Formulation and Evaluation of Labetalol Fast Dissolving Tablets

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Abstract

Fast dissolving tablets or mouth disintegrating tablets are those oral delivery systems formulated for rapid break down of dosage form in the mouth or oral cavity when compared to other conventional dosage forms. Labetalol is a third-generation alpha-1-adrenergic antagonist which has vasodilatory and anti-hypertensive properties. It is used in treating hypertension and angina. The objective and aim behind this research work is to prepare and evaluate labetalol fast dissolving tablets using the novel co-processed super disintegrants and physical mixtures which includes crospovidone and croscarmellose in ratios of 1:1, 1:2, 1:3, 2:1 and 3:1. The tablets were prepared using direct compression method. As the tablets are orally disintegrating and fast dissolving, they give immediate action. Orally disintegrated tablets are more convenient, and can be swallowed easily like the liquid dosage forms. Disintegrants are important excipients in solid dosage forms which are added to break or disintegrate tablet in the aqueous medium. By adding the disintegrants to the formulation, surface area of the formulation i.e. tablet increases and it overcomes the cohesive forces which help in binding the particles together.

Keywords: *Fast dissolving tablets, co-processed super disintegrants, crospovidone, croscarmellose, direct compression*

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1. Introduction

For any drug to show its therapeutic action, it should be formulated into various dosage forms. This dosage forms helps the drug to show its therapeutic response different dosage forms are present such as solid, semi-solid and liquid dosage forms having different mechanisms of drug delivery. For a drug to show its desired effect, it should be delivered to its particular site of action at a pre-determined rate as well as concentration in order to show the minimum adverse effect and maximum therapeutic effect [1]. To develop a suitable dosage form for a drug, it should be subjected to various physicochemical principles involved in formulation of a drug.

To overcome problems in the conventional tablets, new drug delivery systems called mouth disintegrating tablets or mouth dissolving tablets (MDTs) were developed. These tablets contain ingredients known as super disintegrants which include croscarmellose sodium, crospovidone [2,3,4]. Sodium starch glycolate which disintegrate inside the mouth or oral cavity in a very short span, on contact with the oral fluid or saliva it shows its therapeutic action.

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The objective behind this research work is to prepare and also evaluate fast dissolving tablets to provide better patient acceptability, increasedonset of action, enhanced rate and extent of absorption and better stability [5,6]. FDT's also increase drug absorption due to saliva present inside the mouth which disperses the drug that passes to the stomach which reduces first pass metabolism of the drug as compared to conventional tablets.

Pre gastric absorption takes place in the oral cavity for dispersion of drug in some formulations where there is rapid dissolution of the drug. Therefore, it helps in improving safety profiles of drugs which produce certain amounts of metabolites by first pass metabolism of the liver [7,8,9]. Certain fraction of the metabolized drug gets absorbed orally and in pre gastric segments of GIT [10].

2. Materials and Methods

Materials

Labetalol, MCC (microcrystalline cellulose), sodium starch glycolate, mannitol, crospovidone, magnesium stearate, sodium saccharin, talc.

Equipments

i. Electronic balance: Shimadzu Corporation – BL- 220H**.**
ii. Tablet compression machine: Rimek, Minipress 10 station rotary machine.
iii. Hardness tester – Serve well instruments and equipments pvt ltd**.**
iv. Thickness tester – Screw Gauge.
v. Dissolution test apparatus – Electro lab USP (XXIII) TDT-06T 9911090**.**
vi. **S**ieves – Techno instrument Co.
vii. UV/Visible spectrophotometer – Shimadzu 1700,Shimadzu Corporation, Japan**.**

Methods

Preparation of Standard calibration curve of Labetalol by using phosphate buffer pH (6.8)

Labetalol (100 mg) was weighed accurately and then dissolved in small amount of phosphate buffer 6.8 pH and the total volume was levelled up to 100ml using the same which is called as stock-1 solution. 10ml of the above stock solution was diluted in dry and clean volumetric flask upto 100 ml which is called as stock-II Solution.

Serial dilutions were prepared from this stock-II solution by pipetting out 1ml, 2ml, 4ml, 6ml, 8ml and 100ml to obtain concentration ranging from 10, 20, 40, 60, 80, 100 µg/ml respectively. The total absorbance of the prepared solutions was measured at 303nm with the help of UV-visible spectrophotometer. Based on the observed absorbance values, graph was plotted between concentration and absorbance.

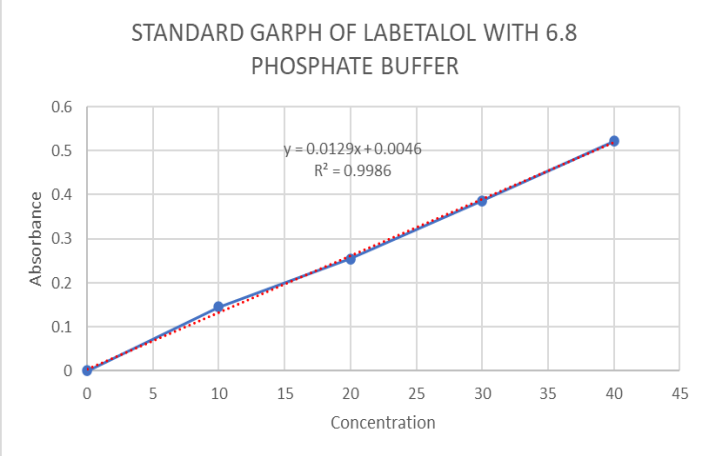
Preparation of Standard calibration curve of Labetalol in methanol:

100 mg of labetalol was weighed and mixed with 100 ml of methanol in a volumetric flask. 1ml of drug solution was taken and was diluted to make up the volume upto 100ml. Concentrations were prepared by taking 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4ml from the stock solution and was diluted upto 10ml to prepare solutions of 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml, 30µg/ml and 40µg/ml concentration. for each solution absorbance was measured at 320nm using Shimadzu UV/visible spectrophotometer, and the graph was drawn between absorbance vs concentration of labetalol.

Table 1 Absorbance of labetalol observed against pH 6.8 phosphate buffer.

Concentration (µg/ml)	Absorbance
0	0
10	0.145
20	0.225
30	0.386
40	0.522
50	0.628

Fig 1 Standard calibration graph of labetalol using phosphate buffer pH 6.8



Formulation of super disintegrant mixture

Step 1 – Preparation of super disintegrant mixture

The mixture of super disintegrant was prepared by two methods :

Method 1: Preparation of super disintegrant by co-processed technique

- These super disintegrants were formulated using solvent evaporation method.
- A mixture of croscarmellose and crospovidone (in different ratios of 1:1, 1:2 and 1:3) was added to 10 ml ethanol.
- The mixture present inside the beaker were mixed thoroughly and stirring was continued until most of the ethanol was evaporated.
- Granules were prepared by passing the wet mass of the super disintegrant mixture through sieve no 44. The granules were allowed to dry in the hot air oven at a temperature of 60ºC for 20 minutes.
- After the granules dried, they were sifted using sieve no 44 and were stored in air tight container until further use.

Method 2: Preparation of super disintegrant by physical mixture technique

- In this method, the super disintegrants were directly added into mortar and pestle according to their ratios and mixed thoroughly and then added to the dry ingredients.

Table 2 Formulation of labetalol fast dissolving tablets

		Co-processed super disintegrants					Physical mixture				
FORMULA CODE	**F0**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
	CF	**(1:1)**	**(1:2)**	**(1:3)**	**(2:1)**	**(3:1)**	**(1:1)**	**(1:2)**	**(1:3)**	**(2:1)**	**(3:1)**
Labetalol	100	100	100	100	100	100	100	100	100	100	100
Co-processed super disintegrants	----	10	10	10	10	10	10	10	10	10	10
MCC	50	40	40	40	40	40	40	40	40	40	40
Mannitol	30	30	30	30	30	30	30	30	30	30	30
Sodium saccharin	8	8	8	8	8	8	8	8	8	8	8
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5
Total weight	198	198	198	198	198	198	198	198	198	198	198

Preparation of labetalol fast dissolving tablets by direct compression method:

Direct compression method was used for the formulation of fast dissolving tablets of labetalol by using co-processed super disintegrants like mannitol, sodium starch glycolate. Crospovidone. The diluent used is microcrystalline cellulose, sodium saccharin is used as a sweetening agent. The lubricant and glidant used were magnesium stearate and talc. Except the ingredients used in the formulation of granules, ingredients were sieved using sieve 60. Finally, ingredients were separated based on their weight, mixed and were further compressed to make tablets each weighing 198 mg using 6 mm round and flat punches on rotary tablet compression machine.

3. EVALUATION

Preformulation studies

1. Pre-compression parameters

a) Angle of repose b) Bulk density c) Tapped density d) Hausner ratio e) Compressibility index (%).

a) Angle of repose (Ɵ)

Angle of repose is the maximam angle possible between the surface of the powder and horizontal plane. The frictional force of the loose powder or granules can be measured by angle of repose.

$\tan Ɵ = h/r$, $Ɵ = \tan^{-1} (h/r)$

Where, Ɵ is the angle of repose, h is height of powder, r is the radius of the base of powder.

Table 3 Different ranges of flowability in terms of angle of repose

Angle of repose (Ɵ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Method:

For this test, funnel was used which was filled with the test sample upto the brim. Then the test sample and was made to pass through the orifice. The area of the test sample was measured from the cone which was formed on the graph paper. Therefore, flow properties and height of the granules were measured.

b) Bulk density

It is defined as total weight of sample divided by its bulk volume. Bulk density of the powder generally depends on particle size distribution, shape of the particle and the adherence of the particles to one and another.

Method:

Powder was accurately weighed from each formula and was taken into a measuring cylinder to measure its volume.

Bulk density = Mass / volume

c) Tapped density

Tapped density was calculated by taking the granules and tapping was done for a fixed interval. The volume of the granules in the cylinder and the mass of granules was measured. The tapped density was calculated using the formula.

Tapped density (ρt) =M/ V

d) Hausner ratio

Hausner ratio is the measure of ease of powder flow.

Hausner ratio = ρt/pd

Where ρt = tapped density

ρd = bulk density.

Lower the hausner ratio i.e. (<1.25), better is the flow properties.

e) Carr's compressibility index

Carr's compressibility index determine granule's compressibility

Carr's compressibility index (%) = Tapped density- Bulk density x 100/ Tapped density.

Table 4 Flow properties of the powders according to carr's index

Consolidation index (carr%)	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
40	Very very poor

Evaluation of tablets

Post compression parameters

1. Hardness
2. Weight variation
3. Uniformity of thickness
4. Wetting time
5. In vitro dissolution studies

1. Hardness

It is the measure of strength or resistance of the tablet to resist the mechanical shocks while handling in manufacturing and packaging. Tablet hardness was measured monsanto hardness

tester. The units of hardness are Kg/cm^2. Five tablets were selected from each formulation in a randomized manner and the mean, standard deviation was calculated.

2. Weight variation test:

From each formulation, tablets were selected randomly and individually weighed to check the variation in the weight.

Table 5 Percentage deviation in weight variation according to IP

Average weight of a tablet	Percentage deviation
130mg or less	10
More than 130 mg and less than 324mg	7.5
324 mg or more	5

In all the formulations the weight of the tablet was found to be more than 350 mg hence 5% of maximum difference was allowed.

3. Uniformity of thickness

Individual tablet thickness can be measured using micrometer which provides accurate variation values between tablets. Other methods include placing 5 or 10 tablets in a tray where the total thickness of the crown can be measured with a sliding caliper scale. The thickness of the tablet was measured using a screw gauge.

4.Wetting time

It is measured by folding a piece of tissue paper twice and was placed in a petri dish which has 10 ml of 6.8 pH phosphate buffer solution. The tablet was placed on the tissue paper, and the time taken for the tablet to get wet completely was measured. For each batch three trials were performed and the standard deviation was calculated.

5. *In vitro* dissolution studies

Dissolution was performed using USP type-II apparatus in phosphate buffer pH (6.8) of 900 ml. Temperature was kept constant at 37±0.5 ˚C. 5 ml of aliquots was collected every minute and was then filtered. Absorbance of the filtered solution was measured using UV spectrophotometer at 320 nm and the drug concentration was determined from the standard calibration curve.

4. Results and discussion

Results

Table 6 Physical appearance of Labetalol tablets

Formulation Code	Colour	Appearance
F0	White	Good
F1	White	Good
F2	White	Good
F3	White	Good

F4	White	Good
F5	White	Good
F6	White	Good
F7	White	Good
F8	White	Good
F9	White	Good
F10	White	Good

Pre-compression parameters:

The powder of the drug and the excipients were evaluated for the loose bulk density, tapped bulk density, angle of repose, carr's index and hausner's ratio. The results of the evaluations are presented below

Table 7 Pre- compression studies of Labetalol

Formulation code	Bulk density(g/cc)	Tapped density(g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
F0	0.49	0.61	38.2	19.6	1.24
F1	0.51	0.62	37.1	17.7	1.21
F2	0.51	0.61	37.3	16.3	1.19
F3	0.53	0.62	36.4	14.5	1.16
F4	0.52	0.63	37.2	17.4	1.21
F5	0.53	0.65	36.2	18.4	1.16
F6	0.50	0.60	36.4	16.6	1.20
F7	0.51	0.61	36.6	16.3	1.19
F8	0.52	0.64	36.1	18.7	1.23
F9	0.51	0.62	36.3	17.7	1.21
F10	0.51	0.63	35.9	19.0	1.23

Table 8 Post-compressional evaluation parameters:

Formulation code	Weight variation	Hardness (kg/cm^2)	Thickness (mm)	Wetting time (sec)
F0	194±0.23	5.1±0.41	6.1±0.16	72
F1	195±0.47	5±0.62	6±0.72	69
F2	199±0.48	5.2±0.31	6.2±0.76	54
F3	195±0.85	5.1±0.76	6.1±0.23	49
F4	198±0.96	5.1±0.23	6.1±0.56	67
F5	197±0.72	5±0.41	6.2±0.11	56
F6	195±0.76	5±0.66	6±0.91	65
F7	198±0.32	5.2±0.35	6±0.71	62
F8	193±0.72	5±0.56	6±0.22	52
F9	197±0.96	5±0.67	6±0.53	59
F10	195±0.09	5±0.23	6±0.41	51

Optimization of F3 and F10 formulations

- Based on pre-compressional and post-compressional parameters especially based on the wetting time, two formulations were opted which were F3 and F10 for further evaluation.
- F3 (1:3 ratio of crospovidone and croscarmellose respectively prepared by coprocessed super disintegrants technique).
- F10 (3:1 ratio of croscarmellose and crospovidone respectively prepared by physically mixed super disintegrants technique).

Table 9 *In vitro* dissolution of formulation F3

Time	% Drug dissolved
0	0
15	44.41
30	50.75
45	53.44
60	58.34
75	58.47
90	72.98
105	85.54
120	97.02

Fig 2 In vitro dissolution profile of formulation F3

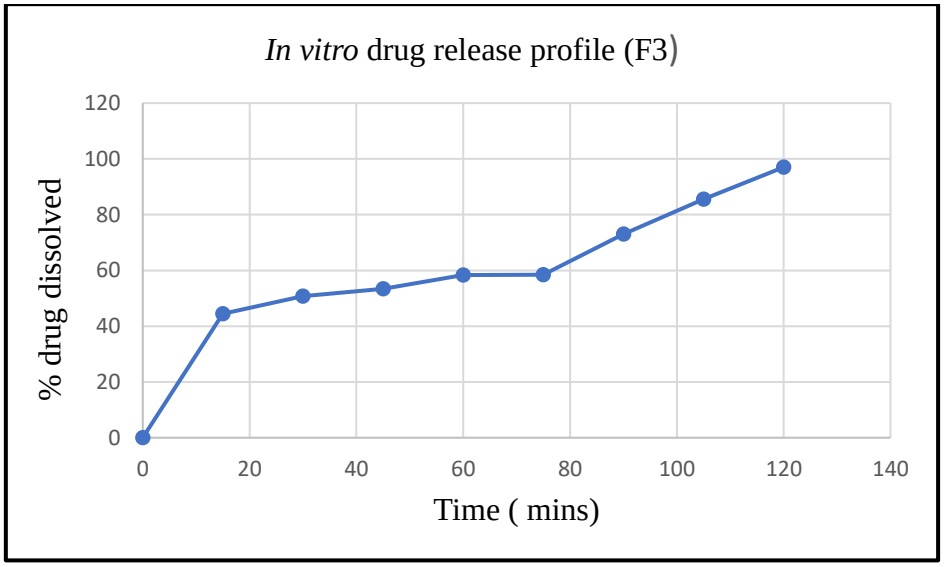


Table 10 In-vitro drug release profile of F10

S.no	Time	% Drug dissolved
1	0	0
2	15	37.3
3	30	42.96
4	45	46.96
5	60	50.47
6	75	50.82
7	90	55.23
8	105	75.92
9	120	78.06

Fig 3 In vitro drug release profile of formulation F10

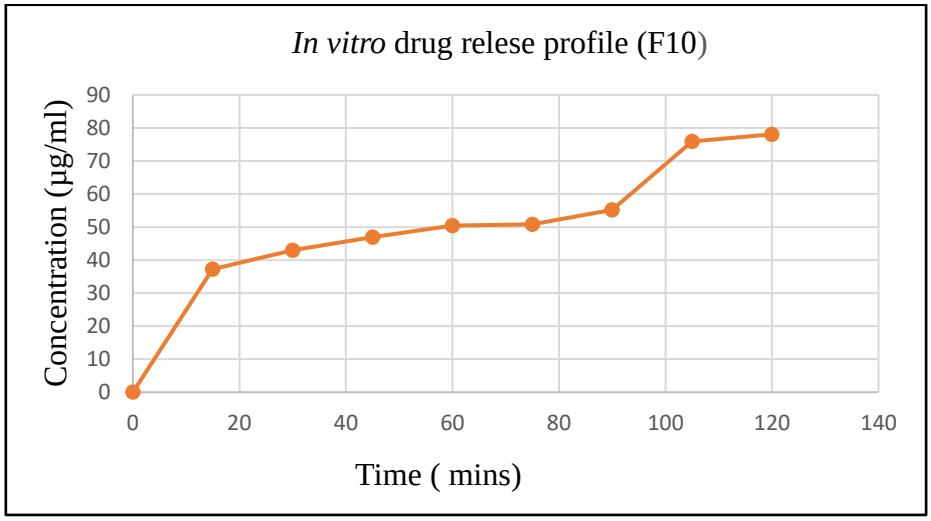
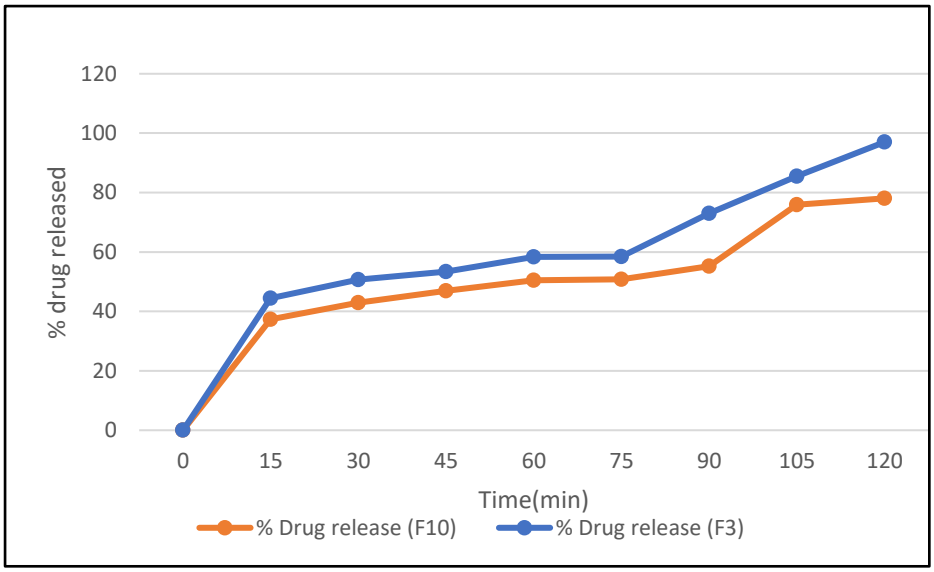


Table 11 Comparison of dissolution profiles of formulations F3 and F10

Time (mins)	% Drug release (F3)	% Drug release (F10)
0	0	0
15	44.41	37.3
30	50.75	42.96
45	53.44	46.96
60	58.34	50.47
75	58.47	50.82
90	72.98	55.23
105	85.54	75.92
120	97.02	78.06

Fig 4 Comparison of dissolution profiles of formulation F3 and F10



Discussion

Labetalol calibration curve was performed and the concentrations between 0-40 µg/ml and its R^2 value was found to be 0.998 according to fig 1 which showed a linear relationship. Therefore, it followed Beer Lambert's law.

Various evaluation parameters of Labetalol tablets

1. Angle of repose: As the angle of repose is between 30 – 40 the flow property of the drug is passable.
2. Hardness: Tablet hardness was around 5 kg/cm² which is according to the I.P limits.
3. Thickness: The thickness of the tablet is around 6 mm which is according to the I.P limits.
4. Wetting time: The wetting time of the tablets is between 50 sec - 75 sec which is according to the I.P limits.

Dissolution studies of Labetalol tablets

5. The formulation F3 with co-processed technique showed 97.02% of the drug release in 120 min and the formulation F10 with physical mixture showed 78.06% of drug release in 120 min according to fig 4
6. Based on the above results we conclude that co-processed super disintegrant technique is giving better result than the physical mixture technique.

Hence, from the present work it can be concluded that co-processed super disintegrants of crospovidone and croscarmellose show better release than its physical mixture and they showed enhanced the dissolution rate.

5. Conclusion

1. Labetalol tablets were formulated and prepared by using co-processed super disintegrants which were crospovidone and croscarmellose in the ratios 1:1, 1:2, 1:3, 2:1, 3:1 of the formulation F0, F1, F2, F3, F4, F5 respectively and physical mixture included 1:1, 1:2, 1:3, 2:1, 3:1 of formulation F6, F7, F8, F9, F10.
2. Pre-compressional and post-compressional evaluation tests were conducted which showed 49 seconds wetting time for the formulation F3 (2:1) i.e using co- processed super disintegrants and 51 seconds for F10 (3:1) i.e using physical mixture.
3. Optimized formulations of F3 and F10 were subjected to *in vitro* dissolution studies where formulation F3 (2:1) showed 97.02% drug release in 120 minutes whereas formulation F10 (3:1) showed 78.06% drug release.
4. From the current study it is concluded that the use of co-processed super disintegrants like crospovidone and croscarmellose enhanced the drug release from the formulation as compared to the physical mixture.

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