Nanotechnology Perceptions
ISSN 1660-6795
www.nano-*ntp.com*

Preformulation Studies Of Semaglutide For The Development Of Extended-Release Tablets

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Preformulation studies play a crucial role in the successful development of a stable and effective dosage form. This study focuses on the characterization of Semaglutide through particle size analysis, flow property assessment, Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and solubility determination. The particle size distribution of three Semaglutide lots was analyzed using the Malvern technique, and Lot-III (D90: 53.219 µm) was selected for further formulation development. Flow properties indicated poor flowability, necessitating the use of aqueous wet granulation. FTIR and DSC studies confirmed drug-excipient compatibility, ensuring formulation stability. Solubility studies demonstrated poor aqueous solubility, classifying Semaglutide as a poorly soluble drug across physiological pH ranges. The findings of this study provide essential preformulation insights for the development of an optimized extended-release tablet formulation of Semaglutide.

Keywords: Semaglutide; Preformulation; Diabetes mellitus; FTIR; DSC.

INTRODUCTION

The development of stable and effective pharmaceutical dosage forms requires a comprehensive understanding of the physicochemical properties of the active pharmaceutical ingredient (API) and excipients. Preformulation studies provide essential data on particle size, flow properties, thermal stability, solubility, and drug-excipient compatibility, which are critical for formulation optimization. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist used in the management of type 2 diabetes mellitus, exhibits poor aqueous solubility and flow properties, necessitating the selection of appropriate processing techniques and excipients [1-4].

This study aims to evaluate the preformulation characteristics of Semaglutide, including particle size distribution, flow properties, identification via FTIR and DSC, and solubility across various physiological pH ranges. These insights will aid in the development of an extended-release tablet formulation, ensuring improved stability and performance[5-8].

MATERIALS AND METHODS

Materials

Semaglutide is purchased from Indaimart and all the other excipients are purchased for sigma Aldrich.

Methods

Preformulation Studies

Preformulation is described as a phase of research and development process, where the physicochemical properties of the drug substances and the excipients used are characterized in order to achieve success in developing a stable formulation.

Particle Size and Flow Properties

The particle size of Semaglutide was determined using the Malvern technique, where laser light scattering measured the intensity of dispersed particles. Flow properties, including bulk density, tapped density, compressibility index, and Hausner's ratio, were evaluated to assess powder flowability. Bulk and tapped densities were determined using a graduated cylinder, while compressibility index and Hausner's ratio were calculated to analyze the compressibility and cohesion of the powder blend [6-9].

Identification studies by fourier transform infrared spectroscopy (FTIR) & differential scanning calorimetry (DSC)

Semaglutide was identified using FTIR spectroscopy and DSC studies to assess drug-excipient compatibility. FTIR spectra were recorded using the KBr pellet method within the 4000–400 cm^{-1} range. DSC analysis was performed by heating samples at 10ºC/min from 30ºC to 110ºC under an inert nitrogen atmosphere to evaluate thermal stability and interactions [10-13].

Solubility determination

The solubility of Semaglutide was assessed in purified water, 0.1 N HCl, acetate buffer (pH 4.5), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4) at 37 ± 0.5ºC. A weighed amount of Semaglutide was added to each medium until saturation, followed by 24-hour stirring. The samples were filtered (0.45 μm), diluted, and analyzed using HPLC to determine drug concentration in each medium [14].

RESULT AND DISCUSSION OF PREFORMULATION STUDIES

Particle size determination and flow property

Particle size of the Semaglutide has a potential effect on In vitro dissolution and in vivo performance. Particle size distribution of Semaglutide was measured by using Malvern particle size analyzer for three lots. The results are shown in the Table 1**.**

Table 1: PSD of different lots of Semaglutide API

Pre-Compression Characteristics	Lot-I	Lot-II	Lot-III
D_{10} (µm)	1.926	6.135	3.276
D_{50} (µm)	5.361	25.033	13.575
D_{90} (µm)	11.372	85.847	53.219

Particle size d_{90} values for three lots of Semaglutide were 11.372 µm (Lot-I), 85.847 µm (Lot-II) and 53.219 µm (Lot III). Lot III with value of d_{90} 53.219 µm was selected for further developmental trials. The optimized formulation was further studied to check the influence of particle size on in vitro dissolution.

Semaglutide was cohesive and displayed poor flowability as evidenced by the compressibility index and Hausner ratio. Poor material flow may produce tablets with high weight and content variability due to an uneven distribution of the drug substance in the blend, uneven bulk density and eventually uneven filling of die cavities on the tablet press. Poor Semaglutide flow rules out the use of direct compression processing (Table 2).

Table 2: Flow properties of three lots of Semaglutide

Pre-Compression Characteristics	Lot-I (D_{90}-11.373 µm)	Lot-II (D_{90} -85.848 µm)	Lot-III (D_{90} -53.220 µm)
Bulk density (g/mL)	0.426	0.251	0.234
Tapped density (g/mL)	0.848	0.410	0.428
Compressibility index (%)	49.76	38.78	45.32
Hausner ratio	1.990	1.633	1.829

Aqueous wet granulation process was preferred in the present study in order to increase the flow properties of the blend. The use of wet granulation method with non aqueous solvent was excluded because of the desire to avoid the environmental considerations involved. Hence, use of wet granulation method with aqueous solvent, purified water, was preferred.

Identification by Fourier Transform Infrared Spectroscopy (FTIR) & Differential Scanning Calorimetry (DSC) studies

Pure Semaglutide API showed distinctive peaks in the following manner (Table 3 and Figure 1):

Table 3: FTIR of Semaglutide with distinctive peaks

Vibrations	Peaks (cm^{-1})
Stretching of N-H bond	3026.64 cm^{-1}
N-H bend	1579.90 cm^{-1}
C-N stretch of alkyl	1107.77 cm^{-1}
Methyl symmetric C–H stretching	2925.62 cm^{-1}
Methyl asymmetric C–H stretching	2888.48 cm^{-1}

C–H bending	790.74 cm^{-1}, 637.87 cm^{-1}(800–600 cm^{-1}) region were characteristic for heterocyclic molecules

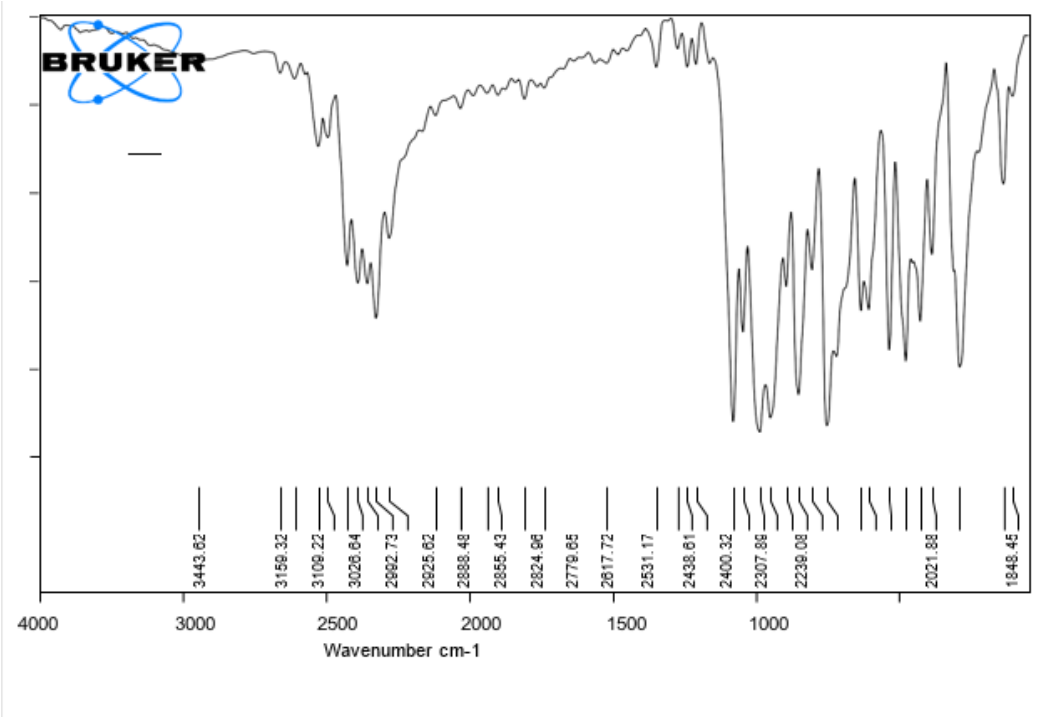

Figure 1: FTIR and DSC of Similitude

Optimization of drug and excipients is mandatory in the development of new dosage forms because an excipient can initiate or propagate or participate in chemical or physical interaction with an active substance. Drug and excipients compatibility study FTIR spectra were shown in the Table 4**.** In all the binary mixtures the characteristic peaks of Semaglutide API were retained. The excipients used were found to be compatible with Semaglutide.

Table 4: Characteristic peaks of Semaglutide and excipients

Characteristic peaks		**Semaglutide API**	**PD+ PVP**	**PD+TRH**	**PD+SSF**	**PD+SiO_2**	**PD+PEO**
stretching of N-H bond	Amine Group	3026.64	3026.23	3030.15	-	3026.98	3024.02
N-H bend		1579.90	1582.84	1580.28	1585.00	1582.13	1580.25
methyl symmetric C–H stretching		2925.62	2920.18	2923.60	2926.40	2927.23	2923.27

Methyl asymmetric C–H stretching		2888.48	2861.28	2891.33	-	2889.67	2887.91
C–H bending bands	Heterocyclic molecule	790.74	789.60	789.73	786.67	789.17	791.46
C–H bending bands		637.87	642.75	635.41	645.53	638.73	637.43

PD = Semaglutide, PVP-Poly vinyl pyrrolidine, TRH = Trehalose dihydrate, SSF = sodium stearyl fumarate, PEO = polyethyleneoxide, SiO_2 = Colloidal silicon dioxide

Solubility studies of Semaglutide API

The solubility of Semaglutide in aqueous media as a function of pH is measured and presented in Table 5.

Table 5: Solubility of Semaglutide in various media with different pH

Media	**Solubility (mg/mL)**
0.1 N HCl	0.955
Acetate buffer (pH 4.5)	0.878
Purified water	0.084
Phosphate buffer (pH 6.8)	0.148
Phosphate buffer(pH 7.4)	0.075

The aqueous solubility of Semaglutide was low and was constant across the physiological pH range due to the lipophilic nature of the molecule. Literature and experimental data support the categorization of Semaglutide is a poorly soluble drugubstance, based on its solubility across various physiological pH values.

DISCUSSION & CONCLUSION

The preformulation assessment of Semaglutide has provided critical insights into its physicochemical characteristics and suitability for development into an extended-release oral dosage form. The particle size distribution of the three Semaglutide API lots revealed significant variation, with Lot-III demonstrating an optimal D90 value of 53.219 µm. This intermediate particle size is conducive to achieving a balance between adequate dissolution and compressibility, which is particularly essential for extended-release formulations. A smaller particle size increases surface area and enhances dissolution but can adversely impact flowability and processing, while a larger size may delay dissolution excessively.

The flow properties of Semaglutide across all three lots were found to be poor, as indicated by high compressibility indices and Hausner ratios. These findings eliminated direct compression

as a viable formulation method. Therefore, aqueous wet granulation was selected to enhance flowability and ensure uniform die filling during tablet compression. This method also aligns with environmental and safety considerations by avoiding organic solvents, while supporting better particle cohesion.

FTIR spectroscopy confirmed the identity of Semaglutide through characteristic peaks corresponding to specific functional groups, such as N–H, C–N, and C–H bonds. More importantly, FTIR and DSC studies revealed no significant interaction between the drug and excipients, as the key functional peaks remained unaltered in the binary mixtures. This confirmed the chemical compatibility and thermal stability of Semaglutide with commonly used excipients, including PVP, trehalose, sodium stearyl fumarate, polyethylene oxide, and colloidal silicon dioxide. Compatibility studies are a crucial component in the development of stable formulations, particularly for peptide-based drugs like Semaglutide, which may be sensitive to processing and storage conditions.

The solubility studies revealed poor aqueous solubility of Semaglutide across all tested pH values, confirming its classification as a poorly soluble drug. The highest solubility was observed in 0.1 N HCl (0.955 mg/mL), while minimal solubility was seen in phosphate buffer pH 7.4 (0.075 mg/mL). This consistent low solubility across the physiological pH range indicates that Semaglutide belongs to the BCS Class II category (low solubility, high permeability). Therefore, formulation strategies aimed at enhancing dissolution, such as incorporation of hydrophilic polymers, solubilizers, or particle size modification, will be critical in ensuring therapeutic bioavailability.

The results of the preformulation studies underscore several formulation challenges and opportunities for Semaglutide. The particle size analysis identified Lot-III as the optimal candidate due to its balanced particle size suitable for sustained release. Poor flowability ruled out direct compression, justifying the selection of aqueous wet granulation. FTIR and DSC studies confirmed that there were no significant interactions between the API and selected excipients, supporting formulation stability. Solubility studies emphasized the need for formulation approaches that enhance dissolution to address Semaglutide's poor aqueous solubility.

These findings collectively provide a robust foundation for the rational design of an extended-release tablet formulation of Semaglutide. Future development should focus on modifying the release kinetics through matrix-forming agents or advanced delivery technologies to achieve consistent drug release, enhanced bioavailability, and improved patient compliance in the management of type 2 diabetes mellitus.

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