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Formulation and Evaluation of Multi-particulate Drug Delivery System for Metformin Hydrochloride by Spray Drying Method

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Authors' contributions

This work was carried out in collaboration between both authors at Bharati Vidyapeeth's College of Pharmacy, Sector-8, CBD, Belapur, Navi Mumbai-400 614, India. Author VK designed the study. Author AS performed the formulation and development studies, wrote the protocol and wrote the first draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus is a serious emergency right now which is considered to be one of the major causes of death in all the nations. MET is considered to be one of the major medications to treat type two or insulin dependent diabetes mellitus. Though this process of oral administration may reduce the level of glucose in the blood, it shows some adverse effect on the kidney. In the presented work, a successful attempt has been taken to formulate the multiparticulate drug delivery system for MET prepared by spray drying technique. The study of *the In-vitro* release profile of spray dried particles produces the desired release profile for SR of MET. The proposed formulations have an excellent floating property which is predictive for gastro retention of the proposed formulation. It was found that concentration of Carbopol 934 and ethyl cellulose affect over the few variables. The desired release of MET was achieved by adjusting the drug and polymer ration and the drug and (polymer: polymer ratio.) SEM studies reflected that the spray dried particles obtained from optimized batch and optimized process parameters have good surface morphological characteristics.

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder resulting from a deficiency in insulin secretion, insulin action, or both. Insulin deficiency, in turn, leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration [1-4]. Thus, diabetes triggers a wide range of heterogeneous diseases. Diabetes is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025 [5-7]. Diabetes mellitus may be categorized into several types but the two major types are type 1 and type 2.

On the basis of etiology, the term type 1 and type 2 were widely used to describe IDDM and NIDDM, respectively [8-10]. Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance [11]. In Western countries, the disease affects up to 7% of the population. Globally, it affects 5-7% of the world's population [12-14].

Metformin hydrochloride (MET) is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type II diabetes, particularly in overweight and obese people and those with normal kidney function. Metformin causes few adverse effects when prescribed appropriately (the most common is gastrointestinal upset) and has been associated with a low risk of hypoglycemia. MET shows incomplete absorption from the gastrointestinal tract; its absolute bioavailability is 50 – 60%. It has a short half-life of 1.5-4 hr. It is absorbed from the proximal part of the intestine within 6 hr, so the repeated administration is required to maintain effective plasma concentration. Since MET belongs to BCS class III, it is necessary to retard dissolution to ensure the extended release of the drug. All above-cited facts make MET, the best-suited drug candidate for the sustained release drug delivery system.

The multi-particulate drug delivery systems namely microspheres, nanospheres offer many advantages over a conventional system. Multiparticulate drug delivery systems are preferred in order to obtain prolonged or controlled drug delivery, to improve bioavailability, to target the drug to specific sites, to avoid variance of gastric emptying and to release the drug in a more predictable way. Microspheres and nanospheres are commonly prepared by different techniques such as solvent evaporation, spray drying etc. Spray drying is advantageous over solvent evaporation technique because it is a single step process, is easy to control and scale up, produces the product with minimum or none residual solvent content and is less dependent on solubility parameter of drug and polymer. Carbopol 934p and Eudragit RS 100 were used as sustained release polymers.

2. MATERIALS AND METHODS

Metformin Hydrochloride was obtained as a generous gift from Wanbury Ltd., Turbhe. Tablets containing 500 mg of MET was procured from the local chemist shop. Carbopol 934p was purchased from S. D. Fine Chemicals Ltd., Mumbai. Eudragit RS 100 was purchased from Evonik Roehm Pharma Polymer.

3. EXPERIMENTAL

3.1 A Preliminary Batch of Sustained Release Particles of MET

MET sustained release particles was prepared using spray drying system.

1 g of MET was weighed and dissolved in 100ml of distilled water in a beaker. The solution was subjected to magnetic stirring for complete solubilization of MET. 1 g of the polymer was accurately weighed and added to this solution and stirring was continued until complete hydration of polymer takes place. After half an hour the resulting solution was subjected to spray drying process, the solution was sprayed using a spray nozzle through a 1 mm diameter. [Spray mate, Jay instruments Pvt. Ltd]. The process parameters were kept as given in Table 1.

Table 1. Initial process parameters

Procecss parameters	Set value
Inlet temperature	150°C
Outlet temperature	80°C
Feed pump RPM	20
Aspirator RPM	1100

3.2 Trial Batches for Screening of Primary Polymer

On the basis of reported studies, various polymers and their combinations were selected to be screened for sustained release profile. For these polymers screening experiments the process parameters were fixed as that of above-mentioned trial batches.

Numbers of trial batches were prepared using different polymers, their combinations by varying polymer-polymer combination ratios, varying drug: polymer ratios to make a proper selection of polymer(s) / drug-polymer ratio. On the basis of reported studies, various grades of Carbopol such as Carbopol 934p and carbopol 940p were used as a primary polymer to achieve sustained drug release rate. The Carbopol trial batches (A1-A6) are shown in Table 2.

Various grades of Eudragit such as Eudragit RS 100 and RL 100 were used as a primary polymer to achieve desired release rate. Eudragit trial batches (B1-B6) are shown in Table 3.

3.3 Batches Using Different Drug: Polymer Ratios

Various batches were taken using variable Drug: polymer ratios, in which two polymers were taken in 1:1 proportion (equal quantities of each polymer). Trial batches with two sustained release polymer are shown in Table 4.

3.4 Batches with Fixed Drug: Polymer Ratio and Variable Levels of Polymer Combinations (Carbopol 934p: Eudragit RS 100)

Various batches were taken to finalize the optimized combination of drug: (Polymer-polymer ratio.) Batches are shown in Table 5.

Table 2. Batches with various grades of Carbopol

	Quantity (mg)					
Batch code	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**
Drug: Polymer Ratio	**1:0.8**	**1:0.8**	**1:1**	**1:1**	**1:1.2**	**1:1.2**
MET	500	500	500	500	500	500
Carbopol 934p	400	-----	500	-----	600	-----
Carbopol 940p	-----	400	-----	500	-----	600
Total	900	900	1000	1000	1100	1100

Table 3. Batches with various grades of Eudragit

	Quantity (mg)					
Batch code	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
Drug: Polymer Ratio	**1:0.8**	**1:0.8**	**1:1**	**1:1**	**1:1.2**	**1:1.2**
MET	500	500	500	500	500	500
Eudragit RS 100	400	-----	500	-----	600	-----
Eudragit RL 100	-----	400	-----	500	-----	600
Total	900	900	1000	1000	1100	1100

Table 4. Batches using different Drug: polymer ratios

	Quantity (mg)					
Batch code	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**
Drug: polymer ratio	**1:0.5**	**1:0.75**	**1:0.8**	**1:1**	**1:2**	**1:3**
MET	500	500	500	500	500	500
Carbopol 934p	125	187.5	200	250	500	650
Eudragit RS 100	125	187.5	200	250	500	650
Total	750	875	900	1000	1500	1800

Table 5. Batches with fixed drug: polymer ratio and variable levels of polymer combinations (Carbopol 934p: Eudragit RS 100)

Ingredients	Quantity (mg)				
Batch code	**F1**	**F2**	**F3**	**F4**	**F5**
Drug: polymer Ratio	**1:0.8**	**1:0.8**	**1:0.8**	**1:0.8**	**1:0.8**
MET	500	500	500	500	500
Carbopol 934p	40	120	200	280	360
Eudragit RS 100	360	280	200	120	40
Total	900	900	900	900	900

4. EVALUATION OF MET SUSTAINED RELEASE PARTICLES

4.1 Percent Yield

Theoretical weight of drug and polymer microspheres is determined by using the formula [15].

Percentage yield = {(Weight of spray dried particles × 100) / Theoretical weight of drug and polymer}

4.2 Entrapment Efficiency

Entrapment efficiency was performed as per the following procedure [16].

The weighed amount of spray dried particles containing 100 mg equivalent of the drug was washed with distilled water to remove the free drug and then crushed in a glass mortar. The powder was suspended in 100 mL of water and was kept for shaking in a water bath shaker at ambient temperature in order to extract the drug, filtered and analyzed spectrophotometrically at 233 nm using double beam UV – Visible Spectrophotometer.

4.3 Surface Morphology

The spray dried particles were characterized by their properties such as surface morphological study and particle size using scanning electron microscopy (SEM).

The procedure followed for preparation of a sample for scanning electron microscopy (SEM) study: Shape and surface characteristics of the sustained release spray dried particles of MET were investigated and using scanning electron microscopy (Philips XL – 30 SEM, CIRCOT). The samples were mounted on an aluminum stage using adhesive carbon type and placed in a low humidity chamber for 12 hr prior to analysis. Samples were coated with gold-palladium for 60 sec under an argon atmosphere using sputter coater in a high vacuum evaporator equipped with an omnirotary stage tray.

4.4 *In-vitro* Drug Release Study

In-vitro dissolution test for spray dried particles of MET was carried out using following protocol.

The *In-vitro* release study of spray dried particles of MET was carried at 75 rpm using in USP dissolution apparatus (Type II). Spray dried particles equivalent to 500 mg of metformin were kept in a muslin cloth and that muslin cloth was fixed tied to the paddle of dissolution. At 0, 0.5, 1, 2, 4, 6, 8, 10, 12 hr, 10 ml samples was withdrawn and replaced by an equal volume of fresh dissolution medium. The samples were then subjected to suitable dilution and analyzed spectrophotometrically at 322 nm using double beam UV – Visible Spectrophotometer. The concentration of Metformin in test samples was measured and calculated using a regression equation of the calibration curve.

Table 6. *In –vitro* dissolution study Protocol

Parameter	Specification
Dissolution apparatus	U S P apparatus type II (Paddle)
Temperature	37 ℃ ± 0.5 ℃
Speed	75 rpm
Dissolution medium	Hydrochloric acid buffer pH 1.2
Volume of dissolution medium	900 ml
Sampling intervals	0, 0.5, 1, 2, 4, 6, 8, 10, 12 hrs

Table 7. Drug release kinetic studies

Model	Equation
Zero-order release kinetics	Q = Q0 + K0t
First order release kinetics	dC / dt = k (Cs - Ct)
Hixson-Crowell cube root law	Q01/3 – Qt1/3 = KHCt
Higuchi Model	Qt = kH (t) 0.5
Korsmeyer-Peppas Model	Mt/M N = Ktn.

4.5 Drug Release Kinetic Studies

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. To describe the kinetics of drug release from matrix tablet, mathematical models such as zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The criterion for selecting the most appropriate model is based on the goodness of fit test. Formulas for mathematical model calculation are given Table 7.

5. RESULTS AND DISCUSSION

5.1 Preliminary Batch of Sustained Release Particles of MET

The spray dried particles obtained from preliminary batches were not good in appearance, the particles were not in good texture, and also the particles were not spherical. Percent yield was found to be 32%. Entrapment efficiency was found to be 41%. The entrapment efficiency and percent yield of the preliminary batch were found to be very low, the number of trial batches was tried with different approaches by making variations in polymers, drug-polymer ratio as well as process parameters.

5.2 Trial Batches for Screening of Primary Polymer

The spray dried particles obtained from batches A2, A4, A6 was not good in appearance and texture. These particles were not found spherical after microscopic evaluation. Also, the percentage yield was found to be very low, hence these batches were not considered for further evaluation. Results of entrapment efficiency Carbopol trial batches (A1, A3, A5) are shown in Fig. 1.

The spray dried particles obtained from batches B2, B4, B6 was not good in appearance and texture. These particles were not found spherical after microscopic evaluation, also the percentage yield was found to be very low, hence these batches were not considered for further evaluation. Results of eudragit trial batches are summarised in Fig. 2.

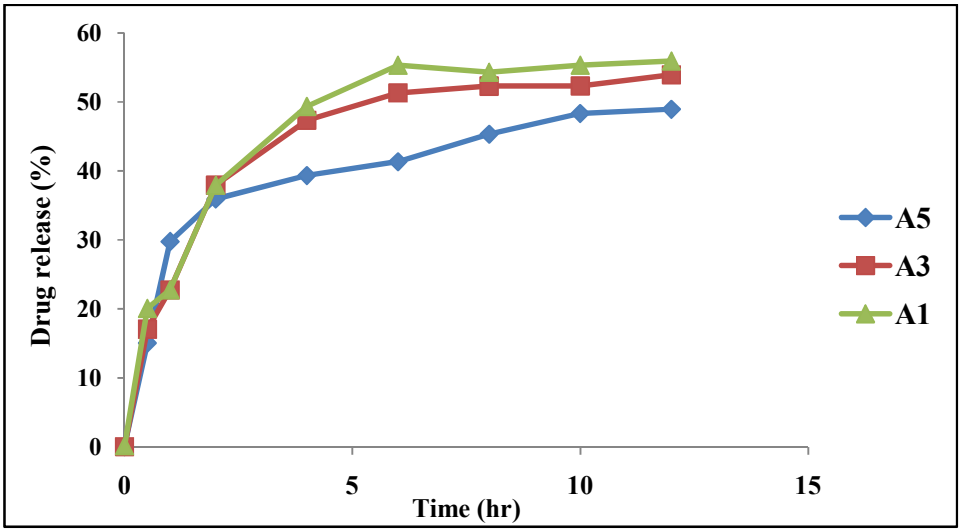

Fig 1. *In-vitro* drug release study of batches A1, A3 and A5

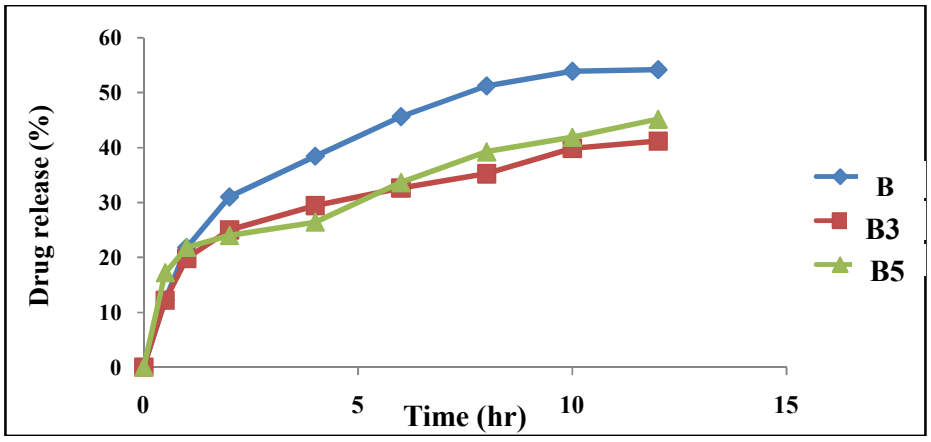

Fig 2. *In-vitro* drug release study of batches B1, B3 and B5

In-vitro drug release profile of batches prepared using carbopol 934p and eudragit RS 100 and their entrapment efficiency is tabulated in Table 8.

The entrapment efficiency was observed to be less. Percent drug release from batches B2, B4 and B6 was found to be incomplete. Hence, further trials with different polymers were tried.

5.3 Characterization of Batches Using Different Drug: Polymer Ratios

The appearance with respect to texture and sphericity of spray dried particles and the product yield was acceptable for all these batches except batch C6. Results entrapment efficiency and percent drug release in batches using different Drug: polymer ratios are tabulated in Table 9.

Table 8. Percent drug release and entrapment efficiency

Time (Hr)	Percent drug release (%)					
	Carbopol 934p			Eudragit RS 100		
	A1	A3	A5	B1	B3	B5
0	0.046	0.066	0.16	0.10	0.08	0.1
0.5	15.06	17.06	20.06	12.27	12.27	17.27
1	29.76	22.76	22.76	21.86	19.86	21.86
2	35.93	37.93	37.93	31.06	25.06	24.06
4	39.33	47.33	49.33	38.47	29.47	26.47
6	41.32	51.32	55.32	45.68	32.68	33.68
8	45.31	52.31	54.31	51.26	35.26	39.26
10	48.32	52.32	55.32	53.91	39.91	41.91
12	48.93	53.93	55.93	54.20	41.20	45.20
% Entrapment	**55**	**53**	**48**	**54.2**	**41.2**	**45.20**

Table 9. *In-Vitro* drug release profile of batches using different Drug: polymer ratios

Time (hr)	Percent drug release (%)				
	C1	C2	C3	C4	C5
0	2.45	0.05	0.48	0.18	0.037
0.5	45.95	1.66	13.45	12.75	12.07
1	56.07	16.52	23.51	24.13	18.04
2	60.78	31.32	33.43	46.82	35.39
4	62.78	45.59	55.32	64.18	54.64
6	62.20	57.52	67.06	70.08	61.43
8	63.25	64.61	72.95	72.89	70.86
10	64.31	74.30	79.24	74.29	72.05
12	64.60	74.09	83.17	78.46	76.78
% Entrapment	**67**	**75**	**80**	**71**	**70**

5.4 Batches with Fixed Drug: Polymer Ratio and Variable Levels of Polymer Combinations (Carbopol 934p: Eudragit RS 100)

Entrapment efficiencies and percentage yield of prepared spray dried batches (F1- F5) and *In-Vitro* drug release profile of batches F1 to F5 are given in Fig. 3 and Table 10.

After evaluation, all the parameters Batch F3 was selected as an optimised batch of MET spray dried sustained release particles. Entrapment efficiency of batch F3 was found to be 90% and its percent yield was found to be 90%. So batch F3 was selected as the optimized batch of spray dried multi-particulate drug delivery system.

5.5 Surface Morphology

Morphological evaluation of final optimized batch (F3) was carried out using scanning electron microscopy. An electron micrograph is shown in Figs. 4a, 4b, 4c, and 4d.

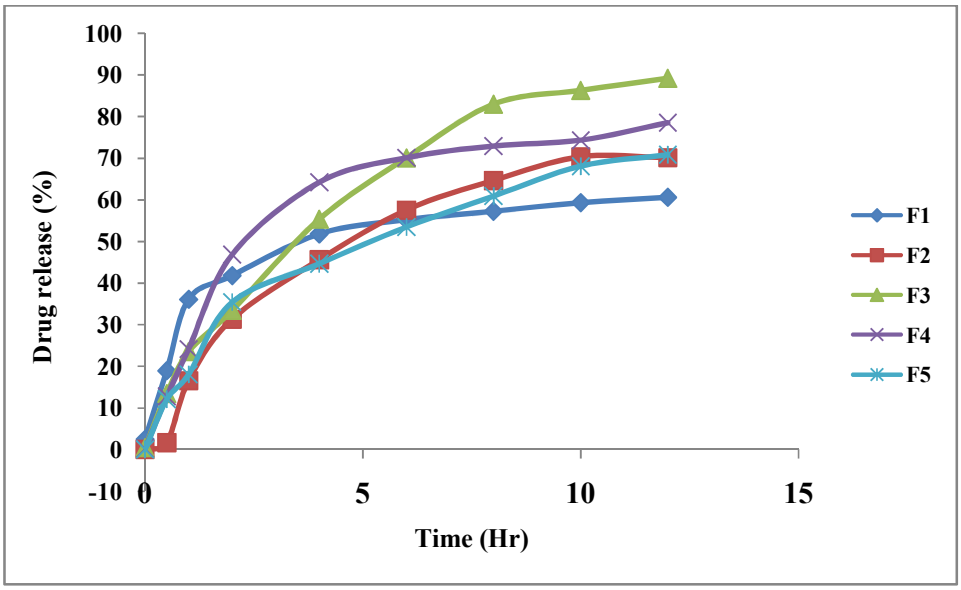

Fig. 3. *In-Vitro* drug release profile of fixed drug: Polymer ratio and variable levels of polymer combinations

Table 10. *In-vitro* drug release profile of fixed drug: Polymer ratio and variable levels of polymer combinations

Time (Hr)	Percent drug release (%)				
	F1	**F2**	**F3**	**F4**	**F5**
0	2.45	0.05	0.48	0.18	0.03
0.5	18.95	1.66	13.45	12.75	12.07
1	36.07	16.52	23.51	24.13	18.04
2	41.78	31.32	33.43	46.82	35.39
4	51.78	45.59	55.32	64.18	44.64
6	55.20	57.52	70.06	70.08	53.43
8	57.25	64.61	82.95	72.89	60.8
10	59.31	70.30	86.24	74.29	68.05
12	60.60	70.09	89.17	78.46	70.78
% Entrapment	**65**	**79**	**90**	**83**	**72**
Percentage Yield	**75**	**81**	**90**	**78**	**70**

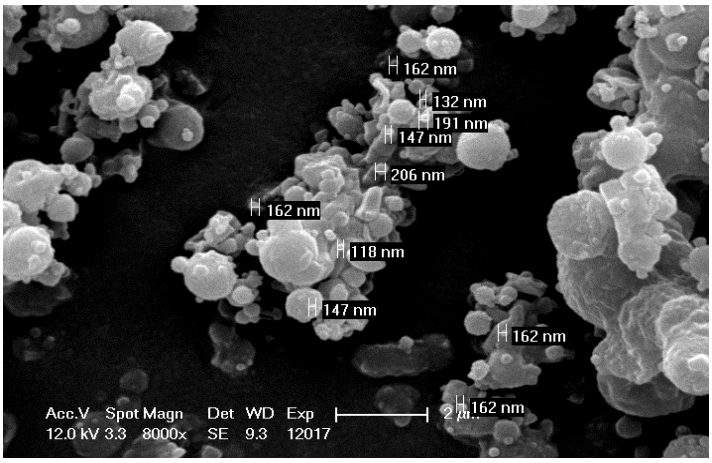

Fig. 4a. Electron micrograph of optimized batch F3 showing particles in the range of 893 nm to 4.32 micrometer

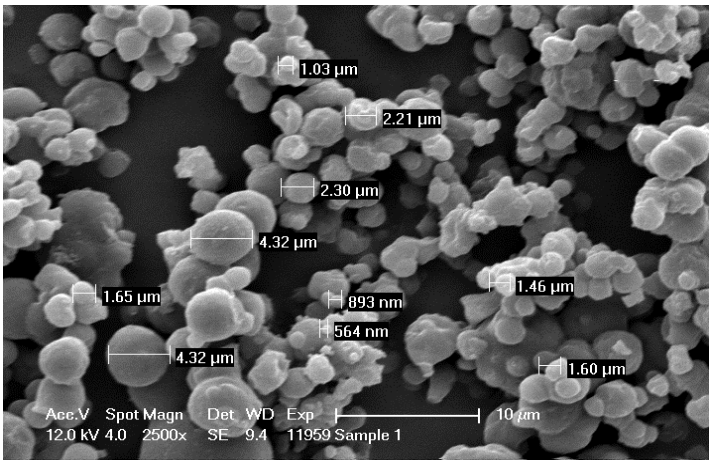

Fig. 4b. Electron micrograph of optimized batch F3 F3 showing particles in the range of 118 nm to 206nm

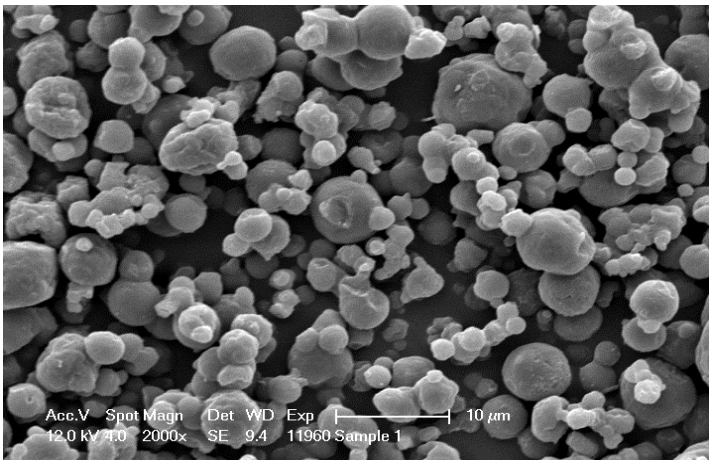

Fig. 4c. Electron micrograph of optimized batch F3

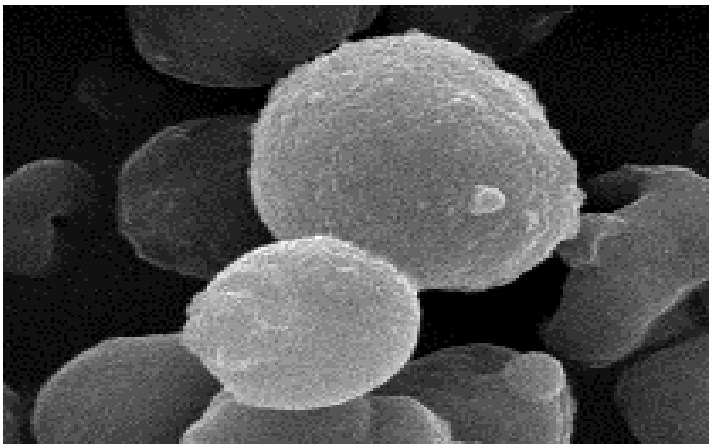

Fig. 4d. Electron micrograph of optimized batch F3 showing surface morphology

SEM studies reflected that the spray dried particles obtained from optimized batch F3 and optimized process parameters have good surface morphological characteristics. The particle size range was observed to be in the broad range of 118 nm to 4.32 micrometers. Thus we could prepare multiparticulate system having a particle size in the range of nanospheres as well as microspheres. It can be considered as a mixture of nanospheres and microspheres, we have referred these spray dried particles as “semi-nano-microspheres”.

6. CONCLUSION

A successful attempt has been made to formulate multiparticulate drug delivery system for MET could be prepared by spray drying technique. The study of the *In-vitro* release profile of spray dried particles produces the desired release profile for sustained release of MET. The prepared formulations have excellent floating properties which is predictive for gastro retention of the proposed formulation. It was found that concentration of Carbopol 934 and ethyl cellulose affected the few variables such as drug entrapment efficiency, *In-vitro* drug release of MET etc. The desired release of MET was achieved by adjusting the drug and polymer ration and the drug and (polymer: polymer ratio.) SEM studies reflected that the spray dried particles obtained from optimized batch F3 and optimized process parameters have good surface morphological characteristics. In the context of different parameters, it may be concluded that F3 (1:0.8 ratio) formulation shows comparatively better results hence F3 batch was selected as an optimised batch. These sustained release multi-particulate drug delivery may fulfill the need of diabetic patients those who regularly consume the drug orally.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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