



Suggested Formula	Estradiol 0.4 mg, Estriol 1.6 mg Oral Rapid-Dissolve Tablets (Solid Suspension, 96 x 750 mg [0.93 mL] Tablets)	FIN	F 005 475v4
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SUGGESTED FORMULATION

Ingredient Listing	Qty.	Unit	NDC #	Supplier	Lot Number	Expiry Date
Estradiol 2% Stock Powder Blend †	1.920	g				
Estriol (Micronized), USP	0.154	g				
Orange Flavor (Powder)	0.40	g				
Vanillin Flavor (Powder)	0.20	g				
Stevia Powder (Stevioside)	0.10	g				
Medi-RDT Base	TBD					
† Estradiol 2% Stock Powder Blend						
Estradiol (Micronized), USP	TBD					
Medi-RDT Base	q.s. to 5.00	g				

SPECIAL PREPARATORY CONSIDERATIONS

Ingredient-Specific Information

Light sensitive (protect from light whenever possible): *Estradiol*

Hygroscopic (protect from moisture whenever possible): *Estradiol, Medi-RDT Base, Stevia Powder*

Suggested Preparatory Guidelines

Non-Sterile Preparation Sterile Preparation

Processing Error / Testing Considerations: To account for processing errors and considerations during preparation, it is suggested to measure an additional **5 to 9%** of the required quantities of ingredients.

Special Instruction: Protective apparel, such as a lab coat, disposable gloves, eyewear and face-masks should always be worn.

This procedure requires the use of very small quantities of ingredients. All calculations and preparation techniques must be verified before dispensing the final product.

IMPORTANT: This procedure involves heating the tablet mold at temperatures reaching 110°C. Ensure that your molds are able to withstand this temperature.



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SUGGESTED PREPARATION (for 96 Tablets)

Weigh and / or measure the following ingredients when appropriate:

Ingredient Listing	Qty.	Unit	Multiplication factor ^(*) : ____	Processing Error	Qty. to measure
Estradiol 2% Stock Powder Blend † §	1.920	g			
Estriol (Micronized), USP	0.154	g			
Orange Flavor (Powder)	0.40	g			
Vanillin Flavor (Powder)	0.20	g			
Stevia Powder (Stevioside) §	0.10	g			
Medi-RDT Base §	TBD				
† Estradiol 2% Stock Powder Blend					
Estradiol (Micronized), USP §	TBD		---	---	
Medi-RDT Base §	q.s. to 5.00	g	---	---	

* Takes into account increased batch size conversions and density conversions, if required.

§ Weigh / measure just prior to use.

Preparatory Instruction

1. **Mold calibration:**

Determine the required quantity of Medi-RDT Base for 96 tablets based on the actual size of the tablet mold being used. Refer to the Appendix for details.



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2. **Ingredient quantification:**

A. Determine the potency of Estradiol (Micronized) based on the certificate of analysis:

	100%
MINUS	
Water Content (from certificate of analysis)	_____ %
DIVIDED BY	100
EQUALS	
Quantity of water free Estradiol (Micronized), in decimal	_____
MULTIPLY BY	
Assay on anhydrous basis result (from certificate of analysis)	_____ %
DIVIDED BY	100
EQUALS	
i. Potency of Estradiol (Micronized), in decimal	_____

3. **Ingredient quantification:**

A. Determine the quantity (in g) of Estradiol (Micronized) to make an Estradiol 2% Stock Powder Blend (5 g):

Quantity of Estradiol (Micronized) required for the Stock Powder Blend	0.100 g
DIVIDED BY	
Potency of Estradiol (Micronized), in decimal (Step 2Ai)	_____
EQUALS	
i. Quantity of Estradiol (Micronized) needed for the Stock Powder Blend	_____ g



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4.	<p>† <u>Estradiol 2% Stock Powder Blend preparation:</u></p> <p>A. Combine and mix the following ingredients together to form a homogeneous powder blend:</p> <ul style="list-style-type: none">-Estradiol (Micronized) (amount calculated in Step 3Ai)-Medi-RDT Base (q.s. to 5.00 g)
5.	<p><u>Powder preparation:</u></p> <p>A. Pass the Medi-RDT Base through a 40 or 50 mesh sieve and weigh the required quantity (amount calculated in Appendix Step 5Aiii).</p> <p>B. By geometric addition, combine and triturate the following ingredients together to form a homogeneous powder blend:</p> <ul style="list-style-type: none">-Estriol (Micronized)-Estradiol 2% Stock Powder Blend (1.920 g <i>plus</i> processing error adjustments)-Orange Flavor (Powder)-Vanillin Flavor (Powder)-Stevia Powder (Stevioside) <p>C. By geometric addition, combine and mix (DO NOT TRITURATE) the following ingredients together to form a homogeneous powder blend:</p> <ul style="list-style-type: none">-Sieved Medi-RDT Base (Step 5A)-Homogeneous powder blend (Step 5B) <p><u>Note:</u> Do not use excessive force as Medi-RDT Base should not be triturated.</p> <p>D. Prior to filling the tablet mold cavities, pass the homogeneous powder blend (Step 5C) through a 40 or 50 mesh sieve to improve flow properties and obtain content uniformity.</p>
6.	<p><u>Mold filling and heating:</u></p> <p>A. Fill the 96 tablet mold cavities by tapping and pressing the sieved homogeneous powder blend (Step 5D) into the cavities using the upper part of the mold. Repeat at least three times to ensure the cavities are completely filled. If necessary, add additional powder blend.</p> <p>B. Gently heat the powder blend to 105°C – 110°C for 10 – 15 minutes. Do not overheat.</p> <p><u>Specifications:</u> Heat by placing the filled mold (base cavity plate only) in an appropriate oven, preheated to 105°C – 110°C.</p> <p><u>End Result:</u> Homogeneous solid dispersion.</p>



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7.	<p><u>Cooling:</u></p> <p>A. Carefully remove the tablet mold from the heated oven, using a hot hand protector.</p> <p>B. Immediately remove the tablets by flipping over the mold onto a piece of wax or ointment paper and gently tapping the mold with a mini mallet.</p> <p><u>Note:</u> Hold the tablet mold in place while tapping to avoid shaking and breaking the tablets.</p> <p>C. Allow the tablets to cool for an additional 30 minutes at controlled temperature and relative humidity.</p>		
8.	<p><u>Validation technique:</u></p> <p>A. Weigh 20 tablets separately.</p> <p>B. The final weight of each tablet from Step 8A (not including the weight of the tablet mold) should be between 90 and 110% of the theoretically calculated weight (Appendix, Step 4B), in accordance to USP guidelines.</p>		
9.	<p><u>Product transfer:</u></p> <p>Transfer the final product into the specified dispensing container (see “Packaging Requirements”).</p>		



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SUGGESTED PRESENTATION

Estimated Beyond-Use Date	6 months, as per USP*.	Packaging Requirements	Manually put into light-resistant Medi-RDT blisters and cold seal with foil labels.	
Auxiliary Labels	1	Use as directed. Do not exceed prescribed dose.	6	Discard container after use.
	2	Keep out of reach of children.	7	Keep at room temperature (20°C – 23°C).
	3	Keep in a dry place.	8	Consult your health care practitioner if any prescription or over-the-counter medications are currently being used or are prescribed for future use.
	4	Protect from light.	9	Do not take with alcohol, sleep aids, tranquilizers or other CNS depressants.
	5	May impair mental and/or physical ability. Use care when operating a car or machinery.		
Pharmacist Instructions	Add any auxiliary labels specific to the API to the dispensing container as deemed necessary.			
Patient Instructions	Contact your pharmacist in the event of adverse reactions.			

* The BUD is not later than the time remaining until the earliest expiration date of any API or 6 months, whichever is earlier.



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REFERENCES

1.	Tablets. In: Allen, LV, Jr. <i>The Art, Science and Technology of Pharmaceutical Compounding Third Edition</i> . American Pharmaceutical Association; 2008: 145.
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4.	Estradiol (Monograph). In: O'Neil MJ. <i>The Merck Index 14th Edition</i> . Whitehouse Station, NJ: Merck & Co, Inc.; 2006: Monograph #3703.
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Appendix	Tablet mold calibration		
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SUGGESTED CALCULATION

Preparatory Instruction

1. **API weighing:**

- A. Pass the Medi-RDT Base through a 40 or 50 mesh sieve.
- B. Weigh and / or measure the following ingredients:

Ingredient	Quantity
Medi-RDT Base	9.08 g

Notes: Measure the exact amount specified. Do not consider processing error for calibration step.
Data within this calibration table are based on a 0.93 mL mold size.

2. **Mold filling and heating:**

- A. Fill 5 tablet mold cavities by tapping and pressing the Medi-RDT Base into the cavities using the upper part of the mold. Repeat at least three times to ensure the cavities are completely filled. If necessary, add additional Medi-RDT Base.
- B. Gently heat the powder blend to 105°C – 110°C for 10 – 15 minutes. Do not overheat.

Specifications: Heat by placing the filled mold (base cavity plate only) in an appropriate oven, preheated to 105°C – 110°C.

End Result: Homogeneous solid dispersion.



Appendix	Tablet mold calibration		
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3. **Cooling:**

- A. Carefully remove the tablet mold from the heated oven, using a hot hand protector.
- B. Immediately remove the tablets by flipping over the mold onto a piece of wax or ointment paper and gently tapping the mold with a mini mallet.

Note: Hold the tablet mold in place while tapping to avoid shaking and breaking the tablets.

- C. Allow the tablets to cool for an additional 30 minutes at controlled temperature and relative humidity.

4. **Calculate the average tablet weight:**

- A. Weigh the five tablets and record the total weight here (not including the weight of the empty tablet mold): _____ g

- B. Calculate the average tablet weight:

Combined weight of the tablets (from Step 4A)	_____ g
DIVIDED BY	
Number of Tablets	5
EQUALS	
Average (theoretical) tablet weight*	_____ g

***Note:** The weight of the Rapid-Dissolving Tablets is mainly affected by factors such as compression force, flow properties of the powder mixture (flow properties will vary depending on the Active Pharmaceutical Ingredient(s) and excipients in the formulation) and particle size distribution. The mixture must be sieved prior to filling.

The expected average weight of RDT's are as follows (data based on various experiments/troubleshooting completed in the past):

- 750mg ± 30mg (720mg - 780mg)
- 200mg ± 10mg (190mg - 210mg)
- 150mg ± 7.5mg (142.5mg - 157.5mg)
- 75mg ± 5mg (70mg - 80mg)



Appendix	Tablet mold calibration		
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5. **Ingredient calculation:**

A. Calculate the quantity of excipient blend required for 96 tablets:

Average tablet weight (from Step 4B)	_____ g
MINUS	
Total quantity (in g) of Estradiol 2% Stock Powder, Estriol and Flavors per tablet	0.0289 g
EQUALS	
i. Quantity of Medi-RDT Base required per tablet	_____ g
MULTIPLY BY	
Number of tablets required	96
EQUALS	
ii. Total quantity of Medi-RDT Base required for 96 tablets	_____ g
MULTIPLIED BY	
Processing error adjustments (5 to 9%)	1.05 to 1.09
EQUALS	
iii. Total quantity of Medi-RDT Base required <i>plus</i> processing error adjustments	_____ g

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