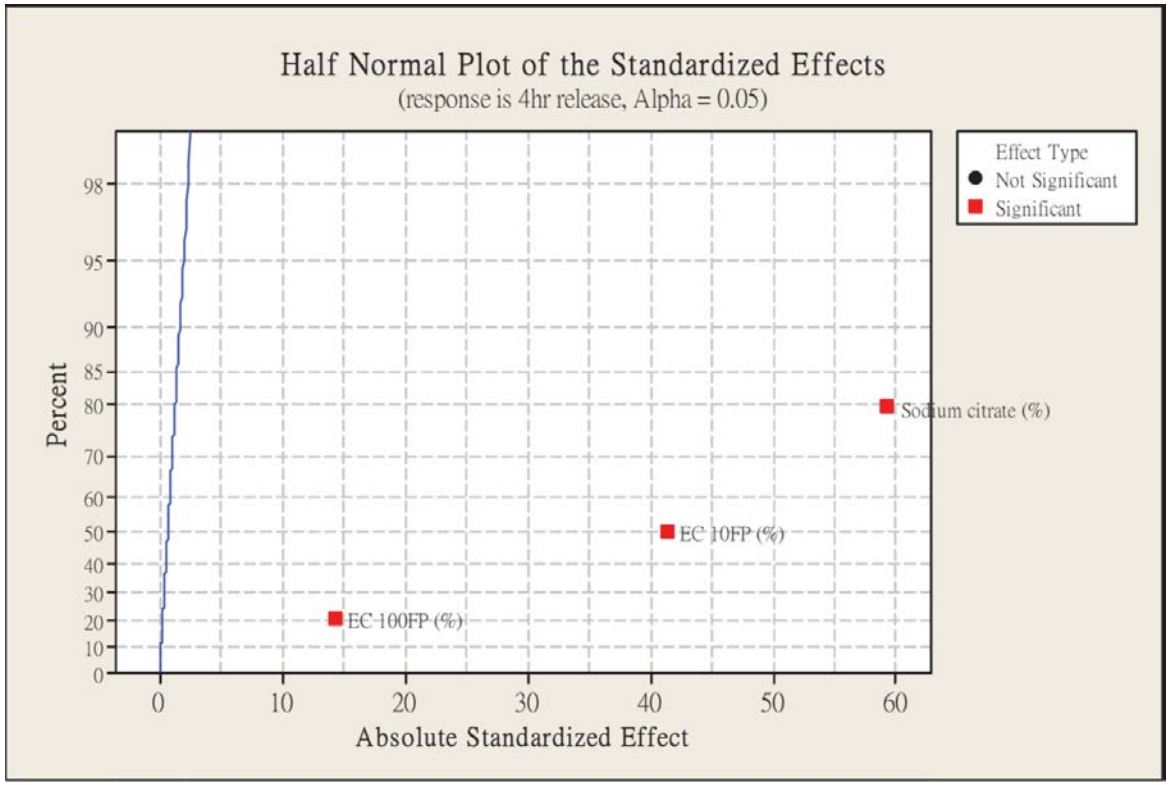
Response: drug release at 4 hour (%)

- Formulation design and results

	EC 10	EC 100	Sodium citrate	Drug release at 4 hour (%)
F1	8	16	11	70
F2	7	15	12	98
F3	9	15	10	70
F4	7	17	10	77
F5	9	17	12	83

Case A2 _Effect of Excipients on Dissolution

Drug release at 4hr (%)



Ethylcellulose 10, ethylcellulose 100 and sodium citrate have an impact on drug dissolution rate.

Summary

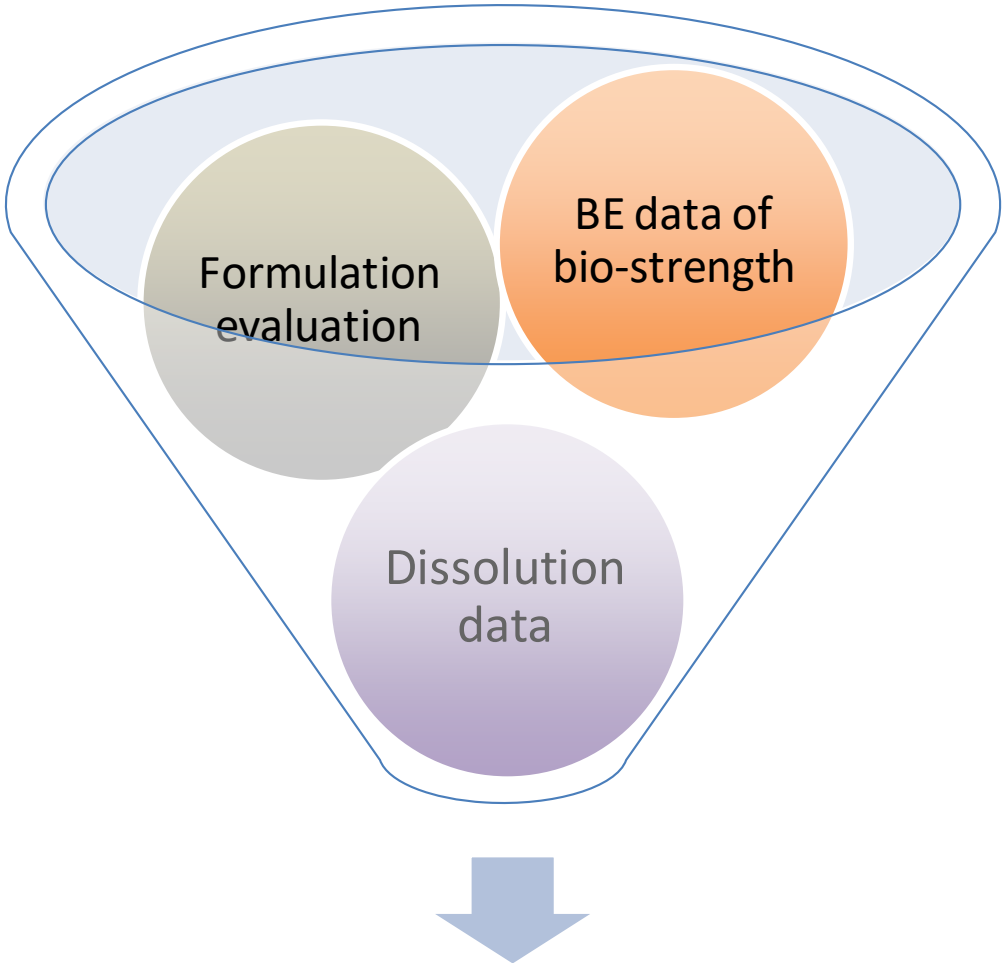
- An excipient may be an RCE or NRCE depending on the formulation design:
  - In Case A1, ethylcellulose is considered as an NRCE in barrier coating but is an RCE in diffusion coating

- Case A2 shows that ethylcellulose 10, ethylcellulose 100 and sodium citrate are considered as RCEs

- The RCE can be determined with a suitable study design

- The RCE determination could affect the compositional proportionality evaluation

BE Demonstration of Additional Strengths -Totality-of-Evidence



Case Examples to Illustrate Various Considerations for BE Demonstration of Additional Strengths

- RCE evaluation based on drug delivery mechanism (Case B1)
- Change of NRCE (Case B2)
- Pattern of RLD vs. Test (Cases B3, B4)
- Dissolution data and BE study results on bio-strength (Case B5)

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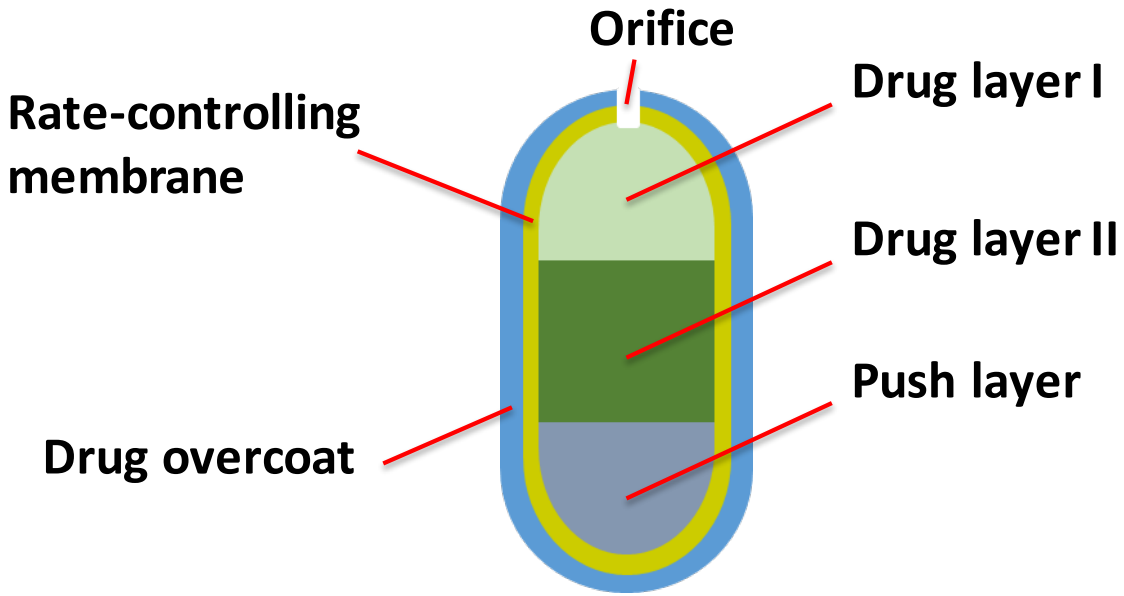
Case Study-B1

Taking Drug Delivery Mechanism into Account for Evaluation of RCEs

Drug Product with Osmotic Pump Formulation

- RLD: An extended release (ER) tablet that uses osmotic pump design to deliver the drug product over a 12-hour period.
  - When the osmotic pump design is ingested, the drug in the overcoat is quickly released; then an osmotic gradient is established across the rate-controlling membrane.
- Test: Similar osmotic pump design was adopted.
  - The API is delivered by a combined process of aqueous dissolution of the drug overcoat (IR) and osmotic delivery of the core drug (ER).

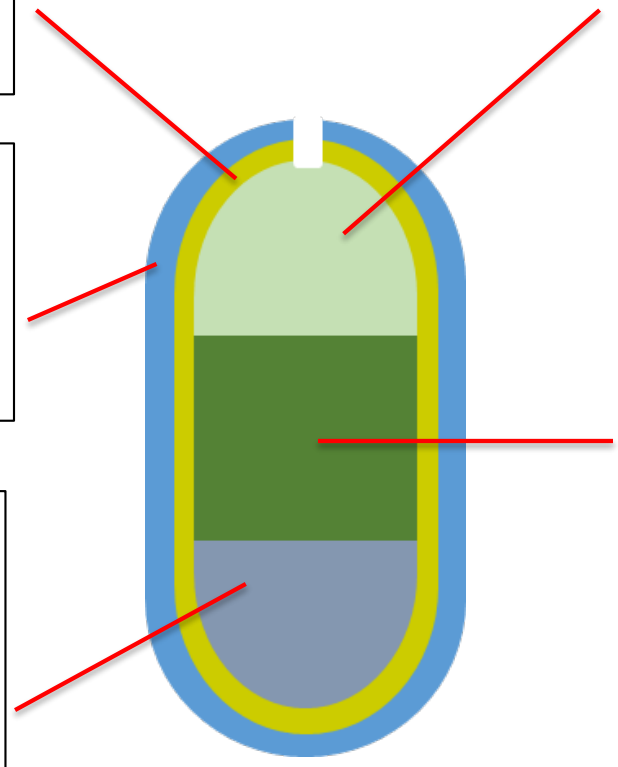


Test Formulations (20 mg and 60 mg Strengths)

Rate-controlling membrane
- Ingredients
  - Cellulose Acetate
  - PEG (MW 3350)

Immediate release coating layer
- Ingredients
  - API
  - Opadry Blue

Push layer
- Ingredients
  - Polyethylene Oxide, NF (700 K)
  - Povidone, USP (Plasdone-K29/32)
  - Sodium Chloride, USP
  - Stearic Acid, NF
  - Ferric Oxide Yellow, NF



API layer I
- Ingredients
  - API
  - Polyethylene Oxide, NF (200 K)
  - Povidone, USP (Plasdone-K29/32)
  - Stearic Acid, NF

API layer II
- Ingredients
  - API
  - Polyethylene Oxide, NF (200 K)
  - Povidone, USP (Plasdone-K29/32)
  - Stearic Acid, NF
  - FD&C GREEN No. 3 Powder

Evaluation of RCEs When Sodium Chloride is Included

Release Controlling Excipient	Function	Quantity of Release Controlling Excipient per Tablet (mg)		Quantity/Total Release Controlling Excipients (w/w%)		Difference in Percentage in each RCE between Bio-strength and lower strength
		20 mg	60 mg (bio-strength)	20 mg	60 mg (bio-strength)	20 mg vs 60 mg
Cellulose Acetate	Rate Controlling Polymer	21.6	24.3	10.3	6.1	4.2
PEG (MW 3350)	Rate Controlling Polymer	2.4	2.7	1.1	0.7	0.4
Polyethylene Oxide, NF (200 K)	Rate Controlling Polymer	95	194	45.5	48.4	-2.9
Polyethylene Oxide, NF (700 K)	Rate Controlling Polymer	70	140	33.5	34.9	-1.4
Sodium Chloride	Osmotic Agent	20	40	9.6	10	-0.4
Total Difference of RCEs						**9.3**

Evaluation of NRCE

Non-Release Controlling Excipient	Function	Quantity of NRCE per Tablet (mg)		Quantity /Total Tablet Weight (w/w%)		Difference in Percentage in each NRCE between Bio-strength and lower strength
		20 mg	60 mg (bio-strength)	20 mg	60 mg (bio-strength)	20 mg vs 60 mg
Povidone	Binder	11	23.35	4.13	4.36	-0.23
Stearic Acid	Lubricant	1.05	2.2	0.39	0.41	-0.02
FD&C GREEN No. 3	Colorant	0.04	0.08	0.02	0.01	0.01
Ferric Oxide Yellow, NF	Colorant	0.55	1.1	0.21	0.21	0
Opadry Blue	Film Coat	24.5	48.0	9.2	9.0	0.2
Total Difference of NRCEs						**0.46**

Demonstrating BE for 20 mg Strength between Test and RLD Products

- Formulations are compositionally proportional between 20 mg and 60 mg of the test products
  - The total difference of RCEs is considered acceptable
    - Sodium Chloride as an osmotic agent should be considered as a RCE in the current formulation
  - The total difference of NRCEs is minimal
- Acceptable fasting and fed BE studies comparing the bio-strength, 60 mg of test product with 60 mg of the reference product
- Comparable dissolution profiles between 20 mg and 60 mg of the test products under quality control (QC) method (water as dissolution medium) and multi-media (pH 1.2, 4.5 and 6.8) conditions

Case Study-B2

Non-Release Controlling Excipients are Not Compositionally Proportional

Matrix tablet

Test Formulations (10 mg, 20 mg & 30 mg strengths)

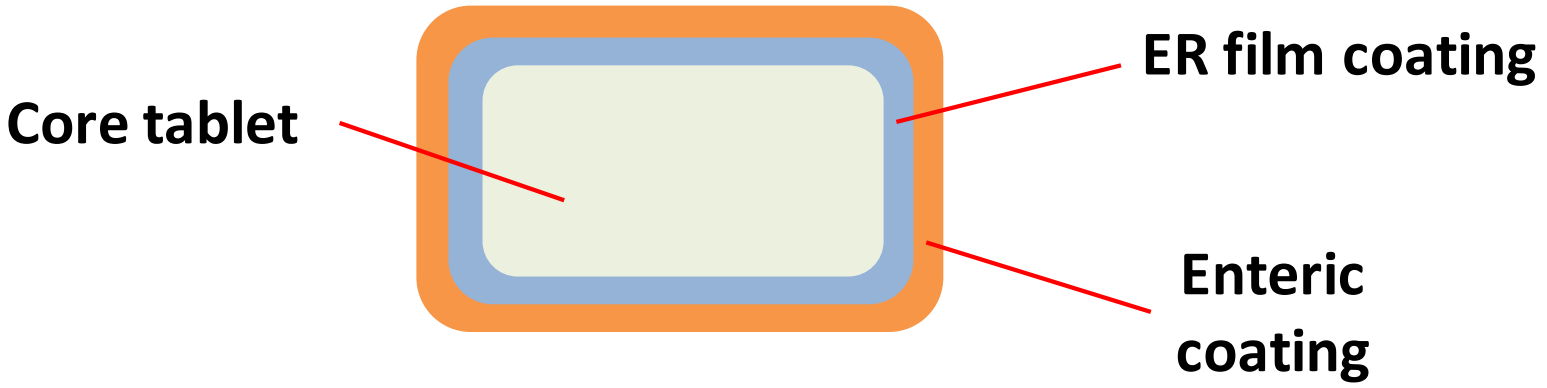
Ingredient	Function	Quantity/Tablet (mg)			Quantity/Tablet (w/w%)		
		10 mg	20 mg	30 mg (bio-strength)	10 mg	20 mg	30 mg (bio-strength)
API	API	10	20	30	11.11	22.22	33.33
Hypromellose, K4M	Rate Controlling Polymer	45	45	45	50	50	50
Microcystalline Cellulose (Avicel PH-302)	Filler	34.1	24.1	14.1	37.89	26.78	15.67
Colloidal Silicon Dioxide	Glidant	0.45	0.45	0.45	0.5	0.5	0.5
Magnesium Stearate	Lubricant	0.45	0.45	0.45	0.5	0.5	0.5
Total weight or w/w% of Core Tablet		90	90	90	100%	100%	100%

Demonstrating BE for 10 mg and 20 mg between Test and RLD Products

- Formulations of 10 mg and 20 mg are considered proportionally similar to 30 mg of the test product
  - There is no difference in RCE across all strengths.
  - The change in NRCE (microcrystalline cellulose, NF) between the bio-strength and other strengths is considered acceptable
    - To achieve the constant core tablet weight across the strengths, it is allowable to vary the amount of the non-release controlling excipient
    - This is the only difference across all strengths
- Acceptable BE studies comparing 30 mg of the test and RLD products
- Comparable dissolution data (10 mg vs 30 mg, 20 mg vs 30 mg) under the QC method condition and multi-media (pH 1.2, 4.5 and 6.8) conditions

Case Study-B3

Formulations Coated with Both ER and Delayed Release (DR) Coatings



Test Formulations (100 mg & 200 mg Strengths)

	Ingredient	Function	Quantity/Tablet (mg)		Quantity /Tablet (w/w%)	
			100 mg	200 mg, (bio-strength)	100 mg	200 mg, (bio-strength)
Core tablet	API		100	200	74.62	78.25
	Hydroxypropyl Cellulose	Binder	6	12	4.48	4.69
	Colloidal Silicon Dioxide	Glidant	4	8	2.99	3.13
	Glyceryl behenate	Lubricant	10	20	7.46	7.82
ER film coating	Ethyl Cellulose	ER polymer	3.0	3.5	2.24	1.37
	Hydroxypropyl cellulose	Pore former	5.5	6.0	4.1	2.35
Enteric coating	Methacrylic acid copolymer	Enteric Polymer	2.5	3.6	1.87	1.41
	Silicon Dioxide	Glidant	0.5	1.0	0.37	0.39
	Copovidone	Pore former	1.5	2.5	1.12	0.98
Total Tablet Weight or w/w%			*134*	*255.6*	*100%*	*100%*

Evaluation of RCEs from both ER Film Coating and Enteric Coating

Release Controlling Excipient	Function	Quantity/Tablet (mg)		Quantity /Total (w/w%)		Change in Percentage in each RCE between 100 mg vs. 200 mg
		100 mg	200 mg	100 mg	200 mg	
Ethylcellulose	ER polymer	3	3.5	24	22.44	1.56
Hydroxypropyl cellulose	Pore former	5.5	6	44	38.46	5.54
Methacrylic Acid	Enteric Polymer	2.5	3.6	20	23.08	-3.08
Copovidone	Pore former	1.5	2.5	12	16.02	-4.02
Total Weight or w/w% of RCEs	---	12.5	15.6	100%	100%	---
Total Difference of RCEs						**14.2**

Evaluating of ER Film and Enteric Coating Separately

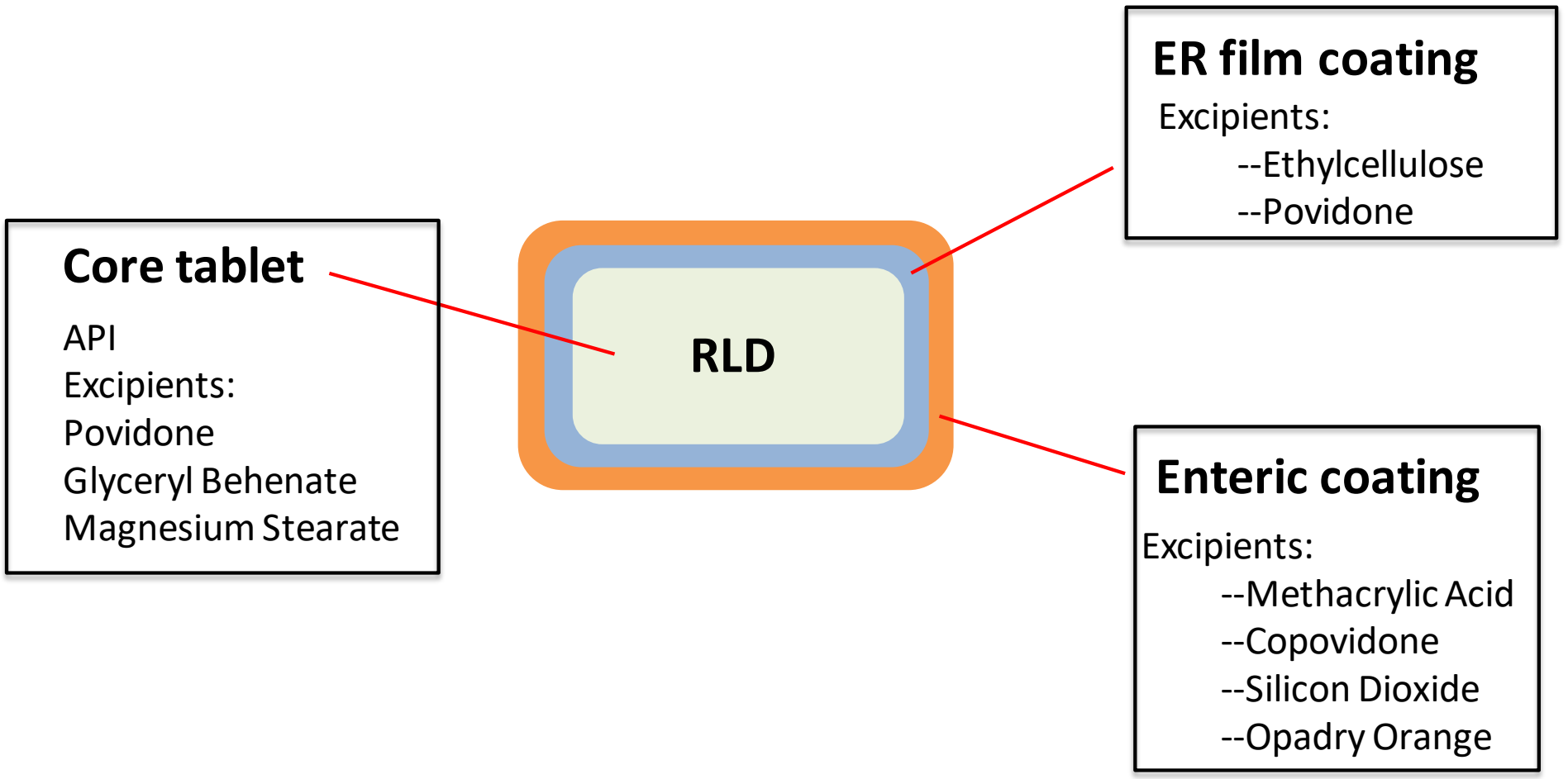
Evaluation of ER film coating

Release Controlling Excipient	Quantity/Tablet (mg)		Quantity/Total Release Controlling Excipients (w/w%)		Difference in Percentage in each RCE between 100 mg vs. 200 mg
	100 mg	200 mg	100 mg	200 mg	
Ethylcellulose	3	3.5	35.29	36.84	-1.55
Hydroxypropyl cellulose	5.5	6	64.71	63.16	1.55
Total weight or w/w% of RCEs	*8.5*	*9.5*	*100%*	*100%*	---
Total Difference of RCEs					**3.1**

Evaluation of enteric coating

Release Controlling Excipient	Quantity/Tablet (mg)		Quantity/Total Release Controlling Excipients (w/w%)		Difference in Percentage in each RCE between 100 mg vs. 200 mg
	100 mg	200 mg	100 mg	200 mg	
Methacrylic Acid	2.5	3.6	62.5	59.02	3.48
Copovidone	1.5	2.5	37.5	40.98	-3.48
Total weight or w/w% of RCEs	*4*	*6.1*	*100%*	*100%*	
Total Difference of RCEs					6.96

RLD Formulation (100 mg and 200 mg Strengths)

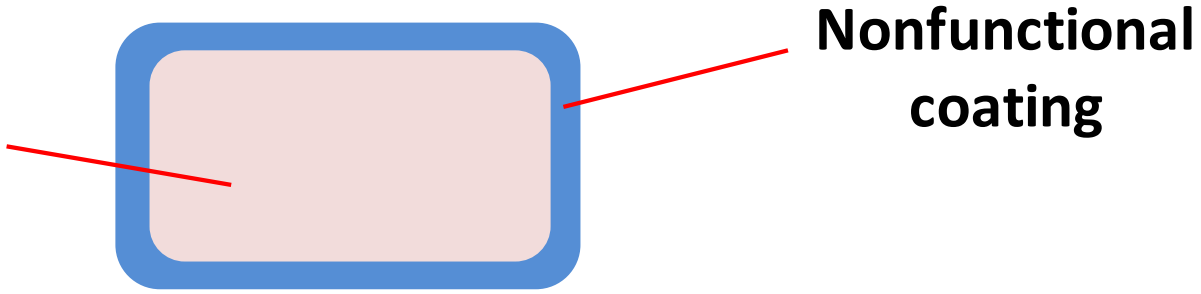


Demonstrating BE for 100 mg between Test and RLD Products

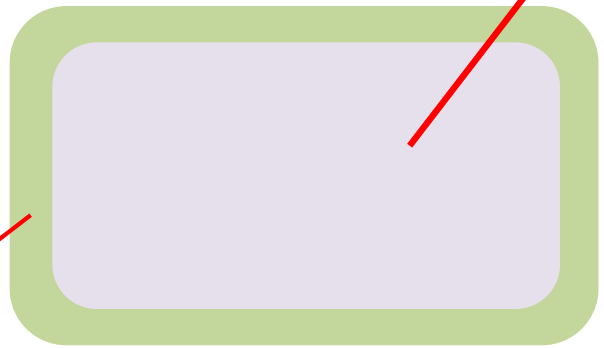
- The test and RLD formulations exhibit similar pattern when comparing 100 mg with 200 mg strength
  - Difference in RCEs of Total RCE Weight between 100 mg and 200 mg of the RLD Product
    - when combining all RCEs from both ER and DR layers
    - when the difference in RCEs was calculated in each individual layer
  - The test formulation has the same release controlling polymer and delayed release enteric polymer as those in the RLD formulation
  - Difference in NRCEs (total difference in w/w% of total tablet weight) is minimal across two strengths
- Acceptable BE studies comparing 200 mg of the test and RLD products
- Comparable dissolution data (100 mg vs. 200 mg) under the QC method condition and multi-media (pH 1.2, 4.5 and 6.8) conditions

Case Study-B4

RLD and Test Formulations Exhibit Similar Pattern



Test Formulations (15 mg and 30 mg Strengths)



- API
- Excipients
  - Hypromellose, K 100 LV CR
  - Hypromellose, E4M CR
  - Lactose
  - Magnesium Stearate

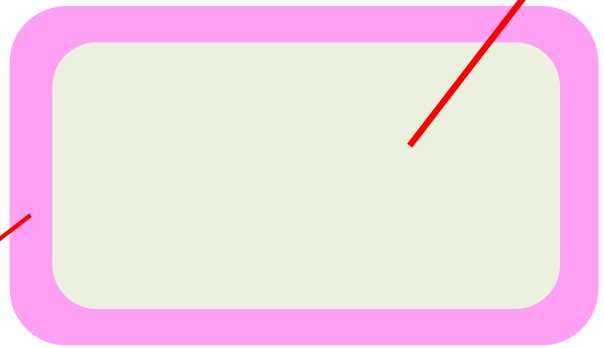
Opadry, Green (30 mg) or
Opadry, Yellow (15 mg)

Test Formulation Comparison between 15 mg and 30 mg

Non-Release Controlling Excipient	30 mg (bio-strength)	15 mg	Difference in percentage in each NRCE between 30 mg and 15 mg
Lactose	53.02% (167 mg)	49.05% (103 mg)	-3.97%
Magnesium Stearate	0.95% (3 mg)	0.95% (2 mg)	0%
Total Tablet Weight	315 mg	210 mg	---
Total Difference of NRCEs			3.97%

Release Controlling Excipient	30 mg (bio-strength)	15 mg	Difference in percentage in each RCE between 30 mg and 15 mg
Hypromellose, E4M CR	66.67% (80 mg)	43.75% (35 mg)	-22.92%
Hypromellose, K 100 LV CR	33.33% (40 mg)	56.25% (45 mg)	22.92%
Total Weight of RCEs	120 mg	80 mg	---
Total Difference of RCEs			**45.84%**

RLD Formulation (15 mg and 30 mg strengths)



- API
- Excipients
  - Hypromellose, 2910
  - Hypromellose, 2208
  - Lactose
  - Magnesium Stearate

Opadry Pink (30 mg) or
Opadry White (15 mg)

RLD Formulation Comparison between 15 mg and 30 mg

Non-Release Controlling Excipient	30 mg (bio-strength)	15 mg	Difference in Percentage in each NRCE between 30 mg and 15 mg
Lactose	56.2% (177 mg)	56.2% (118 mg)	0 %
Magnesium Stearate	0.95% (3 mg)	0.95% (2 mg)	0%
Total Tablet Weight	315 mg	210 mg	---
Total Difference of NRCEs			0 %

Release Controlling Excipient	30 mg (bio-strength)	15 mg	Difference in percentage in each RCE between 30 mg and 15 mg
Hypromellose, 2910	67.50% (81 mg)	42.50% (34 mg)	-25.00%
Hypromellose, 2208	32.50% (39 mg)	57.50% (46 mg)	25.00%
Total Weight of RCEs	120 mg	80 mg	---
Total Difference of RCEs			**50.00%**

RCE Comparison: Test and RLD

RCEs of Test Formulation

Release Controlling Excipient	30 mg (bio-strength)	15 mg	Difference in percentage in each RCE between 30 mg and 15 mg
Hypromellose, E4M CR	66.67% (80mg)	43.75% (35 mg)	-22.92%
Hypromellose, K100 LV CR	33.33% (40 mg)	56.25% (45 mg)	22.92%
Total Weight of RCEs	120 mg	80 mg	---
Total Difference of RCEs			45.84%

RCEs of RLD Formulation

Release Controlling Excipient	30 mg (bio-strength)	15 mg	Difference in percentage in each RCE between 30 mg and 15 mg
Hypromellose, 2910	67.50% (81 mg)	42.50% (34 mg)	-25.00%
Hypromellose, 2208	32.50% (39 mg)	57.50% (46 mg)	25.00%
Total Weight of RCEs	120 mg	80 mg	---
Total Difference of RCEs			50.00%

Demonstrating BE for 15 mg between Test and RLD Products

- Dissolution Data Comparison

Dissolution Testing	F2 Values			
	Test 15 mg vs 30 mg	RLD 15 mg vs 30 mg	Test 15mg vs RLD 15 mg	Test 30 mg vs. RLD 30 mg
FDA Method (QC Method)	39.09	37.60	65.2	78.4
0.1 N HCl	78.2	52.3	51.8	62.5
pH 4.5 Acetate Buffer	50.1	63.5	52.4	57.1
pH 6.8 Phosphate Buffer	34.5	39.7	85.6	75.2

Based on the totality of the evidences (acceptable BE studies on bio-strength, and similar dissolution and formulation patterns observed in test and RLD products when comparing lower strength to bio-strength), 15 mg strength of the test product is deemed bioequivalent to the corresponding 15 mg strength of RLD product.

Case Study-B5

(Compositionally proportional formulation failed to yield desirable dissolution profiles)

Matrix tablet

Test Formulations

Ingredient	Function	200 mg (bio-strength)		150 mg (submitted formulation)	
		mg/tablet	% w/w	mg/tablet	% w/w
API		200	38.5	150	38.6
HPMC K4M	Rate controlling polymer	49.5	9.5	47.4	12.2
HPMC K100M	Rate controlling polymer	88	16.9	66	17.0
Lactose	Filler	56.7	10.9	37.4	9.6
MCC	Filler	117.3	22.6	82.2	21.1
Magnesium Stearate	Lubricant	8	1.5	6	1.5
Total		*519.5*	*100*	*389*	*100*

Formulation Evaluation

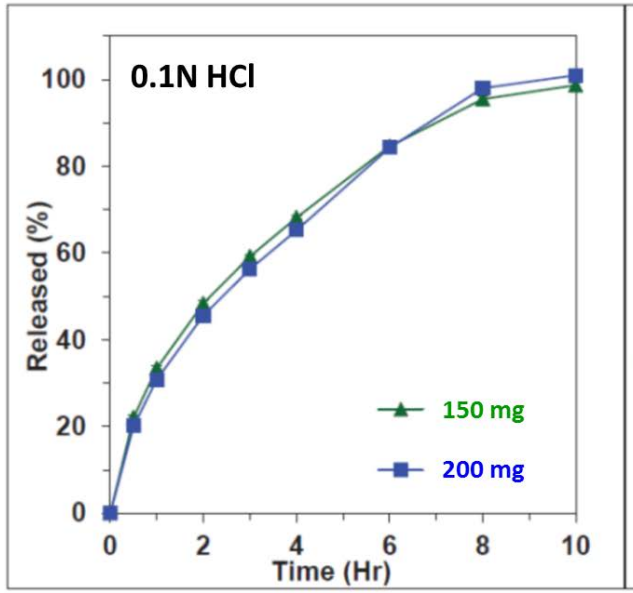
% Difference in NRCE

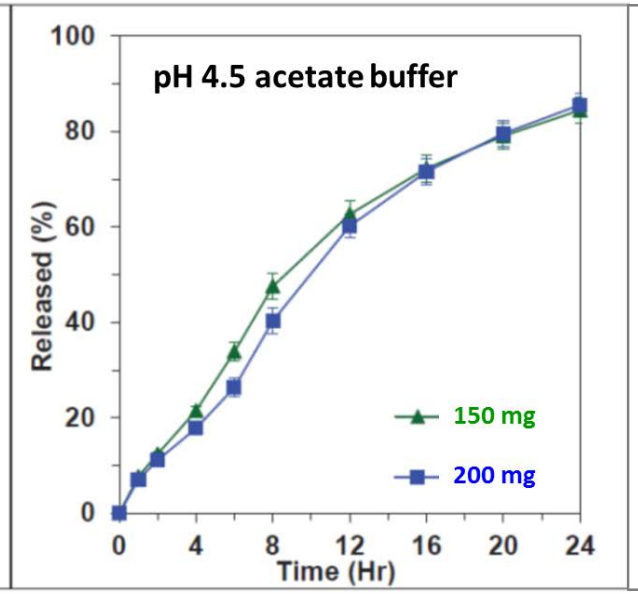
	200 mg		150 mg (submitted formulation)		% Difference between 200 mg and 150 mg
	mg/tablet	% (Tablet wt.)	mg/tablet	% (Tablet wt.)	%
Lactose	56.7	10.9	37.4	9.6	-1.3
MCC	117.3	22.6	82.2	21.1	1.4
Magnesium stearate	8	1.5	6	1.5	0.0
Total difference					**2.7**

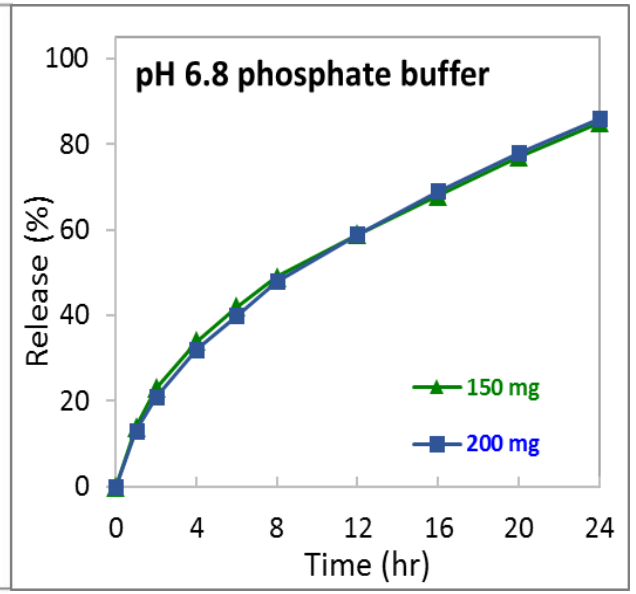
% Difference in RCE

	200 mg		150 mg (submitted formulation)		% Difference between 200 mg and 150 mg
	mg/tablet	% (total RCE)	mg/tablet	% (total RCE)	%
HPMC K4M	49.5	36.0	47.4	41.8	5.8
HPMC K100M	88	64.0	66	58.2	-5.8
Total difference					**11.6**

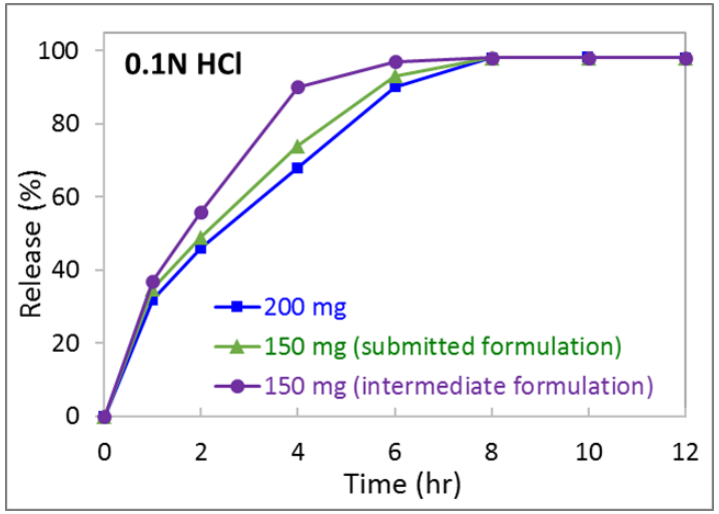
Dissolution _200 mg vs. 150 mg







Similarity factor (f2) ranges from 70 to 93 under different dissolution media comparing 150 mg to 200 mg strengths



- Dissolution profiles of the 200 mg, 150 mg (submitted formulation) and 150 mg (intermediate formulation)
- The 150 mg (intermediate formulation) strength was compositionally proportional to the 200 mg strength but exhibited much faster dissolution rate

BE Data of the 200 mg strength

Fasting BE study

	Ratio (T/R)	90% CI
AUC_{0-t} (ng·hr/ml)	1.07	102.0 – 112.8
AUC_{0-inf} (ng·hr/ml)	1.08	102.0 – 113.4
C_{max} (ng/ml)	1.03	93.3 – 113.1

Fed BE study

	Ratio (T/R)	90% CI
AUC_{0-t} (ng·hr/ml)	0.98	91.2 – 104.8
AUC_{0-inf} (ng·hr/ml)	0.98	91.5 – 105.1
C_{max} (ng/ml)	1.00	91.6 – 108.6

BE Justification for the 150 mg Strength

- The BE of test 150 mg strength to the corresponding reference product strength was demonstrated based on:
  a) During the product development, the formulation of the 150 mg strength (intermediate formulation) was compositionally proportional to that of the 200 mg strength. However, the % drug release of 150 mg strength (intermediate formulation) is much faster than that of the 200 mg formulation.
  b) The dissolution profiles of the submitted formulation for the 150 mg strength and the 200 mg strength in multimedia are comparable ($f2 > 50$).
  c) The 90% CI for PK parameters (i.e., AUC, C_{max}) between the test and reference of the 200 mg strength in both fasting and fed BE studies were well within the acceptance limit of 80.00% - 125.00% and were not marginal.
  d) The total additive difference on RCE between the 200 mg and submitted 150 mg strengths is not substantially higher than the acceptable limit.

Conclusions

- Formulation evaluation across strengths involves separate assessment of the differences in RCEs and NRCEs.
  - Assessment of RCEs through DOE studies facilitates justifications of formulation similarity.
- Multiple factors need to be taken into considerations to use alternative methods to support BE for additional strengths of oral MR products under 21 CFR 320.24(b)(6)—a totality of evidence approach.
  - Formulation composition
  - Release mechanism
  - Dissolution comparison
  - BE data of bio-strength

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