EXAMPLE QUALITY OVERALL SUMMARY[1]

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product:

Non-Proprietary Name of Drug Product: Ersatzine Tablets, USP

Non-Proprietary Name of Drug Substance: Ersatzine

Company Name: ANDA Sponsor

Dosage Form: Immediate Release Tablets

Strength(s): 2 mg

Route of Administration: Oral

Proposed Indication(s): Depression

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

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

Chemical Name:	[full chemical name]
CAS #:	[CAS#]
USAN:	Ersatzine
Molecular Structure:	[chemical structure]
Molecular Formula:	$C_xH_yO_zN$
Molecular Weight:	300

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

Physical Description: Ersatzine is a white, crystalline powder, practically insoluble in water at pH 7.0, freely soluble in methylene chloride, sparingly soluble in acetone and alcohol.

pKa: The pKa of the secondary amine group in Ersatzine is 5.5.

Polymorphism: There are two anhydrous polymorphic forms, Forms I and II, and no known hydrate forms. Form I is the most stable form and is used for the manufacture of the drug product. Form I and II can be produced by crystallization from ethanol at different cooling rates.

Solubility Characteristics: The aqueous solubility as a function of pH at 37º C is:

[1] This Quality Overall Summary does not contain real data and information and is meant only to demonstrate examples of information/data/tests that may be used for scientific & regulatory justification of a drug product.

Solvent Media	Solubility Form I	Solubility Form II
0.1 N HCl, pH 1.2	0.10 mg/ml	0.40 mg/mL
0.15 M acetate buffer, pH 3.0	0.09 mg/ml	0.40 mg/mL
0.15 M acetate buffer, pH 4.5	0.011 mg/mL	0.033 mg/mL
0.15 M phosphate buffer, pH 6.8	(< 0.001 mg/ml)	(< 0.001 mg/ml)

Calculated dose solubility volume: 2 mg (highest strength)/(0.001 mg/mL) = 2000 mL > 250 mL. Therefore, Ersatzine is considered a low solubility according to the Biopharmaceutics Classification System (BCS).

Hygroscopicity: Water uptake for the drug substance was less than 0.1% by weight after one week at 25ºC/75±5% RH. (Details in 3.2.P.2.1.1)

Melting Point: The melting point of Form I and Form II are 225 ºC and 210 ºC, respectively.

Partition Coefficient: ClogP = 4.251.

2.3.S.2 Manufacture

Who manufactures the drug substance?

Drug Substance Maker Ltd (DMF nnnn)
111 Main Street
City 1, County 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 Ersatzine. DMF holder for Ersatzine has proposed validated methods that are suitable for stability-indicating purposes, and has documented stability data for the drug substance.

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized?

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

How were potential 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?

A summary of drug substance tests, analytical procedures, acceptance limits and results for the drug substance batch (Lot #15531) (COAs located in 3.2.S.4.4) used for the manufacturing of the submission batch (Lot #9A) is given in the table below.

Tests	Acceptance criteria	Analytical procedure	Test results for Lot#15531
Appearance	A white, crystalline powder.	Visual	Complies
Identification A: IR B: UV	 A. IR: Corresponds to RS B. UV: Absorptivities at xxx nm, do not differ by more than 3.0% from the reference standard.	 USP<197M> USP<197U>	 Complies Complies
Heavy metals	NMT 20 ppm	USP<231>	LT 20 pm
Assay	98.0-102.0%	USP method	99.5%
Residual solvents	Methanol: NMT 3000 ppm Methylene Chloride: NMT 600 ppm Toluene NMT 890 ppm	USP <467>	 300 ppm 150 ppm 80 ppm
Related Substances	Specified Impurities* RC 1: NMT 0.15% RC 2: NMT 0.25% RC 3: NMT 0.25 % Any unspecified impurity: NMT 0.10% (each) Total impurities: NMT 0.75%	method #41	 LT 0.05% LT 0.05% 0.10% LT 0.05% 0.30 %
Polymorphic Form (XRD)	Ratio of peak at 2θ= xx to peak at 2θ=yy: LT 5%	method #47	LT 1%
Particle size (Laser Diffraction)	D90: NMT 30 µm D50: NMT 15 µm D10: NMT 5 µm	method #48	20 µm 10 µm 2.5 µm

*RC 1: [impurity identity]
RC 2: [impurity identity]
RC 3: [impurity identity]

There is an official monograph in USP for Ersatzine drug substance and tests from the USP monograph are shaded. Limits for these tests are those found in the monograph. Related compounds are specified in the USP monograph, but the USP analytical procedure was not acceptable because it was not able to resolve impurity RC1 and was replaced.

The specification includes all the critical drug substance attributes that affect the manufacturing and quality of the drug product. In addition to the tests found in the USP monograph, we include specifications for polymorphic form and particle size. In our drug product manufacturing process, the aqueous granulating fluid contains suspended drug. The particle size and the polymorphic form of the drug substance therefore affect these attributes in the drug product. Our development studies indicated that the drug substance particle size and polymorphic form are critical to product performance (see 2.3.P.2.2).

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

The drug substance is visually inspected to verify that it is a white, crystalline powder.

Identity

The identification tests, a specific IR test and a UV test, are per the USP monograph for Ersatzine.

Assay

In accordance with the USP monograph, the assay limit is set at 98.0% to 102.0%. Assay is determined by the USP method. Test procedures along with chromatograms of test samples and the reference standard are located in 3.2.S.4.2 and 3.2.S.4.4.

Impurities (Related Substances)

Related compounds potentially present in the drug substance are:

Name	Structure	Origin
RC1	Structure of Impurity RC1	Process impurity
RC2	Structure of Impurity RC2	Process impurity/ degradation product (exposure to light)
RC3	Structure of Impurity RC3	Process impurity/ degradation product (exposure to light)

The limits for RC2, RC3, any unidentified impurity, and total impurities are found in the USP monograph. RC1 was identified by the DMF holder as a process impurity and is not specified in the USP monograph; its limit is justified as the ICH Q3A qualification threshold. Justification for impurities limits are summarized in the table below. Batch analysis of the drug substance (Lot #15531) indicated that impurities levels fall well within the proposed limits.

Name	Ersatzine (Lot #15531)	USP Limit for Drug Substance	ANDA Drug Product (Lot #9A)	Proposed Acceptance criteria	Justification
RC1	LT 0.05%	Not applicable	LT 0.05%	NMT 0.15%	ICH Q3A qualification threshold
RC2	LT 0.05%	0.25%	0.2%	NMT 0.25%	USP Limit
RC3	0.10%	0.25%	0.2%	NMT 0.25%	USP Limit
Any Unspecified Impurity (each)	≤ 0.05%	0.1%	≤0.05%	NMT 0.10%	ICH Q3A identification threshold
Total Impurities	0.30%	0.75%	0.65%	NMT 0.75%	Within USP Limit

There is a USP method for related compounds in the drug substance monograph. The USP method was not acceptable because it could not resolve process impurity RC1 from RC2. For this reason, we developed an in-house HPLC method (#41), which uses a reverse phase column (C18 column), an isocratic mobile phase, and UV detection (220 nm) for quantitation of related compounds. The HPLC test method meets the USP system suitability requirements and is comparable to the USP method for identification of impurities.

Name	USP Method	In house HPLC #41
RC 1	N/A	LT 0.05%
RC 2	0.08%	LT 0.05%
RC 3	0.10%	0.10%
Largest Unspecified Impurity	LT 0.05%	LT 0.05%
Total Impurity	0.30%	0.30%

The HPLC test method (#41) is accurate, precise, linear, sensitive, and suitable for use.

Name	Acceptance criteria	Linearity	Precision	Accuracy	LOD	LOQ
RC 1	NMT 0.15%	r^2 = 0.997 RSD = 2.1%	Mean 0.15% RSD 7.12%	90-112% RSD = 2.5%	0.025%	0.075%
RC 2	NMT 0.25%	r^2 = 0.996 RSD = 1.5%	Mean 0.13% RSD 6.45%	92-110% RSD = 2.8%	0.025%	0.075%
RC 3	NMT 0.25%	r^2 = 0.996 RSD = 1.5%	Mean 0.14% RSD 5.7%	91-110% RSD = 2.9%	0.035%	0.1%

The specificity of the method is demonstrated by stress testing described in section 3.2.S.4.3 which showed no interference between the impurity peaks. For details regarding the HPLC test procedure, chromatograms of test samples, and reference standards (including impurity standards) refer to 3.2.S.4.2 and 3.2.S.4.4.

Impurities (Residual Solvents)

The solvents used in the manufacturing process are methanol, methylene chloride, and toluene. Methanol, methylene chloride, and toluene are class 2 solvents that are controlled at the levels found in the USP, which are the same as the ICH Q3C recommendations. The test is conducted using USP <467> Procedure A (GC method). For test procedures, chromatograms of test samples Lot# 15531, and reference standard, refer to modules 3.2.S.4.2 and 3.2.S.4.3.

Impurities (Inorganic)

The drug substance supplier certifies that no transition metal catalysts are used in the manufacture of Ersatzine**,** therefore only heavy metals are included as part of routine release testing using USP Method Heavy Metals Test, with a limit of NMT 20 ppm in accordance with USP.

Polymorphic Form

To evaluate the relative amounts of Form I and Form II in the drug substance we use the relative ratio of the main peaks in the X-ray diffraction pattern of the two known forms. We prepared physical blends with known compositions of pure form I and form II to validate the method. The LOQ is 2% and the LOD is 1%. Details are found in 3.2.S.4.2 and 3.2.S.4.3. The acceptance limit of NMT 5% of Form II is justified because the presence of Form II will not affect bioavailability (see 2.3.P.2.2).

Particle Size

Particle size is determined by laser diffraction (Malvern Mastersizer). The limits were set based on product development studies that evaluated the dissolution of drug product produced with different particle sizes of the drug substance (see 2.3.P.2.2). Drug product manufactured using drug substance with D90 less than 30 μm provided an acceptable dissolution profile. Method validation is found in 3.2.S.4.2 and 3.2.S.4.3.

2.3.S.5 Reference Standards

How were the primary reference standards certified?

The reference standard used to test drug substance batch (15531) which was used to manufacture the exhibit batch (#9A) was a working standard (WS1321) that was qualified against the compendial reference standard: USP Standard Lot# H. The qualification report and COA are in 3.1.S.5.

2.3.S.6 Container Closure System

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

Ersatzine drug substance is packaged in a clear polyethylene bag placed inside a black light protective polyethylene bag and they are placed in fiberboard drum that is sealed. 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.

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 of each excipient?

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

Ingredient	Function	Weight/tablet	% (w/w)
Ersatzine, USP	Active	2.00 mg	0.83
Lactose Monohydrate, NF	Filler	160.00 mg	66.67
Microcrystalline Cellulose, NF	Filler	61.61 mg	25.67
Povidone, NF	Binder	7.20 mg	3.00
Crospovidone, NF	Disintegrant	7.20 mg	3.00
Magnesium Stearate, NF	Lubricant	1.20 mg	0.50
FD&C Blue #2	Colorant	0.80 mg	0.33
Purified Water	Granulation Solvent*		
Total Weight		240.0 mg	

* Removed during the manufacturing process

Does any excipient exceed the IIG limit for this route of administration?

All excipients fall below the IIG limits for this route of administration.

Ingredient	Amount per unit of Ersatzine Tablet, 2 mg	IIG levels
Lactose Monohydrate, NF	160.00 mg	889.42 mg
Microcrystalline Cellulose, NF	61.61 mg	1385.3 mg
Povidone, NF	7.20 mg	49.55 mg
Crospovidone, NF	7.20 mg	300 mg
Magnesium Stearate, NF	1.20 mg	400.7 mg
FD&C Blue #2	0.80 mg	21 mg

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

No, both the proposed formulation and the RLD contain standard excipients consistent with the design of an IR solid oral dosage form. Our developmental studies also reveal that these

differences are not important with respect to therapeutic equivalence or stability of our product. Our excipients-active compatibility studies did not reveal any incompatibilities.

According to the package insert, the RLD contains the following ingredients. Also listed in the table are their functions that are inferred by us.

Reference Listed Drug	Proposed Generic Drug Product	Function
Cellulose	Microcrystalline Cellulose	Filler
	Povidone	Binder
Corn Starch	Crospovidone	Disintegrant
Lactose Monohydrate	Lactose Monohydrate	Filler
Magnesium Stearate	Magnesium Stearate	Lubricant
FD&C Blue #2	FD&C Blue #2	Coloring Agent

2.3.P.2 Pharmaceutical Development

Our pharmaceutical development process for this product involved the following sequential steps (a detailed summary of each step is found in the responses to the questions)

- An analysis of the reference product identified a target product profile (2.3.P.2.2) that included rapid dissolution and other aspects of product quality and equivalence.
- Preformulation characterization of the drug substance (2.3.P.2.1.1) identified particle size and polymorphic form as mechanistic factors critical to product performance.
- A list of mechanistic factors (2.3.P.2.2) that are needed to reach the target product profile was identified.
- The need for content uniformity of the low dose API and its poor flow properties led us to choose wet granulation as the manufacturing process (2.3.P.2.3)
- Since the amount of active ingredient is less than 1%, we selected an established set of excipients known to provide pharmaceutically acceptable tablets by wet granulation.
- We evaluated the compatibility of these excipients with the active and found no evidence of incompatibility (2.3.P.2.1.2).
- During process development the manufacturing steps and critical process parameters that controlled each of the mechanistic factors were identified (2.3.P.2.3).
- During formulation optimization (2.3.P.2.2), we identified the disintegrant level and uniformity as critical and added it to the list of mechanistic factors. In this step, we propose a design space for the formulation composition.
- Diagram 1 summarizes our understanding of the process (raw materials and manufacturing process steps) which allow us to control the mechanistic factors that determine the desired quality.

2.3.P.2.1 Components of the Drug 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 drug substance attributes that were considered during product development were:

- The drug substance solubility and its pH dependence.
- The multiple polymorphic forms of the drug substance.
- The drug substance stability
- The flow properties of the micronized drug substance.
- The particle size of the drug substance.

Solubility

Solubility data is summarized in 2.3.S.1. According to the Biopharmaceutical Classification System (BCS), Ersatzine is categorized as a poorly soluble drug. The highest solubility is at low pH which motivates a rapidly dissolving formulation such that drug can be released and absorbed before the drug reaches regions of the intestine where a higher pH reduces the solubility and dissolution rate.

Polymorphic Form

The polymorphic forms are discussed in 2.3.S.1. Because stability testing on Form II indicated that it is significantly less stable than Form I, maintaining Form I in the drug product is critical to product quality. We evaluated whether dissolution testing would be able to distinguish polymorphic forms in the drug product and whether polymorphic form changes could affect bioequivalence.

Figure 1 demonstrates that when both polymorphs of the drug substances were micronized to the same particle size (D90 = 30 μm), the less stable form (Form II) has much faster dissolution than the more stable form (Form I) used in the drug product. Dissolution profile comparison using an f2 test would be able to distinguish the two forms in the drug product.

Because we use the more stable form, the solubility of drug substance in the granulation media is low, and the drug substance is not subject to extreme mechanical stress, there is a low risk of polymorphic form transformation during the manufacturing process. During process development we compared dissolution profiles using an f2 test and observed no evidence of formation of Form II under any process conditions studied. Dissolution testing using the f2 test will be used during scale up and to support any subsequent process changes.

Transformation to the faster dissolving Form II would not be expected to alter the bioavailability because the slower dissolving RLD is already bioequivalent to an oral solution (the oral solution can be considered to represent an infinitely rapidly dissolving form). Combined with our process development experience, this allows use to conclude that a single point dissolution specification (as in the USP monograph) is appropriate for release testing.

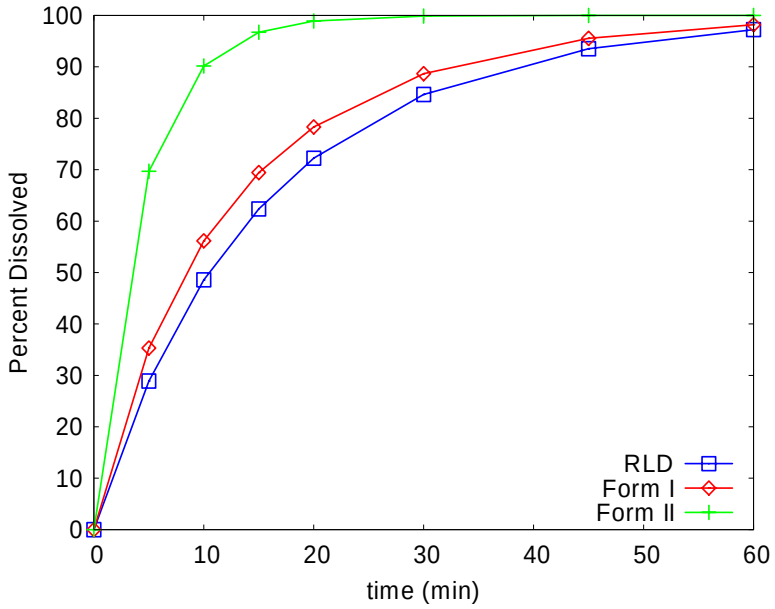


Figure 1: Dissolution profiles in USP apparatus 2 at 50 rpm and pH 4.5 for product produced with different polymorphic forms of the drug substance.

Stability Studies

- Literature Study: There are literature reports of accelerated thermal, hydrolytic, and photochemical degradations of ersatzine performed under several reaction conditions. Studies revealed the photolability of the drug substance as the most adverse stability factor and the main degradation route for ersatzine tablets[2].
- Sponsor Study: We evaluated drug substance in polymorphic forms I and II. Under accelerated stability conditions (40°C/75% RH), Form II degrades much more quickly than Form I, resulting in twice as much impurity RC2 as Form I. (Details in 3.2.P.2.1.1)

Flow Properties

The poor flowability of the drug substance and tendency of the micronized drug substance to form agglomerates and adhere to equipment led us to use a manufacturing process of wet granulation rather than direct compression.

Particle Size

Because the drug substance is low solubility, particle size in the drug product was potentially critical. Figure 2 shows that the dissolution of the drug product is a strong function of the particle size. We therefore concluded that particle size of active ingredient in the drug product would be a significant factor in determining the overall dissolution rate. The particle size in the drug product could potentially be altered by recrystallization or agglomeration during the granulation process.

[2] Literature Reference

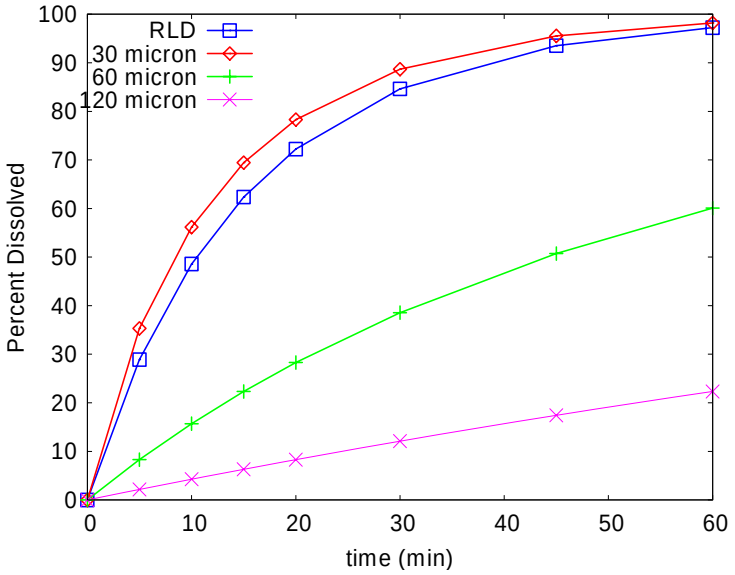


Figure 2: Dissolution profiles in USP apparatus 2 at 50 rpm and pH 4.5 for product produced with different particle size (D90) of the drug substance.

2.3.P.2.1.2 Excipients

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

Lactose monohydrate, magnesium stearate, and microcrystalline cellulose are found in the RLD product so these excipients were presumed compatible with the drug substance. This hypothesis was tested in a set of compatibility screening studies. Closed vials containing 200 mg of drug-excipient blends (1:100 ratio of drug to excipient prepared as physical blend) at 75% RH were incubated in ovens at 50 °C (3 weeks). The three week compatibility studies with various excipients suggested that the major degradation pathways are not connected with excipient interactions.

Excipient/Grade	Ersatzine Assay (%)	Impurity RC2 (%)	Impurity RC3 (%)
No Excipient (Control)	97.0	0.11	0.12
Microcrystalline Cellulose	98.0	0.10	0.13
Povidone	98.0	0.09	0.12
Lactose Monohydrate	96.5	0.15	0.10
Magnesium Stearate	97.2	0.09	0.11
Crospovidone	97.1	0.08	0.10

No degradation of the drug substance in the processing solvent (water) over the time and temperature of use was observed.

2.3.P.2.2 Drug Product

What attributes should the drug product possess?

This IR product is intended to have the following attributes:

- Rapid and complete dissolution
- The correct amount of active ingredient in each tablet
- Stability
- Purity

- Acceptable tablet characteristics

This list serves as the definition of quality for our product. Assay, Stability, Purity, and Content Uniformity are necessary for all drug products. The reasons for selection of the other attributes are:

Acceptable Tablet Characteristics

The tablet look and feel must meet consumer expectations for pharmaceutical tablets.

Rapid Dissolution

- The RLD product is rapidly dissolving. USP monograph states the dissolution of the RLD is conducted in pH 4.5 buffer with immediate release within 30 minutes.
- The RLD is similar in pharmacokinetic performance to an oral solution (information obtained from FOI on the RLD and presented in Figure 4)

Both factors indicate very rapid dissolution as the formulation design goal. Based on the bioequivalence of the RLD product to an oral solution, rapid dissolution should ensure a bioequivalent product.

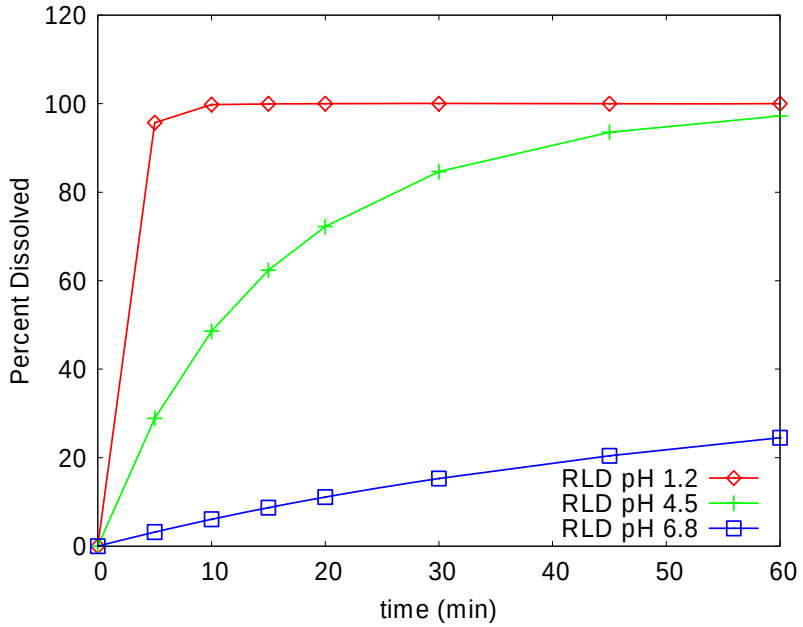


Figure 3: RLD dissolution in USP apparatus 2 at 50 rpm as a function of pH.

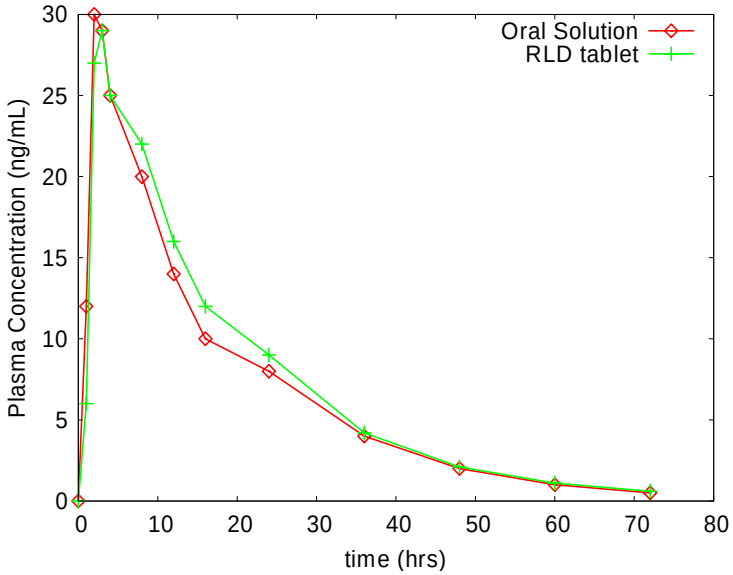


Figure 4: Publicly available data demonstrating the RLD provides similar pharmacokinetics to an oral solution. This plot contains the mean data from 12 subjects.

How was the product designed to have these attributes?

As a target for the development of a manufacturing process, we identified the following attributes that will ensure the desired final product quality:

- Particle size of the drug substance in the drug product
- Polymorphic form of the drug substance in the drug product
- Assay of drug substance in the drug product
- Content uniformity of drug substance in the drug product
- Level of disintegrant in the drug product
- Content uniformity of disintegrant in the drug product
- Tablet friability
- Tablet hardness
- Level of degradation products
- Container closure protects drug product from light

Not all of these attributes will be measured directly, some will be ensured through indirect tests or control of raw materials and the manufacturing process as described in Diagram 1.

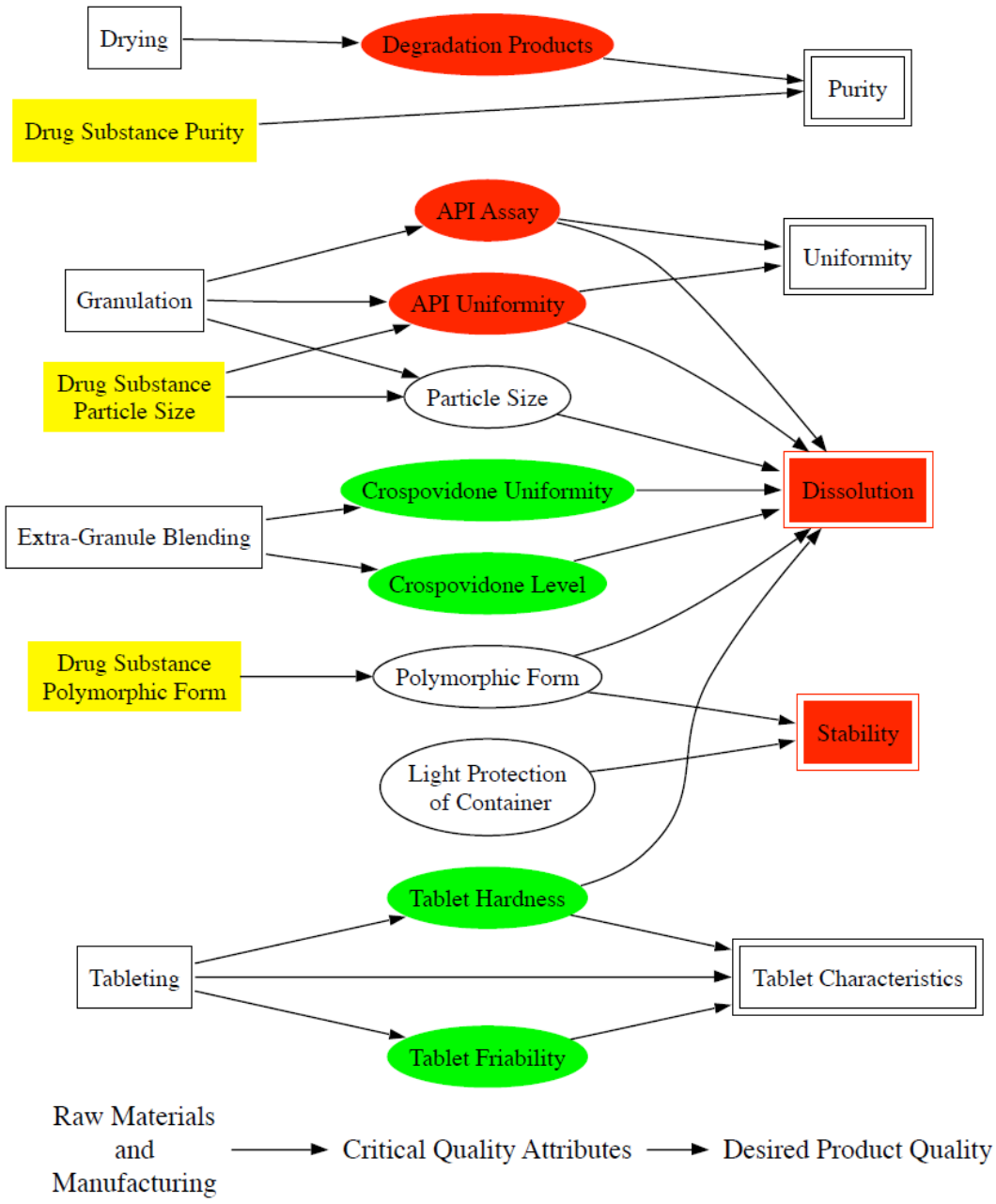


Diagram 1: Depicts our approach to reach the desired product quality. The selection of raw materials and the design of the manufacturing process determine the properties of the drug product need to reach the desired quality. Our testing process, indicated in red for end product tests, green for in process tests, and yellow for raw material controls verifies the execution of the design.

Were alternative formulations or mechanisms investigated?

No alternative formulations or mechanisms were investigated.

How were the excipients and their grades selected?

The ratio of lactose monohydrate and microcrystalline cellulose used (160/61.6 or 2.59) was chosen based on our previous experience with scaling up the wet granulation equipment (see ANDA xx-xxxx and yy-yyyy). This choice provided acceptable tableting and dissolution when the levels of magnesium stearate and crospovidone were adjusted based on the trial formulations.

The lactose monohydrate grade selected was a pharmaceutical grade (Lactose #312, Foremost Farms) recommended for use in wet granulation. This grade is passed through a 200 mesh sieve before release and the supplier's particle size limits are NLT 99.5%<75µm and 20-30%<45µm.

The microcrystalline cellulose grade used (Avicel PH-101, FMC) is the grade recommended by our supplier for use in wet granulation processes. It has a mean particle size of 50 µm, moisture content of 3.0-5.0%, and a bulk density of 0.26-0.31 g/mL.

The grade of povidone used (Plasdone K-29/32, ISP) is the grade recommended for use in wet granulation. It has a molecular weight of 58,000 and is highly soluble in water at room temperature. Tap and bulk densities are 0.43 and 0.34 g/mL and the mean particle size is 100 µm.

The grade of magnesium stearate used (Hyqual NF, Mallinckrodt) has particle size limits of D50 10.5 - 16.5µm and D90 35µm.

How was the final formulation optimized?

To establish the robustness of the proposed formulation, the following ranges around the target formulation were investigated using design of experiments:

Factors	Range
Lactose/ MCC ratio (RATIO)	2.4 to 2.6
Disintegrant level (DISINT)	2.0% to 4.0%
Lubricant level (LUB)	0.25% to 0.75%
Binder level (BIND)	2.0% to 4.0%

Based on prior experience, we expected these ranges to lead to acceptable product. Using SAS (v8) a response surface design using the Small Composite: Hartley Method was constructed and dissolution at 30 minutes (DISS), and the RSD of the content uniformity (RSD) were evaluated for tablets produced from each formulation (tablets were produced in 2kg lab scale batches).

Experiment Number	Binder level (%)	Disintegrant level (%)	Lubricant level (%)	Lactose/ MCC ratio
1	2.00	2.00	0.25	2.80
2	4.00	2.00	0.25	2.80
3	2.00	4.00	0.25	2.40
4	4.00	4.00	0.25	2.40
5	2.00	2.00	0.75	2.40
6	4.00	2.00	0.75	2.40
7	2.00	4.00	0.75	2.80
8	4.00	4.00	0.75	2.80
9	1.31	3.00	0.50	2.60
10	4.68	3.00	0.50	2.60
11	3.00	1.31	0.50	2.60
12	3.00	4.68	0.50	2.60
13	3.00	3.00	0.08	2.60
14	3.00	3.00	0.92	2.60
15	3.00	3.00	0.50	2.26
16	3.00	3.00	0.50	2.93
17	3.00	3.00	0.50	2.60

For all formulations, acceptable tablets were produced and the RSD was less than 2.0% and judged to be acceptable. For DISS a model was fit to the data:

DISS = -184.493 + 7.708959***BIND** + 41.01166***DISINT** + 274.2326***LUB** + 92.77734***RATIO** - 0.87802***BIND*BIND** + 0.375***BIND*DISINT** + 1.5***BIND*LUB** - 1.875***BIND*RATIO** - 8.479439***DISINT*DISINT** - 0.121591***DISINT*LUB** + 8.530532***DISINT*RATIO** - 39.50422***LUB*LUB** - 95.07233***LUB*RATIO** - 13.11169***RATIO*RATIO**

From the model, the disintegrant is the most important factor. The following contour plots (Figure 5) show that a disintegrant level greater than 2.5% is needed to ensure rapid dissolution (>80% in 30 minutes). For the other variables, dissolution was acceptable over the ranges studied.

This indicates the potential design space around the to be marketed formulation.

Factors	Design Space
Lactose/ MCC ratio (RATIO)	2.4 to 2.6
Disintegrant level (DISINT)	2.5% to 4.0%
Lubricant level (LUB)	0.25% to 0.75%
Binder level (BIND)	2.0% to 4.0%

2.3.P.2.4 Container Closure System

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

The container/closure should protect the drug product from light based on the results of the stress testing reported in 2.3.P.2.1. Thus, we selected a container that met USP <661> limits on light protection. The container is enclosed in a secondary packaging carton for additional light protection.

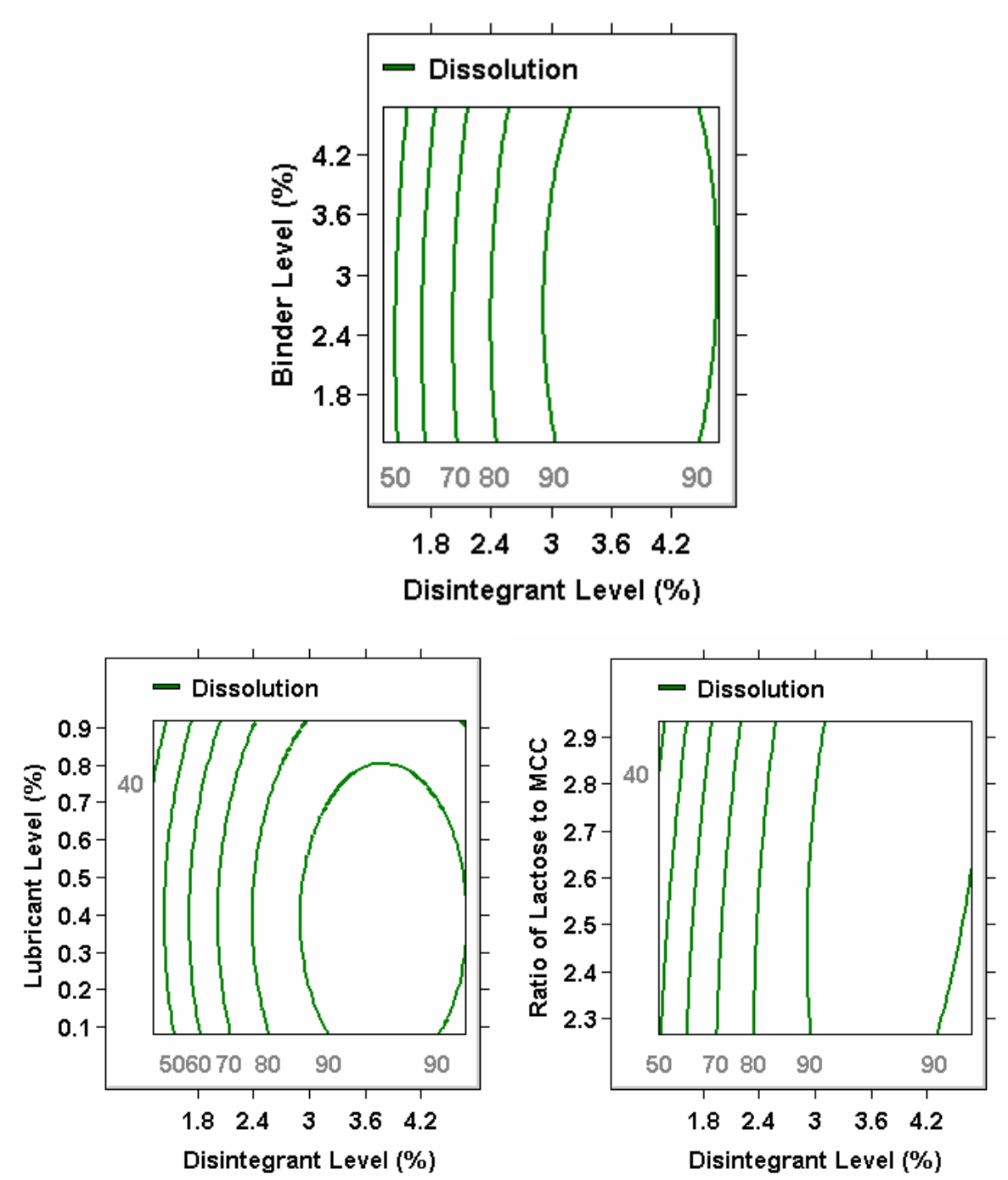


Figure 5: Contour plots of dissolution as a function of composition. The true space is four dimensional so these plots show slices with the other two factors fixed. The green lines are contours of constant percent dissolution in 30 minutes. The proposed formulation is at the center of each plot. The region of dissolution greater than 80% should be considered the potential design space.

2.3.P.3 Manufacture

Who manufactures the drug product?

ANDA Sponsor at site 21 in
This place, That state, USA.

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

Process Flow Diagram and Narrative Summary

The manufacturing process involves the following steps:

a. Lactose monohydrate, povidone, and microcrystalline cellulose (MCC) were mixed in a high shear mixer.

b. Separately a suspension of drug substance in water was prepared.

c. The suspension of drug substance was sprayed onto the dry mix and mixed with the impeller on fast speed and the chopper off.

d. After addition of the liquid, mixing continued with the chopper on until the power consumption endpoint was reached (an additional 5 min) to provide for a homogenous mix of the active and the excipients.

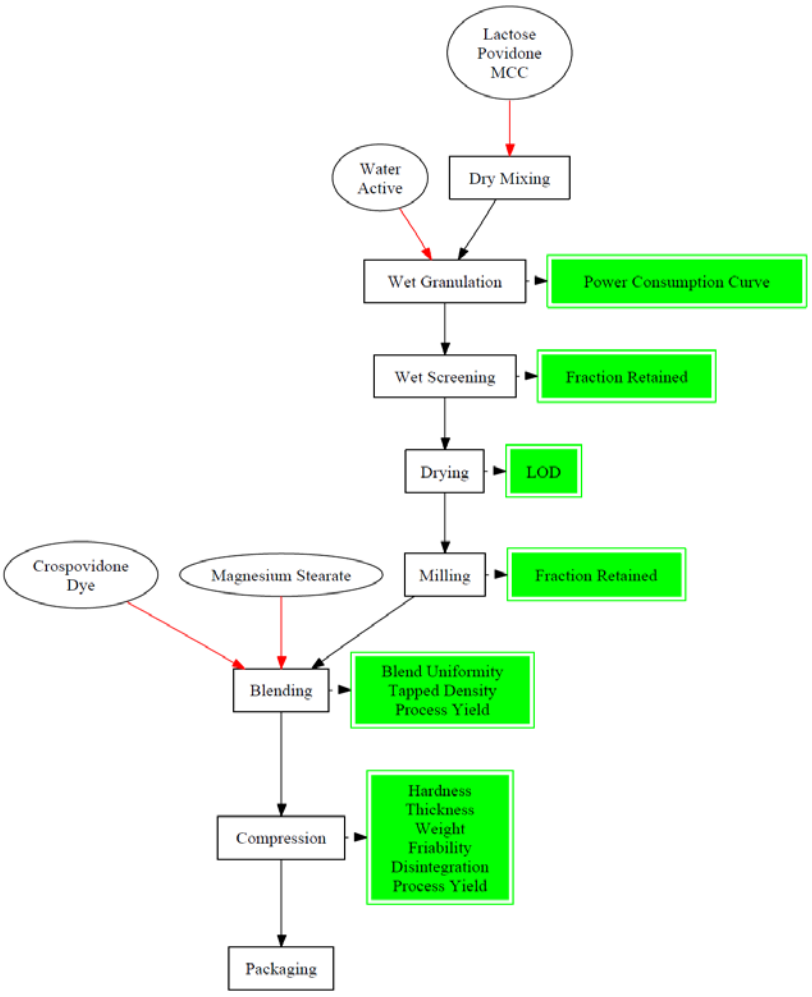
e. The wet mass was passed through a 6 mesh (3.3 mm) screen to remove large agglomerates that would not dry uniformly.

f. Granules were dried at an inlet temperature of 60±5°C (to an LOD 0.5 %) in a fluid bed dryer

g. Dry granules were milled through a 12 mesh (1.1 mm) screen in an impact mill with knives forward.

h. Milled granules were blended in a bin-blender with dye and Crospovidone for 5 min, and subsequently blended with magnesium stearate for 2 minutes.

i. Blend was compressed into tablets using suitable tooling and packaged



Reprocessing statement: There is no reprocessing. The reprocessing statement is at 3.2.P.3.3

What is the reconciliation of the exhibit batch?

The reconciliation of the executed batch record for the exhibit batch at each stage is provided below. For exhibit batch records, refer to Module R.1.P.

Process Step	Lot #9A	Target	Limit
Blend (after drying)			
Yield	45.629 kg (98%)	46.56 kg (100%)	96%
Blending of Extra-Granular Material			
Yield	47.04 kg (98%)	48 kg (100%)	96%
Tablet Compression			
Yield	46.70 kg (97.3%)	48 kg (100%)	96%
Tablets Produced	225,420	231,000	93%
500 count bottles	198 bottles	200 bottles	
100 count bottles	950 bottles	1010 bottles	
60 count bottles	500 bottles	500 bottles	
Tablets Packaged	224,000 (96.9%)	231,000	93%
Accountability	99%	100%	97%

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

Batch Formula:

Component	Pivotal ANDA Batch 230,000 Units	Commercial Batch 2,300,000 tablets	% (w/w)
Ersatzine, USP	0.40 kg	4.0 kg	0.83
Lactose Monohydrate, NF	32.00 kg	320.00 kg	66.67
Microcrystalline Cellulose, NF	12.32 kg	123.20 kg	25.67
Povidone, NF	1.44 kg	14.40 kg	3.00
Crospovidone, NF	1.44 kg	14.40 kg	3.00
Magnesium Stearate, NF	0.24 kg	2.4 kg	0.50
FD&C Blue #2	0.160 kg	1.60 kg	0.33
Purified Water	9.6 L	96 L	
Total Weight	48 kg	480 kg	

Batch records:

Batch records for the ANDA batch and proposed commercial batches are found in section R.1.P. There are no overages in the process.

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

In-Process Test	Acceptance Criteria	Analytical Procedure	Results Pivotal Batch #9A
Granulation:			
Power consumption curve	Conforms to in house standard	M-1231	Complies
Wet Screening:			
Fraction Retained	NMT 1.0%	M-1233	0.1%
Drying:			
LOD	NMT 0.5%	M-1232	0.3%
Milling:			
Fraction Retained	NMT 1.0%	M-1233	0.2%
Blend Samples:			
Appearance	White to off-white granules	M-1234	Complies
Blend Uniformity	90.0-110.0%, RSD NMT 5.0%	M-1235	99.1%, RSD 2.0%
Tapped Density	0.65-0.85 g/mL	M-1236	0.73 g/mL
Process Yield	96.0-100.5%		47.04 kg (98%)
Compression:			
Hardness	8-12 Kp (Target = 10 Kp)	M-1238	9.96 Kp
Thickness	3.5 – 3.9 mm (Target = 3.7 mm)	M-1239	3.72 mm
Weight		M-1240	
Average of 10 Tablets:	228-252 mg (Target = 240 mg ±5%) 222-258 mg (Target = 240 mg ±7.5%)		241.2 mg 235.5-243.9 mg
Individual:	NMT 1.0%	M-1241	0.6 %
Friability	NMT 5 minutes	USP <701>	1 min
Disintegration	93-101%		225.420 tablets
Process Yield			(97.3%)

Three of the in-process tests (hardness, disintegration, friability) were identified as critical to product quality in diagram 1 in 2.3.P.2.2. The limits of the hardness range were verified as meeting the desired dissolution profile, the friability limit of NMT 1.0% is an acceptable pharmacopeial limit, and the disintegration in less than 5 minutes is correlated with obtaining the desired rapid dissolution. Limits on the other in-process tests were chosen to monitor process consistency as described in the process development reports available for inspection.

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

The commercial scale process contains the same unit operations and utilizes equipment of the same design and operating principles as used to produce the exhibit batch.

Unit Operation	Equipment	Development Studies	ANDA batch	Commercial batch
		2 kg batch 10,000 tablets	48 kg batch 230,000 tablets	480 kg batch 2,300,000 tablets
Wet Granulation	High Shear Granulator	PMA 10	PMA 300	PMA 1800
Wet Screening	Impact Mill (FitzSieve)	FS 75	FS 200	FS 200
Drying	Fluid Bed Dryer	STREA 1	MP 4	MP 6
Milling	Impact Mill (FitzSieve)	FS 75	FS 200	FS 200
Extra-Granule Blending	Bin-Blender	Size: 5L	Size: 100 L	Size: 1000L
Tableting	Tablet Press	Beta	Beta	Beta

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

Controls on these excipients will be based upon specifications defined by the USP/NF. In the development studies, excipient characterization beyond the supplier's grade was not found to be critical to product performance.

Ingredient	Manufacturer	Grade	Lot Numbers*		Complies with USP/NF Tests
			Supplier	Applicant	
Lactose Monohydrate, NF	Foremost Farms	Lactose #312	P3455	6543	Yes
Microcrystalline Cellulose, NF	FMC	Avicel PH-101	B323	1235	Yes
Povidone, NF	ISP	Plasdone K-29/32	N/A	5309	Yes
Crospovidone, NF	ISP	Polyplasdone XL	N/A	2336	Yes
Magnesium Stearate, NF	Mallinckrodt	Hyqual, NF	A3253	4478	Yes

* Lot numbers used in production of the exhibit batch

Non-Compendial Excipients

The only non compendial excipient is a certified color additive which may be safely used for coloring drugs (i.e., FD&C Blue #2 (21CFR 74.1102)).

Excipients from Animal Origin

Magnesium Stearate and Lactose Monohydrate are of animal origin. Details are found in 3.P.4.5.

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	Batch #9A
Appearance	Blue, rectangle shaped, debossed, "ABCD" on one side and "DEF2' on the other side.	Visual	Complies
Identification A. IR	IR absorption spectrum maxima correspond to reference standard	USP	Complies
Assay	90.0% to 110.0% of labeled amount of Ersatzine	USP	98.8%
Content Uniformity	USP <905>	USP	Mean: 99.1%RSD=0.8% Range: 98.2%- 100.1%
Degradation Products	RC2: NMT 0.5% RC3: NMT 0.5% Largest Unspecified Impurity: NMT 0.2% Total Degradation Products: NMT 1.5%	method #41	0.2% 0.2% 0.1% 0.65%
Dissolution (HPLC)	NLT 80% (Q) of the labeled amount in 30 minutes. USP <711>	USP	Mean: 88% Range: 85%-90%

The product has a USP monograph. USP tests are shaded in the table. All acceptance criteria meet the USP limits. The product specification includes a different dissolution medium than is used in the USP monograph.

The specification does not include a test for moisture because development studies did not indicate any moisture sensitive degradation pathways and an in-process test for LOD is used for the endpoint determination of the drying unit operation.

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

Tablets will be examined by visual inspection for color, shape, and general appearance.

Identification

A specific IR method from the USP monograph is used for identification.

Assay

The 90.0-110.0% limits are based on the USP monograph for this product.

The USP method is used. There was no interference from placebo. For chromatograms of the test samples, placebo formulation, and reference standard, refer to 3.2.P.5.2 and 3.2.P.5.4. Stress testing to demonstrate the assay is stability indicating is described after related compounds.

Content Uniformity

The acceptance criteria described in the USP Content Uniformity test <905> will confirm acceptable content uniformity in the final dosage form.

Impurities (Degradants)

Two major degradation products of ersatzine were found in the drug product:

Name	Chemical name/ Identification	Chemical Structure	Proposed Acceptance Criteria
RC2	[Chemical Name]	[Chemical Stucture]	NMT 0.5%
RC3	[Chemical Name]	[Chemical Stucture]	NMT 0.5%

The limits are from the USP monograph for this drug product.

Impurity	Proposed Acceptance Criteria	Justification	ANDA Drug Product (Lot #9A)
RC2	NMT 0.5%	USP Limit	0.2%
RC3	NMT 0.5%	USP Limit	0.2%
Largest Unspecified Impurity	NMT 0.2%	ICH Q3B identification threshold	0.1%
Total Degradation Products	NMT 1.5%	USP Limit	0.65%

The method for detection of related compounds is method (#41) described in 2.3.S.4 with the addition of a sample preparation stage (full method details are in 3.2.P.5.2 and 3.2.P.5.4). The USP method was not used because it was unable to resolve a process impurity as described in 2.3.S.4. The HPLC test method (#41) is accurate, precise, linear, specific, and suitable for use.

Test	Acceptance Criteria	Linearity	Precision	Accuracy	LOD	LOQ
RC2	NMT 0.5%	r^2 = 0.996 RSD = 1.5%	Mean 0.13% RSD 6.45%	92-110% RSD = 2.8%	0.025%	0.075%
RC3	NMT 0.5%	r^2 = 0.996 RSD = 1.5%	Mean 0.14% RSD 5.7%	91-110% RSD = 2.9%	0.035%	0.1%

Method (#41) meets the USP system suitability requirements and is comparable to the USP method for identification of drug product impurities. In event of dispute, the USP method will prevail.

Test	USP Method (DP)	In house HPLC #41
RC2	0.2%	0.2%
RC3	0.2%	0.2%
Largest Unspecified Impurity	0.1%	0.1%
Total Degradation Products	0.65%	0.65%

Stress testing was conducted to ensure that the assay and impurity methods are specific and stability indicating when used with this proposed formulation. The drug product was subjected to acid, base, oxidation, heat, and light. The product was analyzed by HPLC with peak purity analysis (PDA). Degradation peaks were well resolved from peak of interest. The peak purity of the major peak (drug substance) was observed to be >0.99. The peak purity angle was less than the peak purity threshold, indicating no interference. There was no interference of degradants with the main peak or the RC2 and RC3 impurity peaks. For full details, refer to 3.2.P.5.3.

Stress conditions	Assay Method		Impurity Method	
	% Assay	Peak Purity	Observed Degradants	Peak Purity
Untreated	99%	>0.99	N/A	>0.99
0.1N HCl/70°C/14 h	97%	>0.99	RC2:2%	>0.99
0.1N NaOH/70°C/30 min	98%	>0.99	RC2:1%	>0.99
3% H_2O_2/60°C/2 h	97%	>0.99	RC2:1% RC3:1%	>0.99
Purified water/60°C/13 h	99%	>0.99	N/A	>0.99
Expose to humidity (90% RH)/25°C/7 days	99%	>0.99	N/A	>0.99
Expose to sun light 408 days	55%	>0.99	RC2:25% RC3: 20%	>0.99
UV light (short and long wave length) 7 days	27%	>0.99	RC2:35% RC3: 30%	>0.99
Dry heat /105^{0}C/14 h	97%	>0.99	RC2:2%	>0.99

Dissolution

The dissolution method is the USP method. The acceptance criteria are appropriate because all rapidly dissolving formulations would be expected to be bioequivalent to solution formulations.

Parameter	Value
Medium	pH 4.5 buffer
Volume	900 mL
Temperature	37ºC
Apparatus	2 (Paddle)
Rotational Speed	50 rpm
Specification	NLT 80% (Q) in 30 minutes

2.3.P.6 Reference Standards and Materials

How were the primary reference standards certified?

The reference standards are the same as were used for the drug substance.

2.3.P.7 Container Closure System

What container closures are proposed for packaging and storage of the drug product?

Ersatzine Tablets 2 mg will be marketed in the following containers:

- HDPE (white, square) plastic bottles
    - 60-mL bottle (60 and 100 count) with 28-mm neck and PP CRC with Al induction seal
    - 325-mL (500 count) with 45-mm neck and PP CT closure with Al induction seal

Summary of the container closure system:

Type	Description (Tablet Count)	Supplier	DMF
Bottle	60mL, white square HDPE, (60, 100 tablets)	Bottle Co.	xxxx
Bottle	325mL, white square HDPE, (500 tablets)	Bottle Co.	xxxx
HDPE Resin	HDPE resin 456 HDPE	E Chemicals	xxxx
Closure	28mm CR cap white HDPE Outer Shell clear PP CRC	Bottle Co.	xxxx
Closure	45mm PP white CT Fine Ribbed Closures	Bottle Co.	xxxx
PP Resin	PP resin 120 resin	PP Co.	xxxx
Closure Liner	Pulp backing wax-bonded to PE-faced Al inner seal (induction sealed)	Plup Inc.	xxxx
	Heat Seal	S Liner	xxxx

Has the container closure system been qualified as safe for use with this dosage form?

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 (ANDA YYYY and ANDA YYYY). For full details, refer to Module 3.2.P.2.4.

2.3.P.8 Drug Product Stability

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

The proposed stability specifications are:

Tests	Acceptance Criteria	Analytical Procedure
Appearance	2 mg: Blue, rectangle shaped, debossed, "ABCD" on one side and "DEF2' on the other side.	Visual
Assay (HPLC)	90.0% to 110.0% of labeled amount of Ersatzine	USP method
Related Compounds (HPLC)	RC2: NMT 0.5% RC3: NMT 0.5% Largest Unspecified Impurity: NMT 0.2% Total Degradation Products: NMT 1.5%	method #41
Dissolution (HPLC)	NLT 80% (Q) of the labeled amount in 30 minutes. USP <711>	USP method

All attributes used to confirm the quality of the finished drug product on batch release are evaluated during stability testing, with the exception of identity and content uniformity testing which 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 on batch release (see Module 2.3.P.5 for justification of these limits).

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

Accelerated stability (40°C/75% RH) at 0, 4, 8, and 12 weeks, and room temperature (25°C/60% RH) stability data at 0, 3, 6, 9, and 12 months has been provided for the drug product packaged in the proposed 60-unit and 500-unit packaging configurations, which bracket the 100-unit packaging configuration. The stability data is summarized in the table below. Refer to Modules 3.2.P.8.1 and 3.2.P.8.3 for full details regarding stability studies and data.

Three months of accelerated stability data studies indicates that all monitored attributes of the drug product fall well within the proposed stability specifications. Comparison of accelerated (3 months) and room temperature (12 months) stability data suggests that the observed trends are overestimated by the accelerated stability studies. A tentative 2 year expiration dating period is proposed, which will be confirmed by real-time room temperature stability data. The tentative 2 years expiration dating period at room temperature reflects the recommended storage conditions specified in the labeling: *"Store at controlled room temperature, 20-25°C (68-77°F). Protect from Light"*.

Stability protocol

Strength	Container/Closure	Conditions	Sample Times	Batches
2mg	60 unit bottle	40° C ± 2°C 75% ± 5% RH	0, 4, 8, and 12 weeks	Lot #9A
2mg	60 unit bottle	25° C ± 2°C 60% ± 5% RH	0, 3, 6, 9, and 12 months	Lot #9A
2mg	500 unit bottle	40° C ± 2°C 75% ± 5% RH	0, 4, 8, and 12 weeks	Lot #9A
2mg	500 unit bottle	25° C ± 2°C 60% ± 5% RH	0, 3, 6, 9, and 12 months	Lot #9A

Summary of stability test results

	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 98-102.1%	No Trend All values vary between 98.7-101.5%
Impurity RC 2 (NMT 0.5%)	No Trend All Values (0.1-0.2%)	No trend All Values (0.1-0.2%)
Impurity RC 3 (NMT 0.5%)	No Trend. All values are (0.1-0.2%)	No Trend. All values are (0.1-0.2%)
Any Unspecified Impurity (NMT 0.2%)	No Trend All values are (0.05-0.1%)	No Trend. All values are (0.05-0.15%)
Total Impurities (NMT 1.0%)	Upward Trend (0.7%). All values are (0.5-0.8%)	No Trend (<0.3%). All values are (<0.3%)
Dissolution	All Comply (93-98%) S1 stage dissolution testing only	All Comply (95-100%) S1 stage dissolution testing only
Moisture (NMT 6.5%)	No Trend Values vary between 5.1-5.5%	Values vary between 5.1-5.5%
Description and Physical Appearance	All Comply	All Comply

What is the post-approval stability protocol?

- We commit to place the first three commercial production batches (packaged in the smallest and largest configurations) on stability ($25^{o}C \pm 2^{o}C/60\% \pm 5\%$ RH) and test at intervals of 0, 3, 6, 9, 12, 18, 24 months and 36 months (if applicable) until the desired expiration date is reached. The data will be reported to FDA in the annual report.
- Yearly thereafter, a minimum of one production batch (packaged in the smallest and largest configurations) will be added to the long-term stability program.
- Expiration dates may be extended based upon room temperature stability data from a minimum of three production batches.
- If, in these post-approval stability studies, any lots are found to fall outside the approved specifications, these lots may be withdrawn from the market.
- Deviations that 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.