(Research Article)

# FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF LABETALOL HYDROCHLORIDE

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## ABSTRACT

Labetalol hydrochloride is used in treatment of hypertension. It has a short half life and undergoes extensive first pass metabolism. In the present study, labetalol hydrochloride 300 mg controlled release matrices were prepared by wet granulation method and invitro drug dissolution studies were performed to find out the drug release rate and patterns. HPMC (K4 M, K15 M ), Eudragit S100, carbopol and their combination were used as rate controlling polymers. Tablets were formulated using different polymer ratios. as In-vitro drug release was carried out using USPType II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 2 hours, followed by 900 ml alkaline dissolution medium (pH 6.8) upto 12 hours. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. When HPMC K4 M and HPMC K15 M were used alone as the only retarding polymer, a sustained drug release pattern were not observed while, combination in the matrix almost doubled the time required for releasing the drug. Several kinetic models were applied to the dissolution profiles to determine the drug release kinetics.

**Keywords:** Labetalol Hydrochloride, Eudragit S100, HPMC (K4 M and 15M), Carbopol.

## INTRODUCTION

Controlled release oral dosage forms are in the focus of interest for several reasons. Customer compliance with the trend to simplicity and more comfort of use, the prolonged drug release with more reliable blood levels than those obtained with conventional dosage forms and life-cycle management of existing API's directed the pharmaceutical development towards sustained release formulations. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration. HPMC and Carbopol are used as matrix materials. The matrix may be tableted by wet granulation tech. Antihypertensive drugs are used for prevention of stroke. Stroke is associated with a wide variety of reasons and hence the presence of adequate amounts of plasma drug levels becomes very necessary for efficient treatment of hypertension. Antihypertensive drugs have short half-lives, extensively metabolized in the liver and are highly bound to plasma proteins. Hence if the release of drug is sustained for a longer period of time, will result in efficient management of hypertension. Labetalol hydrochloride is a selective α- and nonselective β-adrenergic blocking agent. It is used in management of hypertension, alone or in combination with other classes of antihypertensive agents. Labetalol hydrochloride is one of several preferred initial therapies in hypertensive patients with heart failure, post-MI, high coronary disease risk, or diabetes mellitus. It can be used as monotherapy for initial management of uncomplicated hypertension. Labetalol hydrochloride is also effective in controlling blood pressure in pregnant women with moderate to severe hypertension and severe pregnancy-induce hypertension. Labetalol hydrochloride has a dosage of 300 mg twice daily initially. For maintenance, manufacturer recommends a usual dosage of 200–400 mg twice daily. Manufacturer states that some adults with severe hypertension may require up to 1.2 g–2.4 g administered in 2 or 3 divided doses daily. Labetalol hydrochloride is rapidly and almost completely absorbed (i.e., 90– 100%) from the GI tract following oral administration. It undergoes extensive first-passmetabolism in the liver and/or GI mucosa. Absolute bioavailability is about 25%. Therefore to improve bioavailability and patient compliance in this study attempt has been made to develop a controlledrelease dosage form.

## MATERIALS AND METHODS

### Materials

Labetalol hydrochloride was obtained as gift sample from aurobindo pharma Pvt. Ltd.

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Hyderabad,india. HPMC ,Eudragit S100 and Carbopol obtained as gift sample from Loba Chemie Pvt.Ltd Mumbai, . Other materials used were of analytical grade and procured from commercial sources.

### Preparation of controlled release matrix tablets of labetalol hydrochloride

Controlled release tablets were prepared by Wet granulation tech . HPMC and Carbopol used as retardant material for preparation of tablets. Other excipients were magnesium stearate is a lubricant and Talc as a glidant.Specified quantity of all materials were weighed and then active ingredient and polymers were mixed by mortor pestle.A liquid binder solution of PVP K30 is added to the mixture to facilitate adhesion.A dump mass resembling dough is formed and used to prepare the granules by 10 number sieve.The granules were dried in hot air oven at 60º c for 1to2 hr.After drying granules are passed through sieve number 20 and sizing the granules.After sizing the granules were mixed with magnesium stearate and talc .After blending with the polymers the granules were subjected to the compression using 10 station tablet punching machine.. Tablet compression weight was adjusted to 300mg.In total, 9formulations containing different amounts of HPMC K4 M (F1,F2,F3),HPMC K15 M (F4,F5,F6) and combination of HPMC K15 M and Carbopol (F7,F8,F9) were prepared.The formula for various formulations attempted have been given in **table1.**

### Physical characterization of fabricated tablets

The quality control tests for the tablets, such as hardness, friability, weight variation etc.were determined using reported procedure. The tablet crushing strength was tested by commonly used Dial tablet hardness tester. Friability was determined by Roche® friabilator (Electro lab Pvt. Ltd., India), which was rotated for 4 min at 25 rpm. After dedusting, the total remaining mass of the tablets was recorded and the percent friability was calculated.Weight variation was determined by weighing 20 tablets individually, the average weight Physical characters observed for various batches is given in **table3**.

### Estimation of drug content

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount. Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to average weight of three tablets of Labetalol was transferred to a 100 ml volumetric flask containing 6.8 pH Phosphte buffer solution and the volume was made upto the mark. From this 10ml was taken and shaken by mechanical means using centrifuge at 3000rpm for 30min. Then it was filtered through whatman filter paper. From this resulted solution 1 ml was taken, diluted to 10 ml with 6.8 pH Phosphate buffer solution and absorbance was measured against blank at 302 nm.

### In vitro release studies

The in vitro dissolution studies were pe rformed using USPtype 2 dissolution apparatus (paddle) at 50 rpm

in 900 ml of and the phosphate buffer ph 6.8 upto 12 hrs and temperature was maintained at 37±0.5ºC .An aliquot (5ml) was withdrawn at specific time intervals and replaced with same volume of prewarmed fresh dissolution medium And drug content in each sample was analyzed by UV-Visible spectrophotometer at ±302 nm. Results are tabulated in table 2. Results of in-vitro dissolution studies are shown graphically in figure 1.

### Kinetics of *In-vitro* drug release

In-vitro release data obtained was treated to zero order rate equation, Higuchi's equationand Korsmeyer-Peppasequation to know precisely the mechanism of drug release from matrix tablet.Release data obtained is treated with following modles of data treatment. Zero order equation - Cumulative percentage drug release vs. Time in hours. First order equation – Log cumulative percentage drug remained vs. Time in hours.Higuchi's Diffusion equation – Cumulative percentage drug release vs. Square root time.Korsmeyer- Peppasequation - Log cumulative percentageof drug release vs. Log time. Results are tabulated in table 5

## RESULT AND DISCUSSION

In present work an attempt has been made to formulate and evaluated controlled release matrix tablets of labetalol hydrochloride using hydrophobic polymers namely hpmc,eudragit s100 and carbopol rate controlling polymers and effect on in vitro drug dissolution were studied by addition of these polymers at concentrations of 20%, 30% and 40%.

### Pre comprssional studies

The results obtained by evaluating the powder blends of drug and excipients are shown in table no??? Bulk density and tapped density were found in the range 0.52-0.56 g/cc and 0.62-0.69 g/cc respectively. The value of hausner's ratio was in between 1.16-1.25 (< 1.3) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 19.65-25.8 showing that blend of powder mass was Good flowing.Results are tabulated .in table 2

### Weight variation and Thickness

The average weight in all the 9formulations was found to be 498.7mg to 501.3 mg. In all 9 formulations no tablets were outside the ±10%of tablet weight in weight variation test. The thickness varies between 3.4 to 3.72mm. In all formulations tablet thickness of all formulations was within ±5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 4 to 5 kg/cm$^2$ for all the formulations. Assay was performed and percent drug content of all the tablets were found to be between 96.5 % and 100.38% of Labetalol hydrochloride which was within the acceptable limits,see in table number 3.

### In vitro dissolution

*In vitro* dissolution studies are performed for controlled tablets of Labetalol mixture of solvent 0. Linearly with increasing concentration of polymer. The optimized formulations are HPMC K4M combination containing tablets (F3).Formulation have recorded drug 97.65respectively in 12 hrs.1N HCl using USP

dissolution apparatus type 2. The dissolution rate was found to increase.

## Kinetics of drug release

In vitro release data of all the Sustained formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in table??? and plots shown in figures. From the above data, it can be seen that optimized formulation shows zero order release kinetics ('r' values in the range of 0.98). From Higuchi and Peppas data, it is evident that the drug is released by non-fickian diffusion mechanism (n<0.5). From the kinetic data of factorial formulations. It is evident that F3 formulation has shown drug release by zero order kinetics. This data reveals that drug release follows non-Fickian diffusion Supercase –II mechanism Peppas model.

**Table 1:** Composition of controlled release labetalol hydrochloride tablets

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Labetalol hydrochloride** | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| **Eudragit S 100** | 35 | 30 | 20 | 40 | 35 | 25 | - | - | - |
| **HPMC K4 M** | 35 | 40 | 50 | - | - | - | - | - | - |
| **HPMC K15 M** | - | - | - | 30 | 35 | 45 | 30 | 35 | 40 |
| **Carbopol** | - | - | - | - | - | - | 40 | 36 | 31 |
| **MCC** | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| **PVP K30** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Magnesium stearate** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **Sodium propyl paraben** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Talc** | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Table 2:** Pre compression parameters

| Code | Bulk density ( g/ml) | Tapped density ( g/ml) | Carr's index (%) | Hausner's ratio | Angle of Repose |
|---|---|---|---|---|---|
| **F1** | 0.55±0.08 | 0.65±0.17 | 13.1±1.25 | 1.14±0.25 | 23.4±2.9 |
| **F2** | 0.54±0.06 | 0.62±0.13 | 14.1±1.19 | 1.17±0.16 | 19.6±1.7 |
| **F3** | 0.56±0.09 | 0.64±0.15 | 15.1.231± | 1.21±0.18 | 22.3±2.4 |
| **F4** | 0.54±0.04 | 0.63±0.12 | 13.2±1.12 | 1.16±0.11 | 20.6±2.1 |
| **F5** | 0.50±0.02 | 0.67±0.17 | 15.1±1.24 | 1.23±0.22 | 20.8±1.7 |
| **F6** | 0.53±0.04 | 0.64±0.09 | 15.9±1.23 | 1.15±0.18 | 20.7±2.3 |
| **F7** | 0.51±0.03 | 0.67±0.13 | 14.2±1.24 | 1.25±0.19 | 20.8±1.8 |
| **F8** | 0.52±0.06 | 0.69±0.16 | 14.1±1.3 | 1.18±0.23 | 20.7±1.9 |
| **F9** | 0.56±0.08 | 0.68±0.11 | 13.2±1.12 | 1.17±0.17 | 22.6±2.5 |

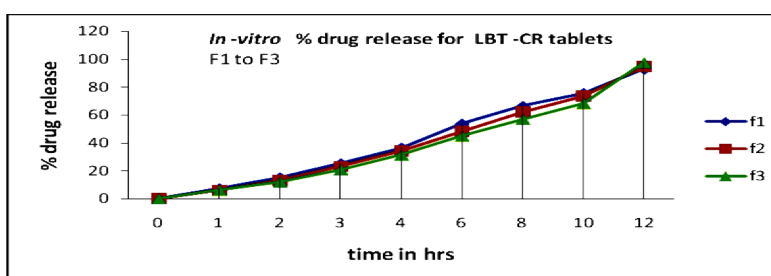**Table 3:** Evaluation of physical characters of labetalol hydrochloride tablets

| Code | weight variation(mg) | Thickness (mm) | Hardness (Kg/cm²) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| **F1** | 299.29 ±7.63 | 3.00±0.03 | 4.03±0.09 | 0.26±0.01 | 99.0±2.4 |
| **F2** | 298.29 ±7.53 | 3.01±0.04 | 4.02±0.10 | 0.56±0.02 | 98.3±1.7 |
| **F3** | 298.29 ±7.83 | 3.42±0.02 | 5.05±0.10 | 0.66±0.04 | 98.9±2.8 |
| **F4** | 299.29 ±7.53 | 3.81±0.03 | 4.61±0.08 | 0.67±0.01 | 99.4±2.3 |
| **F5** | 298.28 ±7.63 | 2.91±0.02 | 4.03±0.10 | 0.65±0.02 | 98.7±1.7 |
| **F6** | 297.29 ±7.63 | 3.41±0.05 | 5.04±0.04 | 0.78±0.05 | 97.6±2.4 |
| **F7** | 299.28 ±7.63 | 3.52±0.03 | 5.06±0.05 | 0.47±0.03 | 99.5±2.4 |
| **F8** | 299.28 ±7.73 | 3.60±0.04 | 4.51±0.08 | 0.28±0.01 | 97.3±1.7 |
| **F9** | 299.27 ±7.83 | 3.61±0.02 | 5.02±0.10 | 0.35±0.02 | 98.9±2.8 |

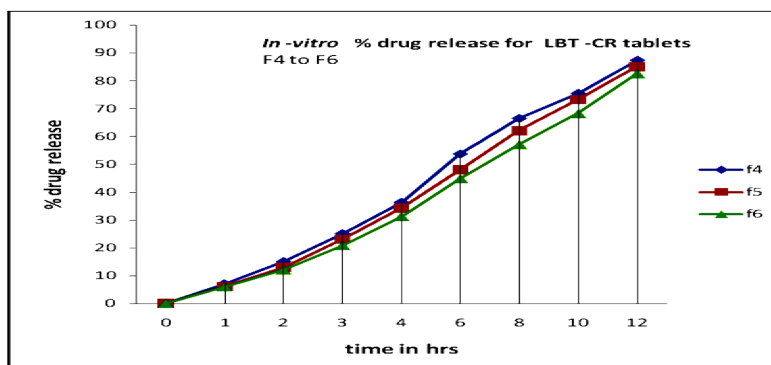**Table 4:** *In-vitro* drug release studies of labetalol hydrochloride tablets

| Sampling time(hr) | F1 | F2 | F3* | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 8.22±1.24 | 8.01±0.44 | 6.81±0.45 | 7.1±1.05 | 6.10±1.35 | 6.01±2.12 | 5.11±1.04 | 4.10±1.30 | 4.01±2.16 |
| 2 | 16.13±0.42 | 16.01±0.30 | 13.98±0.50 | 15.08±1.30 | 13.02±1.54 | 12.02±2.17 | 10.08±1.30 | 7.02±1.50 | 6.02±2.16 |
| 3 | 25.80±0.65 | 24.51±0.50 | 23.81±0.53 | 25.09±1.75 | 23.14±1.09 | 20.82±2.09 | 14.09±1.72 | 9.14±1.60 | 8.82±2.10 |
| 4 | 37.13±0.52 | 36.45±0.65 | 35.72±0.47 | 36.34±1.14 | 34.28±2.10 | 31.28±1.95 | 18.34±1.14 | 15.28±2.10 | 13.28±1.95 |
| 6 | 55.43±0.43 | 52.01±0.56 | 50.81±0.80 | 53.69±1.25 | 48.04±1.01 | 44.85±1.07 | 28.69±1.22 | 22.04±1.01 | 18.85±1.90 |
| 8 | 71.90±1.01 | 68.01±0.47 | 65.76±0.94 | 66.44±1.33 | 62.16±0.81 | 57.09±1.01 | 36.44±1.30 | 28.16±0.81 | 26.09±1.21 |
| 10 | 87.13±0.54 | 85.51±0.81 | 78.88±0.91 | 75.50±1.58 | 73.28±1.09 | 68.23±1.04 | 52.50±1.51 | 37.28±1.09 | 35.23±1.01 |
| 12 | 92.99±1.02 | 94.71±0.30 | 97.65±0.66 | 87.33±1.69 | 85.11±0.91 | 82.55±1.08 | 67.33±1.60 | 58.11±0.91 | 54.55±1.01 |

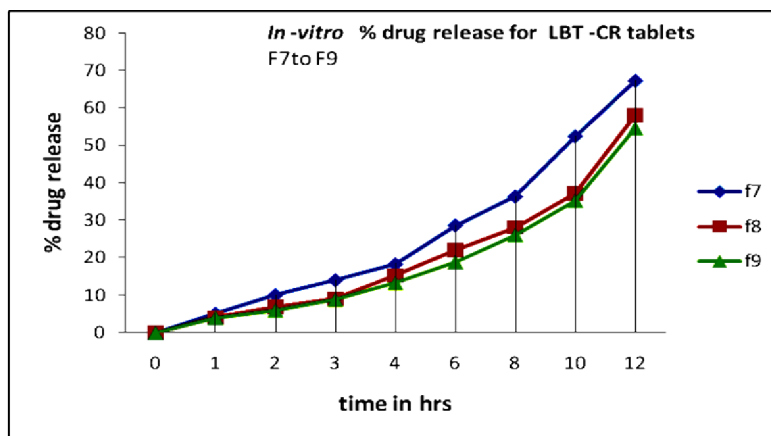**Table 5:** Different kinetic models for labetalol hydrochloride tablets

| Formulation code | Zero order | First order | Higuchi | Peppas | |
|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | N |
| F3 | 0.98 | 0.73 | 0.86 | 0.98 | 1.02 |



*In -vitro* **% drug release for LBT -CR tablets** F4 to F6



*In -vitro* **% drug release for LBT -CR tablets** F7 to F9

## CONCLUSION

In this study matrix tablet of labetalol hcl were prepared by wet granulation technique, using HPMC K-4M, and HPMC k-15 and cardopol polymers as retardant. The drug-polymer ratio was found to influence the release of drug from the formulations. It was found that increase in the concentration of HPMC K-4M in polymeric ratio decreases the drug release. HPMC K-4M is non carcinogenic, biocompatible and has high drug holding capacity at the same time it is effective in retarding the drug release. The formulations F-3, showed good drug release with good matrix integrity. Different parameters like hardness, friability, weight variation, drug content uniformity, in-vitro drug release were evaluated. Based on these results formulation F-3was found to be the most promising formulations. The results suggest that the developed controlled-release matrix tablets of labetalol hcl could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance. Thus the aim of this study was achieved. Further preclinical and clinical studies are required to evaluate the efficacy of these formulations of labetalol hcl in the management of Hypertension.

## REFERENCES

1. Anderson NR et al., 1982. Quantitative evaluation of pharmaceutical effervescent systems II: stability monitoring by reactivity and porosity measurements.J Pharm. Sci. 71(1): 7–13.
2. Phadke DS, Eichorst JL., 1991. Evaluation of particle size distribution and specific surface area of magnesium stearate.DrugDevInd Pharm. 17: 901–906.
3. Brahmankar D M, Jaiswal SB. "Biopharmaceutics and pharmacokinetics a treatise 1st ed.vallabh prakashan. New delhi.1995:64-70.
4. Amelia avachat, Vikram kotwal. Design and evaluation of matrix based controlled release tablets of Diclofenac Sodium and chondrotin Sulphate. AAPS PharmSciTech. 2007; 8(4): E1-E6
5. Rao K P et al., 2005. Impact of solid-state properties on lubrication efficacy of magnesiumstearate. Pharm.Dev Technol. 10(3): 423–437.
6. Phadke DS, Collier JL., 1994. Effect of degassing temperature on the specific surface area and other physical properties of magnesium stearate.Drug DevInd Pharm. 20(5): 853–858.
7. S.M. Herbig., J.R Cardinal., R.W. Korsmeyer and K.L. Smith., J. Controlled Release. 35. 127-136., 1995.
8. Y. Qiu., H. Cheskin., J. Briskin and K. Engh., J. Controlled Release. 45. 249-256., 1997.
9. Welling P.G and Dobrinska M.R., Controlled drug delivery: fundamentals and applications. 2nd ed., Marcel Decker Inc., 29, 254-289., 1978.
10. Longer M.A and Robinson J.R., Remington's pharmaceutical sciences, 18th edition, Mack Publishing Company., 1675-1684., 1980.
11. N.C. Healey., J.G. Haedy., S.S. Davis and C.G. Wilson., eds., Drug Delivery to the GastroIntestinal Tract, Ellis Horwood, Chichester, England, 83-96., 1989.
12. Raymond C Rowe, Paul S Sherkey and Marian E Quinn., Handbook of Pharmaceutical Excipients., 6th ed., 326-329., 2009.
13. Raymond C Rowe, Paul S Sherkey and Marian E Quinn., Handbook of Pharmaceutical Excipients., 6th ed., 629-632., 2009.
14. www.drug store.com.