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FORMULATION AND EVALUATION OF PROPRANOLOL HYDROCHLORIDE ORAL DISINTEGRATING TABLETS

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Keywords:

Propranolol hydrochloride, Oral disintegrating tablets, Super disintegrants, *In-vitro* dissolution profile

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ABSTRACT: Background and purpose of the study: Propranolol hydrochloride beta-adrenergic receptor antagonist utilized in the treatment of high blood pressure, atrial fibrillation, myocardial infarction, angina and migraine headaches. The pharmacokinetic parameters make Propranolol hydrochloride an appropriate candidate for oral disintegrating tablets. This work aims to develop orally disintegrating tablets for Propranolol hydrochloride and to evaluate their pre-compression, physicochemical properties and water absorption ratio, disintegrating time, wetting time, *in-vitro* dispersion, time, and *in-vitro* dissolution. **Research rationale:** To attain rapid disintegration, dissolution/absorption, and further improving the bioavailability of the drug. To resolve swallowing issues in geriatric, pediatric patients by rapid disintegration in saliva and to treat high blood pressure, angina, atrial fibrillation, myocardial infarction, migraine. **Methods:** Oral disintegrating tablets prepared by direct compression technique using super disintegrants like Crospovidone, Croscarmellose sodium, Sodium starch glycolate, and Pregelatinised starch in several concentrations. The prepared batches of tablets were evaluated for pre-compression parameters and weight variation, thickness, hardness, friability, drug content, wetting time, disintegrating time, *in-vitro* dispersion time and *in-vitro* dissolution. The physicochemical interaction between drug and excipients were investigated by Fourier transform infrared spectroscopy. **Results:** Among the prepared formulations, F5 (Crospovidone 6%) was optimized and shows the maximum cumulative amount of drug release 97.05% in 14 min and disintegration time is 14.25 sec. Spectroscopic studies showed no evidence of interaction between the drug and excipients. **Conclusion:** Propranolol orally disintegrating tablets were found to possess faster disintegration time and drug release.

INTRODUCTION: Among the various routes of drug delivery system oral route is the most preferred route to the patient because of their convenience in self-administration, pain avoidance, and most significantly the patient compliance. However, people experience inconvenience in swallowing conventional forms, such as when water is not available. To overcome this drawback, a new drug delivery system has been developed known as orally disintegrating tablets (ODT) [1].

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US Food and Drug administration center for drug evaluation and research (CDER) defines an ODT as " A solid dosage form containing medicinal substances, that disintegrates quickly, typically at usually within a matter of seconds, once placed upon the tongue". ODT is that the most popular route for low bioavailability as a result of the

tablets disintegrate within the mouth; drugs may undergo pre gastric absorption, thereby avoiding the first-pass metabolism; moreover, it provides fast onset of action [2]. Propranolol hydrochloride is a synthetic beta-adrenergic blocking agent antagonist used to treat high blood pressure, myocardial infarction, angina, and migraine [3-5]. It has 26% oral bioavailability because of aqueous solubility that produces absorption and dissolution rate-limited [6-8]. In the present study, to develop orally disintegrating tablets of Propranolol Hydrochloride (HCl) to attain fast disintegration, dissolution/absorption and further improving the bioavailability of the drug and additionally to resolve to swallow issues in geriatric, pediatric patients by fast disintegration in saliva and improve patient compliance [9].

From the pharmacokinetics (absolute bioavailability 26%) Propranolol HCl may be an appropriate candidate for ODT. Different concentrations of super disintegrants like Cross Povidone, Croscarmellose, Pregelatinised starch, Sodium starch glycolate are used to increase drug release [10]. The present investigation aim was to develop ODT for Propranolol and to evaluate for pre-formulation, physicochemical and wetting time, disintegrating time, *in-vitro* dispersion time, and *in-vitro* dissolution release [11].

MATERIALS AND METHODS:

Materials Used: Propranolol hydrochloride gift sample from Hetero Drugs, Hyd. Crospovidone, Croscarmellose sodium obtained from Hi media chemicals, sodium starch glycolate from Loba cheme, magnesium stearate, and lactose from Qualikem fine chem. Pvt. Ltd. Pregelatinised starch from Hetero Drugs, Hyd. Avicel pH-101 and potassium dihydrogen phosphate, from SD fine chemicals Mumbai, sodium hydroxide from Finar chemicals limited, Ahmedabad, and Eosin (dye) from Selkrom, Mumbai.

Preparation of Tablets: All the desired ingredients were passed through 40 mesh to get uniform size particles and weighed accurately. Drugs and excipients were mixed within the increasing order of the weights in a mortar **Table 1**. To this mixture, lubricant was added. This powder was passed through the hopper of the 16 station rotary tableting machine and punched into tablets using 7 mm. The method is similar for all the formulations, which are prepared by the direct compression technique [12].

TABLE 1: COMPOSITION OF PROPRANOLOL HCl ODT

Ingredients/code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Propranolol (mg)	40	40	40	40	40	40	40	40	40	40	40	40
Sodium starch glycolate (%)	3	6	9	-	-	-	-	-	-	-	-	-
Crospovidone (%)	--	-	3	6	9	-	-	-				
Croscarmellose sodium (%)	--	-	-	-	-	-	3	6	9	-	-	-
Pregelatinized starch (%)	-	-	-	-	-	-	-	-	-	3	6	9
Lactose (mg)	21.4	17.8	14.2	21.4	17.8	14.2	21.4	17.8	14.2	21.4	17.8	14.2
Avicel pH (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Magnesium stearate (mg)	5	5	5	5	5	5	5	5	5	5	5	5

Evaluation of Pre and Post Compression Characteristics: Fourier transform infrared spectroscopy studies (FTIR) were carried out to determine possible interaction studies between drug and excipients [13, 14].

The blend was subjected to various pre-compression parameters like bulk density, tapped density, Carr's index, Hausner ratio and angle of repose.

The compressed tablets were characterized for various physicochemical parameters like weight variation, thickness, hardness, friability, drug content, wetting time, disintegration time and dissolution test.

Weight Variation, Hardness and Thickness: Twenty tablets were randomly chosen from each formulation weighed individually, and their average weight was calculated, and percentage deviation was determined. Not more than two of the weight of the individual tablets deviated from the average weight [15]. Thickness was measured by randomly selecting ten tablets from each formulation utilizing vernier calipers [15]. The tablet hardness of different formulations was measured using the Monsanto hardness tester. Generally, a minimum hardness of 4 kg/cm^2 is considered acceptable for uncoated tablets [16]. The hardness for ODTs ought to be ideally 1-3 kg/cm^2.

Friability: It is measured by the mechanical strength of tablets. This test is performed employing a laboratory friability tester known as Roche Friabilator. The friability was determined as the percentage loss of tablet weight was calculated [17].

% Friability = (initial weight-final weight) / (final weight) × 100

Drug Content: Randomly 10 tablets were selected, weighed, and finely powdered, and the amount of powder equivalent to one tablet was added to 100 ml of 0.1N HCL in a conical flask and placed on a rotary shaker. An aliquot of the solution was centrifuged, and therefore, the supernatant was filtered through a 0.22 µ filter; absorbance was measured against blank using UV Visible spectro-photometer at 229 nm [18].

Wetting Time and Water Absorption Ratio: Wetting time is closely related to the inner structure of tablets and the hydrophilicity of the excipients. A tissue paper folded twice was placed in a small petri dish containing water. The time needed for water to succeed in the upper side of the tablet to completely wet them was noted as the wetting time. The water absorption ratio, R, was determined according to the following equation:

$$R = (W_a - W_b)/W_b \times 100$$

Where, W_b, W_a is the weight before and after water absorption, respectively [14].

***In-vitro* Disintegration Time:** It was determined using the USP disintegration apparatus (Electrolab ED-2L, India), a tablet was added in each tube placed in the disintegration medium maintained at 37 ± 0.5 ºC. The time taken for the tablet to disintegrate completely was noted as Disintegration time [15].

***In-vitro* Dissolution Test:** The dissolution test was carried out utilizing USP type II apparatus at 50 rpm in 900 ml of 6.8 pH phosphate buffer and methanol (1:1) as dissolution medium maintained at 37 ± 0.5 ºC.

Periodically 5 ml of samples were withdrawn, filtered, and analyzed at 229 nm with a UV spectrophotometer. Each dissolution study was performed in triplicate [16-18].

RESULTS AND DISCUSSION: Pre-formulation studies were carried, and therefore the results obtained by evaluating the powder blends of drug and excipients were recorded in **Table 2**. Bulk density and tapped density were found within the range of 0.413-0.437 g/cc and 0.507-0.528 g/cc, respectively. The value of Hausner's was between 1.15-1.23 (<1.25), indicating that all batches of powder blends had good compressibility. Values of the angle of repose (Ɵ) were found within the range of 15.92-22.32, showing good flowability and compressibility and may be used for direct compression. The powder blends were free-flowing, as indicated by the values.

TABLE 2: PROPRANOLOL ODTs PRE-FORMULATION STUDIES

Formulation	Bulk density(g/cc)	Tapped density (g/cc)	Hausner ratio	Carr's Index (%)	The angle of repose(θ)
F1	0.428±0.18	0.521±0.21	1.17±0.16	15.85±0.13	19.78±0.19
F2	0.432±0.34	0.516±0.28	1.19±0.30	16.27±0.16	22.32±0.21
F3	0.430±0.21	0.528±0.25	1.18±0.22	15.56±0.12	21.55±0.10
F4	0.420±0.18	0.511±0.13	1.15±0.16	17.21±0.10	18.15±0.33
F5	0.418±0.34	0.515±0.28	1.20±0.11	16.12±0.09	20.22±0.18
F6	0.431±0.15	0.508±0.24	1.20±0.08	14.52±0.18	15.92±0.90
F7	0.419±0.22	0.514±0.30	1.22±0.16	15.53±0.16	19.02±0.18
F8	0.422±0.31	0.521±0.28	1.23±0.11	16.84±0.11	20.24±0.11
F9	0.413±0.26	0.507±0.19	1.22±0.13	12.85±0.13	15.78±0.22
F10	0.432±0.14	0.518±0.17	1.16±0.15	15.02±0.16	18.23±0.24
F11	0.425±0.20	0.520±0.15	1.18±0.13	17.64±0.24	20.54±0.26
F12	0.420±0.16	0.508±0.20	1.17±0.09	15.25±0.40	21.34±0.34

The tablets were prepared by direct compression method, and that they were evaluated for varied post-compression parameters, and the data were tabulated in **Table 3**.

Weight variation was found to be 117.12 ± 0.39 mg to 120.05 ± 0.52 mg. The thickness varies between 3.05 ± 0.10 mm to 3.15 ± 0.09 mm, confirming all the formulations' uniformity.

Friability values were less than 1%; hardness was between 2.78 ± 0.23 to 2.98 ± 0.39 kg/cm^2. From the data, it was cleared that the tablets had enough hardness and friability to withstand stress and were mechanically stable during handling and transportation. It is an indication of the good mechanical resistance of the tablets. Drug content was found to be between 85.48±0.45 mg to 99.09 ± 0.11 mg.

TABLE 3: EVALUATION OF PHYSICOCHEMICAL CHARACTERISTICS

Formulation	Weight	Thickness (mg)	Hardness (mm)	Friability (kg/cm^2)	Drug content (%)
F1	118.05±0.62	3.10±0.10	2.92±0.30	0.59	85.48±0.45
F2	119.01±0.51	3.05±0.12	2.78±0.23	0.65	89.01±0.49
F3	118.03±0.61	3.15±0.09	2.95±0.21	0.58	92.27±0.23
F4	118.01±0.67	3.12±0.11	2.83±0.46	0.68	93.60±0.40
F5	117.12±0.39	3.13±0.16	2.85±0.42	0.41	95.70±0.30
F6	120.05±0.52	3.14±0.14	2.96±0.56	0.47	98.01±0.09
F7	118.25±0.45	3.05±0.10	2.93±0.36	0.56	94.05±0.45
F8	118.04±0.28	3.13±0.05	2.82±0.40	0.45	98.07±0.13
F9	120.01±0.09	3.12±0.07	2.98±0.39	0.58	99.09±0.11
F10	119.03±0.05	3.05±0.12	2.78±0.23	0.65	89.01±0.49
F11	118.05±0.02	3.12±0.11	2.83±0.46	0.68	93.60±0.40
F12	119.05±0.08	3.14±0.14	2.96±0.56	0.47	90.33±0.45

The values of wetting time **Fig. 1** vary between 08.39 ± 0.22 to 25.02 ± 0.48 sec. On comparing the super disintegrants, the formulations containing Crospovidone take less wetting time than the other formulations.

The water absorption ratio **Fig. 2** ranged from 10.23 ± 0.55 to 30.56 ± 0.45%. Tablets containing crospovidone quickly wicked water and were hydrated; however, were soft as compared with tablets prepared with croscarmellose sodium, sodium starch glycolate, and pregelatinized starch. The tablets with Sodium starch glycolate, croscarmellose sodium, and pregelatinized starch remained dry and hard. The wetting time is an important step for the disintegration process; from the wetting time it was reported that a linear relationship exists between wetting time and disintegration time. It was reported that as the disintegration time decreases water absorption ratio increases. The *in-vitro* disintegration time **Fig. 3** for all the 12 formulations varied from 11.47 ± 0.65 to 49.41 ± 0.24 sec.

The disintegration time of formulation (F5) containing 97% Crospovidone was found to be lower than 11.25 ± 0.28 and was selected as the best ODT formulation among all the 12 formulations. This is due to the fast uptake of the water from the medium, swelling, and burst effect. *In-vitro* dispersion **Fig. 4** is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the 12 formulations varied between 5.46 ± 0.35 to 38.94 ± 0.25 sec.

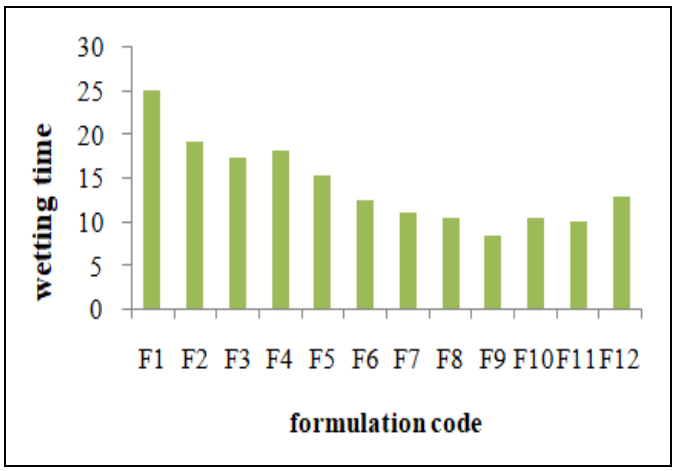

FIG. 1: WETTING TIME OF ODT

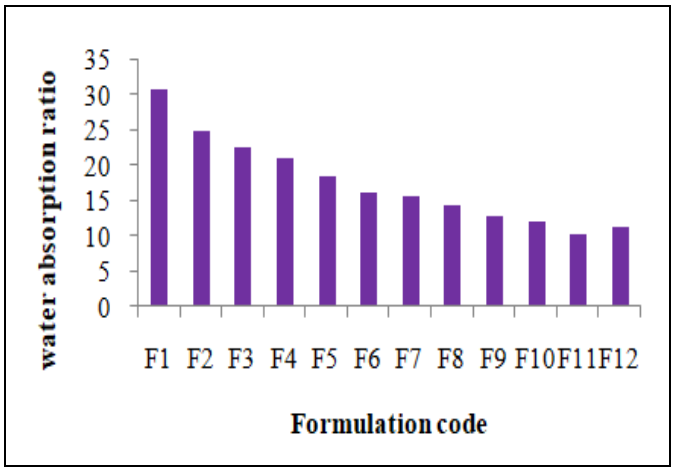

FIG. 2: WATER ABSORPTION RATIO OF ODT

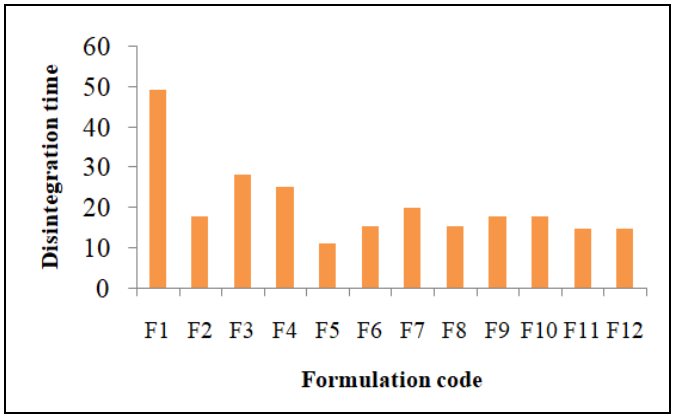

FIG.3: DISINTEGRATION TIME OF ODT

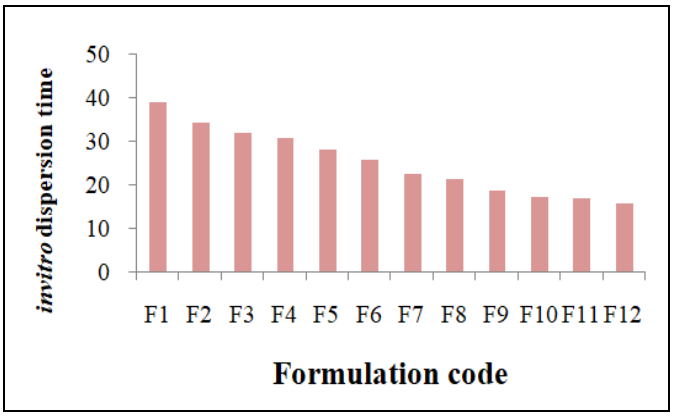

FIG. 4: *IN-VITRO* DISPERSION TIME OF ODT

The dissolution **Table 4** and **5** rate was found to extend linearly with increasing concentration of super disintegrant. Formulations F1, F2, and F3 which contained concentrations of Sodium starch glycolate have recorded drug release 75.6 ± 0.55%, 89.64 ± 0.81%, and 85.52 ± 0.34% respectively within 30 min. Formulations F4, F5, and F6 that contained concentrations of Crospovidone have recorded drug release 95.65 ± 0.35% at 30 min, 97.05 ± 0.25% at 14 min and 90.56 ± 0.76% at 16 min respectively. Formulations F7, F8 and F9 contained concentrations of Croscarmellose sodium 75.56 ± 0.67% at 30 min, 96.85 ± 0.38% at 6 min, and 85.76 ± 0.55% at 30 min. Formulations F10, F11, and F12 containing concentrations of Pregelatinised starch 80.05 ± 0.44, 83.49 ± 0.67, and 81.47 ± 0.56 % respectively at the end of 30 min. Among all the formulation F5 containing 6%, Crospovidone exhibited fast drug release 97.05 ± 0.25% at 14 min compared with other super disintegrants.

TABLE 4: CUMULATIVE % DRUG RELEASE

Time (min)	F1	F2	F3	F4	F5	F6
2	20.26±0.18	15.64±0.20	10.5±0.17	10.06±0.51	18.44±0.09	20.42±0.08
4	32.31±0.19	20.22±0.10	15.12±0.31	25.44±0.15	30.81±0.30	35.02±0.09
6	40.24±0.10	40.58±0.17	30.37±0.11	46.59±0.05	37.08±0.07	40.16±0.12
8	41.68±0.32	51.48±0.11	40.48±0.39	59.56±0.09	69.27±0.27	53.65±0.35
10	44.27±0.27	60.36±0.28	51.48±0.09	61.58±0.51	72.78±0.34	57.25±0.46
12	45.40±0.12	63.09±0.21	54.27±0.13	61.86±0.39	75.05±0.37	60.01±0.09
14	48.20±0.20	68.05±0.25	63.27±0.15	76.55±0.34	97.05±0.25	62.45±0.65
16	52.5±0.51	70.55±0.34	69.25±0.25	80.33±0.45	84.55±0.65	90.56±0.76
18	61.5±0.42	75.34±0.54	75.34±0.44	83.25±0.55	82.65±0.45	80.45±0.55
20	66.3±0.34	78.56±0.76	81.63±0.22	90.34±0.65	80.75±0.75	75.76±0.35
30	75.6±0.55	89.64±0.81	85.52±0.34	95.65±0.35	75.85±0.97	60.55±0.45

The FTIR **Table 6** spectral analysis of Propranolol alone showed that the principal peaks were observed at wavenumbers of 3437.47 cm^{-1} (N-H stretching), 1431.12 cm^{-1} (C-H stretching), 1679.09 cm^{-1} (C=O stretching). These results recommend that there's no interaction between drug and disintegrants utilized in this study, and the drug was found to be compatible with all the excipients.

TABLE 5: CUMULATIVE % DRUG RELEASE

Time (min)	F7	F8	F9	F10	F11	F12
2	23.18±0.43	45.59±0.17	24.07±0.13	14.22±0.55	18.08±0.76	15.16±0.56
4	35.52±0.12	68.02±0.18	30.06±0.30	15.34±0.65	20.66±0.56	20.65±0.67
6	43.78±0.27	96.85±0.38	42.05±0.31	22.48±0.76	30.76±0.76	43.67±0.78
8	45.22±0.13	90.56±0.24	54.25±0.18	25.32±0.98	35.55±0.34	47.77±0.34
10	46.73±0.22	48.77±0.19	63.65±0.01	27.65±0.65	40.76±0.56	57.44±0.76
12	47.05±0.15	30.07±0.23	67.09±0.11	28.05±0.45	51.66±0.34	60.55±0.56
14	51.45±0.25	22.05±0.65	72.05±0.33	35.76±0.56	62.67±0.67	67.57±0.56
16	52.65±0.76	20.55±0.76	75.76±0.77	44.34±0.97	67.45±0.68	69.44±0.78
18	54.55±0.44	19.76±0.78	77.97±0.45	60.21±0.43	69.77±0.34	70.33±0.46
20	63.24±0.45	18.43±0.65	78.04±0.98	73.23±0.56	75.78±0.45	75.23±0.34
30	75.56±0.67	15.75±0.98	85.76±0.55	80.05±0.44	83.49±0.67	81.47±0.56

TABLE 6: FTIR STUDIES OF PROPRANOLOL ODT (WAVELENGTH CM^{-1})

	IRN-H	C-O	C-N	O-H
Propranolol HCl	2942	1393	1265	3269
F5 (optimized formulation)	2918	1367	1265	3858

CONCLUSION: It was concluded that Orodispersible tablets are a promising carrier for Propranolol HCl designed to treat high blood pressure, atrial fibrillation, myocardial infarction, migraine. ODTs were prepared by direct compression method using different concentrations of super- disintegrants. Among all ODT's, the Formulation F5 containing 6% Crospovidone exhibited the lowest disintegration time and rapid drug release compared with other super disintegrants.

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