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Original Article

Optimized Vildagliptin Microsphere Formulation and *in vitro* Characterization Using 2^3 Factorial Design Analysis

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ABSTRACT

Background: Vildagliptin is a dipeptidyl peptidase-4 inhibitor employed for the intervention of non-insulin-dependent diabetes mellitus which has a short half-life. The intention of this work is to devise and qualify vildagliptin microspheres to analyse the impact of two different-polymers, encapsulating agents, and stirring speeds for sustained drug release. **Materials and Methods:** The formulations were crafted by method of solvent evaporation and developed by applying 2^3 complete factorial designs. The independent variables are the polymers (X1), encapsulating agents (X2) and stirring speed (X3). The dependent variables are particle size (Y1), degree of swelling (Y2), encapsulation efficiency (Y3), *in vitro* drug release studies (Y4). The kinship between independent and dependent variables were demonstrated using response surface diagrams. Additionally, the formulated microspheres were analysed for the parameters practical yield, kinetics of drug release and morphology. **Results:** The particle size and degree of swelling of microspheres were influenced substantially by the hydrophilic characteristic of the polymer used. The loading efficiency and the percentage of drug release was found to be ameliorated in water insoluble Eudragit RS 100 microspheres. The microspheres batch VGM6 prepared was observed to be suitable in accordance with loading efficiency 76.3% and slow percentage of drug release 71.78% in 8 hr following Hixson-Crowell kinetics and was characterized by SEM for morphology. **Conclusion:** The similarity and dis-similarity factors show that the rate of drug profiles were similar to each other and the formulation releases the drug slower than that of the innovator brand.

Keywords: Vildagliptin, Microsphere, Solvent evaporation, Response surface.

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INTRODUCTION

Vildagliptin forms a complex with dipeptidyl peptidase-4, resulting in its inhibition and elevating the levels of Glucagon-Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP) hormones. These hormones play a crucial role in maintaining glucose homeostasis by stimulating insulin release from the pancreatic islet, increasing pancreatic β cell mass and inhibiting apoptosis. They also decrease glucagon levels and suppress hepatic glucose production in the short term.[1]

The limitations associated with current immediate-release formulations of vildagliptin offer opportunities for researchers to develop controlled and modified delivery systems that can enhance therapeutic efficacy, reduce dosing frequency, minimize side effects, improve patient adherence and ultimately achieve better management of diabetes.[2]

Due to its brief biological half-life of 1 to 3 hr, frequent dosing is necessary to sustain plasma concentrations of Vildagliptin. This frequent dosing regimen can be inconvenient for patients and may lead to fluctuations in drug levels, potentially jeopardizing therapeutic outcomes. However, advanced controlled-release formulations address these challenges by decreasing dosing frequency, thereby enhancing patient adherence. As a result, there is a growing interest in the development of sustained-release Vildagliptin formulations to optimize treatment, reduce fluctuations in drug levels, minimize adverse effects and lessen the need for frequent administrations.[3]

Hydroxypropyl Methylcellulose (HPMC) is a commonly used polymer in the formulation of oral controlled drug delivery systems. To achieve controlled release using water-soluble polymers like HPMC, rapid hydration of the polymer on the tablet's surface is essential, forming a gel-like layer. This gel layer should exhibit adequate cohesion and continuity to slow down water penetration and control drug diffusion. HPMC products display variations in chemical and physical properties, primarily due to variations in methoxyl substitution level, hydroxypropoxyl substitution moles and polymerization degree. Different products with varying ratios of hydroxypropyl and methyl substitution

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can impact characteristics such as solubility in organic solvents, gelation onset temperature of aqueous solutions and hydration properties.[4]

Eudragit RS100 is a copolymer comprising ethyl acrylate, methyl methacrylate and a small amount of methacrylic acid ester containing quaternary ammonium groups. Its permeability can be enhanced by the addition of salt. Eudragit RS100 is characterized by colourless granules with a faint amine-like odour and a molecular weight exceeding 32,000 g/mol. It demonstrates low permeability and exhibits swelling behaviour independent of pH. This polymer is utilized to achieve specific and controlled release profiles in various ratios.[5]

To stabilize an emulsion formed between a polymer and a drug solution in water, an emulsifier like polyvinyl alcohol can be employed. The hydroxyl groups in polyvinyl alcohol interact with the water phase, while the vinyl chain interacts with the organic solvent, thereby enhancing the stability of the formed emulsion. The stability of the emulsion can be influenced by varying the concentration and volume of polyvinyl alcohol.[6]

Polyvinyl alcohol can be designed either as matrix or reservoir drug delivery systems. Strategies such as modifying gelling properties, solubility and incorporating copolymers have been utilized to control drug release from polyvinyl alcohol hydrogels.[7]

Polyvinylpyrrolidone (PVP), also called polyvidone or povidone, is a biodegradable, water-soluble polymer, derived from its monomer N-vinylpyrrolidone. In addition to being a hydrophilic polymer, PVP has excellent solubility in solvents of different polarities, good binding properties and a stabilizing effect for suspensions and emulsions.[8] PVP is an inert, non-toxic, temperature-resistant, pH-stable, biocompatible, biodegradable polymer that helps to encapsulate and cater both hydrophilic and lipophilic drugs.[9]

MATERIALS AND METHODS

Vildagliptin was kindly gifted by Aurobindo Pharma, Hyderabad, India. HPMC K4M, Eudragit RS100, polyvinyl alcohol and polyvinyl pyrrolidone were procured from Yarrow Chem Products, Mumbai. All the remaining chemicals, reagents and solvents used were of analytical grade.

Formulation of Vildagliptin microspheres

Vildagliptin microspheres are prepared by emulsion solvent evaporation method. The organic phase or polymeric solution for emulsion is prepared by dissolving the polymer HPMC K4M or Eudragit RS 100 in a known quantity of acetone. The measured amount of Vildagliptin drug is then allowed to disperse thoroughly in the organic phase with mechanical stirring. The aqueous phase of the emulsion is then prepared by dissolving completely the given quantity of polyvinyl alcohol or polyvinyl pyrrolidone K 30 in distilled water. Then, the emulsion is prepared by dispersing the polymeric solution slowly in the aqueous phase. The emulsion is allowed to run for minimum 3 hr using magnetic stirrer and the solvent is allowed to evaporate at the interface of air and water. Ascertaining the evaporation of volatile solvent, the emulsion is then filtered and washed with distilled water at least 3 times. The microspheres thus filtered is allowed to dry in air at room temperature and stored in desiccator for further studies.[10]

Experimental Study Design for Optimization

Response surface methodology is a tool to analyse the impact of independent variables on dependent variables with the collection of statistical and mathematical techniques. The 2^3 factorial design was espoused to optimize the responses and to find optimum process parameters with 3 variables at 2 levels. The two polymers (X1) HPMC K4M and Eudragit RS 100, two encapsulating agents/ emulsifiers (X2) polyvinyl alcohol and polyvinyl pyrrolidone K 30 and stirring speed (X3) 250 rpm and 500 rpm were considered as independent variables in the preparation of microspheres by emulsion solvent evaporation method. Each variable were studied at two levels (-1 and +1) (Table 1) as given the formulation Table 2. The dependent variables (Table 3) selected were particle size analysis (Y1), swelling index (Y2), drug entrapment efficiency (Y3) and percentage drug releasae (Y4). Minitab® Statistical Software (Version 17.1) was used to perform the statistical analysis. The best optimized microspheres can be deliberated for farther field of study. The statistical model incorporating interactive and polynomial terms was used to evaluate the response:

$$Y=b0+b1X1+b2X2+b3X3+b12X1X2+b13X1X3+b23X2X3+b123X1X2X3$$

Standard curve of Vildagliptin

Vildagliptin 100 mg was dissolved completely in 100 mL 0.1 N HCl using sonicator to prepare the main stock solution. Series of stock solutions were prepared using the main stock solution in different volumetric flasks and diluted with the same solvent. The concentrations ranging from 2 μg/mL to 12 μg/mL were obtained and the solutions were analysed by using UV spectrophotometry at 210 nm.

Table 1: Independent Variables.

Code	Independent Variables	Level (-1)	Level (+1)
X1	Polymer	HPMC K4M	Eudragit RS 100
X2	Emulsifier	PVP K 30	PVA
X3	Stirring Speed	500 rpm	250 rpm

Table 2: Formulation of Vildagliptin microspheres.

F. Code	Vildagliptin (parts)	HPMC K4M (parts)	Eudragit RS 100 (parts)	PVP K 30 (%)	PVA (%)	Stirring Speed
VGM1	1	5		1		500
VGM2	1	5		1		250
VGM3	1	5			1	500
VGM4	1	5			1	250
VGM5	1		5	1		500
VGM6	1		5	1		250
VGM7	1		5		1	500
VGM8	1		5		1	250

Table 3: Dependent Variables

Code	Dependent Variables
Y1	Particle size
Y2	Degree of swelling.
Y3	Drug entrapment efficiency %.
Y4	% drug release in 8 hr.

Evaluation of microspheres

Entrapment efficiency

A precisely measured amount of microspheres equivalent to 100 mg of Vildagliptin was squashed and dissolved in 100 ml of phosphate buffer with pH 6.8 in a volumetric flask and invoked for 12 hr. Subsequent to mixing, the solution was sifted through Whatman filter paper and the filtrate was thinned utilizing phosphate buffer pH 6.8 and absorbance was estimated for the finding the un-entrapped drug at 210 nm utilizing UV spectrophotometer. Values are taken to ascertain the entrapment efficiency.[11]

$$Entrapment\ efficiency = \frac{Calculated\ drug\ content}{Theoretical\ drug\ content}\ x\ 100$$

Particle size analysis

The particle size of the microsphere was estimated utilizing optical microscopic strategy. The microspheres were enumerated roughly for particle size utilizing a fine-tuned optical microscope equipped with an eyepiece micrometer and a stage micrometer.[12]

Yield of microspheres

The devised microspheres were gathered and gauged. The ratio of real weight of prevailed microspheres and the overall quantity of drug and polymer substance that was utilized for the formulation throws the yield of microspheres.[13]

$$\%\ Yield = \frac{Real\ weight\ of\ prevailed\ microspheres}{Overall\ weight\ of\ drug\ and\ polymer} \times 100$$

Degree of swelling of microspheres

The degree of swelling can be estimated utilizing phosphate buffer pH 6.8. The amount of microspheres were precisely gauged and laid in the Petri dish which was totally drenched in the phosphate buffer pH 6.8. After 2 hr, the microspheres were taken out, dried using filter paper and gauged precisely once more. Then, the degree of swelling was calculated using the following formula:[14]

$$Degree\ of\ Swelling = \frac{[W2 - W1]}{W1}\ x\ 100$$

Where, W1=Initial weight of the dried microspheres.

W2=Final weight of the swollen microspheres.

In vitro drug release

The *in vitro* drug release rate of microspheres was calculated in 900 mL of phosphate buffer pH 6.8 utilizing USP XXII type 2 paddle type dissolution apparatus. An equally weighted measure of microspheres tantamount to 100 mg was laid in the apparatus with proper setting. The temperature of the dissolution medium was kept up at 37.0±0.5°C at 50 rpm. The aliquots were gathered at indicated time gaps, thinned with the same dissolution medium and analysed at 210 nm for Vildagliptin drug. Samples receded were substituted with equivalent volume of the dissolution medium to keep up with *in vitro* sink condition.[15]

Kinetics of drug release

To cognize the mechanism of the drug release from the microspheres, the outcomes incurred from the *in vitro* dissolution process were gibed into various kinetic equations and coefficient of correlation (r) values were calculated by regression analysis as follows:

Zero-order drug release: Cumulative % drug release versus time,

First-order drug release: Log cumulative % drug remaining versus time,

Higuchi's equation: Cumulative % drug release versus square root of time,

Korsmeyer-Peppa's equation: Log cumulative % drug release versus log time,

Hixson-Crowell cube root plot: Cube root of % drug release versus time.[16]

Comparison with the Marketed Product

The *in vitro* dissolution profile of optimized microsphere formulation VGM6 containing Vildagliptin microspheres equivalent to 50 mg was compared with the marketed innovator brand. The similarity factor and dissimilarity factor are calculated.[17]

RESULTS

Standard curve of Vildagliptin

Absorbance of the series of solutions with different concentrations were observed at 210 nm using UV-visible spectrophotometer and the same were plotted in graph which has the regression value of R^2=0.9998 in the equation y=0.0296x+0.0019 (Figure 1).

Particle size

The average particle size of Vildagliptin microspheres ranged from 180 µm to 249 µm. The particle size of formulations VGM1 to VGM4 (212 µm to 249 µm) are higher when compared to that of the particle size of formulations VGM5 to VGM8 (180 µM to 198 µM). This may be attributed due to the hydrophilic nature and rapid swelling behaviour of HPMC K4M which resulted in the formation of slightly larger microspheres (Figure 2 and Table 4).

Encapsulation Efficiency

The entrapment efficiency ranged from 68.8% to 77.1%. The HPMC K4 M microspheres exhibited entrapment efficiency from 68% to 74% and the Eudragit RS 100 microspheres exhibited the entrapment efficiency from 73% to 77%. The highest was found in VGM8 batch of Eudragit RS 100 microspheres and was noted to be 77.1% (Figure 3 and Table 4). Eudragit RS 100 is known for its ability to form a dense and cohesive matrix, which can facilitate better entrapment of the drug molecules within the microspheres. This dense matrix structure may contribute to higher entrapment efficiencies compared to HPMC K4M. Eudragit RS 100 is insoluble in water but has good permeability which can allow for better diffusion of the drug molecules into the polymer matrix during the microsphere formation process. This enhanced permeability may contribute to higher entrapment efficiencies.

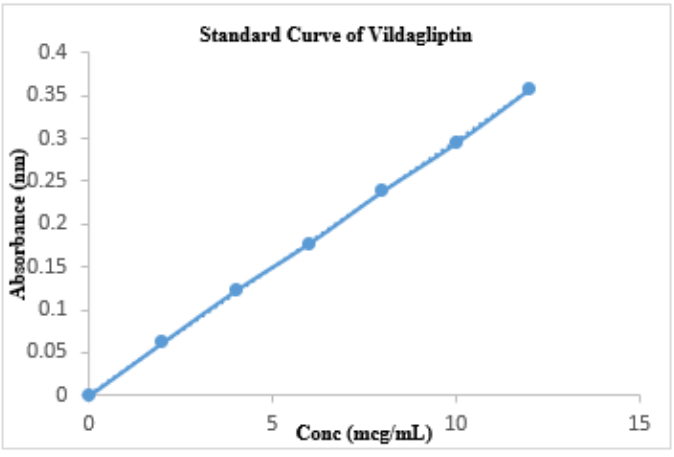

Figure 1: Standard Curve of Vildagliptin.

Degree of swelling

The degree of swelling ranged from 3.12 to 4.75. The HPMC K4 M microspheres exhibited the degree of swelling from 4.21 to 4.75 and the Eudragit RS 100 microspheres exhibited the degree of swelling from 3.12 to 3.52. The highest was found in VGM4 batch of HPMC K4M microspheres and was noted to be 4.75 (Figure 4 and Table 4). HPMC K4M swells primarily due to hydration of its hydrophilic groups, which leads to an increase in polymer volume as water is absorbed into the polymer matrix. Eudragit RS 100 may swell to a lesser extent due to its lower hydrophilicity and its swelling mechanism may involve different interactions such as relaxation of polymer chains rather than extensive hydration.

In vitro drug release studies

The HPMC K4 M microspheres exhibited the *in vitro* drug release from 83.46% to 87.31% and the Eudragit RS 100 microspheres exhibited the *in vitro* drug from 71.78% to 74.93%. The lowest was found in VGM6 batch of Eudragit RS 100 microspheres and was noted to be 71.78 (Figure 5 and Table 4).

HPMC K4M typically forms microspheres with a more porous and hydrated matrix structure due to its hydrophilic nature. This allows for faster diffusion of the drug molecules through the polymer matrix, leading to higher drug release rates. HPMC K4M swells rapidly upon exposure to aqueous media, leading to increased porosity and facilitating drug release. The rapid swelling and hydration of HPMC K4M microspheres can enhance the penetration of dissolution medium into the matrix, promoting faster drug release.

Eudragit RS 100, being less hydrophilic, forms microspheres with a denser matrix structure. This denser matrix may hinder the diffusion of drug molecules, resulting in slower drug release rates compared to HPMC K4M microspheres. Eudragit RS 100,

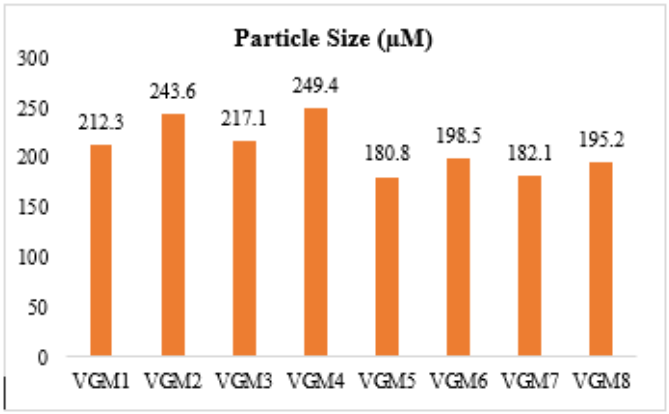

Figure 2: Graphical illustration of Particle Size.

while capable of swelling to some extent, exhibits lower water uptake compared to HPMC K4M. The slower swelling behaviour of Eudragit RS 100 microspheres may result in slower penetration of dissolution medium into the matrix and consequently slower drug release rates.

Upon comparing the regression coefficient values of zero-order and first order it is evident that on average, the First-order model provides a slightly better fit to the data for these microspheres following linear kinetics. Upon probing the regression coefficient values of Higuichi model, Korsmeyer-Peppa model and Hixson-Crowell model, it is discernible that on average, the Hixson-Crowell values are better. This suggests that the Hixson-Crowell model is likely more appropriate for describing the release behaviour of these microspheres and the drug release is by dissolution (Table 5).

DISCUSSION

Shape and surface morphology

SEM of best formulation VGM6 shows that Eudragit RS 100 microparticles are discrete, spherical and poriferous with a rough outer surface (Figures 6 and 7).

Regression Equations

(Y1) Particle size analysis (μm)=304.2-41.45 Polymer (X1)+2.15 Emulsifier (X2)-0.0944 Stirring Speed (X3)

(Y2) Degree of swelling=5.973-1.0975 Polymer (X1)+0.0925 Emulsifier (X2)-0.001550 Stirring Speed (X3)

(Y3) Encapsulation efficiency=73.25+3.450 Polymer (X1)+0.450 Emulsifier (X2)-0.01560 Stirring Speed (X3)

(Y4) *In vitro* drug release (8h)=93.46-12.232 Polymer (X1)+0.488 Emulsifier (X2)+0.00927 Stirring Speed (X3)

Interpretation of Regression Equations

Predictor variables of particle size (Y1) (Figure 8): Polymer (X1): The results of regression equation shows that the particle size with the use of Eudragit RS 100. This may be due to the hydrophobic nature of the polymer. The predicted particle size decreased by 41.45 μm holding other variables constant. Emulsifier (X2): The results of regression equation shows that use of polyvinyl alcohol had increased the particle size giving a positive coefficient of 2.15. The coefficient implies that the change in the emulsifier variable, the predicted particle size increased by 2.15 μm, holding other variables constant. Stirring Speed (X3): As the stirring speed increases, the particle size decreases, given the negative coefficient. The coefficient implies that for every unit increase in stirring speed, the predicted particle size decreases by 0.0944 μm, holding other variables constant.

Table 4: **Physicochemical Evaluation of the Vildagliptin microspheres.**

F. Code	Particle size analysis(μm)	(%) Yield of microspheres	Degree of swelling	Encapsulation efficiency (%)	*In vitro* drug release (8 hr)
VGM1	212.3±0.703	89.6	4.19	69.9±0.825	86.13
VGM2	243.6±0.980	93.7	4.58	73.2±0.081	83.46
VGM3	217.1±0.974	83.3	4.21	68.8±0.081	87.31
VGM4	249.4±0.385	90.1	4.75	74.2±0.286	84.84
VGM5	180.8±1.46	86.8	3.12	72.7±0.793	74.93
VGM6	198.5±0.216	88.9	3.46	76.3±0.454	71.78
VGM7	182.1±0.910	83.2	3.24	73.8±0.286	73.54
VGM8	195.2±0.778	86.5	3.52	77.1±0.294	72.56

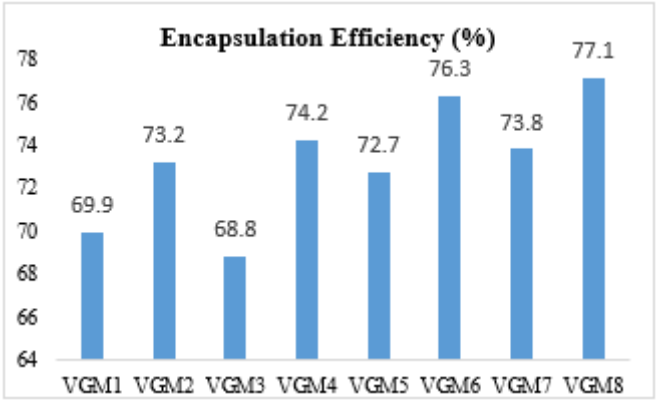

Figure 3: Graphical illustration of Encapsulation Efficiency.

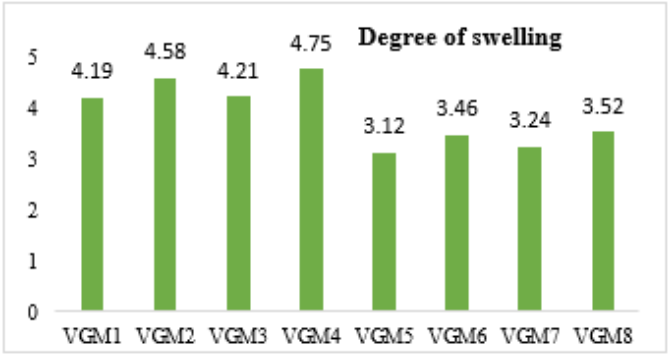

Figure 4: Graphical illustration of Degree of Swelling.

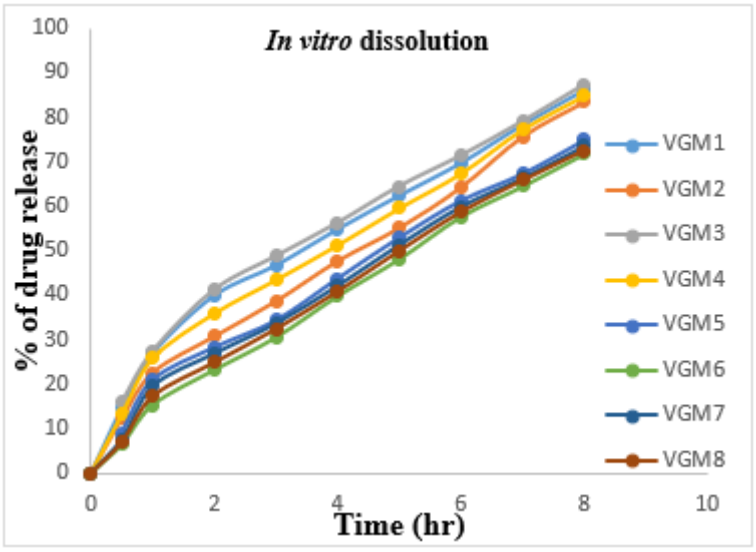

Figure 5: *In vitro* drug release studies

Table 5: Kinetic values of formulations VGM1-VGM8.

F. Code	Zero-order	First-order	Higuichi	Peppa's		Hixson-Crowell
	R^2	R^2	R^2	R^2	n	R^2
VGM1	0.955	0.971	0.992	0.499	0.987	0.985
VGM2	0.983	0.954	0.969	0.547	1.020	0.980
VGM3	0.951	0.971	0.994	0.487	0.978	0.986
VGM4	0.968	0.965	0.984	0.520	1.003	0.984
VGM5	0.980	0.986	0.973	0.591	1.055	0.992
VGM6	0.993	0.985	0.957	0.673	1.138	0.994
VGM7	0.983	0.987	0.970	0.620	1.087	0.993
VGM8	0.989	0.987	0.964	0.648	1.115	0.995

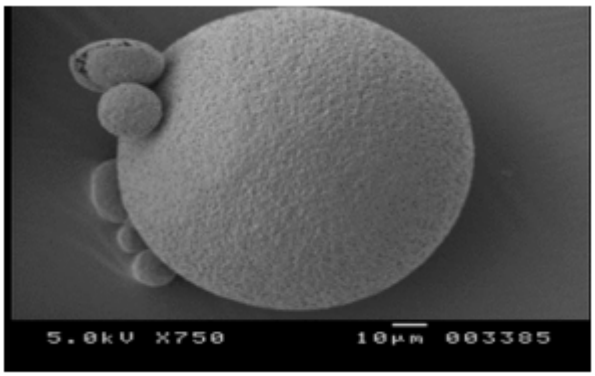

Figure 6: SEM of VGM3.

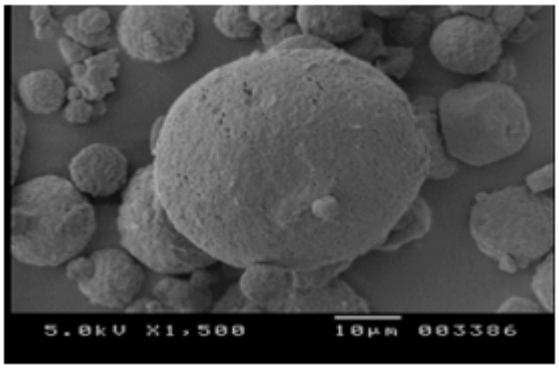

Figure 7: SEM of VGM6.

Predictor variables of degree of swelling (Y2) (Figure 9): Polymer (X1): The negative coefficient suggests that as the change of polymer to Eudragit RS 100, the degree of swelling decreases. The predicted degree of swelling decreased by 1.0975 units, holding other variables constant. Emulsifier (X2): The positive coefficient indicates that the change of emulsifier to polyvinyl alcohol causes increase the degree of swelling. The predicted degree of swelling increased by 0.0925 units, holding other variables constant. Stirring Speed (X3): The negative coefficient suggests that as the stirring speed increases, the degree of swelling decreases. The predicted degree of swelling decreases by 0.001550 units, holding other variables constant.

Predictor variables of encapsulation efficiency (Y3) (Figure 10): Polymer (X1): The coefficient associated with polymer is positive suggesting that the change in polymer to Eudragit RS 100 increased the encapsulation efficiency. The predicted encapsulation efficiency increases by 3.450 percentage points, holding other variables constant. Emulsifier (X2): The coefficient associated with emulsifier is positive, indicating that the change of emulsifier increases the encapsulation efficiency. The predicted encapsulation efficiency increases by 0.450 percentage points,

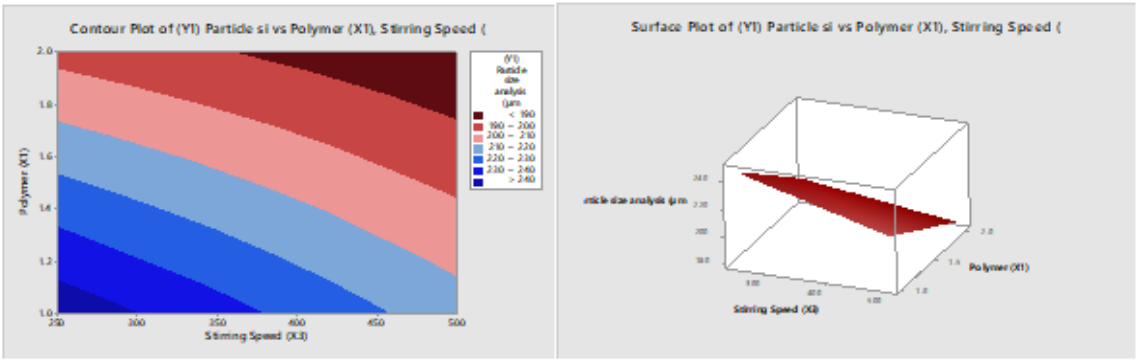

Figure 8: Contour and Surface plots of Particle size (Y1) vs. Polymer (X1) and Stirring Speed (X3).

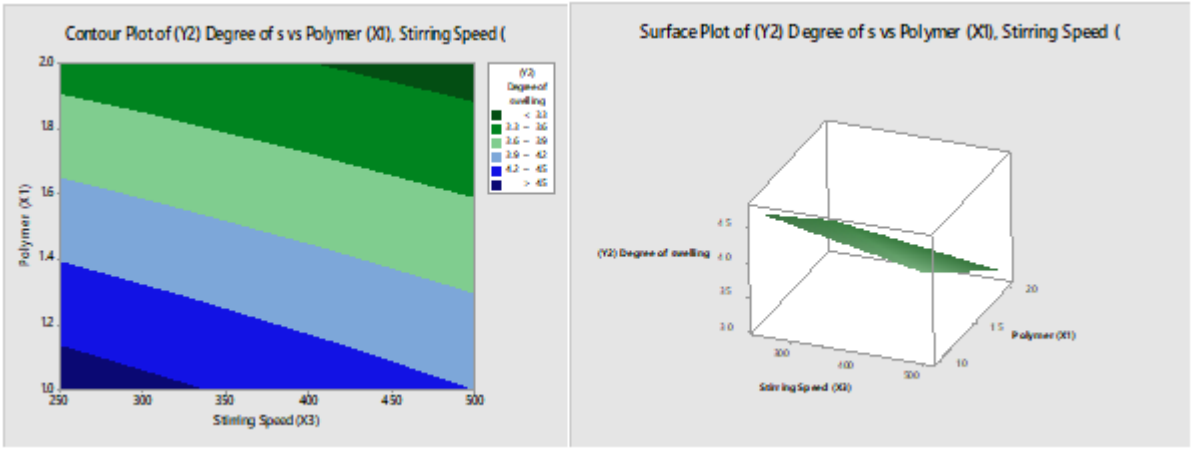

Figure 9: Contour and Surface plots of Degree of swelling (Y2) vs. Polymer (X1) and Stirring Speed (X3).

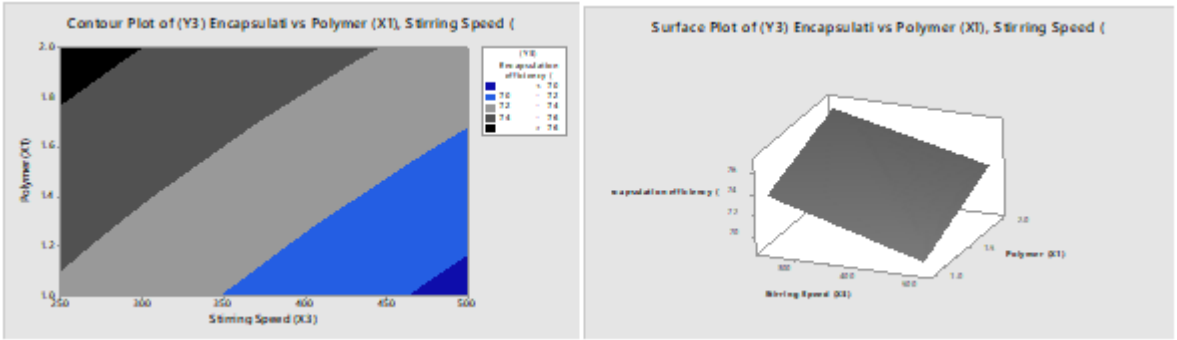

Figure 10: Contour and Surface plots of Encapsulation Eff. (Y3) vs. Polymer (X1) and Stirring Speed (X3).

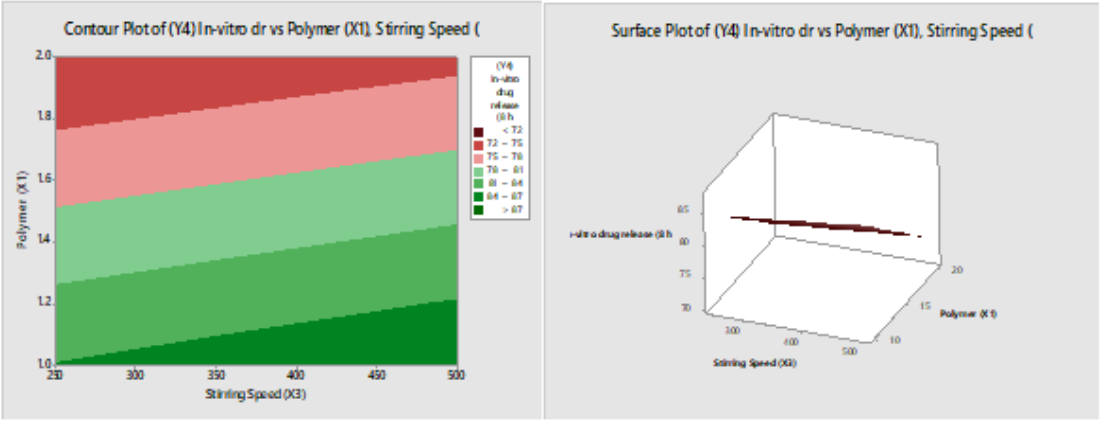

Figure 11: Contour and Surface plots of *In vitro* DR (Y4) vs. Polymer (X1) and Stirring Speed (X3).

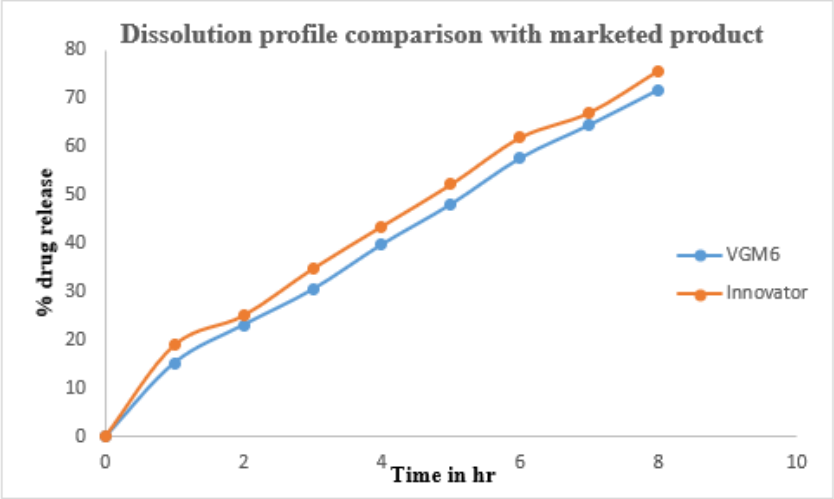

Figure 12: Dissolution profile comparison with the marketed formulation.

Table 6: *In vitro* dissolution profile comparison with marketed innovator product.

Time (hr)	VGM6 (%)	Marketed innovator product %
0	0	0
1	15.32	18.97
2	23.19	25.11
3	30.52	34.78
4	39.81	43.56
5	48.13	52.24
6	57.64	61.93
7	64.49	67.12
8	71.78	75.84

holding other variables constant. Stirring Speed (X3): The coefficient associated with stirring speed is negative suggesting that as the stirring speed increases the encapsulation efficiency decreases. The predicted encapsulation efficiency decreases by 0.01560 percentage points, holding other variables constant.

Predictor variables of *in vitro* drug release (Y4) (Figure 11): Polymer (X1): The coefficient associated with polymer is negative indicating that the change of polymer to Eudragit RS 100 the *in vitro* drug release decreases. The predicted drug release decreases by 12.232 units or percentage points, holding other variables constant. Emulsifier (X2): The coefficient associated with emulsifier is positive suggesting that the change of the emulsifier to polyvinyl alcohol increased the *in vitro* drug release. The predicted drug release increased by 0.488 units or percentage points, holding other variables constant. Stirring Speed (X3): The coefficient associated with stirring speed is positive indicating that as the stirring speed increased the *in vitro* drug release also increased. The predicted drug release increases by 0.00927 units or percentage points, holding other variables constant.

Comparison with the Marketed Innovator Product

The *in vitro* dissolution profile of optimized formulation VGM6 was compared with the marketed innovator brand (Figure 12 and Table 6). The similarity factor *f*2 was found to be 72% and the difference factor *f*1 was found to be 8 for the formulation VGM6 and the marketed formulation which indicates that the drug release rate of VGM6 formulation was slower than that of the marketed formulation. The value of *f*2 from 50 to 100 shows similarity in *in vitro* release profiles and the value of *f*1 below 15% show that drug release profiles are like each other.

CONCLUSION

In the current research endeavour, the microspheres were prepared with two different polymers using two different emulsifiers at two different stirring speeds. The reason for using two different polymers is to observe the release-modifying characteristics of the polymers. The shape of the microspheres is found to be spherical in shape. The HPMC K4M-Vildagliptin microspheres evinced a percentage drug release of 83% to 87% in 8 hr while Eudragit RS 100-Vildagliptin microspheres evinced a percentage drug release of 71% to 74% in 8 hr. This may be because of the polymer Eudragit RS 100 which is not aqueous soluble, diffusivity of the drug through it is difficult and starts releasing the drug only in alkaline pH. The HPMC K4M microspheres demonstrated faster drug release than Eudragit RS 100 microspheres in 8 hr than Eudragit RS 100 due to aqueous solubility, more porous hydrated matrix structure due to its hydrophilic nature. Based on the percentage of drug release and encapsulation efficiency, the formulation VGM6 appears to be the best formulation among the other optimized formulations showing the sustained dissolution drug release of about 71.78% following first-order model and Hixson-Crowell kinetics. The similarity and dis-similarity factors show that the rate of drug profiles were similar to each other and the formulation releases the drug slower than that of the innovator brand.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

VGM: Vildagliptin Microspheres; **GLP-1:** Glucagon-like peptide-1; **GIP:** Glucose-dependent insulinotropic polypeptide; **HPMC:** Hydroxypropyl methylcellulose; **PVP:** Polyvinylpyrrolidone; **PVA:** Polyvinyl Alcohol; **HCl:** Hydrochloric acid; **UV:** Ultraviolet; **USP:** United States Pharmacopoeia; **SEM:** Scanning Electron Microscopy.

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