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Research Article

Formulation and *In-Vitro* Evaluation of Taste Masked Fast Disintegrating Tablets of Labetalol Hydrochloride by Wet Granulation Technique

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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 the 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 superdisintegrants 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 Co-precipitation method. Using the drug HP- β -CD complex, Fast Disintegrating tablets were prepared by Wet granulation Technique 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 WG9 (Sodium Starch Glycolate 15mg and Starch paste 18mg) has shown the % Drug release of 99.97%, In-vitro Dispersion time of 16 Secs respectively.

Keywords: Solid dispersions, fast disintegrating tablets, Labetalol, Crospovidone, Croscarmellose sodium and Sodium starch glycolate.

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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 delivery of drugs to patients using conventional drug delivery system. 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 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 an 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 is used as an antihypertensive agent. Labetalol is used parenterally for immediate reduction in blood pressure in severe hypertension or in 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), Crospovidone 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, 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 behaviour of labetalol hydrochloride and mixture of drug and polymers. (Figure no. 3,4)

Preparation of Solid Dispersion by Co - Precipitation Method:

Drug was dissolved in ethanol at room temperature and 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 cyclodextrine	100	200	300	-	-	-
HP-Beta cyclodextrine	-	-	-	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. (Table no. 3, Figure no. 5)

Preparation of Labetalol HCl of fast disintegrating tablets by Wet granulation technique

All the powders were passed through #80 mesh sieve. Required quantity of drug mixture (Solid dispersion) and

excipients were mixed thoroughly. Mixture was then granulated using Starch paste and granules were made. Granules were dried at 40°C for about 15 min. After drying super disintegrants was added externally. Talc and magnesium stearate were added as glident and lubricant respectively. The tablet was compressed using 9mm round flat punches to get tablets of 300mg weight on 10 station rotary tablet machine (CLIT).

Table no. 2. Formulation Design of Labetalol HCl using Wet Granulation Technique

Ingredients (mg)	WG0	WG1	WG2	WG3	WG4	WG5	WG6	WG7	WG8	WG9
Labetalol+HP Betacyclodextrine (SD6)	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
Starch paste	8	12	12	12	15	15	15	18	18	18
Mannitol	84	75	70	65	72	67	62	69	64	59
Talc	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Pippermint 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

Angle of repose was determined using cylinder method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated using the formula (Table no.4)

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

Bulk density:

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

$$\text{Bulk density} = \frac{\text{weight of sample in gram}}{\text{volume occupied by the sample}}$$

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 tapped density is calculated using following formula.¹⁰

$$\text{Tapped density} = \frac{\text{Wt. of sample in gm}}{\text{Tapped volume}}$$

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

$$I = \text{Tapped density} - \text{Bulk Density} / \text{Tapped density}$$

Hausner's Ratio:

Hausner's Ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.¹¹

$$\text{Hausners Ratio} = \text{Tapped Density} / \text{Bulk density}$$

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 was calculated. (Table no. 5)

b. Thickness:¹³

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

c. Hardness:

Hardness was measured using the Monsanto hardness tester. Measure the pressure required to break 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 (W_{initial}) and transferred into the friabilator. 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

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

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 makeup the volume up to 100ml. The solution was filtered; 1ml of 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 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 $37 \pm 2^\circ\text{C}$ 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 (pH 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 dissolution medium. Temperature was maintained at $37 \pm 0.5^\circ\text{C}$. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals at 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. 6 Fig no. 6)

g. Stability studies:

Stability studies were performed at a temperature of $25 \pm 2^\circ\text{C}$ / $65 \pm 5\% \text{RH}$ & $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$, over a period of three months (90 days) on the promising FDT of Labetalol HCl formulation (Table no. 8)

RESULTS AND DISCUSSION:

FT-IR Spectroscopic Analysis:

Fig 1 FTIR graph for Labetalol HCl (Pure Drug)

Fig: 2 FTIR graph for Labetalol HCl + Excipients

Differential Scanning Calorimetry (DSC) Studies

Fig : 3 DSC of Pure Drug

Fig:4 DSC of Optimized Formulation (WG9)

DSC thermogram of untreated/ pure drug shows an endothermic peak at 158°C, which is related to its melting point. Physical mixture of excipients and the drug of the Optimized Formulation WG9 showed endothermic peaks at 174.51°C. 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 :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±0.019	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

Fig 5: Comparative dissolution profile for labetalol HCl Solid Dispersion

Table 4: Pre compression studies of Labetalol HCl fast disintegrating tablets (Wet Granulation Technique)

Formulation Code	Bulk density	Tapped density	Cars index	Hausners ratio	Angle of repose (°)
WG0	0.26±0.07	0.30±0.06	13.84±0.04	1.16±0.04	33.72±0.03
WG1	0.28±0.09	0.32±0.09	12.95±0.13	1.15±0.11	32.62±0.15
WG2	0.29±0.12	0.31±0.11	8.29±0.15	1.09±0.12	29.47±0.18
WG3	0.29±0.14	0.31±0.12	4.90±0.16	1.05±0.15	25.58±0.14
WG4	0.32±0.15	0.34±0.13	5.66±0.18	1.06±0.16	26.77±0.17
WG5	0.31±0.17	0.34±0.14	7.99±0.14	1.09±0.20	28.47±0.19
WG6	0.32±0.18	0.35±0.17	7.79±0.12	1.08±0.19	27.17±0.23
WG7	0.30±0.16	0.32±0.18	8.83±0.16	1.10±0.16	29.58±0.22
WG8	0.29±0.15	0.32±0.16	9.70±0.17	1.11±0.14	30.11±0.15
WG9	0.28±0.08	0.32±0.09	10.52±0.10	1.12±0.18	31.42±0.11

Table: 5 Post compression studies of Labetalol HCl fast disintegrating tablets (Wet Granulation Technique)

Formulation Code	% weight variation	Thickness (mm)	Hardness (Kg/cm ²)	% friability	Disintegration time (Sec)	In-vitro Dispersion time (Sec)	Water absorption ratio	% Drug Content
WG0	293.2	3.59±0.10	2.5±0.20	0.45±0.05	62.54±0.11	58.39±0.10	62.48±0.23	101.42±0.18
WG1	300.5	4.17±0.17	3.2±0.05	0.38±0.15	56.49±0.16	49.58±0.14	73.58±0.31	99.86±0.15
WG2	301.4	4.12±0.25	3.4±0.11	0.28±0.11	42.47±0.21	35.39±0.17	79.68±0.29	99.35±0.23
WG3	298.9	4.08±0.10	3.5±0.15	0.51±0.15	39.59±0.29	34.96±0.20	76.4±0.19	100.83±0.31
WG4	299.1	4.18±0.17	3.3±0.15	0.37±0.13	41.59±0.28	40.87±0.19	89.57±0.16	100.43±0.49
WG5	301.3	4.1±0.10	3.5±0.25	0.54±0.07	25.39±0.31	21.98±0.16	91.47±0.14	101.16±0.66
WG6	299.4	4.16±0.11	3.5±0.10	0.28±0.09	30.59±0.42	24.51±0.29	92.48±0.16	100.34±0.52
WG7	298.1	4.12±0.05	3.5±0.10	0.36±0.06	28.49±0.17	21.43±0.25	87.48±0.15	99.38±0.41
WG8	302.4	4.19±0.10	3.1±0.10	0.34±0.10	29.51±0.22	19.39±0.20	88.39±0.22	99.51±0.53
WG9	299.5	4.07±0.05	3.5±0.10	0.36±0.11	22.94±0.19	16.49±0.18	85.39±0.10	99.61±0.33

Table :6 Dissolution data of various fast disintegrating tablets of Labetalol HCl (Wet Granulation Technique)

Time (min)	WG0	WG1	WG2	WG3	WG4	WG5	WG6	WG7	WG8	WG9
0	0	0	0	0	0	0	0	0	0	0
5	2.98±0.12	30.29±0.15	32.94±0.20	32.19±0.12	31.84±0.29	42.98±0.21	43.29±0.29	35.38±0.30	39.29±0.21	43.19±0.24
10	6.75±0.09	47.28±0.19	54.27±0.22	63.86±0.19	63.29±0.32	76.37±0.29	73.49±0.27	54.12±0.29	71.39±0.29	75.47±0.29
15	8.19±0.12	71.39±0.20	77.47±0.19	87.97±0.21	87.46±0.30	99.71±0.19	93.74±0.20	74.25±0.21	92.38±0.20	99.97±0.16
20	10.92±0.15	88.27±0.22	92.46±0.18	99.46±0.18	98.46±0.16	99.70±0.16	99.96±0.19	91.38±0.19	99.51±0.17	99.96±0.16
25	13.05±0.08	99.31±0.30	99.21±0.21	99.45±0.18	99.93±0.11	99.69±0.17	99.95±0.18	99.73±0.15	99.50±0.16	99.95±0.16
30	16.95±0.17	99.30±0.34	99.19±0.21	99.44±0.18	99.92±0.11	99.70±0.16	99.94±0.19	99.72±0.15	99.48±0.17	99.97±0.16

Fig: 6 Comparative dissolution profile

Table :7 Comparative dissolution profile for Marketed formulation (Trandate) and WG9

Time(min)	Marketed formulation	WG9
0	0	0
5	23.21±0.21	43.19±0.20
10	42.83±0.19	75.47±0.16
15	64.53±0.26	99.92±0.18
20	79.32±0.22	99.96±0.19
25	91.43±0.19	99.95±19
30	99.65±0.18	99.93±17

Fig:7 Comparative dissolution profile for WG9 and Marketed formulation

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

Table :8 Stability studies for optimized formulation WG9

Formulation Code	In-vitro Dispersion time (Sec)	% Drug Content	% Drug released	
			25±2°C / 65±5%RH	40±2°C / 75±5%RH
Fisrt day	16.49±0.14	99.61±0.11	99.61±0.19	99.61±0.20
30 days	16.51±0.11	99.41±0.23	99.53±0.16	99.59±0.18
60 days	16.33±0.15	99.24±0.19	99.42±0.27	99.52±0.29
90 days	16.22±0.14	99.06±0.27	99.32±0.30	99.45±0.22

CONCLUSION

For this study Fast disintegrating tablet are prepared by using Labetalol HCl as a model drug is used as Anti-Hypertensive. From the Solid Dispersion studies it can be concluded that *In vitro* dissolution studies for solid dispersion has been performed and the results shows 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 ensolubility of the drug.

Labetalol HCl Fast Disintegrating Tablets was successfully prepared by using Direct compression Technique. Evaluation parameters like Weight variation, Thickness, Hardness, Friability, and drug content indicate that values were within permissible limit for all formulations. *In vitro* drug release study was carried out Fast disintegrating tablets prepared by Wet Granulation technique and based on the results; WG9(Containing 15mg of Sodium Starch Glycolate) showed the % Drug release of 99.97%, In-vitro Dispersion time of 16 Secs respectively was identified as the best formulation among all the other formulations. The Sodium Starch Glycolate 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 WG9 0.998 respectively. Stability studies indicate that the formulated oral disintegrating tablets are stable for a period of 3 months under two different conditions.

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

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