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Research Article

EFFECT OF EFFERVESCENCE IN COMBINATION WITH SUPERDISINTEGRANTS IN THE FORMULATION OF PROPRANOLOL HCL ORAL DISINTEGRATING TABLETS

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ABSTRACT

Objective: The current research work is intended to formulate propranolol HCl (PLH) as orally disintegrating tablet (ODT). It is also intending to check the superiority in a combination of superdisintegrants and effervescent mixture than the use of superdisintegrants alone by a direct compression technique. To fasten the onset of action and thereby enhancing the bioavailability of PLH in comparison to its conventional tablets.

Methods: Standard calibration curve of PLH was obtained in pH 6.8 phosphate buffer by spectrophotometric method, drug-excipient compatibility studies were carried by Fourier transform infrared (FT-IR) studies. All the formulations were evaluated for pre and postcompression studies. Accelerated stability studies were carried out up to 6 months for the optimized formulation, EF_3.

Results and Discussion: Superdisintegrants used in the study are compatible with PLH. Pre- and post-compression parameters were within the acceptable limits for all formulations. *In vitro* dissolution kinetic studies indicate the release of PLH from ODT increases as the concentration of superdisintegrants as well as the ratio of citric acid: $NaHCO_3$ of effervescent mixture increases. Formulations with an effervescent mixture are having rapid disintegration and dissolution rate when compared to the formulations with superdisintegrants alone. The order of superdisintegrants in enhancing the dissolution rate of PLH is crospovidone (CPV) > croscarmellose sodium (CCS) > sodium starch glycolate (SSG). Formulation, EF_3 (10% CPV and 1:3, citric acid: $NaHCO_3$ ratio, respectively) had the highest dissolution efficiency at 10 minutes (DE_{10}=82.74%); the first order dissolution rate constant (K_1=0.141/minutes) with a regression coefficient (r^2=0.974) and lesser time for 90% of drug release (t_{90}=4 minutes), was considered as the optimal ODT in this study. Formulation EF_3, passed the test for stability.

Conclusion: Hence, an effective PLH ODT was formulated by the direct compression technique with disintegration by combination of superdisintegrants and effervescent mixture, will fasten the onset of action and enhances the bioavailability of PLH in comparison to its conventional tablets.

Keywords: Propranolol HCl, Orally disintegrating tablet, Sodium starch glycolate, Croscarmellose sodium, Crospovidone, Direct compression, *In vitro* dissolution studies.

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INTRODUCTION

The most preferred route of administration of dosage forms is oral route, due to its potential advantages such as ease of administration, convenient dosing, self-medication, no pain, and patient compliance. Hence, tablets and capsules are the most popular dosage forms [1]. However, the important drawback of these dosage forms is dysplasia [2]. The above-mentioned problem can be solved by developing a fast disintegrating/dissolving drug delivery, i.e., oral disintegrating/dissolving tablet, disintegrates and dissolves rapidly in the saliva, Within a few seconds without the need of drinking water or chewing [3]. In pharmaceutical sciences, disintegration usually means the process by which a solid dosage form breaks up when it comes in contact with aqueous medium. This promotes the rapid release of drug and faster absorption too [4]. A rapid disintegration process is the prerequisite for a good bioavailability [5]. Orally disintegrating tablets (ODT) provides ease of administration, immediate action, convenient dosing, self-medication, no pain, and increases patient compliance [6]. The medications of fast-acting, compliance critical, and pediatrics are commonly suitable for ODT [7]. Propranolol HCl (PLH) is a nonselective beta blocker, which blocks the action of epinephrine and norepinephrine on both β1- and β2-adrenergic receptors. It has little intrinsic sympathomimetic activity but has strong membrane stabilizing activity. It is mainly used in the treatment of hypertension, supraventricular, tachyarrhythmia, ventricular arrhythmias, pheochromocytoma, thyrotoxicosis, and vascular headache. PLH is highly lipophilic and is almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of PLH reaches the systemic circulation [8]. Clinically, orotransmucosal drug delivery is reported to be the most promising alternative approach for enhancing the bioavailability and fastening the onset of action in comparison to its conventional tablets because it has the high blood supply, a very thin membrane barrier (190 μm), and an ability to bypass hepatic first-pass metabolism [9]. The properties of PLH, like low molecular weight (295.81 g/mol); lesser oral dose (20-40 mg) and lesser biological half-life (3-5 h), makes it an ideal candidate, to select for the formulation of ODT [10,11]. This study was aimed to optimize the type and concentration of superdisintegrant by taking batches with 6%, 8%, and 10% w/w of different superdisintegrants (crospovidone [CPV], croscarmellose sodium [CCS], and sodium starch glycolate [SSG] only); (i.e., batches from: DC_1 to DC_9) and to study the effect of the effervescent mixture in combination with superdisintegrants by taking batches with 10% w/w different superdisintegrants along with different ratios (1:1; 1:2, and 1:3) of citric acid: $NaHCO_3$, respectively (i.e., batches from: EF_1 to EF_9).

MATERIALS AND METHODS

Materials

PLH, SSG, CCS (Ac-DI-Sol), CPV (polyplasdone XL-10), citric acid, sodium bicarbonate ($NaHCO_3$), mannitol (PERLITOL-SD-200), aspartame, powder vanilla flavor, magnesium stearate, talc, and sodium lauryl sulfate (SLS) are received as gift samples from Richer Pharmaceuticals Ltd., Bengaluru, India. All the excipients used in the study are of pharmaceutical grade.

Methods

Standard calibration curve of PLH in pH 6.8 phosphate buffer [9]

Was obtained at the λ_{max} 279 nm using an ultraviolet (UV)-visible spectrophotometer (UV-1700, Shimadzu, Mumbai, India) and represented in (Fig. 1). Which was further used for drug release calculations of *in vitro* dissolution studies and assay.

Drug-excipient compatibility/Fourier transform infrared (FTIR) studies [10]

FTIR studies were performed on drug and drug: Superdisintegrants (1:1). The samples were appropriately diluted with dried KBr (2 mg sample in 200 mg KBr) and crushed to make pellets under hydraulic pressure of 600 kg and then the resulting pellets were subjected to analysis by an IR spectrophotometer (Shimadzu, FTIR 8700), in the region between 400 and 4000/cm. FTIR spectra of pure PLH and drug: Superdisintegrants (1:1) samples were represented in Fig. 2.

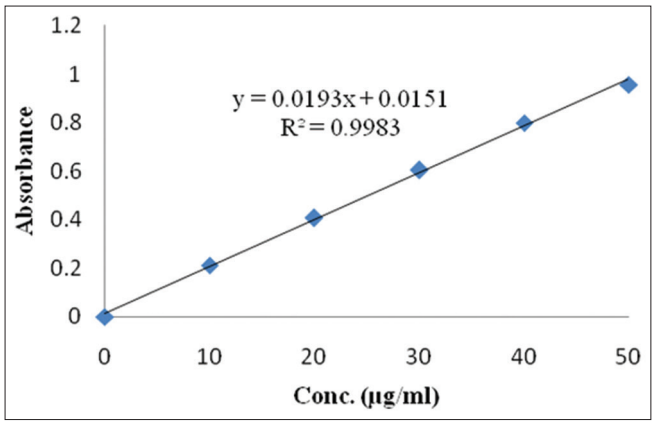

Fig. 1: Standard calibration curve of propranolol HCl in pH 6.8 phosphate buffer

Preparation of PLH ODT [9]

All the formulations were prepared by direct compression method by keeping the amount of PLH constant at 40 mg. The composition of other excipients is varied as mentioned in formulation tables (Tables 1 and 2). In these formulations SSG, CCS and CPV are used as superdisintegrants, mannitol as a directly compressible diluent, aspartame is an artificial sweetener, powder vanilla flavor as flavoring agent, magnesium stearate as a lubricant, talc as glidant, SLS as a surfactant solubility enhancer, citric acid, and $NaHCO_3$ as effervescent mixture. PLH and all the other excipients excluding magnesium stearate and talc were co-sifted through Sieve No. #40 (ASTM), blended uniformly in a poly bag for 10 minutes and lubricated with Sieve No. # 60 (ASTM), passed magnesium stearate and talc and mixed in a poly bag for an additional 2-3 minutes. Tablets were compressed on a tabulating machine (16 station, Cadmach Pharma Machinery Pvt. Ltd., India) fitted with 8 mm standard round punches with an average weight of 200 mg and hardness of 2-3 kg/cm^2.

Precompression studies [12]

The directly compressible tablet blends were evaluated for precompression studies.

Angle of repose (θ)

Was determined by funnelling method. The blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The blend was

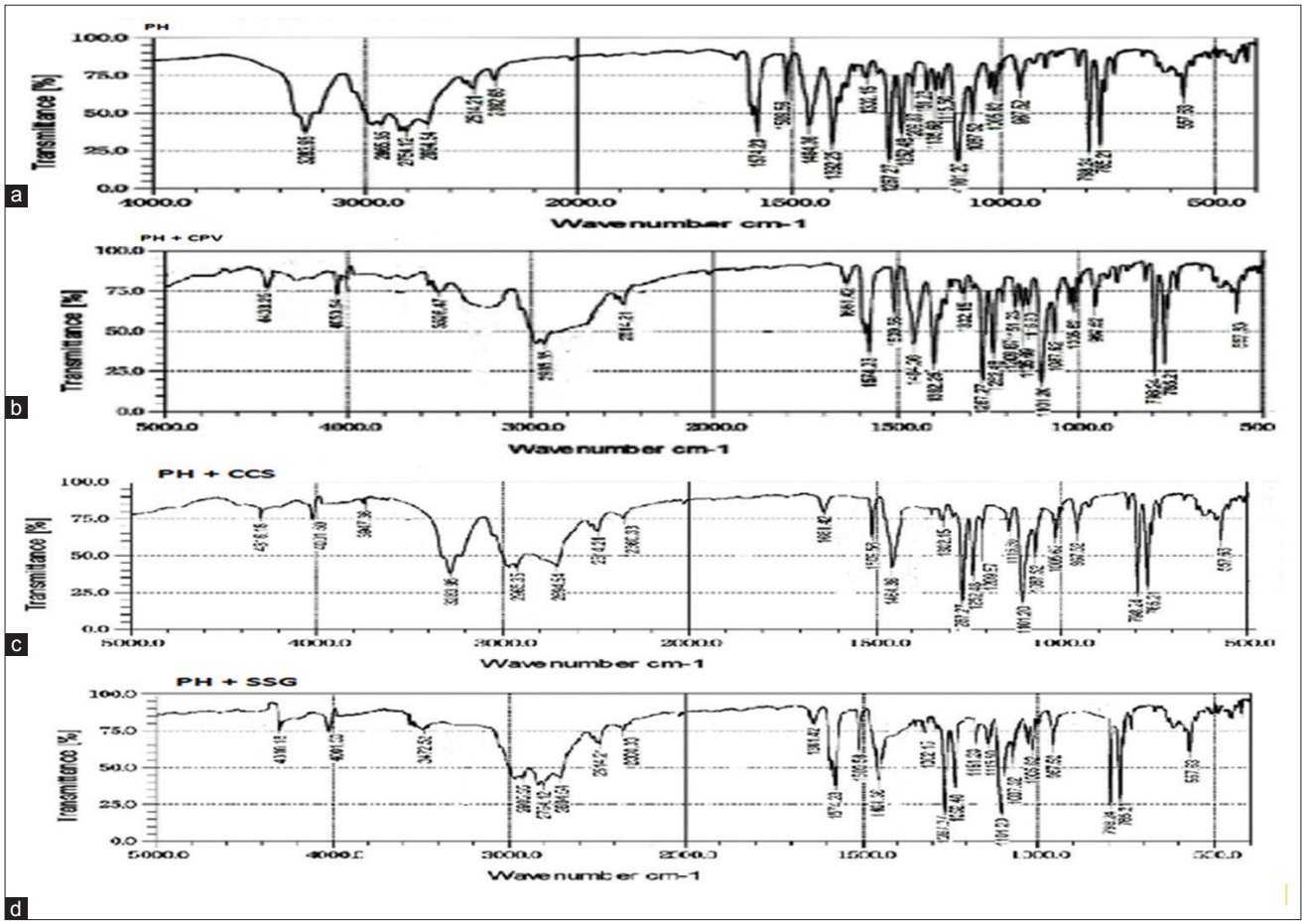

Fig. 2: Fourier transform infrared spectra of (a) propranolol HCl (PH), (b) PH+crospovidone, (c) PH+croscarmellose sodium and (d) PH+sodium starch glycolate

Table1: Formulation table of PH ODT with superdintegrents alone

%w/w superdisintegent	6% CPV	8% CPV	10% CPV	6% CCS	8% CCS	10% CCS	6% SSG	8% SSG	10% SSG
Ingredients*	**DF_1**	**DF_2**	**DF_3**	**DF_4**	**DF_5**	**DF_6**	**DF_7**	**DF_8**	**DF_9**
PH	40	40	40	40	40	40	40	40	40
CPV	12	16	20	-	-	-	-	-	-
CCS	-	-	-	12	16	20	-	-	-
SSG	-	-	-	-	-	-	12	16	20
Aspartame	10	10	10	10	10	10	10	10	10
Powder vanilla flavor	5	5	5	5	5	5	5	5	5
CA	-	-	-	-	-	-	-	-	-
$NaHCO_3$	-	-	-	-	-	-	-	-	-
SLS	4	4	4	4	4	4	4	4	4
Talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6
Mannitol	117	113	109	117	113	109	117	113	109
Total	200	200	200	200	200	200	200	200	200

*Quantity of ingredients per each tablet were expressed in Mg; average weight of a tablet is 200 mg. PH: Propranolol Hcl, ODT: Orally disintegrating tablet, CA: Citric Acid, CPV: Crospovidone, CCS: Croscarmellose sodium, SSG: Sodium starch glycolate, SLS: Sodium lauryl sulphate

Table 2: Formulation table of PH ODT with superdintegrents and effervescent mixture

%w/w superdisintegent	10% CPV			10% CCS			10% SSG		
CA: $NaHCO_3$	**1:1**	**1:2**	**1:3**	**1:1**	**1:2**	**1:3**	**1:1**	**1:2**	**1:3**
Ingredients*	**EF_1**	**EF_2**	**EF_3**	**EF_4**	**EF_5**	**EF_6**	**EF_7**	**EF_8**	**EF_9**
PH	40	40	40	40	40	40	40	40	40
CPV	20	20	20	-	-	-	-	-	-
CCS	-	-	-	20	20	20	-	-	-
SSG	-	-	-	-	-	-	20	20	20
Aspartame	10	10	10	10	10	10	10	10	10
Powder vanilla flavor	5	5	5	5	5	5	5	5	5
CA	10	10	10	10	10	10	10	10	10
$NaHCO_3$	10	20	30	10	20	30	10	20	30
SLS	4	4	4	4	4	4	4	4	4
Talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	6	6	6	6	6	6	6	6	6
Mannitol	89	79	69	89	79	69	89	79	69
Total	200	200	200	200	200	200	200	200	200

*Quantity of ingredients per each tablet was expressed in mg; average weight of a tablet is 200 mg. PH: Propranolol Hcl, ODT: Orally disintegrating tablet, CA: Citric acid, CPV: Crospovidone, CCS: Croscarmellose sodium, SSG: Sodium starch glycolate, SLS: Sodium lauryl sulphate

poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. The θ is calculated by the equation.

$$\theta = \tan^{-1} h/r \quad (1)$$

Where, θ=angle of repose, h=height of heap, and r=radius of the base of heap circle.

Density

Bulk density (BD)

A quantity of 2 g of blend from each formulation (previously lightly shaken to break any agglomerates formed) was introduced into a 10 mL measuring cylinder, and the volume is noted as bulk volume. The BD was calculated by the equation.

Bulk density=weight of powder/bulk volume (2)

Tapped density (TD)

After the determination of BD, the measuring cylinder was fitted with a TD apparatus. The tapped volume was measured by tapping the powder for 500 times. Later the tapping was done for another 750 times, and the tapped volume was noted (the difference between these two volumes should be <2%). If it is more than 2%, tapping is continued for another 1250 times, and the constant tapped volume was noted. The TD was calculated by the equation.

Tapped density=weigh of powder/tapped volume (3)

Carr's index (CI): The percentage of CI is calculated by the equation.

CI=(tapped density-bulk density)×100/tapped density (4)

Hausner's ratio (HR): Is a number that correlates to the flowability of powder. It is calculated by the equation.

HR=tapped density/bulk density (5)

Precompression studies of all the formulations were carried out in triplicate; the consolidated results (mean±SD) were tabulated in Table 3.

Postcompression studies

Tablet weight variation [12]

An electronic balance (Mettler Toledo, 3-MS-S/MS-L, Switzerland) was used to accurately weigh the individual weight of 20 tablets which were randomly selected from each formulation. The (mean±SD) values were calculated.

Friability test [12]

The friability of the 20 tablets from each formulation was tested by a friabilator (ERWEKA, TAR 120, Germany) at a speed of 25 rpm for

Table 3: Precompression studies of propranolol HCl ODT

F code	Angle of repose (θ)	BD (g/cm³)	TD (g/cm³)	Hausner's ratio	Carr's index (%)
DC_1	31.08	0.528	0.692	1.31	23.69
DC_2	30.78	0.541	0.652	1.21	17.02
DC_3	31.92	0.530	0.614	1.16	13.68
DC_4	29.53	0.538	0.639	1.18	15.80
DC_5	29.62	0.512	0.621	1.21	17.55
DC_6	30.12	0.521	0.630	1.21	17.30
DC_7	28.17	0.543	0.640	1.17	15.15
DC_8	29.61	0.509	0.599	1.17	15.05
DC_9	30.09	0.534	0.682	1.27	21.70
EF_1	30.68	0.540	0.633	1.17	14.69
EF_2	29.18	0.543	0.652	1.21	16.71
EF_3	29.72	0.531	0.611	1.15	15.06
EF_4	29.32	0.572	0.670	1.17	14.62
EF_5	27.71	0.552	0.689	1.24	19.88
EF_6	27.32	0.546	0.678	1.24	19.46
EF_7	26.45	0.543	0.689	1.26	21.11
EF_8	29.64	0.580	0.677	1.16	14.32
EF_9	27.29	0.569	0.703	1.23	19.06

ODT: Orally disintegrating tablet, BD: Bulk density, TD: Tapped density

4 minutes, the tablets were then de-dusted, reweighed, and percentage weight loss was calculated by the equation,

% friability=(initial weight-weight after friability) ×100/initial weight (6)

Hardness test [12]

To evaluate the diametrical crushing strength, three tablets from each formulation were tested using a hardness tester (Monsanto type hardness tester, MHT-20, Campbell Electronics, India). The mean±SD values were calculated.

Thickness [12]

Of three tablets from each formulation was determined using a vernier caliper (Mitutoyo Corporation, Japan). The mean±SD values were calculated.

In vitro disintegration time and fineness of dispersion [13]

It is specified in the European Pharmacopeia (EP 6.0) that disintegration time determination procedure for ODT is same as that of conventional uncoated tablets and that the tablets should be dispersed within <3 minutes. The obtained tablet's dispersion was passed through a sieve screen with a nominal mesh aperture of 710 mm to confirm the fineness of dispersion. It was carried out in replicates of three tablets from each formulation and mean±SD values were calculated.

Wetting time and water absorption ratio [14]

A piece of tissue paper folded twice was placed in Petri dish having an internal diameter of 5.5 cm, containing 6 mL of water. A tablet was placed on the paper and the time required for complete wetting was measured as wetting time, using a stopwatch. The wetted tablet was then reweighed and water absorption ratio (R) was determined using following equation.

$$\text{Water absorption ratio } (R)=([W_a-W_b]/W_b)\times 100 \quad (7)$$

Where, W_b and W_a were the weights of the tablet before and after water absorption.

Assay [9]

To evaluate the drug assay, three tablets from each formulation were powdered in motor and pestle. Blend equivalent to 1 mg of PLH was accurately weighed and transferred into a 100 mL volumetric flask. Then, the volume was made up to 100 mL with pH 6.8 phosphate buffer and ultra-sonicated for 2 minutes to extract the PLH from the tablet blend and filtered through 0.45 µm polytetrafluoroethylene (PTFE) filter disc, the filtrate was suitably diluted if necessary and its absorbance was measured by UV-visible spectrophotometer at 279 nm.

Postcompression studies of all the formulations, except friability test were carried out in triplicate (n=3); the consolidated results as (mean±SD) were tabulated in Table 4.

In vitro dissolution studies [9]

Were performed for three tablets form each formulation using the dissolution apparatus (Labindia Disso 2000, Labindia Analytical Instruments Pvt Ltd, India) with USP-II/paddle. Each dissolution flask contains 900 mL of pH 6.8 phosphate buffer; speed of the paddle was maintained at 50 rpm; the temperature was kept stable at 37°C±0.5°C. At required time intervals, 5 mL of dissolution media was withdrawn with a pipette containing 0.45 µ (PTFE) filter disc, suitably diluted if necessary and its absorbance was measured by UV-visible spectrophotometer at 279 nm. Furthermore, 5 mL of fresh pH 6.8 phosphate buffer was replaced to the dissolution flask to keep the volume of dissolution medium constant. The dissolution profiles were represented graphically in Fig. 3.

In vitro dissolution kinetics [15]

The *in vitro* drug release data were fitted into kinetic models to plot dissolution profiles (cum% drug dissolved versus time) and first order plots (log% drug undissolved versus time) as per the following equations.

$$\text{Zero order: } Q_t=Q_0+K_0t \quad (8)$$

$$\text{First order: } \log Q_t=\log Q_0-K_1t/2.303 \quad (9)$$

Where, Q_t is the amount of the drug dissolved in time t, Q_0 is the initial amount of drug in the solution; K_0 and K_1 refers to the rate constants of zero and first order, respectively.

In vitro dissolution kinetic parameters

Dissolution efficiency at 10 minutes (DE_{10}) by trapezoid rule [16]; and time for 90% drug release (t_{90}) were calculated from dissolution profiles. Equations for calculating DE_{10}:

$$[AUC]_{t1}^{t2}=\frac{1}{2}(C_1+C_2)(t_2-t_1) \quad (10)$$

Table 4: Postcompression studies of propranolol HCl ODT

F code	Weight variation	Hardness (kg/cm²)	Thickness (mm)	Friability* (%)	Wetting time (seconds)	*In vitro* DT (seconds)	Water absorption ratio (%)	Assay (%)
DC_1	0.202±2.97	2.8±0.24	3.5±0.24	0.74	50.00±0.01	98.02±0.30	6.21±0.61	94.24±0.97
DC_2	0.205±0.97	2.9±0.16	3.5±0.48	0.66	44.66±1.21	90.12±1.53	9.41±0.02	95.68±0.48
DC_3	0.202±0.99	2.7±0.24	3.5±0.48	0.49	42.66±1.77	89.16±0.90	13.82±0.53	95.47±0.12
DC_4	0.204±1.47	2.9±0.12	3.4±0.97	0.49	58.66±1.10	117.20±1.33	6.53±1.12	94.24±0.44
DC_5	0.201±0.99	2.8±0.12	3.5±0.24	0.49	54.66±2.21	115.5±2.08	8.11±1.55	95.68±0.16
DC_6	0.207±0.48	2.9±0.16	3.5±0.97	0.66	54.25±1.10	102.34±0.88	11.66±0.77	96.47±0.48
DC_7	0.202±1.98	2.9±0.16	3.4±0.79	0.80	59.66±1.10	121.22±2.5	3.41±0.01	95.29±0.12
DC_8	0.204±2.45	2.7±0.24	3.5±0.48	0.82	56.33±0.87	117.23±1.15	4.86±0.99	95.29±0.44
DC_9	0.203±1.47	2.8±0.24	3.5±0.48	0.40	56.12±2.21	113.09±2.10	5.87±1.44	94.66±1.12
EF_1	0.206±1.60	2.6±0.16	3.5±0.48	0.25	16.66±1.12	26.33±0.44	23.31±2.42	96.40±0.44
EF_2	0.202±1.68	2.7±0.24	3.5±0.24	0.49	13.33±0.88	22.00±1.33	23.71±0.71	97.73±1.12
EF_3	0.206±0.97	2.7±0.24	3.5±0.48	0.41	11.00±1.12	13.66±1.11	25.39±5.12	96.57±0.48
EF_4	0.206±0.58	2.7±0.24	3.5±0.79	0.41	16.00±0.66	29.66±0.88	19.36±1.02	95.69±1.11
EF_5	0.208±1.25	2.8±0.24	3.5±0.48	0.33	19.00±0.66	28.24±0.66	21.35±2.45	95.21±1.12
EF_6	0.202±1.13	2.9±0.16	3.4±0.48	0.33	20.32±0.88	27.00±1.33	22.59±2.93	96.02±0.12
EF_7	0.204±0.78	2.6±0.16	3.5±0.97	0.49	24.31±1.11	37.00±1.33	18.45±1.34	98.72±0.16
EF_8	0.202±0.79	2.7±0.24	3.5±0.79	0.49	23.00±0.66	35.66±0.44	20.74±2.25	94.88±0.66
EF_9	0.204±0.58	2.8±0.24	3.5±0.79	0.66	26.33±0.44	34.66±1.78	21.24±1.13	97.57±0.66

*Except friability test all other were performed as n=3 and the values are given as mean±SD. ODT: Orally disintegrating tablet

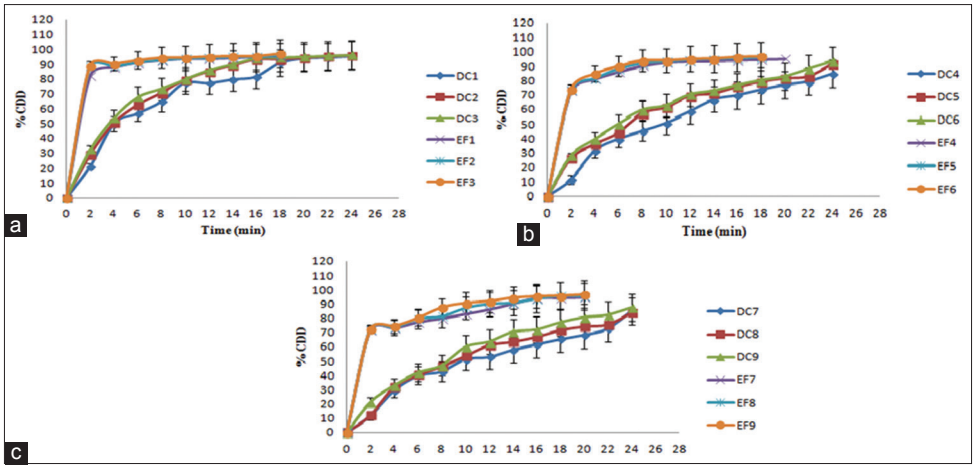

Fig. 3: *In vitro* disso profiles of propranolol HCl orally disintegrating tablet (a) with crospovidone, (b) with croscarmellose sodium and (c) with sodium starch glycolate

$$[AUC]_0^{10}=[AUC]_0^2+[AUC]_2^4+[AUC]_4^6+[AUC]_6^8+[AUC]_8^{10} \quad (11)$$

$$DE_{10}=\frac{[AUC]_0^{10}}{\text{Total area at 10 minutes}}\times 100 \quad (12)$$

Where, $[AUC]_{t1}^{t2}$ =Area under curve between time points t_1 and t_2

Total area at 10 minutes=10×100=1000 cm^2

The first order dissolution rate constant (K_1) and regression coefficient (r^2) of the first order profiles were calculated from first order plots. The consolidated *in vitro* dissolution kinetic parameters of PLH ODT were tabulated in Table 5.

Accelerated stability studies [17]

Of the optimized formulation EF_3, was carried out; by placing 20 tablets each in a 10 CC HDPE bottle; according to ICH guidelines in a humidity chamber (NSW-175, Narang Scientific Work, India) maintained at 45°C±2°C and 75%±5% relative humidity up to 6 month. At the end of 1 month, 2 month, 3 month, and 6 month, the respective samples were withdrawn and evaluated for postcompression studies. The chemical stability of drug in the 6 month-accelerated stability sample of formulation EF_3, was compared with the drug alone by FTIR studies (Shimadzu, FTIR 8700), recorded in the region of 400-4000/cm, by KBr pellet method. The consolidated results of postcompression studies on accelerated stability samples of formulation EF_3; except friability test were carried out in triplicate and the results as mean±SD were tabulated in Table 6. FTIR spectra of pure PLH and 6 month-accelerated stability sample of formulation EF_3 were represented in Fig. 4. *In vitro* dissolution profiles of accelerated stability samples of formulation EF_3 were represented graphically in Fig. 5.

RESULTS AND DISCUSSION

Standard calibration curve of PLH in pH 6.8 phosphate buffer

Based on the measurement of absorbance at 279 nm in pH 6.8 phosphate buffer in the concentration range of 10-50 µg/ml, a straight line with an equation: y=0.0193x+0.0151 and a regression coefficient (r^2) of 0.9983 was obtained (Fig. 1).

Drug-excipient compatibility/FTIR studies

The FTIR spectrum of PLH showed a characteristic secondary amine –NH stretch at 3280/cm, a C–H stretch at 2964/cm, an aryl C¼C stretch at 1579/cm, an aryl O–CH_2 asymmetric stretch at 1240/cm, an aryl O–CH_2 symmetric stretch at 1030/cm, and a peak at 798/cm due to alpha-substituted naphthalene. Comparison of FTIR spectra of pure drug with the drug: Superdisintegrant (1:1 ratio) samples indicate the

absence of chemical interaction between PLH and superdisintegrants used in the study (Fig. 2).

Precompression studies

Of the directly compressible blends of all formulations, reveals that the angle of repose was found between 26° 45' and 31° 92', BD between 0.509 and 0.580 g/cm^3, TD between 0.611 and 0.703 g/cm^3, HR between 1.15 and 1.31, and CI between 15.05% and 23.69%. The micromeritic studies indicate better flow and compression characteristics of all the formulations. In these formulations sugar based excipient (Mannitol) is used as diluent, which impart good flow and compressibility to the directly compressible blends. It also exhibits the high aqueous solubility and sweetness, and hence, impart taste masking property and a pleasing mouth feel [18] (Table 3).

Postcompression studies

Of all the formulations, reveals that the weight variation of tablets was found to be 0.201-0.208%. The average thickness of tablets was found to be 3.4-3.5 mm. The average hardness of the tablets was 2.6-2.9 Kg/cm^2, indicating satisfactory mechanical strength. The % weight loss in the friability test ranges from 0.25% to 0.82%, which was N-methyltryptamine 1% as per official requirement of Indian Pharmacopeia indicating a good mechanical strength of tablets. Assay of all the prepared batches is within 94.24-98.72% of the labeled content, indicating content uniformity of all the formulations. The wetting time of all the formulations was obtained in the range of 11.00-59.66 seconds. As the concentration of superdisintegrant increases, there is a significant decrease in the wetting time and *in vitro* disintegration time. Wetting is related to the inner structure of the tablets, hydrophilicity of the components and swelling mechanism of superdisintegrant. The water absorption ratio was related to the hydrophilicity of the matrix. This phenomenon was similar even with the combination of superdisintegrants with effervescent mixture in different ratios (1:1; 1:2, and 1:3). The order of superdisintegrant's efficiency is CPV>CCS>SSG. The formulation EF_3 (with 10% of CPV+1:3 ratio of citric acid: $NaHCO_3$, respectively) which shows minutes wetting time of 11.00 seconds; minutes *in vitro* disintegration time of 13.66 seconds and max water absorption ratio of 25.39% is an optimized formulation (Table 4). Decrease in the wetting and disintegration times were clearly observed in formulations with a combination of superdisintegrants and effervescent mixture than the formulations with superdisintegrants alone. This is due to the synergistic effect of a combination of two approaches, namely superdisintegrants addition with effervescence approach. The evolved CO_2 gas accelerated the breakdown of the tablets [19].

***In vitro* dissolution studies**

Dissolution profiles are represented graphically in Figs. 1 and 2 indicate that the release rate increases with an increase in concentration of superdisintegrant. Based on the values of K_1, the order of superdisintegrants in enhancing the dissolution rate of PLH in its ODT is (CPV>CCS>SSG). Formulations with a combination of superdisintegrants and effervescent mixture are having rapid disintegration and dissolution rate when compared to the formulations with superdisintegrants alone. A combination of two approaches, namely superdisintegrant addition with effervescence approach resulted in an increase in the drug dissolution rate, could be due to the synergistic effect of superdisintegrant and CO_2 produced due to the wetting of the tablets. The evolved gas accelerated the breakdown of the tablets as indicated by their lesser disintegration times [19]. Dissolution rate also enhances with an increase in citric acid: $NaHCO_3$ ratio of effervescent mixture (1:1<1:2<1:3) as it requires three molecules of sodium bicarbonate to neutralize one molecule of citric acid. Hence, the desired ratio of citric acid: $NaHCO_3$=1: 3.44 by weight [20]. Formulation EF_3 (with 10% CPV AND 1:3, citric acid: $NaHCO_3$ ratio,

Table 5: *In vitro* dissolution kinetics of propranolol HCl ODT

F code	t_{90} (minutes)	DE_{10} (%)	First order dissolution rate constant; K_1 (minutes^{-1})	First order regression coefficient (r^2)
DC_1	18	46.35	0.110	0.667
DC_2	16	50.40	0.113	0.652
DC_3	14	53.44	0.118	0.653
DC_4	>24	30.83	0.123	0.788
DC_5	24	38.92	0.133	0.809
DC_6	24	41.72	0.140	0.802
DC_7	>24	29.97	0.127	0.908
DC_8	>24	31.47	0.131	0.915
DC_9	>24	34.64	0.149	0.927
EF_1	6	80.00	0.129	0.973
EF_2	6	81.84	0.136	0.979
EF_3	4	82.74	0.141	0.974
EF_4	8	75.39	0.074	0.993
EF_5	8	76.32	0.086	0.969
EF_6	6	77.86	0.094	0.966
EF_7	14	68.83	0.064	0.935
EF_8	14	69.89	0.068	0.982
EF_9	10	71.92	0.080	0.993

ODT: Orally disintegrating tablet

Table 6: Postcompression studies on accelerated stability samples of formulation EF_3

Parameter	Initial	45°C/75% RH 1 month	45°C/75% RH 2 month	45°C/75% RH 3 month	45°C/75% RH 6 month
Weight variation (%)	0.206±0.97	0.223±0.21	0.241±0.32	0.244±0.14	0.252±0.52
Hardness (kg/cm^2)	2.7±0.24	2.6±0.12	2.6±0.35	2.5±0.12	2.5±0.33
Thickness (mm)	3.5±0.48	3.5±0.32	3.5±0.11	3.5±0.54	3.5±0.43
*Friability (%w/w)	0.41	0.43	0.51	0.53	0.50
Dissolution (seconds)	11.00±1.12	11.35±0.12	12.35±0.34	12.54±0.38	12.55±0.42
Wetting time (seconds)	13.66±1.11	14.12±0.13	14.76±0.32	14.23±0.45	14.52±0.21
Water absorption ratio (%)	25.39±5.12	25.78±0.15	26.23±0.22	27.35±0.42	27.11±0.35
Assay (%)	96.57±0.48	96.52±0.12	96.40±0.44	95.29±0.44	94.66±1.12

*Except friability test all other were performed as n=3 and the values are given as mean±SD. RH: Relative humidity

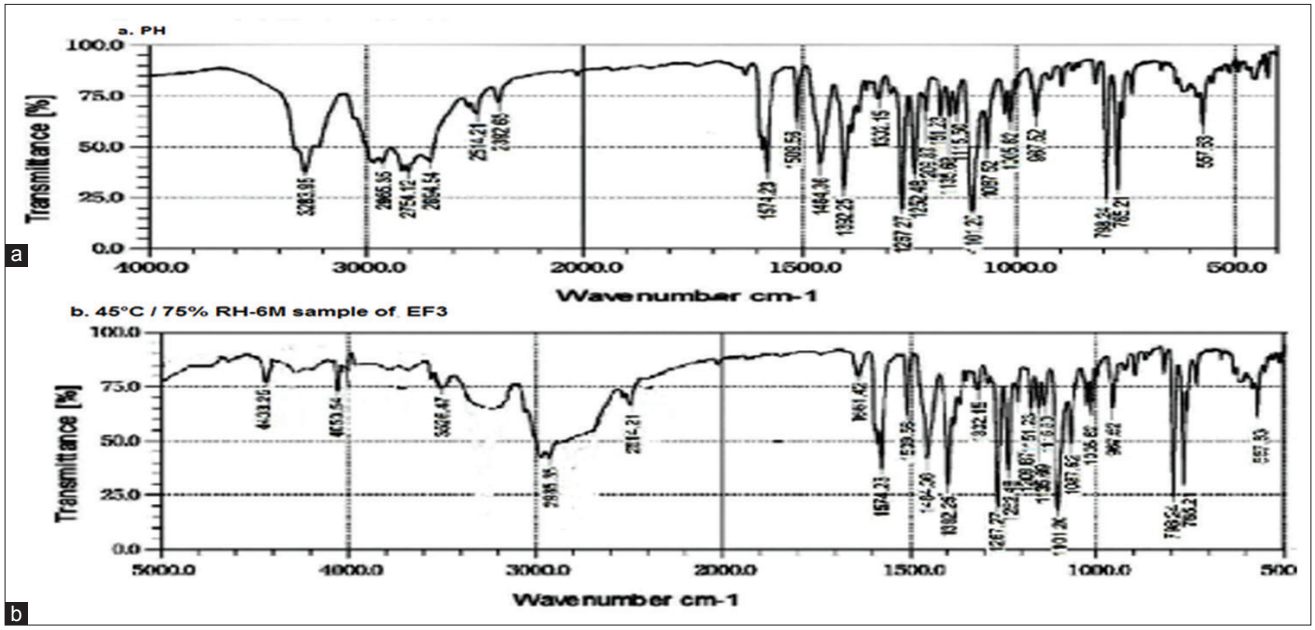

Fig 4: Fourier transform infrared spectra of (a) propranolol HCl and (b) 45°C/75% relative humidity - 6 month sample of formulation EF_3

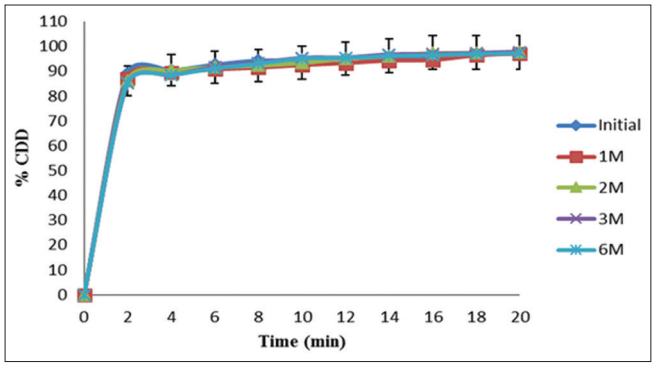

Fig. 5: Dissolution profiles of accelerated stability samples of formulation EF_3

respectively) released 90% of drug within lesser time of 4 minutes than others, was considered as the optimal ODT (Fig. 3).

In vitro dissolution kinetics

Formulation EF_3 had the highest DE_{10} (82.74%); K_1 (0.141/minutes) with r^2(0.974) and the lowest t_{90}(4 minutes). Hence, it is the optimal ODT (Table 5).

Accelerated stability studies

As there were no significant differences in postcompression and *in vitro* dissolution profiles of initial and accelerated stability samples up to 6 months, formulation, EF_3 passes the test for stability. FTIR spectrum of pure PLH is having primary amide group and two secondary amino groups. Two N-H stretching bands resulting from symmetrical and asymmetrical stretching in 3400-3520/cm correspond to primary amide group [18]. An FTIR spectrum of 6 month-accelerated stability sample of optimized formulation (EF_3) shows the same functional groups at the corresponding frequencies as that of pure drug. This, indicates no significant chemical interaction and change in functional groups of PLH occurred during the accelerated stability study of optimized formulation, EF_3 (Table 6, Figs. 4 and 5).

CONCLUSION

In the view of above findings, there is drug-excipient compatibility between PLH and superdisintegrants used in the study. All the formulations passed the pre- and post-compression parameters. The release rate of PLH from ODT increases as the concentration of superdisintegrants as well as the ratio of citric acid: $NaHCO_3$ of effervescent mixture increases. Formulations with an effervescent mixture are having rapid disintegration and dissolution rate when compared to the formulations with superdisintegrants alone. The order of superdisintegrants in enhancing the dissolution rate of PLH is CPV>CCS>SSG. Formulation EF_3 (with 10% CPV and 1:3, citric acid: $NaHCO_3$ ratio respectively) had the highest DE_{10} (82.74%); K_1 (0.141/minutes) with r^2 (0.974) and the lowest t_{90} (4 minutes), was considered as the optimal ODT. An accelerated stability study on EF_3 in the final pack up to 6 months indicates it passed the test for stability. Therefore, an effective PLH ODT was formulated by the direct compression technique with disintegration attained by a combination of superdisintegrants and effervescent mixture. This PLH ODT will better manage the hypertension, by fastening the onset of action and enhancing the bioavailability of PLH in comparison to its conventional tablets.

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