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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS – PROPRANOLOL HCL

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ABSTRACT

Mouth dissolving tablets are patient friendly dosage form that rapidly disintegrate in mouth without need of water. In this present formulation the main objective is to develop mouth dissolving tablets of Propranolol HCl. Propranolol HCl is a β-adrenergic receptor antagonist, it blocks the action of epinephrine and nor epinephrine on both β1- and β2-adrenergic receptors. The present study investigates to development of novel fast dissolving tablet of Propranolol HCl which was by first pass metabolism, rapid disintegration, dissolution/absorption, and further improving the bioavailability of the drugs. The Mouth dissolving tablets were prepared by Direct compression methods using by using super disintegrants like Crospovidone XL, Sodium Carboxymethyl Starch, Pregelatinized starch in several concentrations. The prepared batches of tablets were evaluated post-compression parameters like weight variations, thickness, hardness, friability, drug content, disintegration time, and in-vitro dissolution. The optimized formulation of f5 mouth dissolving tablet containing Crospovidone XL showed maximum cumulative amount of drug release 97.5% in 11min and disintegration time 11sec. Propranolol HCl mouth dissolving tablet containing 9% Crospovidone XL exhibit the lowest disintegration time and rapid drug release compared with other super disintegrants.

Keywords: Propranolol HCl, Mouth dissolving tablets, Super disintegrants, Direct compression.

INTRODUCTION

Orally administered medications reign supreme as the most common and globally preferred route of drug delivery for decades.

Despite their widespread use for convenience, self-administration, and ease of manufacture, tablets can pose swallowing difficulties for pediatric and geriatric patients. To address this challenge, recent

advancements in novel drug delivery systems (NDDS) have prioritized the development of rapidly dissolving and dispersible tablets. These innovative formulations aim to enhance patient compliance and improve the safety and efficacy of medications by providing a more convenient dosage form.

Mouth dissolving tablets (MDTs) are a convenient single-dose medication that disintegrates rapidly in the mouth with saliva, eliminating the need for water. This quick dissolving action allows for faster absorption and onset of medication effects. Additionally, MDTs bypass the first-pass metabolism in the gut, potentially leading to reduced dosage and fewer side effects. Their rapid disintegration is achieved through a porous tablet matrix that readily absorbs saliva. Key factors in developing MDTs include maximizing this porosity, incorporating suitable disintegrants, and using highly water-soluble ingredients. [1,2,3]

MDTs: Rapid Release and Enhanced Bioavailability

Mouth Dissolving Tablets (MDTs) are designed for rapid disintegration in the mouth within minutes, as dictated by the European Pharmacopoeia. This swift breakdown is achieved by incorporating super disintegrants like sodium starch glycolate, carboxymethylcellulose, and polyvinylpyrrolidone into the formulation. These disintegrants cause the tablet to rapidly disintegrate upon contact with saliva, releasing the medication.

MDTs can potentially improve the bioavailability of certain drugs by enabling absorption through the oral cavity in addition to the usual absorption in the stomach. This pre-gastric absorption occurs when the dispersed drug in saliva bypasses first-pass metabolism in the liver, potentially reducing the required dose and minimizing side effects.

Propranolol: A Versatile Beta-Blocker

Propranolol is a medication classified as a non-selective beta-blocker. This means it blocks the effects of adrenaline (epinephrine) and noradrenaline (norepinephrine) on both beta-1 and beta-2 receptors throughout the body. While it has minimal internal stimulant activity (intrinsic sympathomimetic activity), it does possess strong membrane stabilizing properties.

Propranolol finds use in treating various conditions, including hypertension (high blood pressure), supraventricular tachycardia (rapid heart rhythm originating above the ventricles), ventricular arrhythmias (irregular heartbeats in the lower chambers), pheochromocytoma (a tumor of the adrenal gland), thyrotoxicosis (overactive thyroid), and vascular headaches.

This white powder dissolves readily in water and ethanol, but has limited solubility in ether. Notably, only around 26% of orally administered propranolol enters the bloodstream.

METHODS

A. Determination of λ_{max}

To find the wavelength of maximum absorption (λmax) of Propranolol HCl, a solution was prepared by dissolving 10mg of it in water. This solution was then diluted and analyzed using a UV-visible spectrophotometer between 200 and 400 nanometers. The analysis identified the λmax value.

B. Development of standard calibration curve of Drug

A standard calibration curve was created to determine the drug's concentration. This involved dissolving 10mg of the drug in water to make a 100ml solution. Further dilutions were prepared to obtain a range of concentrations between 10 and 50 micrograms per milliliter (µg/ml). Finally, the absorbance of each solution was measured at a wavelength of 290nm using a UV spectrophotometer.

C. PREPARATION OF TABLET

For all formulations, a direct compression technique was used. First, all ingredients were precisely weighed and then sifted through a 40-mesh sieve to ensure uniform particle size. Next, the drug and

excipients were mixed in a mortar, following a weight-ascending order as detailed in Table 1. Finally, a lubricant was added to the mixture, and the entire powder blend was fed through a single-station tableting machine. Using a 7mm punch, the machine compressed the powder into tablets [4].

table 1: composition of propranolol hcl mdt formulation

Ingredients/code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Propranolol (mg)	20	20	20	20	20	20	20	20	20	20	20	20
Sodium starch glycolate (%)	3	6	9	-	-	-	-	-	-	-	-	-
Crospovidone XL (%)	-	-	3	6	9	-	-	-	-	-	-	-
Croscarmellose sodium (%)	-	-	-	-	-	-	3	6	9	-	-	-
Pregelatinized starch (%)	-	-	-	-	-	-	-	-	-	3	6	9
Lactose (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Avicel pH (mg)	40	37	54	57	34	43	40	37	34	40	37	34
Magnesium stearate (mg)	5	5	5	5	5	5	5	5	5	5	5	5

D. EVALUATION POST COMPRESSION CHARACTERISTICS

1. Weight Variation, Hardness and Thickness:

Quality control checks were performed on each formulation. Twenty tablets were randomly selected and weighed individually. The average weight and percentage deviation from the average were then calculated. To ensure uniformity, no more than two tablets were allowed to deviate significantly from the average weight. Additionally, ten tablets from each formulation were randomly chosen to measure their thickness using Vernier calipers. Finally, a Monsanto hardness tester was used to assess the tablet hardness of each formulation. For uncoated tablets, a minimum hardness of 4 kg/cm^2 is generally considered acceptable. However, MDTs ideally require a lower hardness range of 1-3 kg/cm^2.

2. Friability:

Friability, a measure of a tablet's resistance to chipping or breaking during handling, is assessed using a laboratory instrument called a Roche Friabilator. The test involves tumbling the tablets and then calculating the percentage weight loss as an indicator of friability. [7].

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

3. Drug Content:

To determine drug content, ten tablets were randomly chosen, weighed, and ground into a fine powder. A portion of the powder equivalent to a single tablet was then added to 100ml of 0.1N hydrochloric acid (HCl) solution in a conical flask. The flask was shaken on a rotary shaker to aid dissolution. After centrifugation, the clear liquid portion (supernatant) was passed through a 0.22 micrometer filter. Finally, the absorbance of this filtered solution was measured at 290 nanometers using a UV-Visible spectrophotometer, with a blank solution used for comparison[8].

4. Wetting Time and Water Absorption Ratio:

Wetting time is a crucial factor for mouth-dissolving tablets (MDTs) and is influenced by the tablet's internal structure and the water-loving properties (hydrophilicity) of its ingredients. To measure wetting time, a folded tissue paper is placed in a small petri dish filled with water. The tablet is then positioned on the tissue. The time it takes for the water to completely wet the top surface of the tablet is recorded as the wetting time. The water absorption ratio, R, was determined according to the following equation:

$R = (Wa - Wb)/Wb \times 100$

Where, Wb, Wa is the weight before and after water absorption, respectively.

5. In-vitro Disintegration Time:

Disintegration time, a key characteristic of MDTs, was measured using a standard instrument called the USP disintegration apparatus. A tablet was placed in each tube of the apparatus, which contained a disintegration medium maintained at a constant temperature of 37°C ± 0.5°C. The time it took for the tablet to completely disintegrate was recorded as the disintegration time.

6. In-vitro Dissolution Test:

The drug release profile of the tablets was evaluated using a standard dissolution test. This test employed a USP Type II apparatus set at 50 rotations per minute (rpm). The dissolution medium consisted of 900ml of a phosphate buffer solution (pH 6.8) mixed in a 1:1 ratio with methanol, and maintained at a constant temperature of 37°C ± 0.5°C. Samples of the dissolution medium (5ml) were withdrawn periodically, filtered, and analyzed using a UV spectrophotometer at a wavelength of 290nm. The entire dissolution study was repeated three times (triplicate) to ensure accuracy.

RESULT AND DISCUSSION

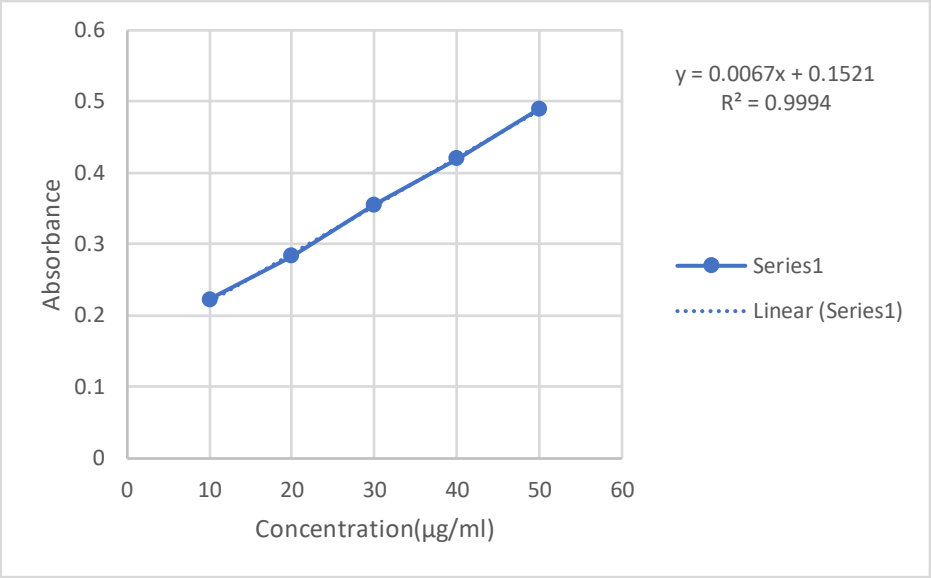
A. DETERMINATION OF λ_{MAX}

Analysis using a UV-visible spectrophotometer revealed a maximum absorption wavelength (λmax) of 290nm for the drug in water.

B. DEVELOPMENT OF STANDARD CALIBRATION CURVE

table no. 2: standard calibration curve of propranolol hcl

Sr.no.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	10	0.222
3	20	0.283
4	30	0.355
5	40	0.42
6	50	0.49



The tablets were manufactured using direct compression and evaluated for various parameters after compression. The results, summarized in Table 3, demonstrate good uniformity across all formulations. Weight variation ranged from 117.12 ± 0.75mg to 120.05 ± 0.52mg, and thickness varied between 3.05 ± 0.10 mm to 3.15 ± 0.09 mm.

Tablet evaluation revealed excellent mechanical properties for handling and transportation. Friability values were all below 1%, indicating minimal weight loss during processing. Hardness ranged from 3.78 ± 0.23 kg/cm2 to 4.00 ± 0.20 kg/cm2, demonstrating sufficient strength to withstand stress. Drug content analysis showed satisfactory levels, ranging from 85.48 ± 0.45 mg to 99.09 ± 0.11 mg.

table 3: evaluation of physicochemical characteristics

Formulation	Weight	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	118.05±0.62	3.10±0.10	3.92±30	0.59	85.48±0.45
F2	119.01±0.51	3.05±0.12	3.78±23	0.65	89.01±0.49
F3	118.03±0.61	3.15±0.09	3.95±21	0.58	92.27±0.23
F4	118.01±0.67	3.12±0.11	3.83±46	0.68	93.60±0.40
F5	117.12±0.75	3.13±0.2	4.00±20	0.31	98.2±0.60
F6	120.05±0.52	3.14±0.14	3.96±56	0.47	98.01±0.09
F7	118.25±0.45	3.05±0.10	3.93±36	0.56	94.05±0.45
F8	118.04±0.28	3.13±0.05	3.82±40	0.45	98.07±0.13
F9	120.01±0.09	3.12±0.07	3.98±39	0.58	99.09±0.11
F10	119.03±0.05	3.05±0.12	3.78±23	0.65	89.01±0.49
F11	118.05±0.02	3.12±0.11	3.83±46	0.68	93.60±0.40
F12	119.05±0.08	3.14±0.14	3.96±56	0.47	90.33±0.45

Wetting time, as illustrated in Figure 1, ranged from 8.39 ± 0.22 seconds to 25.02 ± 0.48 seconds. Notably, formulations containing Crospovidone XL exhibited significantly faster wetting times compared to those with other superdisintegrants.

Water absorption, as shown in Figure 2, ranged from 10.23 ± 0.55% to 30.56 ± 0.45%. Formulations with Crospovidone XL displayed the fastest water uptake and hydration, resulting in a softer texture compared to tablets containing Croscarmellose Sodium, Sodium Starch Glycolate, and Pregelatinized Starch. These latter formulations remained drier and harder.

Wetting time plays a crucial role in disintegration. As Figure 1 demonstrates, a clear correlation exists between faster wetting times and lower disintegration times (Figure 3). This indicates that formulations with quicker water absorption disintegrate faster. The in-vitro disintegration times for all 12 formulations ranged from 11.47 ± 0.65 seconds to 49.41 ± 0.24 seconds.

Formulation (F5) containing 9% Crospovidone XL emerged as the optimal MDT formulation among all twelve due to its superior disintegration time (faster than 11.25 ± 0.28 seconds). This is attributed to Crospovidone XL's ability to rapidly absorb water, causing the tablet to swell and disintegrate quickly. Another crucial parameter is in-vitro dispersion time (Figure 4), which measures how long it takes for the tablet to completely disperse. Dispersion times for all formulations ranged from 5.46 ± 0.35 to 38.94 ± 0.25 seconds.

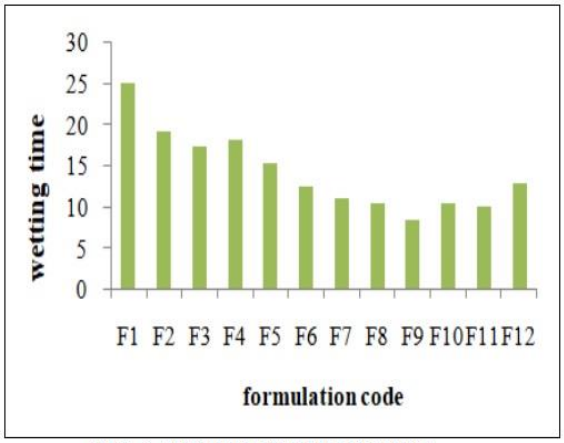


FIG. 1: WETTING TIME OF ODT

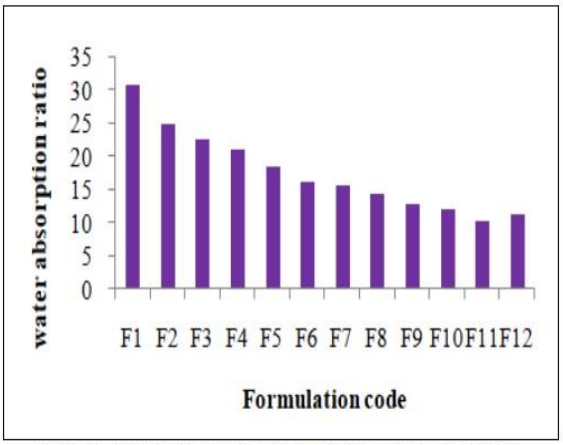


FIG. 2: WATER ABSORPTION RATIO OF ODT

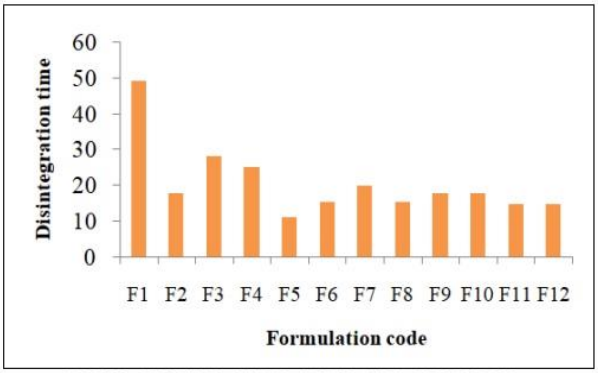


FIG.3: DISINTEGRATION TIME OF ODT

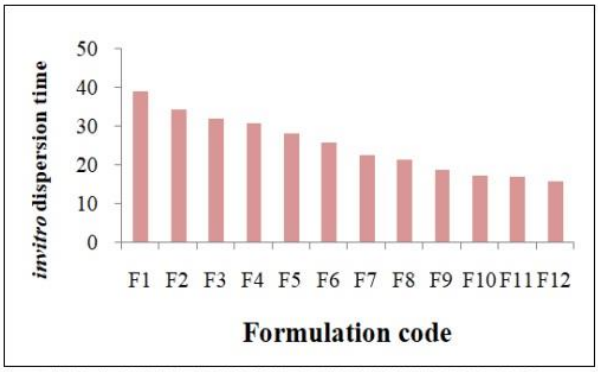


FIG. 4: *IN-VITRO* DISPERSION TIME OF ODT

Dissolution studies (Tables 4 & 5) revealed a positive correlation between superdisintegrant concentration and drug release rate. Formulations containing Sodium Starch Glycolate (F1, F2, F3) achieved moderate drug release (75.6% - 89.6%) within 30 minutes. Notably, formulations with Crospovidone XL (F4, F5, F6) exhibited significantly faster release. Formulation F5, containing 6% Crospovidone XL, achieved the most rapid release, with 97.05% of the drug released within just 14 minutes. Croscarmellose Sodium (F7, F8, F9) offered a mixed performance, with one formulation achieving fast release (96.85% at 6 minutes) and the others showing moderate release by 30 minutes. Finally, Pregelatinized Starch (F10, F11, F12) displayed the slowest release profiles, with all

formulations releasing less than 85% of the drug within 30 minutes. Overall, Crospovidone XL (particularly at 6% concentration in formulation F5) emerged as the most effective superdisintegrant for promoting rapid drug release.

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	97.05±0.25	60.01±0.09
14	48.20±0.20	68.05±0.25	63.27±0.15	76.55±0.34	90.05±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

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

CONCLUSION

This study successfully developed Orodispersible Tablets (ODTs) of Propranolol HCl using direct compression with various superdisintegrants. The ODTs are a promising new dosage form for this medication, offering benefits like rapid disintegration and improved patient compliance for treating conditions like high blood pressure, atrial fibrillation, myocardial infarction, and migraine. Among all formulations, F5 containing 9% Crospovidone XL demonstrated the most favorable results. It achieved the fastest disintegration time and superior drug release compared to formulations with other superdisintegrants.

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