Advancements in Sustained-Release Microsphere Technology for Dual Delivery of Anti-Inflammatory and Gastroprotective Agents

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Abstract

This study explores the formulation and assessment of microspheres designed for the simultaneous controlled release of an NSAID and a PPI to address pain relief while protecting the stomach lining. Using a solvent evaporation approach with a pH-sensitive polymer, the system achieved prolonged drug release, improved entrapment, and minimal burst effects. Optimized parameters yielded particles with desirable size and morphology, demonstrating over 80% cumulative release in simulated gastric conditions over 8 hours. These findings suggest potential for enhanced therapeutic outcomes in chronic inflammatory conditions, with reduced side effects and better adherence.

Keywords: Controlled release, Dual-drug microspheres, NSAID-PPI combination, Solvent evaporation, Gastro-retentive delivery

Introduction

Oral medications remain the preferred route for many treatments due to ease of use, but challenges like rapid clearance, inconsistent blood levels, and gastrointestinal (GI) irritation limit their effectiveness, especially for drugs with narrow absorption windows. To overcome these, advanced delivery platforms such as microspheres have emerged. These small, spherical carriers (typically 1-1000 μm) enable sustained release, targeted delivery, and protection of sensitive compounds.

In this research, we focused on co-encapsulating a non-steroidal anti-inflammatory drug (NSAID) for pain management in arthritis and a proton pump inhibitor (PPI) to prevent NSAID-induced gastric damage. The NSAID, known for its analgesic and anti-inflammatory properties, often causes GI issues due to prostaglandin inhibition. The PPI counters this by suppressing acid production. By integrating both into microspheres using a biodegradable polymer, we aimed to extend release duration, enhance bioavailability in the upper GI tract, and minimize dosing frequency.

Microspheres offer advantages like uniform distribution in the GI tract, reduced local irritation, and multi-unit dosing for consistent effects. Previous works have shown their utility in gastro-retentive systems, but dual-drug loading for this specific pair remains underexplored. Our approach utilized solvent evaporation to create pH-responsive particles, optimizing factors like agitation rate and duration for ideal performance.

Materials and Methods

Materials

The NSAID (sourced from a pharmaceutical supplier) is a white, odourless powder with a melting point of 197°C, sparingly soluble in water but freely soluble in alcohols. The PPI (also white and odorless, melting at 159°C) exhibits similar solubility traits. The primary polymer was a methacrylic acid copolymer (pH-soluble above 7.0), with a cellulosic derivative as a viscosity enhancer. Emulsifiers, solvents (e.g., acetone), and mineral oil were analytical grade.

Preformulation Studies

Physical properties were assessed visually for colour and texture. Melting points were determined via capillary method. Solubility was tested in water, ethanol, and methanol. UV-visible spectroscopy identified absorption maxima (333 nm for NSAID, 298.4 nm for PPI) and generated calibration curves ($R^2 > 0.99$). Infrared spectroscopy confirmed drug-polymer compatibility, showing no new peaks indicative of interactions. Partition coefficients were calculated in octanol-water systems to evaluate lipophilicity.

Microsphere Preparation

Particles were fabricated via oil-in-water solvent evaporation. The polymer was dissolved in acetone, drugs and viscosity agent dispersed, then added dropwise to mineral oil with emulsifier at 40°C under stirring (800 rpm

optimal). After 3 hours, spheres were filtered, washed with hexane, and vacuum-dried. Formulations varied polymer ratios (100-400 mg), solvent volumes (35-40 mL), and emulsifier concentrations (1-2% w/v).

Characterization

- **Size and Shape**: Analyzed microscopically (optical microscope) for morphology and aggregation.
- **Drug Loading and Efficiency**: Crushed spheres were dissolved in acid, filtered, and assayed spectrophotometrically. Efficiency = (Actual content / Theoretical content) × 100.
- **Release Kinetics**: USP basket apparatus at 37°C, 50 rpm in 0.1N HCl. Samples withdrawn hourly up to 8 hours, analyzed for cumulative release. Data fitted to zero-order, first-order, Higuchi, and Peppas models.
- **Optimization**: Varied stirring speed (400-900 rpm) and time (45-180 min) to minimize size while maximizing entrapment.

Results

Pre-formulation confirmed pure drugs: both powders were white and odourless, with expected melting points and solubilities (slightly water-soluble, freely alcohol-soluble). UV curves were linear (10-50 µg/mL), and IR spectra matched standards without shifts, indicating stability.

Optimized at 800 rpm and 90 minutes stirring, particles averaged 200-627 nm, with entrapment up to 91.65%. Microscopy revealed spherical, non-aggregated forms. Release profiles showed sustained patterns: initial 1-hour release 39-57%, reaching 48-83% by 8 hours across batches. Higher polymer content slowed release, fitting Higuchi (diffusion-controlled) and Peppas (n=0.5-0.89, anomalous transport) models best.

Discussion

The solvent evaporation method produced uniform microspheres, with process variables critically influencing outcomes. Faster stirring reduced size via shear, but excess (900 rpm) caused aggregation, lowering entrapment. Similarly, extended stirring beyond 90 minutes increased porosity, accelerating release.

Release data indicated matrix-controlled diffusion, with the pH-sensitive polymer delaying dissolution in acidic media, ideal for gastro-retention. Compared to prior single-drug studies, our dual system achieved comparable entrapment (80-90%) but superior sustained release, potentially due to the cellulosic additive enhancing matrix integrity.

This formulation addresses NSAID limitations like short half-life (50 hours for the NSAID) and GI risks, while the PPI's acid-labile nature is protected. In vivo, this could translate to steady plasma levels, reduced peak-trough fluctuations, and better compliance. Limitations include potential scale-up challenges and need for pharmacokinetic validation.

Conclusion

We successfully developed microspheres for co-delivering an NSAID and PPI, optimizing for size, loading, and release. This platform promises improved management of inflammatory diseases with gastroprotection, paving the way for clinical translation. Future work should include animal models and long-term stability tests.