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Review

Oral Delivery of Semaglutide via Nanostructured Lipid Carriers (NLCs): A Review of Formulation, Stability, and Intestinal Uptake

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Abstract:
Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has demonstrated significant efficacy in obesity management. However, its therapeutic potential is limited by poor oral bioavailability and enzymatic degradation in the gastrointestinal tract, necessitating subcutaneous administration. Nanostructured lipid carriers (NLCs) offer a promising alternative by encapsulating semaglutide within a lipid matrix that enhances stability, protects against proteolysis, and facilitates intestinal absorption. This review explores the formulation strategies, pharmacokinetic improvements, and therapeutic relevance of semaglutide-loaded NLCs. NLCs are composed of solid and liquid lipids stabilized by surfactants such as Tween 80 and Poloxamer 188, which together create a disordered matrix capable of accommodating hydrophilic peptides. Optimization of lipid selection, surfactant concentration, and homogenization parameters is critical to achieving high encapsulation efficiency and sustained release. Pharmacokinetic studies reveal that NLCs significantly improve systemic exposure and half-life of semaglutide, while pharmacodynamic evaluations show enhanced appetite suppression and weight reduction in preclinical models. Despite these advances, challenges remain in formulation stability, mucosal permeability, and large-scale manufacturing. Strategies such as mucoadhesive coatings, PEGylation, and chitosan modification are being explored to improve intestinal uptake. Regulatory harmonization and long-term safety evaluations are essential for clinical translation. Semaglutide-loaded NLCs represent a transformative platform for non-invasive obesity therapy, with the potential to improve patient adherence and therapeutic outcomes. Continued research and innovation in lipid-based nanocarriers may redefine the future of peptide drug delivery.

Keywords: Semaglutide, nanostructured lipid carriers, oral peptide delivery, GLP-1 agonist, obesity, pharmacokinetics, surfactants, mucoadhesion.

1. INTRODUCTION

1.1. Obesity: Global burden and therapeutic challenges

Obesity remains one of the most pressing global health concerns, with its prevalence rising across all age groups and socioeconomic strata. It is now

recognized not merely as a lifestyle condition but as a complex, multifactorial disease with genetic, hormonal, behavioural, and environmental underpinnings [1]. The associated comorbidities type 2 diabetes, cardiovascular disease, non-alcoholic fatty liver disease, and certain cancers have prompted a shift toward precision obesity medicine, where phenotype-guided interventions are prioritized [1]. Despite the availability of pharmacological agents, long-term adherence and tolerability remain significant barriers to sustained weight loss.

1.2. Semaglutide: Mechanism and limitations of current delivery

Semaglutide, a GLP-1 receptor agonist, has emerged as a leading pharmacotherapy for obesity and type 2 diabetes due to its dual action on appetite suppression and glycemic control. It mimics endogenous incretin hormones, enhancing insulin secretion and delaying gastric emptying, thereby promoting satiety and reducing caloric intake [2]. However, its current delivery via subcutaneous injection poses challenges in terms of patient compliance, needle phobia, and long-term acceptability. Oral semaglutide formulations have been explored, but their bioavailability remains low due to enzymatic degradation and poor permeability across the gastrointestinal tract [3].

1.3. Rationale for NLC-based oral delivery

Nanostructured lipid carriers (NLCs) offer a promising alternative for the oral delivery of peptide-based drugs like semaglutide. These lipid-based nanocarriers combine solid and liquid lipids to form a stable matrix capable of encapsulating hydrophilic and lipophilic drugs, protecting them from enzymatic degradation and enhancing mucosal permeability [4]. NLCs have demonstrated improved pharmacokinetic profiles, sustained release, and enhanced bioavailability in various preclinical models [4]. For semaglutide, NLCs could potentially overcome the limitations of conventional oral formulations by facilitating absorption through lymphatic pathways and minimizing first-pass metabolism [5]. Moreover, their scalability, biocompatibility, and ability to incorporate functional excipients (e.g., mucoadhesive polymers, surfactants) make them suitable candidates for translational development.

2. Nanostructured Lipid Carriers (NLCs): An Overview

2.1. Composition and Architecture

Nanostructured lipid carriers (NLCs) are lipid-based nanotherapeutics composed of a blend of solid and liquid lipids, stabilized by surfactants such as Tween 80 and Poloxamer 188. This hybrid matrix creates structural imperfections that enhance drug loading and minimize drug expulsion during storage [6]. The architecture typically features a lipid core surrounded by a surfactant shell, enabling encapsulation of both hydrophobic and amphiphilic drugs [6].

These carriers are designed to overcome the limitations of solid lipid nanoparticles (SLNs), particularly in terms of drug entrapment efficiency and long-term stability. The presence of liquid lipids disrupts the crystalline structure of solid lipids, forming a less ordered matrix that accommodates more drug molecules [6].

2.2. Advantages Over Other Nanocarriers

Compared to conventional systems like liposomes or polymeric nanoparticles, NLCs offer several advantages. Their lipid composition ensures biocompatibility and biodegradability, while their structural design allows for improved solubility, sustained release, and enhanced physical stability [6]. NLCs also provide better protection for labile drugs against enzymatic degradation, especially in the gastrointestinal tract a critical factor for oral delivery of peptides [7].

In anti-obesity therapy, NLCs have shown promise by improving the pharmacokinetics of encapsulated agents and enhancing therapeutic outcomes. Their scalability and adaptability make them suitable for industrial translation, especially for chronic conditions requiring long-term dosing [7].

2.3. Relevance for Peptide Drugs

Peptide-based drugs like semaglutide face significant challenges in oral delivery due to enzymatic degradation and poor intestinal permeability. NLCs offer a lipid matrix that shields peptides from proteolytic enzymes and facilitates transcellular transport [7]. Surfactants such as Tween 80 and Poloxamer 188 enhance mucosal adhesion and membrane fluidity, promoting absorption and bioavailability [7].

Recent advances in targeted nano-based systems have demonstrated that NLCs can significantly improve the therapeutic index of anti-obesity peptides, offering a non-invasive alternative to injectable formulations [7].

3. Semaglutide and NLCs: Formulation Strategies

3.1. Lipid Selection and Compatibility

The formulation of semaglutide-loaded nanostructured lipid carriers (NLCs) begins with selecting lipids that can accommodate and stabilize peptide molecules. Solid lipids such as glyceryl behenate and stearic acid are often paired with liquid lipids like oleic acid or caprylic/capric triglycerides to create a matrix with reduced crystallinity and enhanced drug entrapment [8]. This disordered structure is essential for encapsulating hydrophilic peptides like semaglutide, which are otherwise poorly retained in rigid lipid matrices.

Compatibility between semaglutide and lipid components is typically assessed using thermal and spectroscopic techniques.

These analyses confirm molecular dispersion and absence of unfavourable interactions, which are critical for maintaining peptide stability during storage and transit [9].

3.2. Role of Surfactants: Tween 80 and Poloxamer 188

Surfactants are integral to NLC design, influencing particle size, stability, and mucosal permeability.

Tween 80, a non-ionic surfactant, reduces interfacial tension and facilitates nano-emulsion formation. Poloxamer 188, a triblock copolymer, provides steric stabilization and enhances the interaction of NLCs with intestinal epithelial cells [10].

Recent studies have shown that combining Tween 80 and Poloxamer 188 improves colloidal stability and promotes the formation of reverse micelles within the lipid matrix.

This dual-surfactant approach enhances the encapsulation of semaglutide and supports its transcellular transport across the gut barrier [11].

3.3. Encapsulation Efficiency and Release Kinetics

Achieving high encapsulation efficiency (EE%) is a major challenge in oral peptide delivery. Optimized NLCs using dual surfactants and lipid blends have demonstrated EE% values exceeding 80%, attributed to the formation of internal compartments that trap semaglutide effectively [11].

In vitro release studies reveal a biphasic pattern an initial burst followed by sustained release. This release profile supports prolonged therapeutic action and reduces dosing frequency, which is ideal for chronic conditions like obesity [12].

4. Pharmacokinetic and Pharmacodynamic Enhancements

4.1. Improved Bioavailability and Gastrointestinal Stability

Semaglutide's oral delivery is challenged by enzymatic degradation and limited intestinal permeability. Nanostructured lipid carriers (NLCs) offer a protective lipid matrix that shields semaglutide from gastrointestinal enzymes and facilitates its absorption across epithelial barriers. This encapsulation strategy has shown to significantly improve bioavailability in preclinical models [13].

A pharmacokinetic analysis of oral semaglutide formulations revealed enhanced systemic exposure and prolonged half-life when delivered via lipid-based carriers. These improvements are attributed to sustained release kinetics and reduced first-pass metabolism, which are hallmarks of well-optimized NLC systems [14].

4.2. Appetite Suppression and Weight Reduction Outcomes

Semaglutide's therapeutic effect is primarily mediated through GLP-1 receptor activation, which promotes satiety and reduces food intake. When delivered through NLCs, the extended plasma concentration profile enhances these pharmacodynamic effects, leading to more consistent appetite suppression and weight reduction [15].

In vivo studies have demonstrated that semaglutide-loaded NLCs outperform conventional oral formulations in reducing body weight and improving glycemic control. These outcomes suggest that NLCs not only improve pharmacokinetics but also amplify the drug's therapeutic impact [16].

4.3. Comparative Insights from In Vivo Studies

Comparative trials between injectable semaglutide and oral NLC-based formulations indicate that the

latter can achieve similar efficacy with improved patient compliance. The non-invasive nature of oral delivery, combined with sustained pharmacological action, positions NLCs as a viable alternative for long-term obesity management [17].

5. Challenges and Optimization Parameters

5.1. Formulation Stability and Peptide Integrity

One of the primary challenges in developing semaglutide-loaded nanostructured lipid carriers (NLCs) is maintaining peptide stability during formulation and storage. Semaglutide, being a large and hydrophilic molecule, is prone to degradation under thermal and oxidative stress. Lipid matrices must be carefully selected to avoid interactions that compromise peptide integrity, and antioxidants may be required to stabilize the formulation [18].

Additionally, the encapsulation process must be optimized to prevent aggregation or phase separation, especially when using high-energy emulsification techniques. Studies have shown that improper homogenization parameters can lead to particle size variability and reduced encapsulation efficiency [19].

5.2. Mucoadhesion and Intestinal Permeability

For oral delivery, achieving sufficient mucoadhesion and permeability across the intestinal epithelium is critical. While surfactants like Tween 80 and Poloxamer 188 enhance membrane fluidity, their concentrations must be balanced to avoid cytotoxicity or disruption of tight junctions [20].

Moreover, the presence of mucus can act as a barrier to nanoparticle diffusion, necessitating the use of muco-inert or mucus-penetrating surface modifications.

Recent research has explored the use of PEGylation and chitosan coatings to improve mucosal interaction and facilitate transcellular transport of semaglutide-loaded NLCs [21].

5.3. Scale-Up and Manufacturing Constraints

Translating lab-scale NLC formulations to industrial production presents several hurdles. Maintaining particle size uniformity, zeta potential, and encapsulation efficiency during scale-up requires precise control over mixing speed, temperature, and lipid-to-surfactant ratios. Moreover, regulatory compliance demands rigorous characterization of excipients, reproducibility of batches, and long-term stability data [22].

The use of high-pressure homogenization and microfluidization has shown promise in achieving scalable production, but cost and equipment limitations remain barriers for widespread adoption in low-resource settings.

5.4. Analytical and Regulatory Considerations

Characterizing semaglutide-loaded NLCs involves advanced analytical techniques such as dynamic light scattering (DLS), differential scanning calorimetry (DSC), and high-performance liquid chromatography (HPLC). These methods are essential for confirming particle size distribution, thermal behavior, and drug content, but require specialized instrumentation and expertise [23].

From a regulatory standpoint, peptide-loaded nanocarriers must meet stringent safety and efficacy standards. The lack of harmonized guidelines for lipid-based peptide delivery systems adds complexity to the approval process, especially for oral formulations targeting chronic diseases like obesity.

Conclusion and Future Considerations

Nanostructured lipid carriers (NLCs) have emerged as a transformative platform for the oral delivery of semaglutide, offering a compelling alternative to injectable formulations. By enhancing bioavailability, protecting against enzymatic degradation, and enabling sustained release, NLCs address many of the pharmacokinetic and pharmacodynamic limitations traditionally associated with peptide-based therapies.

However, the path to clinical translation is not without hurdles. Formulation stability, mucosal permeability, and large-scale manufacturing remain critical challenges. Future research must focus on refining lipid-surfactant combinations, integrating mucoadhesive or mucus-penetrating coatings, and developing scalable, cost-effective production methods that meet regulatory standards.

Moreover, long-term in vivo studies and human clinical trials are essential to validate the safety, efficacy, and patient adherence benefits of semaglutide-loaded NLCs. As obesity continues to rise globally, the development of non-invasive, patient-friendly delivery systems like NLCs could

redefine the therapeutic landscape for metabolic disorders.

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