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Strategies for Loading and Releasing Peptide Therapeutics in Biodegradable Carriers

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ABSTRACT

Peptides have become an increasingly important therapeutic modality for diverse diseases (e.g., diabetes and cancer) due to their high potency and specificity, favorable safety profiles, and improved manufacturability. Biodegradable micro- and nanocarriers have consequently been widely investigated to protect peptides from enzymatic degradation and rapid systemic clearance while enabling sustained delivery. Despite substantial progress, biodegradable carrier–based peptide delivery remains limited by several persistent challenges: (i) low peptide loading capacity, (ii) an inherent trade-off between high loading and suppression of initial burst release, and (iii) pronounced peptide-to-peptide variability in loading and release arising from heterogeneous physicochemical properties (e.g., charge, hydrophilicity, and solubility). To present insights for overcoming these unresolved issues, we aim to review recent strategies for efficiently loading and releasing peptide therapeutics in biodegradable carriers. After briefly introducing the properties and types of peptides and biodegradable carriers, the major limitations of biodegradable carrier-based peptide delivery are meticulously discussed. Then, the potential solutions to resolve the limitations are presented based on the recently progressed works. Finally, we outline remaining knowledge gaps and future directions for scalable manufacturing, longer-duration release, and clinical translation of biodegradable carrier-based peptide delivery systems.

1 | Introduction

Peptides are an increasingly important class of therapeutics, typically defined as short chains of fewer than ~50 amino acids with molecular weights in the range of 500–5000 Da [1, 2]. Peptide-based drugs have been investigated across diverse indications, including diabetes [3], cancer [4], Alzheimer's disease [5], and COVID-19 [6]. Relative to small-molecule drugs and therapeutic proteins, peptides offer several advantages. Compared with proteins, peptides generally exhibit lower immunogenicity and toxicity and can be manufactured at a lower cost [1]. Furthermore, the peptide can efficiently penetrate deep tissue and cells [7]. Compared with small molecules, peptides often achieve higher target specificity with reduced off-target toxicity since their degradation products are amino acids, which are endogenous biomolecules [8]. Reflecting these advantages, approximately 100 peptide drugs have been approved for clinical use, and more than 200 candidates are in clinical development [8, 9].

Despite their therapeutic promise, peptides administered without a carrier system face major limitations in vivo, particularly poor stability and limited duration of action. Because peptides are short protein-derived molecules, they are vulnerable to proteolytic degradation in the gastrointestinal tract and the bloodstream [10]. In addition, their relatively small size promotes rapid systemic clearance, especially via renal filtration [11], reducing exposure at target sites and sometimes necessitating higher or more frequent dosing. Consequently, conventional routes such as oral administration, intravenous injection, and subcutaneous injection are often constrained by limited biological stability and low

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