Chapter 1

Introduction

1.1 Background

Type 2 diabetes mellitus (T2DM) is a disease characterized by an uncontrolled increase in blood sugar levels primarily caused by insulin resistance and the inability of the pancreas to produce enough insulin (Goyal et al., 2023). This disease continues to be one of the leading causes of death and other complications related to elevated blood sugar, such as cardiovascular diseases, myopathy, osteoporosis, and liver damage (Farmaki et al., 2020). Recent advances in diabetes research have provided several options for managing T2DM, including the coadministration of drugs with insulin injections. However, even with the many options to choose from, achieving the target HbA1C remains a challenge for most patients (Juarez et al., 2014). This presses the development of new and innovative antidiabetic therapy that is both effective and has good patient acceptability.

One commercially available antidiabetic drug is semaglutide, a GLP-1 receptor agonist. It primarily works to enhance glucose-dependent insulin secretion as well as delay gastric emptying, which promotes better satiety (Kommu & Whitfield, 2024). Despite its proven efficacy, semaglutide is administered by subcutaneous injection, which may be a challenge related to patient acceptability and long-term compliance. In light of this finding, an oral semaglutide tablet, marketed as Rybelsus, has been developed using a permeation enhancer technology to improve systemic absorption. However, research by Overgaard et al. (2021) has shown that oral semaglutide tablets performed poorly in bioavailability tests, which shows systemic bioavailability of less than 1% caused by enzymatic degradation and lowered absorption outside of the stomach. Such a limitation emphasizes the need for better formulation strategies that are capable of improving the drug's physicochemical properties and release profiles to allow better absorption and lead to better bioavailability.

Formulating semaglutide as an oral tablet remains a promising strategy to improve patient acceptability and compliance for T2DM management, given the convenience, non-invasive nature of oral formulations, and the potential manufacturing scalability. However, the currently commercially available oral semaglutide formulation, Rybelsus, is designed for gastric absorption and relies on salcaprozate sodium (SNAC) as a permeation enhancer to facilitate absorption in the stomach. This formulation introduces limitations, including the requirement of taking the drug on an empty stomach, very specific water uptake, and strict dosing timing (Novo Nordisk, 2019). An alternative approach may involve developing an enteric-coated oral semaglutide tablet designed to bypass the stomach and release in the intestines, providing a more suitable environment for semaglutide absorption. The feasibility of this formulation is supported by the addition of a new permeation enhancer, namely sodium caprate (C10). C10 modulates tight junctions to facilitate paracellular transport at lower concentrations, accompanied by mucosal perturbation (Twarog et al., 2019). Utilizing a permeation enhancer may help address issues concerning the oral bioavailability of semaglutide. Despite previous research showing promising effects of permeation enhancers, the concentration-dependent effects of C10 on tablet properties remain underexplored, offering opportunities to optimize the oral semaglutide formulation and improve absorption.

1.2 Objective

To formulate tablets for oral delivery of semaglutide with varying sodium caprate concentrations that possess good mechanical and physicochemical characteristics and release profiles.

1.3 Hypothesis

H_0 : The incorporation of sodium caprate does not improve the physicochemical properties and release profiles of an oral semaglutide tablet.

H_1 : The incorporation of sodium caprate significantly improves the physicochemical properties and release profiles of an oral semaglutide tablet.