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IP International Journal of Comprehensive and Advanced Pharmacology

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Original Research Article

Effect of formulation variables on the characteristics of vildagliptin microspheres

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ARTICLE INFO

Article history:
Received 15-07-2022
Accepted 25-07-2022
Available online 23-08-2022

Keywords:
Vildagliptin
Ethyl cellulose
Polyvinyl Alcohol
Dichloromethane
Microspheres

ABSTRACT

Introduction: Vildagliptin, an antihyperglycemic drug, is having high water solubility and shorter elimination half-life. This leads to administer vildagliptin frequently to maintain its therapeutic efficacy. So the Formulation of vildagliptin microspheres might be beneficial in overcoming the side effects of the conventional drug delivery systems during the prolonged treatment.
Objective: The aim of the work was to evaluate and fabricate the microspheres, which improved the absorption of drug and increase the release kinetics and also to study the effect of formulation variables.
Materials and Methods: The microspheres of vildagliptin were formulated by solvent evaporation technique. The formulation variables were the concentration of Ethyl cellulose (EC), Polyvinyl alcohol (PVA), and stirring speed. The resulting microspheres were evaluated for percentage yield, percentage entrapment efficiency, particle size, surface morphology, drug release rates.
Results: The morphological structure of the microspheres revealed spherical shaped structures. Good entrapment were observed. The in vitro drug release was found to be controlled.
Conclusion: Results indicated that physicochemical properties of microspheres strongly affected by the presence of drug/polymer ratios, changing the concentrations of them and effect of variables.

1. Introduction

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers or polysaccharides which are biodegradable or non-biodegradable in nature and ideally having a particle size less than 200μm.[1] These vary widely in quality, sphericity, uniformity of particle and particle size distribution. This is an important approach in delivering therapeutic substance to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. Controlled drug delivery can be achieved using microspheres as they offer various alterations in their structure for drug release modifications.[2] It has been observed that microspheres are better choice of drug delivery system because it is of the advantage of target specificity and better patient compliance.

In long-term therapy for the treatment of chronic disease conditions like diabetes mellitus type 2 conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[3] Controlled release dosage forms have been demonstrated to improve therapeutic efficiency by maintaining a steady drug plasma concentration. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms.[4]

A promising new approach to treat type 2 diabetes mellitus is to enhance and prolong the physiological actions of the endogenous incretin hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP)

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https://doi.org/10.18231/j.ijcaap.2022.028

by inhibiting dipeptidyl peptidase IV (DPP-4), the enzyme responsible for their degradation and inactivation. Both GIP and GLP-1 have been shown to stimulate insulin release in a glucose-dependent manner.[5] Vildagliptin (VG) is one of the very effective incretin enhancers that functions as a potent inhibitor of DPP-4 also due to its special incretin dependent mechanism of action it may not cause hypoglycemia even after remaining in blood for prolonged duration.[6]

The aim of this study was to formulate Vildagliptin loaded microspheres for controlled delivery. Developed microspheres were characterized for their size, surface morphology, entrapment efficiency and drug release. The influence of formulation variables such as stirring speed, polymer concentration, surfactant, were investigated to achieve the better formulations in order to sustain the action of Vildagliptin; enabling reduction in dosing interval for the treatment of hyperglycemia associated with T2DM.

2. Materials and Method

2.1. Materials

Vildagliptin**,** Ethyl cellulose, PVA, Distilled water, Dichloromethane and n-Hexane.

2.2. Methods

Microspheres of Vildagliptin were obtained by solvent evaporation technique. Firstly, polymer (ethylcellulose) was dissolved in dichloromethane and then the drug (Vildagliptin) were added to the above solution. The polymer drug solution so obtained was injected into the PVA solution maintained at variable speed using mechanical stirrer. Stirring was continued for required duration. The formed microspheres were collected by filtration, washed with n-Hexane and dried to obtain free flowing microspheres.

3. Characterization of Microspheres

3.1. Particle size analysis

Particle sizes of microspheres were determined by optical microscopy. Optical microscope was fitted with eye piece micrometer which was then calibrated with a stage micrometer.[7] About 100 microspheres were randomly selected from each formulation and then the average size was calculated.

3.2. Surface morphology

The prepared vildagliptin microspheres were morphologically examined for shape, size surface morphology and topological properties using scanning electron microscope (FEI, Model NOVANANO 450) after gold sputtering at a pressure of 5.13E to 4 pascal and 5 KV at 0^0 was maintained to get the photographs.

3.3. Determination of percentage yield of microspheres

The prepared microspheres were completely dried and then weighed. The percentage yield was calculated by:[8]

$$\% \text{ Yield} = \frac{Weight\ of\ Microspheres}{Total\ weight\ of\ solid\ material}\ x\ 100$$

3.4. Determination of flow properties of microspheres

The prepared microspheres were evaluated for flow properties including bulk density, tapped density, Carr's index, Hausner ratio and angle of repose.[9]

3.5. Bulk density

It is the ratio of total mass of microspheres to the bulk volume of microspheres. It was measured by pouring the weighed microspheres into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$\text{Bulk density} = \frac{Mass\ of\ microspheres}{Bulk\ volume\ of\ microspheres}$$

3.6. Tapped density

It is the ratio of total mass of microspheres to the tapped volume of microspheres. The tapped volume was measured by tapping the microspheres to constant volume. It is expressed in gm/ml and is given by

$$\text{Tapped density} = \frac{Mass\ of\ microspheres}{Tapped\ volume\ of\ microspheres}$$

3.7. Carr's Index

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$\text{Carr's Index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}\ x\ 100$$

3.8. Hausner ratio

It is an indirect index of ease of flow of microspheres. It is measured by

$$\text{Hausner ratio} = \frac{Tapped\ density}{Bulk\ density}$$

3.9. Angle of repose (θ)

The friction forces in a loose powder can be measured by the angle of repose (θ). It is defined as maximum angle possible between the surface of pile of powder and the horizontal plane.

The microspheres were allowed to flow through a funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of microspheres formed. It is measured by

$$\tan\theta = \frac{Height}{Radius}$$

$$\theta = \tan^{-1}\left(\frac{Height}{Radius}\right)$$

Table 1: Formulation design of vildagliptin loaded microspheres

Formulation Codes	Drug(Vildagliptin) (mg)	Polymer(Ethyl Cellulose) (mg)	Solvent (DCM) (ml)	Medium (PVA) (%)	Stirring rate (rpm)
M1	100	1000	20	0.5	200
M2	100	1000	20	0.5	400
M3	100	1000	20	0.5	600
M4	100	1250	20	0.5	200
M5	100	1250	20	0.5	400
M6	100	1250	20	0.5	600
M7	100	1000	20	0.3	200
M8	100	1000	20	0.3	400
M9	100	1000	20	0.3	600
M10	100	1250	20	0.3	200
M11	100	1250	20	0.3	400
M12	100	1250	20	0.3	600
M13	100	1000	20	0.1	200
M14	100	1000	20	0.1	400
M15	100	1000	20	0.1	600
M16	100	1250	20	0.1	200
M17	100	1250	20	0.1	400
M18	100	1250	20	0.1	600

3.10. Drug entrapment efficiency

To calculate the entrapment efficiency, accurately weighed quantity of microspheres (50 mg) were taken along with 50 ml of phosphate buffer pH 7.4 in a volumetric flask and kept for 24 hours. It was then filtered, suitably diluted and then analyzed by UV spectrophotometry at 210 nm.[10]

$$\% \text{ Entrapment Efficiency} = \frac{Theoretical\ Entrapment}{Practical\ Entrapment} \times 100$$

3.11. In vitro release studies of microspheres

In-vitro release of Vildagliptin microspheres was carried out using the USP dissolution test apparatus at 37±0.5^{0}C in 900 ml of phosphate buffer pH 7.4. Microspheres equivalent to 50 mg Vildagliptin was placed in the muslin cloth and rotated at 100 rpm. A sample of 5 ml was withdrawn at various time intervals and replaced with equal amount of medium to maintain the sink condition. The withdrawn samples were analyzed by UV spectrophotometer at 210 nm using phosphate buffer 7.4 as blank solution.[11]

3.12. Effect of different formulation variables on various evaluation parameters

The influences of different formulation variables on various evaluation parameters were studied. The effects of polymer concentration (Ethylcellulose 1000-1250 mg), emulsifier concentrations (PVA concentration 0.1%-0.5%), and altered stirring speed of a mechanical stirrer (200, 400, 600 rpm) on microspheres characteristics (percentage yield, drug entrapment efficiency, particle size and cumulative drug release) were studied.

4. Results

Bulk density of all the batches was in the range of 0.63 – 0.68 gm/cm^3. Tapped density in the range of 0.71 – 0.78 gm/cm^3. Carr's index in range of 10.95 – 14.86 and Hausner ratio varies from 1.07 – 1.17 indicating excellent flow properties. Angle of repose was also found in the prescribed range showing excellent flow characteristics.

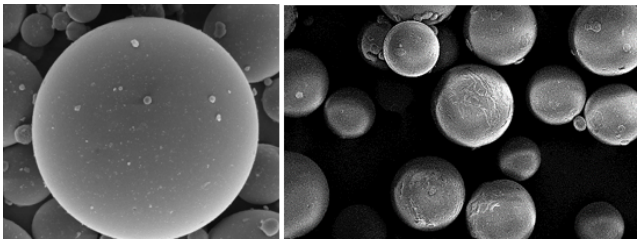

Fig. 1: Scanning electron micrograph of vildagliptin microspheres

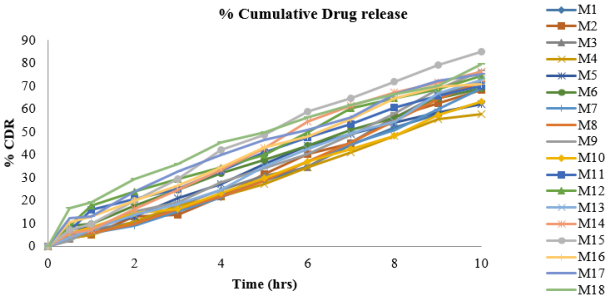

Fig. 2: Cumulative drug release for vildagliptin microspheres

Table 2: Effect of formulation variables on various evaluation parameters

Formulation Code	Particle Size	%EE	% Yield	% CDR
M1	18.45	66.20	84.87	6.3.03
M2	18.30	60.49	79.40	68.38
M3	15.00	54.06	94.00	71.65
M4	23.12	70.57	90.28	57.85
M5	19.10	67.42	86.00	61.95
M6	16.92	63.23	70.34	69.19
M7	21.00	67.81	88.33	69.01
M8	21.00	61.15	92.27	71.79
M9	14.80	52.81	91.73	76.72
M10	22.77	73.31	86.68	63.38
M11	21.87	69.98	86.91	70.14
M12	19.35	66.98	66.63	74.48
M13	26.42	70.15	86.00	72.51
M14	23.80	68.39	84.06	76.45
M15	20.00	63.86	76.67	84.87
M16	26.10	74.42	71.88	71.02
M17	22.45	71.26	88.91	75.11
M18	18.95	67.07	90.11	79.48

Table 3: Flow properties of Vildagliptin microspheres

Formulation Codes	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index	Hausner Ratio	Angle of Repose (θ)
M1	0.66	0.76	13.15	1.15	20.21
M2	0.67	0.78	14.10	1.16	22.47
M3	0.66	0.77	14.28	1.16	19.63
M4	0.64	0.73	12.32	1.14	21.06
M5	0.65	0.73	10.95	1.07	20.13
M6	0.67	0.76	11.84	1.13	16.69
M7	0.68	0.79	13.92	1.13	20.51
M8	0.66	0.75	12.00	1.15	21.13
M9	0.66	0.76	13.15	1.15	18.30
M10	0.66	0.76	13.15	1.15	17.26
M11	0.65	0.75	13.33	1.15	18.14
M12	0.67	0.77	12.98	1.14	16.49
M13	0.64	0.75	14.66	1.17	18.33
M14	0.64	0.74	13.51	1.16	20.54
M15	0.67	0.76	11.84	1.13	17.05
M16	0.63	0.72	12.50	1.14	21.89
M17	0.61	0.71	14.08	1.16	19.94
M18	0.63	0.74	14.86	1.17	21.40

4.1. Effect of concentration of polymer

The increase in the polymer concentration equals an approximately identical increase in the particle size and entrapment efficiency. The increase in the concentration of polymer results in the decrease in the % drug release. The increased polymer concentration might have led to increased density of the polymer matrix, resulting in an increased diffusional path length and consequent retardation of drug release.

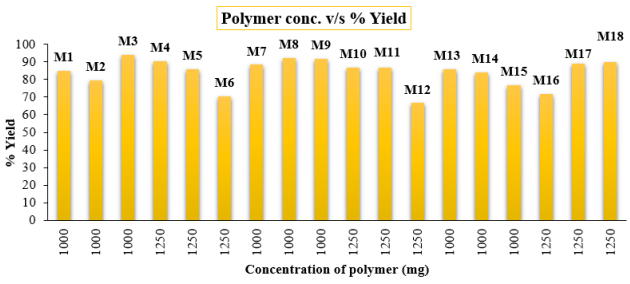

Fig. 3: Effect of polymer concentration on % Yield

Table 4: Effect of variables on various parameters

Formulation Codes	Polymer (mg)	PVA (%)	Stirring rate (rpm)	% Yield	% EE	Particle size (μm)	% CDR
M1	1000	0.5 %	200	84.87	66.20	18.45	63.03
M2	1000	0.5 %	400	79.40	60.49	18.30	68.38
M3	1000	0.5 %	600	94.00	54.06	15.00	71.65
M4	1250	0.5 %	200	90.28	70.57	23.12	57.85
M5	1250	0.5 %	400	86.00	67.42	19.10	61.95
M6	1250	0.5 %	600	70.34	63.23	16.92	69.19
M7	1000	0.3 %	200	88.33	67.81	21.00	69.01
M8	1000	0.3 %	400	92.27	61.15	21.00	71.79
M9	1000	0.3 %	600	91.73	52.81	14.80	76.72
M10	1250	0.3 %	200	86.68	73.31	22.77	63.38
M11	1250	0.3 %	400	86.91	69.98	21.87	70.14
M12	1250	0.3 %	600	66.63	66.98	19.35	74.48
M13	1000	0.1 %	200	86.00	70.15	26.42	72.51
M14	1000	0.1 %	400	84.06	68.39	23.80	76.45
M15	1000	0.1 %	600	76.67	63.86	20.00	84.87
M16	1250	0.1 %	200	71.88	74.42	26.10	71.02
M17	1250	0.1 %	400	88.91	71.26	22.45	75.11
M18	1250	0.1 %	600	90.11	67.07	18.95	79.48

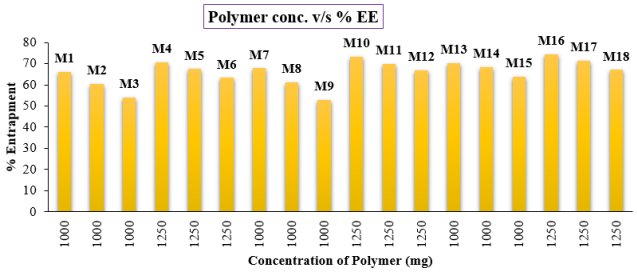

Fig. 4: Effect of polymer concentration on % EE

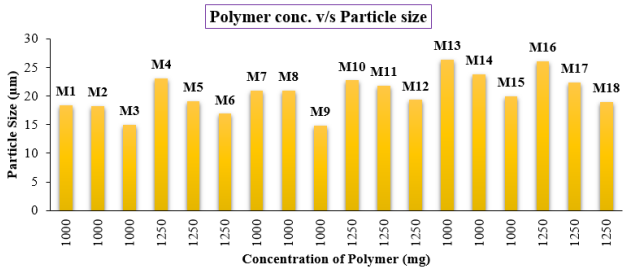

Fig. 5: Effect of polymer concentration on particle size

4.2. *Effect of concentration of PVA*

The increase in the PVA concentration equals an approximately identical increase in the entrapment efficiency. The particle size was dependent on the external phase viscosity, as the increasing concentration decreased the particle size. Increased PVA concentration ensured better system stabilization against coalescence of the emulsion and therefore led to formation of smaller microspheres. The increase in the concentration of PVA

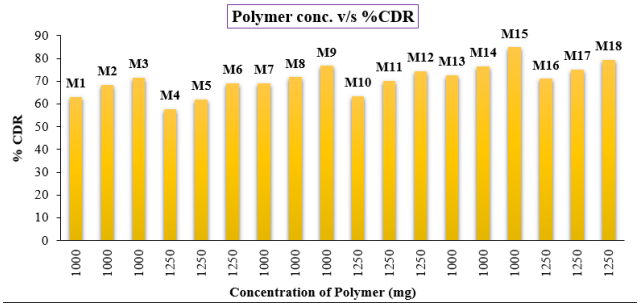

Fig. 6: Effect of polymer concentration on % CDR

results in the decrease in the % drug release. All the formulations prepared at 0.1% concentration exhibited maximum drug release than the formulations prepared with 0.3% and 0.5%. This could be probably due to increasing viscosity of the external phase. [12]

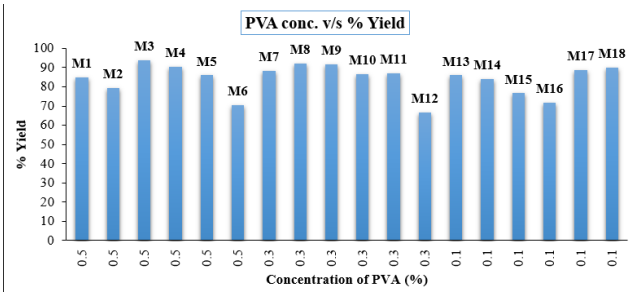

Fig. 7: Effect of PVA concentration on % Yield

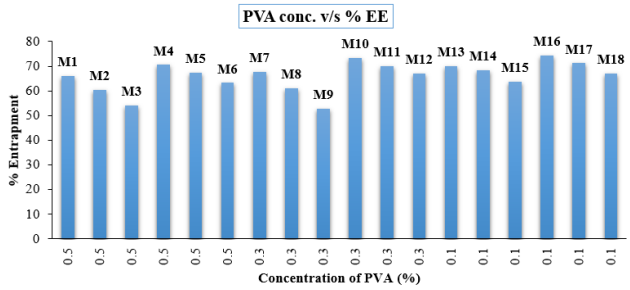

Fig. 8: Effect of PVA concentration on % EE

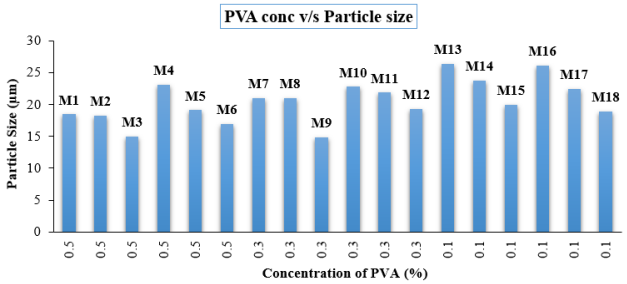

Fig. 9: Effect of PVA concentration on Particle size

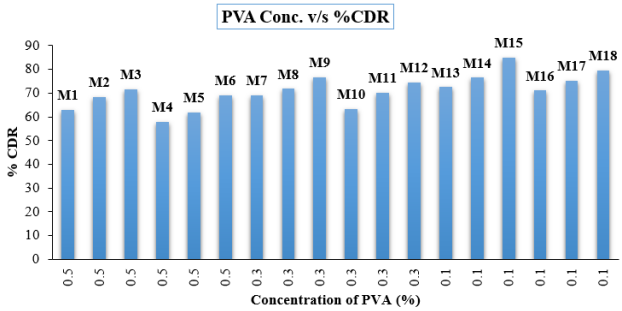

Fig. 10: Effect of PVA concentration on % CDR

4.3. Effect of stirring speed

The increase in the stirring speed equals an approximately identical decrease in the entrapment efficiency. Increasing the stirring speed delivers greater energy to the system, resulting in an increased breakdown of the forming microspheres and lower entrapment efficiency. The results confirmed that the microsphere mean size decreased with an increase in the stirring speed. The force of higher stirring distributes the internal phase into smaller droplets, resulting in the formation of smaller sized microspheres. The increase in the stirring rate results in the identical increase in the % drug release.[13]

5. Conclusion

The Vildagliptin microspheres were formed successfully by solvent evaporation technique using ethyl cellulose as a

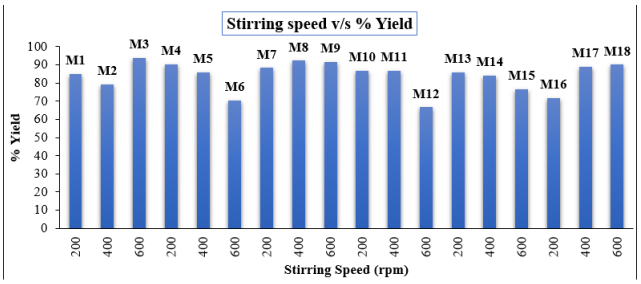

Fig. 11: Effect of Stirring speed on % Yield

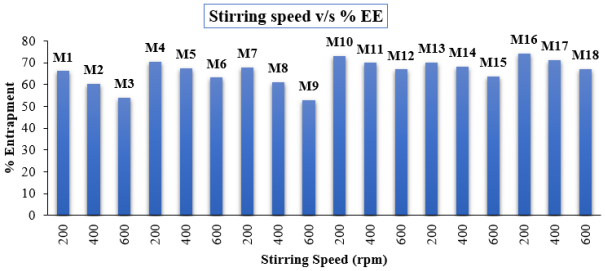

Fig. 12: Effect of Stirring speed on % EE

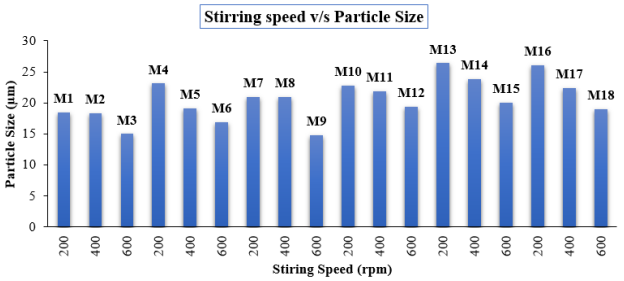

Fig. 13: Effect of Stirring speed on particle size

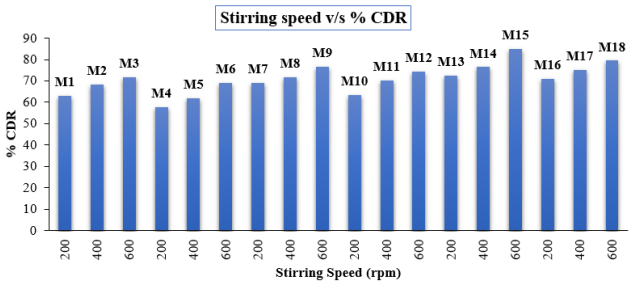

Fig. 14: Effect of Stirring speed on % CDR

polymer, in presence of polyvinyl alcohol as surfactant. Due to the sustained property of polymer and surfactant property of polyvinyl alcohol, formulated microspheres can result in controlled release of drug.

Thus, as the rpm increases, particle size decreases, results in decrease entrapment efficiency and increases the release rate. As the PVA concentration increases, particle size decreases, resulting in decrease of entrapment and release. Hence the present work suggest that, Vildagliptin which has the lower half life and eliminates quickly from the body, when loaded with ethyl cellulose in form of microspheres results in controlled release of drug in diabetes.

6. Acknowledgment

We would like to thank the DAVV UGC Consortium, Indore for providing us with the scanning electron microscopy (SEM), and UV visible spectroscopy facility. Also, we wish to acknowledge the help rendered by Dr. Masheer Ahmed Khan (Lecturer, Stage-II) and Dr. Jitendra Sainy (Lecturer, Stage) of the school of pharmacy, DAVV, Indore for guiding us with our research work.

7. Conflict of Interest

The authors declare no relevant conflicts of interest.

8. Source of Funding

None.

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Cite this article: Mane S, Vinchurkar K, Khan MA, Sainy J. Effect of formulation variables on the characteristics of vildagliptin microspheres. *IP Int J Comprehensive Adv Pharmacol* 2022;7(3):134-140.