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Review Paper

Recent Advancements in Microsphere-Based Novel Drug Delivery Systems for Optimizing the Bioavailability of Acyclovir: A Comprehensive Review

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ABSTRACT

Acyclovir remains the gold standard antiviral agent for managing Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) infections. However, its therapeutic efficacy is heavily constrained by poor oral bioavailability (15–30%), short plasma half-life (2.5–3 hours), and site-specific absorption in the upper gastrointestinal tract. To circumvent these limitations, novel drug delivery systems (NDDS)—specifically polymeric microspheres and micro-nanoparticulate matrices—have emerged as promising solutions. This review systematically analyzes the rationale behind encapsulating acyclovir into polymeric microspheres to achieve gastroretentive, sustained, and targeted release profiles. We discuss the selection criteria for natural, synthetic, and semi-synthetic polymers (e.g., chitosan, PLGA, Eudragit) and critically evaluate dominant fabrication methodologies like solvent evaporation, spray drying, and ionotropic gelation. Furthermore, characterization parameters including entrapment efficiency, zeta potential, surface morphology, and in-vitro kinetic release profiles are scrutinized. Finally, this paper maps current regulatory challenges, industrial scale-up hurdles, and strategic future insights required to translate these laboratory formulations into clinical practice.

INTRODUCTION

1.1 Overview and Clinical Constraints of Acyclovir

Acyclovir (9-[2-hydroxyethoxymethyl]guanine) is a synthetic purine nucleoside analogue possessing highly selective antiviral activity. It acts by inhibiting viral DNA synthesis through competitive inhibition of viral DNA polymerase after cellular phosphorylation by viral thymidine kinase. Structurally, it is categorized under Biopharmaceutics Classification System (BCS)

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Class III, exhibiting high solubility but low permeability across physiological membranes.

The clinical utility of conventional oral dosage forms (tablets and capsules) is significantly hampered by:

- **Low Bioavailability:** Erratic oral absorption leads to only 15–30% of the dose reaching systemic circulation.
- **Frequent Dosing Schedules:** A short elimination half-life of 2.5 to 3 hours necessitates high doses (e.g., 200 mg to 800 mg administered 4 to 5 times daily).
- **Side Effects:** Frequent high dosing induces gastrointestinal distress, renal crystallization, and poor patient compliance.
- **Narrow Absorption Window:** Absorption is predominantly restricted to the upper segment of the small intestine (duodenum and jejunum).

1.2 Rationale for Microsphere-Based Novel Drug Delivery Systems (NDDS)

To eliminate erratic dosing frequencies and improve therapeutic indices, shifting toward microparticulate carriers is essential. Polymeric microspheres are spherical, free-flowing monolithic particles ranging in size from 1 to 1000 μm.

When applied to acyclovir, microsphere encapsulation offers distinct clinical advantages:

- Sustained Release Kinetic Profiles: Provides a continuous release of the antiviral drug over extended intervals, maintaining steady-state plasma concentrations.
- Gastroretentive Mechanisms: Mucoadhesive or floating microspheres prolong the gastric residence time (GRT) of the formulation directly over its absorption window in the upper GIT.
- Dose Dumping **Mitigation:** Spreading the drug across millions of micro-carriers minimizes the risk of local mucosal irritation or abrupt toxic systemic spikes.

2. Polymeric Matrices Used in Formulation

The selection of the polymer matrix governs the entrapment efficiency, particle stability, degradation rate, and drug release kinetics.

2.1 Natural Polymers

- Chitosan: A cationic polysaccharide derived from chitin. It exhibits excellent biocompatibility, biodegradability, and intrinsic mucoadhesiveness. The positively charged amino groups of chitosan interact ionically with the negatively charged sialic acid residues of the gastric mucus layer.
- Sodium Alginate: A natural anionic linear polysaccharide. It undergoes rapid ionotropic gelation in the presence of divalent cations like Ca^{2+}, creating stable crosslinked hydrogel networks ideal for controlled oral drug release.

2.2 Synthetic and Semi-Synthetic Polymers

- **Poly(lactic-co-glycolic acid) (PLGA):** An FDA-approved biodegradable copolymer. It undergoes ester hydrolysis into non-toxic lactic and glycolic acid monomers. PLGA allows precise tuning of drug release by altering the lactide-to-glycolide ratio.
- **Eudragit Polymers (e.g., Eudragit RS100, RL100, S100):** Polymethacrylate-based synthetic polymers. Eudragit S100 provides enteric protection, whereas RS100 and RL100 act as insoluble matrices with varying permeability to deliver sustained release independent of physiological pH.
- **Ethyl Cellulose (EC):** A non-biodegradable, hydrophobic polymer widely used to fabricate core-shell and matrix-type microspheres to

slow down water penetration and drug diffusion.

3. Preparation Techniques and Fabrication Methodologies

Choosing the correct fabrication technique is critical to achieving high entrapment efficiency for water-soluble molecules like acyclovir.

3.1 Solvent Evaporation Method (Single/Double Emulsion)

For hydrophobic drugs, oil-in-water (o/w) single emulsion is used. However, due to the intermediate water solubility of acyclovir, a double emulsion technique water-in-oil-in-water (w/o/w) is highly preferred. The drug is dissolved in an internal aqueous phase, emulsified into an organic polymer solution (oil phase), and then re-emulsified into an external aqueous phase containing a stabilizer (e.g., PVA). The organic solvent (dichloromethane or chloroform) is removed via evaporation or diffusion, forcing polymer precipitation into micro-spherical forms.

3.2 Spray Drying Technique

This method involves atomizing an aqueous or organic suspension/solution of polymer and acyclovir through a nozzle into a drying chamber heated with hot air. The solvent evaporates instantaneously, forming uniform, dry microspheres. This process is rapid, highly reproducible, easily scaled up, and independent of solubility challenges, though thermal stress must be carefully managed.

3.3 Ionotropic Gelation Method

This is a completely aqueous, green synthesis method. Sodium alginate solution containing dispersed acyclovir is dropped through a syringe needle into an aqueous solution of calcium chloride ($CaCl_2$). The counter-ions (Ca^{2+}) displace sodium ions, instantly forming crosslinked calcium alginate beads. This method completely avoids toxic organic solvents.

4. Evaluation and Characterization Parameters

To fulfill pharmacopeial and journal standard benchmarks, the engineered microspheres must undergo rigorous evaluation.

4.1 Particle Size Distribution and Zeta Potential

Particle size is measured via Dynamic Light Scattering (DLS) or laser diffraction. For optimal intestinal uptake and cellular interaction, sizes should ideally range between 10 to 200 µm. Zeta potential indicates the surface charge of the microspheres; a value greater than ±30 mV indicates a stable colloidal system that prevents particle aggregation.

4.2 *Entrapment* Efficiency (EE) and Production Yield

Entrapment efficiency determines the percentage of acyclovir successfully enclosed within the polymer matrix. It is computed via the following formula:

$$\text{Entrapment Efficiency (\%)} = \left(\frac{\text{Mass of actual drug found in microspheres}}{\text{Mass of initial drug added in formulation}} \right) \times 100$$

Production yield measures the physical recovery of the microspheres post-fabrication compared to the initial total solid mass of polymers and drug used.

4.3 Surface Morphology (SEM)

Scanning Electron Microscopy (SEM) reveals the surface topography. Microspheres should present a spherical, smooth matrix or a porous framework depending on the intended release kinetics (porous surfaces facilitate faster water influx and initial burst release).

4.4 *In-Vitro* Drug Release and Kinetics

Dissolution testing is executed using USP Dissolution Apparatus I or II in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 6.8). Data are fitted into mathematical models (Zero-order, First-order, Higuchi, Peppas, and Hixson-Crowell) to identify the underlying transport mechanisms, such as Fickian diffusion or polymer matrix swelling/erosion.

5. Summary of Recent Research Findings (*Comparative* Matrix)

The table below synthesizes performance data extracted from prominent recent studies focused on optimizing acyclovir microsphere formulations:

Polymer Matrix	Fabrication Method	Key Evaluation Metrics / Results	Therapeutic Outcome / Advantage
Chitosan + Sodium Alginate	Ionotropic Gelation	Particle Size: 45-120 µm, Entrapment Efficiency: 72-85%	Exceptional mucoadhesion; sustained drug release extending beyond 12 hours in acidic pH.
PLGA (50:50)	w/o/w Double Emulsion	Particle Size: 5-25 µm, Entrapment Efficiency: 58%	Biphasic release profile: Initial burst release followed by constant diffusion over 48 hours.
Ethyl Cellulose + Eudragit	Solvent Evaporation	Particle Size: 150-300 µm, Floating Efficiency: >80%	Buoyant gastroretentive properties; prolonged gastric residence time for targeted upper GIT absorption.

6. Current Challenges and Future Prospects

Despite successful bench-scale results, several technical hurdles limit commercial translation:

- **Scale-Up Bottlenecks:** Replicating uniform particle size distributions and batch-to-batch consistency in industrial spray dryers or large-scale reactors remains difficult.
- **Solvent Residues:** Traces of organic solvents (like dichloromethane) used in solvent evaporation processes pose significant toxicity concerns, requiring strict compliance with ICH guidelines.
- **Regulatory Pathways:** Establishing clear *in-vitro/in-vivo* correlation (IVIVC) standards for multi-particulate delivery systems is complex.

Future Horizons: Integrating artificial intelligence (AI) to optimize polymer blends, using 3D microfluidic chips to generate highly monodisperse microspheres, and engineering advanced theranostic micro-carriers will shape the next generation of acyclovir therapies.

CONCLUSION

Developing polymer-based microspheres for acyclovir addresses the core limitations of traditional oral dosing schedules. By enhancing mucosal adherence, ensuring buoyancy within the stomach, and modulating drug diffusion kinetics,

microspheres substantially improve acyclovir's bioavailability. Natural polymers like chitosan and biodegradable synthetic matrices like PLGA offer safe and scalable options. Overcoming current industrial scale-up limitations will pave the way for highly compliant, low-dose, and clinically effective antiviral regimens.

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