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PREPARATION AND CHARACTERIZATION OF HOLLOW MICROSPHERE OF VILDAGLIPTIN FOR ENHANCEMENT FOR ORAL BIOAVAILABILITY

Sakshi Kshirsagar*, Kiran Satnami, Deepak Basedia, B K Dubey, Sunil K Shah and Mukesh Patel

Technocrats Institute of Technology Pharmacy, Bhopal (M.P.).

***Corresponding Author: Sakshi Kshirsagar**

Technocrats Institute of Technology Pharmacy, Bhopal (M.P.)

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ABSTRACT

The present investigation was aimed at the development and evaluation of a gastro-retentive hollow microsphere system for the sustained oral delivery of vildagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor used in the management of type 2 diabetes mellitus. Conventional oral administration of vildagliptin is associated with a short biological half-life and frequent dosing, which may compromise patient compliance. To address these limitations, floating hollow microspheres were formulated to prolong gastric residence time and provide controlled drug release. Preformulation studies were carried out to evaluate the physicochemical properties, purity, and stability of vildagliptin, confirming its suitability for formulation development. Vildagliptin-loaded hollow microspheres were prepared by the solvent evaporation technique using hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and guar gum in varying ratios. The prepared microspheres were evaluated for percentage yield, drug entrapment efficiency, buoyancy, particle size, zeta potential, surface morphology, and in vitro drug release behavior. The optimized formulation (F4) exhibited high entrapment efficiency, prolonged buoyancy, acceptable particle size, and good stability. Scanning electron microscopy revealed spherical microspheres with smooth surfaces and a hollow structure. In vitro release studies demonstrated sustained drug release for up to 12 hours, and release kinetics followed the Korsmeyer–Peppas model, indicating a non-Fickian diffusion mechanism. Accelerated stability studies confirmed the stability of the optimized formulation. The developed gastro-retentive hollow microspheres of vildagliptin offer a promising strategy for improving gastric retention, sustaining drug release, and enhancing therapeutic efficacy and patient compliance.

KEYWORDS: Vildagliptin; Gastro-retentive drug delivery; Hollow microspheres; Sustained release; Solvent evaporation; Floating microspheres; Type 2 diabetes mellitus.

INTRODUCTION

Oral drug delivery continues to be the most preferred and convenient route of administration owing to its non-invasive nature, cost-effectiveness, and high patient compliance. Despite these advantages, conventional oral dosage forms often exhibit significant limitations, including unpredictable gastric emptying, short gastrointestinal transit time, and variability in drug absorption due to physiological factors such as pH changes and motility patterns of the gastrointestinal tract (GIT). These limitations are particularly problematic for drugs that exhibit a narrow absorption window in the upper GIT, are unstable or poorly soluble at intestinal pH, or require localized therapeutic action in the stomach.[1,5]

To overcome these challenges, gastro-retentive drug delivery systems (GRDDS) have been developed to prolong the residence time of dosage forms in the stomach, thereby enhancing drug absorption and improving therapeutic outcomes. GRDDS are designed to remain in the gastric environment for extended periods through various mechanisms such as mucoadhesion, flotation, sedimentation, swelling, and modified geometry. By maintaining prolonged gastric retention,

these systems ensure controlled and predictable drug release, reduce fluctuations in plasma drug concentration, and minimize dosing frequency.[3,9]

Among the various gastro-retentive approaches, hollow microspheres have emerged as a promising delivery platform due to their unique physicochemical properties. Hollow microspheres are low-density, spherical particulate systems capable of floating on gastric fluids, thereby achieving extended gastric retention through buoyancy. Their high surface-to-volume ratio allows for efficient drug encapsulation and controlled release behavior. The floating mechanism is primarily attributed to the presence of an internal cavity and the hydration of polymeric matrices, which reduce system density and promote sustained flotation in the gastric medium.[6,12]

Hollow microspheres can be formulated using a wide range of biodegradable and non-biodegradable polymers, including hydrophilic and hydrophobic materials, allowing flexibility in modulating drug release kinetics and stability. These systems offer several advantages such as improved bioavailability, enhanced therapeutic efficacy, reduced drug wastage, and effective site-specific delivery to the stomach and proximal small intestine. Furthermore, hollow microspheres are particularly beneficial for drugs with short biological half-lives, poor aqueous solubility, or extensive first-pass metabolism.[12,15]

Overall, the development of gastro-retentive hollow microspheres represents a rational and effective strategy for overcoming the limitations of conventional oral drug delivery systems. By combining prolonged gastric residence with controlled drug release, hollow microspheres provide a promising approach for improving oral drug bioavailability and achieving sustained therapeutic action.[14,18]

In recent years, increasing attention has been directed toward the development of gastro-retentive microsphere-based systems due to their potential to overcome the limitations of conventional oral dosage forms. By maintaining prolonged contact with the gastric mucosa, these systems enhance drug absorption and improve local therapeutic action. The ability to modulate drug release through polymer selection and formulation optimization further enhances their applicability across a wide range of drugs.[17,20]

In conclusion, gastro-retentive hollow microspheres represent a promising and versatile approach for improving oral drug delivery, particularly for drugs requiring prolonged gastric residence and controlled release. Their ability to combine buoyancy, sustained drug release, and site-specific delivery makes them an effective strategy for enhancing bioavailability and therapeutic outcomes. The development and optimization of such systems continue to be an active area of research in pharmaceutical sciences, offering significant potential for improving patient care and treatment efficacy.

Drug Profile: Vildagliptin

Vildagliptin is an oral antidiabetic drug belonging to the class of dipeptidyl peptidase-4 (DPP-4) inhibitors, used in the management of type 2 diabetes mellitus. It improves glycemic control by inhibiting the DPP-4 enzyme, thereby increasing endogenous incretin hormone levels such as glucagon-like peptide-1 (GLP-1). This leads to enhanced glucose-dependent insulin secretion and reduced glucagon release.

Vildagliptin has a molecular formula of $C_{17}H_{25}N_3O_2$ and a molecular weight of 303.40 g/mol. It appears as a white to off-white crystalline powder and is freely soluble in water. The drug exhibits rapid oral absorption with a bioavailability of approximately 85% and a short elimination half-life of about 3 hours. Due to its short half-life and frequent dosing requirement, vildagliptin is considered a suitable candidate for modified or sustained drug delivery systems to improve patient compliance and therapeutic efficacy.

Preformulation Studies

Preformulation studies represent a critical initial step in the rational design and development of pharmaceutical dosage forms. These studies involve systematic evaluation of the physical, chemical, and physicochemical properties of the drug substance alone and in combination with excipients. The primary objective of preformulation testing is to generate essential information that aids in the development of a stable, effective, and bioavailable dosage form suitable for large-scale manufacturing. The nature and extent of preformulation investigations depend on the intended dosage form and route of administration.

In the present study, preformulation investigations of vildagliptin included assessment of its physicochemical properties, stability characteristics, and compatibility with formulation excipients to minimize formulation failure risks and ensure optimal product performance.

Characterization of Vildagliptin

Physical Evaluation

Vildagliptin was evaluated for organoleptic properties such as color, odor, taste, and appearance. The drug appeared as a white, odorless, fine crystalline powder with a bitter taste, consistent with reported literature, indicating acceptable purity and suitability for formulation development.

Solubility Studies

The solubility of vildagliptin was determined qualitatively in various solvents at room temperature. The drug was found to be freely soluble in distilled water and phosphate buffer (pH 7.2), soluble in ethanol, methanol, and 0.1 N hydrochloric acid, and sparingly soluble in chloroform and 0.1 N sodium hydroxide.

These findings indicate good aqueous solubility, supporting its suitability for oral drug delivery systems.

Melting Point Determination

The melting point of vildagliptin was determined using a digital melting point apparatus. The observed melting point ranged between 155–156°C, which closely corresponds to the reported standard value (155°C), confirming the purity of the drug sample.

FT-IR Spectroscopic Analysis

Fourier Transform Infrared (FT-IR) spectroscopy was employed to confirm the chemical identity of vildagliptin. The FT-IR spectrum exhibited characteristic absorption peaks corresponding to N–H stretching, C–H stretching, C=O stretching, C–N stretching, and C–O stretching, confirming the presence of functional groups consistent with the molecular structure of vildagliptin and indicating no chemical modification.

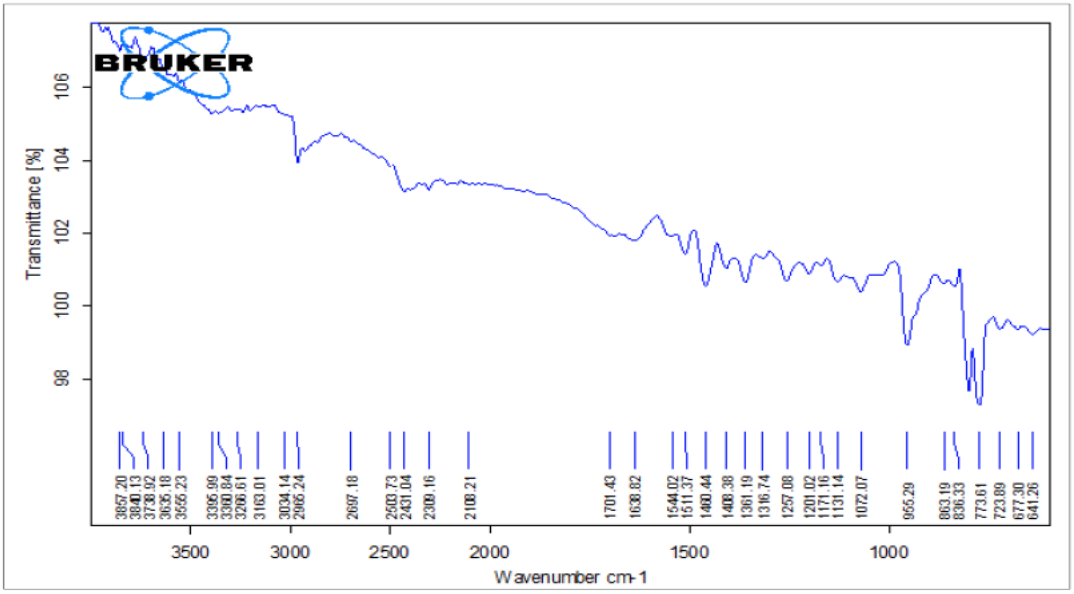

Figure 1 FT-IR spectra of Vildagliptin.

Wavenumber (cm^{-1})	Assignment	Interpretation
3034.14	N–H stretching (secondary amine)	Indicates presence of amine group
2966.24	C–H stretching (alkyl)	Suggests aliphatic –CH bonds
1638.82	C=O stretching (amide group)	Confirms presence of an amide or carbamate functionality
1544.02	N–H bending or C=C aromatic stretching	May relate to the pyrrolidine or imidate structure
1201.02	C–N stretching	Presence of amine or amide C–N bond
1027.07	C–O stretching (ether or secondary OH)	Confirms hydroxyl or ether-like functionality

Loss on Drying and Moisture Content

Loss on drying was determined using an infrared moisture balance and was found to be 0.176 ± 0.002%, indicating low moisture content and good stability. Moisture content was further quantified using Karl Fischer titration, which confirmed minimal water content, supporting the drug's stability during processing and storage.

UV Spectroscopic Analysis

The maximum absorbance (λmax) of vildagliptin was determined using UV–visible spectrophotometry in 0.1 N HCl and was found at 210 nm. A calibration curve constructed over a concentration range of 5–25 µg/mL showed good linearity with a correlation coefficient (R^2) of 0.998, indicating reliability of the method for quantitative drug estimation.

Preparation of Vildagliptin-Loaded Hollow Microspheres

Vildagliptin-loaded hollow microspheres were prepared by the solvent evaporation technique using hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), and guar gum in varying ratios. The drug and polymers were dissolved in a mixture of ethanol and dichloromethane and emulsified into an aqueous polyvinyl alcohol solution under continuous stirring. Solvent evaporation resulted in the formation of hollow microspheres, which were collected, washed, dried, and stored for further evaluation.

Table 1: Formulations of hollow microspheres of Vildagliptin.

S. No.	Formulation Code	Vildagliptin (mg)	HPMC (mg)	EC (mg)	Guar gum (mg)
1.	F1	50	100	25	-
2.	F2	50	100	50	-
3.	F3	50	100	75	-
4.	F4	50	150	25	10
5.	F5	50	150	50	20
6.	F6	50	150	75	30

Evaluation of Hollow Microspheres

Prepared microspheres were evaluated for percentage yield, drug entrapment efficiency, buoyancy, particle size, zeta potential, surface morphology, and in vitro drug release. The optimized formulation (F4) exhibited the highest yield, drug entrapment, buoyancy, and sustained drug release behavior. Particle size analysis revealed nanoscale dimensions, and zeta potential measurements indicated acceptable stability. SEM analysis confirmed spherical morphology with smooth surfaces.

In vitro release studies demonstrated sustained release of vildagliptin over 12 hours. Release kinetics analysis revealed that the optimized formulation followed the Korsmeyer–Peppas model, indicating a non-Fickian diffusion mechanism.

Stability Studies

Accelerated stability studies conducted according to ICH guidelines (40 ± 2°C / 75 ± 5% RH for 3 months) showed no significant changes in physical appearance, drug content, or dissolution profile, confirming the stability of the optimized formulation.

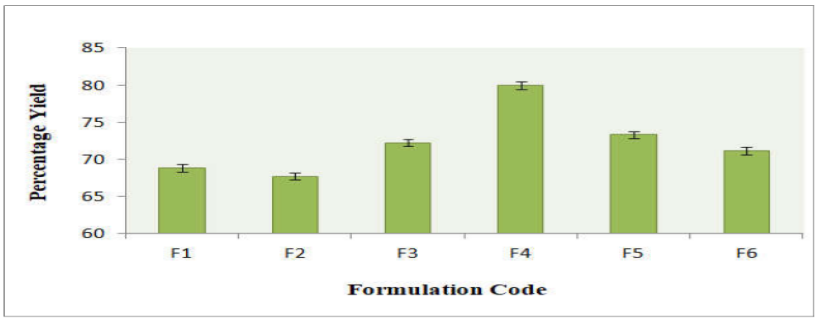

Figure 2. Percentage yield for different formulation.

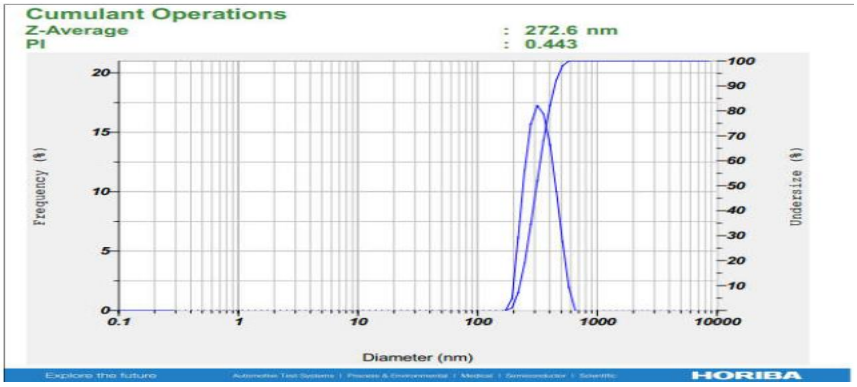

Figure 3: Particle size data of optimized microsphere formulation F4.

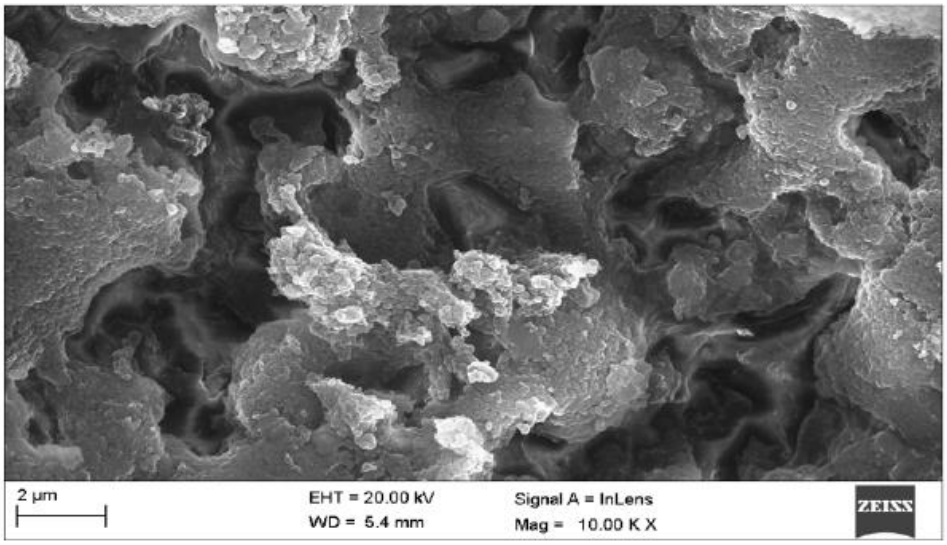

Figure 4: Graph of scanning electron microscopy (SEM) of optimized formulation F4.

Time (hrs)	% of Drug Release						Marketed Formulation (Vildagliptin 50 mg Tablet)
	F1	F2	F3	F4	F5	F6	
0.5	34.85	31.75	27.95	29.85	19.25	12.85	35.95
1	51.45	48.25	34.85	41.45	24.95	19.85	64.85
2	69.25	65.05	54.85	60.55	34.95	29.45	92.85
4	75.95	78.95	68.95	72.65	47.95	35.85	99.25
6	95.85	89.25	74.85	84.75	58.95	44.95	
8	98.85	96.25	89.25	91.65	68.15	59.15	
10	99.25	98.85	97.15	98.45	79.15	73.65	
12	99.65	99.25	99.25	99.68	98.95	90.85	

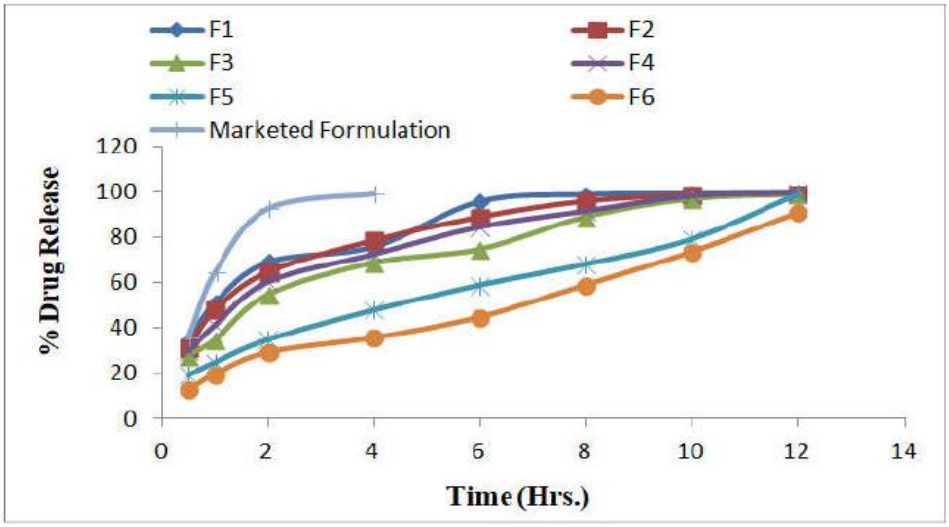

Figure 5: Graph of release study of formulation F1-F6.

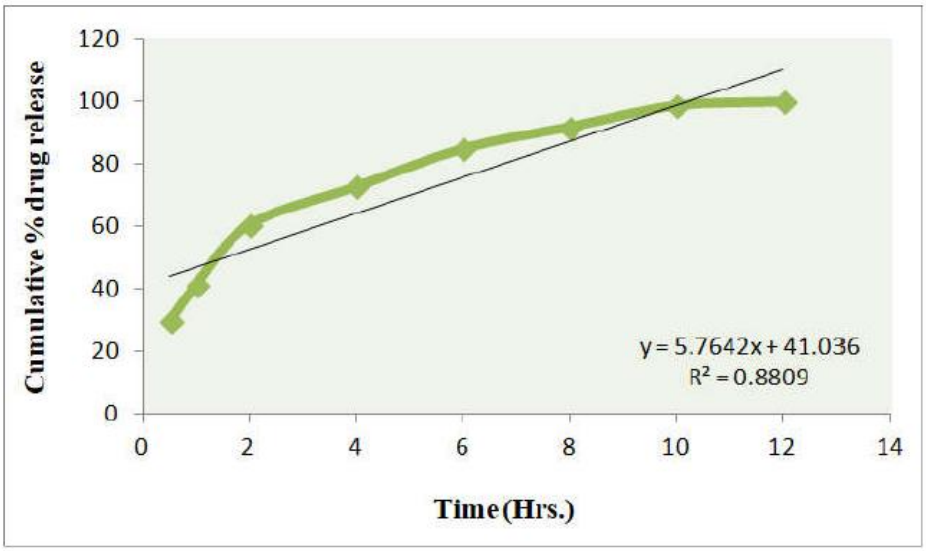

Figure 6: Zero order release kinetics graph of optimized formulations.

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