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Original article

Propafenone HCl fast dissolving tablets containing subliming agent prepared by direct compression method

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ABSTRACT

Propafenone HCl (PPH), an antiarrhythmic drug, has a bitter taste, short half-life, delayed drug dissolution and side effects. Thus, the purpose of this work is to develop orally fast dissolving tablets (OFDTs) containing PPH to provide a rapid drug dissolution and subsequently give rapid onset of action of PPH as an antiarrhythmic drug. Moreover, OFDTs of PPH reduce its side effects and improve its bioavailability. Propafenone HCl (PPH), an antiarrhythmic drug, has a bitter taste, short half-life, delayed drug dissolution and side effects. Direct compression method was used for the preparation of 15 formulations OFDTs containing PPH using directly compressible excipients, subliming agent and superdisintegrants. The prepared tablets were undergone physical characterization, *in vitro* dissolution and stability studies. All pre- and post-compression tests met the pharmacopoeia specifications. *In vitro* dissolution of the prepared PPH OFDTs exhibited high dissolution rate than compared to the marketed tablets. It was found that the tablets prepared by using the higher concentration of crospovidone were found to dissolute the drug at a faster rate when compared to other concentrations. A formula containing croscarmellose sodium showed the higher present of PPH dissolved as compared to the other formulations. It was concluded that PPH OFDTs were formulated successfully with acceptable physical and chemical properties with rapid disintegration in the oral cavity, rapid onset of action, and enhanced patient compliance. It was found that F10 showed good stability upon storage at 25 and 40 °C for 3 months. Formulation of PPH OFDTs can result in a significant improvement in the PPH bioavailability since the first pass metabolism will be avoided.

1. Introduction

Fast-dissolving tablets (OFDTs) were formulated as a substitute to conventional tablets, especially for pediatric and geriatric patients who suffer from swallowing solid dosage forms (Nagaraju et al., 2013). OFDTs have advantages of rapid onset of action, accurate dosing, fast disintegration and dissolution in the oral cavity without the necessity of water (Heer et al., 2013). Moreover, OFDTs have the benefit of avoidance of first-pass hepatic metabolism that occurs during gastric absorption. Thus, OFDTs can improve bioavailability and safety profiles of drugs that changed in liver to toxic metabolites (Sharma et al., 2010).

Several approaches were used for the preparation of OFDTs, such as spray drying, molding, direct compression, lyophilization and sublimation (Patel et al., 2007; Suresh et al., 2007). Many OFDTs contain superdisintegrants, such as crospovidone, croscarmellose sodium (Ac-di-sol) and sodium starch glycolate (SSG), to prompt fast disintegration (Al-Khattawi and Mohammed, 2013). Many OFDTs are highly friable due to its porous structure and to avoid these, mechanically hard OFDTs must be prepared using co-processed excipients (Seong et al., 2008).

Propafenone hydrochloride (PPH) (Fig. 1), an antiarrhythmic drug class IC (sodium channel inhibitor), has been broadly used for the management of certain types of life-threatening irregular heartbeat (ventricular and supraventricular arrhythmias) (Funck-Brentano et al. 1990). In certain patients who are complaining of irregular heartbeat (paroxysmal atrial fibrillation/flutter), PPH

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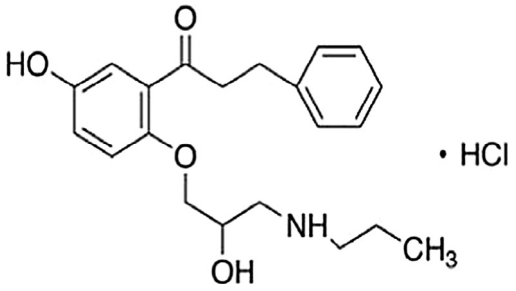

Fig. 1. PPH structure.

can be used to help maintain a normal heart rhythm. It works in the heart to stabilize its action and regulate heartbeat. PPH is undergoing high first pass effect with a mean bioavailability about 4.8%. PPH has a short half-life about 3–4 h (Sestito and Molina, 2012). In addition, PPH has weak beta-blocking activity as well as its local anesthetic effect. Because of the side effect of PPH occurs when it reached the peak plasma concentration, small doses of multiple administrations were advised. Thus, PPH was suggested to be taken 4–6 times per day (Ni, 1994).

Bitter undesirable taste is one of the important pharmaceutical formulation problems occurred with most of the drugs. The techniques, which used for achieving taste masking, include various chemical and physical methods that prevent the drug substance from interaction with taste buds in the oral cavity (Venkata et al., 2010). The simplest and economic method involves the use of flavor enhancers as aspartame and menthol.

The aim of this work was to develop OFDTs containing PPH to provide a rapid drug dissolution and subsequently give rapid onset of action of PPH as antiarrhythmic drug. Moreover, OFDTs of PPH would improve its bioavailability.

2. Materials and methods

2.1. Materials

Propafenone HCl (PPH) was kindly provided from Cairo Pharmaceuticals, Egypt. Magnesium stearate, menthol, Eosin dye, lactose, potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate were purchased from El-Nasr Pharmaceutical Chemicals Co., Egypt. Crosscarmellose sodium, crospovidone and camphor were kindly provided by Sigma Company, Germany. Aspartam was obtained from Alpha Chemika, India. Rytmonorm®150 mg tablets were purchased from Kahira pharmaceuticals, Egypt. Acetonitrile and methanol (HPLC grade) were purchased from Merck-Schuchardt, Germany. Dipotassium hydrogen orthophosphate was supplied by NICE Chemicals (p) LTD, India. All other materials and solvents were of analytical grade.

2.2. Pre compression characterization parameters

The bulk density, Carr's index and Hausner's ratio of the powder blend were calculated according to USP pharmacopeia.

2.3. Preparation of PPH OFDTs

Direct compression method was used for preparation of PPH FDTs (Madgulkar et al., 2009; El-Shenawy et al., 2017). The composition of the prepared tablets formulae is presented in Table 1.

Weighed amount of aspartame and menthol were incorporated for masking the undesirable taste (using digital sensitive electric balance, RADWAG, Poland). Using the bottle method, the amount equal to 150 mg of PPH was mixed with all amount of the excipients for 20 min. The obtained mixture (350 mg) was compressed into a round tablet punch 10 mm (Single punch tableting machine manufactured by Royal artist, India). The compression force was adjusted to attain a tablet hardness of 3–5 kg/cm^2. The prepared PPH FDTs were subjected to sublimation at 60 °C for 12 h in a vacuum oven to ensure full sublimation of camphor, which confirmed by constant weights of the FDTs and hence the porosity and disintegration of the obtained formulae were increased (vacuum oven dryer, SPT-200 Zeamil Horzont co., Poland)

2.4. Differential scanning calorimetric analysis

Drug-excipient interaction was evaluated using differential scanning calorimetry (DSC) (DSC-50, Shimadzu Company. Japan). Weighed samples (3–8 mg) of PPH alone and physical mixture of the drug and excipients (1:1) were poured in aluminum pans and then sealed with lid. The temperature rate was adjusted at 10 °C.

2.5. Fourier transform infrared spectroscopy (FTIR)

Fourier Transform Infrared spectrophotometer (FTIR, Nicolet 6700 FT-IT, Thermo Fisher, Madison, USA) is another tool for drug-excipients interaction. FTIR spectra of PPH alone and physical mixture of the drug-excipients were obtained by scanning the prepared disc with KBr in the range of 500–4000 cm^{-1}.

Table 1
Composition of PPH OFDTs.

Formula No.	Drug and excipients							
	PPH (mg)	CCS (mg)	CP (mg)	CA (mg)	AS (mg)	ME (mg)	MgSt (mg)	LA (mg)
F_1	150	32	32	15	10.5	3.5	3.5	103.5
F_2	150	24	24	15	10.5	3.5	3.5	119.5
F_3	150	24	40	15	10.5	3.5	3.5	103.5
F_4	150	40	24	15	10.5	3.5	3.5	103.5
F_5	150	40	40	15	10.5	3.5	3.5	87.5
F_6	150	32	24	10	10.5	3.5	3.5	116.5
F_7	150	32	40	10	10.5	3.5	3.5	100.5
F_8	150	32	32	15	10.5	3.5	3.5	103.5
F_9	150	32	24	20	10.5	3.5	3.5	106.5
F_{10}	150	32	40	20	10.5	3.5	3.5	90.5
F_{11}	150	24	32	10	10.5	3.5	3.5	116.5
F_{12}	150	40	32	10	10.5	3.5	3.5	100.5
F_{13}	150	24	32	20	10.5	3.5	3.5	106.5
F_{14}	150	40	32	20	10.5	3.5	3.5	90.5
F_{15}	150	32	32	15	10.5	3.5	3.5	103.5

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