EXAMPLE QUALITY OVERALL SUMMARY[1]

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product: Mock® (MK) Controlled Release Capsules

Non-Proprietary Name of Drug Product: MK Controlled Release Capsules

Non-Proprietary Name of Drug Substance: MK

Company Name: Drug Product Maker Ltd.

Dosage Form: Controlled Release Capsules

Strength(s): 32 mg

Route of Administration: Oral

Proposed Indication(s): Treatment of hypertension

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

Nomenclature: MK

Molecular Structure: MK Structure

Molecular Formula: MK Molecular Formula

Molecular Weight: MK Molecular Weight

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

Physical description: MK is a white crystalline powder

pKas: Aqueous acidic/basic potentiometric titration yields two pKa values of 3.2 and 8.1

Polymorphism: MK is reported in the literature to exist in two anhydrous polymorphs: Forms I and II. There are no reported hydrate forms of MK. Form I is the thermodynamically more stable form. Forms I and II are readily distinguished by IR at 1340 cm^{-1}. The process used to manufacture MK consistently yields Form I.

Solubility characteristics: MK is soluble in water, methanol, and ethanol, and insoluble in acetone, hexane, and chloroform

[1] This Quality Overall Summary does not contain real data and information

The aqueous solubility as a function of pH at 37 °C:

Solvent Media	Final pH[1]	Solubility (mg/mL)[2]
0.1 N HCl, pH = 1	1.0	47.2 mg/mL
0.01 N HCl pH = 2	1.7	49.2 mg/mL
0.15 M acetate buffer, pH = 4	3.7	56.8 mg/mL
0.15 M phosphate buffer, pH = 6	5.8	60.8 mg/mL
0.15 M phosphate buffer, pH = 8	7.8	56.0 mg/mL

[1] Refers to the pH of the aqueous media following addition of MK
[2] Solubility measurements were carried out on polymorphic Form I (the most stable form)

Calculated dose solubility volume: 32 mg (highest strength)/(47.2 mg/mL) = 0.68 mL < 250 mL. Therefore MK is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS).

Hygroscopicity: MK is not hygroscopic (<0.5% water uptake at 90% RH)

Melting point: > 240 °C (No melting was observed prior to decomposition)

*Partition Coefficient***:** CLogP = 1.55 (octanol/water (pH 7.0))

Other Applicable Properties:

*UV Max***:** 272 nm (ε = 2265 L/mole•cm) and 222 nm (ε = 732 L/mole•cm)

Specific Optical Rotation: $[\alpha]_D^{25}$ = +67.2 (c=1% in water)

2.3.S.2 Manufacture

Who manufactures the drug substance?

Drug Substance Maker Ltd. (DMF nnnn)
111 Main Street
City 1, Country 2

How do the manufacturing processes and controls ensure consistent production of the drug substance?

Refer to DMF nnnn for information regarding chemistry manufacturing and controls used in the production of MK.

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized?

For full details regarding proof of MK structure, based upon spectroscopy, analytical testing, and inference from synthetic route refer to DMF nnnn.

How were the possible impurities identified and characterized?

For full details regarding the characterization and identification of impurities refer to DMF nnnn.

2.3.S.4 Control of Drug Substance

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

Tests	Acceptance Criteria	Analytical Procedure	Results lot #433
Appearance	White crystalline powder	Visual	Complies
Identification	1. IR spectrum corresponds to that of corresponding preparation of the reference standard	Infrared Absorption, USP <197K>	Complies
	2. Responds to the tests for chloride	Chloride, USP <191>	Complies
Heavy Metals	NMT 20 ppm	Heavy Metals USP <231> Method 2	< 20 ppm
Moisture	NMT 0.5%	Karl Fischer Titration (USP <921> Method 1a)	0.2%
Specific Optical Rotation $[\alpha]_D^{25}$	$+66.4^o$ to $+68.0^o$	In-House Test Method #467	$+67.1^o$
Assay	98.5-101.5% (anhydrous basis)	In-House HPLC Test Method #125a	99.8%
Residual Solvents	Methanol NMT 3000 ppm Toluene NMT 890 ppm Tetrahydrofuran NMT 720 ppm	Residual solvents (USP <467> Procedure C)	200 ppm 80 ppm 300 ppm
Related Substances	Impurity A: NMT 0.5% Impurity B: NMT 0.15% Impurity C: NMT 0.15% Impurity D: NMT 0.15% Impurity E: NMT 1.0% Impurity F: NMT 0.50% Any Unknown Impurity: NMT 0.10% Total Impurities: NMT 2.0%	In-House HPLC Test Method #231a	0.20% 0.10% 0.09% 0.11% 0.30% 0.30% ≤0.07% 1.4%

The specification sheet includes controls on universal attributes that are generally recognized as critical to the quality of the drug substance (e.g. appearance, identification, assay, impurities, etc). The specification sheet however, does not include controls on attributes related to the solid state properties (e.g. polymorphic form and particle size) which are commonly imposed on drug substance raw material used in the manufacture of solid oral dosage forms. The rationale for the exclusion of these controls is based upon the fact that the drug product manufacturing process incorporates a step where MK is fully dissolved prior to layering the drug onto sugar spheres, whereby memory of solid-state properties is lost.

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Appearance

MK is a white crystalline powder. A qualitative visual test for appearance has been incorporated into the specification sheet to confirm that incoming batches of MK drug substance comply with the description as white crystalline powder.

Identity

- A highly specific test for identity has been incorporated whereby the drug substance is compared to the reference standard via IR spectroscopy. Testing is based upon USP <197K>.
- MK is a hydrochloride salt. Therefore, a qualitative test for the chloride counter-ion has also been incorporated into the specification sheet for product identification. Testing is based upon USP <191>.

For full details regarding test procedures and copies of spectra for lot#433 and the reference standard, please refer to Modules 3.2.S.4.2 and 3.2.S.4.4.

Assay

The proposed assay acceptance criteria of 98.5-101.5% are based on general limits applied to pharmacopeial items and allows for analytical variation of the HPLC method. The drug substance HPLC (assay) test method is identical to the drug product HPLC (assay) test method with the exception of sample preparation procedures. For chromatographic conditions refer to the summary table for the drug product HPLC (assay) test method in Module 2.3.P.5. For full details regarding test procedure, and chromatograms of test sample lot #433 and reference standard, refer to Modules 3.2.S.4.2 and 3.2.S.4.4.

The method has been validated for accuracy, precision, specificity, and linearity per ICH Q2A and Q2B recommendations and shown to be stability-indicating. For a summary refer to the information provided for the drug product HPLC (assay) test method under Module 2.3.P.5. For full details refer to Module 3.2.S.4.3.

Impurities (Related Substances)

See table below for name, structure, and origin of related drug substance organic impurities. For additional information regarding impurity structure and origin refer to DMF nnnn.

Name	Structure	Origin
Impurity A	Structure of Impurity A	Degradation impurity (hydrolysis of the ester moiety) Active metabolite of MK
Impurity B	Structure of Impurity B	Process impurity
Impurity C	Structure of Impurity C	Process impurity
Impurity D	Structure of Impurity D	Process impurity
Impurity E	Structure of Impurity E	Degradation impurity (oxidation)
Impurity F	Structure Unknown (RRT 2.55)	Process impurity Levels do not increase on stability/forced stress testing

Applicable data and rationale supporting the justification for the proposed levels of related substances are provided in the table below. The proposed impurity limits are based upon recommendations in ICH Q3A and draft ANDA Drug Substance Impurity Guidances. The observed levels in MK lot #433 fall well within the proposed limits. For additional information refer to Module 3.2.S.4.5.

Name	MK lot #433	Mock® (MK) Controlled Release Capsules (RLD) (lot #22242, Expiration date 10/05)	Proposed Limits	Justification
Impurity A	0.20%	1.5%	NMT 0.5%	Metabolite
Impurity B	0.10%	0.01%	NMT 0.15%	ICH Q3A qualification threshold[2]
Impurity C	0.09%	0.07%	NMT 0.15%	ICH Q3A qualification threshold[2]
Impurity D	0.11%	≤0.02%	NMT 0.15%	ICH Q3A qualification threshold[2]
Impurity E	0.30%	1.0%	NMT 1.0%	Qualified based on RLD
Impurity F (RRT 2.55)[1]	0.30%	0.50%	NMT 0.50%	Qualified based on RLD
Any Unknown Impurity	≤ 0.07%	≤0.05%	NMT 0.10%	ICH Q3A identification threshold[2]
Total Impurities	1.4%	3.7%	NMT 2.0%	Proposed acceptance criterion are below the levels present in RLD

[1]Impurity F is also present is the reference listed drug. This is based on both products exhibiting a peak with the same retention time on the HPLC, identical UV spectra (PDA), and similar mass spectra (MS-electrospray).
[2] The maximum daily dose of MK is 64 mg/day. Therefore the corresponding recommended identification and qualification thresholds are 0.10% and 0.15%, respectively.

The drug substance HPLC (related substances) test method is identical to the drug product HPLC (related substances) test method, with the exception of sample preparation procedures. For chromatographic conditions refer to the summary table for the drug product HPLC (related substances) test method under Module 2.3.P.5. For details regarding the HPLC test procedure, chromatograms of test sample lot #433, and reference standards (including impurity standards) refer to Modules 3.2.S.4.2 and 3.2.S.4.4.

The method has been validated for accuracy, precision, specificity, linearity, and limits of quantitation/detection per ICH Q2A and Q2B recommendations. For a summary refer to the information provided for the drug product HPLC (related substances) test method under Module 2.3.P.5. For full details refer to Module 3.2.S.4.3.

Impurities (Residual Solvents)

The residual solvents utilized in the manufacturing process of MK and the observed levels of these residual solvents in MK lot #433 are listed in the table below. Proposed specification limits are based on the recommendations in ICH Q3C (Option 1 Limits).

Name	MK lot #433	Proposed Limits
Methanol	200 ppm	3000 ppm
Toluene	80 pm	890 ppm
Tetrahydrofuran	300 ppm	720 ppm

Levels are determined based upon a compendial GC test method for residual solvents (USP <467> Procedure C). For full details regarding test procedure, chromatograms of test sample lot #433 and reference standards, refer to Modules 3.2.S.4.2 and 3.2.S.4.3.

Impurities (Inorganic)

Drug Substance Maker Ltd. indicates that no metal catalysts are used in the manufacture of MK. Therefore, only heavy metals will be monitored in MK. The proposed limit of NMT 20 ppm for heavy metals is based upon a general limit applied to pharmacopeial items. Testing is based

upon the USP Heavy Metals Test (<231> Method II).

Moisture

MK is not hygroscopic (<0.5% water uptake at 90% RH). There are also no known hydrate forms of MK. Moisture is not critical to the manufacturing process as MK is fully dissolved in water prior to coating onto sugar spheres. However, due the potential for degradative hydrolysis of the drug substance during storage, a specification limit of NMT 0.5% is proposed for moisture content. Testing for moisture is based upon Karl Fischer Titration (USP <921> Method 1a).

Specific Optical Rotation

MK is optically active having a specific optical rotation ($[\alpha]_D^{25}$) of +67.2 (c=1% in water)). Therefore, a specification for this attribute is proposed for the MK drug substance. The proposed limits of $+66.4^o$ to $+68.0^o$ allow for typical variability in the measurement of optical rotation. For full details regarding the test procedure refer to Module 3.2.S.4.2.

2.3.S.5 Reference Standards

How were the primary reference standards certified?

The MK reference standard (lot #3) was purchased from Drug Substance Maker Ltd. This reference standard was manufactured by the synthetic route as described in DMF nnnn and further purified by two successive recrystallizations. The calculated purity of this reference standard was 99.9%. For further details please refer Module 3.2.S.3.1.

2.3.S.6 Container Closure System

What container closure system is used for packaging and storage of the drug substance?

MK is packaged in two bags: a low density polyethylene inner bag and a heat sealed composite polyethylene-foil outer bag, and these are placed in fibre-board drum. For additional information regarding the container/closure system used to package the bulk drug substance refer to DMF nnnn.

2.3.S.7 Stability

What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

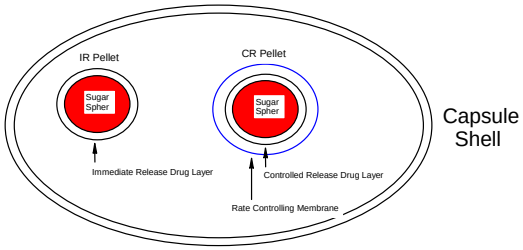
Refer to DMF nnnn for applicable information.

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

What are the components and composition of the final product? What is the function(s) of each excipient?

The drug product consists of a 1:3 mixture of immediate release (IR) and controlled release (CR) pellets filled into a capsule shell, with each unit capsule containing 32 mg of MK.



The quantitative composition and function of each component in the drug product is listed.

Ingredient	Function	Weight
Controlled Release (CR) Pellets		
Core		
Sugar Spheres 25-30 mesh	Base	142.5 mg
Drug Layer		
MK	Active	24.00 mg
Clear Coating 732[2]	Binder	28.48 mg
Butylated Hydroxyanisole	Antioxidant/Stabilizer	0.0225 mg
Purified Water[2]	Solvent	
Rate Controlling Membrane		
Ethylcellulose (20 mPa.s)	Rate controlling polymer component	18.00 mg
Triethyl Citrate	Plasticizer	3.000 mg
Purified Water[2]	Solvent	
Total Weight (CR pellets)		216.0 mg
Immediate Release (IR) Pellets[1]		
Core		
Sugar Spheres 18-20 mesh	Base	47.5 mg
Drug Layer		
MK	Active	8.0 mg
Clear Coating 732[1]	Binder	9.49 mg
Butylated Hydroxyanisole	Antioxidant/Stabilizer	0.0075 mg
Purified Water[2]	Solvent	
Total Weight (IR pellets)		65.0 mg
Hard Gelatin Capsule (Size #1)	**Cap and Body**	
Total Fill Weight		281.0 mg

[1] Components consist of hypromellose and polyethylene glycol 400
[2] Removed during the manufacturing process

Do any excipients exceed the IIG limit for this route of administration?

As depicted in the table below all excipients fall below IIG or other applicable limits.

Ingredient	Amount per unit of MK Controlled Release Capsules, 32 mg	IIG Levels[1] (oral products) or other applicable limits
Sugar Spheres	190 mg	GRAS (21 CFR 184.1854)
Ethylcellulose	18 mg	308 mg
Triethyl Citrate	3 mg	20.18 mg
Polyethylene glycol 400	≤ 37.97 mg	960 mg
Hypromellose	≤ 37.97 mg	480 mg
Butylated hydoxyanisole	0.03 mg	5.0 mg
Gelatin NF	92.35 mg	1000 mg
D&C Yellow #10	0.85 mg	331 mg
FD&C Blue #2	0.019 mg	24 mg
Yellow Iron Oxide[2]	0.065 mg	3.0 mg
Titanium dioxide	1.35 mg	1387 mg
White imprinting ink[3]	0.022 mg	All components present in the white ink have been used in approved drug products

1. http://cdernet.cder.fda.gov/ops/index.htm
2. Complies with the 21 CFR 73.1200 requirement of NMT 5-mg elemental iron/day.
3. Contains pharmaceutical glaze, titanium dioxide, isopropyl alcohol, ammonium hydroxide, n-butyl alcohol, and simethicone

Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

Based upon information in the package insert, the following components are present in the reference listed drug (Mock® (MK) Controlled Release (CR) Capsules): Microcrystalline cellulose, sucrose, eudragit, povidone, talc, hypromellose, titanium dioxide, polysorbate, simethicone, gelatin, and FD&C Blue #1.

Despite the apparent differences in composition between the proposed formulation and the RLD, these differences are considered irrelevant in the context of having a potential effect with respect to therapeutic equivalence. This is based upon the noted similarities between the two products, both in terms of dosage form and dosage form design. For a more detailed summary regarding dosage form design please refer to Module 2.3.P.2.2.

Reference Listed Drug Mock® (MK) CR Capsules	Proposed Generic Drug Product	Significance
Capsule Dosage From	Capsule Dosage Form	Meets applicable requirement for pharmaceutical equivalence
Dissolution testing suggests that the dosage form is designed with both IR (~25% of MK) and CR components (~75% of MK).	Proposed drug product will consist of a mixture of IR and CR pellets, with IR pellets containing 25% of MK dose and CR pellets containing 75% of MK dose	Similar design for in-vivo drug release
Capsules are filled with pellets	Proposed product will consist of pellets	The labeling of the reference product enables patients who may have difficulty swallowing capsules the option of administration by opening the capsule and mixing the pellets with one tablespoon of applesauce. Likewise, this option would be possible for the generic drug product.
RLD label indicates a minimal food effect. Pellet size is 0.8-0.9 mm.	Proposed product will consist of pellets that are ~1.0 mm.	The labeling of the reference product indicates a minimal food effect on the rate and extent of absorption. This design feature will minimize a possible food effect, and enable the generic product, like the RLD, to be taken without regard to meals.

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Product

2.3.P.2.1.1 Drug Substance

Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

The calculated dose solubility volume of MK = 0.68 mL < 250 mL (refer to Module 2.3.S.1). As MK is highly soluble by the BCS, its physical properties (polymorphs, particle size) should have a negligible effect on the biopharmaceutical performance of the finished dosage form. Furthermore, all solid state properties, including particle size and polymorphic form should not be relevant in the context of manufacturability and development as MK is fully dissolved in water for layering the active ingredient onto the sugar spheres. With regard to chemical stability, MK is quite susceptible to oxidation. However, this was remedied by incorporating an antioxidant into the formulation (refer to Module 2.3.P.2.2).

2.3.P.2.1.2 Excipients

What evidence supports compatibility between the excipients and the drug substance?

Compatibility screening of a number of excipients was performed at the early preformulation stage of development to obtain information regarding potential incompatibilities between MK and excipients. Closed vials containing 200 mg of drug-excipient blends with 10% added water were incubated in ovens at 50 °C (3 weeks) to mimic the conditions in the manufacturing process which involve aqueous coating of sugar spheres with MK and excipients, and curing. The preliminary three week compatibility studies with various polymers, fillers, diluents, and plasticizers suggested a potential incompatibility with only lactose, and was attributed to the reaction between the primary amine in MK and the glycosidic hydroxyl of lactose (Maillard

reaction). It was therefore concluded that MK was for the most part compatible with commonly used excipients, including all excipients selected in the final formulation (Module 2.3.P.1). However, formulations containing lactose or other excipients having a glycosidic hydroxyl or aldehyde should be avoided due to the possibility of the Maillard Reaction. For additional details refer to Module 3.2.P.2.1.2.

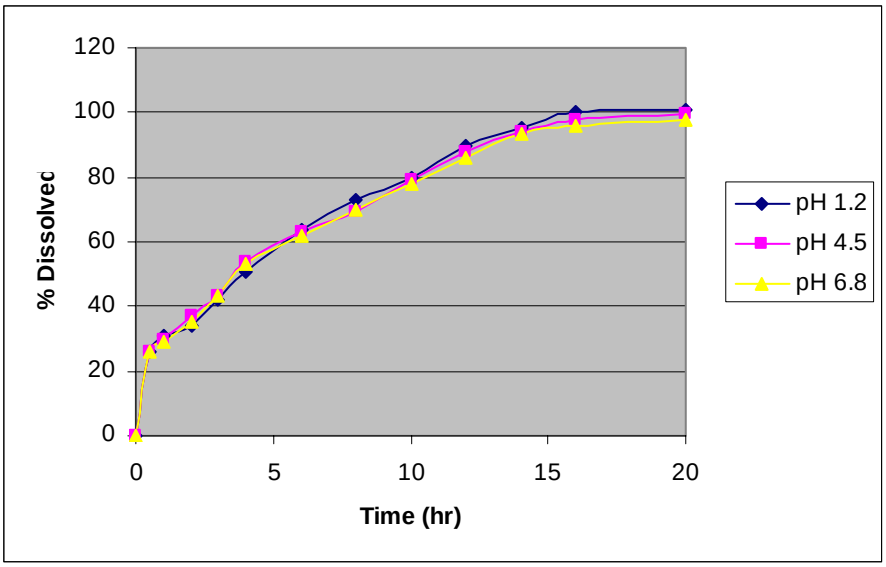
Excipient/Grade	MK Assay (%)	Used in Final Formulation (Y/N)
No Excipient (Control)	91	N/A
Sugar Spheres	90	Y
Ethylcellulose	92	Y
Microcrystalline cellulose	90	N
Lactose	10	N
Hypromellose	91	Y
Triethyl citrate	92	Y
Diethyl phthalate	92	N
Butylated hydroxyanisole	98	Y
Ascorbic acid	95	N
Polyethylene glycol	92	Y

2.3.P.2.2 Drug Product

What attributes should the drug product possess?

Based upon the characterization of Mock® (MK) CR Capsules, it was determined that that the generic formulation would have to have the following four characteristics in order to mimic the reference listed drug. Please refer to Module 3.2.P.2.2.1 for additional information.

1. The product would have to be formulated in a capsule dosage form in order to be considered pharmaceutically equivalent to Mock® CR Capsules.
2. The capsule would have to be filled with coated pellets. The rationale for this is based upon our analysis of the reference listed drug (RLD) and labeling, which allows for patients who may have difficulty swallowing the capsule shell the option of administration by opening the capsule and mixing the pellets with one tablespoon of applesauce. Likewise, this option would also be necessary for the generic drug product formulation.
3. The coated pellets should be ≤ 1.0 mm. The rationale for this design decision rests on the fact that Mock® CR Capsules contain coated pellets having a size of ≤ 1.0 mm. This pellet size is small enough to pass through the pyloric sphincter and as such should show similar gastric residence times under both fasting and fed conditions. This is corroborated by the RLD labeling which indicates the product may be taken with or without food, suggestive of an insignificant food effect. Therefore, since both fed and fasted bioequivalence studies will be required for this product, in order to successfully develop a modified release formulation that is bioequivalent under both fasting and fed conditions, would require in all likelihood, the use of coated pellets ≤ 1.0 mm in the product design.
4. As depicted in the figure below, dissolution testing of the RLD suggested that Mock® CR Capsules consist of both IR (~25% of MK) and CR (~75% of MK) components. Therefore, a similar approach was pursued when designing the generic product prototype, so to mimic MK drug release, and the likelihood of a product that is bioequivalent to the RLD.



Dissolution Profiles of the RLD in USP Apparatus 1 at 100 rpm in pH 1.2, 4.5, and 6.8 dissolution media (37 °C)

How was the drug product designed to have these attributes?

Based upon the observation that Mock® CR Capsules contain both immediate and controlled release components, our product was designed to have a similar release profile through the inclusion of both IR and CR pellets in each capsule.

The CR pellets are coated with a rate controlling membrane that controls drug release; a membrane comprised of ethylcellulose (hydrophobic polymer) and triethyl acetate (plasticizer)[2] was chosen based upon prior experience with this system in an approved and analogous product (e.g. IT ER Capsules (ANDA wwww)). In such a system, drug release is attenuated by virtue of the reduced transport of the water soluble MK active ingredient through the hydrophobic membrane, and functions in a pH independent manner. For full details regarding dosage form design, please refer to Module 3.2.P.2.2.1.

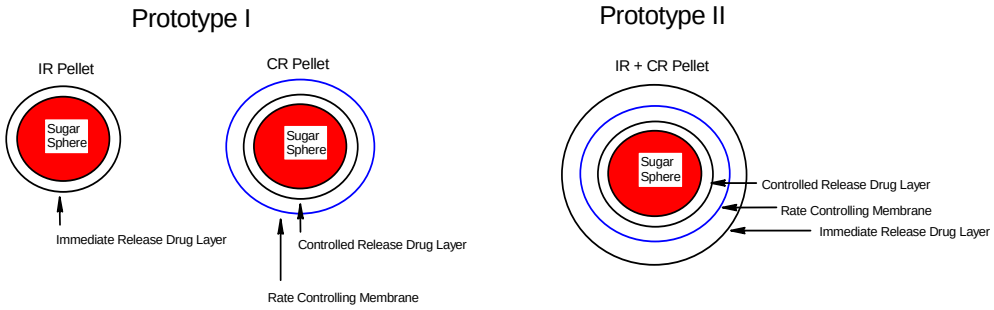
During the development process, the viscosity of the polymer and the thickness of the rate controlling membrane were identified as factors that could change the release profile of the final product.

Were alternative formulations or mechanisms investigated?

Two pellet formulation prototypes were evaluated during product development. The first prototype (Prototype I) consisted of a mixture of two pellets filled into the capsule shell: an IR drug pellet and a CR drug pellet. The second prototype (Prototype II) consisted of a single multilayered pellet having both IR and CR components. Ultimately, it was decided to pursue the first prototype in which a mixture IR and CR pellets would be filled into the capsules shell. The decision to pursue Prototype I was based on prior experience with other products that use this prototype as well as the greater simplicity of the developing separate IR and CR pellets,

[2] Triethyl citrate, a water soluble plasticizer, was chosen based upon previous experience (e.g. IT ER Capsules (ANDA wwww)) in order to ensure coalescence of the membrane as a continuous film during coating, to ensure the CR membrane is free from fractures or cracks, and also to facilitate any curing phenomenon.

compared to the complexities involved in developing a single multilayered IR and CR pellet in Prototype II.



For full details regarding dosage form design, please refer to Module 3.2.P.2.2.1.

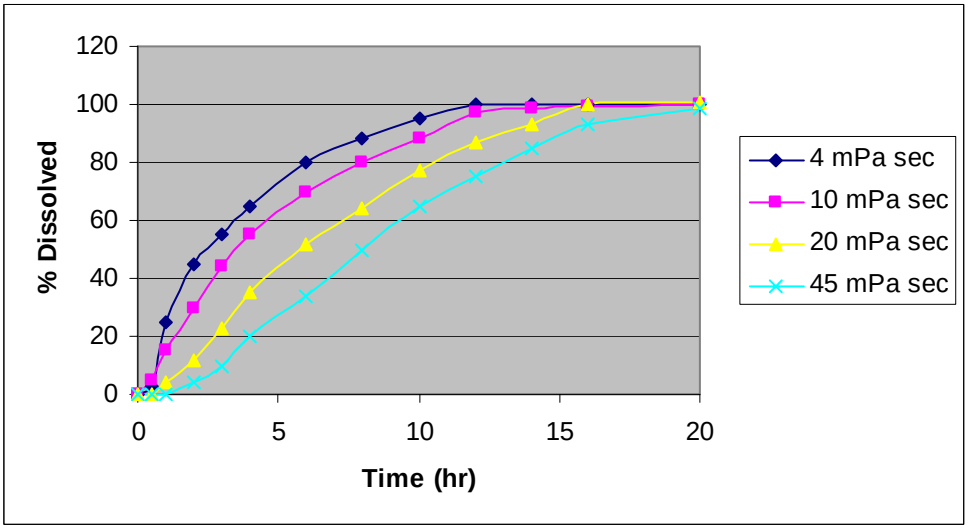
How were the excipients and their grades selected?

***Excipient Selection*:**

Clear coating 732 (comprised of hypromellose and polyethylene glycol) was chosen as a binder to help the MK drug adhere to the sugar spheres. Ethylcellulose (hydrophobic polymer) and triethyl acetate (plasticizer) were chosen as components of the rate controlling membrane. These choices were based upon prior experience with the above excipients in an analogous approved product (e.g. IT ER Capsules (ANDA wwww)) and upon the observed compatibility of these excipients with MK (refer to Module 2.3.P.2.1.2).

Excipient Grade Selection

Ethylcellulose: Ethylcellulose, the hydrophobic polymer that attenuates MK release is commercially available in various grades with differing viscosities (correlated with MW of the polymer). As this excipient exerts a critical function related to product performance, various grades of ethylcellulose having different viscosities (applied at a 10% coating level) were evaluated in small scale laboratory studies to determine whether excipient viscosity would have an effect on product performance.



Dissolution Profile of the MK coated pellets with different ethylcellulose viscosities.

The above results show that the viscosity of ethylcellulose significantly impacts product performance. Therefore, stringent controls were imposed upon the viscosity grade of the excipient, during both development and manufacturing. Although other viscosity grades may have been chosen, the decision to utilize ethylcellulose having a viscosity of 20 mPa.S was based upon convenience, as this grade of ethylcellulose is already used in other pre-existing products (e.g. IT ER Capsules (ANDA wwww)).

Sugar Spheres: During product development, sugar spheres with a particle size distribution of 25-30 mesh were selected. This constraint on the particle size distribution of sugar spheres provides a uniform surface area for coating. Having sugar spheres with uniform surface area enables one to manufacture CR pellets with a membrane of uniform thickness, based upon the level of coating applied, which is essential for ensuring a uniform and reproducible drug release profile. Additionally, the particle size constraint of 25-30 mesh ensures that the coated pellets are $\leq$ 1.0 mm, which is essential for minimizing a possible food effect on the rate and extent of MK absorption (refer to response regarding what attributes the drug product should possess).

For additional details regarding excipient (and grade) selection refer to Module 3.2.P.2.1.2.

How was the final formulation optimized?

Product Stability Optimization

During the initial stages of development, studies on various laboratory scale trial formulations qualitatively similar to the finalized formulation described in Module 2.3.P.1 were investigated under accelerated stability test conditions (40 ^{o}C /75 % RH, 4 weeks). These studies suggested that MK was prone to degradation, particularly oxidation to Impurity E and to a lesser extent, hydrolysis to Impurity A (active metabolite). Since oxidation was the predominant degradation pathway, experimental formulations containing different antioxidants were evaluated under accelerated stability conditions (40 ^{o}C/75% RH, 4 weeks). As illustrated in the table below, while both ascorbic acid and butylated hydroxyanisole provided a stabilizing antioxidant effect, butylated hydroxyanisole was clearly superior and therefore chosen in the final formulation. The amount of 0.03 mg of butylated hydroxyanisole provides the optimum stability of the product.

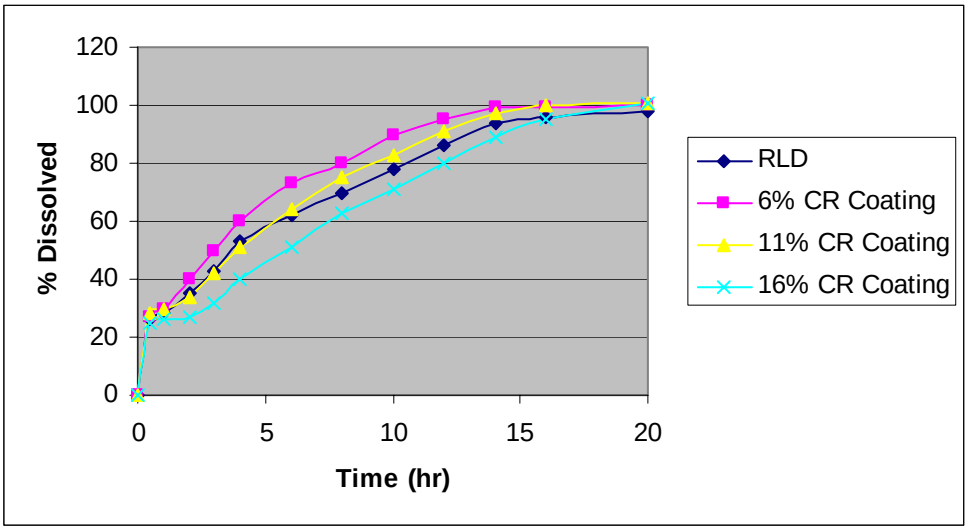
It should be noted that studies to stabilize the product in terms of degradative hydrolysis to Impurity A were not pursued, as this impurity is in fact, the active metabolite, and therefore does not pose safety concerns. Furthermore, the observed level of degradation to Impurity A did not present a realistic potential for drug product assay failure.

	MK Assay (%)	Impurity A (%)	Impurity E (%)
IR Pellet* (No antioxidant)	80	2	17
IR Pellet* (+5.0 mg of ascorbic acid)	87	2	10
IR Pellet* (+10.0 mg of ascorbic acid)	89	2	8
IR Pellet* (+20.0 mg of ascorbic acid)	94	2	3
IR Pellet (+0.01 mg of butylated hydroxyanisole)	96	2	2
IR Pellet (+0.03 mg of butylated hydroxyanisole)	97	2	1
IR Pellet (+0.06 mg of butylated hydroxyanisole)	97	2	1

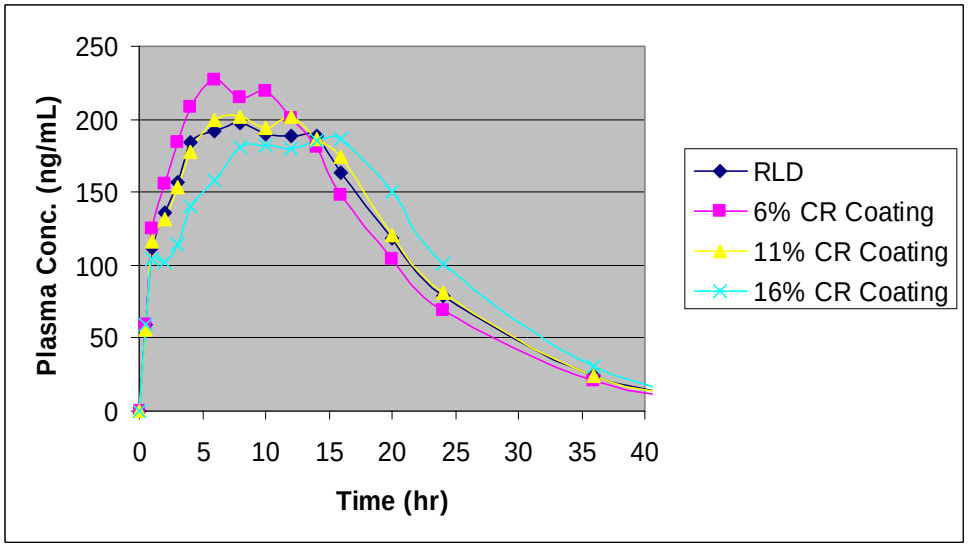
* IR Pellet is qualitatively similar to the formulation listed Module 2.3.P.1 with the exceptions noted in ().

Product Bioequivalence/Bioavailability Optimization

A series of studies were performed to investigate the effect of the thickness of the controlled release membrane on dissolution. Dissolution in the trial formulation was found to proceed in a pH independent manner due to the similar solubilities of MK at various pH levels and the fact that the controlled release mechanism is governed by diffusion. This behavior was consistent with the observed pH dependent release profile of the RLD. Therefore, three trial formulations having differing CR coating levels (6%, 11%, 16%) were designed such that their dissolution profiles (pH independent) would bracket the RLD dissolution profiles at 6.8. Pilot PK studies in 5 subjects were then performed to determine the coating thickness that would best match the pharmacokinetic profile of the RLD. The mean PK profile data from the pilot studies are summarized and plotted in the figure below. Based upon these studies, 11% was determined to be the optimal coating level, and was used in the final formulation for the pivotal bioequivalence studies.



Dissolution testing was performed using the USP Apparatus 1 (900 mL, 100 rpm, 37 ^{o}C) at pH 6.8



	RLD	CR Coating (6%)	CR Coating (11%)	CR Coating (16%)
AUC (ng/ml hr)	4612	4650	4717	4808
C_{max} (ng/ml)	197	226	202	186
AUC ratio		1.01	1.02	1.04
C_{max} ratio		1.15	1.03	0.94

For full details regarding these dosage optimization studies refer to Module 3.2.P.2.2.1.

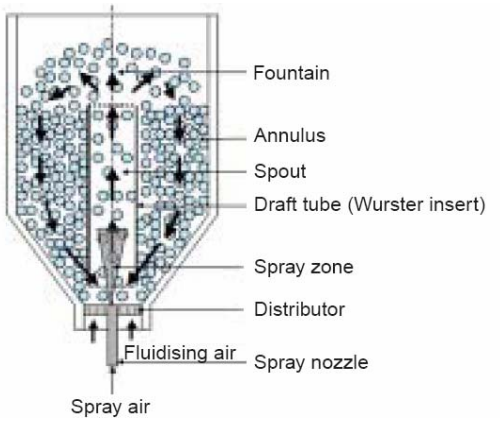
2.3.P.2.3 Manufacturing Process Development (This section is optional for a non critical dose drug formulated in a solution or an immediate release dosage form)

Why was the manufacturing process described in 2.3.P.3 selected for this drug product?

Coating Process:

In order to manufacture the drug product, a bottom spray coating (Wurster coating) process was chosen for both 1) the sugar-sphere-drug layering process that yields the IR pellet component of the final drug product and 2) for the functional CR coating process (onto IR pellets) that yields the CR pellet drug product component. The rationale for selecting this process was two fold:

1. The Wurster process results in highly uniform coating of particulates. In terms of process design, this is essential to ensure both content uniformity (uniform MK coating sugar spheres) and reproducible drug release (uniform CR coating layered on sugar spheres).
2. Prior manufacturing knowledge utilizing a Wurster coating process and similar functional CR coating mechanism is available ((IT ER Capsules (ANDA wwww)).



Principle: Batch fluid bed coating Bottom Spray (Wurster)

Encapsulation:

The encapsulation process using a dosing disk and weight sorting was chosen for filling of the capsules with IR and CR pellets based on prior knowledge of this type of filling process in other products (IT ER Capsules (ANDA wwww)). Moreover, the very fact that that the dosage form has been designed to consist of two pellet components filled within a capsule shell necessitates the utilization of the encapsulation process. For additional details regarding the rationale for manufacturing process refer to Module 3.2.P.2.3.

How are the manufacturing steps (unit operations) related to the drug product quality?

An influence matrix correlating process steps with drug product quality characteristics was constructed. Locations where process steps have a high influence on drug quality are identified. In-process tests/controls are imposed at these locations to ensure the process step has proceeded successfully (refer to question on in-process testing under Module 2.3.P.3).

	Raw Material	Drug Layering	CR Coating	Encapsulation
Purity	**High**			
Assay/Content Uniformity		**High**		**High**
Release Profile	**High**		**High**	**High**
Stability			**High**	

In summary, the product has been designed as an encapsulated combination of IR and CR pellets to yield a drug product with the target of mimicking the drug release profile of the RLD. Based on the desired drug release profile, the critical process steps have been identified as 1) drug layering (yielding the IR pellets); 2) CR coating (yielding CR pellets); and 3) encapsulation (yielding the combined both IR and CR drug release pulses).

How were the critical process parameters identified, monitored, and/or controlled?

Drug Layering Process:
The drug layering process was identified as a critical step in the manufacturing process, as this step directly impacts upon coating efficiency as well as content uniformity of the final product. The critical process parameters and optimum settings for the drug layering process were identified based on prior knowledge on a similar product in which the drug substance is coated on sugar spheres of the same size distribution and porosity (see ANDA wwww). In addition, laboratory scale studies (3 kg batches) were performed in a 7" Wurster at the optimized and extremes (low and high) for the identified critical process parameters. The critical process parameters identified for the drug layering step were the drug layering solution spray rate, product bed temperature, atomizing pressure, and fluidizing air volume. Most importantly, these studies established that a spray droplet size[3] of 20 μm was critical for the optimum drug layering onto the sugar spheres, and was achieved through the appropriate combination of spray rate and atomizing air pressure process parameters.

In summary, in the optimized process, coating efficiency was 98.0% with pellets exhibiting content uniformity values varying between 98 and 101%, thereby demonstrating that MK was uniformly distributed over the entire batch. For detailed results of the laboratory scale batch studies refer to Module 3.2.P.2.3.

[3] Droplet size was measured using a Malvern Spraytec Real Time Droplet Sizing System.

Optimized Drug Layering Process Parameter Settings (7" Wurster (89 mm partition))

Parameter	Settings	Rationale
Fluidizing Air Volume	80-100 m^3/hr	Range for proper fluidization behavior of the sugar spheres. Note: Range setting are based on prior knowledge for coating a similar drug substance on sugar spheres of the same size distribution and porosity (see ANDA wwww), with confirmatory studies in the laboratory scale.
Product Bed Temperature	35–45°C	Lower than optimum led to too little evaporation of the solvent leading to low yield due to core agglomeration. Higher than optimum yielded increased evaporation and poor adherence of drug/binder to sugar pellet core, yielding poor coating efficiency and poor content uniformity.
Spray Rate*	15–20 mL/min	Lower spray rates decreased droplet size, enhancing evaporation and resulted in poor adherence of drug/binder to sugar pellet core, yielding poor coating efficiency and poor content uniformity. Faster spray rates increased the droplet size, leading to low yield due to product agglomeration.
Atomizing Air Pressure	1.0 bar	At the optimized spray rate of 15-20 g/min, an atomizing air pressure of 1.0 bar generates a 20μ droplet size. Atomizing air pressures exceeding 2.5 bar should be avoided due to excessive pellet attrition.
Inlet Air Temperature	45-55°C	Calculated using the drying/humidity chart of the Wurster. This is a dependent process variable that is calculated based upon consideration of spray rate, fluid bed temperature, fluidizing air volume, incoming air RH%, and outlet air temperature/RH% to ensure sufficient evaporative capacity. See Module 3.2.P.2.3 for Wurster drying/humidity chart.

* In the drug layering process, MK (active), clear coating 732 (binder), and butylated hydroxyanisole (stabilizer) are sprayed as a 10% w/v aqueous solution

CR Coating Process:

As per the intended function of the proposed drug product, the functional coating process was identified as a critical step in the drug product manufacturing process.

The critical process parameters for the CR coating process were identified and the impact elucidated using a statistical design of experiments (D.O.E.) with the main objective to determine the influence of the process parameters and maximize coating efficiency. A secondary objective was to ensure that the optimized process yields a fully cured product that maintains a consistent release profile through the shelf life of the product. The D.O.E. was set up to challenge extremes of several process parameters, which were chosen based on prior knowledge of the Wurster coating process for a CR drug product (ANDA wwww) and available literature. Results of the D.O.E. study are summarized below.

D.O.E. CR Process Variables Studied

Process Variable	Minimum	Maximum
Product Bed Temperature	40°C	70°C
Atomizing Air Pressure	1 bar	5 bar
Fluidization Air Volume	70 m^3/h	150 m^3/h
Spray Rate	10 mL/min	70 mL/min
CR Coat Solids Content	10%	30%
Droplet Size	5 μm	70 μm

D.O.E. Response Variables Obtained

	Minimum Observed	Maximum Observed
Coating Efficiency	75.8%	99.2%
Drug Release (1 hr)	2%	25%
Drug Release (4 hr)	25%	64%
Drug Release (8 hr)	55%	88%
Drug release, f_2 values Freshly prepared vs. stored at 60 °C (18 hr)	53.1	97.9

The range of process parameter results showed an expected influence on the drug release profile of the CR coated drug product attributed to variations in coating thickness and coating membrane integrity, based on the range of process parameters. All process parameters were found to have some effect on the coating efficiency, with the maximal effect observed when spray rate and atomizing pressure were varied in the process. With regard to curing, the observed similarity of dissolution profiles ($f_2 > 50$) between freshly coated CR pellets and CR pellets stored in an oven at 60^{o}C (18 hr), suggested that under the range of coating conditions surveyed in the D.O.E., the CR coating was fully coalesced; removing the need for an additional curing step.

The results of the D.O.E. study were then used to choose the process parameters that could be used for the manufacture of a 3 kg lab scale CR coated batch using the optimum conditions, with drug product characteristics of $f_2 > 50$ (freshly coated vs "cured" at 60^{o}C (18 hr)), drug release at 1, 4 and 8 hours of <10%, 35%, and 65% respectively, and coating efficiency of greater than 95%. It is also worth noting, that the results of the D.O.E study indicated a spray droplet size[3] of 30 μm was absolutely critical for optimal coating of the CR membrane, and this was achieved through the appropriate combination of both spray rate and atomizing air pressure process parameters. The optimized process settings are presented in the table below, along with the rationale. The integrity of the CR membrane was further evaluated and confirmed via scanning electron microscopy. The coating process efficiency of the optimized batch was 99.0%.

For full details refer regarding D.O.E setup, lab scale results, rational for the selection optimized process parameters, and results on the optimized 3 kg scale batch, refer to Module 3.2.P.2.3.

Optimized CR Process Settings (7" Wurster (89 mm partition))

Parameter	Settings	Rationale
Fluidizing Air Volume	90–110 m^3/hr	Lower and higher than optimum range led to poor fluidization patterns and loss of coating efficiencies.
Product Bed Temperature	37–43 °C	Lower than optimum led to poor evaporation and pellet agglomeration. Higher than optimum led to case hardening of the pellets (trapping moisture in the product matrix), poor adherence of the CR membrane, and rapid drug release.
Spray Rate	25–30 mL/min	Lower spray rates decreased droplet size, enhancing evaporation resulting in poor coating efficiency and rapid drug release. Faster spray rates increased the droplet size leading to low yield due to product agglomeration.
Atomizing Air Pressure	1.5 Bar	At the optimized spray rate of 25-30 g/min, the atomizing air pressure generates a 30μm droplet size that is critical to ensure adequate CR coating. Atomizing air pressures exceeding 3.0 bar should be avoided due to excessive pellet attrition.
Coating Solids	15% w/v	Lower coating solids led to less viscous coating suspension which affected spray rate. Higher coating solids resulted in a too viscous suspension that was difficult to spray without maximum air pressure utilization
Inlet Air Temperature	55-62 °C	Calculated using the drying/humidity chart of the Wurster. This is a dependent process variable that is calculated based upon consideration of spray rate, fluid bed temperature, fluidizing air volume, incoming air RH%, and outlet air temperature/RH% to ensure sufficient evaporative capacity. Refer to Module 3.2.P.2.3 for Wurster drying/humidity chart.

Encapsulation:

IR and CR pellets are filled into a hard gelatin capsule shell using two independent feeders in an automatic encapsulator. Encapsulation process parameters are based on recommendations of the equipment manufacturer and prior knowledge in the operation of an automated encapsulator in filling a two pellet drug product. Therefore, the encapsulation unit operation did not require extensive development work. Moreover, in-process testing will be performed by a capsule fill machine with 100% weight check of both IR and CR pellets. For a summary of in-process controls used in the encapsulation process please refer to Module 2.3.P.3.

What is the scale-up experience with the unit operations in this process?

Scale-up in the Wurster was successfully accomplished in other products, including ER capsule products (IT ER Capsules (ANDA wwww)). Additionally, based upon the design of experiments on laboratory scale batches, acceptable ranges for critical process parameters for coating of both MK and CR layers onto sugar spheres were determined. This process knowledge was used to successfully scale-up from the laboratory scale to the pilot scale in the production of the pivotal ANDA batch. Applicable changes to process parameters that were used to successfully scale-up from laboratory to pilot scale are provided, along with corresponding rationale. For additional information please refer to section 3.2.P.3.3.

	Laboratory Scale	**Pivotal Batch**	
Equipment: Partitions: Number/Diameter Number of Spray Guns	7" Wurster 1/89 mm 1	18" Wurster 1/219 mm 1	
Batch Load[1]	3 kg (10,700 units)	40 kg (142,000 units)	
MK Drug Layering			
Process Parameters			**Rationale**
Fluidizing air volume (m^3/hr)	80-100	480-600	Linear scale-up based upon distribution-plate area ratio[2]
Inlet air temperature (^oC)	45-55	45-55	Scale-independent variable
Product bed temperature (^oC)	35-45	35-45	Scale-independent variable
Spray rate (mL/min)	15-20	90-120	Linear scale-up based upon distribution-plate area ratio
Atomizing air pressure (bar)	1.0	2.0	Due to the higher spray rate, the nozzle atomizing air pressure was increased[3] to maintain the same median spray droplet size of 20 μm
Coating Efficiency	98%	98%	N/A
CR Layering			
Process Parameters			**Rationale**
Fluidizing air volume (m^3/hr)	90-110	540-660	Linear scale-up based upon distribution-plate area ratio[2]
Inlet air temperature (^oC)	55-62	55-62	Scale-independent variable
Product bed temperature (^oC)	37- 43	37-43	Scale-independent variable
Spray rate (mL/min)	25-30	150-180	Linear scale-up based upon distribution-plate area ratio
Atomizing air pressure (bar)	1.5	2.5	Due to the higher spray rate, the nozzle atomizing air pressure was increased[3] to maintain the same median spray droplet size of 30 μm
Coating Efficiency	99%	99%	N/A

[1] Batch loads are in accordance with recommendations from the equipment manufacturer as well as prior experience.
[2] Maintains the same air velocity during scale-up
[3] Studies performed on the laboratory scale indicated the corresponding increase in nozzle atomizing air pressures would not result in significant pellet attrition.

2.3.P.2.4 Container Closure System

What specific container closure attributes are necessary to ensure product performance?

The container closure system should protect the drug product from moisture due to the potential for degradative hydrolysis of MK. The proposed container/closure system complies with the applicable USP <671> requirements for tight containers (refer to Module 3.2.P.2.4).

2.3.P.3 Manufacture

For All Products:

Who manufactures the drug product?

Drug Product Maker Ltd.
5 Main Street
City 1, Country 2

What are the unit operations in the drug product manufacturing process?

A process flow diagram which illustrates the drug product manufacturing process unit operations is provided below. The manufacturing process can be divided in three parts: 1) manufacture of the IR pellets, 2) manufacture of the CR pellets, and 3) encapsulation.

Manufacture of IR Pellets

1. Drug layering solution: Transfer purified water into a suitable stainless steel vessel, and add clear coating 732, butylated hydroxyanisole, and MK. Mix until completely dissolved.
2. Transfer sugar spheres (25-30 mesh) into the fluidized-bed coating apparatus (with Wurster insert), and spray the drug layering solution onto the sugar spheres. After spraying, dry the MK coated sugar spheres for an additional 10 min while fluidizing.
3. Pass the MK drug layered coated beads through a vibratory/shaker separator using a #20 mesh screen on top and #30 mesh screen at the bottom, and package bulk pellets into suitable bags and seal. The screened beads are either used as the IR pellet of the finished dosage form or are subsequently processed to obtain CR pellets.

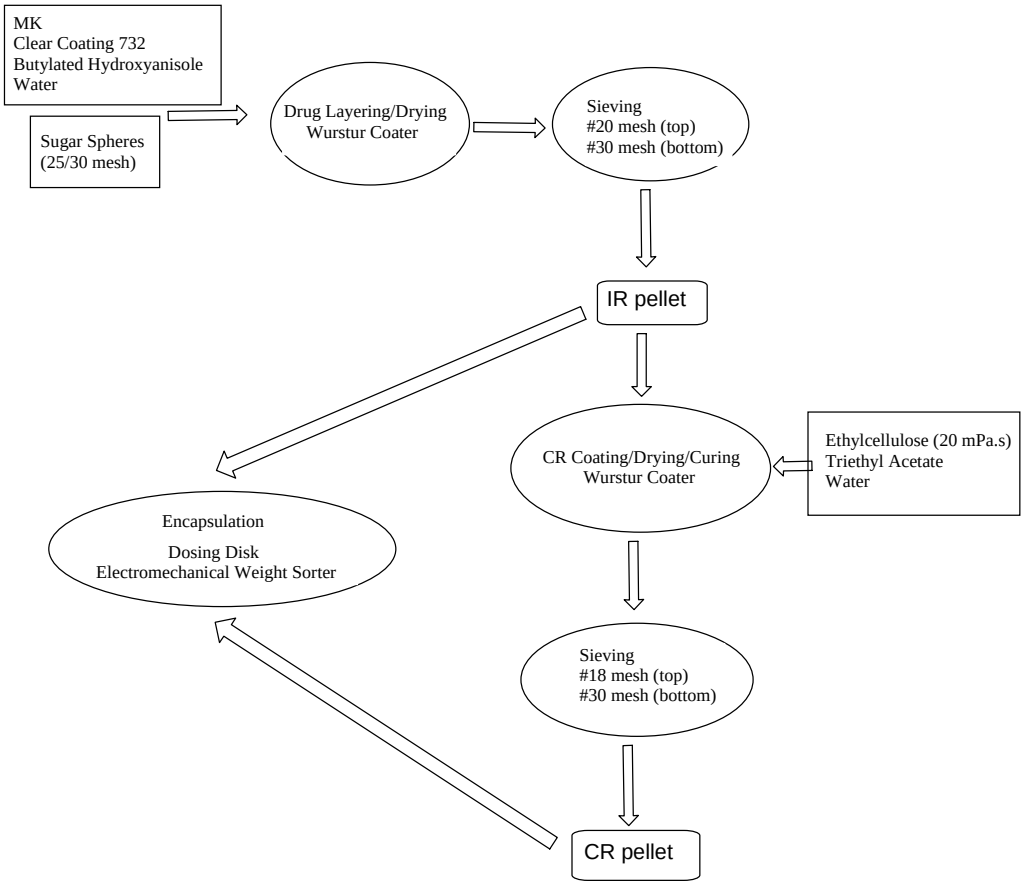
Manufacture of CR Pellets

1. Controlled-release coating suspension: Transfer purified water into a suitable stainless steel vessel equipped with a pneumatic mixer. Add triethyl acetate followed by ethylcellulose (20 mPas) with continuous mixing.
2. Transfer IR pellets into the fluidized-bed coating apparatus (with Wurster insert), and spray coating suspension (mix continuously) onto IR pellets. After spraying, dry the CR coated sugar spheres for an additional 10 min while fluidizing.
3. Pass the CR pellets through a vibratory/shaker separator using a #18 mesh screen on top and a #30 mesh screen at the bottom and package bulk pellets into suitable bags and seal.

Encapsulation

Fill the calculated amount of IR and CR pellets using two independent feeders on an automatic encapsulator, with continuous monitoring, into a #1 gelatin capsule shell.

For details regarding the manufacturing process refer to Module 3.2.P.3.3.



Reprocessing: No reprocessing procedures will be employed in the manufacturing process of MK CR Capsules. For the reprocessing statement refer to Module 3.2.P.3.3.

For batch records of the exhibit batch and proposed commercial manufacturing process refer to Module R.1.P.

What is the reconciliation of the exhibit batch?

A summary of the batch reconciliation data for the ANDA exhibit batch is provided below. For batch records of the ANDA exhibit batch refer to Module R.1.P.

Packaging	Batch #P034	Target (Theoretical)	Yield	OSS Limits
Drug Layering				
	33.60 kg 129,200 units	36.92 kg 142,000 units	91%[1]	85%
CR Coating				
	25.65 kg 118,750 units	27.00 kg[2] 125,000 units	95%[1]	90%
Encapsulation				
	29.98 kg 106,700 capsules	30.91 kg 110,000 capsules	97%[3]	95%
Packaging				
30-Unit Bottles 100-Unit Bottles 500-Unit Bottles Total Packaged	50,500 capsules 40,000 capsules 16,000 capsules 106,500 capsules	106,700 capsules	99.8%	98%

[1] Losses are attributed to rejects of agglomerates and fines following sieving
[2] Number of units is calculated to reflect that the final dosage form is composed of 25% IR and 75% CR pellets.
[3] Losses are attributed to remaining material in the feeder.

Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?

Drug layering step

A coating efficiency of 98% was observed in both laboratory studies and in the pivotal ANDA batch. Therefore, during commercial scale production, the drug layering solution will be sprayed at a 2% overage in order to ensure that sugar spheres are coated with MK at the desired target levels.

Component	Unit Composition	Pivotal ANDA Batch 142,000 Units	Commercial Batch 710,000 Units
Sugar Spheres 25-30 mesh	190.0 mg	26.98 kg	134.90 kg
MK	32.00 mg	4.635 kg[1]	23.17 kg[1]
Clear Coating 732	37.97 mg	5.500 kg[1]	27.50 kg[1]
Butylated Hydroxyanisole	0.03 mg	0.004345 kg[1]	0.02173 kg[1]
Purified Water	n/a	qs to 101 L	qs to 507 L

[1] Sprayed at a 2% overage due to a coating efficiency of 98%

CR coating step

A coating efficiency of 99% was observed in both laboratory studies and in the pivotal ANDA batch. Therefore during commercial scale production, the CR layer coating suspension will be sprayed at a 1% overage to provide for a CR coat with an appropriate thickness that properly attenuates drug release.

Component	Unit Composition	Pivotal ANDA Batch 125,000 Units[1,2]	Commercial Batch 710,000 Units[2]
IR Pellet	260.0 mg	24.375 kg	138.45 kg
Ethylcellulose (20 mPa.s)	24.00 mg	2.273 kg[3]	12.91 kg[3]
Triethyl citrate	4.00 mg	0.3788 kg[3]	2.151 kg[3]
Purified Water	n/a	qs to 17.7 L	qs to 100.4 L

[1] Due to losses during the drug layering step as well as additional testing of the IR pellets in the exhibit ANDA batch, the equivalent of 125,000 (of 142,000) units were carried onto the production of the final drug product
[2] The final dosage form is composed of 25% IR and 75% CR pellets. Therefore, the batch formula is calculated to reflect that only 75% of IR pellets are coated with a CR layer in the final dosage form.
[3] Sprayed at a 1% overage due to a coating efficiency of 99%.

Encapsulation

As per the unit composition of the dosage form, the encapsulation step will provide for the filling of a 1:3 ratio of IR/CR pellets. For additional details regarding the batch formula and justification for the spraying overages please refer to Modules R.1.P, 3.2.P.3.2 and 3.2.P.3.3.

If Product is Not a Solution

What are the in-process tests and controls that ensure each step is successful?

Drug Layering

The drug layering process was identified as a critical step in the manufacturing process as this directly impacts the assay and content uniformity of final dosage form. Therefore, in-process tests for assay, content uniformity, and pellet size are imposed to ensure this step proceeds successfully. In addition, in-process controls for moisture content will be imposed to ensure adequate drying of the pellets during the drug layering process.

In-Process Test	Acceptance Criteria	Results Optimized Laboratory Batch	Results Pivotal ANDA Batch
Description	White to slightly off-white spherical beads	Complies	Complies
Assay	95.0-105.0% of theoretical drug content (123 mg MK/g of IR pellet)	99%	100%
Uniformity of Dosage Units	Mean 90-110%, RSD NMT 5% (Pellet equivalent of 96 mg of MK)	Mean 99% RSD 2%	Mean 100% RSD 1%
Pellet Size	D_{50}: NMT 730 µm D_{90}: NMT 780 µm	700 µm 750 µm	703 µm 755 µm
Moisture	NMT 2.0%	1.5%	1.4%

CR Coating

The CR coating process was identified as a critical step because it directly impacts both coating thickness and integrity, and therefore influences proper attenuation of drug release from the CR pellet. In-process tests for dissolution and pellet size are imposed to ensure this step proceeds successfully. In addition, in-process controls for moisture content will be imposed to ensure adequate drying of the pellets during the CR coating.

In-Process Test	Acceptance Criteria	Results Optimized Laboratory Batch	Results Pivotal ANDA Batch
Description	White to slightly off-white spherical beads	Complies	Complies
Assay	95.0-105.0% of theoretical drug content (111 mg MK/g of CR pellet)	99%	100%
Dissolution	Time % Dissolved in pH 6.8 dissolution media (Apparatus 1, 100 rpm, 37°C) 1 hr: NMT 10% 4 hr: Between 25-45% 8 hr Between 55-75% 12 hr: NLT 80%	 3-5% 33-37% 63-67% 86-91%	 2-5% 32-36% 62-65% 87-92%
Pellet Size	D_{50}: NMT 800 µm D_{90}: NMT 850 µm	775 µm 825 µm	770 µm 825 µm
Moisture	NMT 2.0%	1.3%	1.4%

Encapsulation

The encapsulation process was identified as a critical step as it ensures that the proper ratio (1:3) of IR and CR pellets are filled into a hard gelatin capsule shell, which is essential to achieve the desired release profile of MK. Additionally, this step was also identified as critical because it directly impacts the assay and content uniformity of the finished dosage form. Therefore, in-process controls using a capsule fill machine with 100% weight check of both IR and CR pellets are imposed to confirm that this step has proceeded successfully.

Note that although the capsule fill process provides for a 1:3 ratio of IR and CR pellets, this value may be adjusted within 95%-105% of the theoretical ratio of 1:3, based upon a normalized potency factor using the mean MK assay values of IR and CR pellets. For additional details regarding proposed in-process controls, testing procedures, and batch data please refer to Modules 3.2.P.3.3 and 3.2.P.3.4.

In-Process Test	Acceptance Criteria	Results Optimized Laboratory Batch	Results Pivotal ANDA Batch
Individual Capsule Fill Weight (IR pellets) Theoretical: 65 mg Normalized IR Weight= 65 mg x (IR pellet potency factor[1])	Normalized IR Weight (±8%)	All Comply	All Comply
Average Capsule Fill Weight (IR pellets)	Normalized IR Weight (±3%)	All Comply	All Comply
Individual Capsule Fill Weight (CR pellets) Theoretical: 216 mg Normalized CR Weight= 216 mg x (CR pellet potency factor[2])	Normalized CR Weight (±8%)	All Comply	All Comply
Average Capsule Fill Weight (CR pellets)	Normalized CR Weight (±3%)	All Comply	All Comply

[1] IR pellet potency factor = 1/(Mean Assay Value for IR pellet)
[2] CR pellet potency factor = 1/(Mean Assay Value for CR pellet)

During scale-up and process validation of the commercial manufacturing process, the above in-process tests and controls will be imposed as regulatory commitments to ensure that the critical process steps (drug layering, CR coating and encapsulation) have proceeded successfully.

It should be noted that extensive process development studies have been performed through which the critical process parameters for the drug layering and CR coating process steps were identified, with acceptable ranges for these parameters determined. Therefore, following scale-up and process validation of the commercial scale manufacturing process, a prior approval supplement will be submitted to the Agency, requesting the removal of regulatory commitments on in-process controls for both drug layering and CR coating steps. In the future, these in-process controls will serve as internal controls. However, in-process controls using a capsule fill machine with 100% weight check of both IR and CR will be retained indefinitely.

What is the difference in size between commercial scale and exhibit batch? Does the equipment use the same design and operating principles?

The difference in batch size between the proposed commercial production scale process (200 kg (710,000 units)) and the pivotal ANDA batch (40 kg (142,000 units)) is five fold. The commercial scale process will involve the same unit operations and utilize equipment of the same design and operating principles. For additional information, please refer to subsequent questions regarding the scale-up plan for the commercial process.

If the Product is a NTI Drug or a Non-Simple Dosage Form:

In the proposed scale-up plan what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

The proposed commercial scale process will utilize a 32" Wurster and be at the 200 kg scale. In the proposed scale-up plan the 32" Wurster will contain three separate partitions (219 mm) with each having its own spray gun. Therefore, considering the 32" Wurster is for all practical purposes, comprised of three separate 18" Wurster units, scale-up to commercial production in the 32" Wurster will be based upon simply retaining the process parameters already utilized in the 18" Wurster and adjusting total air-flow to reflect three multiplets of the 18" Wurster insert. The scale up plan is shown below. For additional information please refer to section 3.2.P.3.3.

	Pivotal Batch	Proposed Commercial Scale	
Equipment: Partitions: Number/Diameter Number of Spray Guns	18" Wurster 1/219 nm 1	32" Wurster[1] 3/219 nm 3	
Batch Load[1]	40 kg (142,000 units)	200 kg (710,000 units)	
MK Drug Layering			
Process Parameters			**Rationale**
Fluidizing air volume (m^3/hr)[3]	480-600	1440-1800	Linear scale-up based upon total distribution-plate area ratio[2]
Inlet air temperature (^oC)	45-55	45-55	Scale-independent variable
Product bed temperature (^oC)	35-45	35-45	Scale-independent variable
Spray rate (mL/min)	90-120	90-120/ per spray gun	Spray rate for each spray gun remains unchanged
Atomizing air pressure (bar)	2.0	2.0	Atomizing air pressure in each partition remains unchanged
CR Layering			
Process Parameters			**Rationale**
Fluidizing air volume (m^3/hr)[3]	540-660	1620-1980	Linear scale-up based upon total distribution-plate area ratio[2]
Inlet air temperature (^oC)	55-62	55-62	Scale-independent variable
Product bed temperature (^oC)	37-43	37-43	Scale-independent variable
Spray rate (mL/min)	150-180	150-180/per spray gun	Spray rate for each spray gun remains unchanged
Atomizing air pressure (bar)	2.5	2.5	Atomizing air pressure in each partition remains unchanged

[1] Batch loads are in accordance with recommendations from the equipment manufacturer as well as prior experience.
[2] Maintains the same air velocity during scale-up.
[3] Distributor place configuration will be visually adjusted to achieve the same fluidization levels inside/outside the coating partition.

As the encapsulation process is an inherently scale-independent process, the scale-up plan to the commercial production size will utilize the same process parameters that were used during production of the exhibit ANDA batch.

What evidence supports the plan to scale up the process to commercial scale?

Please refer to the process development information provided in the section 2.3.P.2.3 of the quality overall summary. In summary, there is a reasonable scale-up plan for the following reasons:

- The process steps that are subject to potential scale-up issues have been identified. This is the unit operation (Wurster coating) used for both drug layering and CR coating. The critical process parameters for the unit operation have been identified and acceptable ranges for these parameters have been determined.
- In conjunction with previous scale-up experience in other products, this process knowledge was used to successfully scale-up from the laboratory scale to the pilot scale for production of the pivotal ANDA batch.
- The scale-up plan from the 18" Wurster (pivotal batch) to the 32" Wurster (commercial production) is straightforward. Scaling of these process parameters are based on using three multiplets of the 18" Wurster concept.

- The encapsulation process is an inherently scale-independent process. Therefore, the scale-up plan for this unit operation during commercial production will utilize the same process parameters that were used during production of the ANDA exhibit batch.

2.3.P.4 Control of Excipients

What are the specifications for the inactive ingredients and are they suitable for their intended function?

***Compendial Excipients*:**
The following compendial excipients listed below do not exert critical functional roles in controlling the rate of MK release. Controls on these excipients will be based upon specifications defined by the USP/NF.

Ingredient	Manufacturer	Complies with USP/NF Tests
Sugar Spheres NF, 25/30 mesh*	Sugar Inc.	Yes
Triethyl Citrate NF	Plasticizer Inc.	Yes
Butylated Hydroxyanisole NF	Antioxidant Inc.	Yes
Purified Water USP	In-House	Yes

* The particle size of sugar spheres will comply with the labeled nominal size range of 25/30 mesh. This will ensure the sugar spheres have a uniform surface area for the manufacture of CR pellets which is critical for ensuring a uniform and reproducible MK drug release profile (see section 2.3.P.2.2).

The compendial excipient, ethylcellulose, exerts a critical functional role in controlling the rate of MK release. Furthermore, during product development, studies evaluating varying grades of ethylcellulose indicated that viscosity significantly impacted the rate of MK release through the CR membrane (see section 2.3.P.2.2). Therefore, to ensure a consistent MK release profile, as well as a consistent spray coating process, more stringent specifications than those defined by the USP/NF will be imposed, including controls on viscosity and degree of substitution.

Ingredient	Manufacturer	Complies with USP/NF Tests
Ethylcellulose NF (20 mPa.s)	Control Release Inc.	Yes
Specifications Beyond Pharmacopeial Standards		
Test	Limits	Result
Ethoxy Content (N-Type)	48.0.0-49.5%	48.8%
Viscosity	18.0 – 22.0 mPa.s	20.1 mPa.s

Non-Compendial Excipients

Ingredient	Manufacturer	
Hard Gelatin Capsule Shell	Capsule Maker Ltd.	
Specifications		
Test	Limit	Result
Description and Dimensions	Compares with previously accepted lots as to size, dimensions, imprint, and color hue	Complies

For the composition of the hard gelatin capsule refer to section 2.3.P.1. Capsule Maker Ltd. certifies full compliance with the requirements of the Guidance for Industry: *The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy*

(BSE) in FDA-Regulated Products for Human Use. For chemistry, manufacturing and controls used in the production of the capsule shell refer to Type IV DMF bbbb. For the composition of Clear Coating 732 refer to section 2.3.P.1. For chemistry, manufacturing and controls used in the production of the Clear Coating 732 refer to Type IV DMF bbbb. For copies of certificates of analysis of excipient lots used in the production of the exhibit batch, refer to Modules 3.2.P.4.2 and 3.2.P.4.4.

2.3.P.5 Control of Drug Product

What is the drug product specification? Does it include all the critical drug product attributes?

Tests	Acceptance Criteria	Analytical Procedure	Results lot #P034
Description	No. 1 blue green opaque cap/yellow opaque body hard shell gelatin capsule filled. The capsule is axially printed with "MK" over "32' in white ink on both the cap and body.	Visual	Complies
Appearance	No observation of discoloration, softening, stickiness brittleness, or cracking	Visual	Complies
Identification	1. HPLC: The retention time of the major peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	In-House HPLC Test Method #125b	Complies
	2. UV: Spectrum corresponds to that of corresponding preparation of the reference standard	In-House HPLC (PDA Detector) Test Method #125b	Complies
Drug Release	Time % Dissolved 0.5 hr: Between 25-35% 4 hr: Between 40-60% 8 hr Between 65-85% 12 hr: NLT 85%	Medium: 900 mL, 0.05 M Phosphate Buffer (pH 6.8) at 37 °C. Apparatus: 1 (basket) at 100 rpm	0.5 hr: 27-31% 4 hr: 48-53% 8 hr: 73-78% 12 hr: 90-94%
Uniformity of Dosage Units	USP <905>	In-House HPLC Test Method #125c	99.1-101.3% RSD=0.8%
Assay	95.0-105.0%	In-House HPLC Test Method #125b	101.2%
Degradation Products	Impurity A: NMT 1.5% Impurity E: NMT 1.0% Any Unknown Impurity: NMT 0.2% Total Impurities: NMT 2.5%	In-House HPLC Test Method #231b	0.8% 0.4% 0.07% 1.5%
Moisture	NMT 3.5%	Karl Fischer Titration (USP <921> Method 1a)	2.9%

The specification sheet includes controls for universal attributes which are generally recognized as important to the quality of modified release solid oral dosage forms, including appearance, identity, assay, content uniformity, impurities, and drug release.

For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated? What is the justification for the acceptance criterion?

Appearance

Each batch is visually examined for unique capsule markings, color, and shape. This visual test also examines the integrity of the dosage form to ensure no discoloration, softening, stickiness,

brittleness, or cracking of the capsule shell.

Identification

Controls to ensure that MK is present in the drug product are established by virtue of compliance to cGMPs. However, additional testing to confirm the identity of MK in the drug product are ensured via a

- HPLC chromatographic test in which the retention time of the major peak in of the assay preparation must be shown to correspond to that of the standard preparation as obtained in the assay.
- Spectroscopic test in which the UV spectrum of the major peak (PDA detector) must correspond to the UV spectrum of the standard preparation.

For full details regarding test procedures, copies of chromatograms and UV spectra for lot #P034 and the reference standard, refer to Modules 3.2.P.5.2 and 3.2.P.5.4.

Assay

The proposed drug product assay acceptance criteria of 95.0-105.0% are tighter than the 90.0-110.0% limits that are generally applied to pharmacopeial items. The basis for having these tighter limits is to provide some latitude for degradation, particularly hydrolysis to Impurity A (active metabolite) on storage, in order to ensure that the drug product will comply with the 90.0-110.0% stability limits for assay.

Assay is determined via the chromatographic conditions summarized below. For full details regarding test procedure, and chromatograms of test sample lot #P034 and reference standard, refer to Modules 3.2.P.5.2 and 3.2.P.5.4. The HPLC (assay) test method will also be utilized for the determination of drug product content uniformity and drug release in MK CR Capsules[4].

Mobile Phase	Acetonitrile: Buffer = 30 : 70 Buffer: Dissolve 6.8 g of KH_2PO_4 in 1000 mL of water and adjust pH to 7.4 ± 0.05 with triethylamine
Column	Symtrex C_8, 5 µm, 150 mm × 4.6 mm
Flow Rate	1.5 mL/minute
Temperature	40°C
Detector	UV at 272 nm
Injection Volume	20 µL
Run Time	15 minutes
Retention Time	About 8 minutes
Sample Preparation	Standard and sample solutions contain 0.1 mg/mL of MK
System Suitability	The column efficiency as determined from the MK peak is NLT 5000 theoretical plates. Tailing factor of the same peak is NMT 2.0. RSD of five replicated injections of the standard solution is NMT 1.0%.

The HPLC (assay) test method has been validated for accuracy, precision, specificity, and linearity per ICH Q2A and Q2B recommendations. To further demonstrate specificity and the stability-indicating nature of the HPLC (assay) test method, the drug product was subjected to various stress conditions and analyzed by HPLC equipped with a PDA detector for analysis if peak purity. In all instances degradation peaks were well resolved from MK and the calculated peak purity was >0.99, indicative of MK peak homogeneity. Method validation and stress test studies are summarized below. For full details refer to Module 3.2.P.5.3

[4] With the exception of minor differences related to sample preparation procedures.

Specificity	No interference from placebo, known impurities, peak purity (PDA) > 0.99
Linearity	10-150%, $r^2 = 0.99$
Precision	RSD 0.18%
Intermediate Precision*	RSD 0.5%
Accuracy	98-101%; percentage of recovery of MK at 50%, 100%, 150% of label claim

* Two analysts on different instruments

Stress Conditions	Drug product	MK Peak Purity
Untreated	99%	>0.99
0.1N HCl/70°C/14 h	85%	>0.99
0.1N NaOH/70°C/30 min	30%	>0.99
3% H_2O_2/60°C/2 h	20%	>0.99
Humidity (90% RH)/25°C/7 days	95%	>0.99
UV light (short and long wavelength) 7 days	98%	>0.99
Dry heat /105 ^{o}C/14 h	70%	>0.99

Content Uniformity

Acceptable content uniformity of the drug product is ensured by 1) virtue of the optimized process which results in the uniform coating the MK drug substance onto the sugar spheres and 2) a capsule fill machine which performs a 100% weight check as an in-line monitor. However, additional testing based upon testing of individual capsules using the drug product assay test method and acceptance criteria in USP <905>, will be performed to confirm acceptable MK content uniformity in the finished dosage form. For details regarding analytical testing procedures and results for content uniformity testing for lot #P034, refer to Modules 3.2.P.5.2 and 3.2.P.5.4.

Impurities (Degradants)

See table below for known MK degradation products which will be monitored in the drug product. Impurities B, C, D, and F (refer to Module 2.3.S.4) will not be monitored in the drug product as these process impurities are not degradation products and are controlled in the drug substance.

Name	Structure	Origin
Impurity A	Structure of Impurity A	Degradation impurity due to hydrolysis of the ester moiety Active metabolite of MK
Impurity E	Structure of Impurity E	Degradation impurity due to oxidation

Applicable data and rationale supporting the justification for the proposed levels of degradation impurities in the finished drug product are provided in the table below. The proposed limits for these degradation impurities are based upon recommendations in ICH Q3B and the draft ANDA Drug Product Impurity Guidances. The observed levels in the drug product exhibit batch (lot #P034) fall well within proposed limits. For additional information refer to Module 3.2.P.5.6.

Name	lot #P034	Mock® (MK) Controlled Release Capsules (RLD) (lot #22242, Expiration date 10/05)	Proposed Limits	Justification
Impurity A	0.80%	1.5%	NMT 1.5%	Metabolite
Impurity E	0.40%	1.0%	NMT 1.0%	Equivalent to the level present in RLD
Any Unknown Impurity	≤ 0.07%	≤0.05%	NMT 0.20%	ICH Q3B identification threshold[2]
Total Impurities[1]	1.5%	3.7%	NMT 2.5%	Below the levels present in RLD

[1] Process-related impurities B, C, D, and F are excluded from the calculation of impurities in the drug product.
[2] The maximum daily dose of MK is 64 mg/day. Therefore the corresponding recommended identification threshold is 0.20%.

Impurities (degradants) are determined via the HPLC chromatographic test conditions summarized below. For full details regarding HPLC (related substances) test procedure, and chromatograms of test sample lot #P034 and the reference standards (including impurity standards) refer to Modules 3.2.P.5.2 and 3.2.P.5.4.

Mobile Phase	Phase A: Dissolve 3.2 g of K_2HPO_4 and 0.85 g KH_2PO_4 in 1000 mL of water Phase B: Acetonitrile
Column	Symtrex C_{18}, 5 µm, 250 mm × 4.6 mm
Flow Rate	1.5 mL/minute
Gradient Profile	Time (minute) 0.0 30.0 37.0 Phase A (%) 80 20 20 Phase B (%) 20 80 80
Temperature	40 °C
Detector	UV at 272 nm
Injection Volume	10 µL
Run Time	37 minutes
Relative Retention Time	Impurity E: 0.49 Impurity A: 0.70 Impurity B: 0.89* MK: 1.00 Impurity C: 1.44* Impurity D: 1.66* Impurity F: 2.55*
Sample Preparation	Standard contains 0.01 mg/mL of MK and 0.01 mg Impurity B. Sample solution contains about 2 mg/mL of MK
System Suitability	The column efficiency as determined from the MK peak is NLT 5000 theoretical plates. Tailing factor of the same peak is NMT 2.0. Resolution between MK and Impurity B is NLT 2.0 RSD of five replicated injections of the standard solution is NMT 10%.

* Process-related impurities B, C, D, and F are excluded from the calculation of impurities in the drug product

The HPLC (related substances) test method has been validated for accuracy, precision, linearity, specificity, and limits of quantitation/detection per ICH Q2A and Q2B recommendations. The drug product was also subjected to various stress conditions and analyzed by HPLC equipped with a PDA detector for analysis of peak purity. Degradation peaks were well resolved from MK, and the calculated peak purity for the MK peak was >0.99. Impurity A was the primary degradation impurity generated during heating and exposure to basic and acidic conditions, whereas Impurity E was the primary degradation impurity formed under oxidative conditions. As anticipated, the observed levels of impurities B, C, D, and F remained unchanged during stress testing, confirming that these drug substance process-related impurities are not degradants. Method validation and stress test studies are summarized below. For full details refer to Module 3.2.P.5.3.

	Impurities					
	A	**B[1]**	**C[1]**	**D[1]**	**E**	**F[1]**
Specificity	No interference from placebo and known impurities (refer to chromatogram below) MK Peak purity (PDA) > 0.99					
Linearity	0.05-2.5%, $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$	0.05-1.0%, $r^2 = 0.99$	0.05-1.0% $r^2 = 0.99$
Precision	RSD 6.7%	RSD 4.5%	RSD 6.8%	RSD 5.2%	RSD 3.2%	RSD 4.5%
Intermediate Precision[2]	RSD 8.2%	RSD 9.2%	RSD 10.4%	RSD 9.6%	RSD 8.2%	RSD 9.8
Accuracy[3]	95-104%	80-97%;	88-105%	92-112%	80-101%	82-115%
LOQ	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
LOD	0.02%	0.02%	0.02%	0.02%	0.02%	0.02%

[1] Although process related impurities B, C, D, and F are excluded from the calculation of impurities in the drug product, these were included in these studies to support method validation for the drug substance HPLC (related substances) test method (refer to Module 2.3.S.4).
[2] Two analysts on different instruments.
[3] Percentage recovery for impurities spiked at their upper drug substance/drug product specification limits.

Stress Conditions	Drug product	MK Peak Purity	Observed Degradants
Untreated	99%	>0.99	N/A
0.1N HCl/70°C/14 h	85%	>0.99	Impurity A (12%)
0.1N NaOH/70°C/30 min	30%	>0.99	Impurity A (65%)
3% H_2O_2/60°C/2 h	20%	>0.99	Impurity E (50%) Unknown Impurities (15%)
Humidity (90% RH)/25°C/7 days	95%	>0.99	Impurity A (3%)
UV light (short and long wavelength) 7 days	98%	>0.99	N/A
Dry heat /105 °C/14 h	70%	>0.99	Impurity A (23%)

Dissolution (Drug Release)

The proposed dissolution test method and the rationale for selection are summarized below:

		Rationale
Apparatus	Basket	Typical for capsule dosage forms
Medium	Phosphate buffer (pH 6.8)	Dissolution testing was performed in simulated gastric fluid (pH 1.2), acetate buffer (pH 4.5), and phosphate buffers (pH 6.8) with no significant difference observed as ascertained by the f_2 metric (>50). Therefore, the rationale for selecting a pH 6.8 medium was that it would best mimic the physiological conditions in the intestinal compartment, where the majority of drug release and absorption occur.
Volume	900 mL	Commonly used volume of dissolution medium*
Speed	100 rpm	Typical agitation speed *
Temperature	37°C	Typical dissolution testing temperature *

* See Guidance for Industry: *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*

Acceptance criteria are proposed using four dissolution time points, and based upon observed dissolution data from lot #P034 used in the pivotal bioequivalence studies. Proposed ranges for acceptance criteria allow for ±10% deviation from the mean dissolution profile as recommended in the Guidance for Industry: *Extended Release Solid Oral Dosage Forms: Development, Evaluation, and Application of In-Vitro/In Vivo Correlations.* It should be noted that these ±10% range limits are further justified based upon the fact that the acceptance limits at the 4 hr and 8 hr time points are tighter than the observed dissolution mean data from two development batches having 6% CR and 16% CR coating and PK profiles with AUC and C_{max} point estimate ratios (relative to the RLD) within the upper and lower bioequivalence limits (refer to Module 3.2.P.2.2).

Time point	Observed Values lot #P034	Acceptance Criteria	Rationale
0.5 hr	Average = 29%, Values vary between 27-31%	25-35%	Lower limit: Ensures a 25% immediate drug release pulse necessary for acceptable product performance Upper limit: Detects possible dose dumping
4 hr	Average = 51% Values vary between 48-53%	40-60%	Dissolution data from the batch (lot #P034) used in the pivotal bioequivalence studies with ranges for acceptance criteria allowing for approximately ±10% deviation from the mean dissolution profile.*
8 hr	Average = 75% Values vary between 73-78%	65-85%	Dissolution data from the batch (lot #P034) used in the pivotal bioequivalence studies with ranges for acceptance criteria allowing for approximately ±10% deviation from the mean dissolution profile.*
12 hr	Average = 92% Values vary between 90-94%	NLT 85%	Ensures complete release of MK

*Proposed limits are tighter than the observed dissolution mean data from two development batches having 6% and 16% CR coating and PK profiles with AUC and C_{max} point estimate ratios (relative to the RLD) within the upper and lower bioequivalence limits (refer to Module 3.2.P.2.2).

Moisture

Due to the potential for degradative hydrolysis of MK, controls have been incorporated for moisture content in the drug product. A limit of NMT 3.5% for moisture content is proposed based upon the cumulative upper moisture specification for each component in the formulation (2.8%), and observed values in the drug product at both release (2.9%) and on stability (3.0%). Testing for moisture is based upon Karl Fischer Titration (USP <921> Method 1a). For full details regarding test procedures and justification for moisture content refer to Modules 3.2.P.5.2, 3.2.P.5.4, and 3.2.P.5.6.

2.3.P.6 Reference Standards and Materials

How were the primary reference standards certified?

There are no additional reference standards used for testing of the MK ER Capsules drug that were not previously cited for testing of the MK drug substance (Module 2.3.S.5).

2.3.P.7 Container Closure System

What container/closure system(s) is proposed for packaging and storage of the drug product? Has the container/closure system been qualified as safe for use with this dosage form?

The drug product will be packaged and shipped in 30-unit (60 cc HDPE Bottle, 33 mm CRC), 100-unit (100 cc HDPE Bottle, 38 mm CRC), and 500 unit (300 cc HDPE Bottle, 53 mm CRC) packaging configurations. The proposed container/closure systems comply with USP <661> and USP <671> requirements, and all components used in these container/closure systems have been used in approved CDER products. For full details refer to Module 3.2.P.2.4.

2.3.P.8 Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

Tests	Acceptance Criteria	Analytical Procedure
Description	No. 1 blue green opaque cap/yellow opaque body hard shell gelatin capsule filled. The capsule is axially printed with "MK" over "32' in white ink on both the cap and body.	Visual
Appearance	No observation of discoloration, softening, stickiness brittleness, or cracking	Visual
Dissolution	Time % Dissolved 0.5 hr: Between 25-35% 4 hr: Between 40-60% 8 hr Between 65-85% 12 hr: NLT 85%	Medium: 900 mL, 0.05 M Phosphate Buffer (pH 6.8) at 37 ^{o}C. Apparatus: 1 (basket) at 100 rpm
Assay	90.0-110.0%	In-House HPLC Test Method #125b
Degradation Products	Impurity A: NMT 2.5% Impurity E: NMT 1.0% Any Unknown Impurity: NMT 0.2% Total Impurities: NMT 3.5%	In-House HPLC Test Method #231b
Moisture	NMT 3.5%	Karl Fischer Titration (USP <921> Method 1a)

All attributes used to confirm the quality of the finished drug product at batch release are evaluated during stability testing, with the exception of identity and content uniformity as these are not expected to change over time. The acceptance limits for these attributes remain the same as those used to confirm the quality of the finished drug product at batch release (refer to Module 2.3.P.5) with the exception of the acceptance criteria for assay and degradants. The rationale for relaxing these acceptance criteria are discussed below:

	Drug Product Release Limits	Drug Product Stability Limits	Rationale for Relaxing Acceptance Criteria
Assay	95.0-105.0%	90.0-110.0%	The widening of the assay limits should be considered acceptable as these limits are generally applied to pharmacopeial items. It should be noted that the basis for having tighter limits for assay on drug product release is to provide some latitude for degradation, particularly hydrolysis to Impurity A, in order to ensure that the drug product will comply with the 90.0-110.0% assay limits on stability.
Impurity A	NMT 1.5%	NMT 2.5%	The rationale for relaxing this acceptance limit derives from the observed increase in the level of this impurity during accelerated and room temperature stability testing to levels $\leq$ 2.0%. Despite the fact that the proposed limit of NMT 2.5% exceeds the level observed in the referenced product (1.5%), this should be considered acceptable as such levels are qualified based upon the fact that Impurity A is the active as well as predominant MK metabolite found in human plasma.
Total Impurities	NMT 2.5%	NMT 3.5%	The limit for total impurities has been relaxed by 1.0% to reflect the relaxed stability limit (by 1.0%) for Impurity A.

What drug product stability studies support the proposed shelf life and storage conditions?

Accelerated stability data (40°C/75% RH) and room temperature stability data (25°C/60% RH) have been provided for the drug product in the proposed 30-unit and 500-unit container/closures, and these studies bracket the proposed 100-unit container/closure. The stability data is summarized in the table below. For full details refer to Modules 3.2.P.8.1 and 3.2.P.8.3.

	Accelerated (40°C/75% RH) 0, 4, 8, 12 weeks	**Room Temperature (25°C/60% RH) 0, 3, 6, 9, 12 months**
Assay (90-110%)	No Trend All values vary between 95.9-102.0%	No Trend All values vary between 97.7-102.0%
Related Substances (Degradants)		
Impurity A (NMT 2.5%)	Upward Trend (≤ 1.2%) All values are ≤ 2.0%	Upward Trend (≤ 0.5) All values are ≤ 1.3%
Impurity E (NMT 1.0%)	No Trend All values are ≤ 0.4%	No Trend All values are ≤ 0.25%.
Any Unknown Impurity (NMT 0.2%)	No Trend All values are ≤ 0.09%	No Trend All values are < 0.08%
Total Impurities (NMT 3.5%)	Upward Trend (≤ 1.4%) All values are ≤ 2.8%	Upward Trend (≤ 0.5%) All values are ≤ 2.0%
Dissolution	All Comply L1 stage dissolution testing only	All Comply L1 stage dissolution testing only
Moisture (NMT 3.5%)	No Trend Values vary between 2.6-3.0%	No Trend Values vary between 2.6-2.9%
Description and Physical Appearance	All Comply	All Comply

In summary, the three months of accelerated stability data indicate that all monitored attributes fall well within the proposed stability specifications. Furthermore, a comparison between the accelerated (3 months) and room temperature (12 months) stability data suggests that observable trends such as the increase in the level of impurity A are in fact, overestimated by the accelerated stability studies. Therefore, based upon the totality of stability data, a tentative two year expiry period for the drug product stored under the recommended room temperature storage conditions is proposed. The tentative two year expiry period will also be confirmed by updated real-time room temperature stability data.

In addition, consistent with the known potential for MK degradative hydrolysis, the recommended labeling storage condition indicates: *"Protect from moisture"*.

What is the post-approval stability protocol?

The post-approval stability protocol/commitment requires that the first three commercial production batches (packaged in the smallest and largest configurations) be placed on stability (25°C/60% RH) and tested at intervals of 0, 3, 6, 9, 12, 18, 24 months and 36 months (if applicable) until the desired expiration date is reached. Yearly thereafter, a minimum of one production batch (packaged in the smallest and largest configuration of each container/closure) will be placed on the long-term stability program. Expiration dates may be extended based upon acceptable room temperature stability data from a minimum of three production batches. If during the post-approval stability studies, any lots are found to fall outside the approved specifications these may be withdrawn from the market. Deviations which do not affect the

safety and efficacy of the product will be promptly discussed between the applicant and the reviewing division and must be reported to the FDA under 21 CFR 314.81 (b)(1)(ii). For additional details regarding the post-approval stability protocol refer to Module 3.2.8.2.