



## Development and Characterization of Muco-Adhesive Microcapsules Containing Hypoglycemic Drug

Singh Chhater<sup>1\*</sup>, Kumar Praveen<sup>2</sup>

Shri Venkateshwara University Rajabpur, Gajraula/SVU, (U.P.) India  
S.D. College of Pharmacy & Vocational Studies, Muzaffarnagar, (U.P.) India

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### ABSTRACT

Pioglitazone is a poorly water soluble drug, having short biological half life (3-5 hour) so the present study was aimed to increase the biological half life by develop a sustained release microcapsule. The microcapsules of pioglitazone hydrochloride were prepared by employing sodium alginate as a cell forming polymer and by using a different bio-adhesive polymers as carbopol, HPMC and sodium CMC in a various ratios of 1:1, 3:1, 6:1 & 9:1, by orifice ion gelation method. Scanning electron microscope photographs of samples revealed that all prepared microcapsules were almost spherical in shape and have a slightly smooth surface. The *in vitro* release profile of Pioglitazone hydrochloride indicates that all the batches of microcapsules showed controlled and prolonged drug release over an extended period of 10 h. FT-IR spectra revealed no chemical incompatibility between drug and the polymers.

**Keywords:** Hypoglycemic Drug, Mucoadhesion, Microcapsule, Orifice Ionic Gelation Method.

### 1. INTRODUCTION

Pioglitazone is a Thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action <sup>(1,2)</sup>. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR $\gamma$ ) <sup>(3)</sup>.

Therefore control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patient compliance; there are few reports <sup>(4)</sup> on the formulation of pioglitazone employing coated granules and matrix tablets. Microencapsulation has been accepted as a process to achieve controlled release and drug targeting. The choice of the methods

for the preparation of microcapsules depends on many factors such as the drug solubility and its short half life 3-5 hour <sup>(2)</sup> and is eliminated rapidly. In the present study, an attempt was made to develop sustained release microcapsules to increase half-life of drug concentration in serum by using orifice ionic gelation method. The prepared microcapsules were evaluated for drug content, particle size, surface morphology, muco-adhesive testing and *in vitro* drug release studies. Mucoadhesion has been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form at the site of application or the

\*Corresponding author: Chhater singh | S.D. College of Pharmacy & Vocational Studies, Muzaffarnagar, (U.P.) India  
| Email: [pharma\\_pharm@yahoo.com](mailto:pharma_pharm@yahoo.com) Tel. +919410654914

absorption and to facilitate intimate contact dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs.<sup>(5-7)</sup>

## 2. MATERIALS AND METHODS:

### 2.1 Materials:

Pioglitazone HCl sample from Ontop Pharmaceuticals LTD (Bangalore, India), Sodium carboxymethylcellulose (sodium CMC), Methyl cellulose (Mc) and Hydroxypropylmethylcellulose (HPMC) was purchase in the market; all the chemicals were A.R. Grade.

### 2.2.1 Estimation of Drug

#### 2.2.1.1 Linear regression equation method

Accurately weighed about 100 mg of pioglitazone hydrochloride was dissolved in 100 ml Phosphate buffer (pH 7.4) to obtain 1000 µg/ml concentration of drug (stock A). Stock A (10 ml) was diluted up to 1000 ml with solvent system to obtain 10 µg/ml concentration (Stock B). Aliquots of Stock B were diluted to obtain concentrations of 1, 2, 3, 4, 5 to 10 µg/ml of pioglitazone hydrochloride. All dilutions were scanned from 400 to 200 nm against solvent system as blank (figure 1) and their absorbance were observed at 269 nm (Figure 2). The LRE was developed as  $Y = 0.0202x + 0.0013$ , where Y = absorbance and C = concentration of dilutions in µg/ml, with the correlation coefficient  $r^2 = 0.9998$ .

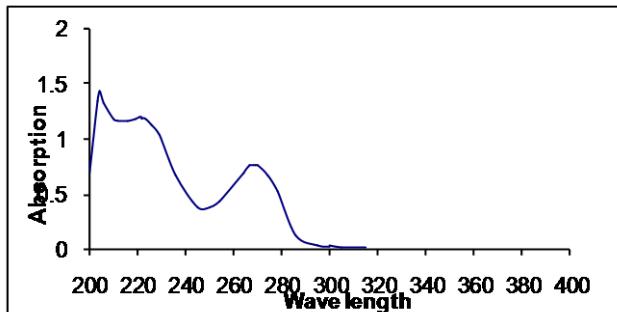


Figure 1: Spectra of pioglitazone HCl in phosphate buffer (pH 7.4)

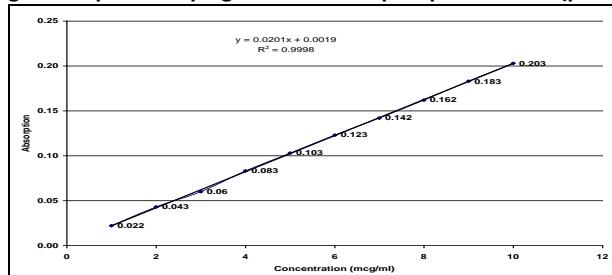


Figure 2: Calibration graph of pioglitazone HCl

### 2.2.1.2 Standard absorptivity method

Five dilutions were prepared in triplicate and the absorbance was observed at 269 nm. The standard absorptivity e was calculated from the above observations (Table 1).

Concentration (mcg/ml)	Absorption			Standard Absorptivity (e=A/BC)		
	I	II	III	I	II	III
1	0.022	0.021	0.023	220.0	210.0	230.0
2	0.043	0.045	0.046	215.0	225.0	230.0
3	0.06	0.064	0.067	200.0	213.3	223
4	0.083	0.082	0.085	207.5	205.0	212.5
5	0.103	0.107	0.105	206.0	214.0	210.0
6	0.123	0.127	0.120	205.0	211.6	200.0
7	0.142	0.146	0.139	202.8	208.5	198.5
8	0.162	0.164	0.167	202.5	205.0	208.7
9	0.183	0.185	0.178	203.3	205.5	197.7
10	0.203	0.205	0.208	203.0	205.0	208.0

\* e = Absorptivity, A= Absorbance, B= Width of cuvette (1 cm), C = Concentration

Table 1: Data of absorption and absorptivity at different concentration on 269 nm

### 2.2.2 Fourier transforms infrared spectroscopy:

FT-IR spectra ( $500\text{-}4000\text{ cm}^{-1}$ ) were obtained on a Nicolet Avatar 37- DTGS FT-IR spectrophotometer (Nicolet) with a resolution of  $4\text{ cm}^{-1}$ . KBr pellets were prepared by gently mixing 1 mg sample with 200 mg potassium bromide (Figure-3).

### 2.3 Preparation of muco-adhesive microcapsules

Microcapsules are prepared by orifice- ionic gelation method<sup>(8, 9)</sup> by employing the Sodium alginate as a cell forming polymer and Sodium CMC, HPMC and Carbopol as muco-adhesive<sup>(10)</sup> polymers are dissolved in purified water in a corresponding ratio 1:1, 1:3 and 6:1 separately to form a homogenous polymer solution. Core material pioglitazone hydrochloride (1 gm) is added to polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion is then added manually drop wise into  $\text{CaCl}_2$  (10% w/v) solution through a syringe with a needle of size no. 18. The added drop lets are related in the  $\text{CaCl}_2$  solution for 15 min to complete the curing reactions and to produce spherical rigid microcapsule. The microcapsules are collected by decantation, and the product thus separated, washed repeatedly with water and dried at  $45^\circ\text{C}$  for 12 hrs. (Table-2)

Formulation code	Composition and ratio	Drug (mg)	Cell forming polymer (mg)	Mucoadhesive Polymer (mg)
MC1	SA: SCMC (1:1)	1000	500	500
MC2	SA: HPMC (1:1)	1000	500	500
MC3	SA: Carbopol (1:1)	1000	500	500
MC4	SA: SCMC (3:1)	1000	750	250
MC5	SA: HPMC (3:1)	1000	750	250
MC6	SA: Carbopol (3:1)	1000	750	250
MC7	SA : SCMC (6:1)	1000	857.14	142.86
MC8	SA : HPMC (6:1)	1000	857.14	142.86
MC9	SA : Carbopol (6:1)	1000	857.14	142.86

Table: 2. Composition of different muco-adhesive microcapsules

Note: Sodium alginate =SA, Sodium CMC = SCMC

## 2.4 Characterization of microcapsules:

### 2.4.1 Physical characterization <sup>(13, 14)</sup>

The surface and inner part of the microspheres was observed through the Scanning Electron microscopy (SEM), (SEM) was performed for surface and inner morphological characterization of microspheres using the scanning electron microscope (SEM- LEICA S430, London, UK). (Fig-4)

### 2.4.2 Particle Size Distribution

Different sizes of microcapsules in a batch were separated by sieving method using a range of standard sieves (#10, #22, #44, #52 and # 60). The amount retained on different sieves was weighed. From the obtained data, weight percent retained on different sieves and average size of microcapsules were calculated.

### 2.4.3 Practical yield:

The percentage yield of Pioglitazone in the microencapsulated product is determined by using the formula:

$$\% \text{ Yield} = \frac{\text{Weight of Microcapsules}}{\text{Theoretical Weight of drug and polymer}} \times 100$$

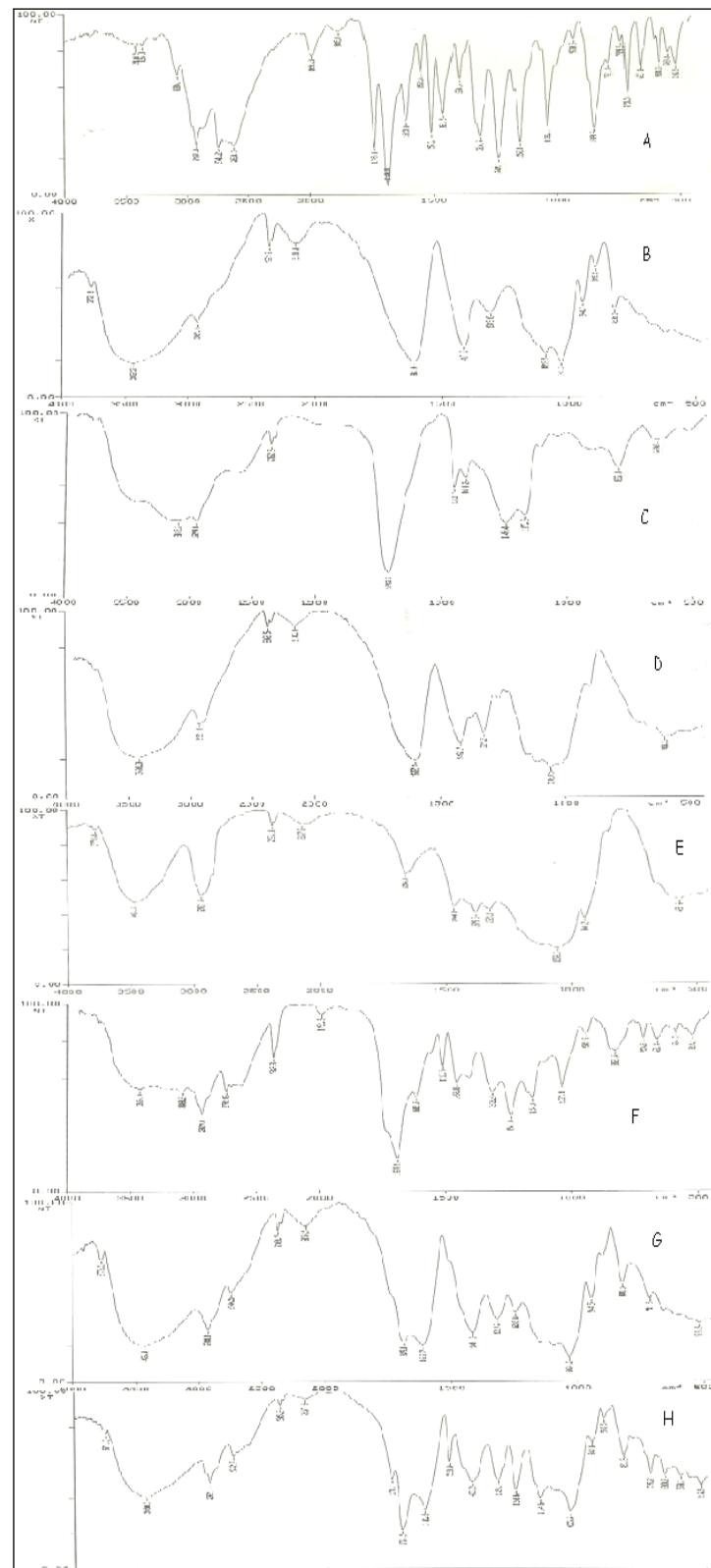
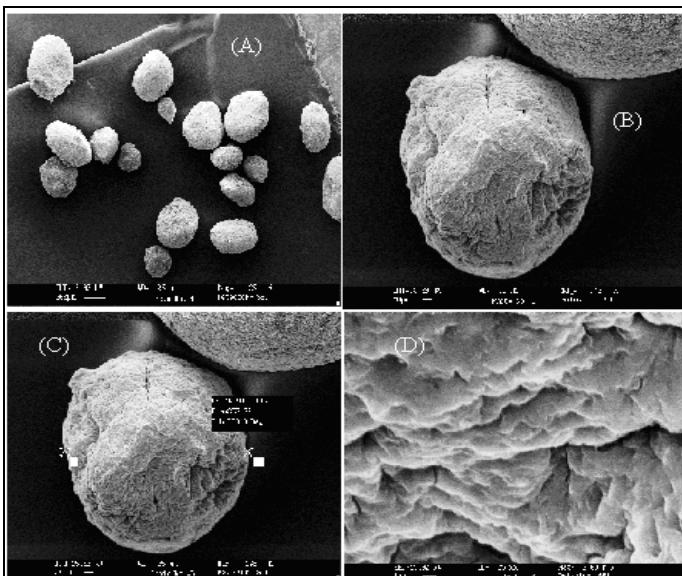


Figure: 3. FIR of (A) Pioglitazone HCl, (B) Sodium alginate, (C) Carbopol, (D) Sodium CMC, (E) HPMC, (F) Mixture of A, B and C, (G) Mixture of A, B and D, (H) Mixture of A, B and E



**Figure.4:** SEM photographs of Pioglitazone (A) microcapsules with size ranging approximately from 300 to 900  $\mu\text{m}$ , (B) Individual microcapsules (C) microcapsules showing the size 353.33  $\mu\text{m}$ , (E) Surface topography analysis of microcapsules

Formulation code	Composition and ratio	Average size ( $\mu\text{m}$ )	% yield	Drug content (mg)	Encapsulation % efficiency
MC1	SA: SCMC (1:1)	350	80.67	185.7	74.28
MC2	SA: HPMC (1:1)	347	83.77	195.42	78.17
MC3	SA: Carbopol (1:1)	389	87.11	169.77	67.91
MC4	SA: SCMC (3:1)	410	89.12	182.8	73.12
MC5	SA: HPMC (3:1)	387	81.27	201.92	80.77
MC6	SA: Carbopol (3:1)	341	86.25	190.62	76.25
MC7	SA : SCMC (6:1)	354	79.87	202.6	81.04
MC8	SA : HPMC (6:1)	372	86.82	198.32	79.33
MC9	SA : Carbopol (6:1)	345	89.77	197.27	78.91

**Table: 3.** Characterization of muco-adhesive microcapsules

#### 2.4.4 Percentage drug content

About 500mg of microcapsule was accurately weighed and transfer in to 1000 ml beaker, which contain 900ml of 7.4 phosphate buffer at 37°C. The phosphate solution was steered continuously until all the microcapsules were dissolved. Drug loading was determined by U.V Photometric method at 269 nm.

(Microencapsulation efficiency) was calculated by the following formula:

$$\% \text{ Drug content} = \frac{\text{Actual drug content of microcapsules}}{\text{Theoretical weight of drug in microcapsules}} \times 100$$

#### 2.4.4 Encapsulation efficiency:

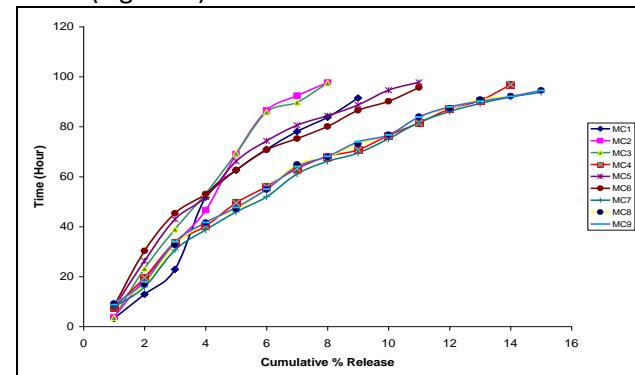
The encapsulation efficiency of microcapsules was calculated by using the formula:

$$\% \text{ Encapsulation efficiency} = \frac{\% \text{ Drug content}}{\% \text{ theoretical drug Content}} \times 100$$

#### 2.5 In-vitro drug release

##### 2.5.1 Release in pH 7.4-phosphate buffer:

*In vitro* release rate of Pioglitazone HCl from microcapsules of different samples was determined using single station USP dissolution test apparatus. The dissolution medium consisted of phosphate buffer (pH 7.4) was used, 9gm of SLS<sup>(15, 16)</sup> mixed in the buffer to enhance the solubility of pioglitazone in the phosphate buffer. Samples of drug, microcapsules equivalent with 100 mg of drug was spread onto the surface of 900 ml of preheated dissolution medium at 37°C. Aliquots of 5 ml were withdrawn at regular intervals of time i.e. (.5, 1, 2, and 3 up to 18 hour) and the same is replaced with fresh dissolution medium each time. The samples obtained were filtered through Whatman filter paper no. 1. The filtrate was diluted up to 6 ml with phosphate buffer (pH 7.4). Then the absorbance was measured at 269 nm (Figure-5).



**Fig: 5.** Comparative drug release of various compositions

#### 2.5.2 Drug release kinetics studies:

In order to understand the kinetics and mechanism of drug release, the results of the *in vitro* drug release study were fitted with various kinetic equations like zero order, first order, Weibull model, Korsmeyer - peppas model, Hill equation, Michaelis- Menten model. The kinetic model that best fits the dissolution data was evaluated by comparing the regression coefficient ( $r$ ) values obtained in various models.

### 3. RESULTS AND DISCUSSION:

#### 3.1 Compatibility Studies:

FTIR studies were done to detect the possible interactions between the drug and the polymers in the

microcapsules. Fig.3 Show the IR spectra of drug and the polymers. Comparing the spectra of individual drug and polymers with those of microcapsules prepared by using different methods revealed that there were no differences in the positions of the absorption bands, hence providing evidence for the absence of hydrogen bonding interactions in the solid state between cell forming polymer (Sodium alginate) and Mucoadhesive polymer (Sodium alginate, Carbopol, Sodium CMC, HPMC) with pioglitazone HCl under investigation. The absence of any significant change in the IR spectral pattern of drug-polymer mixture indicated the absence of any interaction between the drug and the polymer (Figure-3).

Formulation code	Regression Coefficient (r) value					
	Zero order	First order	Weibull	Korsmeyer-peppas	Hill equation	Michaelis - menten
MC1	0.9516	0.7781	0.9888	0.9600	0.9859	0.9484
MC2	0.9774	0.7993	0.9937	0.8988	0.9404	0.9289
MC3	0.9752	0.7383	0.9871	0.9340	0.9522	0.9041
MC4	0.9650	0.7526	0.9854	0.9645	0.9158	0.9735
MC5	0.9279	0.7015	0.9899	0.9310	0.9443	0.9406
MC6	0.9311	0.6859	0.9786	0.9159	0.9571	0.9296
MC7	0.9611	0.7667	0.9949	0.9732	0.9571	0.9888
MC8	0.9503	0.7664	0.9940	0.9722	0.9538	0.9903
MC9	0.9492	0.7562	0.9951	0.9691	0.9578	0.9889

Table: 4. *In vitro* release kinetics studies of Pioglitazone microcapsules

### 3.2 Physical characterization:

The mucoadhesive microspheres of pioglitazone prepared by the orifice-ionic gelatin method were found to be discrete, spherical, free flowing, and the monolithic matrix type. The microcapsules were uniform in size, with size range of 300  $\mu\text{m}$ . The SEM photographs indicated that microcapsules were spherical and completely covered the coat polymer (Figure- 4).

**3.3 Particle Size Distribution:** The average size of microcapsules in various batches was found to be 350  $\mu\text{m}$ , 347  $\mu\text{m}$ , and 389  $\mu\text{m}$ , 410  $\mu\text{m}$  387  $\mu\text{m}$ , 341  $\mu\text{m}$ , 354  $\mu\text{m}$ , 372  $\mu\text{m}$  and 345  $\mu\text{m}$  for MC1, MC2, MC3, MC4, MC5, MC6, MC7, MC8 and MC9 respectively.(Table-3)

**3.4 Practical yield:** The percentage practical yield was found to be in the range of 79.87 to 89.77 %. The

maximum percentage practical yield was found to be 89.77% for MC-9. (Table-3).

**3.5 Percentage drug content and Encapsulation efficiency:** The actual drug content and encapsulation efficiency of all nine formulations are given in Table 3. The encapsulation efficiency ranges from 66.91 to 81.04% for formulation MC1 to MC9. The maximum encapsulation efficiency was found to be 81.04% in MC7.

**3.6 In-vitro drug release:** The *in vitro* release profiles of nine formulations MC1 to MC9 are shown in Fig.5. It shows the plot of cumulative percent drug released as a function of time for different formulations. The cumulative percentage drug released indicates a controlled and prolonged drug release over an extended period of time. From the *in vitro* drug release profiles, it was observed that the drug release from microcapsules was decreased with an increase in cell forming material in the microcapsules (MC7, MC8, and MC9). The regression coefficient (r) values for formulations MC1 to MC9 are tabulated in Table 4. The model that gave higher 'r' value was considered as best fit model. The regression coefficient 'r' values were found to be higher in the zero order models, Hill equation model, Michaelis menten model, Korsmeyer peppas modal and Weibull model respectively, indicating that the dissolution of pioglitazone from all formulations followed following above model. The order of release rate observed with all microcapsules was MC8>MC9>MC7>MC4>MC6>MC5>MC1>MC2>MC3. The drug release from the microcapsules was diffusion controlled.

### 4. CONCLUSION:

Sustained release pioglitazone muco-adhesive microcapsules could be formulated by using cell forming polymer sodium alginate and muco-adhesive polymers (Carbopol, Sodium CMC and HPMC) as a release retardant by orifice ion gelation method. The Muco-adhesive microcapsules of all the formulated batches were spherical, discrete and free flowing. The drug content was found to be almost uniform in a batch of muco-adhesive microcapsules. Increasing the concentration of cell forming polymer (sodium alginate) in microcapsule formulation decreases the rate of drug release, best result were found in alginate Carbopol formulations in both cases

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**Conflict of Interest: None Declared**