

# Formulation and Evaluation of a Tablet Containing Pioglitazone HCl Microspheres

## Abstract

Solubility is an important physicochemical factor for any drug molecule that affects its absorption along with its therapeutic effectiveness. Drug absorption is predominantly dependent upon its prompt dissolution. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Microspheres were prepared by solvent evaporation method using polymers namely Eudragit L100 and Eudragit RL100. Direct compression technique was used for the preparation of tablets. Tablets were prepared with MCC and PVP K-30 as polymers using an 8 mm punch on a rotary press machine with a constant force. Microspheres and the prepared tablets were evaluated using various evaluation tests. The prepared microspheres showed >80% entrapment efficiency and percent yield. Batch F3 exhibited the highest drug release up to 98.30%. Fourier transform infrared (FT-IR) studies revealed no drug-polymer interaction. The results of SEM exhibited that the microspheres are spherical in shape with an average size 5µm. The result of all batches was within an acceptable limit. F2 batch tablet showed a higher drug release of 98.30% as compared with other batches. It was concluded that microcrystalline cellulose or PVP K-30, when used separately, caused retardation in drug release, whereas when used in combination (1:1) it achieved drug release in a controlled manner.

**Keywords:** Direct compression, microspheres, solvent evaporation, tablet

## Introduction

Solubility is an important physicochemical factor for any drug molecule that affects its absorption along with its therapeutic effectiveness. Drug absorption is predominantly dependent upon its prompt dissolution. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption.<sup>[1]</sup> However, the low oral bioavailability of the drug molecule is attributed to poor solubility and low permeability. When a drug is given orally, it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the gastrointestinal tract (GIT) to reach the systemic circulation. Thus, it is necessary to enhance the solubility of poorly soluble drugs to achieve increased absorption and to ensure its maximum therapeutic utility.<sup>[2]</sup> According to the Indian Pharmacopoeia, tablets are solid, flat, or biconvex unit dosage form of a medicament alone or medicament along with excipient(s) prepared by compressing technique.<sup>[3]</sup> The oral route remains to be the preferred route for administration of therapeutic agents rather than other routes

because of its cost therapy, accurate dosage, low self-medication, ease of administration, and noninvasive method, leading to high level of patient compliance.<sup>[4]</sup> The multiparticulate drug delivery system offers an advantage that wide and uniform distribution of drugs throughout GIT is achieved and localized high concentration at a specific point may be avoided. Thus, it leads to reproducible drug absorption and reduces the local irritation as compared to single unit dosage form such as nondisintegrating polymeric matrix tablets. Microspheres are small spherical particles, with diameters 1 to 1000 µm.<sup>[5]</sup> They are characteristically free-flowing powders that are biodegradable.<sup>[6]</sup> These drug delivery systems can easily achieve a therapeutically effective concentration of the drug in the systemic circulation over an extended period of time with better patient compliance.<sup>[7]</sup> According to the BCS classification, pioglitazone belongs to Class II.<sup>[8]</sup> It is an insulin-sensitizing thiazolidinedione (TZD) that activates a specific nuclear receptor [peroxisome-proliferator activated receptor-γ (PPAR-γ)] found in adipose tissue, pancreatic β-cells, vascular endothelium, and macro-phages.<sup>[9]</sup> PPARγ is a transcription factor, which, when

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activated by TZDs, promotes transcription of insulin-sensitive genes involved in fatty acid and glucose uptake and lipogenesis, thereby enhancing or partially mimicking selective actions of insulin.<sup>[10]</sup> It is well absorbed after oral administration and exhibit an oral bioavailability of approximately 83.00% with peak concentrations after approximately 1.5 h after administration.<sup>[11]</sup> It is highly bound to plasma proteins (>99%) primarily to serum albumin and undergoes metabolism mainly by CYP3A4 and CYP 2C8/9.<sup>[12]</sup>

A literature survey revealed that the matrix tablets of pioglitazone exhibited sustained drug release to provide effective and safe therapy for diabetes mellitus with reduced dose and length of treatment as the tablets provide sustained release of drug which also helps to increase its bioavailability.<sup>[13]</sup> Multilayered tablets of pioglitazone also showed better results than their conventional dosage forms.<sup>[14]</sup> However, as solubility is an important physicochemical factor for any drug molecule that affects its absorption along with its therapeutic effectiveness and there are no or less number of methods which cause an increase in the solubility of pioglitazone hydrochloride, the present study was undertaken to increase the solubility of pioglitazone hydrochloride.

## Materials and Methods

Pioglitazone hydrochloride was obtained as a gift sample from Aarti Drugs Ltd. (Mumbai). Microcrystalline cellulose (MCC), polyvinylpyrrolidone K-30 (PVPK 30), sodium starch glycolate, Eudragit (L100 and RL100), polyethylene glycol 6000, and Talc were procured from S.D. FINE Chemicals, Mumbai. Tween 80 and sodium carboxymethyl cellulose (CMC) were purchased from Yarrow Chemicals, Mumbai.

### Preparation of microspheres

Pioglitazone HCl microspheres were prepared by using Eudragit L100 and Eudragit RL100 by the solvent evaporation technique. Accurately weighed quantity of Eudragit L100 and Eudragit RL100 was dissolved in 10 mL of acetone in a separate container to form a homogeneous polymer solution. Weighed quantity of pioglitazone HCl was added to this polymer solution and mixed well. The resulting solution was added drop wise with the help of a syringe in a beaker containing 250 mL of aqueous mucilage sodium CMC (0.5%) and Tween 80 at a stirring rate of 1000 rpm for 2 h. The microsphere was separated by filtration and washed with water. The collected microspheres were dried at room temperature for 24 h in desiccators.<sup>[15]</sup> Compositions of microspheres are shown in [Table 1].

### Characterization of microspheres

#### Fourier transform infrared spectroscopy studies

Fourier transform infrared spectroscopy (FT-IR) studies were carried out to study the compatibility of drug and excipients. To check interaction between pioglitazone and added excipients in the preparation of the microspheres, IR spectra were recorded

on (FT-IR Jasco 4600, Japan) by scanning in the range between 4000 and 650  $\text{cm}^{-1}$ .

#### Saturation solubility study

Solubility studies were carried out by preparing a saturated solution of drug in water. A saturated solution of the drug was prepared in approximately 2 mL of solvent in a vial having a rubber stopper. The vial was kept in a shaker for 24 h at room temperature ( $25 \pm 2^\circ\text{C}$ ). Then, the sample was centrifuged at 300 rpm for 20 min (Remi laboratory centrifuge) at  $25 \pm 2^\circ\text{C}$ . The resulting supernatant liquid was pipetted out from each sample and diluted with a suitable solvent, and the solubility was determined using a UV spectrophotometer (Jasco V630, Japan) at 269 nm.<sup>[16]</sup>

#### Entrapment efficiency

Pioglitazone microspheres were dissolved in 10 mL of methanol with occasional shaking for 2–3 h. The resultant solution was filtered through 0.46  $\mu\text{m}$  filter paper and after suitable dilution, the amount of pioglitazone present in the formulation was determined using a UV Visible spectrophotometer (Jasco V630, Japan) at 269 nm.<sup>[17]</sup>

$$\text{Drug incorporation efficiency} = \left( \frac{\text{Actual drug content}}{\text{theoretical drug content}} \right) \times 100$$

#### Percentage yield

The percentage yield of the prepared pioglitazone HCl microspheres was determined by using the following formula<sup>[18]</sup>:

$$\text{Percentage yield} = \left( \frac{\text{Weight of microspheres obtained}}{\text{total weight of drug and excipients}} \right) \times 100$$

#### Scanning electron microscopy (SEM)

The shape and surface morphology of the pioglitazone microspheres were examined by using a scanning electron microscope (JSM-6390, Japan). Microspheres were dusted on to double-sided carbon dust, which was placed onto a sample carrier in the shape of a cylinder. After fixing the samples on the stubs, a photomicrograph was captured.<sup>[19]</sup>

#### In- vitro release studies

The *in vitro* drug release studies of microspheres were performed by using a USP rotating basket (Apparatus I). Microspheres equivalent to 30 mg of the drug were filled in a capsule, and the capsule was placed in a BASKET for dissolution study. Whereas,

**Table 1: Composition of pioglitazone HCl microspheres**

Composition (mg)	F1	F2	F3	F4
Pioglitazone HCl	1000	1000	1000	1000
Eudragit L100	1000	–	500	750
Eudragit RL100	–	1000	500	250

Each formulation containing sodium CMC 0.5%, Tween 80 1% v/v

the phosphate buffer (pH 7.4) was used as a dissolution medium. The entire system was maintained at  $37.5 \pm 5^\circ\text{C}$  with a stirring rate of 50 rpm. At an appropriate interval of 10 min, 5 mL of the sample was removed and replaced with 5 mL of fresh sample to maintain sink condition up to 240 min. The amount of pioglitazone released in the medium was evaluated by the UV spectrophotometer at 269 nm.<sup>[20]</sup>

### Preparation of tablets containing pioglitazone microspheres

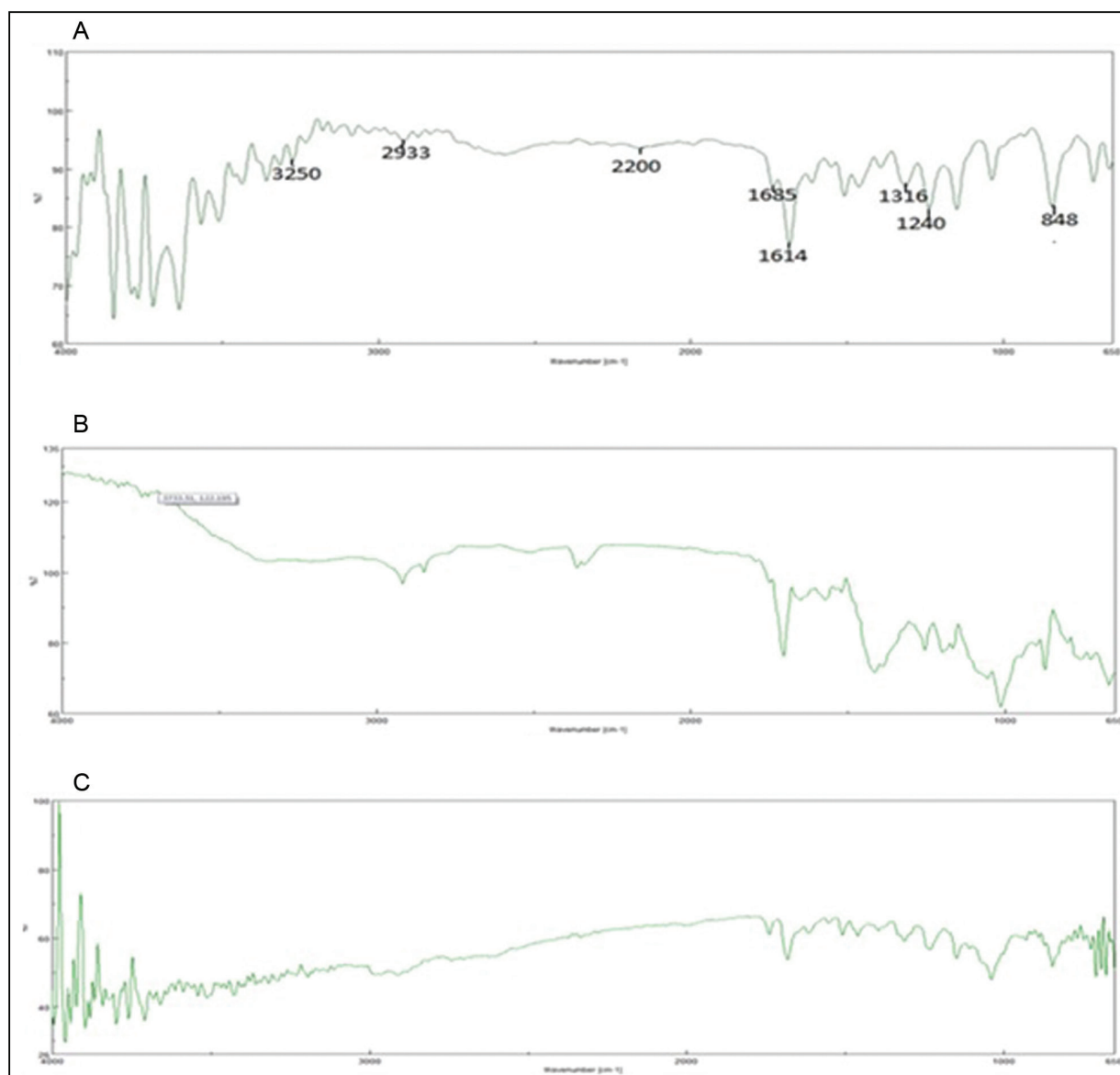
The direct compression method was used to prepare tablets containing pioglitazone microspheres. Batch F3 was used for the preparation of tablets, as it exhibited a higher drug release of 98.30%. Microspheres equivalent to 30 mg were mixed well with other calculated amounts of excipients and compressed by using an 8 mm punch on a rotary press tablet machine. Compositions used in the formulation of the tablet are shown in Table 2.<sup>[21]</sup>

### Fourier transform infrared spectroscopy

To check the interaction between pioglitazone microspheres and excipients used in the preparation of tablets, FT-IR studies were performed. IR spectra were recorded on FT-IR (Jasco 4600, Japan) by scanning in the range between 4000 and  $650\text{ cm}^{-1}$ .<sup>[22]</sup>

**Table 2: Compositions of tablet containing pioglitazone microspheres**

Composition (mg)	F1	F2	F3	F4
Microspheres	60	60	60	60
MCC	37.5	18.75	–	30
PVPK 30	–	18.75	37.5	7.5
PEG 6000	2.5	2.5	2.5	2.5
Total weight (mg)	100	100	100	100



**Figure 1: FT-IR spectra of (A) pure pioglitazone, (B) physical mixture, (C) tablet formulation**

### Precompression studies

The powder blend was evaluated for different flow properties which included angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, and drug content.<sup>[23]</sup>

### Evaluation of tablets containing pioglitazone microspheres

#### Thickness and hardness

Thickness of the prepared tablets was determined by using Vernier caliper. Hardness and crushing strength of the tablets were measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly, and an average reading was noted.

#### Weight variation

Weight variation test was performed by weighing 20 tablets individually, calculating average weight, and comparing the individual tablet weight to the average weight.

#### Friability

Twenty tablets weighed were weighed, placed in a Roche friabilator, and rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed, and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula:

$$\text{Percentage friability} = \left[ \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \right] \times 100$$

#### Disintegration time

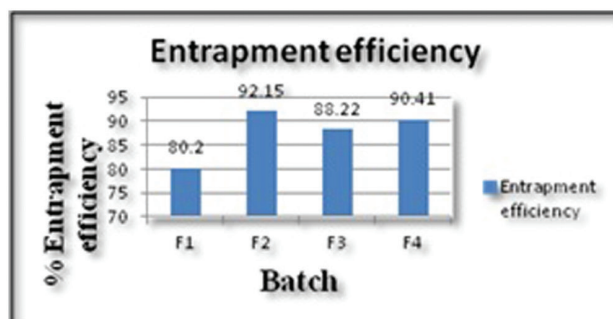
The tablet was placed in a beaker containing 20 mL of phosphate buffer (pH 7.4) at  $37 \pm 0.5^\circ\text{C}$ . Time for complete disintegration of the tablet was measured in triplicate.<sup>[24]</sup>

#### Drug content

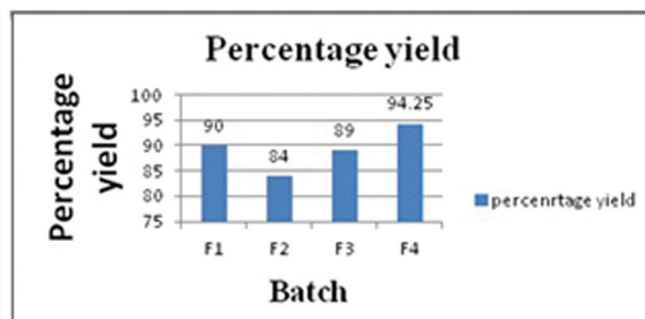
Five tablets from each formulation were weighed individually and crushed to a fine powder. Powder equivalent to 30 mg of pioglitazone was transferred into a 100 mL volumetric flask and extracted using phosphate buffer (pH 7.4). This solution obtained was filtered, and the filter was suitably diluted with

**Table 3: Interpretation of IR spectra of pioglitazone**

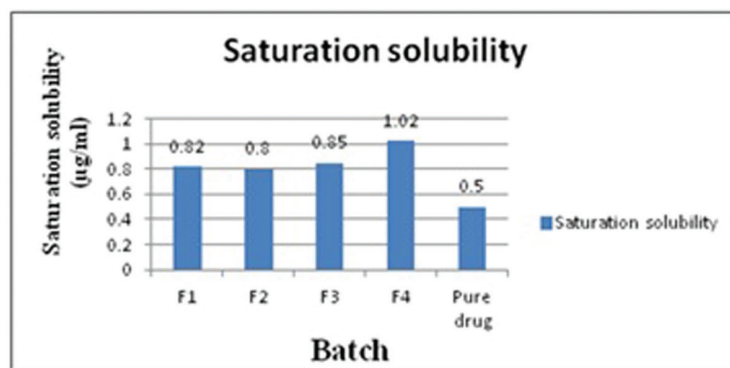
Peak no.	Peak position	Functional group
1.	NH stretching	$3250 \text{ cm}^{-1}$
2.	C-H stretching	$2933 \text{ cm}^{-1}$
3.	C=N stretching	$2200 \text{ cm}^{-1}$
4.	C=C bending	$1316 \text{ cm}^{-1}$
5.	C=O stretching	$1685 \text{ cm}^{-1}$
6.	C-O aromatic group	$1037 \text{ cm}^{-1}$
7.	C=C aromatic	$1614 \text{ cm}^{-1}$
8.	C-S bending	$1240 \text{ cm}^{-1}$
9.	Cl stretching	$848 \text{ cm}^{-1}$



A



B



C

Figure 2: (A) Entrapment efficiency of formulated microspheres, (B) Percent yield of formulated microsphere batches, (C) Saturation solubility of batches F1-F4 and Pure drug

phosphate buffer (pH 7.4). Finally, the solution was analyzed by measuring the absorbance at 269 nm by a UV–visible spectrophotometer.<sup>[25]</sup>

### *In vitro* dissolution study

*In vitro* release of drugs from tablets was monitored by using USP apparatus type II (paddle). Phosphate buffer (pH 7.4) was used as a dissolution media. The whole assembly was maintained at  $37 \pm 0.5^\circ\text{C}$  with a stirring rate of 50 rpm. The sample was withdrawn at a predetermined time 10 min for 120 min and replaced immediately with the same volume of fresh buffer medium to maintain sink condition. Finally, appropriate dilutions were made and analyzed by spectrophotometrically at 269 nm.<sup>[26]</sup>

## Results and Discussion

### FT-IR studies

FT-IR spectrum of pioglitazone HCl is shown in Figure 1A, FT-IR spectrum of pure drug pioglitazone exhibits characteristics peak at  $3250\text{ cm}^{-1}$ ,  $2933\text{ cm}^{-1}$ ,  $2848\text{ cm}^{-1}$ , and  $2200\text{ cm}^{-1}$  due to N–H cyclic stretching, C–H stretching, C–H aliphatic stretching, C=N aromatic stretching, respectively. Whereas,  $1685\text{ cm}^{-1}$ ,  $1614\text{ cm}^{-1}$ ,  $1316\text{ cm}^{-1}$ , and  $1240\text{ cm}^{-1}$  were to be noted for C=O amide stretching, C=C stretching, C=C bending, C–S bending, respectively [Table 3]. All peaks observed in IR spectra confirmed the purity of pioglitazone HCl. The FT-IR spectrum of prepared formulation showed no significant difference in the parent peaks compared with pure drug IR spectra. From the FT-IR spectroscopic study of drugs and polymers, it can be concluded that there is no chemical interaction between drug and polymers. However, drugs and polymers used in this study are compatible to each other [Figure 1].

### Entrapment efficiency

The entrapment efficiency of the formulated microsphere batches is highlighted in Figure 2A. It was observed that Batch F1 showed minimum entrapment efficiency, i.e., 80.20% and batch F2 exhibited maximum entrapment efficiency of 92.15%. However, the F2 batch comprises of only Eudragit RL100 at a concentration of 1000 mg [Table 1], which may attribute to its entrapment efficiency.

### Percent yield

The results revealed that all formulated batches of microspheres exhibited yield greater than 80%. Batch F4 showed a higher percent yield than other. The yield profile of all batches is highlighted in Figure 2B.

### Saturation solubility study

As shown in Figure 2C, Batch F4 exhibited maximum saturation solubility found to be  $1.02\text{ }\mu\text{g mL}^{-1}$ , therefore considered as an optimized batch and subjected to further studies. Saturation solubility of the optimized batch of microsphere and that of the pure drug was found to be 1.02 and  $0.5\text{ }\mu\text{g mL}^{-1}$ , respectively. Thus,

there is an approximately 2-fold increase in the saturation solubility of pioglitazone when it is formulated in the form of a microsphere.

### Scanning electron microscopy

Pioglitazone microspheres prepared by the solvent evaporation technique were found to be discrete, free-flowing, spherical, and of the monolithic matrix type. The microspheres were uniform in size with an average of  $5\text{ }\mu\text{m}$ . The SEM of optimized Batch F3, shown in Figure 3, indicated that microspheres were spherical and completely covered with the coating polymer.

### *In vitro* dissolution study of microspheres

*In vitro* dissolution studies of microspheres were carried out up to 240 min using freshly prepared phosphate buffer (pH 7.4). The depicted result showed an effect of polymer on drug release when they were used alone or in combination. Batch F3 exhibited a higher drug release of 98.30% than other formulations with an equal amount of Eudragit L100 and Eudragit RL100. Whereas the other batches F1, F2, and F4 showed drug release greater than 80%. The drug release pattern of all batches F1–F4 is shown in Figure 4.

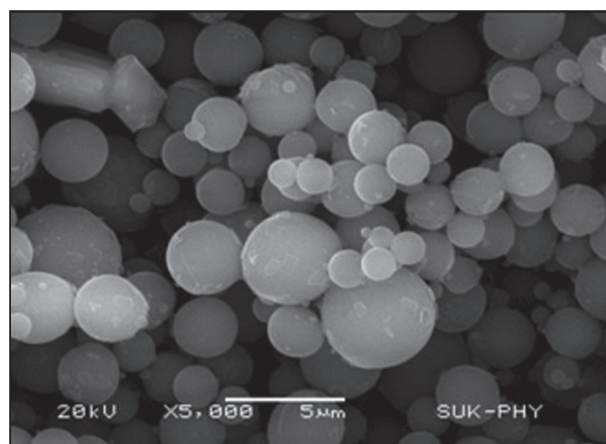


Figure 3: Scanning electron microscopy

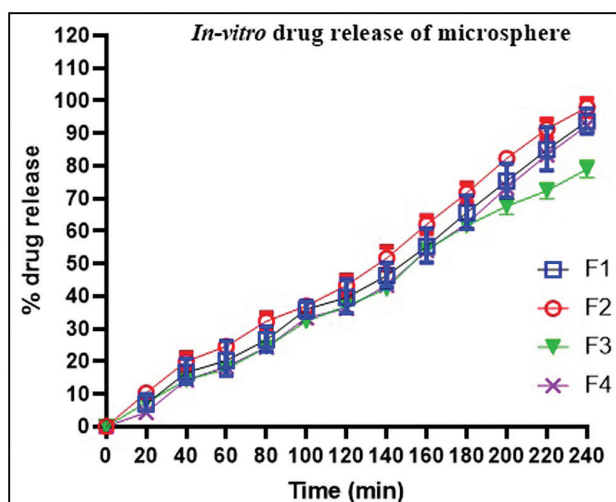


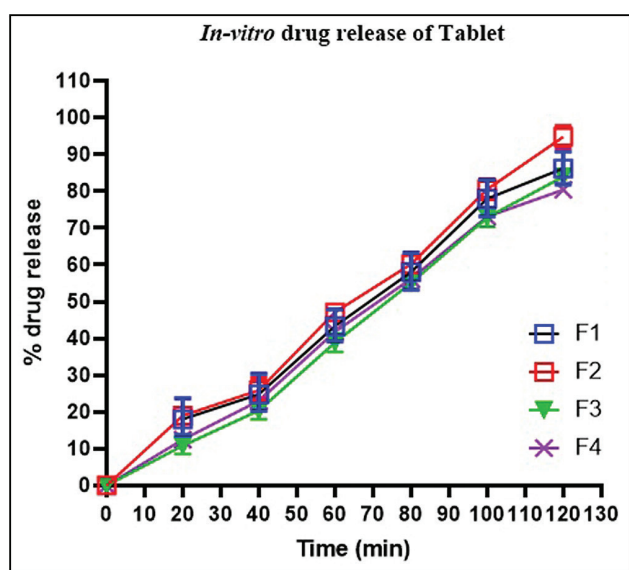
Figure 4: *In vitro* drug release of microsphere

**Table 4: Precompression of the powder blend**

Formulations code	Angle of repose ( $\theta$ )	Bulk density (g/mL)	Tapped density (g/mL)	Carr's compressibility (%)	Hausner's ratio (%)
F1	17.36 $\pm$ 1.14	1.30 $\pm$ 0.20	1.59 $\pm$ 0.32	17.24 $\pm$ 1.53	1.12 $\pm$ 0.8
F2	14.80 $\pm$ 1.32	1.25 $\pm$ 0.23	1.1 $\pm$ 0.18	15.41 $\pm$ 1.29	1.15 $\pm$ 0.5
F3	15.28 $\pm$ 1.36	1.28 $\pm$ 0.21	1.48 $\pm$ 0.25	16.34 $\pm$ 1.14	1.13 $\pm$ 0.7
F4	14.35 $\pm$ 1.21	1.26 $\pm$ 0.17	1.15 $\pm$ 0.19	12.12 $\pm$ 1.02	1.19 $\pm$ 0.6

**Table 5: Evaluation of tablets**

Formulation code	Hardness (kg/cm <sup>2</sup> )	Friability (% w/w)	Thickness (mm)	Weight variation	Disintegration time (min)
F1	3.60 $\pm$ 0.6	0.74 $\pm$ 0.7	3.2 $\pm$ 0.2	150.4 $\pm$ 0.7	9 $\pm$ 0.5
F2	3.58 $\pm$ 0.4	0.58 $\pm$ 0.6	3.06 $\pm$ 0.1	150.7 $\pm$ 0.6	17 $\pm$ 0.3
F3	3.46 $\pm$ 0.3	0.47 $\pm$ 0.8	3.04 $\pm$ 0.3	151.1 $\pm$ 0.5	12 $\pm$ 0.6
F4	3.15 $\pm$ 0.2	0.33 $\pm$ 0.3	3.01 $\pm$ 0.1	150.6 $\pm$ 0.2	8 $\pm$ 0.5

Figure 5: *In vitro* drug release of a tablet

### Precompression characterization

The result of evaluation of the powder blend is presented in Table 4. All formulation showed angle of repose, flow property, Hausner's ratio, and Carr's index within the standard limit.

### Evaluation of tablets

The thickness and hardness of tablets were determined and were found to be in the range of 3.2 to 3.6 mm and 3.15 to 3.60 kg/cm<sup>2</sup>, respectively. Friability was observed to be less than 1%, which indicated that the tablet possesses good mechanical resistance. Weight variation and disintegration time of tablets were observed within the specified limit [Table 5].

### *In vitro* dissolution study of tablet

The *in vitro* release profile of tablets containing microspheres of pioglitazone was monitored up to 120 min [Figure 5]. All formulations exhibited a drug release of more than 80%. Batch F3 formulated by using PVP K-30 showed a lower drug release of 83%, whereas Batch F2 formulated with MCC and PVP

K-30 (1:1) showed higher drug release up to 98.30%. From drug release studies, it is clear that MCC or PVP K-30 when used alone retard drug release, whereas the same ingredients, when used in a combination of 1:1 ratio, achieved release of drug in a controlled manner.

### Conclusion

It can be concluded that monolithic matrix type of microspheres can be prepared by using the solvent evaporation technique. Eudragit L100 and Eudragit RL100 are suitable for microspheres which release the drug in a controlled manner. Microspheres can be compressed into tablets by using MCC and PVPK 30, these polymers are suitable for maintaining tablet characteristics and optimum drug release.

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### Conflict of interest

The author claims that there is no conflict of interest.

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