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DEVELOPMENT AND CHARACTERIZATION OF GASTRO-RETENTIVE MUCOADHESIVE MICROSPHERES LOADED WITH ANTI DIABETIC DRUG BY USING SUITABLE POLYMER

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ABSTRACT

Vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, possesses a short half-life and low protein binding, necessitating frequent dosing. To address this limitation, this study aimed to develop and evaluate gastro-retentive mucoadhesive microspheres of Vildagliptin using the ionic gelation method. The objective was to prolong the drug's retention time in the gastrointestinal tract, thereby maintaining steady plasma levels and enhancing bioavailability while reducing dosing frequency. Microspheres were prepared and characterized for physicochemical properties, including FT-IR, DSC, mucoadhesive wash-off, drug content, drug release, SEM, and stability studies. Results demonstrated no significant drug-polymer interaction and showed drug content ranging from 86% to 93%, with entrapment efficiency between 88% and 95%. In vitro drug release varied from 77% to 89% over 12 hours, indicating effective sustained release. These findings suggest that the prepared microspheres are a promising deliverysystem for Vildagliptin. The ionic gelation method offers a viable approach for once-daily dosing, improving therapeutic outcomes in the management of type 2 diabetes mellitus.

KEYWORDS: Microspheres, Mucoadhesion, Control-release, Gastro-retentive, Drug targeting.

INTRODUCTION

The oral route is the most common and preferred way of administering drugs because it is non-invasive, convenient, safe, cost-effective, and has high patient acceptance. Drugs given orally can be formulated in various dosage forms (tablets, capsules, liquids, etc.) and may allow controlled or sustained release to maintain therapeutic drug levels and reduce the frequency of dosing. However, the oral route has challenges too: variable gastric pH, enzymatic degradation, first-pass metabolism in the liver, and unpredictable gastric emptying can all reduce bioavailability and make formulation design more complex.[1]

Mucoadhesion dosage forms have received substantial attention as novel drug delivery systems able to improve the bioavailability of drugs by prolonging their residence time and controlling the drug release characteristics. Mucoadhesion refers to the adhesion between a dosage form (or polymeric material) and the mucosal surface, exploiting the mucus layer to keep the dosage form in place. Mucoadhesive dosage forms can be tablets, microspheres, patches, films, gels, etc., that adhere to mucosal tissues (including gastric mucosa) to prolong residence time, enabling controlled drug release and potentially enhancing absorption and bioavailability by keeping the drug close to the absorption site.[2]

Gastroretentive drug delivery systems are specialized oral dosage forms designed to remain in the stomach for extended periods of time to improve drug absorption (especially of drugs with narrow absorption windows), increase bioavailability, and achieve sustained or controlled release in the upper GI tract. They may work via various mechanisms (floating, swelling/expanding, mucoadhesive, high density, or delayed gastric emptying devices) to prevent or delay gastric emptying, localize the drug in the stomach, or both. Advantages include lowered dosing frequency, more stable plasma concentration, better therapeutic efficacy for suitable drugs, and improved patient compliance.[3]

Gastroretentive mucoadhesive microspheres combine the benefits of both mucoadhesion and prolonged gastric residence to significantly improve therapeutic outcomes. Because they adhere to the gastric mucosa, they remain at the absorption site for extended periods, which enhances bioavailability especially for drugs with narrow absorption windows or those degraded in distal parts of the gut. Their small size and high surface-to-volume ratio create intimate contact with the mucus layer, allowing more effective absorption and controlled, sustained release of the drug over many hours, reducing the frequency of dosing and

smoothing out peaks and troughs in plasma levels. In addition, these microspheres can localize drug action (both systemically and locally) and reduce dose-related adverse effects by limiting drug exposure elsewhere, while also protecting the drug from harsh gastric or intestinal conditions (pH, enzymes) until released. All of this contributes to improved patient compliance, better therapeutic efficacy, and potentially lower required dose.[4]

Type-2 diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance (reduced responsiveness of peripheral tissues to insulin) and often impaired insulin secretion, leading to persistent hyperglycaemia (high blood glucose levels). Over time, if uncontrolled, it can cause serious complications such as cardiovascular disease, kidney damage, neuropathy, retinopathy, and more. Effective glycemic control is important in management, using lifestyle changes and pharmacotherapy (oral agents or insulin) to reduce risks.[5]

Vildagliptin is an oral antidiabetic drug belonging to the class of DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors). It works by inhibiting DPP-4 enzyme, which breaks down the incretin hormones (GLP-1 and GIP); this inhibition prolongs the activity of active incretins, increasing insulin secretion in a glucose-dependent manner and suppressing glucagon release. Clinical trials have shown that vildagliptin lowers fasting plasma glucose, postprandial glucose, reduces HbA1c, and improves β-cell function with relatively low risk of hypoglycaemia compared to some other agents.[6,7]

The conventional dosage forms of VLG needs frequent dosing for achieving plasma peak level for the effective diabetic's treatment. Recently, the drug loaded into biocompatible polymer was used for the elimination of adverse effects and frequent dosing problem of drugs. Researcher also reported that drugs encapsulation by polymeric materials will improve therapeutic efficiency, bioavailability and patient compliance.[8]

Hence, the aim of this study was to development and characterization of gastro- retentive muco-adhesive microspheres loaded with anti-diabetic drug by using suitable polymer and their evaluation to improve patient compliance.

Table 1: Formulation code for Microspheres preparation.

Formulation code	Vildagliptin (mg)	Sodium alginate %	Carbopol %	HPMC %	Calcium chloride %
F1	100	2.5	0.05	0.2	2
F2	100	2.5	0.05	0.8	2

F3	100	1.5	0.05	0.2	2
F4	100	2.5	0.2	0.2	2
F5	100	1.5	0.2	0.2	2
F6	100	2.5	0.2	0.8	2
F7	100	1.5	0.05	0.8	2
F8	100	1.5	0.2	0.8	2

Table 2: Formulation code for coating of microspheres.

Formulation code	rospheres (mg)	Chitosan (%)
MF6-1	50	0.25
MF6-2	50	0.5

MATERIALS AND METHOD:

Materials

Vildagliptin was kindly gifted by Medreich pharma, Bangalore. Chitosan was provided by Shreeji Chemicals, Mumbai. Carbopol 924, and other solvents like methanol was purchased from S D Fine Chem limited, Mumbai.

Methods

A. Preparation Of Mucoadhesive Microspheres

Ionic gelation technique[9]

Preparation of mucoadhesive microsphere were conducted according to ionic gelation technique, microspheres was obtained by dissolving sodium alginate (2.5%) in water(100ml) and then after dissolving it add HPMC and then Carbopol to form a polymeric solution, to this solution add 100mg of vildagliptin drug. After, the Drug-polymeric solutions were added drop by drop using 21-gauge needle, under magnetic agitation to 20 mL of an aqueous solution containing the crosslinking agent (cacl2nm 3% w/v). Microspheres were then recovered by filtration, washed with distilled water and finally, 24 h dried in an oven at 40°C, and then the microspheres were collected and stored.

B. Coating of Microspheres[10]

The prepared drug-loaded microspheres were converted into mucoadhesive microspheres by surface coating with chitosan polymer. For this, chitosan solutions were prepared at two different concentrations, 0.25% w/v and 0.5% w/v, using dilute acetic acid as the solvent. An accurately weighed number of microspheres (50 mg) was dispersed in each chitosan solution under gentle magnetic stirring to facilitate uniform coating of the polymer over the microsphere surface. The dispersion was maintained for a suitable period to allow sufficient interaction between the cationic groups of chitosan and the microsphere matrix, thereby

enhancing mucoadhesive properties. Following the coating process, the microspheres were collected by filtration, rinsed carefully with distilled water to remove unbound chitosan, and dried at room temperature until a free-flowing, stable mucoadhesive microsphere formulation was obtained.

EVALUATION PARAMETERS OF MUCOADHESIVE MICROSPHERES[11-14]

The prepared Microsphere and coated Mucoadhesive microsphere formulation were evaluated for different parameters like Drug-Excipients compatibility, Particle size analysis, Drug content, Entrapment efficiency determination, *In vitro* dissolution study, *In vitro* wash-off test for mucoadhesive test and Stability studies as per ICH guidelines.

In vitro drug release

The drug release study was carried out in the United States of Pharmacopeia (USP) dissolution apparatus II using the formulation containing 100 mg equivalent drug at 37±0.50C. For the simulation of physiological conditions, the study was carried out at pH 1.2. Initially, the drug release was determined in 900mL of 0.1N (pH 1.2) hydrochloric acid for 12 hrs. The samples were withdrawn at suitable intervals and replaced with fresh medium and analyzed UV spectrophotometrically at 204nm. The drug release mechanism was determined by finding the best fit of the release data.

In Vitro Wash-Off Test for Mucoadhesion

A freshly cut small intestinal tissue obtained from local abattoir within 1hr of killing of the goat, was cleaned by washing with isotonic saline solution. Jejunum was separated and soaked in receptor medium (Buffer pH-7.4). This tissue represents a significant portion of the overall gastrointestinal tract and is therefore a good representative of the target tissue for orally administered bio-adhesive drug delivery systems. Therefore, for experimentation, a piece of jejunum mucosa (2×3 cm) was mounted onto glass slide. An accurate number of microparticles was placed on mucosal surface. The glass slides were put in the grooves of the USP tablet disintegrating test apparatus and regular up and down movement was given in a beaker containing buffer pH 7.4. The duration for complete washing of microparticles from goat intestinal mucosa was recorded and averaged from three determinations.

Amount of drug remaining in mucosa

$$Mucoadesion(\%) = \frac{\text{Amount of drug remaining in mucosa}}{\text{Amount of drug taken}} \times 100$$

RESULT

Drug-excipients compatibility studies were carried out using FT-IR. FTIR spectra of pure Vildagliptin pure drug and polymers mixtures showed sharp characteristic peaks for functional groups. The results revealed that there was no deviation in the wave number of the peaks nor in the intensity of peaks of the pure drug, polymers mixture, confirms that there is no interaction between drug and polymer.

The size analysis of the prepared microsphere formulation was done by optical microscope. The polymer concentration increases particle size also increases there is a Similar relationship between the polymer concentration and the particle size. F6 formulation containing highest concentration of both polymers hence the particle size larger than other formulations found to be 605.94 μm.

The % Drug content was found by estimating uniform distribution of drug within the various batches of microspheres prepared. The drug content results suggest a negligible loss of drug during the formulation Higher values of drug content were observed in the microsphere with increased polymer concentration, ranging from 86.2 % to 93.6% for F1 to F8.

The % Entrapment efficiency, in order to diminish polymer toxicity, a polymeric drug delivery system must be made with the minimum possible amount polymer yet able to entrap as much drug as possible. Hence, an optimal ratio between the entrapped drug and the polymer amount for the highest EE must be obtained. Entrapment efficiency of was ranged from for 88.2% to 95.1% for formulation. The % entrapment efficiency was found to increase with increasing the concentration as a gelling agent in the microsphere and the highest drug loading was found to be 95.1 for F6.

In vitro release study of Vildagliptin microsphere formulations F1 to F8 was conducted for 12 hrs, by using USP type II dissolution test apparatus, using 7.4 pH phosphate buffer. The amount of drug release from formulation F3 was showed 89.5% which was higher among formulations F1 to F8. In 12hr dissolution F6 shows 77.6 % lowest drug release and F3 shows 89.5% highest drug release. It has been concluded that, if we increase the concentration of matrix polymers the release of drug also decreases. The mucoadhesive microsphere confirmed that the rate of drug release in a control matter at 12 hrs.

In vitro, mucoadhesion studies of all formulations are summarized in Table 5.16 and Fig 5.14. In vitro mucoadhesion study of Vildagliptin microsphere formulations F1 to F8 was conducted for 12 hrs., by using a Tablet Disintegrating test apparatus, using pH 6.8 buffer. The amount of mucoadhesion from formulation MF6-1 was showed 41% which was higher among the formulations F1 to F8. From the results, we observed that the mucoadhesion of the drug from the microsphere was varied according to concentration of chitosan and polymers content. It has been concluded that, if we increase the concentration of polymers. the mucoadhesion of drug also increases.

Graphical representation of results

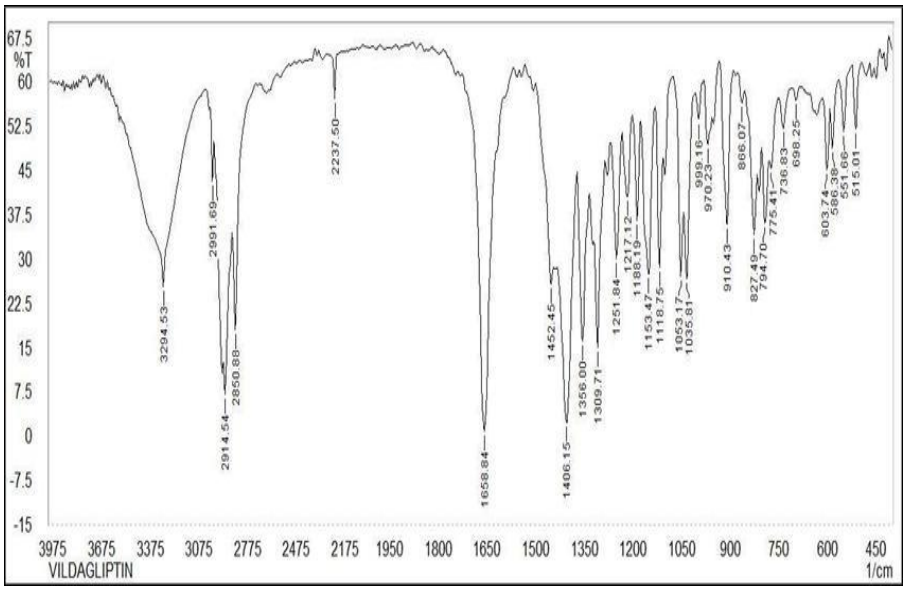

Figure 1: FT-IR spectrum of Vildagliptin.

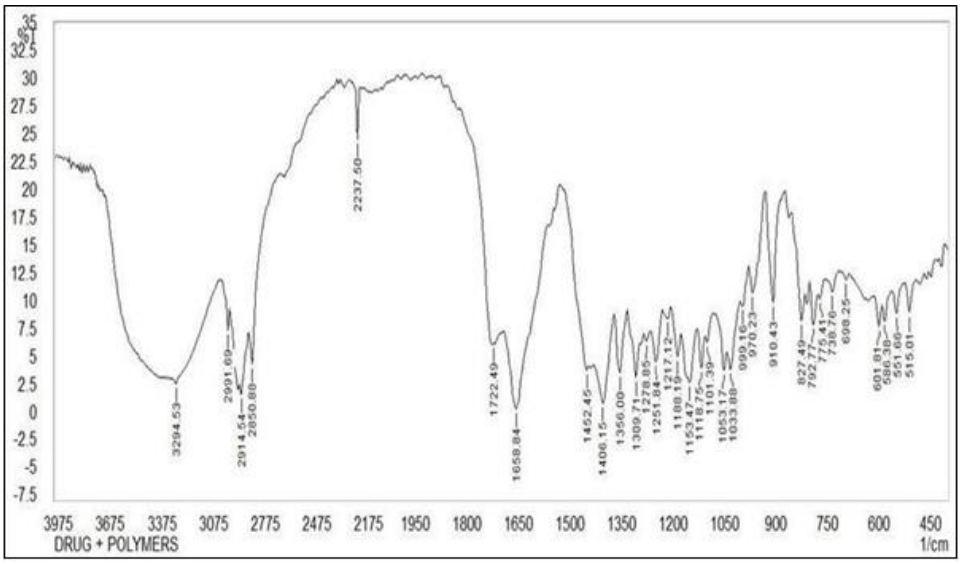

Figure 2: FTIR spectrum of drug and polymers mixture.

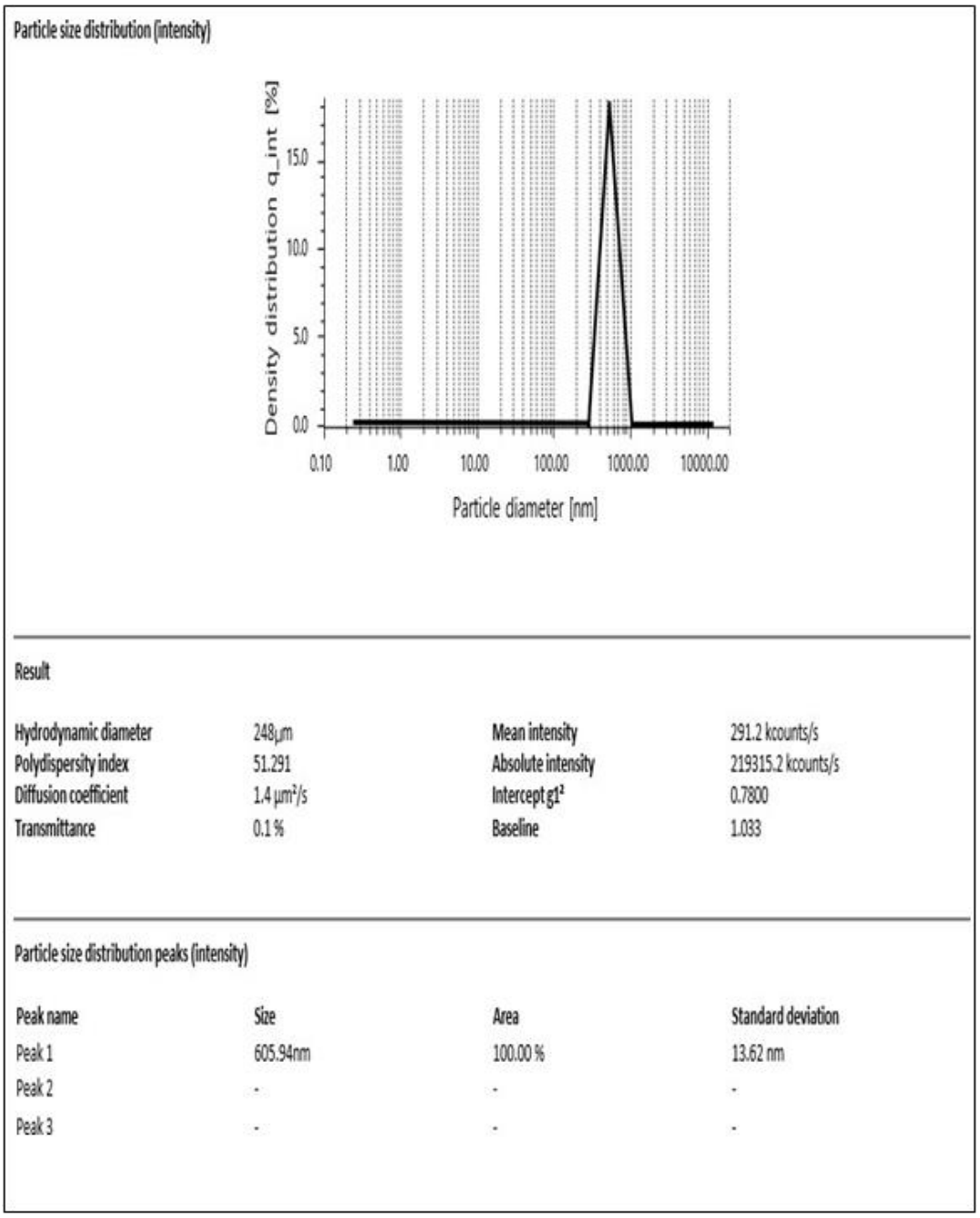

Figure 3: Particle size analysis of Mucoadhesive Microspheres.

Table 3: %Drug content and % Entrapment efficiency for microspheres F1-F8.

Formulation code	% Drug content	% Entrapment efficiency
F1	89.3	92.4
F2	92.5	94.1
F3	87.2	88.2
F4	91.5	93.06
F5	86.2	89.7
F6	93.6	95.1
F7	87.5	90.2
F8	88.3	91.9

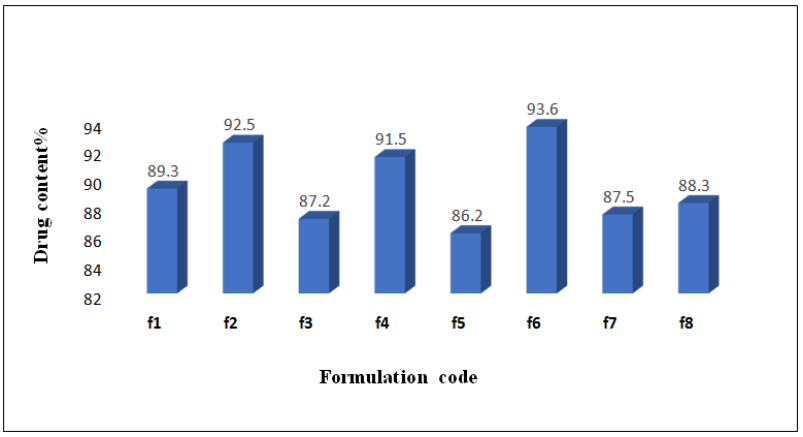

Figure 4: Percentage drug content of formulations F1-F8.

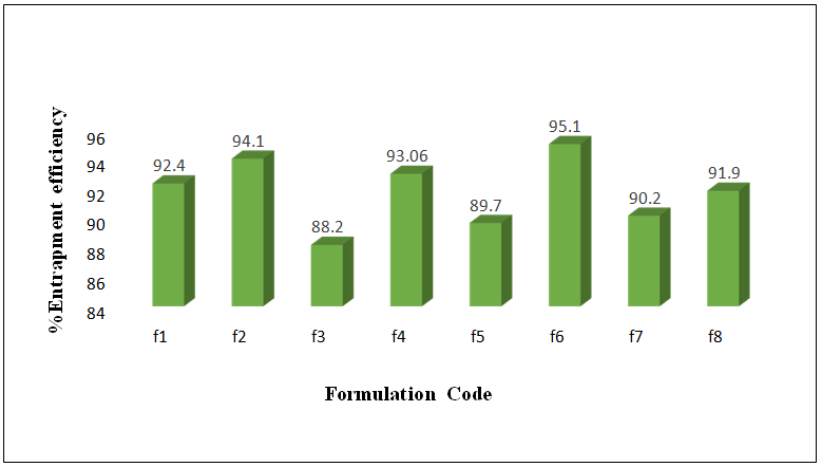

Figure 5: Percentage Entrapment efficiency of formulation F1-F8 Table 4: Drug dissolution study of microspheres.

Time(hrs)	% Cumulative Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	7.105	5.732	9.047	7.105	8.526	5.495	8.289	8.526
2	15.158	11.889	19.421	16.579	17.053	11.842	17.147	16.911
4	31.737	24.726	39.789	34.105	35.526	24.632	35.147	30.316
6	46.421	38.368	50.211	46.421	48.316	38.368	49.737	48.316
8	57.316	51.632	65.842	58.226	62.526	51.632	67.737	60.632
10	68.211	65.368	77.211	69.158	76.263	65.368	79.579	73.421
12	83.368	79.105	89.526	80.053	88.579	77.684	87.158	85.737

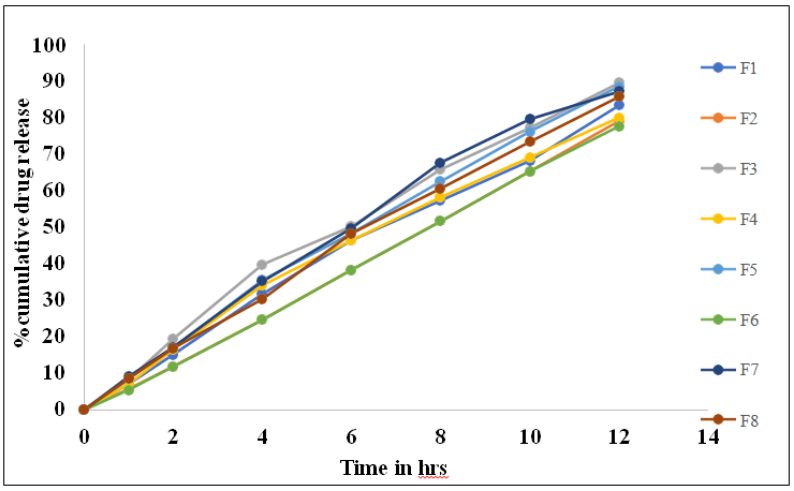

Figure 6: % Cumulative drug release of formulation F1-F8.

Table 5: Drug Mucoadhesion study of mucoadhesive microspheres MF6-1 and MF6-2.

Time(hrs)	MF6-1	MF6-2
0	100%	100%
1	92%	96%
2	84%	88%
4	76%	80%
6	64%	72%
8	52%	64%
10	40%	56%
12	28%	44%

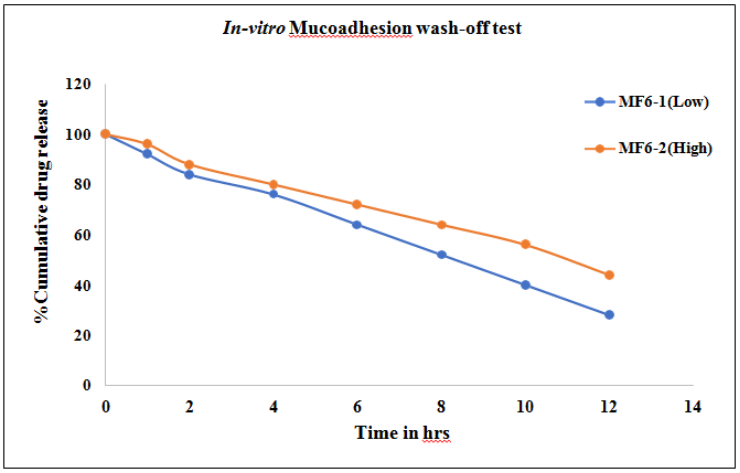

Figure 7: Drug mucoadhesion study of mucoadhesive microspheres MF6-1 and MF6-2.

CONCLUSION

The formulated gastro-retentive mucoadhesive microspheres of Vildagliptin were successfully prepared using suitable polymers. The microspheres showed desirable particle size, high entrapment efficiency, and good mucoadhesive strength. The optimized formulation provided

prolonged drug release, ensuring sustained therapeutic effect. Chitosan-coated microspheres exhibited improved adhesion and controlled release compared to uncoated ones. Thus, the developed formulation can enhance gastric retention and improve the bioavailability of vildagliptin.

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