DESIGN, DEVELOPMENT AND ASSESSMENT OF QUICK DISSOLVING TABLETS OF AN ANTI-HYPERTENSIVE DRUG USING NATURAL SUPERDISINTEGRANT

Srishti Tyagi*[1], Narendra Ahirwal[2]

[1] Student, Agra public college of higher education & research centre

[2] Assistant Professor, Agra public college of higher education & research centre

* Corresponding Author

Srishti Tyagi

e-mail: bpart0001@gmail.com

ABSTRACT

In the current investigation, Quick Dissolving Tablets containing the medicine labetalol hydrochloride were successfully made using the direct compression method and *Plantago ovata* natural superdisintegrant. The formulation of the Quick Dissolving Tablets, which is based on labetalol hydrochloride, offers quick release of the medication. the immediate entry of these pills into the bloodstream. Six formulations in all were created. The tablet formulation number F6 (which contains 18 mg of *plantago ovata*) provides the drug with 99.80% of its maximum release out of the six tablet formulations that were produced. Based on the results of the disintegration time and dissolving profile, the formulation F6 was found to be the best of all the produced formulations. Particularly in cases of hypertension, Quick Dissolving Tablets containing Formulation F6 and 18 mg of *plantago ovata* can be used effectively. *Plantago ovata* was determined to be the optimum superdisintegrant for the production of Labetalol hydrochloride Quick Dissolving Tablets based on the aforementioned findings.

KEYWORDS: Quick dissolving Tablets, *Plantago ovata*, Superdisintegrant, Labetalol HCl,

Hypertension

INTRODUCTION

A formulation a tablet consists of API, excipients is placed upon the tongue then its disintegrate quickly, within a few seconds of time[1]. For much better and more acceptable conventional way of administration of medication for patients the concept of development of orally disintegrating tablets has been emerged[2]. Swallowing of conventional solid dosage forms becomes difficult in patients diseases or health problems included surprising or sudden coughing and recurring emesis and also motion sickness[3]. This drug delivery system is an effective way of release of drug[4]. Having the advantages of each of liquid formulations and usual tablet dosage forms is major advantage of Quick Dissolving Tablets and provide solution to the patients suffering from problem of swallowing[5]. On administration of oral disintegrating tablet there is an easy and rapid dissolution or disintegration of tablet in contact with saliva in a few seconds[6]. Quick Dissolving Tablets are of low-cost and mainly made by a direct compression method called[7]. The Quick Dissolving Tablets with an advantage of increased bioavailability because when administered then these tablets are absorbed from oral cavity through saliva and then as a results the first pass metabolism is bypass, also superior mouth feel generally for children and bitter taste masked by taste masking procedure[8]. Improve patient compliance in case of geriatrics, pediatrics, psychiatric and other patients having swallowing problems[9].

Oral administration of labetalol hydrochloride as tablet dosage form is rapidly absorbed but experience first pass metabolism which causes degradation of drug and shows only 25% oral bioavailability having half-life of 4-6 hours. To overcome this problem, Quick Dissolving Tablets of labetalol hydrochloride will be prepared using natural superdisintegrant *i.e. plantago ovata* by direct compression method, which disintegrates in a few seconds in oral cavity without water need and reaches systemic circulation with better bioavailability by avoiding first pass metabolism and offer reduces dose and side effects.

MATERIALS AND METHOD

Labetalol HCl was obtained from Triveni Interchem, 134 Pancharatna, Char Rasta G.I. D.C., Vapi-396-195. Gujrat, India, as gift. Plantago ovate purchased from Modern Agro Forestry, Lucknow, Mannitol from Mannitol Qindao Bright Moonsea Wood Group Co. Ltd. and

Microcrystalline cellulose from International Speciality Product Technologies limited, USA. All chemical reagents used in this work were of analytical grade.

Preformulation studies

Physical appearance: Drug sample shows was noted for its organoleptic properties complied fully with pharmacopoeial specifications.

Melting point: Labetalol HCl drug melting point determination by Macro scientific works apparatus of melting point determination. The stuff that want to be tested to a very fine powder was reduced. At one end capillary was sealed and filled with sufficient tapping with enough powder of drug. The thermometer was put in silver pocket and capillary was put in capillary holder/pocket. The light button was switched ON. The temperature was set at 0^{o}C. Continuous heating was required for complete melting of the drug and noted down the reading of thermometer. This study was performed in triplicate.

Solubility studies: Solubility of Labetalol HCl was determined in Ethanol, Methanol, Water, and 0.1 N HCL and in different basic pH buffers of 6.8, 7.2, 7.4, and 7.8.

Ultraviolet-visible spectroscopy:

Scanning and determination of maximum wavelength (lambda max): In range of 200-400 nm means UV wavelength region light absorb by most of drugs, because of aromatic structure and double bonds presence. On electronic balance weighed Labetalol HCl 100 mg quantity was and in 6.8 pH phosphate buffer (100ml) dissolved to gives-1000 µg/ml concentration. Labetalol is soluble in water. To gives 10 µg/ml concentration diluted this solution 1 ml with 6.8 pH phosphate buffer (100ml) in separate volumetric flask and scanned on a UV-visible spectrophotometer (UV-2203 Systronics, Germany) between 200 to 400nm.

Preparation of Phosphate buffer Solution pH 6.8: In 200 ml volumetric flask to 0.2 M Potassium dihydrogen phosphate (50 ml) a 0.2 M NaOH (22.4 ml) was added after that made up the volume upto 200ml with water.

Standard calibration curve of Labetalol in 6.8 pH Phosphate buffer: A Labetalol Hydrochloride drug 100 mg was dissolved in 6.8 pH phosphate buffer small amount after that

make up the volume up to 100 ml using same 6.8 pH phosphate buffer which is called as stock-I solution.

In another volumetric flask 10 ml of the above prepared solution (stock-I solution) is diluted upto 6.8 pH Phosphate buffer (100 ml) which is known by name means Stock-II solution. By pipetting out 1 ml, 2 ml, 4 ml, 6 ml, 8 ml and 10 ml serial dilutions were made from the stock-II solution to obtain solutions of drug in the concentration ranging from 10, 20, 40, 60, 80, 100 µg/ml. At 303 nm solutions absorbance using UV-visible spectrophotometer was measured. A concentration Vs absorbance graph was plotted.

Drug polymer compatibility studies by FTIR spectroscopy: The interaction between the Labetalol HCl and natural superdisintegrant were determined by using the FT-IR spectrophotometer (Agilent Cary 630 FTIR spectrophotometer) where in infrared spectra of Labetalol HCl and plantago ovata were carried out using the KBr disk method. 450 to 4000 cm -1 was the scanning range and 1/cm was resolution. With FT-IR analysis every change in drug chemical composition were investigated after in combination with polymers.

Formulation Development

Method of preparation of Quick Dissolving Tablets of Labetalol HCl: A well-known methodology indicates that the direct compression procedure is the simplest and most straightforward way to make tablets. Quick Dissolving Tablets based on labetalol HCl were created via direct compression. The drug candidate and other formulation components were weighed with the use of an analytical weighing balance. The aforementioned blend of additives also contained a medication. then blended well, after which they were sieved for uniform size. thereafter, they were then compacted into tablets.

Isolation of Mucilage: Mucilage was extracted from Plantago ovata seeds by soaking them in distilled water for 48 hours to act as a solvent. Following a brief period of boiling, the seeds' entire mucilage release occurred into the distilled water that had been holding them. The material that was released after being squeezed out of muslin fabric for filtering and marc separation was then collected from the water. An equivalent volume of acetone was added to the filtrate before the mucilage was precipitated. The precipitated separated mucilage was then collected and oven dried at less than 60°C before being stored for further use in a desiccator.

Table No. 1: Composition of different batches Oral disintegrating Labetalol HCl tablets

S. No.	Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
1.	Labetalol HCl	100	100	100	100	100	100
2.	Plantago Ovata	8	10	12	14	16	18
3.	Microcrystalline Cellulose	40	38	36	34	32	30
4.	Mannitol	30	30	30	30	30	30
5.	Magnesium stearate	5	5	5	5	5	5
6.	Talc	5	5	5	5	5	5
7.	Aspartame	10	10	10	10	10	10
8.	Mint	2	2	2	2	2	2

Evaluation of Quick Dissolving Tablets

Pre-compression parameters

Angle of repose: Angle of repose was determined using the cylinder technique. In this approach, a powder combination is poured through a funnel to create a cone with the greatest possible height (h). The funnel can be lifted vertically to achieve this. The value of the heap radius (r) allowed for the calculation of the angle of repose (q):

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

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

Bulk density: Through a glass funnel, a powdered combination is gradually poured into a graduating cylinder (50 ml) to determine bulk density. occupied volumes while recording the samples.

Bulk density = sample weight (gram) / sample occupied volume

Tapped density: A graduated cylinder was filled with a carefully measured amount of powder mixture added with a funnel. First, record the beginning volume of the powder blend in the graduated cylinder. Next, tap the powder mixture for 500, 750, or 1250 times until the volume

decline stops. Finally, record the final volume of the powder mixture after tapping, which is the tapped volume.

Tapped density = sample weight (gram)/ volume after tapping

Carr's index: Carr`s Index or Compressibility index is one of the vital measures that from densities determination means bulk and tapped density determinations can be obtained.

CI = Tapped density –Bulk Density/ Tapped density

Hausner's ratio: It is defined as a parameter for inter particulate interactions measurement.

Hausner's Ratio= Tapped Density/ Bulk density

Post-compression parameters

Weight variation: A graduated cylinder was filled with a carefully measured amount of powder mixture added with a funnel. First, record the beginning volume of the powder blend in the graduated cylinder. Next, tap the powder mixture for 500, 750, or 1250 times until the volume decline stops. Finally, record the final volume of the powder mixture after tapping, which is the tapped volume.

Hardness: Hardness metre made by Monsanto (Harrison's Machinery, New Delhi) used to shatter a tablet that has been put at an angle in order to determine the hardness or crushing strength. A tablet was held in the tester's two jaws, which were positioned parallel to one another. The reading at this moment ought to be 0 kg/cm2. After then, a consistent force was given by moving the knob until the tablet broke. Now, the value was recorded.

Thickness: Six tablets from each batch were chosen, and their thickness and diameter were measured using digital venire callipers (Vernier calliper, Mitutoyo, India).

Friability: The friability of the tablets was assessed using the Friabilator (VTP-2D Veego, India). Ten pills were first weighed, and then they were transferred to the friabilator. The friabilator was run for four minutes at a speed of 25 rpm. Again weighing the pills was done (Wfinal). The following formula was used to calculate % friability:

% friability = (initial weight–final weight x 100) / initial weight

Wetting time and water absorption ratio: A piece of tissue paper that had been folded twice was put in a tiny petri dish with 6ml of water. A tablet was put gently on the tissue paper surface. The time of wetness, or how long it takes water to reach the tablet's upper surface, was then observed.

A Formula which is used to calculate Water absorption ratio (R) are as follows:

R= 100 x [tablet weight after absorption – tablet weight before absorption] / tablet weight before absorption.

Percent drug content: Ten pills Chosen pulverised them. One tablet equivalent of powder was weighed and dissolved in 10ml of phosphate buffer before being added to 100ml of volume. filtered above the remedy. One millilitre of the filtrate was collected, diluted with 6.8 phosphate buffer to the mark, and spectrophotometrically analysed at 303 nm.

In-vitro **Disintegration time:** A tablet and discs are inserted in each of the six tubes of the disintegration test instrument (Electrolab). The water-maintained temperature of 37.2°C and the duration of the whole tablet's total disintegration.

In-vitro **dissolution studies:** The release profile of the medication was investigated in an in-vitro dissolving system (TDT-08L Electrolab, India) at 50 rpm in phosphate buffer pH-6.8 (900ml) of dissolution media. The temperature was held at 37.50°C. Five millilitres of the dissolving medium were removed and filtered every five minutes. The UV-Visible spectrophotometer measured the quantity of medication emitted at 303 nm, and the standard calibration curve revealed the drug concentration

RESULTS AND DISCUSSION

Preformulation Studies

Physical appearance: The drug sample was found to be white with bitter and without any odor.

Melting point: Found to be 180-182˚C by capillary tube method.

Solubility studies: Labetalol HCl's solubility was assessed in water, 0.1N HCl, ethanol, methanol-like organic solvents, and several basic pH buffers of 6.8, 7.2, 7.4, and 7.8. It was shown to be soluble in several basic pH buffers of 6.8, 7.2, 7.4, and 7.8 as well as in ethanol, methanol, water, and 0.1 N HCl.

Ultraviolet-visible spectroscopy: A UV-visible spectrophotometric technique was used to estimate the UV-visible content of labetalol HCl. 6.8 pH calibration curve for phosphate buffer was created and regressed for a straight line. The 0.998 R2 value in the phosphate buffer at 6.8 pH indicates good linearity. The calibration curve was following Beer Lambert's law.

Scanning and determination of maximum wavelength (lambda max): The phosphate buffer with a pH of 6.8 was determined to be the solvent medium with the highest solubility for labetalol HCl. prepared the standard stock solution and used the UV spectrophotometer to scan it in accordance with the methodology section's instructions. Labetalol HCl was detected at 303 nm with a maximum concentration against phosphate buffer in 6.8 pH as a blank.

Standard calibration curve of Labetalol in 6.8 pH Phosphate buffer:

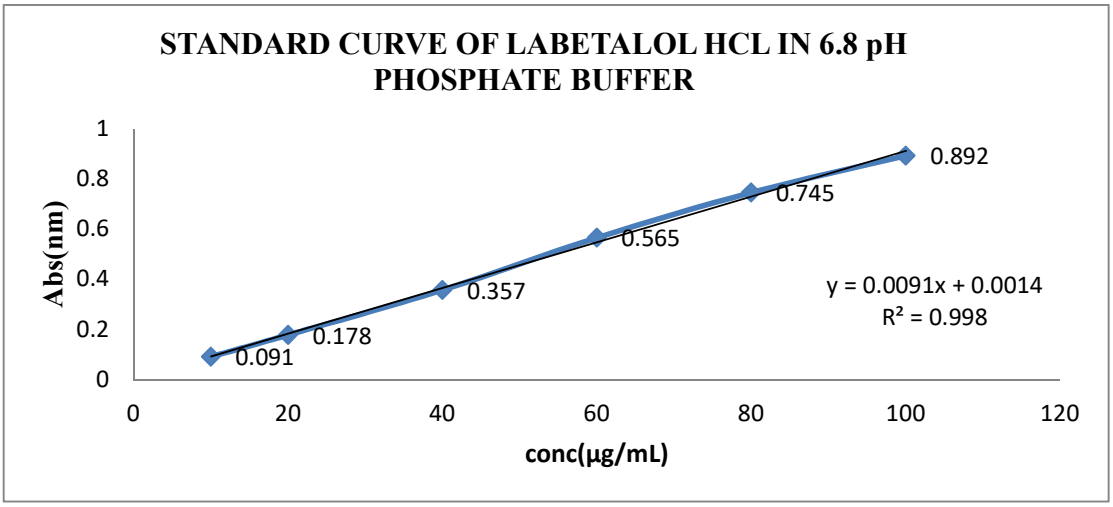

Figure 1: Standard calibration curve for Labetalol HCl in phosphate buffer 6.8 pH.

Correlation coefficient R^2 – 0.998 and linearity equation Y= 0.0091x + 0.0014

Drug polymer compatibility studies by FTIR spectroscopy: Taken are labetalol HCl, a natural superdisintegrantplantago ovata and a physical blend of medication and polymer. There was no discernible interaction, indicating compatibility, between the medication and excipients.

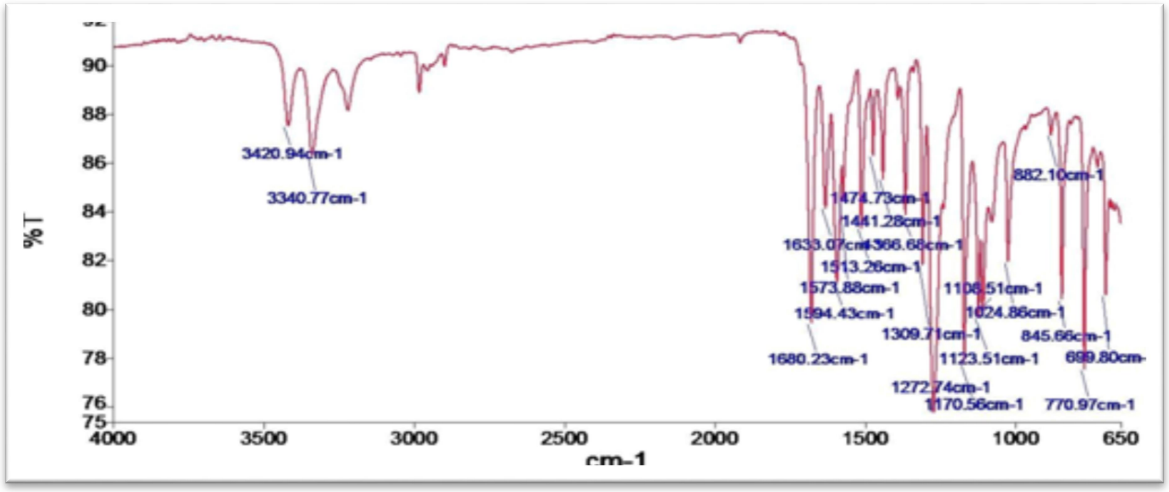

Figure 2: Labetalol HCl FT-IR Spectrum peaks

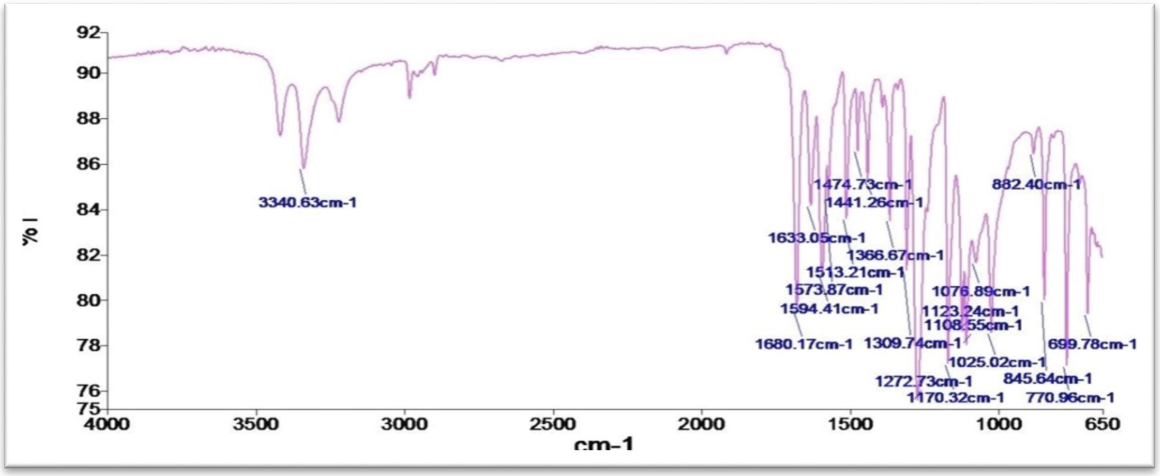

Figure 3: Plantago ovata FT-IR Spectrum peaks

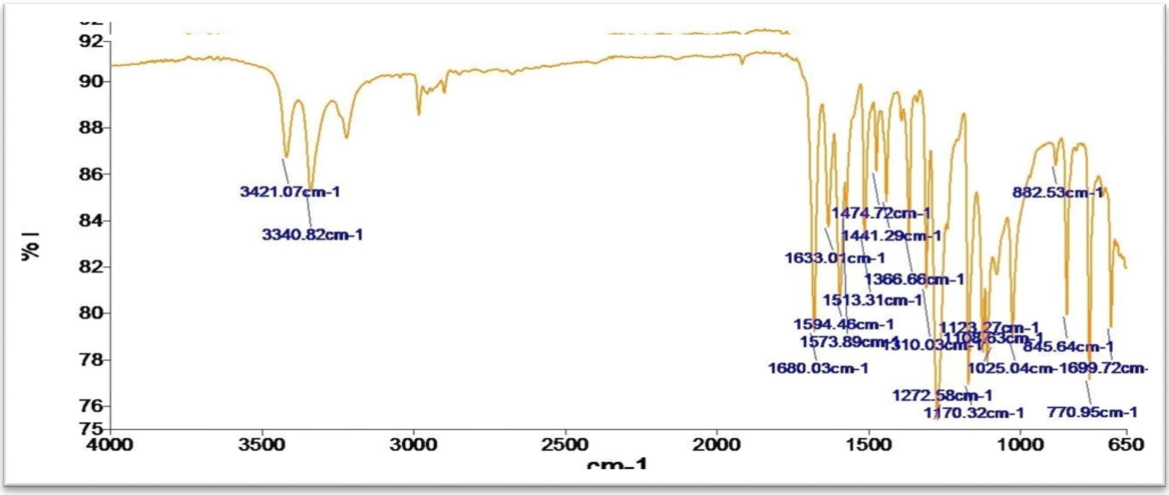

Figure 4: Formulation F6 FT-IR Spectrum peaks

Formulation Development

Prepared overall six F1 to F6 formulations by direct compression. Each formulation consist of 100mg of drug Labetalol HCl with a natural superdisintegrantplantago ovata 8mg, 10mg, 12mg, 14mg, 16mg, 18mg and with other excipients in a measured quantity discussed under section methodology in chapter 5.

Evaluation of Quick Dissolving Tablets

Pre compression parameters

Table No. 2: Pre compression Evaluation of Quick Dissolving Tablets

Formulation code	Angle of repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	30.02	0.517	0.625	14.88	1.174
F2	29.08	0.503	0.636	15.75	1.187
F3	29.55	0.508	0.627	16.57	1.199
F4	27.40	0.516	0.621	17.38	1.220
F5	26.68	0.504	0.618	16.10	1.191
F6	24.28	0.509	0.610	11.20	1.125

Post-compression parameters

Table No. 3: Post-compression Evaluation of Quick Dissolving Tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Wetting time (seconds)	Water absorption ratio(%)
F1	200.78	4.67	3.92	0.24	40.96	84.16
F2	199.92	4.47	3.90	0.28	35.52	86.17
F3	200.21	4.35	3.84	0.47	34.96	87.1
F4	199.79	4.21	3.81	0.53	31.15	89.09
F5	201.21	4.09	3.88	0.69	29.06	89.76
F6	200.24	3.91	3.94	0.70	26.23	91.06

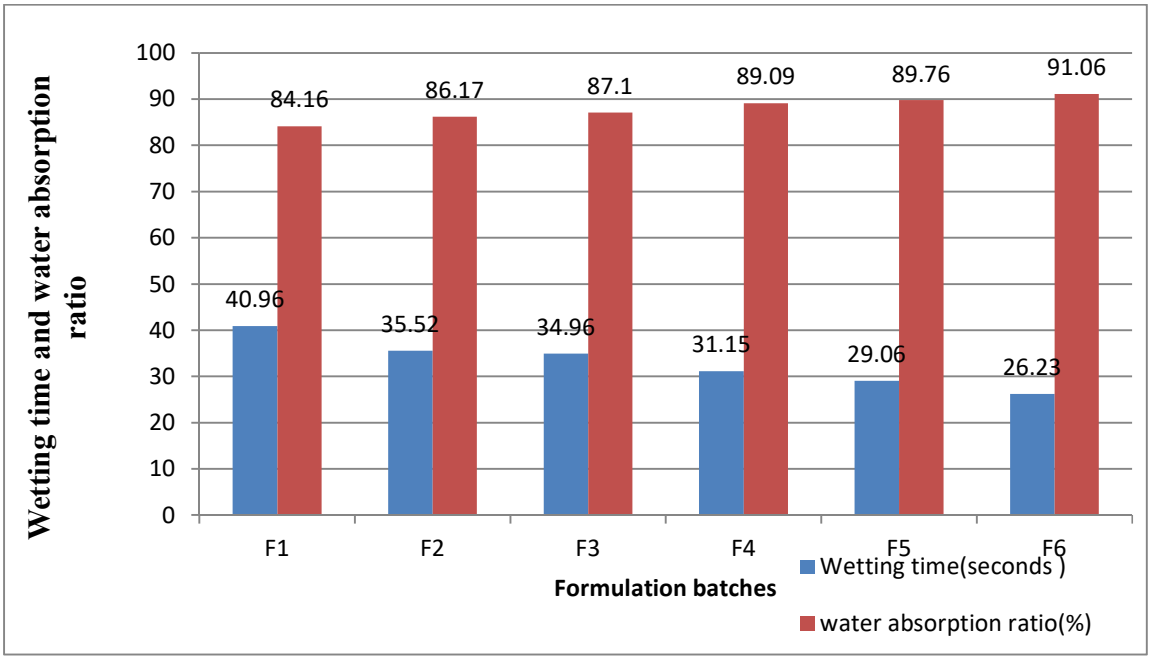

Figure 5: Wetting time and water absorption ratio of F1-F6

Percent drug content:

The drug content of the optimised formulation (F6) was determined to be 99.52%. For all formulations, the drug concentration ranged from 98.42 to 99.52%.

Table No. 4: Weight variation of F1-F6 formulations

Formulation code	% Drug content
F1	98.42
F2	98.64
F3	98.96
F4	98.71
F5	99.44
F6	99.52

***In-vitro* Disintegration time**

Formulations created using the direct compression approach displayed a disintegration time between 20 and 40 seconds. The disintegration time of the optimised formulation (F6) was discovered to be 20 seconds.

Table No. 5: *In-vitro* Disintegration time of F1-F6

Formulation code	In-vitro Disintegration time (seconds)
F1	40
F2	35
F3	32
F4	29
F5	26
F6	20

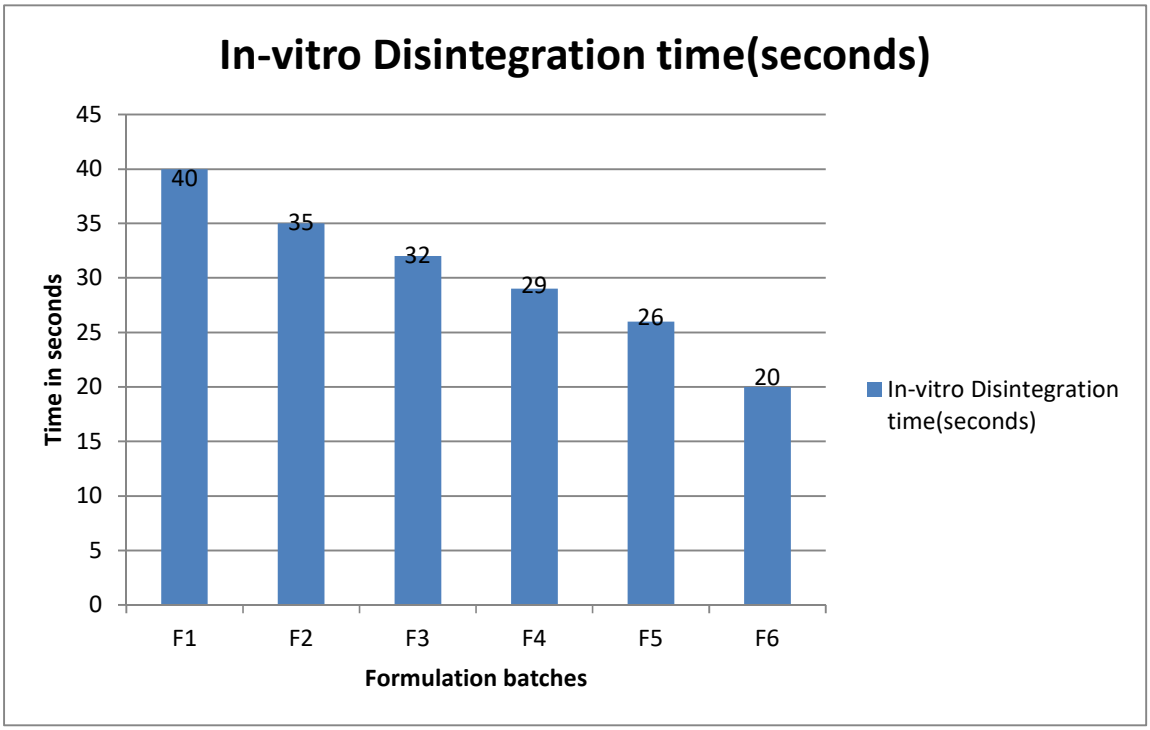

Figure 6: *In-vitro* Disintegration time of F1-F6

***In-vitro* dissolution studies:** *In-vitro* drug release for the optimized formulation (F6) was 99.80% within 25 minutes. Using an in-vitro dissolving device (TDT-08L Electrolab, India), a drug research was conducted in vitro for 25 minutes in a phosphate buffer with a pH of 6.8. According to in-vitro dissolution data, formulations F1, F2, and F3 each released 78.881%, 80.598%, and 88.983% of the medication after 20 to 25 minutes, whereas formulations F4, F5, and F6 each released 93.234%, 98.283%, and 99.80% of the drug within the same time frame.

Table No. 6: Comparative percent cumulative drug release of F1-F6 formulations of labetalol HCl in phosphate buffer 6.8 pH

Time (min)	Cumulative Percentage of Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	24.145	27.100	28.960	31.607	32.896	33.034
10	50.434	54.303	57.680	61.050	64.757	64.835
15	66.778	70.401	76.091	79.058	84.820	86.188
20	71.540	77.050	84.598	88.785	93.568	95.246
25	73.881	80.598	88.983	93.234	98.283	99.800

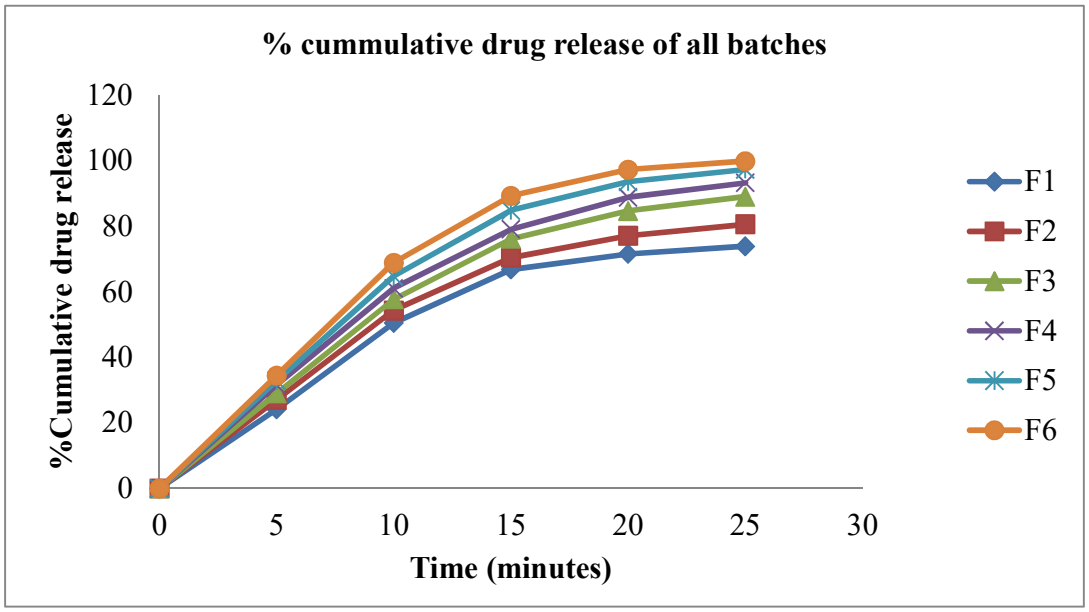

Figure 7: All formulation F1-F6 *in- vitro* dissolution profile in phosphate buffer pH 6.8.

CONCLUSION

The Quick Dissolving Tablets formulation provides speedy release of the medicine and is based on labetalol hydrochloride. The direct absorption of these tablets into the systemic circulation ocured. When FTIR indicated that a medicine and its excipients were compatible, it meant that there was no physico-chemical interaction between the two. Plantago ovata natural superdisintegrant was used to effectively create labetalol hydrochloride drug-based Quick Dissolving Tablets utilising the direct compression method, and these tablets were determined to

be better since they did not chip, cap, or stick. Drug distribution inside the formed tablet is uniform, as seen by the identical drug content in every prepared tablet. Out of all six tablets that were created, tablet formulation number F6 (which includes 18 mg of plantago ovata) offers the medication 99.80% of its maximal release. It was discovered that the optimised formulation F6 worked well with all parameters. The formulation F6 was determined to be the best among all developed formulations based on the findings of disintegration time and dissolving profile. Clinical formulation for Quick Dissolving Tablets that contains Formulation F6 and 18 mg of plantago ovata can be used successfully, particularly in situations of hypertension. Based on the aforementioned findings, plantago ovata was shown to be the best superdisintegrant for the preparation of Labetalol hydrochloride Quick Dissolving Tablets.

CONFLICTS OF INTERESTS

There are no Conflicts of interests.

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