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Formulation and Optimization of Betahistidine Microspheres

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Abstract - Betahistidine is an active histamine analog primarily used in the treatment of vertigo, tinnitus, and Meniere's disease—conditions related to vestibular disorders and inner ear dysfunction. However, Betahistidine's clinical efficacy is hindered by its short half-life, rapid clearance, and limited oral bioavailability. Polymeric microspheres, especially those made from biodegradable materials such as Poly(lactic-co-glycolic acid) (PLGA) and Chitosan, have shown considerable potential for controlled drug release. The current research work focused on preparation and optimization of Betshistidine microspheres which can be scaled up and used commercially in future.

***Key Words*:** PLGA, Chitosan, Microspheres, solvent evaporation

1.INTRODUCTION

This project focuses on developing Betahistine microspheres using PLGA (Poly(lactic-co-glycolic acid)) and Chitosan to enhance the drug's delivery for treating vertigo and Ménière's disease. Betahistine, a histamine analog with a short half-life and frequent dosing needs, suffers from fluctuating plasma levels and poor patient compliance in its conventional oral form. By encapsulating it in microspheres, this study aims to achieve controlled release, leveraging PLGA's biodegradable, tunable properties for sustained delivery and Chitosan's mucoadhesive, biocompatible nature to improve stability and retention. Through techniques like solvent evaporation or emulsification, the project will synthesize and characterize these microspheres, assessing their size, encapsulation efficiency, and release profile, with the goal of overcoming current therapeutic limitations and advancing efficient drug delivery systems..

2. Materials and Methods

Materials

a) Drug:

Betahistine Dihydrochloride – The active pharmaceutical ingredient (API) used in the formulation. Betahistine is usually available as a white, crystalline powder, which is soluble in water.

b) Polymers:

Polymers are key to controlling the release rate of the drug and ensuring the stability of the microspheres. Commonly used polymers in solvent evaporation techniques include:

Natural polymers:

Chitsoan is used as natural polymer

Synthetic Polymers:

Poly(lactic-co-glycolic acid) (PLGA): A biodegradable polymer widely used in controlled drug delivery applications due to its ability to degrade into non-toxic metabolites (lactic acid and glycolic acid).

c) Solvents:

Organic Solvents – Used for dissolving the polymer and/or drug. Common solvents include:

Dichloromethane (DCM): Often used for its low boiling point and ability to dissolve hydrophobic polymers.

Chloroform: A widely used solvent that can dissolve both hydrophobic polymers and some drugs.

Methodology

a) Preparation of Polymer Solution:

Polymer Selection and Dissolution:

Select the polymer based on the desired drug release profile and prepare a polymer solution by dissolving a suitable amount of the polymer (e.g., PLGA or gelatin) in an organic solvent (e.g., dichloromethane or chloroform). The concentration of the polymer solution typically ranges from 1% to 10% (w/v), depending on the desired final microsphere characteristics.

Drug Loading:

Betahistine is dissolved or dispersed in the polymer solution. The concentration of the drug is typically adjusted based on the desired drug load (e.g., 10–50% w/w of the polymer). The drug is either dissolved in the organic solvent along with the polymer or suspended if it is poorly soluble in the solvent.

b) Emulsion Formation:

Preparation of the Aqueous Phase:

The aqueous phase is prepared by dissolving stabilizers like polyvinyl alcohol (PVA) in water. The concentration of PVA is usually between 1% to 2% (w/v). The purpose of the aqueous phase is to prevent the coalescence of the organic phase (which contains the polymer and drug) during emulsification.

Emulsification Process:

The organic phase (containing the polymer and drug) is added dropwise to the aqueous phase under continuous stirring. This forms a primary emulsion (O/W: oil-in-water). High-speed homogenization or sonication may be applied to reduce the droplet size and ensure uniform emulsification. This step is crucial for achieving microspheres with uniform size and drug distribution**.**

The emulsion is typically prepared under cold conditions (e.g., using an ice bath) to prevent premature evaporation of the solvent**.**

c) Solvent Evaporation:

Evaporation of the Organic Solvent:

After emulsification, the solvent is evaporated to harden the microspheres. This is achieved by stirring the emulsion at room temperature or under reduced pressure (using a rotary evaporator). During this step, the organic solvent (e.g., dichloromethane or chloroform) evaporates, leaving behind solidified microspheres of the polymer and encapsulated drug.

Completion of Microsphere Formation:

As the solvent evaporates, the polymer solidifies, trapping the betahistine inside the microsphere matrix. This results in the formation of spherical microparticles.

d) Isolation of Microspheres:

After complete solvent evaporation, the microspheres are separated from the aqueous phase by centrifugation or filtration. The collected microspheres are then washed several times with water to remove any residual surfactant or unencapsulated drug.

e) Drying of Microspheres:

The microspheres are typically freeze-dried or air-dried to remove any residual water content. Freeze-drying helps preserve the microsphere structure and drug loading.

3. Results

Entrapment efficiency

Table -1: Formulation and Encapsulation efficiency

Formulation code	PLGA: Chitosan	Drug Load (%w/w)	Encapsulation Efficiency (EE) (%)
R1L1	PLGA 70%: Chitosan 30%	10% w/w	82
R1L2	PLGA 70%: Chitosan 30%	20% w/w	79
R1L3	PLGA 70%: Chitosan 30%	30% w/w	72
R2L1	PLGA 50%: Chitosan 50%	10% w/w	90
R2L2	PLGA 50%: Chitosan 50%	20% w/w	88
R2L3	PLGA 50%: Chitosan 50%	30% w/w	80

The entrapment efficiency (EE) of microspheres refers to the percentage of the total drug (or active ingredient) that is successfully encapsulated within the microspheres, compared to the total amount of drug that was initially added during the preparation process

Dissolution of Betahistidine Microspheres

Dissolution of Microspheres carried out in PBS 7.4 using USP type II apparatus for 8 hours

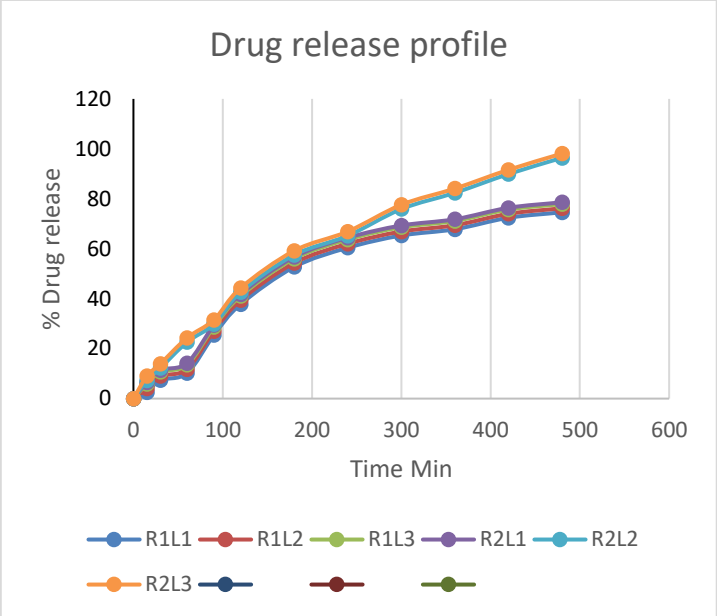

Fig -1: Dissolution data

3. CONCLUSIONS

Among the various formulations, R2L2 emerged as the optimum formulation, exhibiting favorable characteristics in terms of drug entrapment efficiency and controlled drug release. This formulation demonstrated an initial burst release, followed by a sustained release profile, making it a suitable candidate for extended drug delivery

Further optimization in polymer ratios and process parameters may refine the formulation, enhancing reproducibility and clinical applicability. Future studies should focus on in vivo pharmacokinetic assessments and stability studies to validate the formulation's potential for therapeutic applications.

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