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ORIGINAL ARTICLE

Formulation and optimization of orodispersible tablets of flutamide

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Effervescence

Abstract The present study aimed to formulate orodispersible tablets of flutamide (FTM) to increase its bioavailability. Orodispersible tablets were prepared by direct compression technique using three different approaches namely; super-disintegration, effervescence and sublimation. Different combined approaches were proposed and evaluated to optimize tablet characteristics. Sodium starch glycolate (SSG) was used as the superdisintegrant. The prepared powder mixtures were subjected to both pre and post compression evaluation parameters including; IR spectroscopy, micromeritics properties, tablet hardness, friability, wetting time, disintegration time and in-vitro drug release. IR studies indicated that there was no interaction between the drug and the excipients used except Ludipress. The results of micromeritics studies revealed that all formulations were of acceptable to good flowability. Tablet hardness and friability indicated good mechanical strength. Wetting and dispersion times decreased from 46 to 38 s by increasing the SSG concentration from 3.33 to 6.66% w/w in tablets prepared by superdisintegration method. The F8 formulation which was prepared by combined approaches of effervescence and superdisintegrant addition gave promising results for tablet disintegration and wetting times but failed to give faster dissolution rate. The incorporation of 1:5 solid dispersion of FTM: PEG 6000 instead of the pure drug in the same formulation increased the drug release rate from 73.12 to 96.99% after 15 min. This increase in the dissolution rate may be due to the amorphization of the drug during the solid dispersion preparation. The presence of the amorphous form of the drug was shown in the IR spectra.
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1. Introduction

Flutamide (FTM) is an oral, non-steroidal antiandrogen drug primarily used to treat prostate cancer. It competes with testosterone and its powerful metabolite, dihydro-testosterone (DHT) for binding to androgen receptors in the prostate gland. By doing so, it prevents them from stimulating the prostate cancer cells to grow. Flutamide may also be used to

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treat excess androgen levels in women – especially those with Polycystic Ovarian Syndrome (PCOS) George et al., 2001. It is a poorly water-soluble drug; its dissolution is the rate-limiting step in the process of drug absorption that in turns dependent on disintegration. The low bioavailability of FTM after oral formulations may be due to poor wettability, low aqueous solubility, poor permeability, rapid first pass hepatic metabolism and low concentration at the absorption surface (Zuo et al., 2000). FTM undergoes a rapid first pass hepatic metabolism after oral administration resulting in a relatively short half-life of 5–6 h, thus it is usually given 250 mg three doses per day (Zuo et al., 2000). Therefore, developing novel formulations that mitigate solubility and dissolution will produce higher concentrations of FTM in solution at the absorption site and may overcome the first pass effect-mediated poor bioavailability.

The dissolution rate and bioavailability of a poorly soluble drug from solid dosage form depend much on formulation additives and formulation characteristics. On the basis of these considerations, in the present study it was proposed to formulate an oral delivery system, in the form of orodispersible tablet of flutamide to increase its bioavailability.

Orodispersible tablets were prepared by direct compression technique using three different approaches namely; superdisintegrant addition, effervescence and sublimation. In addition combination between different approaches was proposed and evaluated to optimize tablet characteristics. The prepared tablets were subjected to both pre and post compression parameters' evaluation, including; IR spectroscopy, Carr's index, angle of repose, Hausner ratio, hardness, friability, wetting time, disintegration time and dissolution rate. Solid dispersions in the ratios of 1:2 and 1:5 (FTM: PEG 6000) were prepared to increase the solubility and hence the dissolution rate of the drug from the orodispersible tablets.

2. Experimental

2.1. Materials

FTM was kindly donated by Archimica (Origgio, Italy). Sodium starch glycolate (Explotab), spray dried lactose (Ludipress) (El-Amreya Pharmaceutical Co., Alexandria, Egypt). Microcrystalline-cellulose (Avicel pH 102) (FMC Co., USA). Mannitol (Pearlitol SD 200) (BDH, United Poole, England). Polyethylene glycol (PEG 6000) (Pharaonia Pharmaceuticals, Alexandria, Egypt). Sucralose (McNeil Nutritional, LLC, Washington, PA, USA). Sodium bicarbonate, citric acid, sodium tribasic phosphate and camphor (WINLAB, UK). All other chemicals were of analytical reagent grades.

2.2. Preparation of FTM orodispersible tablets

Orodispersible tablets of FTM were prepared by direct compression method using three different approaches; superdisintegrant addition, effervescence, and sublimation, in addition to combined approaches according to the formulae given in Table 1. FTM 300 mg tablets each containing 125 mg of drug were prepared. In all formulations spray dried lactose (Ludipress) and mannitol were used as diluents. The specified quantity of the drug and the other excipients were weighed accurately and passed through 100 # screen prior to mixing. All the materials were transferred to mortar in geometrical order and co-grounded for 15 min. The resulting powder mixture was compressed into tablets using single punch tablet machine (Erweka, Germany) using 8 mm flat surface punches (Nayak and Gopalkumar, 2004). The compression force was adjusted to give tablet hardness in the pharmacopeial range of orodispersible tablets (2–4 kg/cm^3). For tablets prepared by sublimation technique using camphor as a sublimating agent, the tablets were dried at 60 °C in an oven till constant weight was obtained (Gohel et al., 2004). For tablets prepared by the effervescence method, sodium bicarbonate and citric acid were accurately weighed and preheated at a temperature of 80 °C. In all formulations the weighed amounts of drug and Ludipress were mixed first then other excipients were mixed thoroughly to load the drug on the surface of water soluble carriers. Ten formulations were designed, one of which is a control and two others were prepared using solid dispersions of FTM (Table 1).

2.3. Preparation of FTM solid dispersions

FTM solid dispersions (SDs) were prepared by fusion method using PEG 6000 as the polymeric carrier in drug to polymer ratios of 1:2 and 1:5. The weighed amount of the polymer was melted in a porcelain dish placed in a water bath at 60 °C, and then the calculated amount of the drug was added while stirring till homogeneity. The melted mixtures were left to con-

Table 1 Formulations of orodispersible tablets of flutamide.

Ingredients (mg)	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	125	125	125	125	125	125	125	125	SD # 125	SD #125
Mannitol		15	15	15	15	15	15	15	15	15
Avicel 102	45	45	45	45	45	45	45	45	45	45
SSG		10	15	20		20		20	20	20
Sodium bicarbonate							30	30	30	30
Citric acid							24	24	24	24
Camphor					60	60				
Sucralose	3	3	3	3	3	3	3	3	3	3
PEG 6000	6	6	6	6	6	6	6	6	6	6
Ludipress qs	121	96	91	86	26	96	52	32	32	32
TW* (mg)	300	300	300	300	300	300	300	300	550	800

TW* = Total weight of tablet in mg.

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