Original Article

Dissolution enhancement of Tibolone by micronization technique

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ABSTRACT

Objectives: Tibolone is an estrogen-like compound used for the treatment of the symptoms associated with the menopausal transition and also for the treatment of osteoporosis. The aim of this study was to evaluate impact of micronization on the dissolution profile so as to improve the release rate of Tibolone drug from tablet dosage form.
Materials and Methods: Tibolone oral tablet 2.5 mg is formulated using micronized and unmicronized drug in a preoptimized formula and was evaluated for drug content, dissolution, hardness, thickness, and disintegration time. Particle size reduction of Tibolone drug was achieved by Air Jet Milling and evaluated by using Malvern mastersizer instrument.
Results: Micronization of Tibolone enhanced its dissolution rate to a significant extent when compared with unmicronized material. The dissolution profile of formulation with micronized Tibolone was similar to that of European market product (Livial tablet 2.5 mg).
Conclusion: Micronization technique has a significant impact on the dissolution of Tibolone. The experimental findings suggest that micronization can be used for the preparation of rapidly dissolving formulations of Tibolone, and could potentially lead to improvement in the *in-vivo* bioavailability of Tibolone oral tablets.

Key words: Air jet mill, *in-vitro* dissolution, *in-vivo* bioavailability, micronization, Tibolone

INTRODUCTION

The dissolution rate is one of the important factors for attaining good bioavailability. In pharmaceutical products, the particle size of drugs and components may affect the processing and bioavailability.[1-4] A number of compounds 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 technique to increase dissolution rate and, in turn, the bioavailability of poorly water-soluble and steroidal compounds.[5-7] According to the Noyes–Whitney equation, the rate of dissolution (dC/dt) depends on the effective surface area (A) of the particles of the active pharmaceutical ingredient.[8] The present study aimed to improve dissolution profile of Tibolone from the tablet dosage form by using micronization techniques to reduce particle size. Two different formulations of Tibolone containing micronized and unmicronized drug were prepared and the dissolution profile was compared with reference product procured from European market.

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MATERIALS AND METHODS

Tibolone (Symbiotica, Malaysia), lactose monohydrate (DMV Fonterra Excipients GmbH, Germany), starch 1500 (Colorcon, India), potato starch (Roquette, France), magnesium stearate (Ferro Corporation, USA). All the chemicals were of commercial purity grade.

Micronization

Milling of Tibolone was done by using Air Jet Mill (Promas Engineering, Mumbai). Milling

performed at primary pressure 4.5-5.0 kg/cm^2, secondary pressure 4.0-4.5 kg/cm^2, and screw feeder speed 6-7 rpm.

Particle size analysis

Particle size analysis of micronised and unmicronised Tibolone was done using Malvern Mastersizer 2000 (Scirocco 2000) that is based on laser diffraction technique – a nondestructive, nonintrusive method, which can be used for size determination of either dry or wet samples.

Formulation of Tibolone tablets

Tibolone drug of two different particle size distributions was used in two batches F1 (with unmicronized Tibolone, Figure 1) and F2 (with micronized Tibolone, Figure 2) prepared using lactose monohydrate, starch 1500 as diluent, starch paste as binder, and magnesium stearate as lubricant in the preoptimized quantities to make a 100 mg tablet containing 2.5 mg Tibolone [Table 1].

Lactose monohydrate and starch 1500 were sifted through sieve #40. Dry mixing was done in rapid mixer granulator (Ganson, Mumbai) for 10 minutes keeping impeller at slow speed. Starch paste slurry was added over a time of 2 minutes 40 seconds at impeller slow speed. Kneading (Wet mixing) was done at impeller fast and chopper slow speed for 1 minute. Drying of granules was done using a table top fluidized bed dryer (Retsch GmbH, Germany) at 55°C ± 5°C inlet temperature for 60 minutes. Dried granules were milled in Multimill (Ganson, Mumbai) at Slow Speed Knife Forward using 1.0 mm screen.

Tibolone and ascorbyl palmitate were mixed thoroughly and then blended with a part of dummy granules. The blended granules were sifted through #30 and sieve was rinsed with remaining dummy granules. Lubrication was performed in octagonal

Table 1: Batch formula

Ingredients	Qty/Unit (mg)
Tibolone	2.50
Lactose monohydrate	86.30
Starch 1500	8.50
Ascorbyl palmitate	0.20
Potato starch	1.50
Purified water	q.s.
Magnesium stearate	1.00
Total weight	100.00

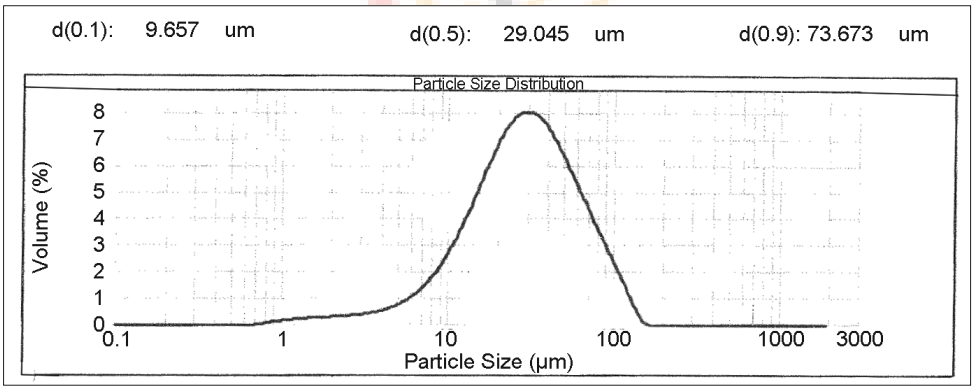

Figure 1: Particle size distribution of Tibolone (unmicronized)

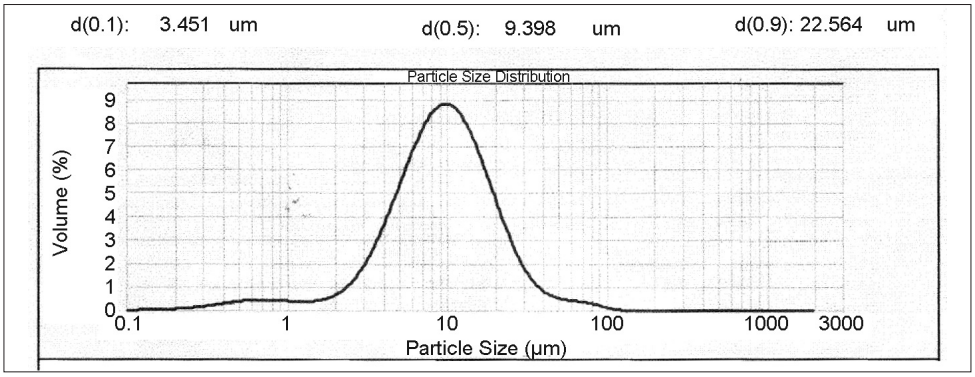

Figure 2: Particle size distribution of Tibolone (micronized)

blender (Ganson, Mumbai) for 5 minutes with addition of magnesium stearate. 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 2]. 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, namely, average weight, thickness, hardness, friability, and disintegration time [Table 3].

Drug content

The content of Tibolone in the formulated tablets was determined on HPLC as per In-House method, as given below:

Column : ZORBAX ODS250 × 4.6
Column temperature : 40°C
Flow rate : 1.0 ml/minute
Mobile phase : Methanol: Water (80:20)
Injection volume : 10 µL
Detector wavelength : 205 nm
Run time : 8 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°C ± 0.5°C and 50 rpm using 500 ml deaerated media containing 0.25% sodium lauryl sulfate (SLS) in purified water. Samples were withdrawn after 5, 10, 15, 20, 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 4] of unmicronized and micronized Tibolone depicted that percentage of fines was found to be highest with micronization using Air Jet Mill.

The appropriate diluents and binder was included in the formulation of wet granulation as shown in Table 1.

The formulations made using unmicronized (F1) and micronized Tibolone (F2) exhibited flow properties in a narrow range such as bulk density, tap density, Hausner ratio, and compressibility index [Table 2].

The formulations F1 and F2 exhibited nearly alike physical properties such as average weight, thickness, hardness, friability, and disintegration time [Table 3].

However, significant difference was observed in percent dissolution at 5, 10, 15, 30 and 45 minutes [Table 5]. Dissolution of formulations F1 and F2 was compared with European market product. The comparative dissolution profile study of formulations F1, F2 and marketed product of Tibolone [Figure 3] exhibit that percentage drug released from marketed product was similar to that of formulation F2. Formulation F1 showed slow dissolution profile, which indicates the superiority of micronized form of Tibolone.

Table 2: Evaluations of flow properties granules

Properties	F1	F2
Bulk density (g/ml)	0.57	0.59
Tapped density (g/ml)	0.69	0.71
Compressibility index (%)	17.39	16.90
Hausner ratio	1.21	1.20

Table 3: Tablet quality parameters for marketed product and formulations F1 to F2

Parameter	Marketed product	F1	F2
Average weight (mg)	100.20	100.21	100.08
Thickness (mm)	2.60±0.05	3.10±0.05	3.10±0.03
Diameter (mm)	6.00±0.02	6.00±0.04	6.00±0.04
Hardness (*N*)	30±5	40±4	40±5
Friability (%w/w)	0.16	0.11	0.14
Disintegration time (minutes)	1 minute 58 seconds	2 minute 15 seconds	2 minute 07 seconds
Drug content (%)	99.32±0.05	99.75±0.05	100.24±0.06

Table 4: Particle size analysis of Tibolone (before and after micronization)

Particle size	Unmicronized Tibolone	Micronized Tibolone
d (0.1)	9.657 µ	3.451 µ
d (0.5)	29.045 µ	9.398 µ
d (0.9)	73.673 µ	22.564 µ

Table 5: Comparative dissolution profile of formulations and reference product

Cumulative percent drug release (%) (media: 0.25% SLS, purified water, USP II, speed 50 rpm, volume 500 ml)

Time (minutes)	Marketed product	Formulation code	
		F1	F2
05	46±3.8	30±3.3	42±3.6
10	63±1.8	45±2.5	59±2.4
15	70±2.5	57±2.4	68±2.0
30	85±1.2	63±2.6	84±2.3
45	90±1.5	68±2.2	87±2.4

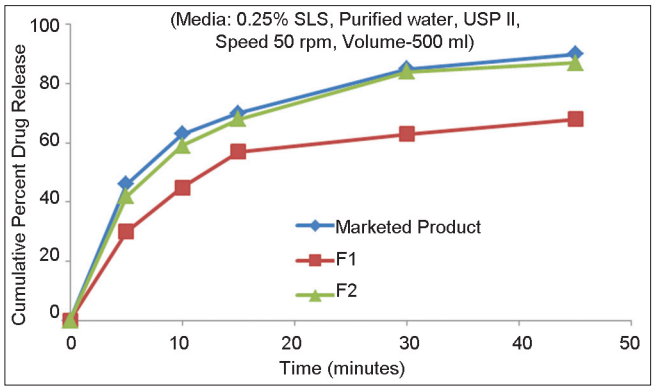

Figure 3: Comparison of dissolution profile of formulations and marketed product

CONCLUSION

The unmicronized form of Tibolone showed significant lower dissolution in 45 minutes, which led an impetus to search for an appropriate formulation that can give better dissolution profile. Mechanical modes of micronization are established simple, efficient, and cost-effective way of achieving particle size reduction. The formulation developed using micronized Tibolone produced a higher rate of dissolution than the formulation made with unmicronized Tibolone. Increase in dissolution rate to such an extent by using micronization technique 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 European market to assess its pharmacokinetic profile and therapeutic efficacy.

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