RESEARCH ARTICLE

Development and Characterization of Modified Release Dosage Form Utilizing Semaglutide

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ABSTRACT

An agonist of the glucagon-like peptide-1 (GLP-1) receptor, semaglutide, when administered as a pure medication solution, has a significant degree of variability in bioavailability due to its low solubility and low permeability. This variability is reflected in the wide range of plasma concentration values (5.85–38.14), affecting its therapeutic effectiveness. The present study aimed to develop and characterize a modified-release dosage form (FPR-8) to enhance the pharmacokinetic profile of Semaglutide by ensuring controlled and sustained drug release over 24 hours, thereby reducing fluctuations in plasma concentration and improving bioavailability. The optimized formulation FPR-8 was developed and evaluated for its drug release profile, pharmacokinetic parameters, and in vivo performance in animal models. The improved formulation's plasma concentration values were contrasted with those of a pure drug solution. Administration of FPR-8 resulted in significantly reduced variability in plasma concentration values (4.12–19.46) compared to the pure drug suspension. The controlled-release formulation facilitated slow and gradual absorption, ensuring prolonged systemic circulation of Semaglutide over 24 hours. This sustained-release effect contributed to enhanced bioavailability and reduced fluctuations, addressing the limitations associated with the pure drug's pharmacokinetic profile. The development of a modified-release dosage form (FPR-8) successfully optimized the pharmacokinetic behavior of Semaglutide, ensuring consistent absorption, prolonged circulation, and reduced intersubject variability. This approach holds promise for improving therapeutic efficacy and patient compliance in the clinical use of Semaglutide.

Keywords: Semaglutide, modified-release formulation, bioavailability, pharmacokinetics, sustained release, drug absorption.

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INTRODUCTION

One of the most popular medications for type 2 diabetes mellitus (T2DM) is semaglutide, an agonist of the glucagon-like peptide-1 (GLP-1) receptor. It helps control blood sugar levels and encourages weight reduction. Its poor permeability and solubility, which lead to uneven plasma drug concentrations and significant bioavailability fluctuation, restrict its therapeutic potential. Conventional formulations of Semaglutide often lead to rapid drug elimination, necessitating frequent dosing, which can impact patient adherence and overall treatment efficacy.[1-3] Modified-release drug delivery systems have been investigated as a viable tactic to enhance semaglutide's pharmacokinetic profile in order to overcome these difficulties. Longer systemic drug exposure, fewer doses, and improved patient compliance can all be attained by creating a controlled-release dosage form. In order to minimize variations in plasma drug levels and enhance bioavailability, the current study intends to create and describe an optimal modified-release formulation (FPR-8) of semaglutide that guarantees continuous drug release over a 24-hour period.[4-5] Semaglutide is extracted from plasma samples, an *in vivo* assessment of the pharmacokinetic characteristics of the improved formulation is conducted, and an analytical technique for quantifying Semaglutide in rat plasma with the use of HPLC is done. Comparative bioavailability study between the developed formulation and a conventional drug suspension highlights the benefits of a sustained-release system in enhancing therapeutic efficacy. This research contributes to the advancement of Semaglutide-based therapy by offering an improved dosage form with better pharmacokinetic stability and clinical utility.

MATERIALS AND METHODS

Materials

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

Methods

Extended Release Tablets Preparation

The wet granulation method was used to create the Semaglutide extended release tablets. Polyethylene oxide was used as a rate-retarding polymer and trehalose dihydrate as a diluent. The granulating agent was a 15% w/w solution of polyvinylpyrrolidone (PVP-K30) in water.

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Table 1: Semaglutide formulation details

Formulation	Ingredients (mg per tablet)					
	Semaglutide	PEO	Trehalose dihydrate	PVP K 30 (Plasdone K 29/32)	Colloidal Silicon dioxide (Aerosil 200)	Sodium stearyl fumarate
FP-1	50	30 (WSR N-750)	93	20	5	2
FP-2	50	40 (WSR N-750)	83	20	5	2
FP-3	50	50 (WSR N-750)	73	20	5	2
FP-4	50	30 (WSR N-60K)	93	20	5	2
FP-5	50	40 (WSR N-60K)	83	20	5	2
FP-6	50	50 (WSR N-60K)	73	20	5	2
FP-7	50	30 (WSR 301)	93	20	5	2
FP-8	50	40 (WSR 301)	83	20	5	2
FP-9	50	50 (WSR 301)	73	20	5	2
FP-10	50	30 (WSR coagulant)	93	20	5	2
FP-11	50	40(WSR coagulant)	83	20	5	2
FP-12	50	50(WSR coagulant)	73	20	5	2

Sodium stearyl fumarate was utilized as a lubricant and colloidal silicon dioxide as a glidant.[6]

Procedure

PVP-K 30 was dissolved in filtered water while being constantly stirred to provide a transparent solution with a 15% w/w binder concentration. The accurately weighed pure drug, rate retardant polymer, and trehalose dihydrate were sifted through an ASTM #20 mesh and manually blended for ten minutes to ensure uniform mixing. The binder solution was then added to this dry mixture, and the resulting wet mass was then run through an ASTM #18 screen to produce homogeneous granules. After being wet, the granules were dried in a tray dryer at 45 ± 5°C using an infrared moisture analyzer set to auto mode at 60°C. The process was continued until the loss on drying (LOD) was below 1.0% w/w. After being dried, the granules were moved to a polyethylene bag and sieved through an ASTM #25 screen. Colloidal silicon dioxide and sodium stearyl fumarate were sifted separately through ASTM #30 and ASTM #60 meshes, respectively. The dried granules were blended with colloidal silicon dioxide for 10 minutes, followed by the addition of sifted sodium stearyl fumarate, and further blended in a polybag for 5 minutes to achieve uniform lubrication. To form the tablets, the final mixture was compressed using a 16-station rotary tablet punching machine from M/s Cadmach in India. The machine had round punches with concave faces that measured 9 mm. No adherence was observed during compression, indicating homogeneous lubrication of the blend. To regulate the dosage, researchers used polyethylene oxide of several viscosities, including PEO WSR N-750, PEO WSR N-60K, PEO WSR-301, and PEO WSR Coagulant. Prior to their post-compression and in vitro dissolving assessments, formulations such as PEO WSR N-750 were developed. In light of these findings, further formulations were made using other PEO grades (Three PEO WSR models: WSR-301, PEO WSR N-60K, and PEO WSR Coagulant) at 15%, 20%, and 25% concentrations in order to examine their effects on drug release behavior.[6-9]

Pre compression characteristics

The bulk density, tapped density, and compressibility index of the matrix granules were measured before compression.

Evaluation of Extended Release Tablets

Tests were conducted on the tablets to determine their in vitro drug release, hardness, friability, and weight uniformity.

Verification of uniformity of weight, thickness and hardness

Twenty pills were chosen at random to ensure weight uniformity. An electronic digital balance (Citizen, India) was used to weigh each of the 20 tablets both collectively and separately. The percentage deviations and mean were calculated. If the percentage difference between the average

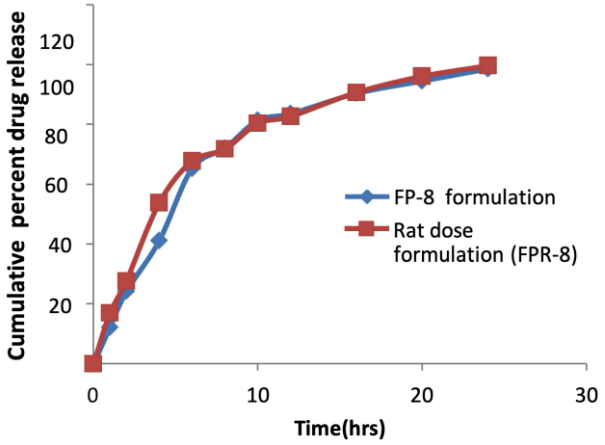

Figure 1: Comparative dissolution profile of FP-8 and FPR-8 formulations

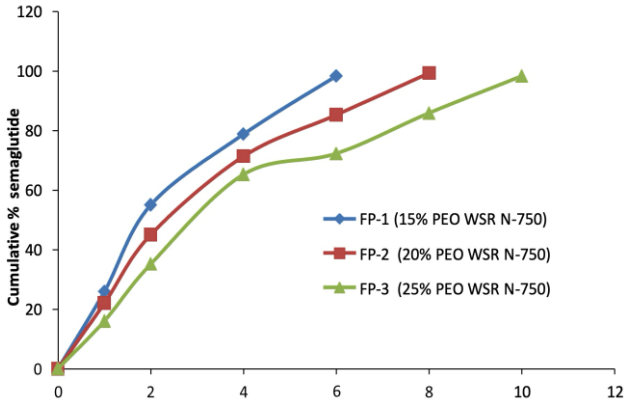

Figure 2: Dissolution of Semaglutide extended release tablets containing PEO WSR N-750 at various proportions

Table 2: Composition and post compression characteristics of Semaglutide Rat dose formulation (FPR-8)

Formulation Ingredients (mg per tablet)	FPR-8
Semaglutide	5
PEO WSR 301	3
Trehalose dehydrate	9.3
PVP K 30 (Plasdone K 29/32)	2
Purified Water	Q.S
Colloidal Silicon dioxide (Aerosil 200)	0.5
Sodium stearyl fumarate	0.2
Total Weight (mg)	20
Post compression characteristics of tablets	
Friability (%)	0.65
Assay (%)	98.5±0.5
Mean Thickness (mm)	1.2±0.05
Hardness (Kg cm^{-2})	6.3±0.7
Uniformity of weight (mg)	20.6±0.9

Table 3: Comparative dissolution profile of FP-8 formulation and Rat dose formulation (FPR-8)

Dissolution time(hr)	FP-8 formulation	Rat dose formulation (FPR-8)
0	0	0
1	12.15	16.94
2	24.22	27.66
4	41.14	53.83
6	65.31	67.78
8	72.12	71.77
10	81.41	80.44
12	83.59	82.73
16	90.38	90.71
20	94.51	96.12
24	98.58	99.68
Similarity factor	66.56	

weight and any two individual weights is less than or equal to the percentages given below, then the produced tablets are considered to pass the test (IP 2007-Uniformity of weight).

Every batch was evaluated by measuring the thickness of six tablets using digital vernier calipers.(Mitutoyo Corporation, Kaisaki, Japan); the results were reported in millimeters. Average values and standard deviations were computed and presented using each of these individual data. Using an Electrolab hardness tester, the hardness (Banker GS and Anderson NR) of six tablets with known weight and thickness was determined. The results were expressed in kg/cm^2.

Friability (IP 2007-Friability)

Randomly selected tablets weighing 6.5 grams from each batch were subjected to a friability test. Following dedusting, the tablets were put in a revolving drum and the starting weight (Wo) was noted. They were subjected to 100 rotations at a height of 6 inches at a speed of 25 rpm for a duration of 4 minutes using a friability test instrument manufactured by Electro Lab in Mumbai, India. After each dose, the tablets were reweighed (W) to get the final weight. To find the percentage of friability, we divided the weight loss before and after the revolutions by 100%. Then, we applied the following formula.: Percentage Friability = $(1 - W/Wo) \times 100$.[10]

Assay by HPLC

Chromatographic conditions and mobile phase were as per the procedure described

Preparation of standard stock solution

This material was dissolved by carefully measuring 50 mg of semaglutide into a 50 mL volumetric flask, adding 20 mL of methanol, and then subjecting the mixture to sonication. Lastly, methanol was used to get the amount up to 50 mL.

Preparation of standard solution

Five milliliters of the standard stock solution were added to a 100 milliliter volumetric flask, well mixed, and brought to volume using the mobile phase. The drug's concentration in this solution was 50 µg/mL.

Preparation of sample solution

Each batch consisted of twenty tablets, which were then triturated in a mortar. A 50 mL volumetric flask was filled with powder that weighed 50 mg. After adding 20 milliliters of methanol, the liquid was subjected to a 15-minute sonication (Remi, India). The sample solution was filtered using 0.45µ filter paper after 50 mL of methanol was added. A 100 mL volumetric flask was filled with the aforementioned solution after 5 mL was added. The volume was then adjusted with the mobile phase.

Procedure

Chromatograph received two injections of sample solutions, five duplicate injections of standard solutions, and 10 µL of diluent. Peak responses were measured and the chromatograms were recorded.[10-11]

System suitability

Consistency in the analytical procedure is ensured when the relative standard deviation of five duplicate injections of standard solutions does not exceed 2%. Additionally, the tailing factor of the Semaglutide peak must be no more than 2% to maintain peak symmetry and accuracy. The assay percentage of Semaglutide is determined using the formula: % Assay = (AT / AS) × (WS / WT) × (DT / DS) × (P / 100) × (AW / LC) × 100, where AT represents the peak area of Semaglutide in the sample solution, AS is the average peak area of Semaglutide in the standard solution, WS is the weight of the Semaglutide standard taken (mg), and WT is the weight of the Semaglutide sample taken (mg). DS and DT represent the dilution factors of the standard and test solutions, respectively, while P indicates the potency of Semaglutide on an as-is basis. Finally, AW refers to the average tablet weight, and LC corresponds to the label claim. This formula ensures accurate quantification of Semaglutide content in the sample, ensuring compliance with analytical standards.[12]

In vitro drug dissolution studies

Using 900 mL of suitable dissolving fluid kept at 37 ± 0.5ºC at 50 RPM for 24 hours, in vitro dissolution tests were

Table 4: Composition and pre and post compression characteristics of tablets of Semaglutide with PEO WSR N-750

Formulation Ingredients	FP-1	FP-2	FP-3
Semaglutide	50mg	50 mg	50 mg
PEO WSR N-750	30 mg	40 mg	50 mg
Trehalose dehydrate	93 mg	83 mg	73 mg
PVP K 30 (Plasdone K 29/32)	20 mg	20 mg	20 mg
Purified water	Q.S	Q.S	Q.S
Colloidal Silicon dioxide (Aerosil 200)	5 mg	5 mg	5 mg
Sodium stearyl fumarate	2 mg	2 mg	2 mg
Total Weight	200 mg	200 mg	200 mg
Pre compression characteristics			
Loose bulk density (g/mL)	0.25 ± 0.3	0.27 ± 0.2	0.26 ± 0.1
Tapped bulk density (g/mL)	0.31 ± 0.1	0.34 ± 0.1	0.31± 0.2
CI value (%)	19.4 ± 1.5	20.6 ± 1.1	16.1 ± 2.1
Post compression characteristics of tablets			
Friability[a] (%)	0.3	0.2	0.5
Assay[b] (%)	99.1± 0.1	99.8 ± 0.3	100.9 ± 0.2
Mean Thickness[c] (mm)	3.1 ± 0.05	3.0 ± 0.04	2.9 ± 0.04
Hardness[d] (Kg cm^{-2})	5.5 ± 0.3	5.6 ± 0.2	6.0 ± 0.1
Uniformity of weight[e] (mg)	202 ± 1.6	199 ± 2.0	200 ± 0.8

a: mean ± % deviation, n=33; b: mean ± S. D, n=20 c: mean ± S. D, n=6; d: mean ± S. D, n=6; e: mean ± S. D, n=20

conducted in a USP Type II (Paddle) dissolution test equipment (Electro lab, TDT-08L, India). Initial 2 hours dissolution study was performed in pH 1.2 hydrochloric acid (0.1N HCl) and the remaining time in a solution of phosphate buffer media of pH 6.8 (United States Pharmacopeial Conventions. 2011). Five milliliter aliquots of the samples were taken out of the medium at predetermined intervals of one, two, four, six, eight, ten, twelve, sixteen, twenty, and twenty-four hours. After passing them through a 0.45 µ filter, the identical amount of brand-new media was utilized in their stead. Samples were analyzed by HPLC and from these values the percentage drug release was calculated. Three tablets were used for each formulation's dissolution. The chromatograph was filled with five replicates of the standard solution and 10 µL of samples. Chromatograms were taken, and measurements were made of the peak responses.[10]

Dissolution parameters

Dissolution apparatus parameters were set as mentioned and the dissolution apparatus was operated. Samples of five mL solution were withdrawn at specific time intervals mentioned, from each dissolution jar. Using a 0.45 µ filter, the solutions were filtered. The approach used was in accordance with the HPLC protocol outlined in the preceding sections.

Standard

Dissolution Medium: 0.1N HCl; Volume: 900 mL: Temperature: 37°C ±0.5°C; Apparatus: USP Type II (Paddle); Time (Hours): 1 hours & 2 hours

Test

Dissolution Medium: 6.8 pH phosphate buffer; Volume: 900 mL; Temperature: 37°C ±0.5°C; Apparatus: USP Type II (Paddle); Time (Hours): 4, 6, 8, 10,12, 16, 20 and 24 hours

Ten microliters each of the standard and sample solutions were extracted and fed into the HPLC apparatus at predetermined intervals. The concentration of semaglutide in the sample was determined by recording the chromatograms. To know % of dissolved semaglutide:

(AT / AS) × (WS / DS) × (900 / LC) × (P / 100) × 100 is the percentage of semaglutide dissolved.

The sample solution's peak area of semaglutide is denoted by AT, while the standard solution's peak area is denoted by AS. P stands for the Semaglutide working standard's purity in its unaltered state, whereas WS represents the weight of the standard measured in milligrams. LC is the dosage

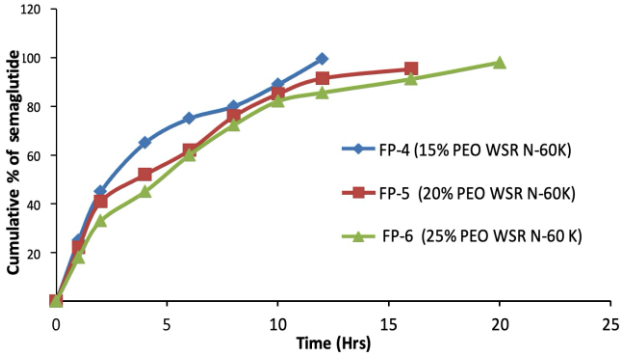

Figure 3: First Order plot for Semaglutide extended release tablets containing PEO WSR N-60K

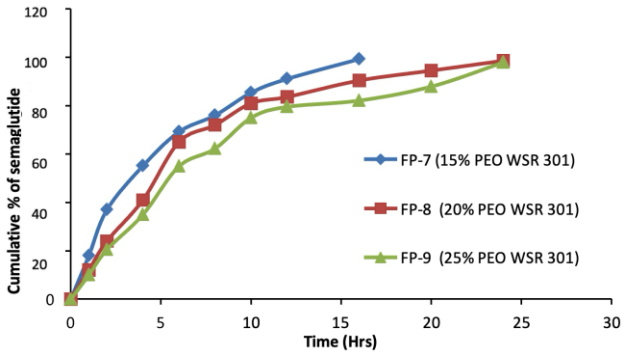

Figure 4: Dissolution of Semaglutide from extended release tablets containing PEO WSR 3

Table 5: *In vitro* dissolution of matrix systems with PEO WSR N-750 as a polymer (Mean ± S.D, n=3) in 0.1 N HCl with pH 6.8 phosphate buffer

Time (Hours)	Cumulative %drug release		
	FP-1	FP-2	FP-3
0	0	0	0
1	25.87 ± 3.6	29.11 ± 3.4	16.23± 1.6
2	53.24 ± 4.6	51.43 ± 4.8	35.13 ± 2.2
4	78.65 ± 2.8	74.21 ± 5.3	65.19 ± 2.6
6	98.21 ± 4.2	85.43 ± 2.8	72.22 ± 3.3
8	--	97.38 ± 3.3	85.79 ± 3.2
10	--	--	98.17 ± 1.2
12	--	--	--
16	--	--	--
20	--	--	--
24	--	--	--

form's label claim. This calculation ensures an accurate determination of the percentage of Semaglutide dissolved in the dissolution study, helping to evaluate the drug release profile and ensure compliance with regulatory standards.[10-12]

Comparison of dissolution data

To quantify the observed variation in the rate and quantity of drug release caused by formulation and process factors, dissolution data were quantitatively compared. Both model independent and model dependent techniques were used to accomplish this.

Stability studies

In accordance with ICH requirements, stability experiments were conducted on the optimized formulation. FTIR analyses were performed on the optimized formulation both before and after stability tests. For 180 days, the optimized formulation was maintained at accelerated temperatures (40± 2ºC/75± 5% RH) in an aluminum foil that was hermetically sealed and bonded with polyethylene. Long-term stability samples were kept at 25± 2ºC/60±5%. At certain intervals, samples were assessed for FTIR research, drug content, drug release, and other physicochemical characteristics.[6]

Modification of optimized formulation FP-8 to dose of a Rat

Results from in vitro investigations performed in this research project informed the selection of the FP-8 formulation for pharmacokinetic (PK) tests. The PK study was designed to be carried out on rats, as administering the human dose to rats is not feasible. To ensure appropriate dosing, the drug dose for rats was calculated to be approximately one-tenth of the human dose. Accordingly, it was planned to formulate and produce a Semaglutide dosage suitable for rats at a reduced concentration. This study involved several key steps, including calculating the required Semaglutide dose for rats, developing and producing the reduced-dose formulation, evaluating its physicochemical properties and dissolution profile, and finally conducting pharmacokinetic studies to assess its absorption, distribution, metabolism, and elimination. These steps were essential to ensure the suitability of the formulation for PK evaluation in animal models before further studies.[7,13]

Rat dose calculation

The rat dose of Semaglutide was calculated using the human dose and species-specific Km values, which are derived from body weight and SA. Rat dosage (mg/kg) equals human dose (mg/kg) multiplied by (Human Km / Rat Km), according to the formula employed. Substituting the values, (50/60) × (37/12) = 2.58 mg/kg, determining the appropriate dose for rats. This adjustment ensures accurate preclinical evaluation before human trials.[7,14]

Formulation and evaluation of FPR-8

Rat dose formulation prepared and evaluated the details of composition and physicochemical evaluation tests are provided**.** Similarity factor was found to be 66.56 for the optimized FPR-8 and Rat dose formulation. Hence, this Rat

Table 6: Composition pre and post compression characteristics of Semaglutide tablets with PEO WSR N-60K

Formulation Ingredients	FP-4	FP-5	FP-6
Semaglutide	50	50	50
PEO WSR N-60K	30	40	50
Trehalose dehydrate	93	83	73
PVP K 30 (Plasdone K 29/32)	20	20	20
Purified water	Q.S	Q.S	Q.S
Colloidal silicon dioxide (Aerosil 200)	5	5	5
Sodium stearyl fumarate	2	2	2
Total Weight (mg)	200	200	200
Pre compression characteristics			
Loose bulk density (g/mL)	0.27 ± 0.2	0.28 ± 0.2	0.29 ± 0.1
Tapped bulk density (g/mL)	0.33 ± 0.2	0.35 ± 0.1	0.33± 0.3
CI value (%)	18.2 ± 1.3	20.0 ± 1.2	12.1 ± 1.6
Post compression characteristics of tablet			
Friability[a] (%)	0.2	0.4	0.35
Assay[b] (%)	98.5± 0.1	99.4 ± 0.6	99.9 ± 0.3
Mean thickness[c] (mm)	3.0 ± 0.05	2.9 ± 0.03	3.0 ± 0.06
Hardness[d] (Kg cm^{-2})	5.6 ± 0.3	5.8 ± 0.2	6.1 ± 0.2
Uniformity of weight[e] (mg)	201 ± 1.1	203 ± 0.4	198 ± 0.6

a: mean ± % deviation, n=33; b: mean ± S. D, n=20 c: mean ± S. D, n=6; d: mean ± S. D, n=6; e: mean ± S. D, n=20

Table 7: *In vitro* dissolution of matrix systems with PEO WSR N-60K (Mean ± S.D, n=3) in 0.1 N HCl with pH 6.8 phosphate buffer

Time (Hours)	Cumulative %drug release		
	FP-4	FP-5	FP-6
0	0	0	0
1	24.96 ± 3.6	22.11 ± 2.4	17.79± 1.3
2	44.89 ± 4.6	40.23 ± 2.8	33.11 ± 2.1
4	64.77 ± 2.8	52.32 ± 3.3	44.67 ± 1.6
6	74.92 ± 4.2	62.19 ± 1.6	60.13 ± 3.2
8	79.76 ±3.1	75.88 ± 0.9	72.32 ± 3.2
10	88.78 ± 1.8	85.21 ± 0.9	82.15 ± 1.1
12	97.52 ± 2.2	91.62 ± 1.8	85.61 ± 1.9
16	--	95.41 ± 2.5	91.22 ± 3.5
20	--	--	98.22 ± 2.3
24	--	--	--

dose formulation was to be similar to the optimized formulation. Hence, it was taken up for the pharmacokinetic study.

RESULTS AND DISCUSSION

Evaluation of Semaglutide extended release tablets with polyethylene oxide (PEO) WSR N-750

FP-1, FP-2, and FP-3 were the first designations for extended-release tablets made with low-viscosity grade PEO WSR N-750 (molecular weight 300,000) in varying concentrations (15, 20%, and 25%). Matrix granules and tablets were tested for pre- and post-compression qualities; the ranges for TBD and LBD values were 0.31 ± 0.1 to 0.34 ± 0.1 g/mL and 0.25 ± 0.3 to 0.27 ± 0.2 g/mL, respectively. Compressibility index (CI) ranged from 16.1 ± 2.1 to 20.6 ± 1.1, indicating superior flow properties compared to Semaglutide API. The hardness of the tablets was 5.5 ± 0.3 to 6.0 ± 0.1 kg/cm², with a thickness of 2.9 ± 0.04 to 3.1 ± 0.05 mm, drug content of 99.1 ± 0.1 to 100.9 ± 0.2%, and friability below 1%. These findings confirm that all prepared tablets met the required quality control standards.

In vitro dissolution studies

A minimum of three items should be included in the dissolution criterion for modified-release formulations, excluding delayed-release formulations. After an hour or two of testing, or at a dissolved level of 20 to 30 percent of the prescription material as labeled, the first limit should be established to avoid dosage dumping. The second restriction should be established at about 50% release of the drug ingredient that is labeled in order to characterize the dissolving pattern. The ultimate limit, which is typically considered to be 80%, is specified to assure (nearly) quantitative medication release. As a result, the quality control dissolving run should be prolonged until at least 80% of the medication material has been dissolved. Shorter test periods could be suitable in some circumstances; nevertheless, they should last at least 24 hours and be backed by an in vitro-in vivo comparative studyCase-by-case decisions regarding the acceptable dissolution pattern at the specified time intervals should be made after considering the in vitro-in vivo comparison study, the capability of the manufacturing process, and the generally accepted range of 95 to 105% for the average drug substance content. 0.1N HCl was used for the first two hours of drug dissolving experiments in two different media, and phosphate buffer with a pH of 6.8 was used for the remaining period. Within 10 hours, the total percentage of medication release for all three formulations was around 98% (Table 5 and Figure 2). In two hours, all of these formulations displayed burst release, with above 30% release. Surface erosion or the extended release tablet's early disintegration before the gel layer forms around the tablet core might be the cause of this event. According to published research, a medication release of over 30% within the first two hours of dissolution suggests the potential for dosage dumping. Additionally, there was no discernible

Table 8: Composition pre and post compression characteristics of Semaglutide tablets with PEO WSR 301

Formulation Ingredients	FP-7	FP-8	FP-9
Semaglutide	50mg	50 mg	50 mg
PEO W SR 301	30 mg	40 mg	50 mg
Trehalose dehydrate	93 mg	83 mg	73 mg
PVP K 30 (Plasdone K 29/32)	20 mg	20 mg	20 mg
Purified water	Q.S	Q.S	Q.S
Colloidal silicon dioxide (Aerosil 200)	5 mg	5 mg	5 mg
Sodium stearyl fumarate	2 mg	2 mg	2 mg
Total Weight	200 mg	200 mg	200 mg
Pre compression characteristics			
Loose bulk density (g/mL)	0.29 ± 0.1	0.30 ± 0.3	0.31 ± 0.1
Tapped bulk density (g/mL)	0.36 ± 0.4	0.34 ± 0.2	0.35 ± 0.4
CI value (%)	19.4 ± 1.5	11.8 ± 1.2	11.4 ± 1.4
Post compression characteristics of tablets			
Friability[a] (%)	0.6	0.35	0.42
Assay[b] (%)	99.8± 0.3	100.4 ± 0.6	99.5 ± 0.2
Mean thickness[c] (mm)	3.1 ± 0.01	3.0 ± 0.04	3.1 ± 0.08
Hardness[d] (Kg cm^{-2})	5.9 ± 0.8	6.2 ± 0.4	6.0 ± 0.6
Uniformity of weight[e] (mg)	198 ± 2.5	201 ± 0.6	199 ± 0.5

a: mean ± % deviation, n=33; b: mean ± S. D, n=20 c: mean ± S. D, n=6; d: mean ± S. D, n=6
e: mean ± S. D, n=20

Table 9: *In vitro* dissolution of matrix systems with PEO WSR 301 as a polymer (Mean ± S.D, n=3)

Time (Hours)	Cumulative % drug release		
	FP-7	FP-8	FP-9
0	0	0	0
1	23.12 ± 2.5	12.15±3.4	10.14± 1.6
2	34.23 ± 4.4	24.22±2.6	20.51 ± 1.1
4	55.24 ± 3.8	41.14±1.8	35.17 ± 1.8
6	69.29 ± 2.9	65.31±1.9	55.23 ± 3.1
8	76.12 ± 3.4	72.12±3.4	62.28 ± 2.2
10	85.49 ± 2.6	81.41±3.1	75.13 ± 1.8
12	95.18 ± 0.6	83.59±2.6	79.59 ± 1.6
16	97.37 ± 0.7	90.38±1.8	85.21 ± 2.5
20	--	94.51±1.4	92.12± 2.6
24	--	98.58±1.6	98.45 ± 1.8

impact on medication dissolution by further increasing the PEO WSR N-750 mix. Therefore, using a larger molecular weight of PEO was seen to be more prudent than increasing the amount of a low molecular weight polymer in order to achieve tablet integrity and the intended release profile.

Preparation and evaluation of Semaglutide extended release tablets with polyethylene oxide (PEO) WSR N-60 K

Since the formulations F1 to F3 could not give the required release profile formulations F4 to F6 were designed with a PEO of higher molecular weight (MW 2,00,000). Extended-release tablets known as FP-4, FP-5, and FP-6 were created with high viscosity grade PEO WSR N-60K (MW 20,00,000) in varying amounts (15, 20%, and 25%). A variety of post-compression properties were assessed for matrix granules and tablets. Table 6 shows the composition and post-compression properties of tablets and granules.

For TBD, the range was 0.33 ± 0.2 to 0.35 ± 0.1 g/mL; for LBD, it was 0.27 ± 0.2 to 0.29 ± 0.1 g/mL. The compressibility index (CI) readings fell between 12.1 ± 1.6 to 18.2 ± 1.3. These findings demonstrated that granules' flow characteristics and CI values outperformed those of API.

The tablets' mean thickness ranged from 2.9 ± 0.03 to 3.0 ± 0.06 mm, their hardness ranged from 5.6 ± 0.3 to 6.1 ± 0.2 kg/cm2, their percentage of drug content ranged from 98.5 ± 0.1 to 99.9± 0.3, and their friability was less than 1%. According to these findings, every pill that was made fell within the necessary quality control ranges.

In vitro dissolution studies

After 12 and 16 hours of dissolution, the cumulative percent drug release values from FP-4 and FP-5 (Table 7 and Figure 3) were 97.52% and 95.41%, respectively. The results show that because the polymer is less viscous, medication release occurs more quickly. Over 20 hours, FP-6 released 98.22% of the medication. Despite a steady medication release over 20 hours, all of these formulations demonstrated more than 30% release in 2 hours, indicating burst release. The medication release increased from 12 hours to 20 hours when the polymer concentration rose from 15% to 25%.

These findings demonstrate that the rate of semaglutide release falls as the polymer fraction rises. As a result, the drug to polymer ratio and viscosity grade both affect drug release. The drug release from these three formulations is uncontrollable for up to 24 hours. As compared to previous formulations, these formulations showed more extended release.

Preparation and evaluation of Semaglutide extended release tablets with polyethylene oxide (PEO) WSR 301

Formulations F3 to F6 did not meet the specification limits of dissolution and also release was not controlled upto 24 hours, so further formulations were prepared with higher molecular weight 4,00,000 PEO. The FP-7, FP-8, and FP-9 extended release tablets were made with varying amounts of high viscosity grade PEO WSR 301 (MW is 40,00,000) and numbered accordingly: FP-7, FP-20, and FP-25. Matrix granules and tablets were evaluated for various pre and post compression characteristics. The composition, pre and post compression characteristics were depicted in the Table 8. The range of findings for TBD was 0.34 ± 0.2 to 0.36 ± 0.4 g/mL, whereas for LBD it was 0.29 ± 0.1 to 0.31 ± 0.1 g/mL. The results of compressibility index (CI) values were in the range from 11.4 ± 1.4 to 19.4 ± 1.5. These results point out that flow properties of granules were superior to those of the API. The tablet hardness values varied from 5.9 ± 0.8 to 6.2 ± 0.4 kg/cm2, the mean thickness values reached 3.0 ± 0.04 to 3.1 ± 0.08 mm, and the percentage of medication content varied from 99.5 ± 0.2 to 100.4 ± 0.6. There was less than 1% friability. The findings show that every single pill that was made was within the specified quality control limits.

In vitro dissolution studies

Formulation FP-7 released 97.4% of the drug after 16 hours, whereas formulations FP-8 and FP-9 released 98.6% and 98.5% of the drug, respectively, after 24 hours of dissolution (Table 9 and Figure 4). All the extended release tablets prepared were found to be non disintegrating in both dissolution media. The rate and extent of drug release are significantly reduced when the viscosity and fraction of PEO polymer rise [10].

There was no burst release with formulations FP-8 and FP-9, as evidenced by less than 30% drug release in 2 hours. These findings demonstrate that the rate of semaglutide release falls as the polymer fraction rises. Drug release is therefore influenced by both the drug to polymer ratio and the polymer grade. Up to 24 hours of slow and progressive medication release were provided by these two formulations.

CONCLUSION

The present study successfully developed and characterized a modified-release formulation (FPR-8) of Semaglutide, addressing the challenges associated with its low solubility and permeability. The optimized formulation demonstrated controlled and sustained drug release over 24 hours, reducing fluctuations in plasma concentration and improving bioavailability compared to the conventional drug suspension. Pharmacokinetic evaluation revealed that the mean peak plasma concentration (Cmax) of the optimized formulation was slightly lower than that of the drug suspension, but the overall drug exposure (AUC) was significantly higher, indicating improved systemic absorption and prolonged residence time. The effectiveness of the modified-release system in improving medication absorption was further shown by the fact that the relative

bioavailability of the modified formulation was 2.44 times higher than that of the pure drug solution. The sustained-release effect of FPR-8 ensured a gradual and consistent absorption profile, reducing intersubject variability and maintaining therapeutic plasma drug levels over an extended duration. Potential clinical benefits of this controlled-release strategy for the treatment of type 2 diabetes mellitus include decreased dosage frequency, better patient adherence, and improved therapeutic results. Conclusion says, the development of a modified-release dosage form of Semaglutide presents a promising strategy to optimize its pharmacokinetic profile, improve bioavailability, and ensure prolonged drug action. Further clinical investigations are warranted to validate the formulation's efficacy and safety in human subjects, paving the way for its potential application in diabetes management.

REFERENCES

1. Maharjan R, Lim DS, Baik HJ, Park HE, Kim MS, Kim KH, Jeong SH. Preparation of semaglutide long-acting injectable microcapsules with physicochemical properties, long-term stability, and pharmacokinetics and pharmacodynamics. J Pharm Investig. 2024;54(5):667–81.
2. Alhashem G, Raghif ARA, Abbas AA. The Effects of Liraglutide on Biochemical Markers of Bone Turnover in Rats Treated by Dexamethasone. International Journal of Drug Delivery Technology. 2022;12(2):598-602.
3. Zeng H, Song J, Li Y, Guo C, Zhang Y, Yin T, et al. Effect of hydroxyethyl starch on drug stability and release of semaglutide in PLGA microspheres. Int J Pharm. 2024;654:123991.
4. Bhavani MS, Saravanan R. Beyond Syringes and Pills: Advances in Drug Delivery Systems for Diabetes. International Journal of Drug Delivery Technology. 2023;13(3):1069-1077.
5. Manasa M, Aanandhi VM. Stability indicating method development and validation of semaglutide by RP-HPLC in pharmaceutical substance and pharmaceutical product. Res J Pharm Technol. 2021;14(3):1385–9.
6. Barzeh H, Sogali BS, Shadvar S. A review on extended release matrix tablet. J Pharm Res. 2016;15(4):147–52.
7. Huang YB, Tsai YH, Yang WC, Chang JS, Wu PC, Takayama K. Once-daily propranolol extended-release tablet dosage form: formulation design and in vitro/in vivo investigation. Eur J Pharm Biopharm. 2004;58(3):607–14.
8. Gunde MC, Jambulkar AD, Suruse PB. Formulation and Evaluation of Extended-release Capsule of Propranolol Hydrochloride. International Journal of Drug Delivery Technology. 2022;12(3):1282-1285.
9. Mansour NM, El-Masry AA, El-Sherbiny DT, Moustafa MA. Blueness, Whiteness, and greenness Appraisal of sensitive chromatographic approach for determination of semaglutide concurrently with Pioglitazone and metformin using green mobile phase; alongside with pharmacokinetic study. Microchem J. 2024;207:111686.
10. Indian Pharmacopoeia Commission. Indian Pharmacopoeia. 8th ed. Vol. 1. Ghaziabad: Indian Pharmacopoeia Commission; 2018.
11. Wang B, Su Z, Kuang M, Luo Y, Xu M, Sun M, et al. Chitosan hydrochloride coated and nonionic surfactant modified niosomes: a better way for oral administration of semaglutide. Biomed Mater. 2025.
12. Bairagee D, Verma P, Jain N, Jain N. Fabrication and in vitro characterization of Niosomal formulations for controlled delivery of ranitidine HCl. Lat Am J Pharm. 2022;41(1):85–91.
13. Lewis AL, McEntee N, Holland J, Patel A. Development and approval of Rybelsus (oral semaglutide): ushering in a new era in peptide delivery. Drug Deliv Transl Res. 2022;12(1):1–6.
14. Yang W, Gadgil P, Krishnamurthy VR, Landis M, Mallick P, Patel D, et al. The evolving druggability and developability space: chemically modified new modalities and emerging small molecules. AAPS J. 2020;22:1–14.