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Formulation and *In-Vitro* Evaluation of Taste Masked Fast Disintegrating Tablets of Labetalol Hydrochloride by Direct Compression Method

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ABSTRACT

Labetalol Hydrochloride is a β-blocker generally indicated for the treatment of hypertension, and it is extensively metabolized due to hepatic metabolism. In the present work, an attempt was made to mask the taste by Solid Dispersion technique, with a formulation into Fast Disintegrating dosage form, using super disintegrants such as Cross carmellose sodium (CCS), crospovidone (CP) and sodium starch glycolate (SSG). The complexes of Labetalol hydrochloride with HP-β-CD (1:3 ratio) were prepared by the Co-precipitation method. Using the drug HP-β-CD complex, Fast Disintegrating tablets were prepared by direct compression method and evaluated for hardness, friability, weight variation, thickness, disintegrating time (DT), *In-vitro* dispersion time and dissolution rate. The results of Direct compression optimized formulation DC6 (Croscarmellose sodium 15 mg and MCC 30mg) have shown the % drug release of 95.95%, In-vitro Dispersion time 15 Secs respectively.

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. For many decades treatment of an acute disease or chronic illness has mostly accomplished by the delivery of drugs to patients using conventional drug delivery systems. Even today these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption.[1]

Difficulty in swallowing (dysphagia) is common among all age groups, especially in the elderly, and is also seen in swallowing conventional tablets and capsules. The novel technology of fast-disintegrating dosage forms is known as fast dissolve, rapid dissolve, rapid melt, and quick disintegrating tablets. A solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as a fast-disintegrating dosage form.[2]

Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs. Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist.[3-6]

Labetalol HCl is a blocker of both alpha- and beta-adrenergic receptors that are used as an antihypertensive agent. Labetalol is used parenterally for an immediate reduction in blood pressure in severe hypertension or hypertensive crises when considered an emergency, for the control of blood pressure in patients with pheochromocytoma and pregnant women with preeclampsia, and to produce controlled hypotension during anesthesia to reduce bleeding resulting from surgical procedures. Absorption Completely absorbed (100%) from the gastrointestinal tract with peak plasma levels occurring 1 to 2 hours after oral administration. The absolute bioavailability of labetalol HCl is increased when administered with food.[7-8]

MATERIALS AND METHODS

Labetalol HCl supplied by Pharma Train, HP-Betacyclo dextrin Purchased from Signet Chemicals Co. Ltd., (Mumbai, India), Crosspovidone was and Croscarmellose sodium, was

purchased from Yaroow Chemicals and Pharmaceuticals (Mumbai, India) Sodium Starch Glycolate and MCC was obtained as a gift sample from Maple Biotech India Pvt, Ltd (Pune, India), Talc, Mannitol, Magnesium Stearate Purchased from S.D. Fine Chem. Ltd.

Drug polymer compatibility studies:

1. Fourier Transform Infrared Spectroscopy (FTIR):

Ten milligrams of drug alone, a mixture of drug and polymer were weighed and mixed properly with KBr uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR-spectrum of the pellet from 450-4500cm^{-1}. **(Figure no. 1, 2)**

2. Differential Scanning Calorimetric (DSC):

Differential scanning calorimeter (DSC) was performed using Perkin Elmer instruments, (Perkin Elmer DSC-7, Norway, USA.) to study the thermal behavior of labetalol hydrochloride and a mixture of drugs and polymers. **(Figure no. 3,4)**

PREPARATION OF SOLID DISPERSION BY CO – PRECIPITATION METHOD:

The drug was dissolved in ethanol at room temperature and the polymer was dissolved in distilled water. Different molar ratios of Drug and polymer (1:1, 1:2 and 1:3) were taken. The mixture was stirred at room temperature, for one hour and then slowly evaporated on a boiling water bath. The inclusion complex precipitated as a crystalline powder was pulverized and passed through sieve No. 80 and stored in a desiccator till free from any traces of the organic solvent.

Table No.1: Formulation codes for the Labetalol HCl solid dispersions

Ingredients (mg)	Formulation code					
	SD1	SD2	SD3	SD4	SD5	SD6
Labetalol HCl	100	100	100	100	100	100
Beta cyclodextrin	100	200	300	-	-	-
HP-Beta cyclodextrin	-	-	-	100	200	300

- In both the Polymer's used HP-Betacyclodextrine > Betacyclodextrine

- Drug: Polymer complex of SD6 (Drug: HP-Betacyclo dextrin 1:3 & by Co-precipitate method) is having the better solubility enhancement.

Preparation of Labetalol HCl of fast disintegrating tablets by direct compression method

All the ingredients were passed through #60 mesh separately. The Drug Mixture (Solid dispersion) and MCC were mixed by taking a small portion of both each time and blending it to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using 9mm round flat punches to get tablets of 300mg weight on 10 stations rotary tablet machine (CLIT).

Table No. 2. Formulation Design of Labetalol HCl using Direct Compression Technique

Ingredients (mg)	DC0	DC1	DC2	DC3	DC4	DC5	DC6	DC7	DC8	DC9
Labetalol+HP Betacyclodextrine	200	200	200	200	200	200	200	200	200	200
Crospovidone	-	5	10	15						
Cross carmellose sodium	-				5	10	15			
Sodium starch glycolate	-							5	10	15
MCC	10	0	15	30	0	15	30	0	15	30
Mannitol	82	87	67	47	87	67	47	87	67	47
Talc	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Peppermint flavor	2	2	2	2	2	2	2	2	2	2
Total weight	300	300	300	300	300	300	300	300	300	300

Pre Compression Parameters

Angle of Repose

The angle of repose was determined using the cylinder method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and the angle of repose (q) was calculated using the formula. **(Table no.5)**

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

Bulk density:

The bulk density of the powdered blend was determined by pouring gently through a glass funnel into a 50 ml graduate9d cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density *= weight of sample in gram /volume occupied by the sample*

Tapped density:

An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%. A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and taped density is calculated using the following formula.[10]

Tapped density *= Wt. of the sample in gm / Tapped volume*

Compressibility Index:

One of the important measures that can be obtained from bulk and tapped density determinations is the percent Compressibility or the Carr`s Index, I which is determined by the following equation.[11]

I = Tapped density –Bulk Density/ Tapped density

Hausner`s Ratio:

Hausner`s ratio is defined as a ratio of a tapped density to bulk density. It is a measure of the relative importance of inter particulate interactions. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.[11]

Hausner's Ratio= Tapped Density/ Bulk density

EVALUATION OF POST-COMPRESSION PARAMETERS:

a. Weight variation test:[12]

Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight were calculated. **(Table no. 6)**

b. Thickness:[13]

Six tablets of each batch were selected and measured for thickness and diameter using the digital venire calipers. The extent to which the thickness of each tablet deviated from ±5% of the standard value was determined.

c. Hardness:

Hardness was measured using the Monsanto hardness tester. Measure the pressure required to break the diametrically placed matrix tablet, by a coiled spring.

d. Friability test:

The friability of the tablets was determined by using the Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($_{Initial}$) and transferred into the friability. The friabilator was operated at 25 rpm for four minutes. The tablets were weighed again (W_{final}). The percentage friability was then calculated using the equation:

$$F= (W_{initial} – W_{final} \times 100) / W_{initial}\%$$

Friability of tablets less than 1% was considered acceptable. The friability was expressed as the loss of mass and was calculated as a percentage of the initial mass.

e. Drug Content:

10 Tablets were taken and powdered. Powder equivalent to one tablet was weighed accurately and allowed to dissolve in 10ml phosphate buffer and make up the volume up to 100ml. The solution was filtered; 1ml of the filtrate was taken in 50ml of volumetric flask and diluted up to the mark with 6.8 phosphate buffer and analyzed spectrophotometrically at 305nm.[14]

f. Wetting time and water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the table was noted as the wetting time.

Water absorption ratio (R) was calculated using the formula:

$$R=100 \times [W_a - W_b] / W_b,$$

Where, W_a=weight of tablet after absorption, W_b=weight of the tablet before absorption.

g. *In*-vitro disintegration time:

The disintegration time for all formulations was carried out using a tablet disintegration test apparatus. Six tablets were placed individually in each tube of the disintegration test apparatus and the disks were placed. The water was maintained at a temperature of 37±2°C and the time taken for the entire tablet to disintegrate completely was noted.

h. *In*-vitro dispersion time: *In-vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated saliva fluid (p^H 6.8). Three tablets from each formulation were randomly selected and *in-vitro* dispersion time was expressed in seconds.

i. *In*-vitro drug release studies:

In-vitro drug release studies were carried out using the USP XXIII Dissolution Apparatus II (Paddle Type) at 50 rpm. The drug release profile was studied in 900 ml of phosphate buffer pH-6.8 as a dissolution medium. The temperature was maintained at 37±0.5°C. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals every five minutes and filtered. The amount of drug released was determined by the UV-Visible spectrophotometer at 305nm and concentration of drug was determined from standard calibration curve.[16] **(Table no. 7 Fig no. 6)**

g. Stability studies:

Stability studies were performed at a temperature of 25±2^{0}C / 65±5%RH & 40±2^{0}C/75±5%RH, over three months (90 days) on the promising FDT of Labetalol HCl formulation. (**Table no. 9)**

RESULTS AND DISCUSSION:

FT-IR Spectroscopic Analysis:

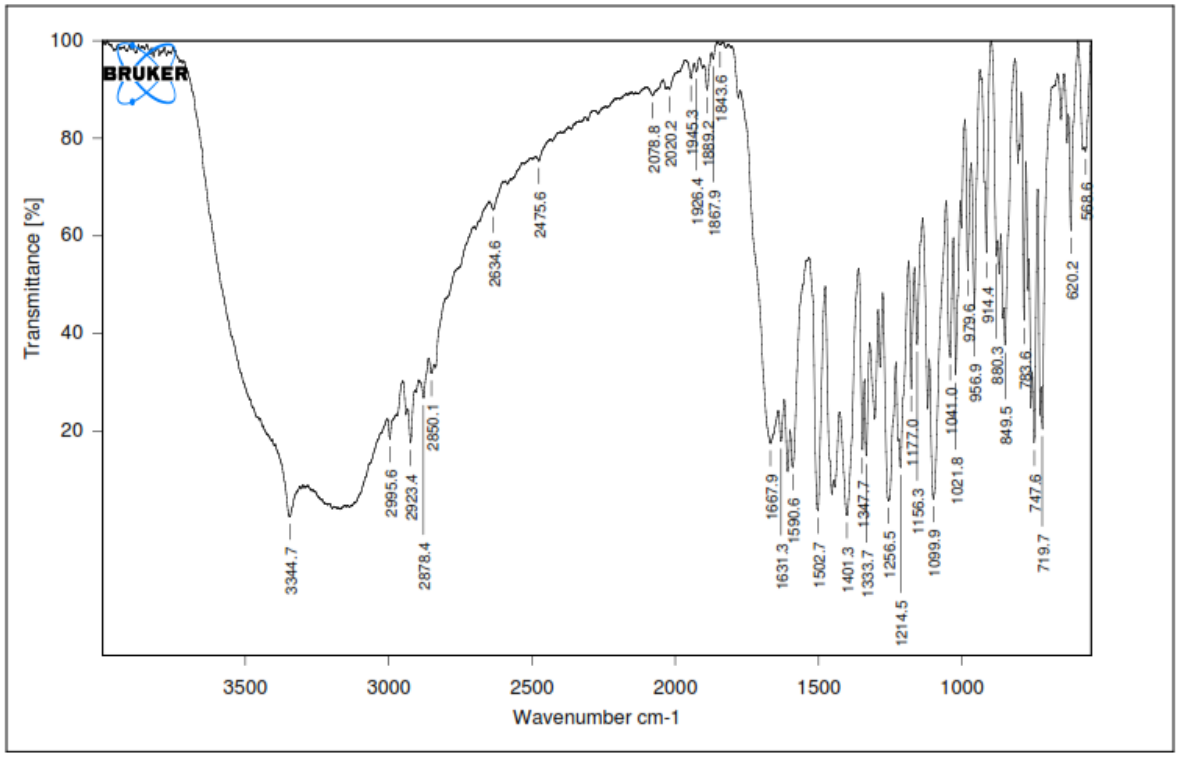

Figure No: 1 FTIR graph for Labetalol HCl

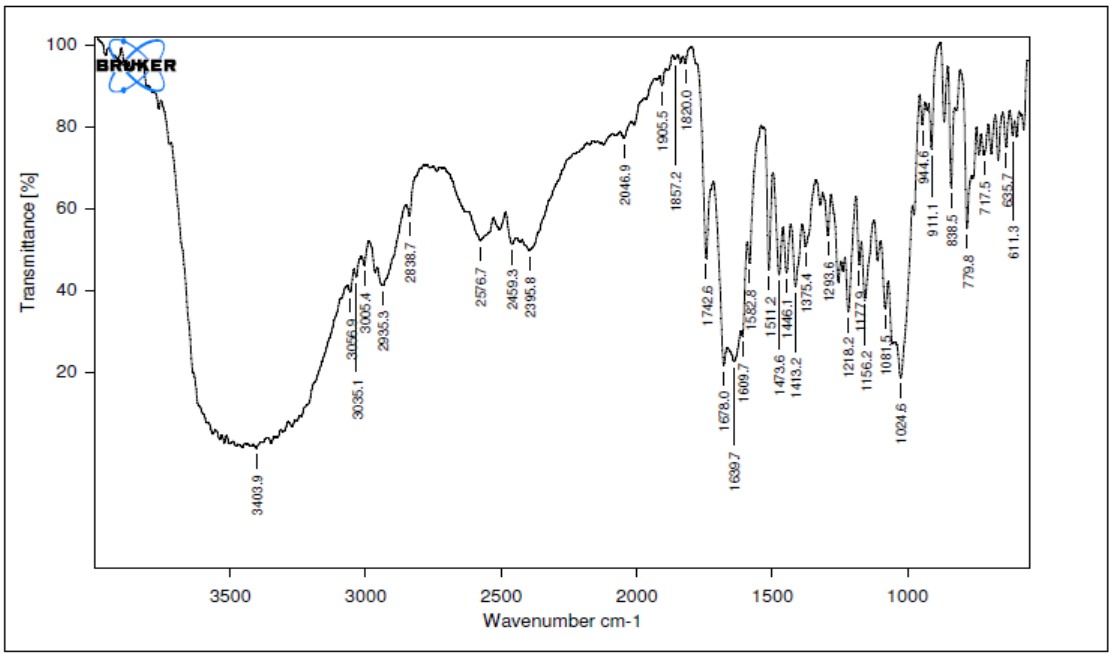

Figure No: 2 FTIR graph for optimized formulation (DC6)

Differential Scanning Calorimetry (DSC) Studies

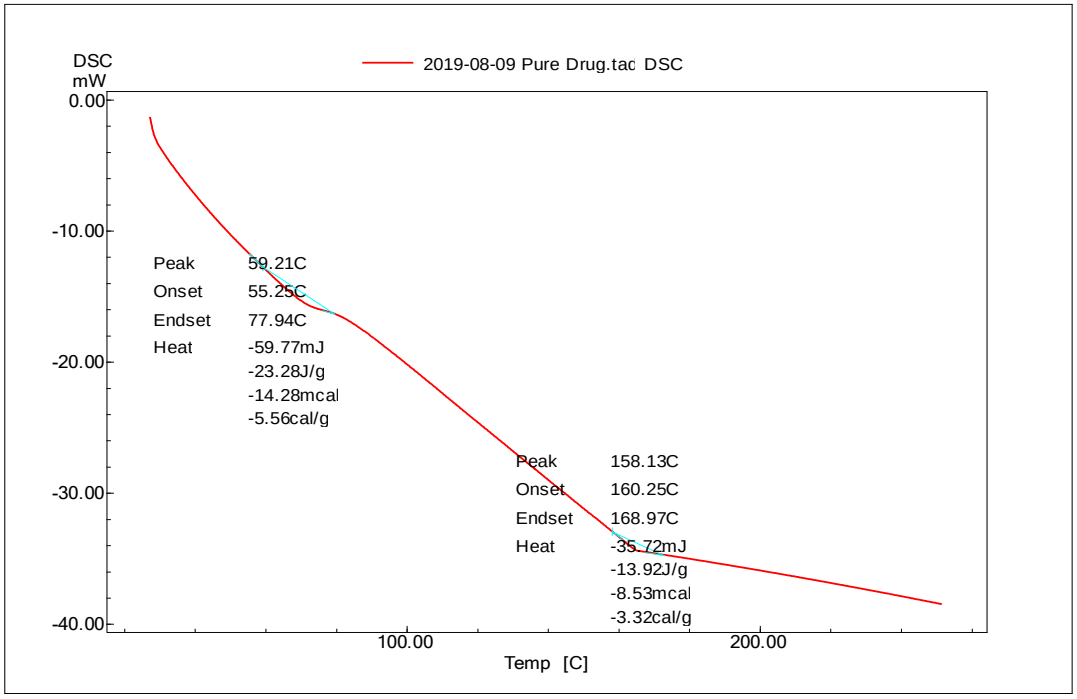

Figure No: 3 DSC of Pure Drug

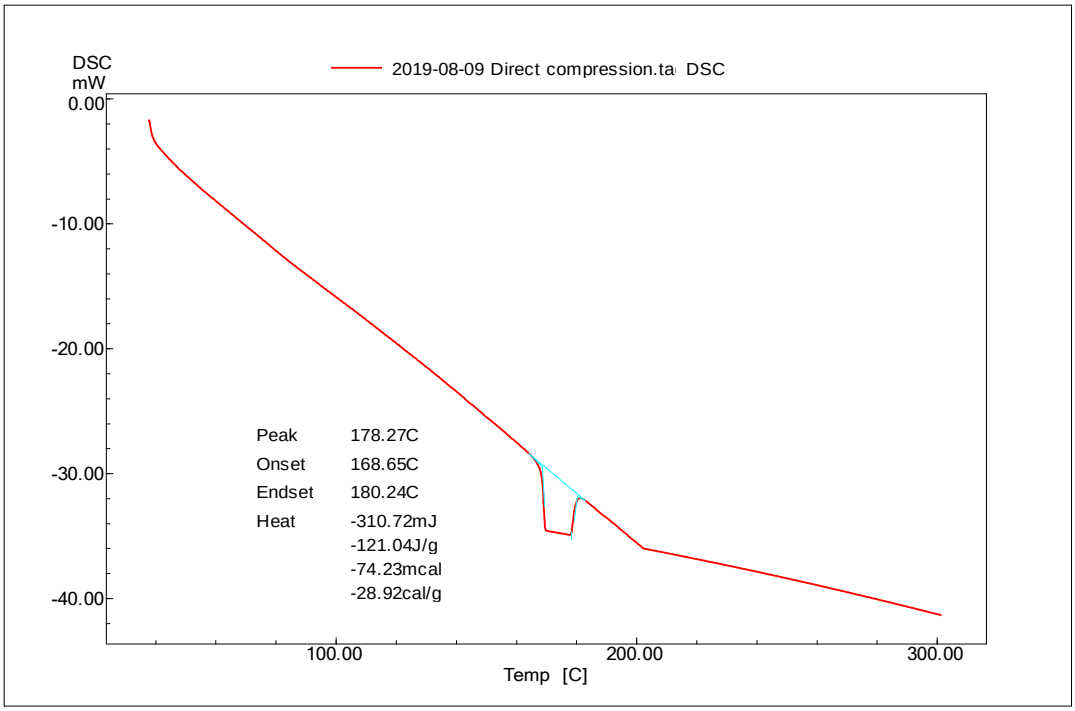

Figure No 4 DSC of Optimized Formulation

DSC thermogram of untreated/ pure drug shows an endothermic peak at 158℃, which is related to its melting point. A physical mixture of excipients and the drug of the Optimized Formulation DC6 showed endothermic peaks at 178.27℃. It was found that there are no new peaks appeared in the thermogram of the drug and excipients. Thus, there is no interaction between the drug and the tablet excipients, was observed. However, there is a very slight shift in the drug peak and this might be due to a reduction of the purity of components by mixing**.**

Table No:3 Dissolution data of Labetalol Solid dispersions

Time(min)	SD1	SD2	SD3	SD4	SD5	SD6
0	0	0	0	0	0	0
5	8.91±0.052	15.02±0.054	12.76±0.068	9.28±0.01	15.43±0.012	26.65±0.025
10	11.55±0.020	18.85±0.056	18.28±0.011	12.26±0.065	20.68±0.0.019	35.05±0.043
15	15.56±0.078	21.9±0.067	24.36±0.025	16.15±0.087	26.97±0.053	46.15±0.044
20	19.34±0.049	28.22±0.078	31.16±0.045	20.86±0.054	32.87±0.045	56.35±0.062
30	23.19±0.067	34.8±0.023	37.88±0.034	24.31±0.054	39.45±0.054	67.6±0.068
40	27.75±0.087	42.92±0.034	44.49±0.053	28.4±0.053	47.58±0.052	82.6±0.079
50	29.47±0.067	45.3±0.051	48.44±0.791	30.46±0.078	50.76±0.088	86.9±0.062
60	31.26±0.003	46.87±0.33	51.28±0.34	32.09±0.04	54.38±0.02	93.12±0.022

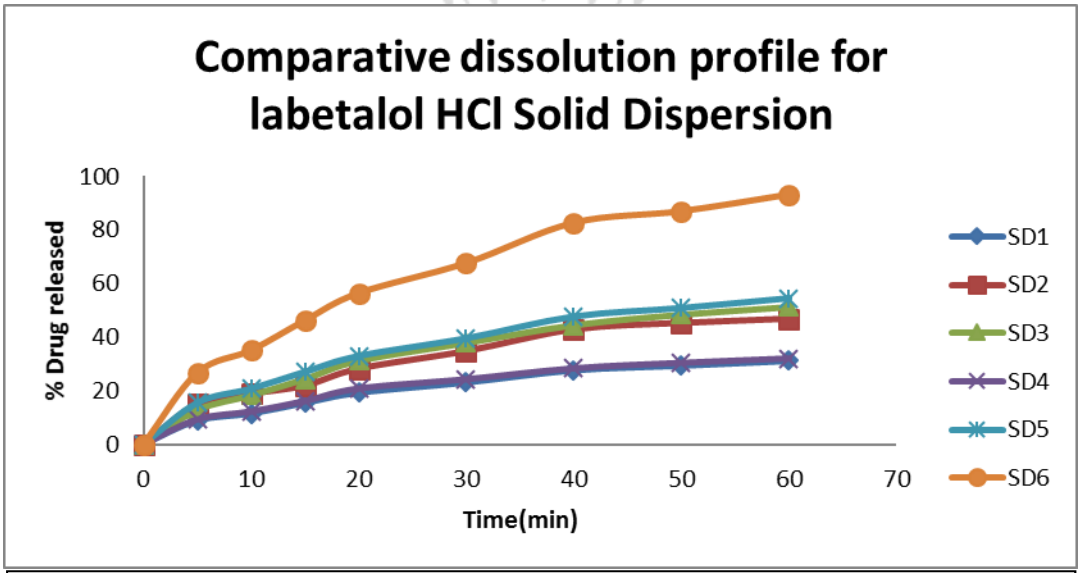

Figure No 5: **Comparative dissolution profile for labetalol HCl Solid**

Taste evaluation of granule

A sensory test on taste of all granule preparations was performed using 6 healthy adult volunteers from whom informed consent was first obtained. They rinsed their mouthcavities sufficiently before and after tasting. The prepared granules were kept in the volunteers mouth for 30s and then spit out. The taste score was set to the range of 0-4 based on the degree of taste masking (0-Good,1-Taste less,2-Slightly bitter, 3-bitter ,4-very bitter.) Then based on scores, the best taste masked (1:3) Drug:HP beta cyclodextrin granules were selected as optimized. **(Table no. 4**)

Table no:4 Scores of taste masking

Ratio	Scores given by Six Volunteers						Total score
	I	II	III	IV	V	VI	
1:1	3	2	2	3	3	2	16
1:2	1	2	2	1	1	2	09
1:3	0	0	1	0	0	0	01

Table No: 5 Pre compression studies of Labetalol HCl fast disintegrating tablets (Direct Compression Method)

Formulation Code	Bulk density	Tapped density	Cars index	Hausner's ratio	Angle of repose (˚)
DC0	0.27±0.15	0.31±0.18	11.42±0.19	1.13±0.17	32.81±0.16
DC1	0.29±0.18	0.31±0.19	6.23±0.17	1.07±0.18	26.58±0.19
DC2	0.29±0.12	0.31±0.17	6.44±0.16	1.07±0.16	27.35±0.10
DC3	0.29±0.13	0.30±0.16	5.54±0.14	1.06±0.14	25.97±0.15
DC4	0.30±0.12	0.31±0.15	5.28±0.13	1.06±0.13	26.05±0.17
DC5	0.29±0.14	0.31±0.16	6.52±0.14	1.07±0.12	26.52±0.18
DC6	0.29±0.15	0.31±0.16	6.60±0.14	1.07±0.12	27.17±0.19
DC7	0.29±0.15	0.32±0.15	9.11±0.15	1.10±0.11	28.31±0.09
DC8	0.29±0.14	0.32±0.15	9.08±0.16	1.10±0.10	28.88±0.14
DC9	0.28±0.13	0.32±0.15	12.45±0.17	1.14±0.16	33.27±0.06

Table No: 6 Post compression studies of Labetalol HCl fast disintegrating tablets (Direct compression method)

Formulation Code	% weight variation	Thickness (mm)	Hardness (Kg/cm^2)	% friability	Disintegration time (Sec)	*In*-vitro Dispersion time (Sec)	Water absorption ratio	% Drug Content
DC0	291.1	3.62±0.2	3.5±0.14	0.49±0.19	58.69±0.29	52.48±0.09	62.48±0.07	99.85±0.5
DC1	298.6	4.21±0.1	3.6±0.15	0.45±0.22	42.58±0.17	36.58±0.13	73.58±0.23	99.32±0.30
DC2	299.1	4.25±0.4	3.5±0.16	0.17±0.20	52.56±0.19	47.75±0.29	79.68±0.31	99.94±0.45
DC3	299.4	4.27±0.5	3.7±0.13	0.21±0.19	38.69±0.21	32.68±0.24	76.4±0.29	99.59±0.29
DC4	297.4	4.23±0.1	3.5±0.14	0.38±0.23	32.58±0.28	28.69±0.17	89.57±0.21	99.95±0.43
DC5	298.2	4.19±0.3	3.5±0.12	0.26±0.24	25.49±0.20	19.68±0.19	91.47±0.11	99.21±0.32
DC6	297.7	4.25±0.1	3.6±0.11	0.31±0.18	21.48±0.11	15.68±0.23	92.48±0.11	100.04±0.29
DC7	300.6	4.28±0.6	3.6±0.10	0.350±0.24	29.46±0.10	19.99±0.26	87.48±0.14	99.32±0.54
DC8	299.9	4.15±0.4	3.7±0.12	0.22±0.20	26.38±.18	22.59±0.32	88.39±0.16	99.57±0.28
DC9	298.49	4.18±0.7	3.5±0.13	0.25±0.22	35.3±0.27	26.70±0.31	85.39±0.15	100.02±0.10

Table No: 7 Dissolution data of various fast disintegrating tablets of Labetalol HCl (Direct compression method)

Time (min)	DC0	DC1	DC2	DC3	DC4	DC5	DC6	DC7	DC8	DC9
0	0	0	0	0	0	**0**	0	0	0	0
5	2.19±0.14	31.38±0.16	32.39±0.18	34.29±0.15	30.85±0.16	40.19±0.19	**41.19**±0.18	30.29±0.14	35.57±0.12	39.42±0.15
10	6.06±0.09	45.23±0.21	52.39±0.22	65.39±0.19	58.32±0.22	73.21±0.21	**73.86**±0.29	51.38±0.31	69.43±0.15	71.28±0.28
15	13.12±0.15	69.27±0.24	76.39±0.27	89.12±0.09	83.29±0.29	91.83±0.16	**95.95**±0.27	73.29±0.39	87.32±0.32	88.32±0.22
20	18.54±0.18	87.39±0.19	91.23±0.20	91.42±0.18	90.38±0.30	92.81±0.29	95.95±0.27	89.14±0.21	91.29±0.22	93.89±0.19
25	28.91±0.16	90.94±0.29	92.83±0.29	93.41±0.21	91.18±0.12	92.82±0.28	95.95±0.26	91.25±0.19	92.28±0.21	93.87±0.16
30	32.21±0.15	90.93±0.29	92.82±0.30	93.45±0.21	91.19±0.11	92.82±0.29	95.95±0.27	91.23±0.19	92.28±0.21	93.88±0.19

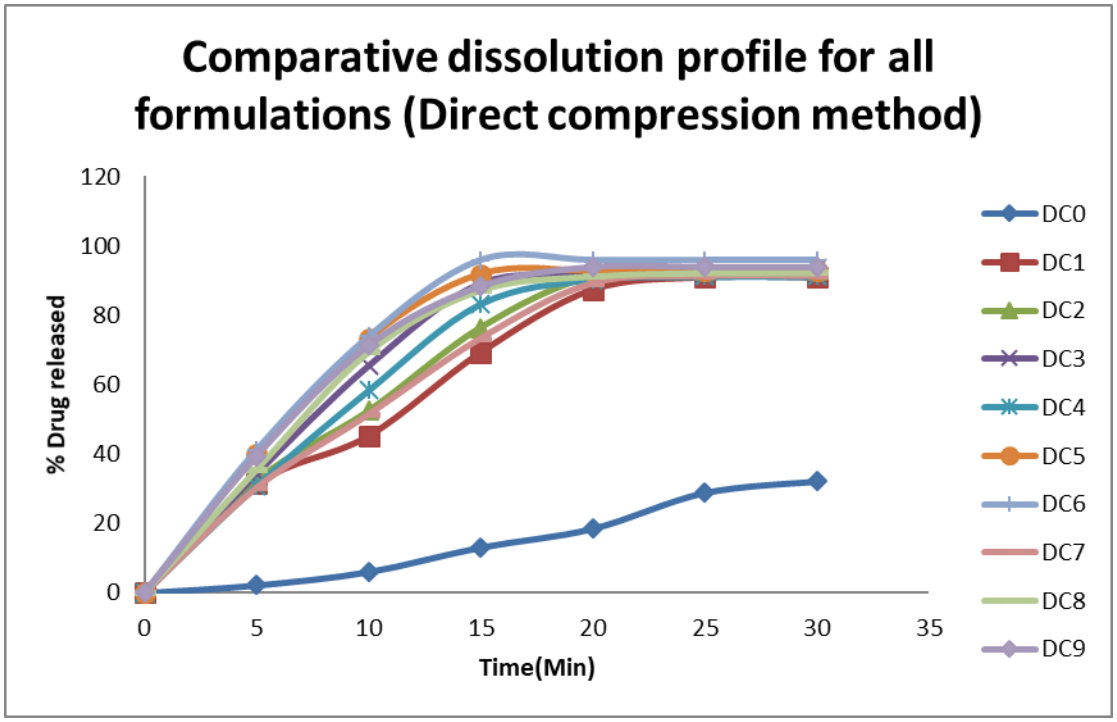

Figure No: 6 Comparative dissolution profile for Labetalol HCl Fast disintegrating tablets

Table No: 8 Comparative dissolution profile for Marketed formulation (Trandate) and DC6

Time(min)	Marketed formulation	DC6
0	0	0
5	23.21±0.21	**41.19**±0.18
10	42.83±0.19	**73.86**±0.29
15	64.53±0.26	**95.95**±0.27
20	79.32±0.22	95.95±0.27
25	91.43±0.19	95.95±0.26
30	99.65±0.18	95.95±0.27

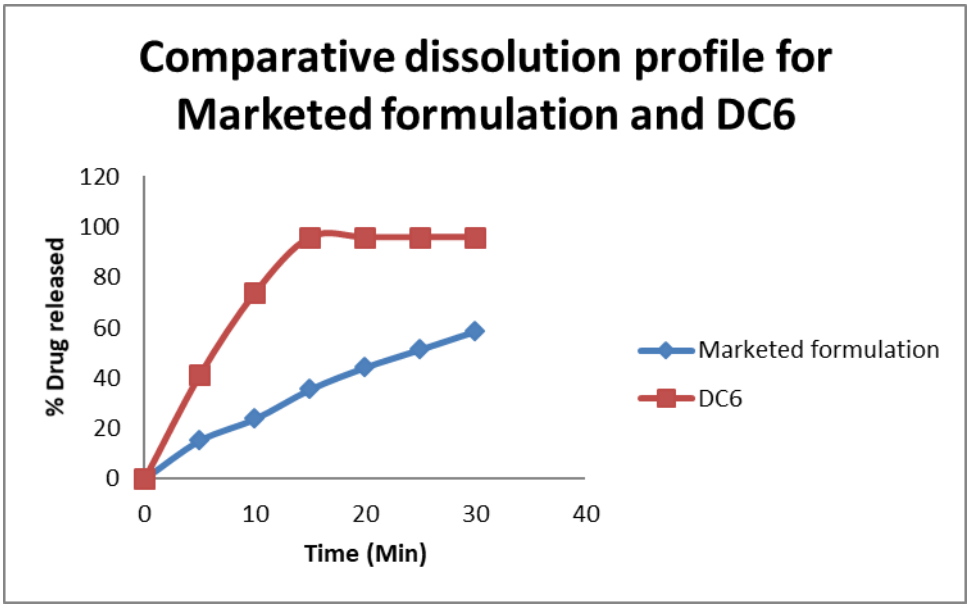

Figure No: 7 Comparative dissolution profile for DC6 and Marketed formulation

Stability studies: There is no change in drug content and % drug release for 3 months, so it is continued for the next three months as per ICH guidelines for stability studies.

Table No: 9 Stability studies for optimized formulation DC6

Formulation Code	*In*-vitro Dispersion time (Sec)	% Drug Content	% Drug released	
			25±2^{0}C / 65±5%RH	40±2^{0}C / 75±5%RH
Fisrt day	19.68±0.11	99.21±0.14	95.95±0.14	95.95±0.13
30 days	19.71±0.14	99.19±0.17	95.67±0.16	95.73±0.18
60 days	19.73±0.12	99.13±0.29	95.48±0.19	95.42±0.29
90 days	19.75±0.12	99.04±0.22	95.12±0.28	95.15±0.26

CONCLUSION

For this study, a Fast disintegrating tablet is prepared by using Labetalol HCl as a model drug that is used as an Anti- Hypertensive. From the Solid Dispersion studies, it can be concluded that *In vitro* dissolution studies for solid dispersion have been performed and the results show that SD6 shows the greater drug release than compared to the other dispersions. SD6 containing 1: 3 concentration of Drug and HP Beta cyclodextrin shows the best suitable Solid dispersion to be used for taste masking and to enhance the solubility of the drug.

Labetalol HCl Fast Disintegrating Tablets was successfully prepared by using the Direct Compression Technique. Evaluation parameters like Weight variation, Thickness, Hardness, Friability, and drug content indicate that values were within the permissible limit for all formulations. *In* vitro drug release study was carried out Fast disintegrating tablets prepared by Direct Compression technique and based on the results; DC6(Containing 15mg of Cross Carmellose Sodium) showed Drug Release of 95.95% and *In* vitro Dispersion time of 15 seconds respectively was identified as the best formulation among all the other formulations. The Croscarmellose sodium used formulation has shown better release profile than compared with other formulations by Direct Compression Technique. The optimized formulation follows first-order kinetics with regression coefficient DC6 0.998 respectively. Stability studies indicate that the formulated oral disintegrating tablets are stable for 3 months under two different conditions.

Conflict of interest: The authors declare no conflict of interest.

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