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Formulation and Evaluation of Enteric Coated Microspheres of Paracetamol

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ABSTRACT:

This study focuses on the formulation and evaluation of enteric-coated microspheres containing paracetamol, aimed at enhancing drug targeting and sustained release while minimizing gastric irritation. Microspheres were prepared using the ionotropic gelation technique with sodium alginate as a matrix-forming polymer and calcium chloride as a cross-linking agent. Selected batches were coated with Hydroxypropyl Methylcellulose Phthalate (HPMCP) to provide enteric protection. The micromeritic properties, including bulk density, tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose, were evaluated to assess the flow characteristics of the microspheres. The results demonstrated that the microspheres had good flow properties and uniform particle size distribution. The enteric coating effectively protected the drug from the acidic environment, suggesting the potential of microspheres as a reliable carrier for controlled drug delivery to the intestine, thereby improving patient compliance and therapeutic efficacy.

INTRODUCTION:

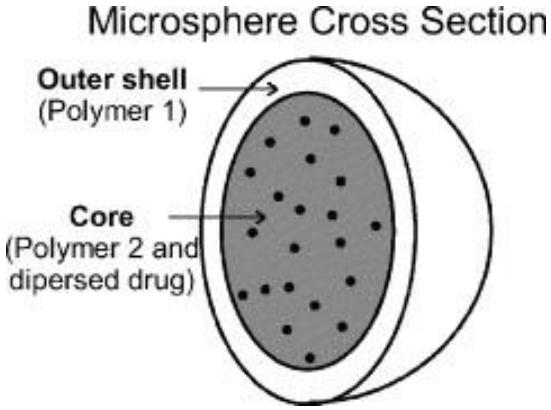
MICROSPHERES

Microspheres are free-flowing polymeric microparticles that can be loaded with biologically active drugs to provide a sustained and consistent therapeutic effect. This approach reduces the frequency of dosing and enhances patient compliance. In addition to extended drug release, microspheres can also facilitate targeted drug delivery to specific sites in the body, which helps minimize potential side effects. Applying a suitable coating to microspheres is an important formulation technique, as it allows for further modification of their properties, particularly the in vitro release profile of the incorporated drug.(1,2)

Microspheres are powders composed of natural proteins or synthetic biodegradable polymers, typically ranging in size from 1 to 1000 μm. These systems are generally divided into two categories:

- **Microcapsules:** in which the encapsulated drug is enclosed within a distinct shell or capsule wall.
- **Microspheres (or micrometrics**): where the drug is uniformly dispersed throughout the polymer matrix.

Solid biodegradable microspheres containing a drug either dissolved or dispersed within the matrix hold significant potential for controlled drug release. They are formulated from various materials, including biodegradable synthetic polymers, modified natural substances, or waxy compounds, acting as protective carriers for the drug.[3,4,5]



Preparation of Stock Solutions for Calibration Curve:

Stock Solution 1:

A primary stock solution of the drug at a concentration of 1 mg/ml was prepared by dissolving 100 mg of the drug in a mixture of methanol and phosphate buffer (pH 6.8) within a 100 ml volumetric flask. The mixture was shaken thoroughly and sonicated for approximately 10 minutes to ensure complete dissolution, resulting in a 1000 µg/ml solution.

Stock Solution 2:

From Stock Solution 1, 10 ml was transferred to a separate 100 ml volumetric flask and diluted to volume with phosphate buffer (pH 6.8). This resulted in a secondary stock solution with a concentration of 100 µg/ml.

Stock Solution 3:

Subsequently, 1 ml of Stock Solution 2 was diluted to 10 ml using phosphate buffer (pH 6.8), yielding a tertiary stock solution with a drug concentration of 10 µg/ml.

Preparation of Sample Solutions:

To generate the calibration curve, a series of solutions with concentrations of 2, 4, 6, 8, and 10 µg/ml were prepared by appropriately diluting Stock Solution 3 with phosphate buffer (pH 6.8). The absorbance of each solution was measured at 245 nm using a UV spectrophotometer, with phosphate buffer (pH 6.8) serving as the blank. A standard calibration curve was then constructed by plotting drug concentration on the X-axis and the corresponding absorbance on the Y-axis. [6,7]

FORMULATION OF ENTERIC COATED MICROSPHERES OF PARACETAMOL:

Microspheres were formulated using the ionotropic gelation technique with sodium alginate as the matrix-forming polymer and calcium chloride as the cross-linking agent. A 2% sodium alginate solution was prepared by dissolving the polymer in 100 mL of distilled water under magnetic stirring. The required amount of paracetamol was uniformly dispersed in this solution.

Cross-linking solutions with calcium chloride concentrations of 10%, 15%, and 20% w/v were prepared separately in distilled water. Using a syringe, the drug-polymer solution was dropped into these cross-linking baths from a height of approximately 6 inches, maintaining a drop rate of about 50 drops per minute. The interaction with calcium ions resulted in microsphere formation through ionic cross-linking.

The formed microspheres were collected by decantation, followed by centrifugation, then air-dried overnight and stored in vacuum desiccators for stability.

For enteric coating, selected batches of microspheres were immersed in a 2%solution of Hydroxypropyl Methylcellulose Phthalate (HPMCP) in water for 30minutes. After coating, the microspheres were again collected by decantation, centrifuged, air-dried overnight, and stored. Based on the concentration of calcium chloride used during cross-linking.[8]

Evaluation of Enteric-Coated Paracetamol Microspheres: Micromeritic Properties:

1. **Bulk Density:** A specific weight of microspheres was placed into a measuring cylinder, and the volume they occupied (Vo) was recorded. Bulk density was then calculated using the formula:

Bulk Density = Mass of microspheres (W) / Bulk volume of microspheres (Vo).

2. **Tapped Density:** A known quantity of microspheres was filled into a measuring cylinder. The cylinder was gently tapped against a wooden surface at regular intervals, up to 100 times, until the volume minimized. The tapped volume (Vf) was noted, and tapped density was calculated as:

Tapped Density = Mass of microspheres (W) / Tapped volume of microspheres (Vf).

3. **Flow Properties:** The flow behavior of the uncoated microspheres was evaluated using Carr's compressibility index and Hausner's ratio, calculated from bulk and tapped densities.
    - **Carr's Compressibility Index:** Indicates the compressibility of the powder and is calculated as:

Carr's Index = [(Tapped Density − Bulk Density) / Tapped Density] × 100.

    - **Hausner's Ratio:** Used to predict flowability and calculated as:

Hausner's Ratio = Tapped Density / Bulk Density.

4. **Angle of Repose:** This parameter measures the resistance to flow of the microspheres and was determined using the funnel method. A known amount of microspheres was allowed to flow through a funnel onto a paper surface, forming a conical pile. The diameter and height of the pile were recorded, and the angle of repose (θ) was calculated by:

$\theta = \tan^{-1}(h / r)$

where,

- θ = Angle of repose,
- h = Height of the pile,
- r = Radius of the base of the pile.[9]

CONCLUSION:

The enteric-coated microspheres of paracetamol were successfully formulated using sodium alginate and calcium chloride through ionotropic gelation. The micromeritic evaluation revealed favorable flow and compressibility properties, essential for manufacturing and handling. The enteric coating with HPMCP provided protection against premature drug release in acidic conditions, ensuring targeted release in the intestinal environment. This approach

offers a promising strategy to minimize gastric side effects, improve drug stability, and achieve sustained drug release. Further in vivo studies are recommended to validate the therapeutic benefits of these enteric-coated microspheres

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