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Formulation and Evaluation of Sustained Release Floating Microspheres of Labetalol HCl

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Abstract

This research paper details the development and characterization of sustained-release floating microspheres containing Labetalol HCl, a drug used to treat hypertension. The aim of this formulation is to enhance the drug's oral bioavailability and prolong its therapeutic effect by increasing its gastric residence time. The microspheres were prepared using the emulsion solvent diffusion method with varying compositions of Ethyl Cellulose and Eudragit RS100. The formulated microspheres were evaluated for various parameters, including percentage yield, particle size, drug entrapment efficiency, and
in vitro buoyancy. The drug release kinetics were also studied to understand the release mechanism. The results show that the optimized formulation (F3) has a high yield, excellent buoyancy, and a sustained drug release profile over 12 hours, making it a promising platform for controlled drug delivery.

Keywords

Labetalol HCl, Floating Microspheres, Ethyl Cellulose and Eudragit RS100

1. Introduction

Sustained-release drug delivery systems are designed to deliver a specific drug at a constant rate over an extended period, which is particularly beneficial for drugs that are rapidly metabolized and eliminated from the body. This approach helps maintain a steady drug concentration within the therapeutic window, thereby reducing the frequency of dosing, improving patient compliance, and minimizing fluctuations in plasma drug levels (1-8).

Microspheres are a type of sustained-release system consisting of small spherical particles ranging from 1 µm to 1000 µm. They can be manufactured from various natural and synthetic polymers and are widely distributed throughout the gastrointestinal tract (GIT), which can improve drug absorption and reduce side effects. Floating microspheres are a specific type of microsphere with a bulk density lower than gastric fluid, allowing them to remain buoyant in the stomach for an extended period, which prolongs gastric residence and ensures a prolonged therapeutic effect. Labetalol HCl is a drug used to treat hypertension, and a sustained-release formulation is desirable to manage this chronic condition (9-12).

Benefits of Sustained-Release Medications

Sustained-release medications offer several benefits over immediate-release formulations. These include the ability to maintain a constant rate of drng delivery, resulting in a more consistent drug concentration in the body (8-12).

This also allows for reduced frequency of dosing and avoids peak and trough concentrations, which can be associated with adverse effects or decreased efficacy.

Sustained-release medications provide a valuable option for treating chronic conditions and improving patient outcomes.

Polymers used in sustained release tablet

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

a) Hydrophilic Polymers: Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and copolymers of acrylic acid.[3]•[4]

b) Hydrophobic Polymers: This usually includes waxes and water insoluble polymers in their formulation (5,12-19).

c) Natural polymers: Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan.[5]

d) Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.[6]

e) Non-biodegradable polymers: Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

Advantages of sustain release dosage forms (20-26)

1. Reduce the toxicity by slowing drug absorption.
2. It maintains a therapeutic concentration over a prolonged period.
3. Reduction in frequency of intakes.
4. Reduce side effects.
5. Uniform release of drug over time.
6. Better patient compliance
7. The total amount of drug administered can be reduced, thus:

i) Maximizing availability with minimum dose

ii) Minimize or eliminate local side effects

iii) Minimize or eliminate systemic side effects

iv) Minimize drug accumulation with chronic dosing

Disadvantages of conventional dosage forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under medication or over Medication.

3. A typical peak-valley plasma concentration time profile is obtain which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effect especially of a drug with small Therapeutic Index whenever over medication occur.

Microsphere

Microspheres are small spherical particles, with diameters in the micrometer range (typically I µm to I000 µm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available.[8] Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material (24-30).

2. Materials and Methods

The study utilized Labetalol HCl as the active pharmaceutical ingredient. Other materials included polymers such as Ethyl Cellulose and Eudragit RS100. The preparation of the sustained-release floating microspheres was performed using the emulsion solvent diffusion method.

2.1. Preformulation Studies

Preformulation studies were conducted to characterize Labetalol HCl. Organoleptic characteristics revealed it is a white to off-white crystalline powder with a bitter taste. The solubility was assessed in various solvents, finding it freely soluble in ethanol and 0.1 N HCl. A calibration curve for Labetalol HCl was created, showing a strong linear relationship (R^2 = 0.998). FTIR analysis was also performed to confirm the drug's chemical structure and compatibility with the polymers, showing no significant interaction.

2.2. Preparation of Microspheres

Floating microspheres of Labetalol HCl were prepared with varying compositions and ratios of Ethyl Cellulose and Eudragit RS100. Six different formulations (F1-F6) were developed.

Table 1 Formulations of sustain release floating microspheres of Labetalol HCl

S. No.	Formulation Code	Labetalol HCl (mg)	HPMC (mg)	EC (mg)	Guar gum (mg)
1.	F1	50	150	25	-
2.	F2	50	150	50	-
3.	F3	50	150	75	-
4.	F4	50	150	-	25
5.	F5	50	150	-	50
6.	F6	50	150	-	75

2.3. Evaluation of Microspheres

The prepared microspheres were evaluated for several parameters:

- **Percentage Yield:** Calculated by weighing the recovered microspheres and comparing the mass to the total weight of non-volatile components.
- **Drug Entrapment Efficiency:** Determined by crushing the microspheres, dissolving the powder in 0.1 N HCl, and measuring the absorbance using a UV-Visible spectrophotometer against a calibration curve.
- **Floating Behavior:** Assessed by dispersing the microspheres in 0.1 N HCl and measuring the floating lag time and percentage buoyancy over a period of 10 hours.
- **Particle Size Analysis:** The mean particle size was measured using Photo Correlation Spectroscopy (PCS).
- **In Vitro Drug Release Study:** The drug release profile was studied using the dissolution apparatus with 0.1N HCL buffer as the medium.

3. Results and Discussion

The study found that the percentage yield for all formulations ranged from 48.33% to 86.25%. The particle size was found to be between 55.4 µm and 219.33 µm. The drug entrapment efficiency ranged from 80.5% to 97.2%.

Among all the formulations, F3 was identified as the optimized formulation because it exhibited the best characteristics. It had the highest percentage yield of 83.32% and the highest drug entrapment efficiency of 78.98%. Furthermore, F3 showed excellent floating behavior with a percentage buoyancy of 86.65% and a short floating lag time of 65 seconds.

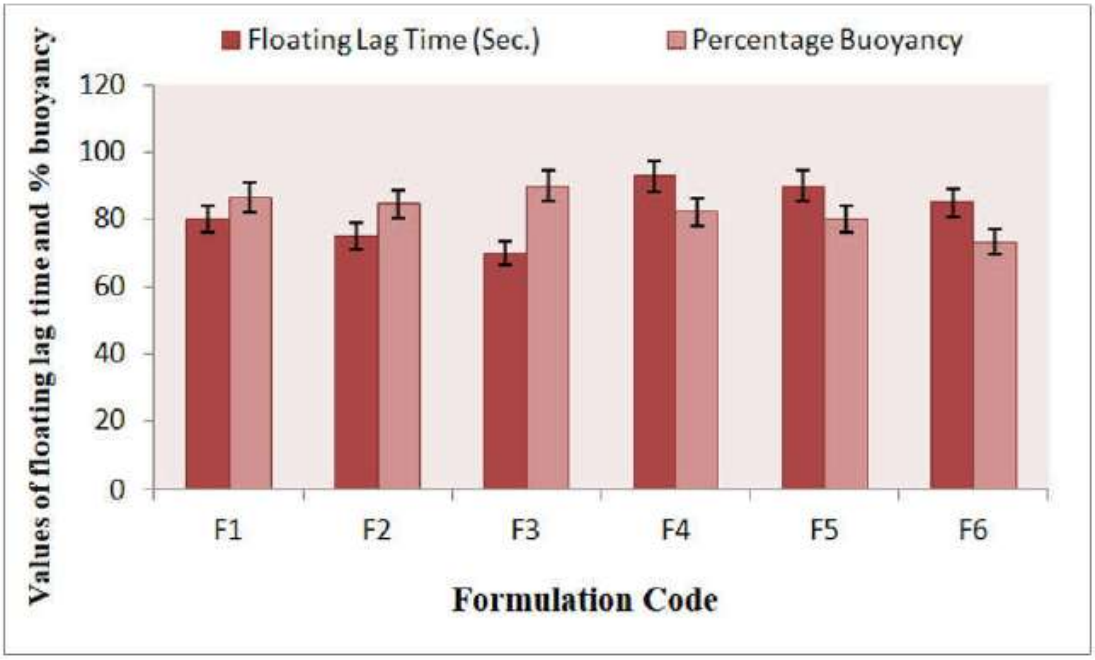

Figure 2. Floating lag time and percentage buoyancy for different formulation

The in vitro drug release studies demonstrated a sustained release profile for all formulations over 12 hours. The optimized formulation F3 released 99.12% of the drug over 12 hours, which was comparable to a marketed formulation. The release kinetics of F3 were analyzed using various models. The data best fit the Higuchi model (R^2 = 0.9932) and the Korsmeyer-Peppas model (R^2 = 0.9893), indicating a diffusion-controlled mechanism.

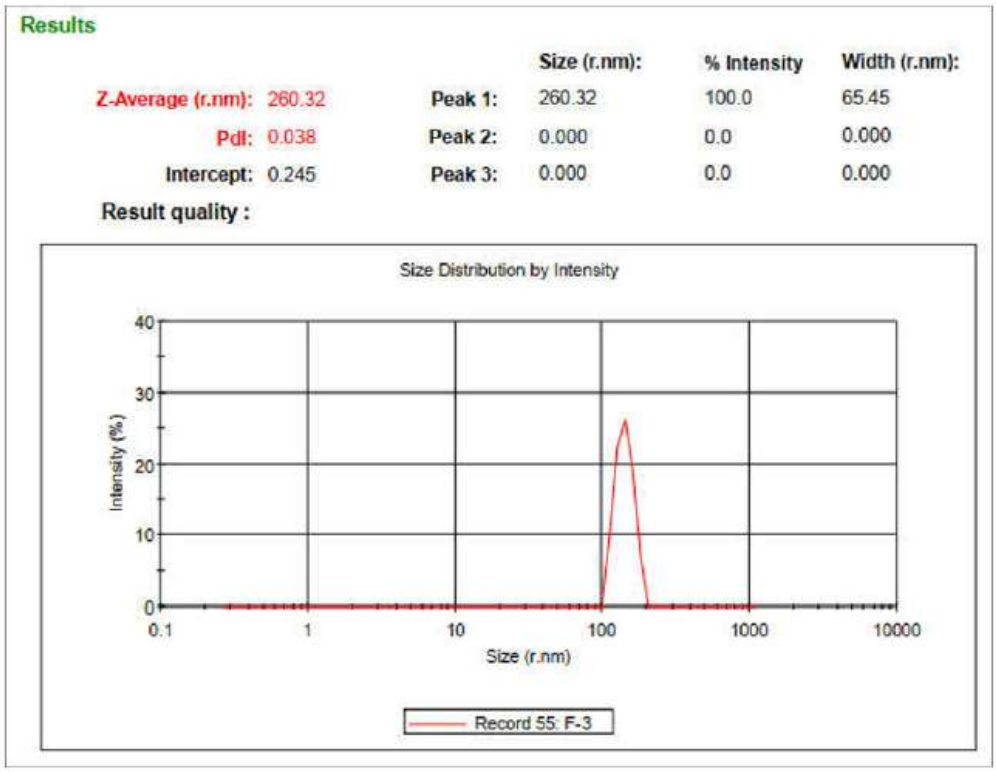

Figure 3. Particle size data of optimized microsphere formulation F3

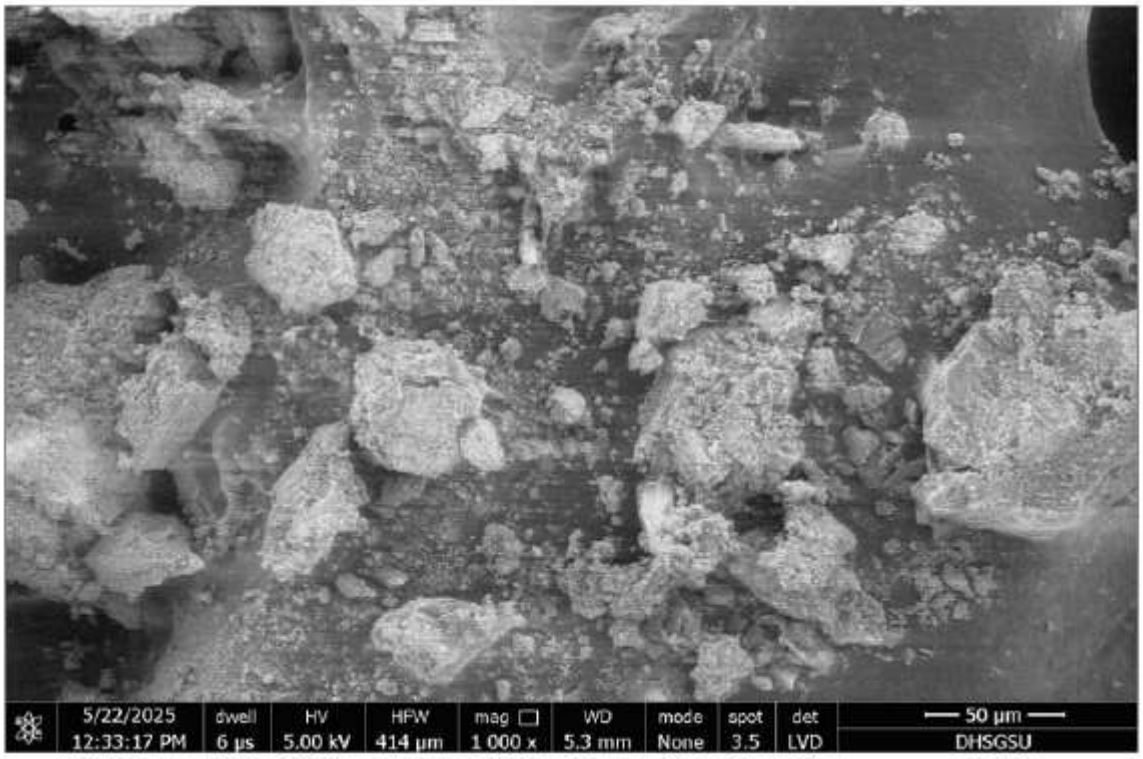

Figure 4: Graph of scanning electron microscopy (SEM) of optimized formulation F3

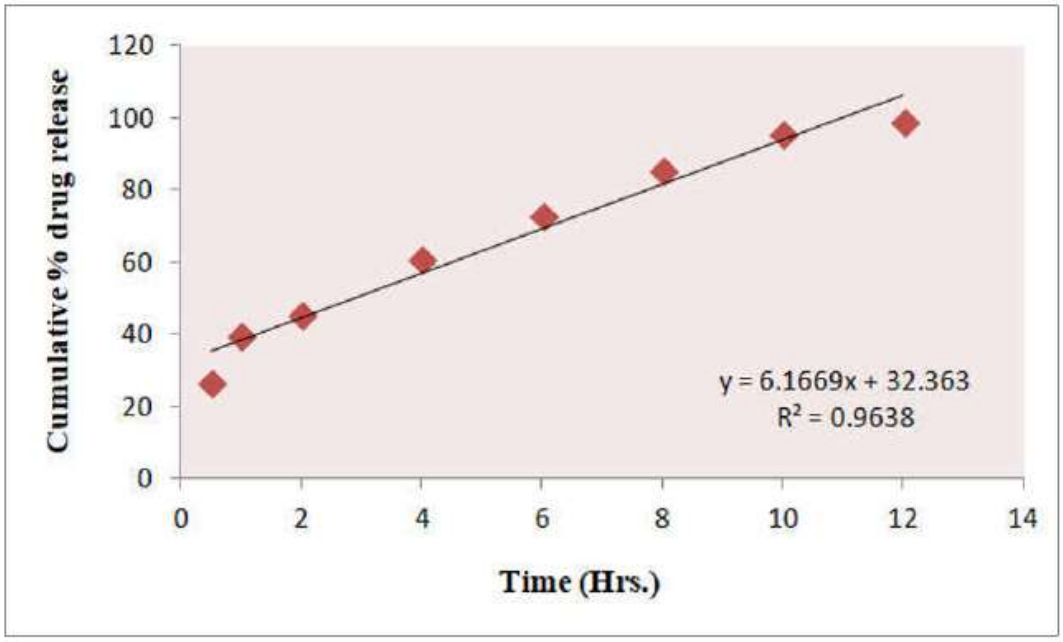

Figure 5: Zero order release kinetics graph of optimized formulations

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