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# Preparation, Optimization and Characterization of Labetalol Nanoparticles Via Precipitation Method

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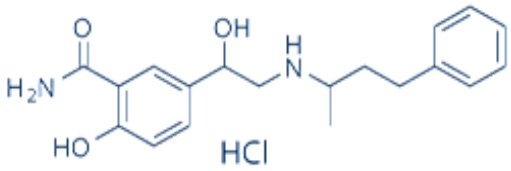
**ABSTRACT**
The aim of this study was to develop controlled-release nanoparticles of Labetalol Hydrochloride to improve its bioavailability. Nanoparticles were fabricated using polymers including Gelatin, HPMC, and Eudragit S100 via a precipitation technique. FT-IR analysis confirmed no chemical interactions between drug and polymers. The nanoparticles exhibited spherical morphology with smooth surfaces, uniform size distribution ranging from approximately 122 to 642 nm, and high encapsulation efficiency that increased with polymer concentration. Zeta potential measurements indicated good colloidal stability, with the best formulations showing values around 20 mV. The drug release was sustained and prolonged, following Super case-II transport mechanisms, with an optimized formulation releasing about 86% of the drug over 12 hours. These results demonstrate the potential of such polymeric nanoparticles for enhancing therapeutic efficacy of Labetalol HCl, warranting further in vivo evaluation in suitable models. This approach yields controlled drug delivery suitable for lipophilic drugs with limited water solubility, possibly improving antihypertensive therapy through reduced dosing frequency and enhanced bioavailability.
**Keywords:** polymeric carriers, precipitation technique, sustained release, bioavailability

## INTRODUCTION

Name: Labetalol HCl
Chemical Name:3-Carboxamido-4-hydroxy-alpha-((1-methyl-3-phenylpropylamino) methyl) benzyl alcohol5-(1-Hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl)salicylamide
Formula: C19H25ClN2O3
Synonyms: Normodyne, Trandate
Molecular Weight: 364.9g/mol
**Structure:**




**Category:** Antihypertensive
**Description:**
Labetalol is a racemic combination of two diastereoisomers, with dilevalol, the R,R' stereoisomer, accounting for 25% of the total. To treat hypertension, labetalol is available as an injectable or as tablets. On August 1, 1984, the FDA approved labetalol.
**Storage:** Do not freeze**,** Protect from light**,** Store at controlled room temperature (between 68 and 77o F)
**Administration:**
**Oral Administration**
Because the full antihypertensive effect of labetalol is typically observed within the first 1 to 3 hours of the underlying portion or portion increase, the absence of an exaggerated hypotensive response can be clinically established in the workplace setting. The antihypertensive effects of continued dose can be assessed at subsequent visits, typically 12 hours following a portion, to determine whether further titration is required.
**Administration of Injectable**
Examine parenteral products for particle problem and discoloration before organisation at whatever point arrangement and compartment licence are required.
**Administration intravenously**
Patients must be maintained supine throughout IV treatment since standing causes a drop in blood pressure. Before allowing ambulation, determine the patient's ability to endure an upright position.
**Mechanism of action** :
Selectively blocks alpha-1 receptors and non selectively blocks beta-receptors to decrease BP, heart rate and myocardial oxygen demand.
**Pharmacokinetics:**
Labetalol is administered orally and iv. The half-life is 2.5-8hours. Labetalol is widely distributed throughout the body, crosses the placenta, and is found in breast milk. Limited amounts cross the blood-brain barrier. It metabolized in the liver by glucuronidation and is excreted in the feces via biliary elimination (30%) and in the urine (55-60% as metabolites and 5% as unchanged drug).

# MATERIALS AND METHODS

## DRUG IDENTIFICATION TESTS

**Description of drug**

Description of drug is observed by the naked eye.

**Determination of melting point**[37]

Digital melting point apparatus was used to estimate the melting point of the Labetalol HCl.

**Determination of λmax**[36]

The first part of Pre-plan is to construct a fundamental explanatory approach with the purpose of making every future prediction measurable. Because most drugs are sweet-smelling and have two fold bonds, they absorb light in the brilliant frequency (190-390 nm) range. 100 mg of Labetalol was precisely weighed on an electronic balance and dissolved in 100 ml of 6.8 pH phosphate buffer, yielding a concentration of 1000 g/ml. Water dissolves labetalol. In a separate volumetric flask, 1 ml of this solution was diluted with 100 ml of 6.8 pH phosphate buffer, yielding -10 g/ml conc., and scanned on a UV-visible spectrophotometer (Shimandzu 1700) between 190 and 390 nm. The drug's maximum was determined to be 303 nm.

**Calibration curve of Labetalol HCl**[36]

Labetalol (100 mg) was dissolved in a tiny amount of 6.8 pH Phosphate buffer and a volume of 100 ml was created using the same, which is known as the stock-I solution. In another volumetric flask, 10 ml of the aforementioned solution is diluted to 100 ml to form the Stock-II solution. Pipetting out 1 ml, 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml of this stock-II solution yielded solutions of the medication with concentrations ranging from 10, 20, 40, 60, 80, and 100 g/ml, respectively. The absorbance of the solutions was measured using a UV-visible spectrophotometer at 303 nm.

**Solubility**[37]

The drug's solubility was determined using a conventional technique in distilled water and a pH 7.4 phosphate buffer. To obtain a saturated solution, an excess amount of the medication was obtained and separately dissolved in an amount of the aforesaid solvents in a glass beaker. This solution was shook intermittently to help the undissolved drug particles reach equilibrium. After 24 hours, the filtered drug solution was removed and gradually diluted with the appropriate solvents, and the concentration was determined spectrophotometrically. The averages of three readings were obtained.

**Partition coefficient**[37]

In n-octanol, a pharmaceutical solution (1mg/ml) was prepared. In an isolating pipe, 25ml of this arrangement was agitated for 10 minutes with an equal amount of pH 7.4 phosphate support (watery stage) and allowed to represent for 2 hours. At that time, the fluid and natural stages were separated and centrifuged separately at 2000 rpm. A UV spectrophotometer was used to separate the two stages of drug fixation. The parcel coefficient was regulated by adjusting the fraction of medicine fixation in n-octanol used to calm the attention in the fluid stage. Readings were taken in triplicate.

**Permeability coefficient**[37]

The equation called "Potts and Guy equation" was used to calculate the permeability coefficient.

**Log Kp = - 2.7 + 0.71 x log Ko/w - 0.0061 x Molecular weight**

Where, Log Kp=Permeability coefficient and Ko/w = Partition coefficient

**Loss on drying:** Dry it in a vacuum at 105$^{o}$C for 4 Hrs: It loses not more than 1.0% of its weight.

**Identification of Drug by FTIR**[37]

**Procedure:** The medication (3 milligrammes) was weighed and combined with 100mg of potassium bromide (dried at 40-50oC). The mixture was collected and compacted in a hydraulic press at 10-ton pressure to form a translucent pellet. The IR spectrophotometer was used to scan the pellet. A similar technique is utilised for all relevant excipients.

**Preparation of Nanoparticles:**[38-42]

- With minor modifications, nanoparticles were produced using the nanoprecipitation technique.
- In brief, 200 mg of medication and 200, 400 mg of polymer (HPMC, Eudragit S100, and gelatin) were dissolved individually in 25 ml of Methanol, forming an organic phase.
- An aqueous phase consisting of 40ml of water and 1% polyvinyl alcohol.
- The organic phase was slowly introduced into the aqueous phase while being continuously stirred.
- Nanoparticles were formed instantly by precipitation of the polymer in a restricted composition window, followed by evaporation of the organic solvent under continuous stirring for 3- 4 hours.

**SEM Analysis:**

SEM was used to determine the form, surface topography, and texture, as well as to analyse the morphology of a fractured or sectioned surface. Because of the ease of sample preparation and operation, scanning electron microscopy (SEM) is a popular approach for characterising drug delivery systems. For 5-6 minutes, the sample is distributed on a tiny square plate and coated with a gold ion. The prepared sample was held within the chamber, and photos were taken at various magnifications. (10,000, 15,000 and 20,000).

**In vitro dissolution studies**[48]

A dialysis membrane with a pore size of 2.4 mm (LA-395-5Mt Himedia Pvt. Ltd, Mumbai, India) and 75 ml of pH 7.4 phosphate buffer were used to evaluate the dissolution profiles of Labetalol Nanoparticle at 37°C. 75ml of pH 7.4 phosphate buffer was placed in a 100 ml beaker. Two millilitres of formulation were placed in a dialysis bag and dipped into the buffer solution. Earlier, the dialysis membrane was activated by soaking it in 1% w/v NaOH overnight. A magnetic stirrer was used to keep the flask stirred. Stirring was kept at 250 rpm, and the buffer temperature was kept at 37°C. Sampling was accomplished by taking 1 ml aliquots from a beaker. To maintain the sink state, 1 mL of fresh buffer was introduced right away. After properly diluting with methanol, samples were analysed using a UV/Spectrophotometer (UV/VIS-Double beam Spectrophotometer, V-530, Jasco, Tokyo, Japan) at 303 nm. Each test was repeated three times, with the average value used in the computation.

**Release kinetics of the optimized formulations**

**Drug Release Kinetics**

The data from the in vitro release research was applied to various motor circumstances. Zero request (aggregate level of medication discharge versus time), first request (log total level of medication remaining versus time), Higuchi model (total

level of medication discharge versus square base of time), and Korsmeyer-Peppas (log combined percent sedate delivery versus log of time) were the active models used. Relapse (r2) values were calculated for the direct bends obtained from relapse research.

**Kinetic analysis:** The grid frameworks were accounted for in order to follow the zero-request discharge rate and the Diffusion component for pharmaceutical arrival. The information obtained was fitted into the Zero request, First request, Higuchi lattice, and Peppa's model to break down the system for the delivery and delivery rate energy of the measurements structure. The best fit model was picked in this case based on the r Values obtained.

**Kinetics of zero order:** The following equation can be used to depict drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the medication slowly, provided that the area does not change and no equilibrium conditions are established.

$$Qt = Q0+K0t$$

Where Qt represents the quantity of drug dissolved in time t, Q0 represents the starting amount of drug in the solution, and Ko represents the zero order release constant. To investigate first order release kinetics, the release rate data were fitted to the following equation.

$$Qt = \log Q0 + k1t/2.303.$$

Where Qt represents the quantity of drug released in time t, Qo represents the initial amount of drug in the solution, and K1 represents the first order release constant.

**Higuchi model:** Higuchi created many theoretical models to investigate the release of water-soluble and low-soluble medicines integrated in semisolids and/or solid matrices. For drug particles distributed in a uniform matrix acting as a diffusion medium, mathematical formulas were developed. And the formula is Qt = KH.t1/2.

Where Qt represents the quantity of medication released in time t and KH represents the Higuchi Dissolution constant.

The Korsmeyer and Peppa model: To investigate this concept, the following equation is fitted to the release rate data.

$$Mt/M = Ktn$$

Where Mt/M is the drug release percentage, K is the release constant, t is the release period, and n is the drug release diffusion exponent that depends on the geometry of the matrix dosage form.

## RESULTS AND DISCUSSION

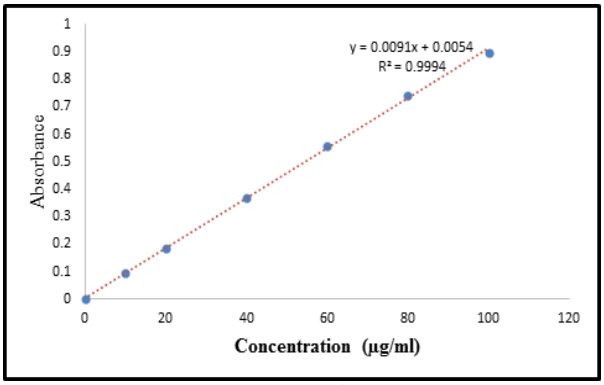



**Fig.1:** Standard graph of Labetalol HCl

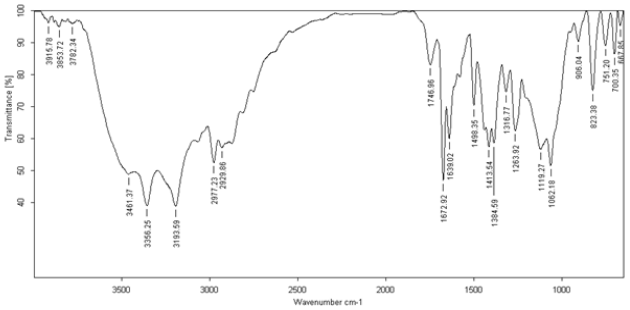



**Fig.2:** FTIR Spectra of Labetalol HCl

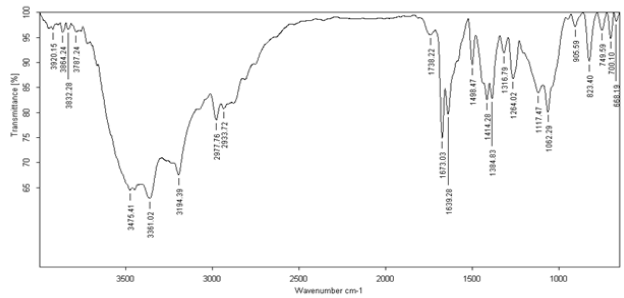



**Fig.3:** FTIR Spectra of Labetalol HCl + Eudragit S 100

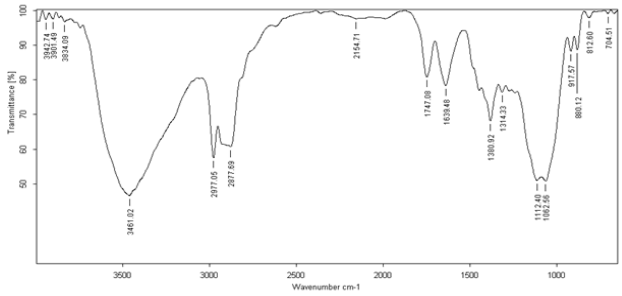



**Fig.4:** % FTIR Spectra of Labetalol HCl + HPMC K4M

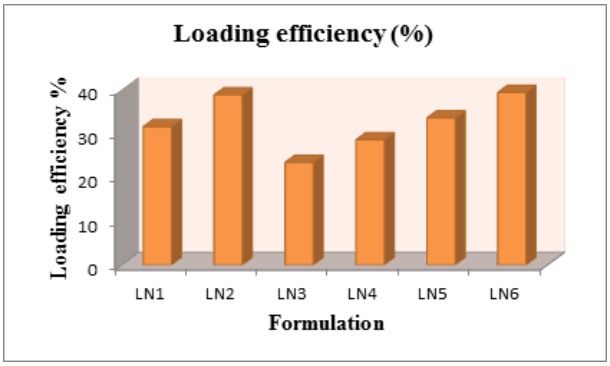



**Fig.5:** Loading efficiency (%) of Labetalol Nanoparticles

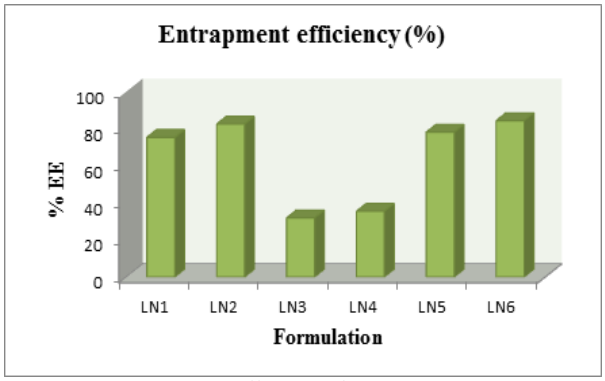



**Fig.6:** % Entrapment efficiency of Labetalol Nanoparticles

**Table 1:** Drug loading and Entrapment efficiency

| Formulation code | Polymer | Drug : Polymer ratio | Loading efficiency (%) ± SD | Entrapment efficiency (%) ± SD |
|---|---|---|---|---|
| LN1 | HPMC K 4M | 1:1 | 31.47 ± 04 | 75.5 ± 0.8 |
| LN2 | | 1:2 | 38.72 ± 01 | 82.7 ± 1.0 |
| LN3 | Eudragit S100 | 1:1 | 23.34 ± 0.2 | 32.0 ± 0.4 |
| LN4 | | 1:2 | 28.48 ± 0.4 | 35.6 ± 0.3 |
| LN5 | Gelatin | 1:1 | 33.47 ± 03 | 78.3 ± 0.4 |
| LN6 | | 1:2 | 39.31 ± 02 | 84.5 ± 0.6 |

* = Average of three determinations

**Table 2:** Drug polymer ratio, mean particle size, particle size distribution, poly dispersity index (PDI) and zeta potential.

| Formulation code | Polymer | Drug : Polymer ratio | Mean Particle Size (nm) ± SD | PDI ± SD | Zeta Potential (mV) ± SD |
|---|---|---|---|---|---|
| LN1 | HPMCK 4M | 1:1 | 122.01 ± 4 | 0.12±0.13 | 24.4±1.3 |
| LN2 | | 1:2 | 142.05 ± 2 | 0.13±0.15 | 20.1±1.4 |
| LN3 | Eudragit S100 | 1:1 | 210.30 ± 4 | 0.16±0.11 | 16.4±1.5 |
| LN4 | | 1:2 | 298.12 ± 7 | 0.18±0.14 | 11.3±1.7 |
| LN5 | Gelatin | 1:1 | 502.30 ± 5 | 0.50±0.11 | 14.1±1.5 |
| LN6 | | 1:2 | 642.30 ± 3 | 0.70±0.13 | 12.3±1.2 |

**Table 3:** *In vitro* Drug release kinetics of LN1

| Formulation code | Zero order | | First order | | Higuchi model | | Korsmeyer-peppas | | Release Mechanism transport |
|---|---|---|---|---|---|---|---|---|---|
| | Slope | $R^2$ | Slope | $R^2$ | Slope | $R^2$ | n | $R^2$ | |
| LN1 | 5.18 | 0.840 | -0.060 | 0.974 | 23.41 | 0.978 | 0.992 | 0.520 | Super Case II transport |

## DISCUSSION

The objective of this study was to develop controlled-release nanoparticles of Labetalol Hydrochloride to enhance drug bioavailability. Nanoparticles of Labetalol were prepared using Gelatin, HPMC, Eudragit S100 through precipitation techniques. The IR spectrum analysis confirmed that there were no interactions between the polymers and the drug. The resulting nanoparticles exhibited small, spherical shapes with smooth surfaces, high yield, and uniform encapsulation efficiency. The size of Labetalol nanoparticles ranged from 122.01±4nm to 642.30±3nm. Zeta Potential analysis demonstrated the colloidal dispersion stability of the nanoparticles, with the best formulations showing an excellent stability of 20.1±1.4mV. Encapsulation efficiency for Labetalol nanoparticles varied from 32.0 ± 0.4% to 84.5 ± 0.6%, with an increase in polymer concentration leading to higher encapsulation efficiency. The release of Labetalol from the nanoparticles was slow and prolonged, attributed to the increased polymer concentration. The release mechanism for all formulations followed the Super case – II transport model. Formulation LN1 exhibited a drug release of 86.01% over a 12-hour period, following the Super case – II transport model. Overall, the nanoparticles prepared through the precipitation method showed promising results for drug delivery, suggesting the need for further in vivo evaluation using appropriate animal models.

## CONCLUSION

The Nano precipitation process was used to create labetalol-loaded polymeric nanoparticles. FT-IR tests demonstrated the compatibility of drug-polymer excipients. The approach produced smaller size nanoparticles with a narrow size distribution and high entrapment efficiency on a regular basis. In vitro release tests revealed that the designed polymeric nanoparticles might increase Labetalol bioavailability. The formed polymeric nanoparticles demonstrated slower drug release with lower burst release than pure drug. These findings might pave the way for the formulation to be used as an adjuvant anti-hypertensive medication for a longer period of time. As a result, polymeric nanoparticles may enable excellent drug delivery for lipophilic medicines that are weakly water soluble.

## ACKNOWLEDGMENT

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## CONFLICT OF INTERESTS

The authors declare no conflict of interest

## ETHICS APPROVAL

Not applicable

## FUNDING

This study received no specific funding from public, commercial, or not for profit funding agencies.

## AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

## DATA AVAILABILITY

Data will be available on request

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