# *Manufacture and Evaluation of an Experimental 37.5 kg Scale Batch of 0.103% w/w Ethinyl Estradiol Triturate (Formulation Number WC3074-01I)*

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***Abstract*** *— Actavis Fajardo, is a Pharmaceutical company dedicated to the manufacturing and packaging of oral contraceptive products. Ethinyl Estradiol is an intermediate product used to incorporate Ethinyl Estradiol active in tablet formulations. Ethinyl Estradiol is a high potency drug; therefore, low dosages are required to achieve its therapeutic range (for example 10µg equivalent to 0.014% of the powder blends of the formulations). The triturate is prepared as an intermediate product to aid in the distribution of the active ingredient in the final blend tablets formulation. The manufacturing process of the intermediate product consists of wet massing and drying cycles in a solid processor. Tablet formulations containing this Ethinyl Estradiol triturate are showing a significant variability in the In Process Content Uniformity Test. Therefore, one of the solution was identified to improve the variability in the In Process Content Uniformity Test is to change the formulation of the Ethinyl Estradiol from a concentration of 0.206% w/w to 0.103% w/w. This report will shows the new formulation, manufacturing process and results obtained for a new Ethinyl Estradiol Triturate with a concentration of 0.103% w/w.*

***Key Terms*** *— Blend Uniformity, Ethinyl Estradiol, Formulation Triturate.*

## PROBLEM STATEMENT

Actually, Actavis Fajardo site is manufacturing Oral Contraceptive products which show variability in the content uniformity test. This test is pharmaceutical analysis required for the quality control of tablets as per USP 905 [1]. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. To perform this test multiple tablets are selected randomly and a suitable analytical method is applied to assay the individual content of the active ingredient in each tablet. Tablets manufactured at Actavis, Fajardo site contains a very low quantity of Ethinyl Estradiol active. This active is manufactured as a triturate due to the low quantity of active that required each tablet. This triturate is manufactured individually and then is blending with other active depends of the tablet. Currently, there are three different tablets showing variability in the content uniformity test of the Ethinyl Estradiol active. Tablets are identified at Actavis, Fajardo as WC3016-21C which contains 1mg of Norethindrone Acetate and 10 mcg of Ethinyl Estradiol, WC3016-20C which contains 10mcg of Ethinyl Estradiol and WC3026-5C which contains 0.8mg of Norethindrone and 25mcg of Ethinyl Estradiol. These three tablet formulations can be considered as one product family due to them sharing similar formulations and routes of manufacture. All of these three products are prescribed for the prevention of pregnancy in the US and Canada market. The Ethinyl Estradiol triturate is added to each formulation: WC3016-21C, WC3016-20C and WC3026-5C.

The main problem was presented in the WC3016-21C formulations. Some lots using this formulation were found out of trend (OOT) in the In Process Content Uniformity (IPCU) test results. The specification limit for the sample mean is 90.0% - 110.0% and two stages were reported OOT whit 110.7% and 110.0%. As a manufacturing investigation performed at Actavis, Fajardo the segregation mechanisms of fluidization and elutriation were impacting the IPCU (In-Process

Content Uniformity) of NA (Norethindrone Acetate) and EE (Ethinyl Estradiol) in WC3016-21C tablets. Specifically, a trend to low NA IPCU results and high EE IPCU results had been observed at the start of batches. Conversely, a trend to high NA IPCU results and low EE IPCU results had been observed at the end of batches. These mechanisms were promoted by the long transition chute transfer of the granulation from the second floor to the tablet press located at the first floor. These trends were addressed initially by implementing beginning and end of batch discards in the compression process. As a more permanent solution, the installation of the mass flow bins directly on top of the tablet press hopper was implemented, eliminating the long transition tube.

Two commercial lots of WC3016-21C were evaluated under a process validation protocol. The bins were installed directly on top of the tablet press using a bin lifter. The qualification considered compliance with the finished product specification including IPCU (In-Process Content Uniformity) of both active pharmaceutical ingredients: NA and EE.

IPCU samples collected from 20 locations throughout the compression process, including the beginning and end of lot, were analyzed for each lot. The two lots met IPCU acceptance criteria with mean results within target potency (90.0% – 110.0% weight corrected. All individual results were also within target potency (75.0% – 125.0% as is).

Forty-five (45) lots containing WC3016-21C tablets have been manufactured with the changes. The lots manufactured have met release specification for both tests. The beginning and end of batch trends observed previously were eliminated. However, five (5) lots have reported OOT (out of trend) results in IPCU or CU (Content Uniformity) tests for EE in WC3016-21C tablets. All lots manufactured after implementing the bin on top of the tablet press have met the specification limits for IPCU test. The beginning and end of batch trends observed previously were eliminated. However, OOT results have been reported for five (5) WC3016-21C lots. Due to the results obtained after the implementation of these changes, was recommended to take additional actions to address the EE variability in WC3016-21C, WC3016-20C and WC3026-5C lots. An evaluation following an experimental design was conducted.

This report will be focused in one of the actions identified to address the EE variability to the three manufacturing formulations (WC3016-21C, WC3016-20C and WC3026-5C). One of the actions identified is to reduce the Ethinyl Estradiol concentration from 0.206% w/w to 0.103% w/w in WC3016-21, WC3016-20C and WC3026-5C tablets. The use of a lower concentration of Ethinyl Estradiol EE triturate will improve the IPCU test in tablets.

## LITERATURE REVIEW

As per FDA Content Uniformity (CU) testing is an important assessment of unit dosage form performance because pharmacological responses are dynamic, variable, and their manifestations easily confounded, clinical response alone cannot serve as an arbiter of adequate CU performance. CU testing is usually destructive and consumes resources (wet chemical analyses) [2].

The United States Pharmacopeia (USP) is a pharmacopeia (compendium of drug information) for the United States published annually by the United States Pharmacopoeia Convention (usually also called the USP), a nonprofit organization that owns the trademark and copyright. Drugs subject to USP standards include both human drugs (prescription, over-the-counter, or otherwise), as well as animal drugs. USP has no role in enforcing its standards; enforcement is the responsibility of FDA and other government authorities in the U.S. and elsewhere. The USP <905> Uniformity of Dosage Units applies to many dosage forms in the industry. As per USP <905> to ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each

unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for external, cutaneous administration. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of the UPS <905> chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified elsewhere in this Pharmacopeia [3].

The uniformity of dosage units can be demonstrated by either of two methods, Content Uniformity or Weight Variation. The test for Content Uniformity of preparations presented in dosage units is based on the assay of the individual content of drug substance(s) in a number of s dosage units to determine whether the individual content is within the limits set. The Content Uniformity method may be applied in all cases.

## METHODOLOGY

The Ethinyl Estradiol (EE) triturate is currently manufactured at Actavis Fajardo with a concentration of 0.206% w/w. This concentration was reduced to 0.103% w/w which is exactly the half of the original concentration. A new formulation was created to manufacture the EE triturate with the new concentration. The batch formula for 37.5-kg scale, 0.103% w/w EE triturate is detailed in Table 1.

### Equipment

The Ethinyl Estradiol (EE) triturate 37.5-kg scale, 0.103% w/w was manufactured in a Pilot Plant designed to manufacture and package pilot batches. The batch was manufactured using the following equipment listed in Table 2.

### Manufacturing Process

The batch was manufactured and sampled using an experimental batch record. The following process was detailed in the experimental study plan:

- Measure and blend the alcohol and purified water in a stainless steel container to make the granulation solvent.
- Reserve about 0.75 L of the granulation solvent for rinsing the container and the transfer line.
- Add vitamin E to the container and dissolve in the granulation solvent.
- Rinse the vitamin E container with 150 mL of the reserved granulation solvent from Step 2 and add to the container.
- Add EE to the container and dissolve in the granulation solvent.
- Rinse the EE container with the povidone and add to the container. Continue mixing until a clear solution is formed.

**Table 1**
**37.5-kg Scale, 0.103% w/w EE Triturate Batch Formula**

| Component | Function | Specification | % w/w | Quantity / Batch (kg) |
|---|---|---|---|---|
| Ethinyl estradiol | API | 10000548 | 0.103% | 0.03863 |
| Lactose monohydrate | Diluent | 001A071 | 99.25% | 37.22 |
| Vitamin E | Anti-oxidant | RM-10021 | 0.40% | 0.1500 |
| Povidone (Plasdone K29/32) | Binder | 343A003 | 0.25% | 0.09375 |
| Total (solids) | | | **100%** | **37.50** |
| Purified water | Solvent | 000A179 | --- | 0.4995 |
| Alcohol**Error! Reference source not found.** | Solvent | 10000796 | --- | 4.500 |

**Table 2**
**37.5-kg Scale, 0.103% w/w EE triturate Process Equipment**

| Process | Equipment | Model |
|---|---|---|
| Granulation solvent preparation | Solution mixer and vessel | Lightnin' mixer or similar<br>Stainless steel tank |
| Milling (Delumping) | Rotating impeller mill | Quadro Comil 197S fitted with a size 2A032R screen |
| Granulation | V-blender/processor | Patterson Kelley 3 cu ft solids processor |
| Drying | V-blender/processor | Patterson Kelley 3 cu ft solids processor |

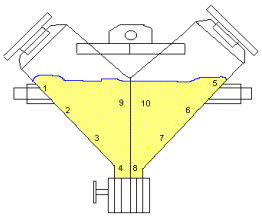
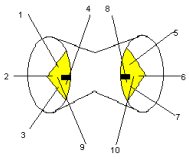
- Pass lactose monohydrate through the rotating impeller mill equipped with a size 2A032R screen operating at 1100 ± 100 rpm and load into the v-blender/processor.
- Transfer the solution from Step 6 into the v-blender/processor using a peristaltic pump (375 ± 25 mL/min), while operating the shell at 24 ± 1 rpm and the intensifier bar (I-bar) at 1500 ± 100 rpm.
- Rinse the solution tank with the 0.6 L of reserved solvent from Step 2 and pump the rinse into the v-blender/processor. Continue mixing at 24 ± 1 rpm with the I-bar at 1500 ± 100 rpm for 10 minutes.
- When the blender stops, remove the connection hose to the pump. Open the v-blender/processor lids and scrape granulation from the lid openings.
- Operate the v-blender/processor at 24 ± 1 rpm with I-bar at 1500 ± 100 rpm for 1 minute.
- Operate the v-blender/processor at 3 ± 1 rpm with I-bar off.
- Turn on the v-blender/processor heat and vacuum (jacket temperature setting = 46°C ± 3°C, target vacuum ≤ 150 mbar).
- Dry the granulation to a target loss on drying of ≤ 0.4%. Once a LOD of 0.4% has been achieved repeat the LOD test as detailed in Table 4.
- Cool the v-blender/processor jacket with the vacuum on for approximately 15 minutes or until a product temperature of ≤ 30°C is achieved, then discharge the dried granulation into suitable containers.
- Mill the granulation through the rotating impeller mill equipped with a size 2A032R screen operating at 1100 ± 100 rpm.
- Transfer the milled triturate into the v-blender/processor and mix the contents for 10 minutes at 24 ± 1 rpm with the I-bar off.
- Sample the blend as detailed in Table 4 before and during discharge into suitable containers.

**Sampling and Testing**

The following tests were performed on 37.5-kg scale, 0.103% w/w EE triturate batch:

- Screen Analysis for 300g sample of lactose monohydrate from the raw material used.
- Loss on drying was performed triplicate. 5g samples were removed from 3 separate locations across the top of the v-blender.
- Ethinyl Estradiol assay. Blend samples were collected in triplicate (80-150mg each) using sample thief and sampling die from the following v-blender locations:

**Table 3**
**37.5-kg Scale, 0.103% w/w EE Triturate Unit-Dose V-blender Sampling Positions**

| Container | Position | Description |
|---|---|---|
| 3 cu. Ft. V-blender     | 1 / 3 | Left front top / bottom |
| | 2 / 4 | Left rear top / bottom |
| | 6 / 8 | Right front top / bottom |
| | 5 / 7 | Right rear top / bottom |
| | 9 | Middle front |
| | 10 | Middle rear |

## RESULTS

A 37.5-kg scale batch of Ethinyl Estradiol (EE) triturate 0.103% w/w (Batch Number 538048X) was manufactured. The batch was sampled and tested for loss on drying, particle size distribution, bulk and tapped density and assay for Ethinyl Estradiol.

Loss on drying (LOD) results met the protocol drying target of ≤ 0.4%. The batch was dried until a product temperature of 40ºC was achieved. Loss on drying (LOD) testing was performed at the end-point of drying and repeated in triplicate. The LOD results all met the Actavis protocol drying and point of 0.4%.

**Table 4**
**Particle Size Distribution Results for EE Triturate 0.103% w/w**

| Sieve Size | | Quantity Retained (%w/w) | |
|---|---|---|---|
| US Mesh No. | µm | Lactose | Final Blend |
| Pan | Pan | 4.6 | 13.6 |
| 325 | 45 | 17.8 | 27.1 |
| 200 | 75 | 23.6 | 19.4 |
| 140 | 106 | 34.1 | 20.7 |
| 100 | 150 | 15.9 | 7.2 |
| 80 | 180 | 3.8 | 9.5 |
| 60 | 250 | 0.1 | 2.3 |

Particle size analysis indicated that EE triturate 0.103% w/w had a greater proportion of particles <45 µm than the lactose monohydrate raw material. The particle size distribution of the lactose monohydrate and EE Triturate 0.103% final blend are illustrated in Figure 1. The results indicated that EE triturate 0.103% w/w had a greater proportion of particles <45 µm than lactose monohydrate raw material. The quantity of material retained in the pan during sieve analysis (<45 µm) increased from 5% to 14%.

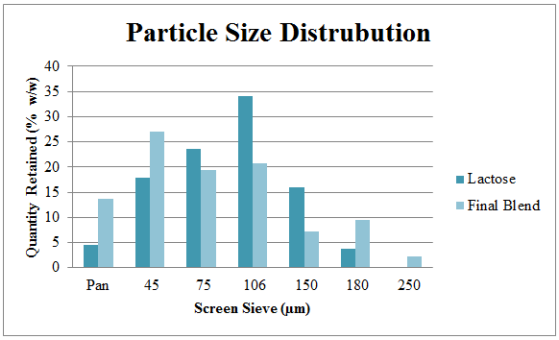



**Figure 1**
**Particle Size Distribution for Lactose Monohydrate Raw Material and EE Triturate 0.103% w/w Final Blend**

Assay testing results for EE indicated that the EE was uniformly dispersed in the granulation. The results indicate that the EE was uniformly dispersed within the triturate and the RSD of 2.3%, met the blend uniformity requirement detailed in FDA draft guidance for stratified blend sampling and testing (< 5.0%). Blend uniformity test was performed for Ethinyl Estradiol Triturate 0.103% batch with a specification limits from 90.0% to 110.0% and %RSD ≤ 5.0%. Average value obtained is within the specification limits (90.0% to 110.0%) and RSD% value is below ≤ 5.0%. The assay results for EE triturate 0.103% w/w are presented in Table 5.

**Table 5**
**Assay Results for EE Triturate 0.103% w/w**

| Results | | |
|---|---|---|
| **Sample #** | **Position Description** | **EE** |
| 1 | Left Front Top (LFT) | 105.6% |
| 2 | Left Rear Top (LRT) | 109.4% |
| 3 | Left Front Bottom (LFB) | 110.6% |
| 4 | Left Rear Bottom (LRB) | 103.3% |
| 5 | Right Rear Top (RRT) | 110.0% |
| 6 | Right Front Top (RFT) | 105.6% |
| 7 | Right Rear Bottom (RRB) | 104.7% |
| 8 | Right Front Bottom (RFB) | 106.8% |
| 9 | Middle Front (MF) | 107.5% |
| 10 | Middle Rear (MR) | 105.2% |
| Average: | | 106.9% |
| Minimum: | | 103.3% |
| Maximum: | | 110.6% |
| % RSD | | 2.3% |

## CONCLUSION

A 37.5-kg scale batch of ethinyl estradiol (EE) triturate 0.103% w/w (Batch Number 538048X) was manufactured at Actavis Fajardo satisfactorily. A new formulation was created and a batch was manufactured using this new formulation. Test required during the manufacturing of the lots were performed satisfactorily. Loss on drying results met the Actavis protocol drying target of ≤ 0.4%. Particle size analysis indicated that EE triturate 0.103% w/w had a greater proportion of particles < 45µm than the lactose monohydrate raw material. Assay testing results for EE indicated that active was uniformly dispersed in the granulation. Actavis Protocol and Batch record were executed satisfactorily without deviations. Therefore, one of the proposed solutions for the improvement of the variability in the content uniformity test for the formulation tablets WC3016-21C, WC3016-20C and WC3026-5C was completed and the results were the expected.

The manufactured lot will be used to evaluate effect of Ethinyl Estradiol Triturate 0.103% w/w instead of a 0.206% w/w formulation and blend time increase from 15 to 20 minutes on the IPCU (in-process content uniformity) of the following tablet formulations: NA (Norethindrone Acetate) 1 mg and EE (Ethinyl Estradiol) 10 µg (WC3016-21C), EE 10 (WC3016-20C) and NE (Norethindrone) 0.8 mg / EE 25 mcg (WC3026-5C) This study plan will be applicable to the manufacturing of two pilot scale batches of WC3016-21C, two of WC3016-20C and two of WC3026-5C containing EE triturate 0.103%. A separate study plan will be generated to provide the manufacturing instructions, sampling, testing and cleaning plan for pilot-scale (36 kg size) batches of WC3016-21C, WC3016-20C, and WC3026-5C tablets. The resulting tablets will be evaluated for quality attributes including blend uniformity test.

## REFERENCES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