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# Formulation and Evaluation of Floating Tablets of Labetalol Hydrochloride

**Subhash Kumar V, Saranya Nair P*, Hitesh Vekariya**

**Department of Pharmaceutics, Smt.R.B.Patel college of Pharmacy, Atkot, Rajkot, Gujarat, India**

**ABSTRACT:**

Labetalol HCl is mainly used in the treatment of hypertension. The characteristic of the drug is it has short half life (3-6 hrs) and undergoes first pass metabolism.It is PH dependent with solubility range of 6-10. This research work was carried out to improve the bioavailability, patient compliance & solubility on oral floating drug of Labetalol HCl. 300mg of Labetalol HCl sustained controlled release tablets were formulated by wet granulation method and in vitro dissolution studies were performed to study drug release rate and patterns. HPC, HEC, Xanthum gum were used as rate controlling polymers. Tablets were prepared using different polymer ratios. Dissolution profiles are determined using USP XXII at 50 rpm in 99ml of acidic medium (PH 1.1) for 2 hrs followed by 900 ml alkaline dissolution medium (PH 7.4) upto 12hrs. To determine the drug release kinetics several kinetic models were applied to the dissolution profiles.

**KEY WORDS:** HPC ( Hydroxy propyl cellulose), HEC ( Hydroxy ethyl cellulose), GRDDS(Gastroretentive drug delivery system), FDDS(Floating drug delivery system), GRT (Gastric retention time), GET(Gastric emptying time).

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***For Correspondence:***

**Nair Saranya P. Mohan**

Department of Pharmaceutics,
Smt.R.B.Patel college of Pharmacy,
Atkot, Rajkot, Gujarat, India.



## INTRODUCTION:

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration

of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.[1-5]

**Matertial & methods :**

Labetalol hydrochloride was obtained from gift sample (Mercury Labs. Ltd., Baroda, Gujarat, India)..HPC, HEC, Xanthum Gum, Sodium Bicarbonate, PVP-K30, MCC, Talc, Magnisium Stearate was procured from the college laboratory. All the chemicals and materials used were of analytical grade. Single punch tablet compression machine was used to punch tablets. In addition digital weighing balance, density & hardness tester, rotary compression machine, roche friabilator, electrolab dissolution tester (USP)TDT-08L, stability control oven,in-vitro-dissolution test apparatus, UV visible spectrophotometer (Shimadzu,800,Japan), FTIR (Shimadzu,FTIR,8300,Japan) was used in this study.

**UV analysis of drug[6,7,8]**

**Preparation of 0.1 n HCl solution**

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

**Preparation of standard stock solution**

Accurately weighed 1 0 mg of Labetalol HCl was dissolved in 100 ml of 0.1 N HCl which gives 100 µg/ml standard stock solution.

**Determination of Analytical Wavelength ($\lambda_{max}$)**

The standard stock solution of 100 µg/ml of Labetalol HCl was estimated by UV-Visible Spectrophoto metric method and the absorption maxima were determined. The $\lambda_{max}$ of Labetalol HCl was found to be 299.60 nm (≈ 300 nm ).

**Standard calibration curve of labetalol HCl**

From standard stock solution of 100 µg/ml, appropriate aliquots were taken into different volumetric flasks and volume was made up to 10 ml with 0.1 N HCl so as to get drug concentrations of 20, 30, 40, 50, 60, 60, 70, 80, 90 a nd 100 µg/ml. The absorbencies of these drug solutions were estimated at $\lambda_{max}$ 300 n m.

**Drug excipients compatibility study[6]**

Drug: Excipients compatibility study was carried out for any interference of drug and excipients used for the formulation of gastro retentive floating tablet of Labetalol HCl. It was carried out using Fourier Transformed Infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) analysis. The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm-1 to 400 cm-1. The DSC analysis of pure drug and physical mixture of polymer and drug were carried polymer drug interaction studies out between 50 – 250 $^{o}$ C.

**Bulk density[7,8,9]**

It refers to packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in g/ml.

**$\rho i = m / V_i$**

Where, m = Mass of the blend,$V_i$ = Untapped volume

**Tapped density [7,8,9]**

Tapped density was measured by using formula:

**$\rho t = m/Vt$**

Where, Vt = Tapped volume

**Carr's index (compressibility)[7,8,9]**

The compressibility index is a ratio to measure the property of powder to be compressed.

**Carr's index = [Tapped density - Bulk density/Tapped density] * 100**

**Hausner's ratio [7,8,9]**

It is measurement of frictional resistance of the drug.

**Hausner's Ratio = Tapped density / Bulk density**

**Angle of repose [7,8,9]**

It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane.

**$\theta$ = tan-1 h/r**

Where, θ = Angle of repose,h = Height of powder heap,r = Radius of the powder cone.

**Method used for preparation of labetalol HCl**

Wet granulation method is used for preparation of Labetalol HCl floating tablet.

**Method: -** All the ingredients, except lubricant, glident and binder, were accurately weighed and mixed geometrically. Alcoholic solution of PVP K-30 (5 %w/w) is used as granulating agent. The granules were dried in conventional hot air oven. The dried granules were sieved through 40/60 meshes. Talc and magnesium stearate were added and granules were compressed using multiple rotatory punching machine. Punching was done using 9 mm punch.

**Post compression evaluation of labetalol HCl tablets[8-11]**

**Weight variation**

Twenty tablets were taken randomly, weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

**Hardness**

3 tablets were randomly selected and hardness was measured in monsento hardness tester. The average was taken as hardness of the tablet.

**Thickness**

3 Tablets were selected randomly from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement.

**Friability**

10 tablets were weighed (initial weight) and then transfer into Roche friabilator. It was subjected to 100 revolutions in 4 min. The tablets were de-dusted and reweighed & calculated as follows:

**% Friability = (Initial weight – Final weight) / (Initial weight) × 100**

**Drug content uniformity[11,12]**

Three tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (100 mg) was extracted in 100 ml of 0.1N HCl. The solution was filtered. The drug content was determined by UV spectroscopy at a wavelength of 300 nm after a suitable dilution with 0.1 N HCl.

***In-vitro* buoyancy *study* [11,12,13]**

The tablets were placed in 900 ml 0.1 N HCl in a beaker and the time required to rise to the surface and float (floating lag time) and the duration of time floating on the dissolution medium (total floating time) were determined.

***In-vitro* dissolution study [11,12,13]**

Dissolution profiles of the gastro retentive floating tablet were determined using the USP XXIII dissolution test apparatus II (Electrolab) with 50 rpm and the dissolution medium was 900 ml 0.1 N HCl. Samples (5 ml) were withdrawn with replacement at fixed time intervals and filtered. The filtered samples were then diluted with dissolution medium (when necessary) and the absorbance measured at 300 nm by Shimadzu UV spectrophotometer (Shimadzu-1800, Japan) at 300 nm.

**Drug release kinetic study of optimized formulation[11,12,13]**

**Zero order equation**

A graph of the cumulative percentage drug released from matrix against time is plotted. Zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$$Q_t = k_0.t$$

Where, $Q_t$ is the percentage of drug release at time t and $k_0$ is the release rate constant.

**First order equation**

A graph of Log cumulative % drug release against time is plotted.

$$\ln (100 - Q_t) = \text{in } 100 - k_i.t$$

Where, $k_i$ is release rate constant

**Higuchi's equation**

A graph of cumulative percentage of drug release against square root of time is plotted.

$Q_t = k_H.t^{1/2}$

Where, $k_H$ is higuchi release rate constant.

**Korseymeyers – peppas**

A graph of Log cumulative percentage of drug release against Log time is plotted.

$Q_t/Q_\infty = k_{KP}.t^n$

Where $Q_t/Q_\infty$ is fraction of drug released at time t. $K_{KP}$ is constant and n is release exponent.

**Stability study of optimized formulation**

ICH guidelines were followed for stability study. Short term stability study i.e. accelerated stability study for one month is carried out with temperature 40 $^oC$ ± 2 $^oC$, relative humidity 75 % ± 5 % RH

**Result and Discussion:**

$\Lambda_{max}$ of Labetalol HCl was found to be 299.60 nm (≈ 300 nm).Standard calibration curve is given in fig 1. The results for FTIR study is shown in fig 2. This indicates that no interaction was found between Labetalol HCl and polymer. Micromeretic properties of precomposition mixture is shown in table 2.It was observed that granules prepared by wet granulation of powder blend of Labetalol HCl had Carr's index in range 12.43 to 16.37 and angle of repose within range 24$^o$32' to 26$^o$68' predicted good flow property and compressibility of granules. So wet granulation method was performed for preparation of Labetalol HCl tablets. The results of physico-chemical evaluation of the drug tablets are given in Table 3 & all the physical parameters of the tablets were within control. In the in-vitro buoyancy study, TFT of batches FB4,FB5,FB7,FB8 is found >12hrs and of batch FB5 is 12hrs. From in-vitro dissolution study which is shown in Fig 3, it was found that FB1 to FB5 showed more than 90 % drug release in 12 hrs while FB6 to FB9 had less than 90% release in 12 hrs. It was observed that F1 having both HPC and HEC 40 mg showed fastest release while F8 having HPC and HEC 60:50 mg showed lowest release of drug. It was observes that concentration of HPC strongly affect the drug release. In kinetic study, the best fit model was selected on the basis of R2 values. Thus, Higuchi model and korsmeyerpeppas model were followed by formulation N value between 0.5-0.85 which showed that anomalous (non-Fickian) diffusion.

**Conclusion:**

12 hr release floating tablets of Labetalol HCl were successfully prepared using Hydrophilic polymer. HPC and HEC can successfully be used to obtained desired drug release and gastric retention. Wet granulation is an advantageous method compared to conventional granulation method as it may increase micrometric property of drug.Gastro retentive floating tablets can increase solubility and stability of drugs like Labetalol HCl. By preparing gastro retentive floating tablets of Labetalol HCl solubility and bioavailability of Labetalol HCl can be achieved.

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**Figures and tables:**

| Ingredients | Batch code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | FB1 | FB2 | FB3 | FB4 | FB5 | FB6 | FB7 | FB8 | FB9 |
| Labetalol HCl | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| $NaHCO_3$ | 36 | 36 | 36 | 36 | 36 | 36 | 36 | 36 | 36 |
| PVP K 30 M | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| HPC | 40 | 40 | 40 | 50 | 50 | 50 | 60 | 60 | 60 |
| HEC | 40 | 50 | 60 | 40 | 50 | 60 | 40 | 50 | 60 |
| MCC | 63 | 53 | 43 | 53 | 43 | 33 | 43 | 33 | 23 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Mg. Stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

**Table-1:Composition of Labetalol HCl tablets**

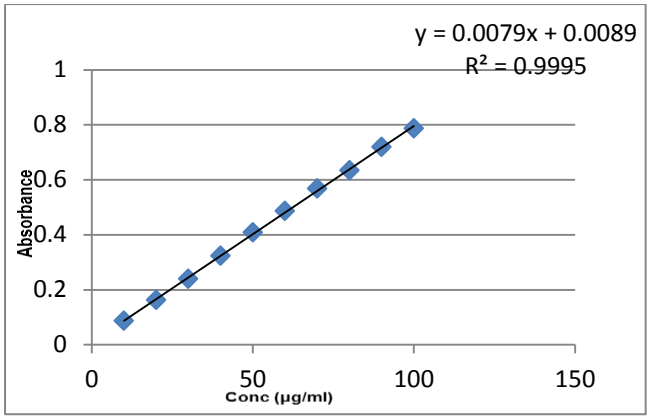



**Figure 1-Standard Calibration curve of abetalol**

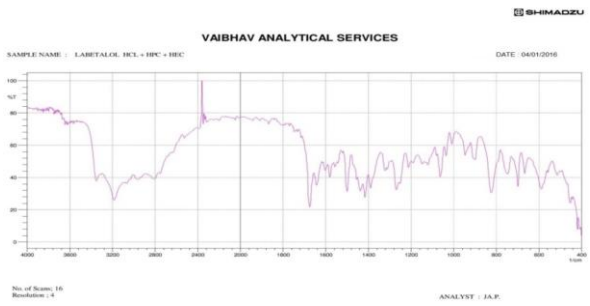



**Figure 2-FTIR study of Labetalol HCl + Polymers**

**Table-2:Micromeretic properties of precompression mixture**

| Batch Code | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index | Hausner's Ratio | Angle of Repose |
|---|---|---|---|---|---|
| **FB1** | 0.33 ± 0.00 | 0.38 ± 0.01 | 13.26 ± 2.94 | 1.15 ± 0.03 | 26°68′ |
| **FB2** | 0.33 ± 0.00 | 0.39 ± 0.01 | 14.92 ± 2.95 | 1.17 ± 0.04 | 25°40′ |
| **FB3** | 0.32 ± 0.01 | 0.38 ± 0.01 | 14.30 ± 1.23 | 1.16 ± 0.01 | 26°50′ |
| **FB4** | 0.32 ± 0.01 | 0.39 ± 0.01 | 16.37 ± 2.60 | 1.19 ± 0.03 | 26°50′ |
| **FB5** | 0.32 ± 0.00 | 0.37 ± 0.01 | 14.04 ± 2.36 | 1.16 ± 0.03 | 24°32′ |
| **FB6** | 0.33 ± 0.00 | 0.40 ± 0.01 | 15.73 ± 1.05 | 1.18 ± 0.01 | 25° 40′ |
| **FB7** | 0.32 ± 0.00 | 0.38 ± 0.00 | 14.83 ± 3.28 | 1.17 ± 0.04 | 26°48′ |
| **FB8** | 0.33 ± 0.00 | 0.38 ± 0.00 | 13.26 ± 1.76 | 1.15 ± 0.02 | 26°50′ |
| **FB9** | 0.32 ± 0.00 | 0.37 ± 0.01 | 12.43 ± 0.99 | 1.14 ± 0.01 | 25°35′ |

**Table –3:Physicochemical evalution of final batches of Labetalol HCl**

| Batch Code | *Weight Variation (mg) | *Hardness (kg/cm2) | *Thickness (mm) | Friability (%) | Drug Content Uniformity (%) |
|---|---|---|---|---|---|
| **FB1** | 249.66 ±3.05 | 4.27± 0.05 | 5.24 ± 0.05 | 0.58 | 99.52 |
| **FB2** | 249.33 ±1.52 | 4.4± 0.1 | 5.23 ± 0.01 | 0.75 | 99.67 |
| **FB3** | 250 ± 1.73 | 4.27 ± 0.5 | 5.25 ± 0.03 | 0.67 | 99.38 |
| **FB4** | 251 ± 3 | 4.37± 0.15 | 5.23 ± 0.03 | 0.68 | 99.24 |
| **FB5** | 254.66 ± 4.16 | *4.37 ± 0.1* | 5.20 ± 0.01 | 0.56 | 100.07 |
| **FB6** | 252.33±4.04 | *4.37 ± 0.1* | 5.33 ± 0.24 | 0.68 | 100.14 |
| **FB7** | 253.66 ± 2.51 | 4.23± 0.05 | 5.20 ± 0.04 | 0.76 | 99.09 |
| **FB8** | 247.66± 1.15 | 4.43± 0.05 | 5.22 ± 0.02 | 0.58 | 98.78 |
| **FB9** | 257.33± 5.13 | 4.23± 0.05 | 5.24 ± 0.02 | 0.42 | 98.94 |

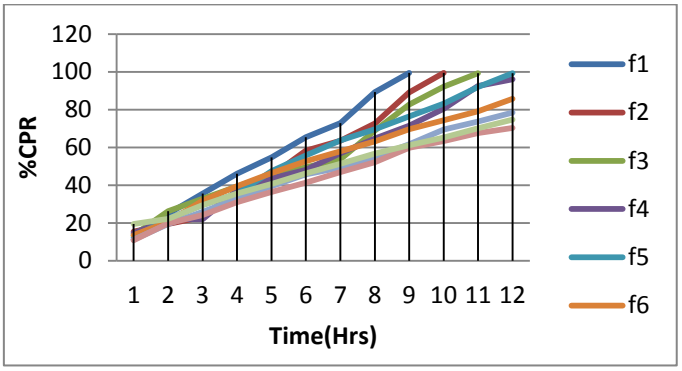
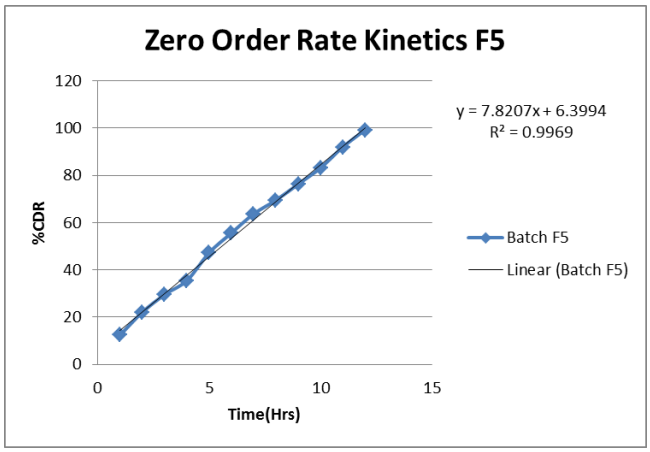
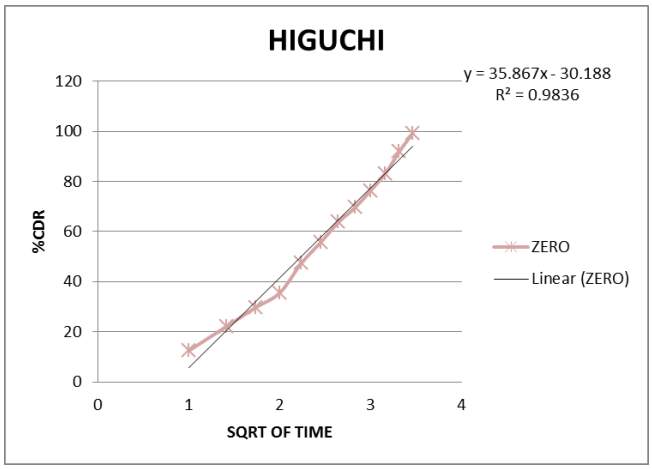



**Figure3-*IN-VITRO* drug release profile**

**Table-4:Kinetic model for drug release**

| Model | Kinetic Model Data of Experimental Work | | | |
|---|---|---|---|---|
| | Zero Order | First Order | Higuchi | Peppas |
| **R2** | 0.996 | 0.906 | 0.983 | 0.997 |
| **Slope(a)** | 7.82 | 0.072 | 35.86 | 0.839 |
| **Intercept** | 6.39 | 1.21 | 30.18 | 1.08 |



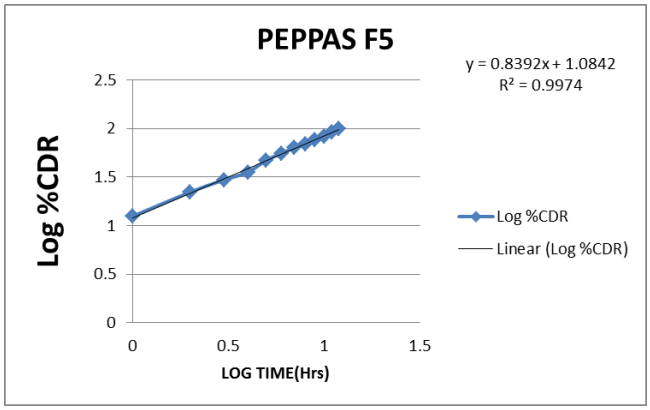




Table -5:Evaluation of stability study

| | In vitro drug release | % Drug content | Floating Time |
|---|---|---|---|
| **Initial(In 5hr)** | 47.33 | 100.07 | 12 |
| **After storage at 40+2°C and 75+5% RH** | 50.28 | 100 | 12 |

**Table-6:Comparison of in vitro drug release study after stability study**

| Time (hr) | % Cumulative Release (Initial) | % Cumulative Release (After storage at 40 ± 2 °C / 75 ± 5 %) |
|---|---|---|
| **1** | 12.49 | 13.45 |
| **2** | 22.14 | 25.66 |
| **3** | 29.61 | 32.55 |
| **4** | 35.54 | 38.15 |
| **5** | 47.33 | 49.29 |
| **6** | 55.65 | 56.88 |
| **7** | 63.74 | 67.04 |
| **8** | 69.54 | 73.21 |
| **9** | 76.35 | 78.95 |
| **10** | 83.19 | 86.37 |
| **11** | 91.99 | 93.79 |
| **12** | 99.24 | 99.98 |

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