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(RESEARCH ARTICLE)

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Formulation and evaluation of extended-release floating tablets of labetalol hydrochloride 200 mg

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Abstract

The aim of present work is to formulate and evaluate extended-release floating tablets of Labetalol HCL to improve the bioavailability, Patient compliance and solubility on oral floating drug of Labetalol HCL. Labetalol HCL is mainly used in the treatment of hypertension, which is BCS Class Ⅰ drug i.e. Highly soluble and highly permeable.

The tablets were prepared by wet granulation method by using different concentrations of HPMC polymer. The tablets were evaluated for Preformulation characteristics, Pre compression parameters and post compression parameters. In-vitro dissolution studies were performed for all prepared formulations by using dissolution test apparatus employing a paddle stirrer at 50 rpm and 37 ± 0.5°C, 0.1N HCL buffer was used as dissolution medium. Samples of 5ml each were withdrawn at different time intervals. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were diluted and assayed at 302 nm using Agilent UV Visible double beam spectrophotometer. The increased drug release is due to the presence of low concentration of HPMC K4 m.

The drug release kinetics was calculated for all the formulations, among all the formulations F8 was taken as optimized formulation whose percentage drug release was found to be 96%. It indicates the release follows zero order and Hixon kinetics. Hence formulation F8 was Considered as the optimized batch and stability studies were conducted at 40°c±2°c/75±5%RH, Storage condition for 3 months and no change was observed.

Keywords: Labetalol HCL; Wet granulation; Floating systems; Hypertension; BCS class

1. Introduction [1,2,3,4]

Oral route is the most common and frequently used route for systemic drug effects facilitating absorption from various sites along the gastrointestinal tract (GIT). It is considered as the most natural, uncomplicated, convenient and safe route of administration. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Controlled release tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and site effects, and increase the safety margin for high-potency drugs. Floating drug delivery systems provide prolonged gastric residence time which increases the duration of drug release, improves bioavailability and reduces drug wastage.

Labetalolhydrochloride,2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]-benzamide, a non-selective α, β-adrenoreceptor antagonist which is used in the treatment of hypertension. It is appreciably soluble in

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lower and higher pH solutions, with minimum solubility between pH 6- 10. The drug shows variable bioavailability ranging from 10-80% which may be attributed to its instability in alkaline pH and poor absorption due to precipitation.

It is administered in doses ranging from 50-200 mg twice a day due to its shorter half-life of 6-8 hrs suggesting the need for sustained release formulation. Thus, the present study was aimed at developing extended-release floating form of Labetalol hydrochloride. [1,2,3,4]

2. Materials and Methods

2.1. Procurement of drug and chemicals

Labetalol Hcl was a gift sample from New land, Lactose monohydrate procured from DMV Fontera, Sodium bicarbonate from Mereck, Hydroxypropyl methylcellulose K_4M was collected from Lotte fine Chemicals, Polyvinyl Pyrrolidone K90 taken from Ashaland, Talc from Emeries, Magnesium stearate was taken from Valtries and Purified Water from In-house.

2.2. API characterization

2.2.1. Physical appearance

The appearance of API was done by visual observation.

2.2.2. Color of the drug sample

The drug sample was viewed visually for the determination of its color using white and dark backgrounds and then the results were compared with pharmacopoeias.

2.2.3. Odor and taste of the drug sample

The odor and taste of the drug sample results were compared with pharmacopoeias.

2.2.4. Solubility

Solubility profiles of Labetalol HCl were done by solubility equilibrium method. It is done by stirring an excess of drug in the water and other solvents like methanol, ethanol, isopropyl alcohol. It is also done in various concentrations of pH buffers.

2.2.5. Melting point

Melting point of Labetalol HCl was found out using traditional melting point apparatus. Labetalol HCl was packed in the capillary tube which was placed in the holder provided in melting point apparatus. Melting range was found out from the reading which was observed visually.

2.2.6. Loss on Drying

Required quantity of drug was weighed and placed on the steel plate provided in the LOD tester and tested for LOD at 105°.

3. Analytical method -standard calibration curve by Ultraviolet visible spectroscopy (UV-Visible)

3.1. Preparation of 0.1 N HCl:

8.5 ml of concentrated hydrochloric acid was taken and diluted with distilled water up to 1000ml.

3.2. Determination of lambda max of drug in 0.1 N HCl

3.2.1. Preparation of drug standard stock solution in 0.1 N HCl (100 µg/ml)

A standard stock solution was prepared by dissolving accurately weighed 25 mg of drug in 0.1 N HCl.

3.2.2. Estimation of λ max of drug

From the standard stock solution, 1 ml was pipette out into 10 ml volumetric flask. The volume was made up with 0.1 N HCL. The resulting solution containing 10µg/ml was scanned between 200 and 400nm.

3.2.3. Calibration curve of drug in 0.1N HCl

An accurately weighed amount of 25 mg of drug was transferred separately into 100ml volumetric flask and then the volume was made up to the mark with 0.1 N HCl.

From the stock solution 2.5,4,5,5.5, and 6ml of sample was taken diluted up to 25 ml using 0.1 N HCl in a 25 ml volumetric flask resulting in concentration of 25,40,50,55,60 µg/ml solution.

These were analyzed at 302 nm and calibration curve was plotted taking concentration on x-axis and absorbance units on y-axis.

3.3. Evaluation of pre compression parameters [23,24]

The final blend of core tablets was evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index, and Hausner's ratio.

3.3.1. Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. A funnel with 10 mm inner diameter of stem was fixed at a height of 2.5 cm over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stem of the funnel. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Calculated by following formula:

$$\text{Tan}Ø = h/r$$

Where, Ø=angle of repose, h= height of the pile, r =average radius of the powder cone.

3.3.2. Bulk density

The ratio of mass (weight) to volume is known as the bulk density of material. The bulk density of a powder depends on particle size distribution. The equation for determining the bulk density is $\rho b = M/V$

Where, M= Mass of particles

V= Total volume of packing.

3.3.3. Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of drug on a mechanical tapper apparatus, which is operated for fixed number of taps (1000) until a powder bed volume has reached the minimum. Using the weight of drug in cylinder and tapped volume, the tapped density is determined.

TD = weight of powder/ Tapped volume

3.3.4. Compressibility index

The compressibility index of the powder was determined by Carr's compressibility index.

Where, Carr's Index $= [(D_t - D_b) \times 100/D_t]$

D_t, is the tapped density

D_b, is the bulk density

3.3.5. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder. [23,24]

Hausner's Ratio = TD/BD

3.4. Formulation of floating tablets

The floating tablets were prepared by wet granulation method. The formula was designed by using the ingredients.

3.5. Formulation development

3.5.1. Sifting

Sift the weighed quantity of Labetalol HCI, Lactose monohydrate, HPMC k-4 m, and Sodium bicarbonate, through #30 mesh and collect in double lined polyethylene bag.

3.5.2. Granulation

Required quantity of binder (PVP K90) was added to the sufficient Demineralized water. Stir the solution for 15 minutes.

Granulation was performed in 2litre RMG.

Table 1 Process parameters of RMG

Time	Impellar@120 RPM	Chopper RPM
Binder addition		
60 Sec	0.89A	-
30 Sec	0.90A	-
Kneading		
60 sec	0.90A	-

3.5.3. Drying

The wet mass obtained after granulation was air dried in rapid driers for 60 min. Later it was subjected to temperature drying in rapid driers till LOD value of NMT 2% was reached. Loss on drying of granules was determined by LOD apparatus at 105°C.

Table 2 Process parameters of Rapid Driers

Time	Temperature	Airflow	LOD @105°c
60 minutes	55°C	20	1.20%w/w

3.5.4. Sizing

The dried granules are sifted through #18 mesh.

3.5.5. Lubrication

Sift accurately weighed magnesium stearate and talc through #60 mesh, which is added to the previously obtained dried granules and blended for 5 min in polyethylene bag.

3.5.6. Compression

Lubricated blend was compressed to obtain tablets.

Table 3 Process parameters of Compression

Process Parameters	Data
Punch shape	Round
Punch size	9mm
Compression Speed	15

Table 4 Formulation table

Composition	F1	F2	F3	F4	F5	F6	F7	F8
Dry Mix								
Labetalol HCL	25	25	25	25	25	25	25	25
Lactose monohydride	1.88	3.38	4.73	5.94	7.04	8.02	8.91	9.71
$NaHCO_3$	4.38	4.38	4.38	4.38	4.38	4.38	4.38	4.38
HPMC K4m	15	13.50	12.15	10.94	9.84	8.86	7.97	7.17
Binder Solution								
Purified water	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
PV PK 90	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Lubrication								
Magnesium stearate	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86
Talc	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63

3.6. Evaluation of post compression parameter: [15]

All the tablets prepared were evaluated for hardness, thickness, friability, weight variation, and In-vitro dissolution studies as follows.

3.6.1. Hardness

The hardness of prepared tablets was determined by using Electro lab digital tester and measured in terms of kg/cm^2.

3.6.2. Thickness

The tablets were randomly selected from each formulation and their thickness was measured by using vernier calipers.

3.6.3. Friability

Friability test was done by Roche friabilator. 6.5 gm of tablets were weighed and were subjected to combined effect of attrition and shock by utilizing a plastic chamber that resolve at 25 rpm dropping the tablets at distance of 6 inch with each revolution. Operated for 100 revolutions, the tablets were dusted and reweighed. The percentage friability was calculated.

%Friability = Initial weight- Final weight/ Initial weight x 100

%Friability of the tablets not more than 1% w/w was considered acceptable.

3.6.4. Weight Variation Test

20 tablets from each formulation were randomly picked up and weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. For the tablets of average weight 350 mg, the % deviation allowed is + 5%.

%deviation=Average weight of the tablets- Individual of the tablet/ average weight of tablet ×100

3.6.5. Floating lag time

The test was performed by placing 1 tablet in 250ml beaker containing 0.1N HCL. How much time required to float the dosage form on its surface is called floating lag time.

3.6.6. Floating time

How much time it will be stable at the surface.

3.6.7. Determination of drug content

Three tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (100 mg) was extracted in 200 ml of 0.1N HCl, sonicate for 30minutes. For Further dilution take 5ml of solution from stock-l and add in 50ml volumetric flask. The solution was filtered. The drug content was determined by UV spectroscopy at a wavelength of 302 nm.

3.6.8. In-vitro Dissolution Study:[23][24]

The In-vitro dissolution study for the Labetalol HCL floating tablets were carried out in USP type-Ⅱ dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCL as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 302 nm using UV Visible spectrophotometer after suitable dilutions. The results are showed in table 10.[15]

3.7. Stability studies:[25]

The optimized formulation batch of Labetalol HCL was loaded for accelerated stability studies at 40±2°C/75±5% RH for approximately 3 months. The tablets were evaluated for Color, Assay, Floating time, Floating lag time, weight variation, Hardness, thickness, Friability and In-vitro Drug release studies and compared with initial tablets (optimized batch), evaluated immediately after manufacturing.[25]

4. Results

4.1. Pre-formulation studies

4.1.1. API Characterization

The following properties of the active ingredient labetalol HCL were evaluated during Preformulation study.

Table 5 Characterization of drug properties

Property	Interference
Organoleptic Characteristics	White coloured powder, Bitter in taste and odourless
Bulk Density(g/ml)	0.42
Tapped Density(g/ml)	0.51
Melting point(^{o}c)	188
LOD (%W/W)	2
Solubility	117mg/l (at 25^{o}c)

4.1.2. Analytical method -standard calibration curve by Ultraviolet visible spectroscopy (UV-Visible)

Table 6 Data for Standard plot of Labetalol HCL in 0.1NHCL

S. No.	Concentration(mg/ml)	Absorbance(nm)
1	25	0.219±0.001528
2	40	0.343±0.002082
3	50	0.430±0.003055
4	55	0.469±0.01528
5	60	0.519±0.002517

*All the values are expressed as mean ± standard deviation (n=3)

4.1.3. Calibration Curve of Labetalol HCL in 0.1N HCL

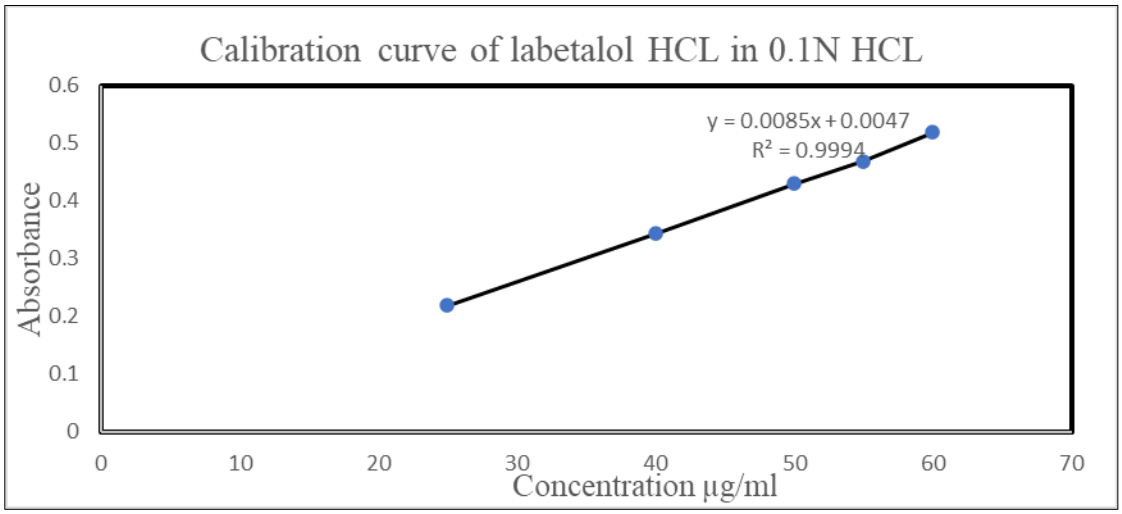

Figure1 Calibration curve of labetalol HCL in 0.1N HCL at λmax 302nm

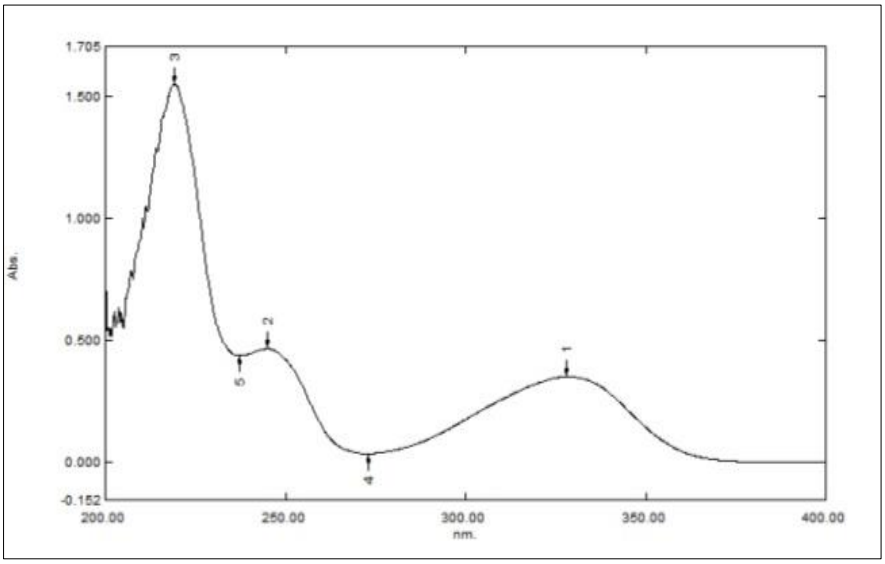

Figure 2 Absorption spectrum of labetalol HCL

4.2. Evaluation of precompression parameters

Table 7 Evaluation of pre compression parameters

Formulation code	Angle of repose	Bulk density(gm/ml)	Tapped density (gm/m)	Carr's index (%)	Hauser's ratio
F1	35.6±0.25	0.47±0.005	0.56±0.01	16.07±0.0	1.19±0.01
F2	36.7±0.25	0.48±0.015	0.62±0.00	22.50±0.2	1.29±0.02
F3	36.7±0.15	0.52±0.005	0.65±0.01	20.00±0.5	1.25±0.01
F4	36.5±0.05	0.43±0.011	0.56±0.00	23.21±0.1	1.30±0.02
F5	36.4±0.152	0.46±0.015	0.58±0.02	20.68±0.0	1.26±0.01
F6	36.2±0.152	0.49±0.015	0.62±0.02	20.96±0.0	1.26±0.01
F7	36.2±0.25	0.42±0.013	0.54±0.03	22.22±0.3	1.28±0.01
F8	36.1±0.15	0.56±0.05	0.63±0.01	11.11±0.0	1.12±0.02

*All the values are expressed as mean ± standard deviation (n=3)

4.3. Evaluation of post compression parameters

Table 8 Evaluation of post compression parameters

Formulation code	Weight variation (mg)	Hardness (kg/cm)	Thickness (mm)	Friability (%)	Drug content (%)
F1	398±0.63	81.9±0.38	5.24±0.01	0.17±0.01	99.5±0.07
F2	397±0.63	85.4±0.08	5.27±0.01	0.12±0.00	99.7±0.01
F3	399±0.63	86.5±0.13	5.29±0.01	0.10±0.00	99.8±0.13
F4	397±0.63	89.9±0.14	5.32±0.01	0.11±0.00	99.5±0.07
F5	396±0.63	85.3±0.08	5.26±0.01	0.12±0.00	99.6±0.13
F6	397±0.63	82.6±0.38	5.28±0.01	0.14±0.01	99.4±0.07
F7	396±0.63	86.1±0.13	5.30±0.01	0.13±0.01	99.6±0.13
F8	399±0.63	86.2±0.13	5.28±0.01	0.12±0.00	99.9±0.13

*All the values are expressed as mean ± standard deviation

In case of weight variation(n=6); Hardness, thickness, Friability and drug content (n=3)

Table 9 Disintegration, Floating lag time, Floating time

Formulation Code	Disintegration time (Hrs)	Floating lag time (Hrs)	Floating time (Hrs)
F1	1	2:20	>12
F2	1	2:10	>12
F3	1	2:15	>12
F4	1	2:10	>12
F5	1	2:10	>12
F6	1	2:20	>12
F7	1	2:15	>12
F8	1	2:20	>12

*All the values are expressed as mean ± standard deviation (n=6)

Table 10 Invitro drug release for F1to F8 formulation

Time Hrs	%CUMULATIVE DRUG RELEASE							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	1±0.54	3±0.54	5±0.75	8±0.81	9±0.75	10±0.10	12±0.70	15±0.80
2	8±0.81	9±0.81	13±0.81	18±0.32	21±0.30	23±0.30	25±0.80	29±0.40
4	16±0.8	18±0.80	22±0.75	27±0.81	31±0.80	34±0.20	37±0.32	38±0.30
6	28±0.2	32±0.50	39±0.10	48±0.32	49±0.10	51±0.70	54±0.70	58±0.53
8	39±0.3	43±0.50	51±0.16	62±0.03	67±0.08	69±0.80	69±0.50	70±0.60
10	46±0.8	59±0.70	62±0.75	74±0.75	78±0.80	79±0.80	83±0.30	84±0.40
12	54±0.8	69±1.10	79±0.81	81±0.04	86±1.00	89±0.90	96±0.02	96±0.40

*All the values are expressed as mean ± standard deviation (n=3)

4.3.1. Comparative Dissolution profiles of formulation (F1 to F8)

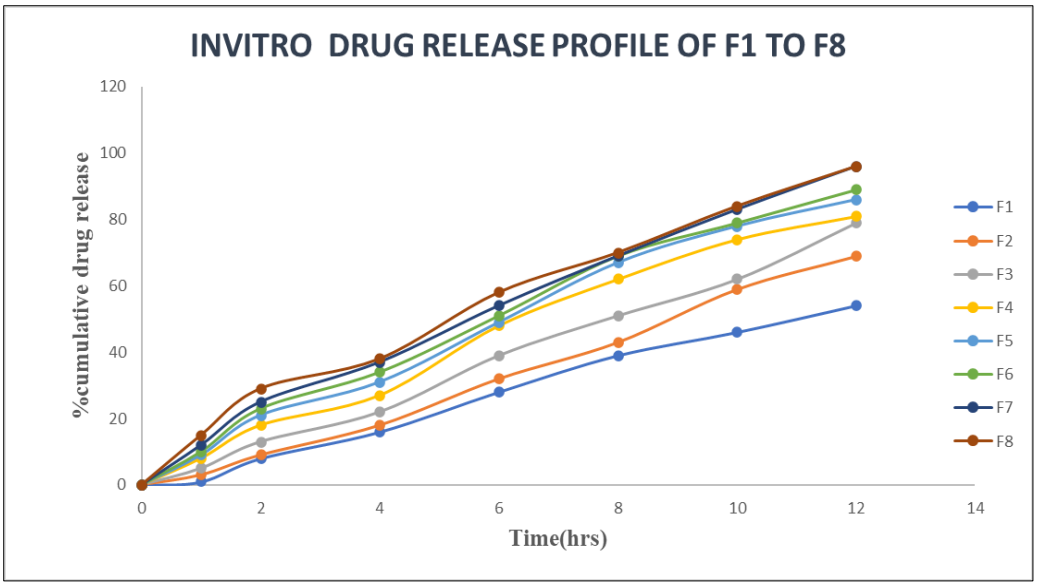

Figure 3 Comparative In-vitro dissolution profiles of formulations (F1 to F8)

4.4. Study of release kinetics

- Cumulative percent drug released versus time (Zero order kinetic model).
- Log cumulative percent drug remained versus time (First order kinetic model).
- Cumulative percent drug released versus square root of time (Higuchi's model).
- Log cumulative % of drug released Vs time. (Korsmeyer equation/Peppa's model)
- Hixson-Crowell cube root law

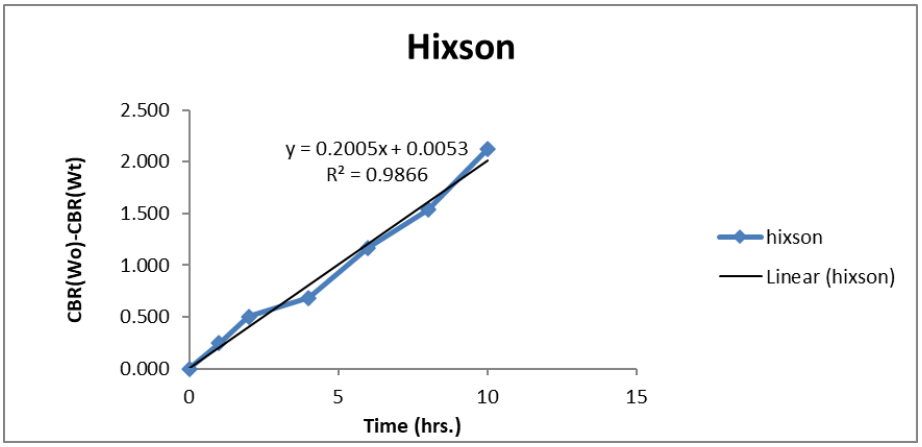

Figure 4 Hixson plot of Optimized Formulation(F8).

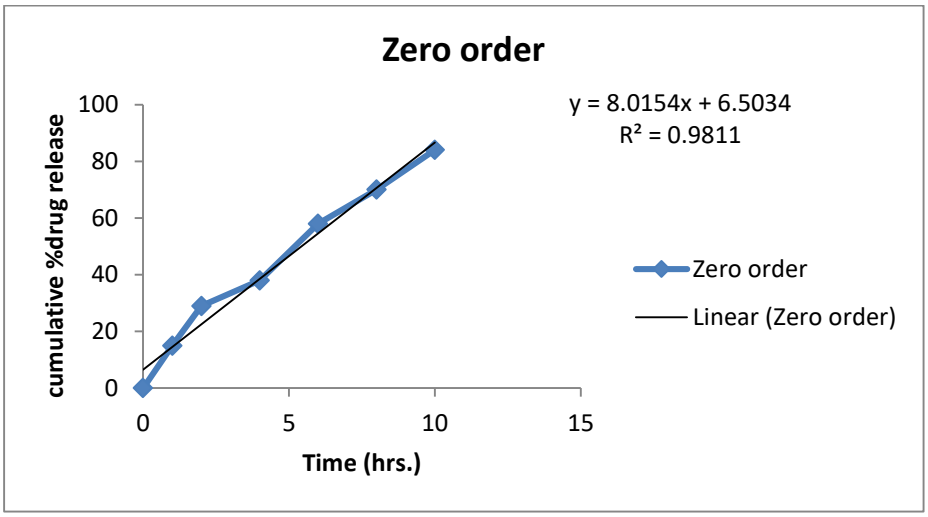

Figure 5 Zero order plot of Optimized Formulation(F8).

Table 11 Drug release Kinetics of Formulations (F1 to F8)

Formulation Code	Zero order R^2	First order R^2	Higuchi R^2	Hixon R^2	Kors-Peppas R^2
F1	0.9927	0.9872	0.8887	0.9904	0.9382
F2	0.9912	0.9564	0.8694	0.9716	0.9001
F3	0.9961	0.9823	0.9086	0.9903	0.9341
F4	0.9938	0.9734	0.9205	0.9867	0.9343
F5	0.9939	0.9692	0.931	0.9858	0.9403
F6	0.9915	0.9749	0.9438	0.9896	0.9501
F7	0.9918	0.9641	0.9543	0.9874	0.9516
F8	0.9811	0.9663	0.9653	0.9866	0.9464

The correlation coefficient of different formulations was shown in the table 11. Among them the optimized formulation release was found to be close to zero order kinetics with a R^2value of 0.9811 indicating the release rate is independent

on concentration. The Hixon plot showed has highest R^2value when compared to Korsmeyer peppas and Higuchi plot. It follows dissolution kind of drug release.

4.5. Stability studies

The stability study was conducted as per ICH guidelines at 40±2°C/75±5% RH for 3months and results are reported. Tablets were observed and there is no significant change in the parameters like Color, Floating time, Floating lag time, Weight variation, Thickness, Hardness, Disintegration, Friability, Assay and In-vitro drug release studies of Optimized formulation F8 at 40±2°C/75±5% RH stability condition for 3 months.

5. Conclusion

Labetalol HCI floating tablets were prepared by using wet granulation method. Labetalol HCI tablets were prepared by using different polymer concentrations (HPMC k4 m). From the results obtained, it was concluded that the formulation F8 is the best formulation as the extent of drug release was found to be around 96% with the increased pattern of release. This batch also showed immediate floatation and has floatation duration of more than 12hrs. The drug release model of this formulation complies with zero order kinetics and Hixon model.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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