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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.
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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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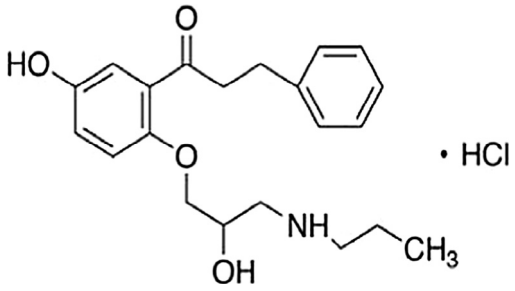

Fig. 1. PPH structure.

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

2.6. Post-compression characterization of PPH OFDTs

2.6.1. Uniformity of weight

This test was being done to verify that the tablets are uniform in weight. Twenty tablets were randomly taken, weighed and then the average weight was calculated (Thahera et al., 2012).

2.6.2. Drug content

One tablet was powdered and sonicated with 100 ml phosphate buffer pH 6.8 for 10 min and the solution was then filtered. The drug content was calculated by analyzing the filtrate spectrophotometrically (Double beam spectrophotometer, UV-1601 Shimadzu Co., Japan) at 305 nm (Krishna et al., 2013).

2.6.3. In-vitro disintegration time

The disintegration time was determined in phosphate buffer pH 6.8 using tablet disintegration test apparatus (Electrolab, ED-21, Mumbai, India) on six tablets according to the USP30-NF25 requirements for immediate release tablets. The tablet was put in 500 ml phosphate buffer pH 6.8 and the time taken for the tablet to disintegrate into fine particles was calculated (Mahrous et al., 2016).

2.6.4. Wetting time

The tablet was placed on folded tissue paper wetted by phosphate buffer pH 6.8 and eosin solution (water soluble dye). The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time (Shailendra et al., 2015).

2.6.5. Hardness, thickness and friability test

The hardness using hardness tester (Pharma test GmbH, Hainburg, Germany), thickness using a micrometer (Starrett, Athol MA, USA) and friability test using the friabilator (Erweka, TA3R, Heusenstamm, Germany) were determined for the prepared PPH OFDTs according to USP Pharmacopeia guidelines USP30-25NF.

2.7. In-vitro dissolution study

Drug dissolution rate from the prepared OFDTs was performed according to USP specification using USP paddle type apparatus (Model 85T, Caleva Ltd., Dorset, United Kingdom), at 50 RPM using a continuous automated monitoring system. This system consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620 (Caleva), Epson FX 850 printer, and Watson-Marlow peristaltic pump using in each flask 500 ml phosphate buffer, pH 6.8. The temperature was maintained at 37 °C ± 1 °C. At scheduled time intervals, absorbances were recorded automatically at 305 nm, and the percentage of PPH dissolved was determined as a function of time in triplicate (Shazly et al., 2012).

2.8. Palatability test

One group, three healthy human volunteers aged from 23 to 43. The study was approved by the Human ethics committee of Assuit University, Assuit, Egypt (IRB Nr. IRB00009982) that ensured the investigations of Human Volunteers followed the Declaration of Helsinki guidelines 1964. The selected tablet F3 was kept in the mouth until complete disintegration occurred, and then disgorged. The test was repeated for three days and the resulted data were collected and evaluated. The acceptability scale was divided into 5 levels (level 1 is the lowest degree of taste masking and level 5 is the highest degree of taste masking).

2.9. Effect of storage on characterization parameters of PPH OFDTs at 25 and 40 °C

Three PPH OFDTs formulations (F3, F10, and F14) were stored at 25 and 40 °C for three months. These formulae were selected because they showed low disintegration time, low% friability, and the highest percent amount dissolved in 10 min. About 110 OFDTs of each formula each containing 150 mg of PPH were stored in a tightly closed, light protected bottles and wrapped within aluminum foil and stored at 25 and 40 °C + RH 75% ± 5 in thermostatically controlled hot air ovens (India). Samples of 18 tablets of each formula from each temperature were taken at zero time and after 1, 2, 3, 4, 8 and 12 weeks and were evaluated for weight variation, drug content, in-vitro disintegration time, wetting time, the% amount dissolved in 10 min,% friability and hardness (Sahitya et al., 2014).

3. Results and discussion

PPH OFDTs were prepared by direct compression method using CP, CCS as superdisintegrants and camphor as a subliming agent in different ratios. Fifteen formulae were designed and evaluated (Table 1).

3.1. DSC

DSC thermogram of untreated drug shows an endothermic peak at 173 °C, which is related to its melting point (Fig. 3A). The physical mixture of excipient used (Placebo) has endothermic peak at 194 °C (Fig. 3B). Physical mixture of excipients and the drug showed endothermic peaks at 164.71 °C and 193.44 °C (Fig. 2C). It was found that there are no new peaks appeared in the thermogram of the drug and excipients. Thus, there is no interaction between the drug and the tablet excipients, was observed. However, there is a very slight shift in the drug peak and this might be due to a reduction of the purity of components by mixing (Tayel, 2013).

3.2. FTIR

FTIR spectroscopy for pure PPH, physical mixture of excipients and physical mixture of excipients and drug was shown in Fig. 4. The spectrum of PPH showed characteristic bands, at wave number 1662 cm^{-1} corresponding to the carbonyl group (C=O), 3421 cm^{-1} corresponding to the tertiary amine group (N—H), 3312 cm^{-1} corresponding to the hydroxyl group (O—H) and another peak at

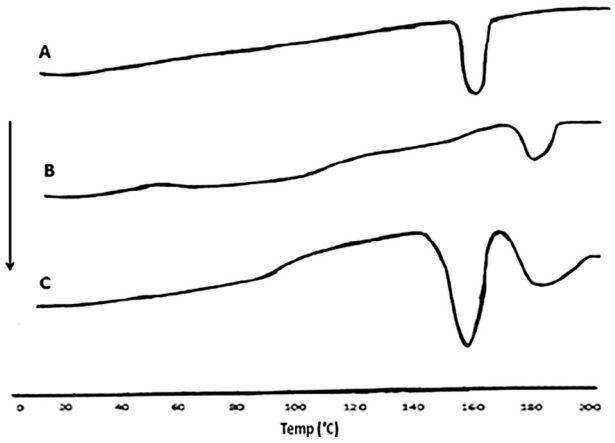

Fig. 2. DSC thermogram of pure PPH (A), physical mixture of excipients (B) and physical mixture of excipients and PPH.

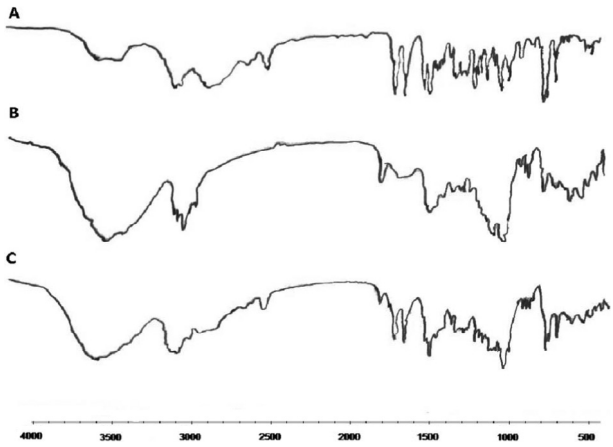

Fig. 3. FTIR spectrum of pure PPH (A), physical mixture of excipients (B) and physical mixture of excipients and PPH.

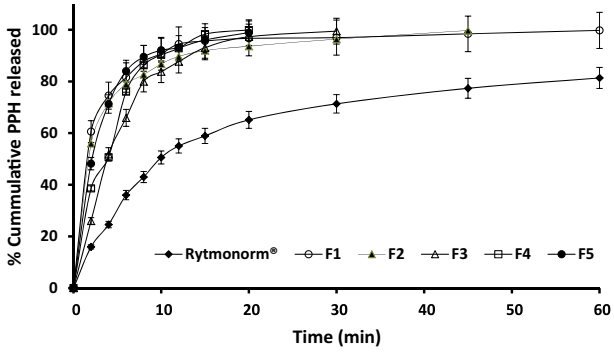

Fig. 4. *In-vitro* dissolution study of PPH FODTs (F1-F5) compared to Rytmonorm® tablets.

2940 cm^{-1} refer to methyl group. From the FTIR spectra, it was found that all the characteristic peaks of PPH were also found in the spectrum of formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the contents (Manju et al., 2016).

3.3. Pre-compression characterization parameters

The values of pre-compression parameters evaluated (angle of repose, bulk density, Carr's index and Hausner's ratio) were investigated. The results indicated, all the examined formulae showed a poor flowability (Carr's index ranged from 21.36 to 28.47) except formulae F4 exhibit a good powder flow. While the values of Hausner's ratio were ranging between 1.27 and 1.44 indicated poor flowing properties (Table 2).

3.4. Post-compression characterization of PPH OFDTs

Uniformity of weight, drug content, *and in vitro* disintegration time, wetting time, hardness, thickness and friability met the pharmacopeia requirements (Table 3). The results indicated that disintegration time ranged between 25.4 s (F_8) and 53.4 s (F_6). The calculated wetting time values were between 20.46 s and 34.93 s for F_{10} and F_{12} respectively. According to the noticed results formulae F_8, F10, and F3 gave the lowest disintegration and wetting time. The hardness of FDTs was between 3.443 and 4.609 kg/cm^2 (Shailendra et al., 2015; El-Shenawy et al., 2017).

3.4.1. In vitro dissolution studies of PPH OFDTs

Figs. 5 and 6 exhibited *in vitro* dissolution of the prepared HPP OFDTs. These studies indicated that all the tablet formulations prepared by using various superdisintegrants were found to exhibit high dissolution rate than compared to the marketed tablets. All the prepared tablets formulae showed a rapid drug dissolution (more than 70% of PPH dissolved within the first 10 min) this attributed to the porosity and capillary action (wicking) of the superdisintegrant and the subliming agent (Vineet et al., 2010). The results illustrated that F_7 and F_{11} gave the highest drug dissolution after 10 min while F_{12} gave the lowest.

Crospovidone is a cross-linked polyvinylpyrolidone. It is insoluble but highly hydrophilic. It was noticed that the tablets prepared by using the higher concentration of crospovidone found to dissolute the drug at a faster rate than those prepared by higher concentrations of croscramellose as superdisintegrant. These results agreed with that obtained by Shailesh et al., 2010, who found that increasing the concentration of Crospovidone during the formulation and optimization of promethazine theoclate FDTs led to increase the amount of drug dissolved after 10 min. Crospovidone facilitates penetration of liquid into the tablet and particles because its particles are porous leading to rapid disintegration (Raymond, 2006). In addition, crospovidone swells rapidly in water without gelling due to its high Crosslink density than other superdisintegrants (Shrivastava and Sethi, 2013). Moreover, Crospovidone displays effectively no affinity toward gel formation, even at high use levels in contrast to other superdisintegrants (Mohanachandran et al., 2011). A pronounced effect of the combination of different ratios of both crospovidone and crosscarmellose sodium as a superdisintegrants on the cumulative amount of drug

Table 2
Pre-compression characterization of parameters of the blended powder.

Formula No.	Loose bulk density	Tapped density	Carr's index	Hausner's ratio
F_1	0.367 ± 0.005	0.510 ± 0.009	28.01 ± 0.56	1.38 ± 0.011
F_2	0.399 ± 0.004	0.557 ± 0.010	28.32 ± 0.583	1.38 ± 0.011
F_3	0.381 ± 0.008	0.517 ± 0.011	26.29 ± 0.047	1.35 ± 0.000
F_4	0.407 ± 0.006	0.588 ± 0.017	30.73 ± 1.388	1.44 ± 0.028
F_5	0.394 ± 0.008	0.538 ± 0.022	26.76 ± 1.500	1.36 ± 0.03
F_6	0.380 ± 0.008	0.529 ± 0.019	28.10 ± 1.151	1.39 ± 0.023
F_7	0.381 ± 0.004	0.492 ± 0.008	22.60 ± 1.22	1.28 ± 0.020
F_8	0.370 ± 0.015	0.472 ± 0.043	21.36 ± 3.75	1.27 ± 0.060
F_9	0.380 ± 0.006	0.499 ± 0.014	23.84 ± 1.33	1.31 ± 0.026
F_{10}	0.347 ± 0.007	0.456 ± 0.011	23.90 ± 3.330	1.31 ± 0.051
F_{11}	0.381 ± 0.011	0.532 ± 0.003	28.47 ± 1.72	1.39 ± 0.032
F_{12}	0.363 ± 0.005	0.484 ± 0.011	24.96 ± 1.28	1.32 ± 0.020
F_{13}	0.400 ± 0.007	0.551 ± 0.016	27.45 ± 2.115	1.37 ± 0.045
F_{14}	0.400 ± 0.007	0.532 ± 0.009	24.81 ± 0.095	1.33 ± 0.000
F_{15}	0.363 ± 0.005	0.484 ± 0.009	24.97 ± 0.500	1.33 ± 0.010

Table 3
Post- compression characterization parameters.

Formula No.	Weight uniformity (mg)	Drug content (%)	Disintegration time (second)	Cum. amount dissolved at 10′	Wetting time (second)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)
F_1	349.33 ± 2.34	98.65 ± 0.01	38.7 ± 4.89	90.70 ± 0.04	31.96 ± 2.40	0.553 ± 1.88	3.861 ± 0.05	3.822 ± 0.03
F_2	348.64 ± 2.67	94.03 ± 0.01	41.40 ± 4.55	86.76 ± 0.04	31.2 ± 2.82	0.521 ± 0.91	4.492 ± 0.15	3.668 ± 0.02
F_3	349.43 ± 1.82	97.99 ± 0.01	33.1 ± 6.14	83.75 ± 0.04	27.86 ± 2.42	0.292 ± 0.65	4.609 ± 0.11	3.690 ± 0.09
F_4	349.96 ± 1.86	94.89 ± 0.01	43.16 ± 6.14	90.28 ± 0.01	28.6 ± 2.93	0.641 ± 0.90	3.616 ± 0.01	3.620 ± 0.07
F_5	349 ± 1.88	92.11 ± 0.01	39.8 ± 1.47	92.10 ± 0.003	28.06 ± 3.19	0.539 ± 2.02	4.302 ± 0.23	3.664 ± 0.07
F_6	349.81 ± 1.88	98.45 ± 0.01	53.4 ± 3.90	92.82 ± 0.02	29.5 ± 2.39	0.659 ± 1.88	4.287 ± 0.06	3.548 ± 0.116
F_7	348.41 ± 2.14	95.21 ± 0.01	51.7 ± 6.45	98.95 ± 0.02	30.7 ± 2.97	0.855 ± 1.79	3.443 ± 0.28	3.558 ± 0.01
F_8	347.93 ± 2.28	97.33 ± 0.01	25.40 ± 1.80	90.70 ± 0.02	22.43 ± 3.13	0.682 ± 0.80	3.554 ± 0.06	3.591 ± 0.01
F_9	348.43 ± 1.77	97.79 ± 0.01	40.53 ± 2.95	74.77 ± 0.06	28.46 ± 2.27	0.757 ± 1.38	3.477 ± 0.06	3.618 ± 0.06
F_{10}	348.27 ± 1.44	96.07 ± 0.01	29.56 ± 2.82	75.61 ± 0.01	20.46 ± 2.43	0.419 ± 0.55	4.260 ± 0.26	3.620 ± 0.08
F_{11}	348.56 ± 1.95	96.93 ± 0.02	51.96 ± 2.17	97.39 ± 0.02	28.26 ± 2.63	0.729 ± 1.74	3.482 ± 0.25	3.501 ± 0.03
F_{12}	349.14 ± 2.25	96.34 ± 0.01	49.1 ± 4.10	70.30 ± 0.02	34.93 ± 5.65	0.573 ± 0.57	3.819 ± 0.11	3.604 ± 0.09
F_{13}	347.87 ± 1.89	96.80 ± 0.01	38.96 ± 2.06	73.40 ± 0.02	34.36 ± 2.85	0.586 ± 1.26	3.719 ± 0.15	3.572 ± 0.02
F_{14}	349.27 ± 3.23	101.09 ± 0.01	38.06 ± 5.78	80.14 ± 0.09	21.36 ± 2.60	0.514 ± 1.65	4.004 ± 0.17	3.640 ± 0.01
F_{15}	348.63 ± 2.14	99.63 ± 0.01	35.16 ± 5.40	89.51 ± 0.02	29.23 ± 2.22	0.712 ± 1.44	3.488 ± 0.26	3.539 ± 0.034

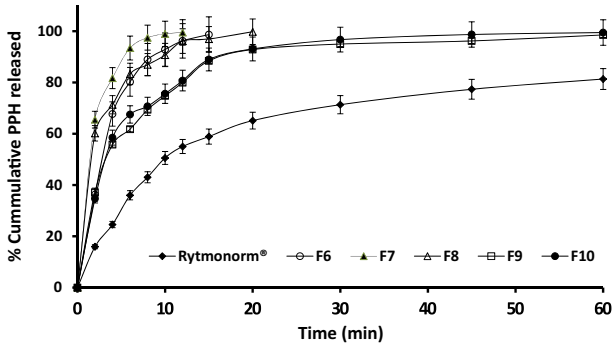

Fig. 5. *In-vitro* dissolution of PPH FODTs compared to Rytmonorm® tablets.

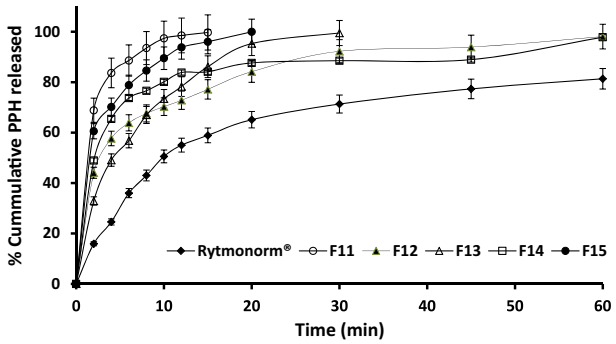

Fig. 6. *In-vitro* dissolution study of PPH FODTs (F11-F15) compared to Rytmonorm® tablets.

dissolved after 10 min was obtained (Patil and Das, 2011). These findings were in a good accordance with Jagdale et al., 2010.

Lactose is an example of water soluble diluents used in these formulations. It was used as a sweetening agent and to enhance the tablets wettability and disintegration (Chandrasekhar et al., 2009).

3.4.2. Rank order of prepared PPH OFDTs

After characterization of the prepared OFDTs of post-compression parameters, the optimized formula which has the best properties (e.g. the lowest % variability, the shorter *in vitro* disintegration time, the fastest wetting time and the maximum % cumulative amount dissolved in 10 min) were selected for further investigation by conduction of rank order. The final rank order showed that F3 was the optimum formula. F10 and F14 were in the next order in OFDTs properties to F3. The total and final rank orders are listed in Table 4.

3.4.3. Palatability test

Table 5 exhibited the evaluation parameters, e.g. degree of the selected fast dissolving tablets F3. The results showed the effectiveness of PPH bitter taste masking as the final rank in the case of the tested formulation. The used amounts of aspartame (3%) with menthol (1%) were powerful in taste masking (Jae-Il and Hoo-Kyun, 2010). The results of the taste evaluation show that the formula was acceptable by more than half of the volunteers, while other volunteers showed good response and acceptable mouth feel with few show gritty mouth feel. The volunteers have no complain of numbness.

Table 4
The total and final rank order of PPH OFDTs.

Formula No.	Hardness	Friability (%)	Wetting time	Disintegration time	Drug content	Cum. amount dissolved at 10′	Total rank	Final rank
F_1	7	5	13	6	4	6	41	5
F_2	2	4	12	10	13	9	50	8
F_3	1	1	4	3	7	10	26	1
F_4	10	9	8	11	14	7	59	9
F_5	3	6	5	8	15	4	41	5
F_6	4	10	10	15	3	3	45	6
F_7	15	15	11	13	12	1	67	13
F_8	11	11	3	1	5	5	36	4
F_9	14	14	7	9	6	13	63	11
F_{10}	5	2	1	2	8	12	30	3
F_{11}	13	13	6	14	11	2	59	9
F_{12}	8	7	15	12	9	15	66	12
F_{13}	9	8	14	7	10	14	62	10
F_{14}	6	3	2	5	1	11	28	2
F_{15}	12	12	9	4	2	8	47	7

Table 5
The degree of acceptability of the selected PPH OFDTs (F_3).

Formula	Volunteer No.	Day 1 Degree of acceptability					Day 2					Day 3					Average Rank
		1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	
F_3	1					√				√					√		4.33
	2			√						√					√		3.66
	3					√					√			√			4.33

Table 6
Characterization parameters of PPH OFDTs formulae after storage at 40 °C + RH 75% for three months compared with the corresponding recently prepared tablets.

Evaluation parameters	Evaluation time								
	Recent tablets (0 week)			Stored tablets (12 weeks)					
				25 °C & RH 75% ± 5			40 °C & RH 75% ± 5		
	F_3	F_{10}	F_{14}	F_3	F_{10}	F_{14}	F_3	F_{10}	F_{14}
Weight variation (mg)	349.4 ± 0.816	348.3 ± 1.44	349.3 ± 3.23	346.9 ± 1.17	345.6 ± 0.7	346.8 ± 1.85	345.8 ± 0.8	344.7 ± 0.7	345.3 ± 0.4
Drug content (%)	97.86 ± 0.01	96.08 ± 0.01	101.2 ± 0.01	93.31 ± 0.01	93.3 ± 0.01	96.87 ± 0.02	92.9 ± 0.01	91.7 ± 0.01	95.7 ± 0.1
Disintegration time (sec.)	35.17 ± 4.55	33.1 ± 2.82	38.07 ± 5.78	32.45 ± 2.65	30.7 ± 5.15	35.2 ± 1.67	30.6 ± 2.76	29.1 ± 1.97	34.2 ± 3.7
Wetting time (sec.)	27.87 ± 2.42	20.5 ± 2.43	21.37 ± 2.60	24.9 ± 2.66	17.9 ± 3.01	19.8 ± 2.25	24.2 ± 2.93	17.1 ± 1.9	18.6 ± 2.2
% Cum. Am. dis. at 10 min. *	83.81 ± 0.04	75.6 ± 0.01	80.14 ± 0.09	91.3 ± 0.01	86.2 ± 0.02	88.1 ± 0.01	96.9 ± 0.01	88.8 ± 0.03	92.8 ± 0.02
% Friability	0.29 ± 0.66	0.42 ± 0.55	0.51 ± 1.65	0.37 ± 1.65	0.51 ± 1.65	0.61 ± 2.06	0.5 ± 1.3	0.580 ± 1.4	0.7 ± 0.9
Hardness (kg/cm^2)	4.61 ± 0.11	4.26 ± 0.26	4.01 ± 0.17	3.76 ± 0.25	3.17 ± 0.19	3.37 ± 0.01	3.01 ± 0.2	3 ± 0.3	3 ± 0.2

* % Cumulative amount dissolved at 10 min.

3.4.4. Effect of storage on the characterization parameters of PPH OFDTs at 25 and 40 °C

Table 6 shows the evaluation parameters (e.g. Weight variation, drug content, in-vitro disintegration time, wetting time, the% amount dissolved in 10 min,% friability and hardness) of the selected formulations F3, F10 and F14 that subjected to storage at 25 and 40 °C. From this table, it is clear that weight variation and drug content showed non-significant variation (p values < 0.05).

For the disintegration time, there is a small decrease in the values for all formulations. The wetting time of F3 and F10 was decreased significantly, but it was not significantly changed in case of F14.

Regarding% amount dissolved in 10 min for all formulations after twelve weeks of storage under the mentioned conditions was markedly increased. The% friability for all formulations was slightly increased. F3, F10, and F14 showed significant decrease in their hardness values.

4. Conclusion

OFDTs containing PPH has been successfully developed and manufactured by direct compression method using different quantities of superdisintegrants and camphor as subliming agent. The tablets have acceptable physical and chemical properties. The use of two superdisintegrants in combination with subliming agent in the formulation resulted in tablet accepted properties. All tablets that were manufactured met the specification limits for all pre- and post-compression characterization parameters. Formulation of PPH as fast dissolving tablets resulted in a significant improvement in the dissolution, which could be reflected in PPH bioavailability enhancement.

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