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Development and Characterization of Carbopol PVP Microspheres of Metformin HCl

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ABSTRACT
The aim of the present work is to investigate the possibility of obtaining a predetermined controlled manner leading to reduction of dosing frequency and enhanced bioavailability for effective level of Metformin loaded microsphere formulations using Carbopol934 and PVP as carriers. In the present study Carbopol-PVP based microspheres bearing metformin were prepared by emulsion cross-linking method. The prepared microspheres were studied for drug loading, particle size distribution, in vitro release characteristics, and stability studies. The microspheres were found to have diameters within the range of 105 to 123 µm and incorporation efficient of 81 to 88% was obtained. Percent drug release after 8 hours was 88.4 3.8% in SGF (pH 1.2), and 95.3 1.4% in PBS (pH 7.4). Stability studies showed that maximum drug content and closest in vitro release to initial data was found in the formulationstored at 4ºC.

Keywords: Metformin HCl, Carbopol934, Microspheres, Emulsion cross-linking, Surfactant, PVP

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder of multiple etiologies. It is characterized by chronic hyperglycemia together with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both.

Diabetes was first documented by the Egyptians and is characterized by weight loss and polyuria; it was the Greek physician Aertaeus who coined the term diabetes mellitus (DM). In Greek, diabetes means “to pass through” and mellitus is the Latin word for honey (referring to sweetness). These are associated with the development of the specific microvascular complications of retinopathy, which can lead to blindness, nephropathy with potential renal failure, and neuropathy. The latter carries the risk of foot ulcers and amputation and also autonomic nerve dysfunction. Diabetes is also associated with an increased risk of macrovascular disease. Diabetes is an important cause of prolonged ill health and premature mortality.

Worldwide the number of adults suffering from diabetes will rise from 194 million in 2003 to nearly 380 million in 2025. The countries most affected by this epidemic in the year 2025 will be India, China and the USA. The change in life expectancy and lack of improvement in healthcare are in part responsible for the astounding rise in the incidence of DM. As a result there is an upward trend of occurrence of diabetes, especially in the urban areas. Consequently, countries across the globe will face a significant increase in the burden for health care, as patients with diabetes are prone to both short-term and long-term complications and premature death.

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Type of Diabetes:

Classification of diabetes

- Type 1 (β cell destruction, usually leading to absolute insulin deficiency)
  - Autoimmune
  - Idiopathic
- Type 2
  - Ranges from predominantly insulin resistant, with relative insulin deficiency, to a predominantly insulin secretory defect, with or without insulin resistance
- Gestational diabetes

- Other specific types
  - Genetic defects of β cell function
  - Genetic defects of insulin action
  - Diseases of exocrine pancreas
  - Endocrinopathies
  - Drug induced or chemical induced, e.g. steroids
  - Infections
  - Uncommon forms of immune - mediated diabetes

Figure: 1 Classification of diabetes

Microsphere as drug delivery systems for management of Diabetes Mellitus:

The use of microspheres as drug delivery systems is thought to be an effective way to precisely deliver the drug to the target site and to maintain the desired concentration at the site of interest without causing any negative side effects. Microparticles are another name for microspheres. For some years, sustained drug delivery has received significant interest in microsphere carrier systems built from naturally occurring biodegradable polymers. There are several methods for delivering a medicinal chemical to the target site with a regulated release that is sustained. Microspheres are small and have a high surface-to-volume ratio. They have colloidal characteristics at the smaller end of their size range.

II. MATERIAL AND METHODS:

Materials

The drug Metformin was genially supplied as a gift sample from Glenmark Pharmaceutical Industries Ltd. Nasik, India. Carbopol was procured from Himedia Laboratories Pvt. Ltd, Mumbai, India. PVP, Span 80 and n-Hexane were procured from central drug house Pvt. Ltd. Mumbai, India. All other chemicals were used of analytical grade.

Methods

- **Tests for Identification**

Dissolve 25 mg in 5 ml of water, add 1.5 ml of 5 M sodium hydroxide, 1 ml of 1- naphthol solution and, drop wise with shaking, 0.5 ml of dilute sodium hypochloride solution; an orange-red colour is produced which darkens on keeping

- **Determination of solubility of various solvents**

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Solubility determination of Metformin was carried out in various common solvent. An accurately weighed quantity (10 mg) of the drug was taken in series of 25 ml volumetric flasks and 10 ml of each solvent was added separately to these flasks. Flasks were clamped and shaken in vortex shaker for 6 hour at room temperature. The flasks were observed visually for the presence of insoluble particle of the drug. The supernatant was taken and filtered. Quantitative determination of metformin was carried out after suitable dilution using UV /Visible spectrophotometer (UV 1800, Shimadzu, Japan).

- **Preparation of Standard Calibration Curve of Metformin**

An accurately weighed quantity of Metformin Hydrochloride (10mg) was dissolved in a 2ml of methanol and volume made up to 100ml with SGF (pH 1.2) to prepare a stock solution of 100µg/ml of drug. It was diluted to 10µg/ml with SGF (pH 1.2) was scanned between 200- 400 nm to obtain the absorbance maxima was obtained at 233nm.

From the above stock solution ,aliquots of 0.2,0.4,……2.0 ml were withdrawn into a series of 10ml volumetric flasks and diluted to 10ml with SGF (pH 1.2). This gave the drug solution in a final concentration range of 2-20 µg/ml. This absorbance of each solution was measured using spectrophotometer at λmax 233nm. (Table. 2)

- **HPLC analysis of Metformin Hydrochloride:**

Accurately weighed 10 mg of Metformin Hydrochloride was transferred into a clean and dry volumetric flask, a minimum volume of 0.1M phosphate buffer (pH 2.5): acetonitrile (25:75 ratio) was added, the volumetric flask was shaken gently to dissolve whole amount of the drug and the volume was made up to 100 mL with the 0.1M phosphate buffer (pH 2.5): acetonitrile (25:75 ratio). Then prepared the proper aliquots having concentration ranging from 2-20 □ g/mL and standard curve of Metformin Hydrochloride was prepared. In this HPLC analysis of Metformin Hydrochloride Mobile Phase- Phosphate Buffer (0.1M, pH 2.5) and Acetonitrile in 25:75 v/v ratio, Flow rate- 1.0 mL/min, Column- C18, λmax-233 nm and temperature- 25±2ºC was taken.

PREPARATION OF MUCOADHESIVE MICROSPHERES:

The Mucoadhesive microspheres were prepared by modified emulsion cross-linking method The aqueous phase was prepared by dissolving CARBOPOL (1g) and PVP (0.2g) in 5 ml of ethanol/water (7/3 v/v) mixture. And then drug 100mg was dissolved in it. The aqueous phase was then added to an organic phase of petroleum ether, light liquid paraffin (60:40 v/v containing 1.5%v/v span 80), under constant stirring at 500 rpm for 10 min at 350C, using a mechanical stirrer (Remi, India) to form w/o emulsion. After 10 min 0.8 ml glutaraldehyde was added as cross-linking agent at 40°C for 4 hours, the prepared microsphere were gradually hardened and collected by filtration. They were washed three times with n-haxane and dried at room temperature.

Table.1 the optimized variables for the preparation of microspheres were selected as follows

S. No.	Variables	Optimized value
1.	Conc. Of polymers	0.2:1
2.	Drug concentration	100 mg
3.	Surfactant concentration	1.5 (% v/v)
4.	Glutaraldehyde	0.8%
5.	Stirring speed	500rpm
6.	Stirring time	4hrs

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CHARACTERIZATION OF PVP-CARBOPOL MUCOADHESIVE MICROSPHERES

A. Particle size

Microspheres were studied microscopically for their size and size distribution using calibrated ocular micrometer.

B. Determination of drug loading in PVP Carbopol microspheres

The amount of Metformin loaded in microspheres was analyzed in terms of surface adsorbed drug and entrapped drug.

C. Degree of Swelling of PVP Carbopol microspheres

For estimating the degree of swelling 1gm of microsphere were suspended in 5 mL of simulated gastric fluid USP (pH 1.2). The particle size was monitored by microscopy technique every 1 hour using an optical microscope (Labomed CX RIII). The increase in particle size of the microspheres was noted for up to 8 hours.

The formula used for calculation of degree of swelling is given below

□= [□g-□0]/□0

Where □ = degree of swelling,

□ 0 = initial weight of microspheres, □ g = final weight of microspheres

D. In Vitro Drug Release Studies from PVP-Carbopol Microspheres in Different pH of Simulated GIT Fluids

The dissolution test of metformin microspheres was carried out by the paddle type-II dissolution apparatus specified in USP XXIII. 500 mg of metformin loaded microspheres was weighed accurately and gently spread over the surface of 900 mL of dissolution medium. The content was rotated at 100 rpm and thermostatically controlled at 37□ 0.5°C. Perfect sink condition was abounding during the drug dissolution. The release was tested in dissolution medium of SGF (pH 1.2), SIF (pH 8.8) and PBS (pH 7.4). An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through 0.45µm- syringe filter (Millipore millex HN) and analyzed spectrophotometrically.

III. RESULTS AND DISCUSSIONS

➢ **Tests for Identification**

The drug, Metformin Hydrochloride was found to be a white, crystalline and odorless powder.

➢ **Determination of solubility of various solvents**

The experiment was repeated with the different volume of the solvents to obtain more appropriate degree of solubility. The solubility profile of metformin in different solvent is given in Table.2

Table 2 solubility profile of metformin in different solvent at room temperature (25±2)

S.No	Solvent (s)	Observed Solubility
1	Water	Very Soluble
2	PBS(7.4)	Freely soluble
3	Ethanol (95%)	Slightly soluble
4	Acetone	Practically insoluble
5	Chloroform	Practically insoluble

➢ **Preparation of Standard Calibration Curve of Metformin**

The standard curve of Metformin Hydrochloride was prepared spectrophotometrically at λmax 233nm by UV –Visible spectrophotometer (UV-1800, Shimadzu, Japan) in SGF (pH 1.2)

A straight line was obtained for 2-20µg/ml concentration with correlation coefficient (r^2) 0.999.

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Table 3 Standard Curve of Metformin Hydrochloride in SGF (pH 1.2) at λmax 233 nm:-

S. No	Concentration µg/ml	Absorbance	Statistical analysis
1	2	0.16	
2	4	0.247	Correlation coefficient R^2 = 0.999
3	6	0.346	Straight line equation Y =0.048x + 0.055
4	8	0.44	
5	10	0.538	
6	12	0.646	
7	14	0.742	
8	16	0.841	
9	18	0.932	
10	20	1.03	

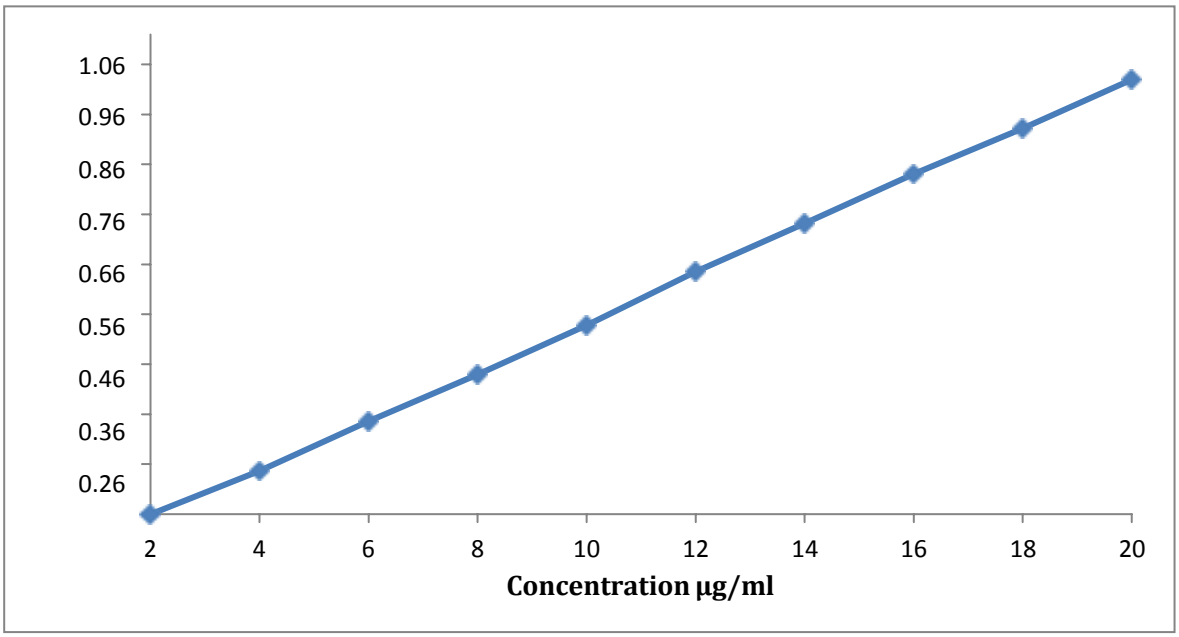

Fig .2 Standard Curve of Metformin Hydrochloride in SGF (pH 1.2) at λ_{max} 233 nm

- **HPLC analysis of Metformin Hydrochloride:**

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In HPLC analysis the retention time for Metformin Hydrochloride was found to be 2.520 min

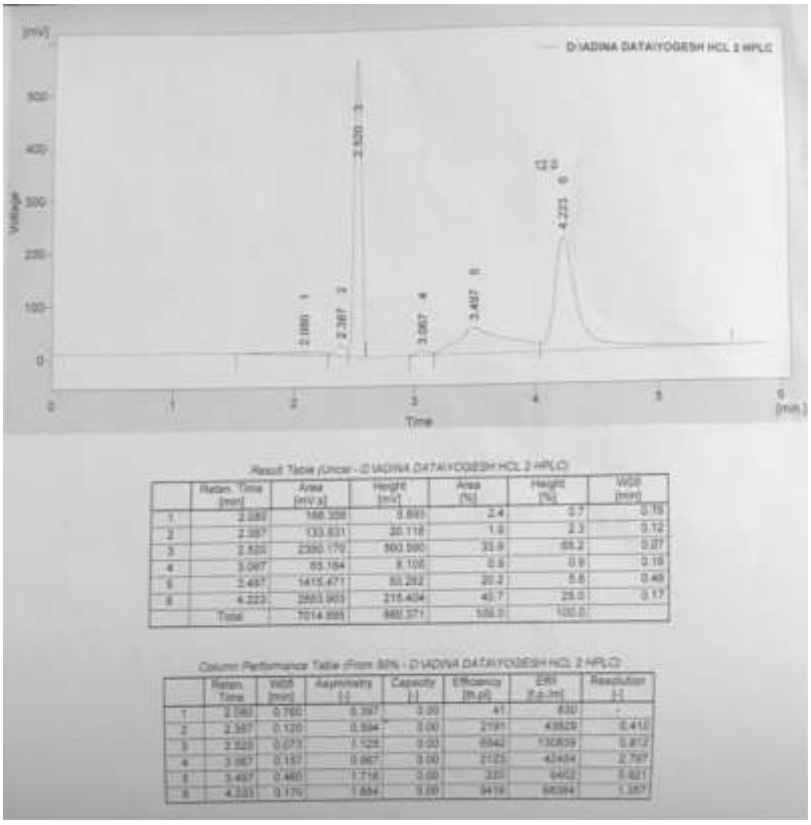

Fig.3 HPLC Curve of Metformin Hydrochloride

CHARACTERIZATION OF PVP-CARBOPOL MUCOADHESIVE MICROSPHERES

A. Particle size & drug loading

The average Particle size of optimized formulation was found to be 109.3±2.3 µm with 91.3±1.2% drug entrapment efficiency. The observation recorded in Table 4.

Table.4 Characteristic of optimized microspheres formulation

S.No.	Formulation	Particle size(µm)	Particle shape	Drug loading (%)
1.	microspheres	109.32±2.3	Circular shape	91. 3 ± 1.2%

B. Degree of Swelling of PVP Carbopol microspheres

The swelling degree of optimized PVP-Carbopol was found to be 1.90 respectively.
The observations are recorded in Table5

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Table 5 Degree of swelling of PVP-Carbopol microspheres

S.No.	Microspheres	Degree of Swelling
1.	PVP-Carbopol microspheres	1.90

C. In Vitro Drug Release Studies from PVP-Carbopol Microspheres in Different pH of Simulated GIT Fluids

In vitro metformin release from optimized microspheres was carried out in SGF (pH 1.2) and PBS (pH 7.4) by dissolution paddle apparatus type-II specified in the U.S.P. XXIII. Nearly linear relationship between the % cumulative release of Metformin and the square root of time was obtained for the first 8 hr. suggested that the microspheres formulation follows a diffusion controlled drug release mechanism. The % Cumulative amount of drug release was found PVP-Carbopol uncoated microsphere 88.4±3.8% in SGF (pH 1.2), and 95.3±1.4% in PBS (pH 7.4) up to 24 hrs. The observations are recorded in Table 6, and graphically shown in Fig.4. The results clearly suggest that microspheres formulation could be utilized for sustained and drug delivery purpose

Table 6 % cumulative metformin release from PVP-Carbopol microspheres in different pH of buffer medium

S No.	**Time interval (hrs)**	**SGF (pH 1.2)**	**PBS (pH 7.4)**
1	0.5	8.5□ 0.9	9.1□ 2.2
2	1	13.6□ 1.4	14.3□ 1.3
3	2	20.3□ 2.3	20.3□ 1.7
4	3	25.6□ 3.1	31.4□ 2.1
5	4	32.2□ 3.4	39.5□ 1.2
6	5	40.6□ 3.2	57.5□ 2.1
7	6	52.7□ 3.1	68.6□ 2.5
8	7	59.2□ 3.5	75.1□ 1.8
9	8	65.3□ 3.2	80.4□ 2.6
10	24	88.4□ 3.8	95.3□ 1.4

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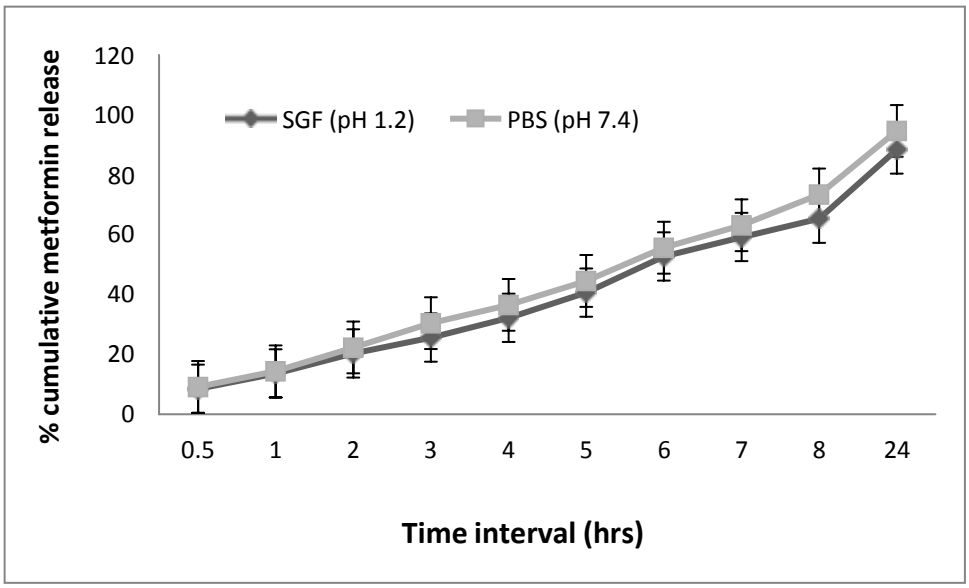

Fig .3 % cumulative metformin release from PVP-Carbopol microspheres indifferent pH of buffer medium

IV. CONCLUSION

Recently microspheres prepared by emulsion cross-linking method have gained importance. By this method, the microspheres could be easily prepared using simple instruments and the drug could be entrapped within PVP-Carbopol microspheres in a completely aqueous environment under mild conditions.

The findings of every experiment conducted for this study revealed that a mixture of PVP-Carbopol polymers might be used to create PVP-Carbopol microspheres with sustained release. By extending the gastric emptying time of the dosage form, the PVP-Carbopol microspheres drug delivery system offers the opportunity to improve the bioavailability and control the release of Metformin, exhibiting an absorption window and ensuring availability of the drug at the site of absorption for the desired period of time. As the PVP-Carbopol microspheres demonstrated good drug release qualities, there is a lot of promise for their application as tablets, both in granular and powder form.

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