Research Article

DISSOLUTION ENHANCEMENT OF LEVONORGESTREL BY MICRONIZATION: COMPARISON WITH COMMERCIAL PRODUCT

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ABSTRACT

Levonorgestrel is a synthetic progestogen. In this study Levonorgestrel Tablet 1.5 mg is being developed for prevention of pregnancy, following unprotected intercourse or a known or suspected contraceptive failure. Micronization is a process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by use of attrition methods (Fluid energy or Air Jet Mill). Micronization is a technique for improving the dissolution of poorly soluble drugs. Particle size reduction was realized by Air Jet Milling. Micronization of Micronization of Levonorgestrel enhanced its dissolution rate in 0.1N HCl with 0.1% Sodium lauryl sulphate compared to nonmicronized material. Levonorgestrel drug products commercially available in USA, German and French markets dissolved similarly to micronized Levonorgestrel, but significantly higher than the nonmicronized Levonorgestrel. The results suggest that micronization technique for the preparation of rapidly dissolving formulations of Levonorgestrel, and could potentially lead to improvement in the bioavailability of oral Levonorgestrel product.

Keywords: Levonorgestrel, Dissolution, Micronization, Air Jet Mill.

INTRODUCTION

In pharmaceutical products, the particle size of drugs and components may affect the processing and bioavailability[1-4]. 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. The dissolution rate is one of the limiting factors for attaining good bioavailability. Particle size reduction, leading to increased surface area, is a very promising approach to enhance dissolution rate and, thus, the bioavailability of poorly water- soluble compounds[5-7]. According to the Noyes- Whitney equation, the rate of dissolution (dC/dt) depends on the effective surface area (A) of the drug particles[8]. The present work attempted to address the problem of slower dissolution of Levonorgestrel from the tablet dosage form by employing micronization techniques as a means of decreasing particle size. Two different formulations of Levonorgestrel, both micronized and nonmicronized were prepared and the dissolution profile was compared with Reference product (Escapelle, Mfg By: Gedeon Richter Ltd., Budapest, Hungary)

MATERIALS AND METHODS

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

Micronization

Milling of Levonorgestrel was done by using Air Jet Mill (Promas Engineering, Mumbai). Milling performed at primary pressure 4.2 kg/cm^2, secondary pressure 4.0 kg/cm^2 and Screw feeder speed 5 rpm.

Particle Size Analysis

Particle size analysis of unmilled and milled Levonorgestrel was done using Malvern Mastersizer 2000 (Scirocco 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 Levonorgestrel tablets

Levonorgestrel of two different particle size distributions was used in two batches F1 (with nonmicronized Levonorgestrel) and F2 (with micronized Levonorgestrel) prepared using Lactose monohydrate, maize starch as diluent, Potato Starch as binder as well as disintegrant and Talc as glidant, magnesium stearate as lubricant in the pre-optimized quantities to make a 200 mg tablet containing 1.5 mg Levonorgestrel (Table 2). Lactose, maize starch and Lactose Monohydrate were passed through sieve #40. Dry mixing was done in rapid mixer granulator (Ganson, Mumbai) for 10 minutes keeping impeller at slow speed. Potato starch paste binder was added over a time of 2 minutes at impellor 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 50^{0}C inlet temperature for 20 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 maize starch and 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 (CIP, Ahmadabad) using 8.00 mm Round flat beveled edged punches. Compressed tablets of formulations F1 and F2 were subjected evaluation viz. average weight, thickness, hardness, friability and disintegration time (Tablet 4).

Drug Content

The content of Levonorgestrel in the formulated tablets was determined on HPLC. Content of Levonorgestrel was calculated on the basis of declared content of Levonorgestrel standard using the area of principal peak by single-point standardization technique.

Dissolution Study

In vitro dissolution studies was carried out using USP Type II Paddle (model TDT-08L, Electrolab, India) at 37°±0.5°C and 75 rpm using 1000ml 0.1N HCl with 0.1% SLS. Samples were withdrawn after 10,20,30,45,60 and 90 minutes and subjected to HPLC analysis by injecting 50 µl of blank, standard solution (five injections), and sample solution. The percent drug dissolved was calculated from the peak area.

RESULTS AND DISCUSSION

Particle size analysis (Table 1) of nonmicronized and micronized Levonorgestrel depicted that percentage of fines was found to be highest with Air Jet Mill micronized Levonorgestrel. The appropriate diluents and binder was included in the formulation of wet granulation as shown in Table 2. The granules made using output of Nonmicronized 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 10, 20, 30, 45, 60 & 90 minutes (Table 5). Formulation F1 and F2 Dissolution compared with Reference product (Escapelle). The dissolution profile study of formulations F1, F2 and Reference product of Levonorgestrel (Figure 3) exhibit that percentage Levonorgestrel released from Reference product was very dissimilar to F1 containing Nonmicronized Levonorgestrel, whereas formulation F2 containing micronized Levonorgestrel provide Similar dissolution Profile.

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

Particle Size	Nonmicronized Levonorgestrel	Micronized Levonorgestrel
d (0.1)	2.491µ	0.859 µ
d (0.5)	13.891 µ	2.275 µ
d (0.9)	54.680 µ	5.497 µ

Table 2: Unit batch formula

S. No.	Ingredients	Qty./Unit (mg)
1.	Levonorgestrel	1.50
2.	Lactose monohydrate	160.50
3.	Maize Starch	29.00
4.	Potato Starch	1.00
5.	Purified Water	q.s
6.	Maize Starch	5.00
7.	Talc	1.00
8.	Magnesium Stearate	2.00
	Total weight	**200.00**

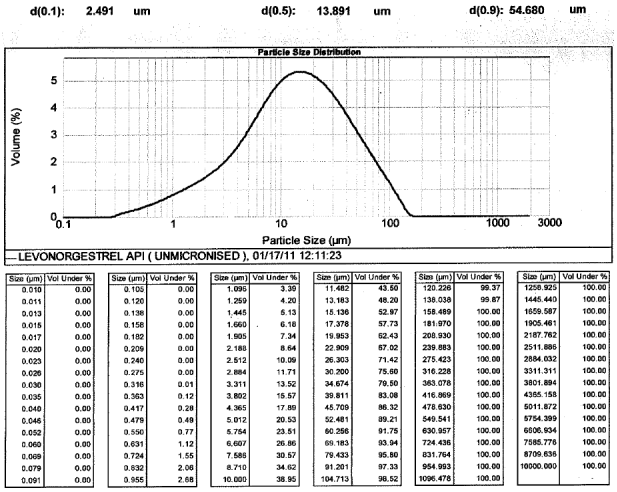

Figure 2: Particle size distribution of Levonorgestrel (Nonmicronized)

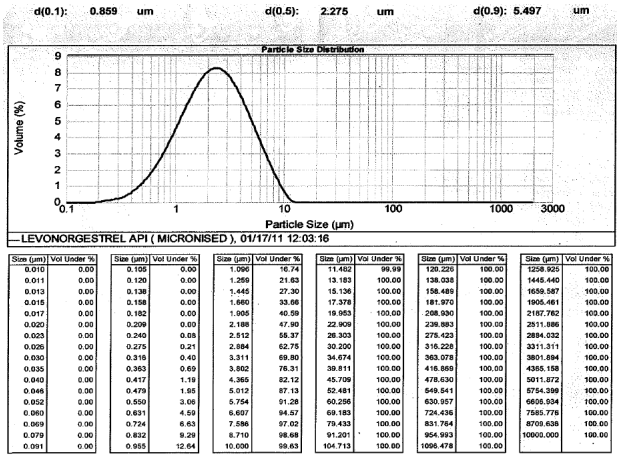

Figure 3: Particle size distribution of Levonorgestrel (Micronized)

Table 3: Evaluations of flow properties granules

Properties	F1	F2
Bulk density(gm/ml)	0.54±0.03	0.53±0.04
Tapped density(gm/ml)	0.69±0.02	0.68±0.04
Compressibility Index (%)	21.65±1.25	24.83±0.98
Hausners Ratio	1.27±0.11	1.33±0.20
Angle of Repose	26.0±0.03	27.5±0.03

Table 4: Tablet quality parameters for formulations F1 to F2.

Parameter	F1	F2
Average Weight (mg)	200.08	200.00
Thickness (mm)	2.98± 0.20	3.00± 0.20
Diameter (mm)	8.03 ± 0.15	8.04 ± 0.12
Hardness (N)	55±5	55±6
Friability (%w/w)	0.05	0.04
Disintegration Time (Sec)	35	30
Drug Content (%)	100.1±0.02	99.9±0.03

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

Time (Minutes)	Cumulative Percent Drug Release		
	Reference	F1	F2
10	56±2.3	15±2.5	55±2.4
20	72±2.2	21±2.1	73±2.5
30	81±2.4	25±2.3	83±2.2
45	89±2.1	30±2.8	90±2.6
60	94±2.2	33±2.4	93±2.8
90	100±2.7	38±2.5	100±2.4

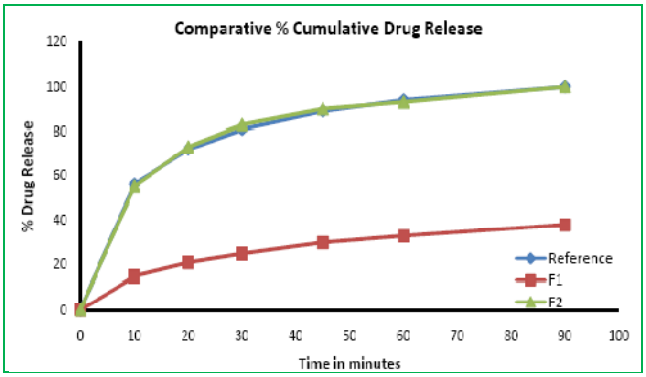

Figure 3: Comparison of dissolution profile of formulations and Reference product

CONCLUSION

The finding that Nonmicronized Levonorgestrel yields less than 40% dissolution in first 30 minutes provided 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 Levonorgestrel produced a higher rate of dissolution than the formulation made with nonmicronized Levonorgestrel. 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.

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