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RAPID COMMUNICATION

Stability-enhanced solid dispersion formulation of amorphous raloxifene hydrochloride

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Abstract−To develop a stabilized formulation of amorphous raloxifene hydrochloride (RXF), solid dispersion granules (SDG) of amorphous RXF were prepared by fluidized bed granulation with non-pareil beads, compressed and film-coated to produce solid dispersion tablets (SDT). Polymorphic changes in RXF were inhibited by SDG formulation. Drug content, impurity, and dissolution profile of SDT revealed that the SDT meets the acceptance criteria, and the content of RXF was maintained over 95% for 5 months at accelerated conditions of 40 °C and 75% R.H. In comparative dissolution study of reference tablet (Evista®) and SDT, the similarity factor (f_2) provided evidence for similar dissolution profiles between two formulations. Therefore, we suggest the usefulness of SDT for the development of generic pharmaceuticals containing amorphous RXF.

Key words: Raloxifene, Polymorphs, Solid Dispersion, Stability, Dissolution

INTRODUCTION

Raloxifene hydrochloride (RXF) was first approved by the Food and Drug Administration in 1997, as a selective estrogen receptor modulator for the treatment of osteoporosis (Fig. 1). Due to the antiestrogenic and antiandrogenic effects, it is also applied to treat breast cancer, prostate cancer, benign prostate hypertrophy, and fibrocystic disease. It is commercially available under the trade name of Evista® (Eli Lilly), which is one of the blockbuster drugs as a film-coated tablet formulated with the excipients of povidone, polysorbate 80®, anhydrous lactose, etc. [1-5]. Several patents are authorized for crystal form of RXF [OPN; 10-1996-0010634, OPN; 10-1996-0010637], and they will expire on Sep. 15, 2015.

Although the amorphous form of RXF could replace the crystal forms, launching as generic pharmaceuticals has been very limited because of the thermodynamic instability problem. In general, metastable polymorphs are converted to a stable form on storage. Although several studies have been performed for the stabilization of amorphous RXF, e.g. inclusion complexation with hydroxybutenyl-beta-cyclodextrin to prevent crystallization [6], spray drying with polymeric carriers, and conjugation with polyethylene glycol [7], nothing has been available for practical or commercial use.

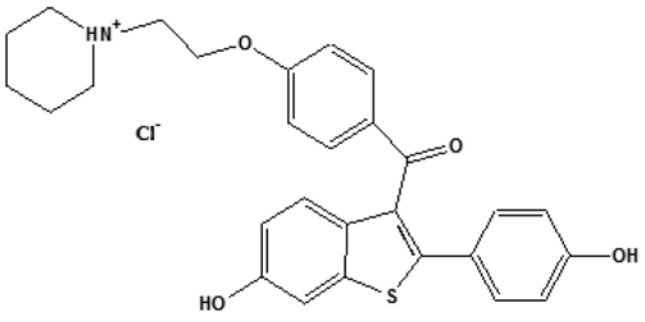

Fig. 1. Chemical structure of raloxifene hydrochloride.

In the present study, solid dispersion granules of amorphous RXF were prepared by fluid-bed granulator, compressed, and further film coated [8]. For the evaluation of the stability of prepared formulations, polymorphic changes, drug content, impurity, and dissolution profile were monitored. In addition, a comparative dissolution study with Evista® was also performed.

EXPERIMENTAL

Amorphous and crystal form of RXF (purity >99%) was purchased from Jiangsu Kangxi Pharmaceutical Co. Ltd. (Jiangsu, China) and Dr. Reddy's Lab. Ltd. (Bollaram, India), respectively. Lactose anhydrous and hydroxypropyl cellulose (HPC) were purchased from DMV International (Netherlands) and Shin Etsu (Japan), respectively. Other chemicals and excipients were of analytical or pharmcopoeial grade and were used as received. Solid dispersion granules (SDG) of RXF were prepared using a fluid-bed granulator (GPCG, Glatt, Germany). Briefly, amorphous RXF and HPC were dissolved in the mixture of ethanol and acetone under continuous stirring with heating at 45 °C. The solution was sprayed through a nozzle onto the fluidized non-pareil beads (mixture of lactose and crospovidone). The operation was performed in the condition of 65-75 °C of inlet air temperature, 30-40% of exhaust air flap, 30-35 °C of outlet temperature, respectively. After mixing SDG with crospovidone and magnesium stearate, the mixtures were compressed, and film coated with hydroxypropyl methylcellulose (HPMC 2910, 4.8/7.2 cps), to prepare solid dispersion tablets (SDT).

Accelerated stability tests were performed at storage conditions of 40 °C and 75% relative humidity (R.H.). Polymorphic changes in raw material and SDG were observed by X-ray diffractometer (XRD; Rigaku D/Max 2500, Japan) using CuKα radiation under 40 kV and 200 mA with 0.02 mm slit [9,10]. Content and impurity

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changes were assayed by HPLC (Waters Alliance, USA) at 280 nm with Capcell Pak C_8 column (4.6×250 mm). Dissolution tests were performed using the paddle apparatus (SR8 Plus, Hanson, USA) under the conditions of 50 rpm at 37±0.5 °C in various media (pH 1.2, pH 4.0, pH 6.8 buffer and water) with and without 0.1% polysorbate 80® for stability specification and comparative dissolution study, respectively. Aliquots were withdrawn at predetermined time intervals and assayed for the amount of dissolved RXF. Dissolution profiles of SDT were plotted versus time and compared with the reference tablet (Evista®) in the point of similarity factor (f_2), calculated by the following equation:

$$f_2=50 \log\{[1+(1/N)(R_t-T_t)^2]^{-0.5}\cdot 100\}$$

where N is the number of time points, R_t and T_t are dissolved amount

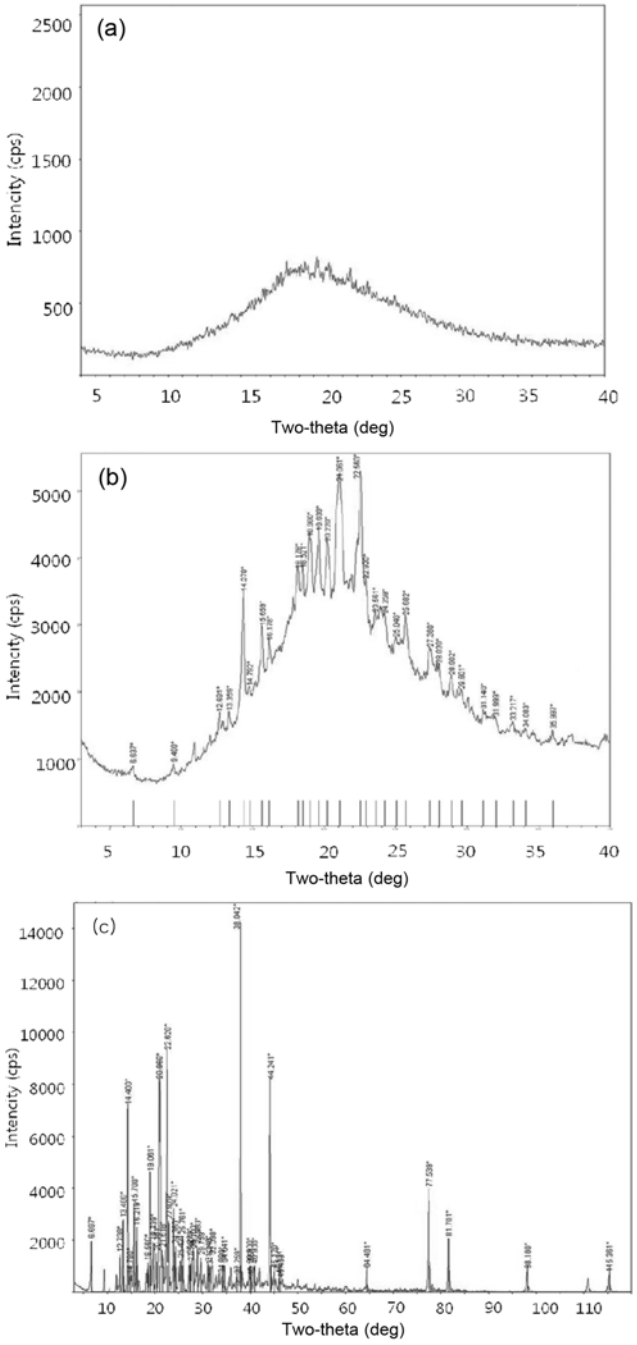

Fig. 2. X-ray diffraction patterns of raloxifene HCl (RXF): (a) amorphous RXF, (b) amorphous RXF after 3 months storage at 40 °C and 75% R.H., (c) crystal form of RXF.

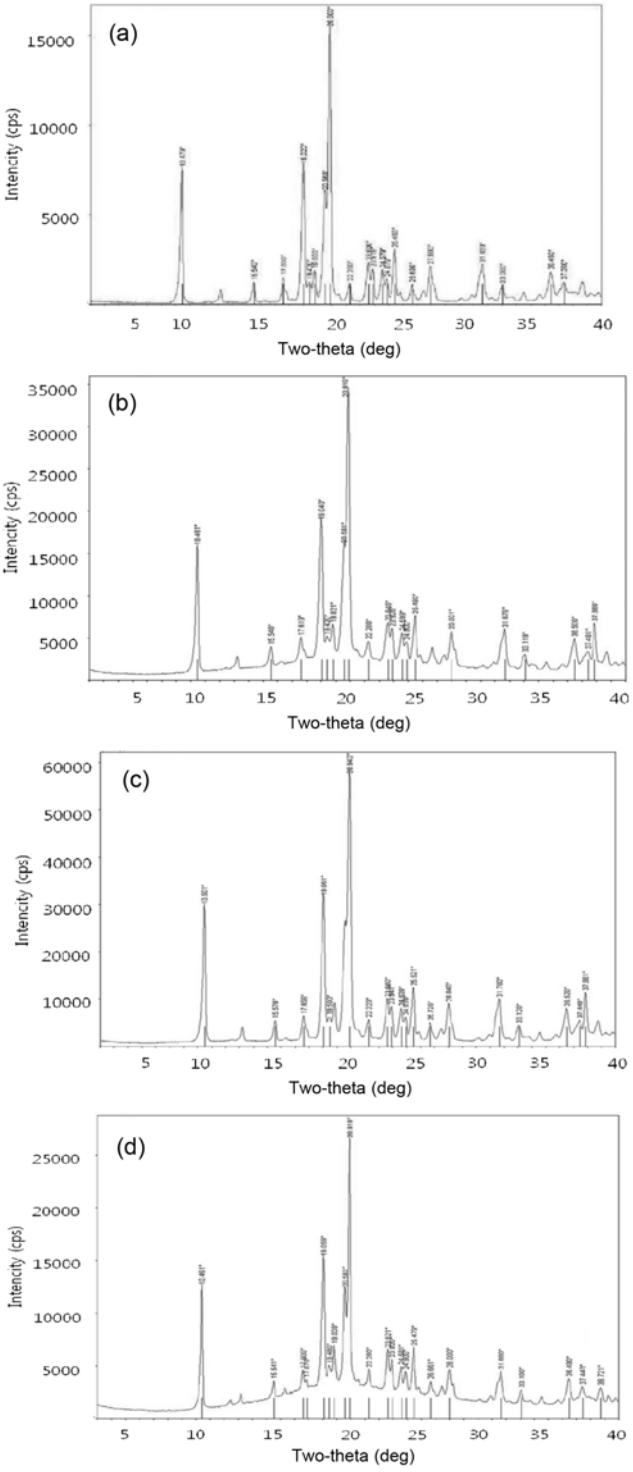

Fig. 3. X-ray diffraction patterns of lactose anhydrous and raloxifene HCl (RXF) SDG. (a) lactose anhydrous, (b) RXF SDG at initial time point, (c) RXF SDG after 6 months storage at 40 °C and 75% R.H., (d) RXF SDG after 14 months storage at room temperature.

of reference and test products at time t, respectively [11]. If f_2 value is greater than 50, it is considered that both products share similar drug release behaviors.

RESULTS AND DISCUSSION

Comparison of XRD pattern of raw material gives a background for physical stability assessment. As shown in Fig. 2(c), crystal RXF has the characteristic diffraction peaks at 2θ=6.697°, 14.400°, 19.061°, 20.060°, 22.620°, and 38.042°, which are not observed in amorphous RXF. However, three months storage of amorphous RXF at accelerated condition brought significant changes in peaks at 2θ=6.637°, 14.318°, 19.039°, and 22.560°, which are comparable to those of crystal form. Therefore, it was evident that polymorphic transformation occurred in the powder state. Meanwhile, as shown in Fig. 3, XRD patterns of RXF-containing SDG were maintained for 6 months at accelerated condition and even after 14 months storage at room temperature. The peaks in initial state SDG (Fig. 3(b)), specifically at 2θ=10.461, 19.059, and 20.919°, are attributed to interference of the excipient. Lactose anhydrous exhibited the typical peaks (Fig. 3(a)), which are same as those of SDG. The absence of diffraction peaks at 2θ=6.697° and 14.400° which are crucial stamps of crystal form is also noticeable. We could conclude that the stability of amorphous RXF was not deteriorated by the dispersion granulation process, but kept for longer period of time on exposure at storage condition. Recently, Jagadish et al. [12] reported that the crystalline nature of RXF was reduced after co-grinding with superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate, using a ball mill. Reduced drug crystallinity was directly related to enhanced dissolution and improved bioavailability of RXF.

Upon storage of RXF-containing SDT at accelerated conditions of 40 °C and 75% R.H., evaluations on drug content, impurity, and dissolution revealed the acceptance to meet requirement of stability specifications (Table 1). The content of RXF was maintained over 95% for 5 months, and the impurities were found to be negligible. Dissolution for 30 min in the medium of polysorbate-containing aqueous solution was about 90% in average, which is much higher than the acceptance criterion of 75% or more. Solid dispersion approach to control the dissolution of poorly water-soluble drug has been demonstrated [13]. Employing povidone and Eudragit as fast- and slow-dissolving polymers in different ratios, solid dispersions of itraconazole were prepared using a twin-screw hot-stage extruder. The combination of the two polymers resulted in a solid dispersion with good dissolution properties and improved physical stability as well. On the other hand, as shown in Fig. 4, comparative dissolution studies between the reference tablet (Evista®) and SDT showed similar profiles. The f_2 values in various dissolution media were in the range of 60 to 90, as listed in Table 2, confirming that the release of RXF from the prepared SDT was similar to that of the marketed tablet. These results clearly indicated the usefulness of SDT for the development of generic pharmaceuticals containing amorphous RXF.

Table 1. Stability specification for solid dispersion tablet (SDT) containing amorphous raloxifene hydrochloride on storage at 40 °C and 75% R.H.

	Spec.	Storage	
		3 Months	5 Months
Drug content (%)	95-105	98.4	97.0
Dissolution (Q, time)[a]	75%, >30 min	87.8-103.1	89.3-101.1
		>30 min	>30 min
Unknown impurity (%)	Not more than 0.3%	0.16	0.14
Total impurity (%)	Not more than 1.0%	0.74	0.67

[a]Polysorbate 80®-containing aqueous medium was used

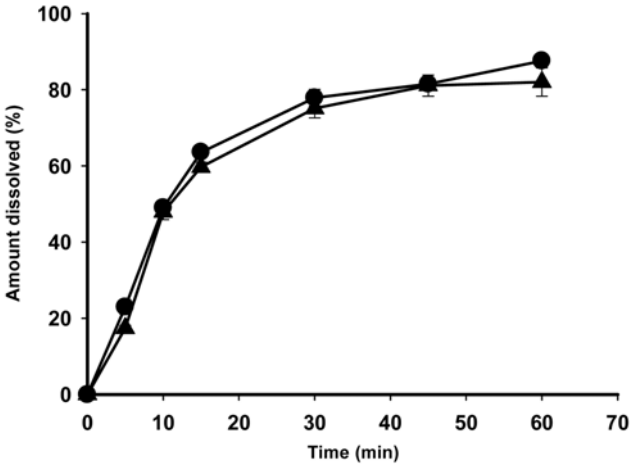

Fig. 4. Dissolution profiles of raloxifene HCl in water: ●; Evista®, ■; SDT. All data are represented as mean±S.D. (n=12).

Table 2. Similarity factors (f_2) for solid dispersion tablet (SDT) versus reference tablet (Evista®) in various dissolution media

	pH 1.2	pH 4.0	pH 6.8	Water
f_2 Value	89.83	61.03	87.01	65.17

CONCLUSION

Stability of amorphous raloxifene hydrochloride was enhanced by solid dispersion formulation using a fluid-bed granulator. The prepared solid dispersion tablet revealed similar dissolution profiles to the reference tablet, suggesting the potential usefulness of SDT for generic product development of amorphous RXF in the future.

ACKNOWLEDGEMENT

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