

MICRONIZATION AND DISSOLUTION ENHANCEMENT OF NORETHINDRONE

Kailash Bansal*, Pankaj Pant, P. Rama Therdana Rao, Kumud Padhee, Ajit Sathapathy
and Prithipal Singh Kochhar

Formulation & Development department, Jagsonpal Pharmaceuticals, Plot No. 14-16, 55-57, Sec-5,
SIDCUL, Rudrapur, Uttarakhand, India.

*Corresponding Author: kls.bansal@gmail.com

ABSTRACT

Norethindrone (or norethisterone) is a molecule used in some combined oral contraceptive pills and in some progestogen only pills. In this study, Norethindrone Oral Tablet 0.35 mg is being developed for use in therapy of premenstrual syndrome, painful periods, abnormal heavy bleeding, irregular periods, or to postpone a period. Micronization is a process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by use of attrition methods (e.g. Fluid energy or Air Jet Mill). Micronization technique is a economic and effective technique for improving the dissolution of Norethindrone, a poorly soluble drug. Particle size reduction was achieved by Air Jet Milling. Micronization of Norethindrone enhanced its dissolution rate to a significant extent when compared with unmiconized material. Norethindrone Oral Tablets commercially available in Indian market dissolved similarly to tablets prepared with unmiconized Norethindrone, while those prepared with micronized Norethindrone showed higher dissolution rate. The experimental findings suggest that micronization technique can be used for the preparation of rapidly dissolving formulations of Norethindrone, and could potentially lead to improvement in the *in-vivo* bioavailability of oral Norethindrone Tablets.

Keywords: *in-vitro* dissolution, *in-vivo* bioavailability, micronization, Norethindrone.

INTRODUCTION

The dissolution rate is one of the limiting factors for attaining good bioavailability. In pharmaceutical products, the particle size of drugs and components may affect the processing and bioavailability¹⁻⁴. A number of compounds that are investigated in pharmaceutical field have low aqueous solubility and fall in class II and IV of the biopharmaceutical classification system. Particle size reduction, leading to increase in surface area, is a very promising tool to increase dissolution rate and, in turn, the

bioavailability of poorly water soluble compounds⁵⁻⁷. According to the Noyes-Whitney equation, the rate of dissolution (dC/dt) depends on the effective surface area (A) of the drug particles⁸. The present work attempted to improve dissolution profile of Norethindrone from the tablet dosage form by using micronization techniques to decrease particle size. Two different formulations of Norethindrone, both micronized and unmiconized were prepared and the dissolution profile was compared with Reference product procured from Indian market.

MATERIALS AND METHODS

Norethindrone (Indo Phyto Chemicals Pvt. Ltd, India), Lactose monohydrate (Friesland Foods, Holland), Maize starch (Roquett, France), Crospovidone (ISP Technologies), Povidone (ISP Technologies), Talc (Luzenac Italy), Magnesium stearate (Ferro Corporation, USA). All the chemicals were of commercial purity grade.

Micronization

Milling of Norethindrone was done by using Air Jet Mill (Promas Engineering, Mumbai). Milling performed at primary pressure 4.9 kg/cm², secondary pressure 4.3 kg/cm² and Screw feeder speed 7 rpm.

Particle Size Analysis

Particle size analysis of micronised and unmicronised Norethindrone was done using Malvern Mastersizer 2000 (Sciocco 2000) that is based on laser diffraction technique - a non-destructive, non-intrusive method, which can be used for size determination of either dry or wet samples.

Formulation of Norethindrone Tablets

Norethindrone drug of two different particle size distributions was used in two batches F1 (with un micronized Norethindrone) and F2 (with micronized Norethindrone) prepared using Lactose monohydrate, Maize starch as diluent, Povidone as binder, Crospovidone as disintegrant, Talc as glidant and Magnesium stearate as lubricant in the pre-optimized quantities to make a 100 mg tablet containing 0.35 mg Norethindrone (Table 2). Norethindrone, Lactose Monohydrate, Maize Starch and Crospovidone were passed through sieve #40. Dry mixing was done in rapid mixer granulator (Ganson, Mumbai) for 10 minutes keeping impeller at slow speed. Povidone binder solution was added over a time of 2 minutes at impeller slow speed. Kneading (Wet mixing) was done at impeller fast and chopper slow speed for 2 minutes. Drying of granules was done using a table top fluidized bed dryer (Retsch GmbH, Germany) at 55±5°C inlet temperature for 60 minutes. Dried granules were milled in Multimill (Ganson, Mumbai) at Slow Speed Knife Forward using 1.5 mm screen and blending was done in Octagonal blender (Ganson, Mumbai) for 10 minutes with addition of Talc, then after add magnesium stearate into

Octagonal blender (Ganson, Mumbai) again blend for 5 minutes. The granules of formulations (F1 and F2) were tested for flow properties such as bulk density, tap density, Hausner ratio, compressibility index and angle of repose (Table 3). Compression of blend was done on 12-station single rotary compression machine (Labpress model by CIP, Ahmedabad) using 6.00 mm diameter, Round flat faced beveled edged punches. Compressed tablets of formulations F1 and F2 were subjected to evaluation viz. average weight, thickness, hardness, friability and disintegration time (Table 4).

Drug Content

The content of Norethindrone in the formulated tablets was determined on HPLC as per Test 1 and Test 2 of monograph of Norethindrone Tablet described by USP 33, page 3105. Content of Norethindrone was calculated on the basis of declared content of Norethindrone standard using the area of principal peak by single-point standardization technique.

Tolerances (as per USP Dissolution Method, Test 1): Not less than 80% (Q) of the labeled amount of C₂₀H₂₆O₂ is dissolved in 30 minutes. Tolerances (as per USP Dissolution Method, Test 1): Not less than 80% (Q) of the labeled amount of C₂₀H₂₆O₂ is dissolved in 45 minutes.

Dissolution Study

In vitro dissolution studies was carried out using USP 33 method which includes Type II Paddle (model TDT-08L, Electrolab, India) at 37° ± 0.5°C and 75 rpm using 500ml deaerated media containing 0.09% sodium lauryl sulfate in 0.1 N hydrochloric acid. Samples were withdrawn after 30 and 45 minutes and subjected to HPLC analysis. The percent drug dissolved was calculated from the peak area.

RESULTS AND DISCUSSION

Particle size analysis (Table 1) of unmicronized and micronized Norethindrone depicted that percentage of fines was found to be highest with Air Jet Mill micronized Norethindrone. The appropriate diluents and binder was included in the formulation of wet granulation as shown in Table 2. The granules made using output of Unmicronized and micronized, i.e., F1 and F2 exhibited flow properties in a narrow range such as bulk density, tap density, Hausner ratio,

compressibility index and Angle of repose (Table 3).

Two formulations F1 and F2 exhibited nearly alike physical properties such as average weight, thickness, hardness, friability and disintegration time (Table No. 4). However, there was significant difference in percent dissolution observed at 15, 30 and 45 minutes (Table 5). Formulation F1 and F2 Dissolution compared with marketed product as per Test 1 and Test 2 of Norethindrone Tablet monograph described by USP 33, page 3105.

The comparative dissolution profile study of formulations F1, F2 and Marketed product of Norethindrone (Figure 3) exhibit that percentage Norethindrone released from Marketed product was similar to F1 containing Unmicronized Norethindrone, whereas formulation F2 containing micronized Norethindrone provide higher and faster dissolution. Formulation F2 passed the Tolerance limit of Test 1 and Test 2 of monograph of Norethindrone Tablet as per USP 33. This proves the superiority of micronized form of Norethindrone.

CONCLUSION

The finding that unmicronized Norethindrone showed significant lower dissolution in 45 minutes and this led an impetus to search for an appropriate formulation that can give better dissolution profile. Mechanical methods of micronization are simple, efficient and cost effective way of achieving particle size reduction. The formulation developed using micronized Norethindrone produced a higher rate of dissolution than the formulation made with unmicronized Norethindrone. Achievement of increase in dissolution rate to such an extent by micronization suggests that such a formulation may offer an advantage in terms of bioavailability and optimum therapeutic effect. However, it would be necessary to conduct more studies like bioequivalence evaluation with formulations available in United States of America to assess its therapeutic efficacy.

ACKNOWLEDGMENTS

The authors are thankful to M/s Indo Phyto Chemicals Pvt Ltd, Nainital for providing generous gift sample of Norethindrone.

Table 1: Particle size analysis of Norethindrone (before and after micronization)

Particle Size	Unmicronized Norethindrone	Micronized Norethindrone
d (0.1)	53.285 μ	0.839 μ
d (0.5)	85.660 μ	2.843 μ
d (0.9)	138.195 μ	7.905 μ

Table 2: Batch formula

S. No.	Ingredients	Qty./Unit (mg)
1.	Norethindrone	0.35
2.	Lactose monohydrate	79.65
3.	Maize Starch	15.00
3.	Crospovidone	1.00
4.	Povidone	1.00
5.	Purified Water	q.s.
5.	Talc	2.00
7.	Magnesium Stearate	1.00
Total weight		100.00

Table 3: Evaluations of flow properties granules

S. No.	Properties	F1	F2
1.	Bulk density(gm/ml)	0.57	0.52
2.	Tapped density(gm/ml)	0.73	0.68
3.	Compressibility Index (%)	21.92	23.52
4.	Hausner Ratio	1.28	1.30
5.	Angle of Repose	25.0	24.3

Table 4: Tablet quality parameters for formulations F1 to F2

S. No.	Parameter	F1	F2
1.	Average Weight (mg)	100.30	100.10
2.	Thickness (mm)	3.29 \pm 0.20	3.25 \pm 0.20
3.	Diameter (mm)	6.00 \pm 0.05	6.00 \pm 0.02
4.	Hardness (N)	50 \pm 5	50 \pm 7
5.	Friability (%w/w)	0.18	0.15
6.	Disintegration Time (minutes)	3-5	3-5
7.	Drug Content (%)	99.9 \pm 0.02	100.6 \pm 0.03

Table 5: Comparative of dissolution profile of formulations and Reference product

Time (minutes)	Cumulative Percent Drug Release (%)		
	Marketed Product	Formulation Code	
		F1	F2
30	63 \pm 2.3	65 \pm 2.8	85 \pm 2.5
45	70 \pm 2.1	69 \pm 2.4	90 \pm 2.9

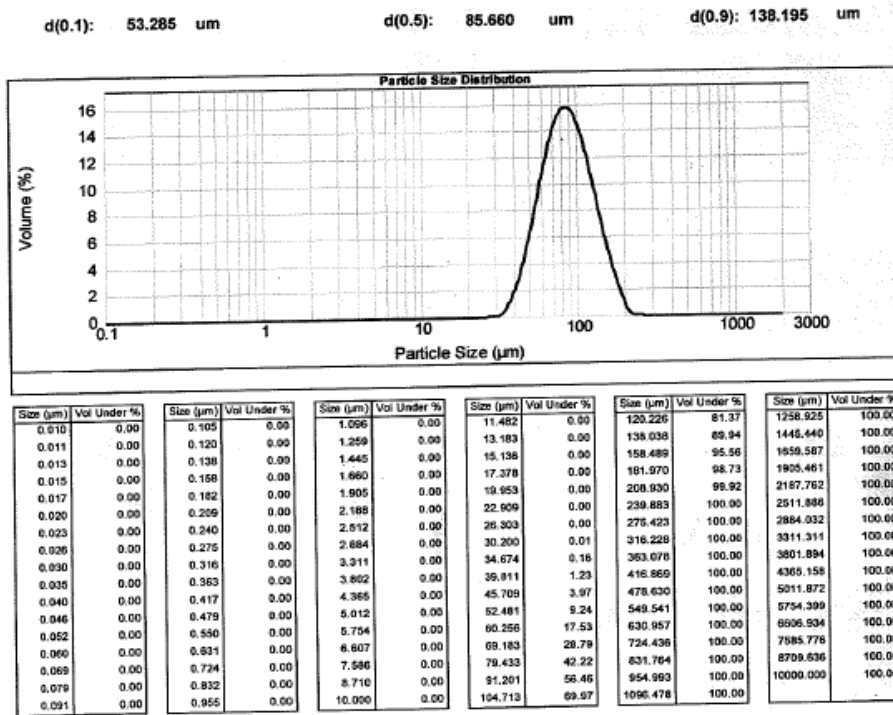


Fig. 1: Particle size distribution of Norethindrone (Unmicronized)

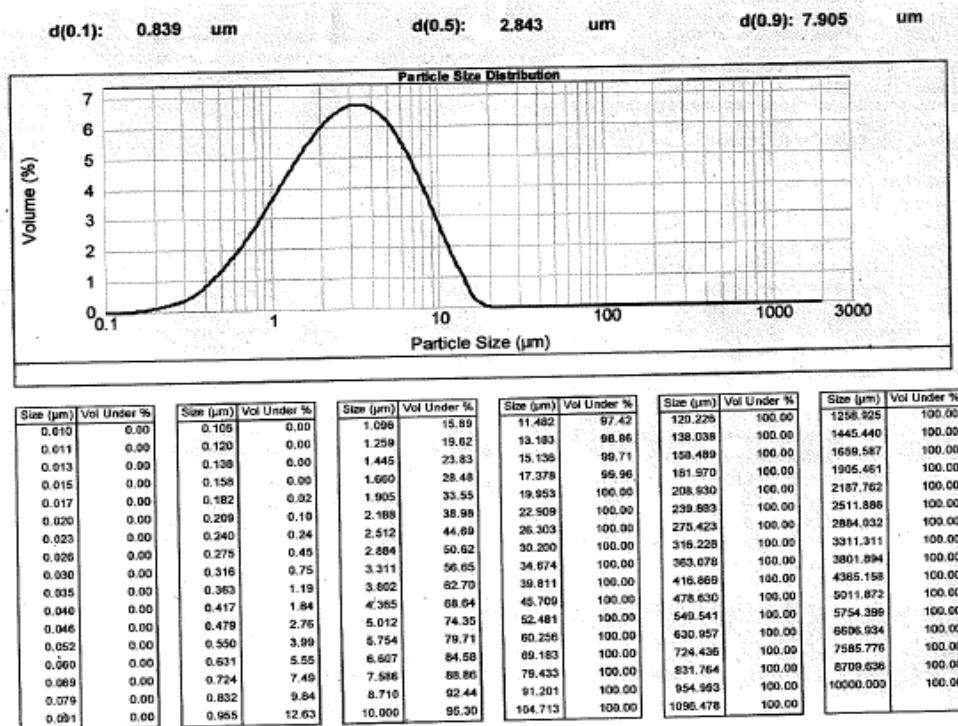


Fig. 2: Particle size distribution of Norethindrone (Micronized)

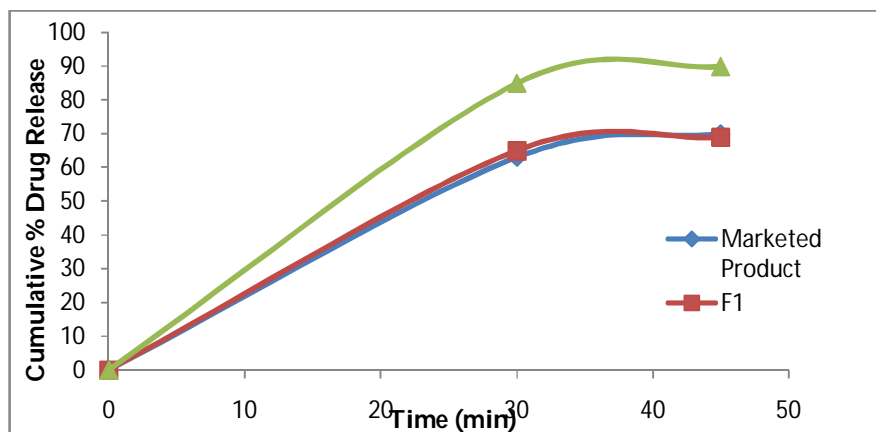


Fig. 3: Comparison of dissolution profile of formulations and Reference product

REFERENCES

1. Jounela AJ, Pentikainen PJ and Sothmann A. Effect of particle size on the bioavailability of digoxin. *European Journal of Clinical Pharmacology*. 1975;8:365-70.
2. Jinno JI et. al. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. *Journal of Controlled Release*. 2006;111(1-2):56-64.
3. Vrana A and Andrysek T. The effect of particle size on bioavailability in cyclosporine preparations based on submicron dispersions. *Biomed Papers*. 2001;145(2):9-15.
4. Nishihata T, Ishizaka M, Yokohama S, Martino AC and Gordon RE. Effects of Particle Size of Bulk Drug and food on the Bioavailability of U-78875 in Dogs. *Drug Development and Industrial Pharmacy*. 1993;19(20):2679-2698.
5. Chaumeil JC. Micronization: A method of improving the bioavailability of poorly soluble drugs. *Methods and Findings*. 1998;20(3):211.
6. Katdare AV, Oddoye DD and Bavitz JF. Effect of micronization of Norfloxacin on Tablet Properties. *Drug development and industrial pharmacy*. 1987;13(2):281-288.
7. Reverchon E, Porta GD, Spada A and Antonacci A. Griseofulvin micronization and dissolution rate improvement by supercritical assisted atomization. *Journal of Pharmacy and Pharmacology*. 2004;56(11):1379-1387.
8. Brahmankar DM and Jaiswal SB. *Biopharmaceutics and Pharmacokinetics- A treatise*. New Delhi: Vallabh Prakashan; 1995.