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Formulation and Characterization of Fast-Dissolving Tablets of Raloxifene Hydrochloride

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ABSTRACT
Fast Dissolving Tablet (FDT) of Raloxifene was prepared by direct-compression method by incorporating super disintegrants like crosscarmellose sodium and sodium starch glycolate. The study was performed by incorporating the super disintegrants in 2 % and 4 % concentration for each and 2 % - 2 % in combination of both super disintegrants. Five formulations having super disintegrants at different concentration levels were prepared to assess their efficiency. Different types of evaluation parameters for tablets were performed. Tablets containing super disintegrants in combination showed excellent in vitro dispersion time and drug release as compared to other formulations

Keywords: Fast dissolving tablets, Direct compression, Raloxifene.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any diseases is one, which immediately attains the desire therapeutic concentration of drug in plasma and maintains it constant for the entire duration of treatment. Drugs are more frequently taken by oral route. Although few drugs taken orally are intended to be dissolved with in the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. Fast dissolving tablet is an important and attractive alternative to liquid dosage form. [1]

Raloxifene hydrochloride (RLH), [6-hydroxy-2-(4-hydroxy phenyl) benzo[*b*]thien-3-yl]-[4-[2-(1-piperinyl) ethoxy]-phenyl] methanone, is an antiosteoporotic. [2] It is a nonsteroidal benzothiophene that is the first selective estrogen receptor modulator to be approved for the prevention and treatment of osteoporosis in postmenopausal women. [3] In the present study, fast dissolving tablets of RLH were formulated by using super disintegrants, which accelerates the disintegration of tablets by virtue of their ability to absorb large amount of water when exposed to aqueous environment. This rapid disintegration of FDTs is due to penetration of saliva into the pores, which lead to the swelling of super disintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablets. This increase bioavailability / rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and esophagus as saliva pass down. [4] The objective of this study was to enhance the efficacy of drug molecule, achieve better compliance, enhance onset of action and provide stable dosage form.

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MATERIALS AND METHODS

Raloxifene was obtained as gift sample from Dr. Reddys Laboratories, Hyderabad. Croscarmellose sodium, sodium starch glycolate, microcrystalline cellulose, aspartame, talc, and magnesium stearate were procured from S. D. fine Chem. Ltd. All other materials were of analytical grade.

Preparation of blends and tablets

Fast dissolving tablets of RLH were prepared by direct compression method as per formulae given in Table 1. The super disintegrants (crosscarmellose sodium, sodium starch glycolate) in varying concentration (2 % and 4 %) and in combination (croscarmellose sodium - Sodium starch glycolate 2-2 %) were used to develop the tablets. All the ingredients were passed through # 60. All the ingredients were mixed in a motor and pestle for 5 min. The mixed blend was compressed into tablets on a Cadmach tablet compression machine to a weight of 200 mg each, with thickness of 2.98±0.15 mm and diameter of 8 mm. The prepared tablets were evaluated for the uniformity of weight, drug content, hardness, friability, dispersion time and disintegration time.

In solid dosage forms the physiochemical properties of blend rules the tablet quality. The mixing step if not properly

optimized can affect the characteristics of blend and thereby tablet produced. The blends were characterized by mass-volume relationship (bulk density, tapped density, Hausner's ratio, compressibility index) and flow properties. [5]

Evaluation of tablets

Prepared tablets were evaluated for hardness (Pfizer hardness tester), friability (Roche friabilator), weight variation, disintegration time, wetting time [6], water absorption ratio [7], *In-vitro* dispersion time [8], drug content and *in vitro* release studies.

The disintegration time was determined using USP tablet disintegration test apparatus (ED 2L, Electrolab, India) using distilled water without disk at room temperature. In weight variation, test twenty tablets were selected at random and average weight was determined using an electronic balance (Shimadzu AX200, Japan). Tablets were weighed individually and compared with average weight. Wetting time was measured by the following method. In this method a piece of tissue paper folded twice in a small culture dish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet is placed on the paper and the time for complete wetting is measured. The wetted tablet is then weighed and the water absorption ratio was calculated by using following equation:

$$R = (W_b - W_a) / W_a$$

Where Wa and Wb are the weights before and after water absorption, respectively. [9-11]

For the determination of *in vitro* dispersion time one tablet was placed in a beaker containing 10 ml of distilled water at 37 ± 0.5ºC and the time required for complete dispersion was determined.

Estimation of Raloxifene

Ten tablets were weighed individually and powdered; an amount equivalent to 50 mg of drug was extracted with 50 ml of methanol and sonicated for 15 min. The volume was made up to 100 ml with 0.1 % polysorbate 80 in distilled water. The mixture was filtered (through 0.45µm), diluted suitably and the drug content was measured at 289 nm using ELICO-167 double beam UV spectrophotometer.

Table 1: Formulation of fast dissolving tablets of Raloxifene

Ingredient	F1	F2	F3	F4	F5
Raloxifene	30	30	30	30	30
Lactose	100	96	100	96	96
Cross carmellose sodium	4	8	---	---	4
Sodium starch glycolate	---	---	4	8	4
Microcrystalline cellulose	50	50	50	50	50
Aspartame	10	10	10	10	10
Talc	4	4	4	4	4
Magnesium stearate	2	2	2	2	2
Total tablet weight (mg)	200	200	200	200	200

Dissolution rate studies

Dissolution rate of Raloxifene from various fast dissolving tablets was studied using USP XXIII six-station dissolution rate test apparatus (DISSO 2000, LABINDIA) with paddle stirrer. The dissolution rate was studied in 900 ml of 0.1 % polysorbate 80 in distilled water maintained at 37 ± 0.5ºC with a speed of 50 rpm. Samples of 5 ml were withdrawn at different time intervals, filtered (through 0.45µ) and replaced with 5 ml of fresh dissolution medium. The samples were suitably diluted if necessary and estimated spectrophotometrically at 289 nm by using ELICO-167 double beam UV-spectrophotometer. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

The use of super disintegrants for preparation of fast dissolving tablets is highly effective and commercially useful. Prepared fast dissolving tablets are dispersed in the mouth quickly and release the drug early as compared to its formulated conventional tablets. The super disintegrants crosscarmellose sodium, sodium starch glycolate alone in varying concentration and both in combination were studies for achieving faster dispersion of tablets.

Since, the flow properties of the powder mixture are important for the uniformity of mass of tablets, the flow of the powder mixture was analyzed before compression of tablets. All the formulations were analyzed for bulk density, tapped density, compressibility index, hausner's ratio and angle of repose. The values are shown in Table 2. As the tablet powder was free flowing, tablets produced were of uniform weight with acceptable weight variation (≤ 0.483 %) due to uniform die fill. Tablets prepared by direct compression method were found to be good, without any chipping, capping and sticking. The most important parameter of fast dissolving tablets is the disintegration time. In the present study, all tablets disintegrated in ≤ 54.69 seconds fulfilling the official requirements (≤ 3 minutes) for dispersible tablets. Formulation F5 showed disintegration of 17.69 seconds. The hardness of tablets was found to be in range of 3.9 – 4.9 kg/cm^2. The friability of all formulation was below 1 % was an indication of good mechanical resistance of tablets. Drug content was found to be in range of 98 – 101 %. The formulation F5 has displayed good water absorption ratio of about 83.54 % which indicates better and faster swelling ability of the super disintegrants in presence of little amount of water. The formulation F5 has displayed wetting time of 17 seconds, which facilitates their faster dispersion in mouth. The dissolution study of the formulation F5 showed that complete drug was released in 60 minutes. The dissolution data was shown in Fig. 1. Thus, it can be concluded that disintegration of raloxifene can be enhanced largely by direct compression technique with the addition of combination of super disintegrants.

Table 2: Evaluation of blend and fast dissolved tablets of Raloxifene

Parameter	F1	F2	F3	F4	F5
Bulk density (gm/cm^3)	0.416	0.476	0.476	0.472	0.476
Tapped density (gm/cm^3)	0.588	0.700	0.700	0.694	0.661
Compressibility index (%)	29.25	31.97	32.00	31.98	28.0
Hausner's ratio	1.413	1.47	1.47	1.47	1.39
Static angle of repose (θ)	35º 52'	31º 00'	30º 54'	30º 75'	31º 52'
Weight variation (mg)	201.8 ±0.82	200.7 ± 0.51	199.2 ± 0.43	201.6 ± 0.91	200.7±0.19
Hardness (kg / cm^2)	4.56 ± 0.130	4.56 ± 0.271	4.91± 0.567	4.12 ± 0.432	3.93±0.15
Friability (%)	0.45	0.54	0.65	0.63	0.71
Disintegration time (sec)	54.69 ± 1.23	31.5 ± 0.76	52.5 ± 1.56	34.4 ± 0.79	17.69±0.23
Wetting time (sec)	87	21	37	26	17
Water absorption ratio (%)	78.53	93.12	71.54	84.19	83.54
In-vitro dispersion time (sec)	29.33 ± 1.155	16.67±1.528	28.0 ± 2.0	25.0 ± 2.0	18.47
Assay (%)	98.96	99.12	96.67	101.23	100.27

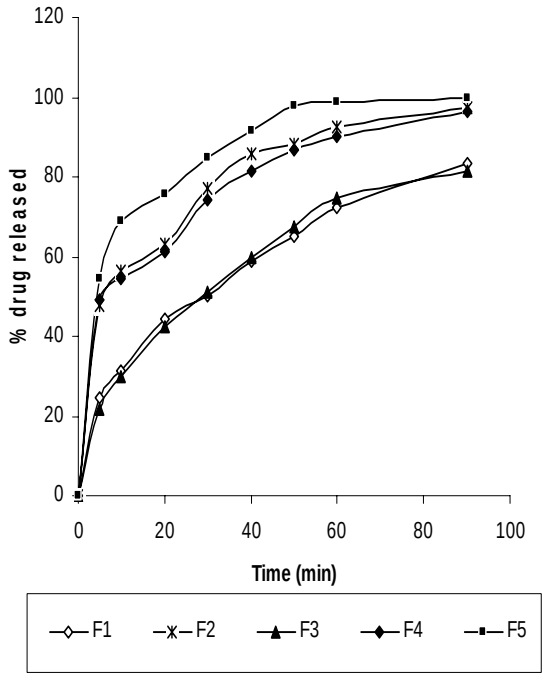

Fig. 1: *In vitro* dissolution profile of Raloxifene tablets containing super disintegrants

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