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Solid Dispersion Incorporated Microcapsules: Predictive Tools for Improve the Half Life and Dissolution Rate of Pioglitazone Hydrochloride

Singh Chhater[1,*], Kumar Praveen[2]

[1]Shri Venkateshwara University Rajabpur, Gajraula/SVU, (U.P.) India
[2]S.D. College of Pharmacy & Vocational Studies, Muzaffarnagar, (U.P.) India
*Corresponding author: pharma_pharm@yahoo.com

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Abstract The present study was aimed to formulate the solid dispersion incorporated microcapsule to improve the dissolution rate and half life of pioglitazone hydrochloride. The solvent evaporation method was used to formulate the solid dispersion resulted increased dissolution rate, bioavailability and stability. Finally increase the half life of the drug by employ the orifice ionic gelation method to formulate solid dispersion incorporated muco-adhesive microcapsule. The solubility of pioglitazone hydrochloride was increase by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 using solvent evaporation methods. The microcapsules of pioglitazone hydrochloride were prepared by (orifice ionic gelation method) employing sodium alginate as a cell forming polymer and 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. FT-IR spectra revealed no chemical incompatibility between drug and polymers. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC), Powder X-Ray Diffraction (PXRD). Scanning electron microscope photographs of samples revealed that all prepared microcapsules were almost spherical in shape and have a slightly smooth surface.

Keywords: *solid dispersion, muco-adhesive microcapsules, orifice gelation method, solvent evaporation method, biological half life*

1. Introduction

Pioglitazone is a Thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action [1,2]. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPARg) [3]. Pioglitazone decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Pioglitazone HCl is a poor water soluble drug and has a short half life (3-5 hour). The formulation of poorly water-soluble drugs has always been a challenging problem faced by pharmaceutical scientists and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programs are poorly water-soluble. It is necessary to improve the solubility and bioavailability and half life.

In the present study, an attempt was made to develop solid dispersion incorporated to increase the dissolution rate and half-life of drug by using solvent evaporation method for sold dispersion and orifice ionic gelation method for solid dispersion incorporated microcapsules. 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 [2] and is eliminated rapidly. 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 absorption and to facilitate intimate contact dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs [4,5,6].

2. Materials and Methods

Pioglitazone HCl sample from Ontop Pharmaceuticals LTD (Bangalore, India), Sodium carboxymethylcellulose (sodium CMC), Methyl cellulose (Mc), Hydroxypropylmethylcellulose (HPMC), Polyvinyl pyrrolidone K30 (PVP K30) and Polyethylene glycol 6000 (PEG 6000) was purchase in the market; all the chemicals were A.R. Grade.

2.1. Estimation of Drug

2.1.1. Linear Regression Equation Method

Accurately weighed about 100mg of pioglitazone hydrochloride was dissolved in 100ml Phosphate buffer (pH 7.4) to obtain 1000µg/ml concentration of drug (stock A). Stock A (10ml) was diluted up to 1000ml with solvent system to obtain 10µg/ml concentration (Stock B). Aliquots of Stock B were diluted to obtain concentrations

of 1, 2, 3, 4, 5 to 10µg/ml of pioglitazone hydrochloride. [7,8] All dilutions were scanned from 400 to 200nm against solvent system as blank (Figure 1A) and their absorbance were observed at 269nm (Figure 1B). The LRE was developed as Y = 0.0202X + 0.0013, where ABC = absorbance and C = concentration of dilutions in µg/ml, with the correlation coefficient r^2 = 0.9998.

2.1.2. Standard Absorptivity Method

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

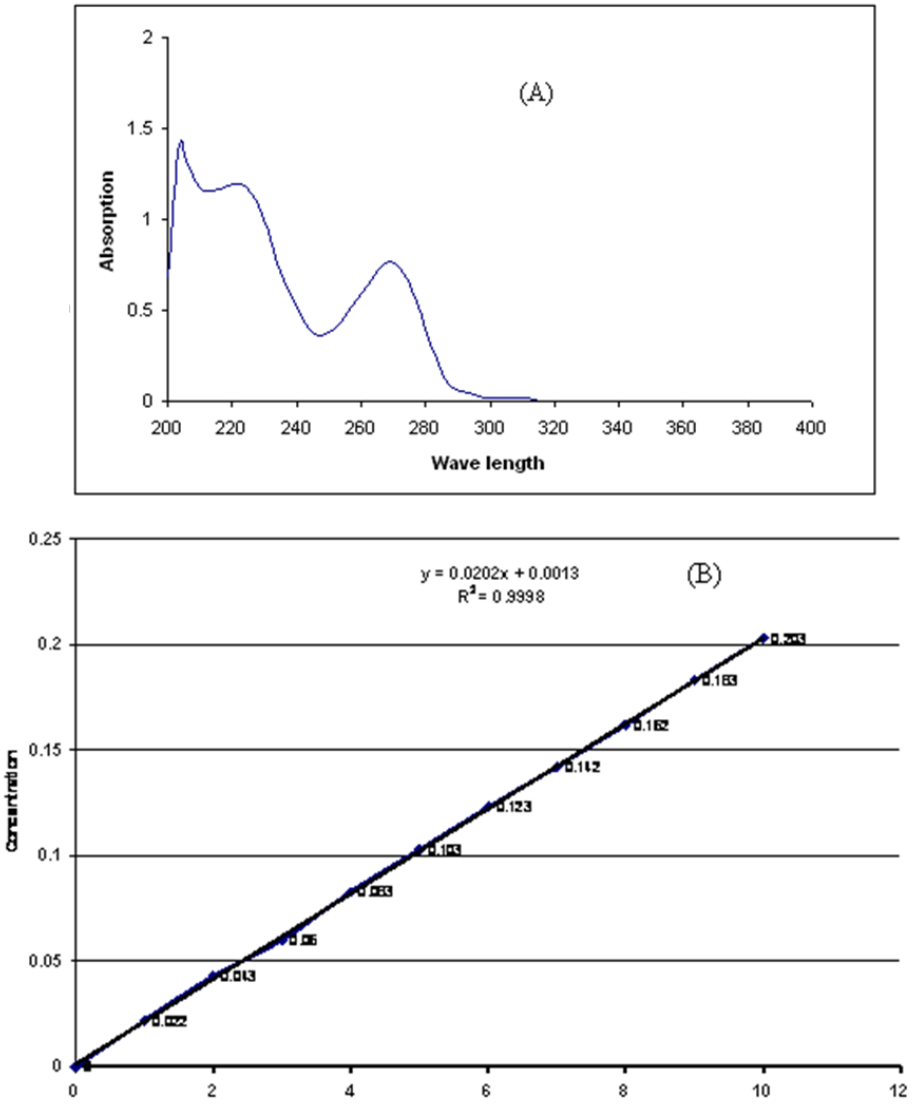


Figure 1. (A) Spectra of pioglitazone HCl in phosphate buffer (pH 7.4), (B) Calibration graph of pioglitazone HCl

Table 1. Data of absorption and standard absorptivity at different concentration

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 (1cm), C = Concentration						

2.2. Phase Solubility Study

Solubility studies were performed according to the Higuchi [9] and Connors method. An excess amount of Pioglitazone hydrochloride was placed in to 50ml flask containing different concentration of polyvinyl pyrrolidone K30 and poly ethylene glycol 6000 separately in 25ml distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent lose. The flasks were kept in the incubator shaker for 72h. After 72h the content of each flask was then filtered through Whatman filter paper; the filtrate was diluted and assayed

spectrophotometrically (Shimadzu 1700UV spectrophotometer) for Pioglitazone HCl content at 269nm. All solubility measurements were performed in triplicate (Figure 2).

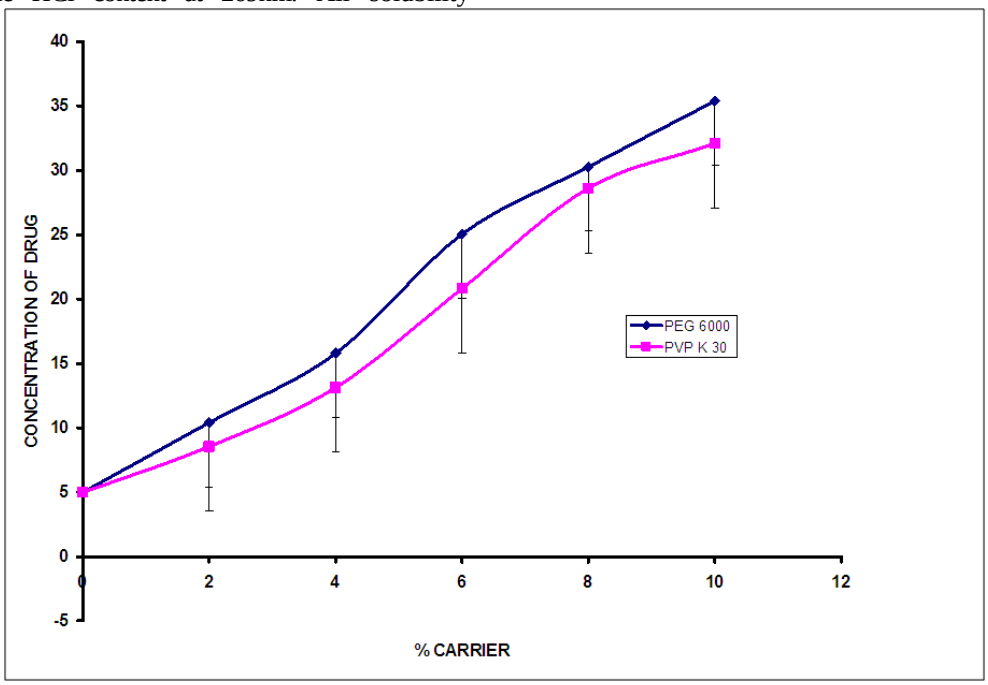


Figure 2. Phase solubility diagram of Pioglitazone hydrochloride in different carrier

2.3. Preparation of Method

2.3.1. Preparation of Physical Mixture and Solid Dispersions

Physical mixtures were prepared by mixing the appropriate amount of Pioglitazone HCl and Polyvinyl pyrrolidone K30 (PVP K30) and Polyethylene glycol 6000 (PEG 6000) in pestle and mortar separately and passed through sieve # 60. Solid dispersions were prepared by solvent evaporation method. The carrier (PVP K30 and PEG 6000) and adding amounts of Pioglitazone HCl corresponding to ratio 1:1, 2:1, 3: 1 and 5:1 was accurately weighed and mixed properly. This physical mixture was solubilized in a common solvent that is in ethanol (25ml). The solvent was allowed to evaporate in hot air oven at 45°C ± 10°C. The process of evaporation was opted until the constant weight was obtained. This formulation was kept in dessicator for 24h under vacuum. Then, solid dispersion formulation was pulverized using a porcelain mortar and pestle. The pulverized powder was classified using the sieves (size 60# and 120# mesh) and the particle size fraction of 100-250mm was used for the study (Table 2).

Table 2. Composition of solid dispersions (SD) and physical mixtures (PM) of Pioglitazone Hydrochloride

S. No.	Name of Carrier	Product Name	Drug (mg)	Carrier (mg)	Drug carrier Ratio	Description of product	Preparation of method
1.	Polyvinyl pyrrolidone K30	A11	1500	1500	1:1	Solid Dispersion	Solvent Evaporation
2.	Polyvinyl pyrrolidone K30	A12	1000	2000	1:2	Solid Dispersion	Solvent Evaporation
3.	Polyvinyl pyrrolidone K30	A13	750	2250	1:3	Solid Dispersion	Solvent Evaporation
4.	Polyvinyl pyrrolidone K30	A15	500	2500	1:5	Solid Dispersion	Solvent Evaporation
5.	Polyvinyl pyrrolidone K30	PMA15	500	1500	1:3	Physical Mixture	----------
6.	Polyethylene Glycol 6000	B11	1500	1500	1:1	Solid Dispersion	Solvent Evaporation
7.	Polyethylene Glycol 6000	B12	1000	2000	1:2	Solid Dispersion	Solvent Evaporation
8.	Polyethylene Glycol 6000	B13	750	2250	1:3	Solid Dispersion	Solvent Evaporation
9.	Polyethylene Glycol 6000	B15	500	2500	1:5	Solid Dispersion	Solvent Evaporation
10.	Polyethylene Glycol 6000	PMB13	500	1500	1:3	Physical Mixture	……..

2.3.2. Preparation of Solid Dispersion Incorporated Muco-Adhesive Microcapsules

Microcapsules are prepared by orifice- ionic gelation method [10,11] by employing the Sodium alginate as a cell forming polymer and Sodium CMC, HPMC and Carbopol as muco-adhesive [12] 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 (solid dispersion of pioglitazone hydrochloride) equivalent to drug (1gm) 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 $CaCl_2$ (10%w/v) solution through a syringe with a needle of size no. 18. The added drop lets are related in the $CaCl_2$ 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°C for 12 hrs. (Table 3).

Table 3. Composition of different muco-adhesive microcapsules

Formulation code	Composition and ratio	SD (A13) equivalent to mg of drug	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

Note: Sodium alginate =SA, Sodium CMC = SCMC, SD = Solid dispersion

3. Characterization of Solid Dispersion

3.1. Physical Characterization

The surface and internal structure of solid dispersion was observed through the Scanning Electron microscopy (SEM), by using the scanning electron microscope (SEM-LEICA S430, London, UK). (Figure 6E, F).

3.2. Practical Yield

The percentage yield of Pioglitazone in solid dispersion was determined by using the formula:

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

3.3. Percentage Drug Content

The dispersion system equivalent to 25mg of Pioglitazone hydrochloride was taken in 25ml volumetric flask and dissolved in phosphate buffer (pH 7.4). The volume was made up to the mark with phosphate buffer (pH 7.4) and filtered. One ml of filtrate was further diluted to 10 ml with phosphate buffer (pH 7.4) and absorbance was recorded at 269nm. The amount of drug in each dispersion system was determined spectrophotometrically (Table 4).

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

Table 4. Drug Content of solid dispersion system

S. No.	Product Name	% yield	% Drug content
1	A11	84.91	97.54
2	A12	87.55	92.22
3	A13	82.98	95.14
4	A15	88.67	89.07
5	PMB13	87.90	97.54
6	B11	81.37	98.02
7	B12	86.56	91.17
8	B13	89.39	86.52
9	B15	82.99	83.37
10	PMB13	85.81	96.02

3.4. In Vitro Drug Release

3.4.1. Release in pH 7.4-Phosphate Buffer

In vitro release rate of Pioglitazone HCl alone and Pioglitazone HCl from solid dispersion of different samples was determined using single station USP dissolution test apparatus. The dissolution medium consisted of phosphate buffer (pH 7.4) was used. Samples of drug, solid dispersion equivalent with 100mg of drug were spread onto the surface of 900ml of preheated dissolution medium at 37°C. Aliquots of 2ml were withdrawn at regular intervals of time i.e. (5, 10, 15, 20, up to 120min) 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 6ml with phosphate buffer (pH 7.4). Then the absorbance was measured at 269nm.

Table 5. Drug release kinetics data of different formulations

Formulation code	Regression Coefficient (r) value					
	Zero order	First order	Weibull	Korsmeyer-peppas	Hill equation	Michaelis-menten
A11	0.2239	0.1183	0.9873	0.9859	0.9892	1.0000
A12	0.3320	0.1223	0.9901	0.9897	0.9927	1.0000
A13	0.3499	0.1223	0.9907	0.9876	0.9945	1.0000
A15	0.3023	0.1203	0.9888	0.9864	0.9920	1.0000
PMA13	0.6156	0.1309	0.9922	0.9903	0.9943	1.0000
B11	0.2520	0.1192	0.9880	0.9863	0.9903	1.0000
B12	0.2689	0.1194	0.9877	0.9861	0.9900	1.0000
B13	0.2943	0.1202	0.9892	0.9865	0.9927	1.0000
B15	0.2686	0.1194	0.9878	0.9861	0.9901	1.0000
PMB13	0.4870	0.1287	0.9928	0.9904	0.9955	1.0000
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

3.4.2. 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. (Table 5).

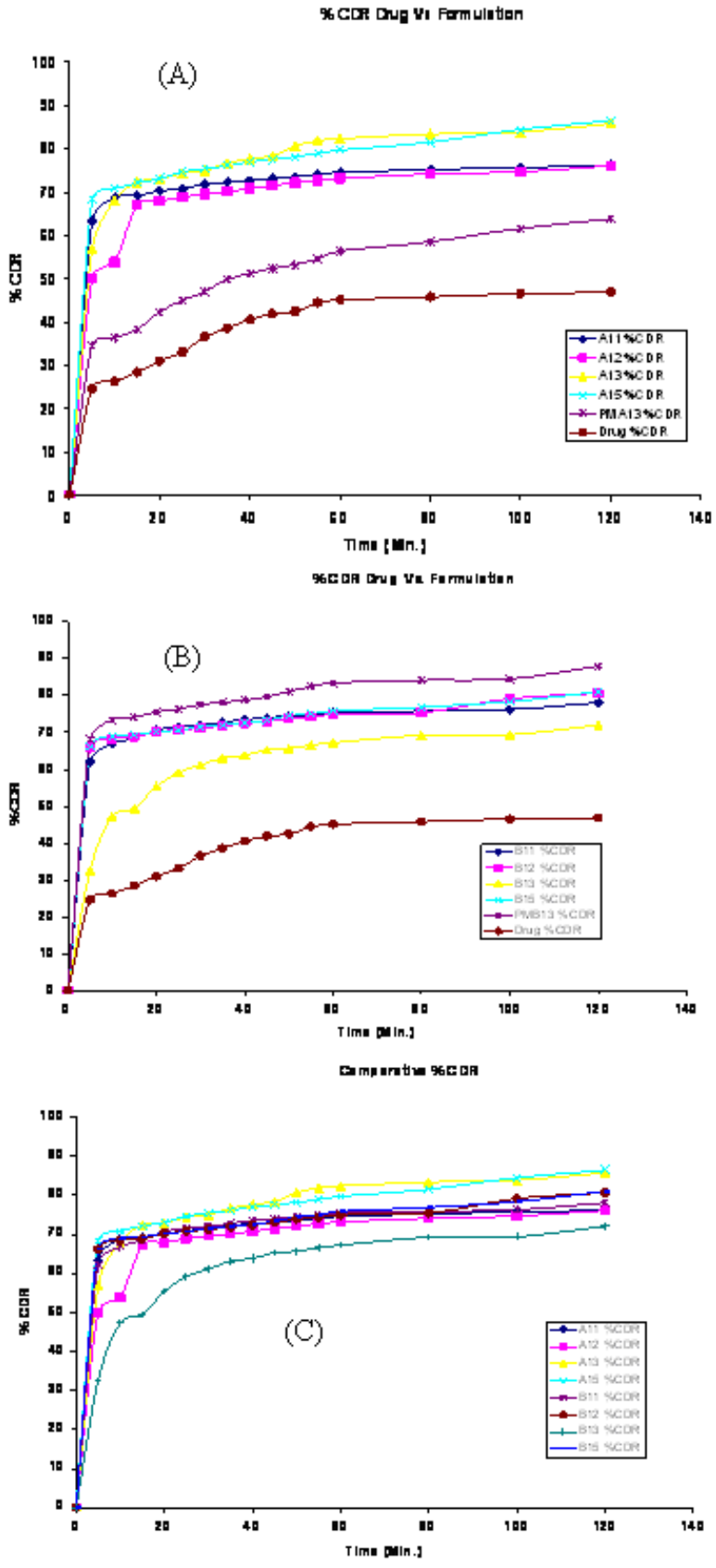


Figure 3. (A) Comparative % release of pure drug and different formulations containing PVP K30 as carrier, (B). Comparative % release of pure drug and different formulations containing PEG 6000 as carrier, (C) Comparative % CDR of different formulations

3.5. Analytical Testing of Solid Dispersion

3.5.1. Fourier Transforms Infrared Spectroscopy

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

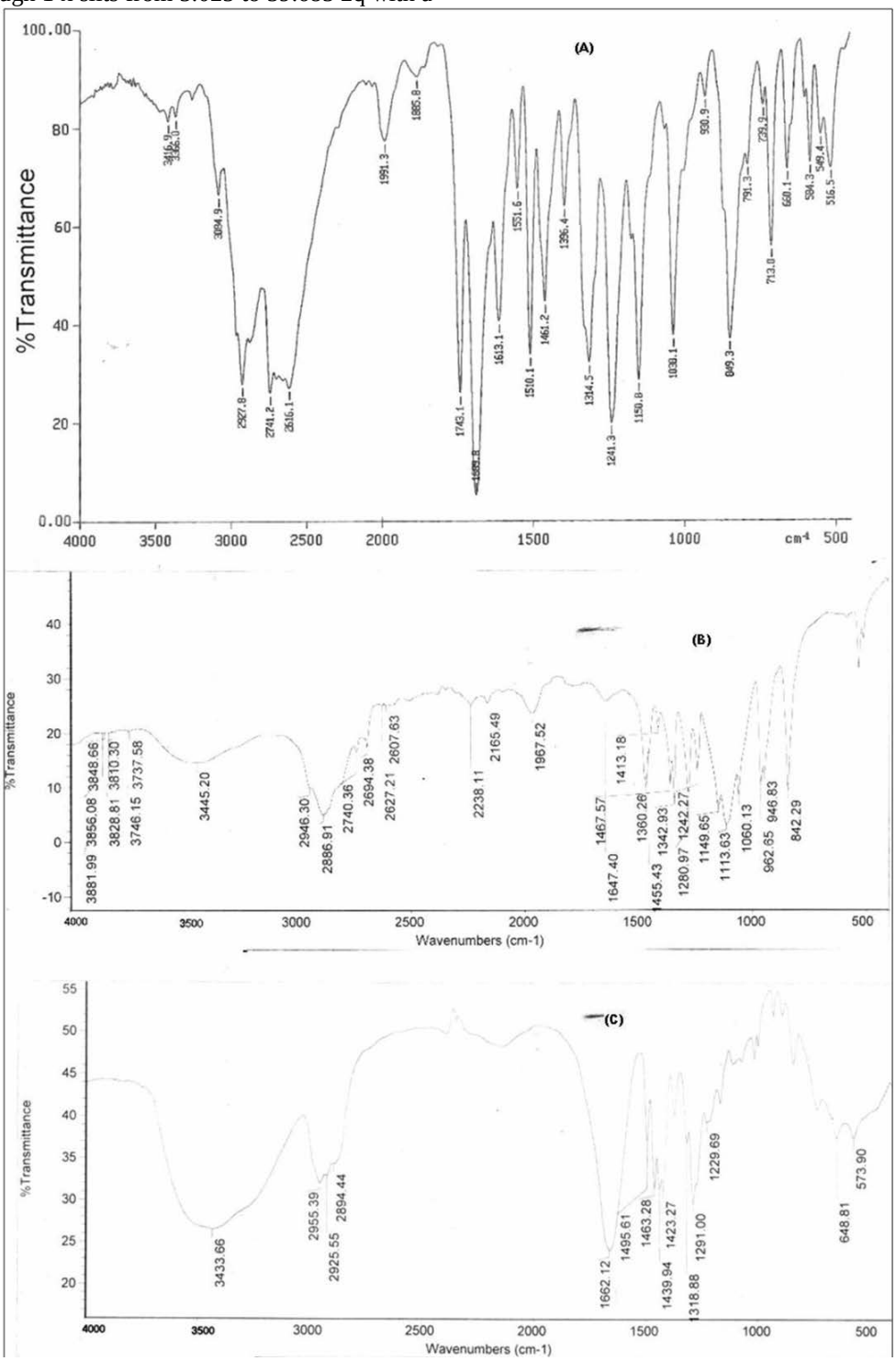
3.5.2. X-Ray Diffraction

Diffraction patterns were obtained at room temperature on a Philips PW 1710 Diffractrometer (Philips, Holland). Samples were exposed to Cu Ka radiation, wavelength 1.54060Å through 1 x slits from 5.025 to 59.685 2q with a step size of 0.60° 2q and a count time of 1 sec. per step; the generator was set to 40 kV and 30mA.

4. Characterization of Microcapsules

4.1. Physical Characterization [13,14]

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). (Figure 6).



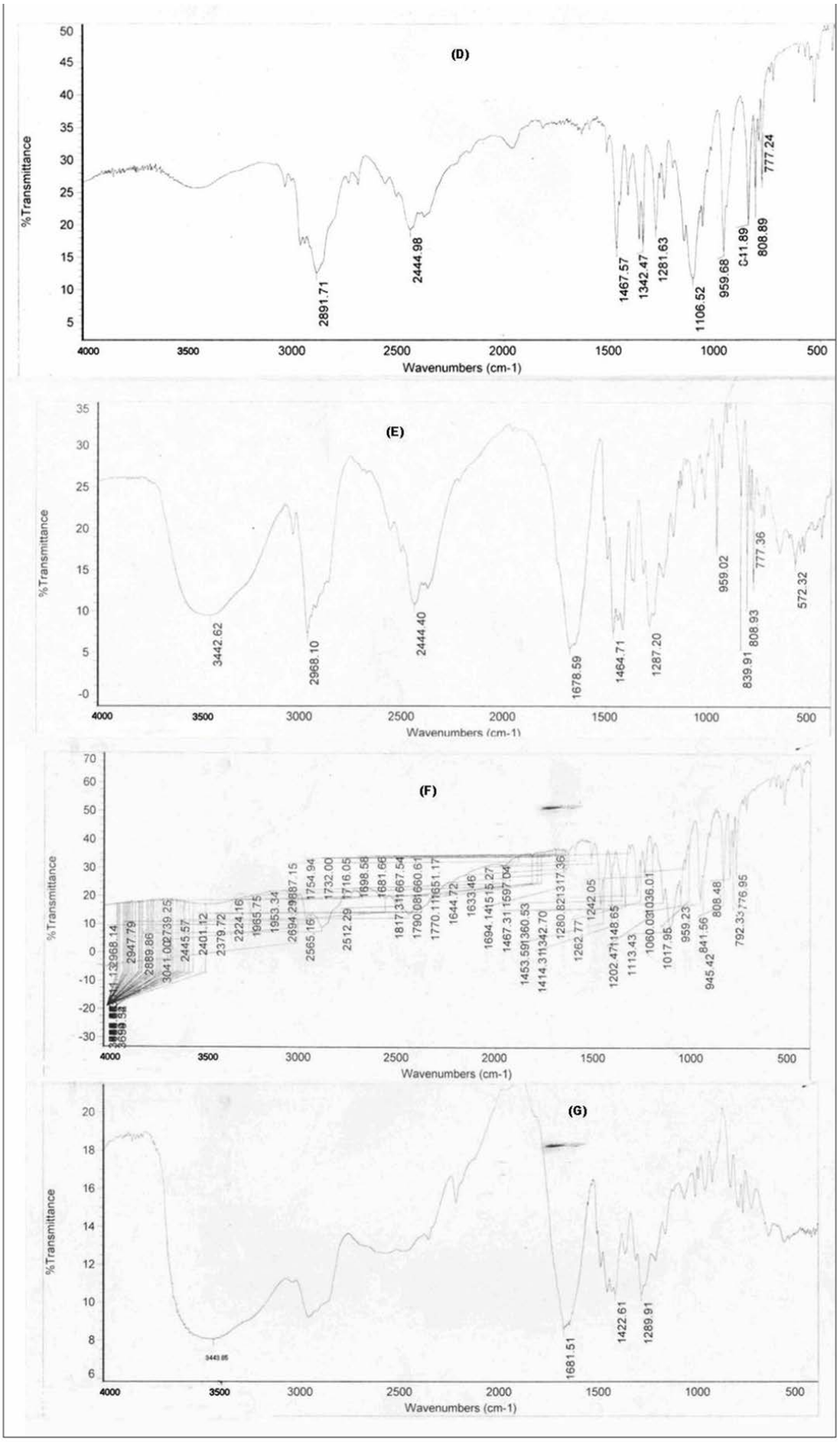


Figure 4. FTIR Spectra of (a). Pioglitazone HCL, (B). PVP K30, (C). PEG 6000, (D). PMA13, (E). PMB13, (F). A13, (G). B13

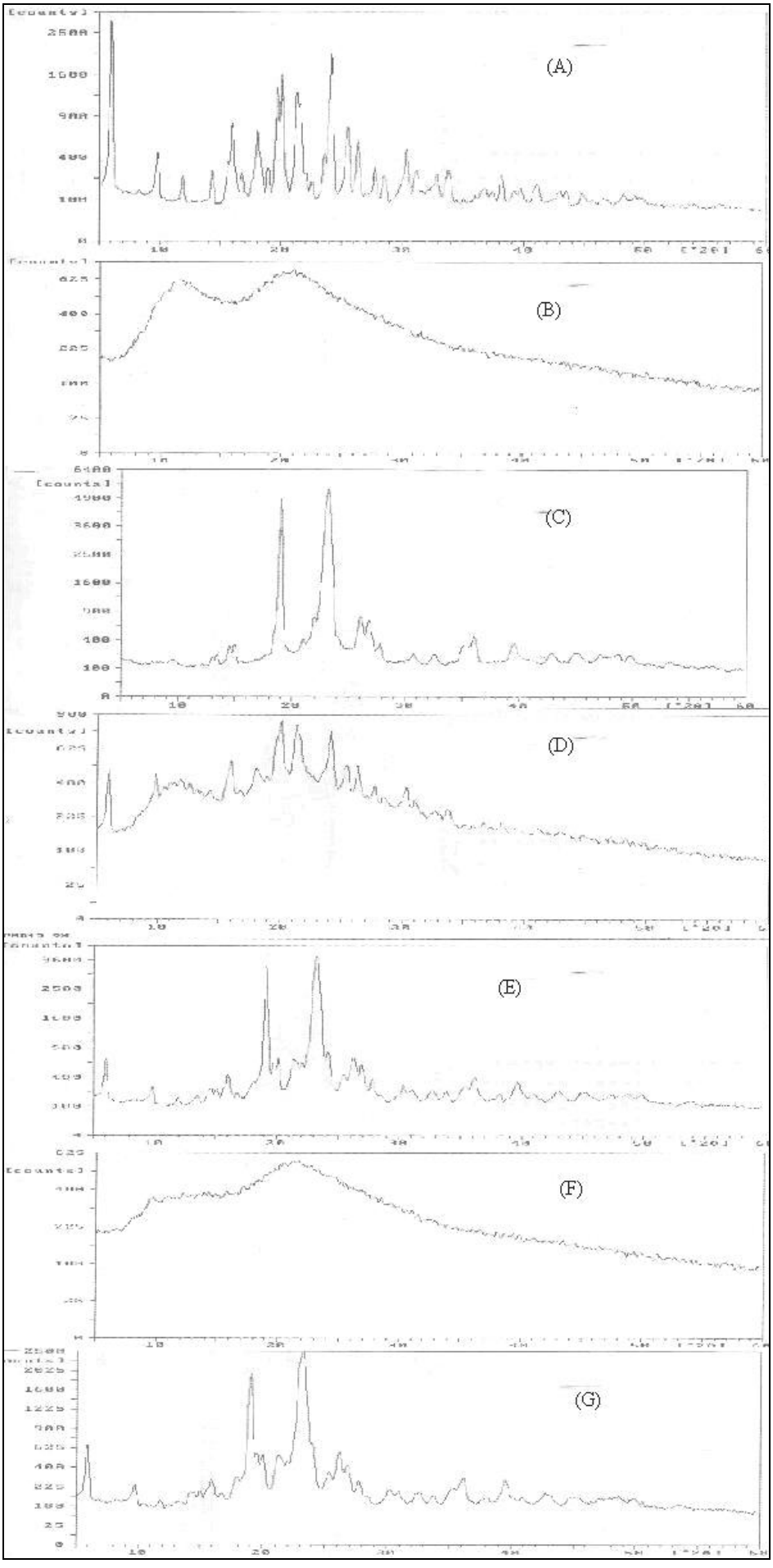


Figure 5. XRD Spectra of (a) Pioglitazone HCL, (B) PVP K30, (C) PEG 6000, (D) PMA13, (E) PMB13, (F) A13, (G) B13

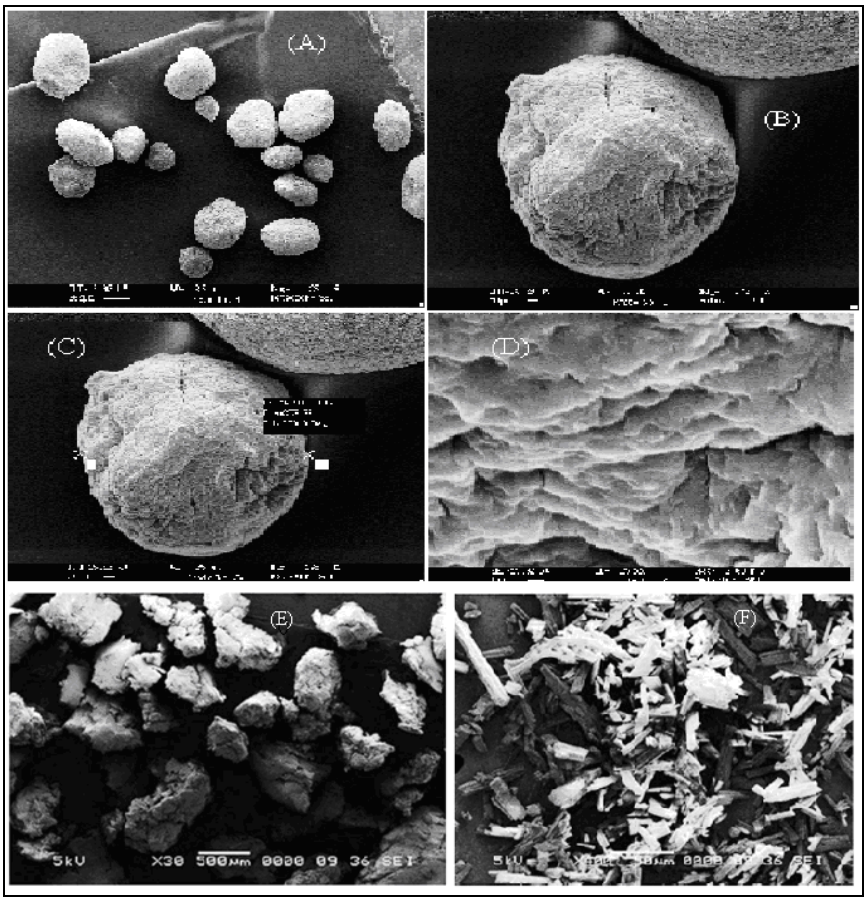


Figure 6. SEM photographs of Pioglitazone (A) microcapsules with size ranging approximately from 300 to 900µm, (B) Individual microcapsules (C) microcapsules showing the size 353.33µm, (D) Surface topography analysis of microcapsules, (E) Internal structure of solid dispersion of sample B13 and (F) show the amorphous and A13 show the crystalline stage

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.

4.3. Practical Yield:

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

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

Table 6. Characterization of muco-adhesive microcapsules

Formulation code	Composition and ratio	Average size (µm)	% 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	195.425	78.17
MC3	SA: Carbopol (1:1)	389	87.11	169.775	67.91
MC4	SA: SCMC (3:1)	410	89.12	182.8	73.12
MC5	SA: HPMC (3:1)	387	81.27	201.925	80.77
MC6	SA: Carbopol (3:1)	341	86.25	190.625	76.25
MC7	SA : SCMC (6:1)	354	79.87	202.6	81.04
MC8	SA: HPMC (6:1)	372	86.82	198.325	79.33
MC9	SA: Carbopol (6:1)	345	89.77	197.275	78.91

4.4. Percentage Drug Content

About 500mg of microcapsule was accurately weighed and transfer in to 1000ml 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 269nm.

(Microencapsulation efficiency) was calculated by the following formula:

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

4.5. Encapsulation Efficiency

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

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

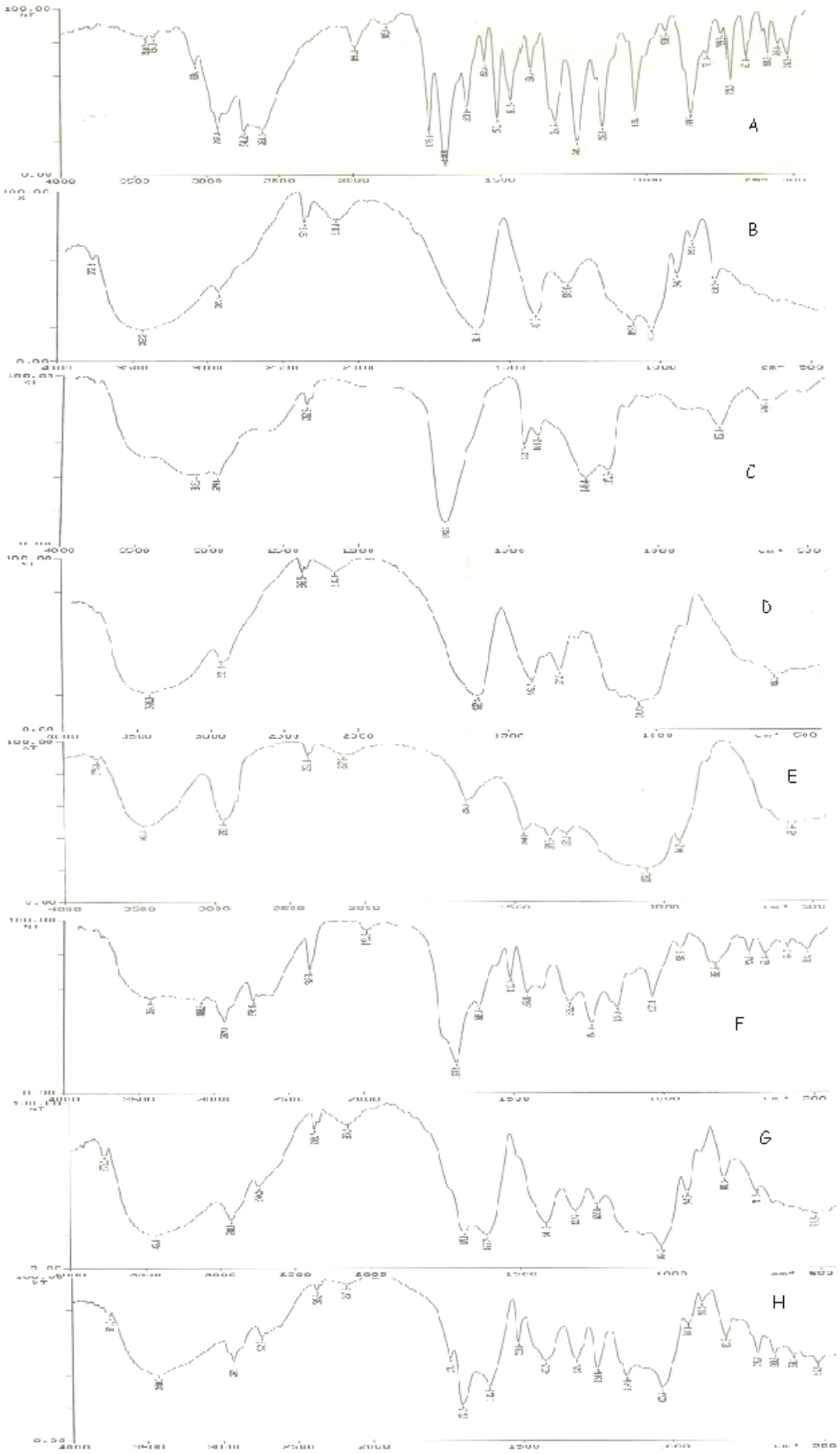


Figure 7. FIR of (A) Pioglitazone HCl, (B) Sodium alginate, (C) Carbopol, (D) Sodium CMC, (E) HPMC, (F) Mixture of A, B and C, (G) Mixture of A, B and D, (H) Mixture of A, B and E

4.6. Fourier Transforms Infrared Spectroscopy

FT-IR spectra (500-4000 cm^{-1}) were obtained on a Nicolet Avatar 37- DTGS FT-IR spectrophotometer (Nicolet) with a resolution of 4 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg sample with 200 mg potassium bromide (Figure 7).

4.7. In-Vitro Drug Release

4.7.1. 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. Samples of drug, microcapsules equivalent with 100mg 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 6ml with phosphate buffer (pH 7.4). Then the absorbance was measured at 269nm (Figure 8).

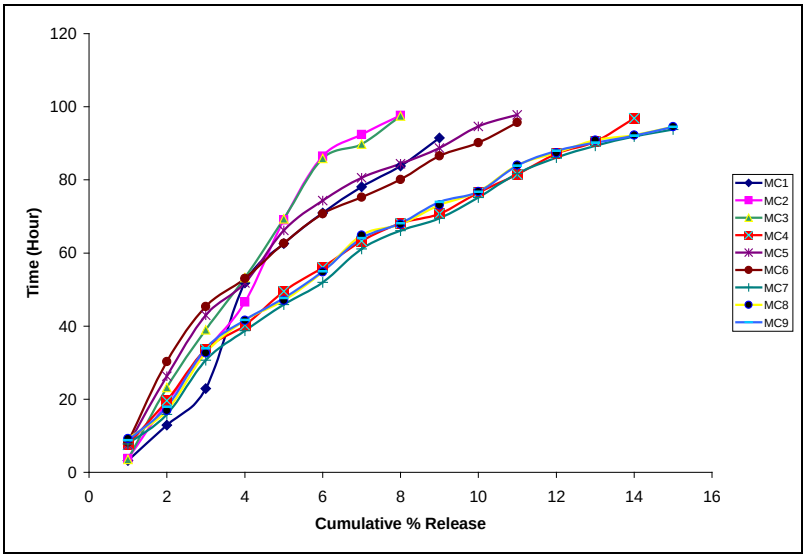


Figure 8. Comparative drug release of various compositions

4.7.2. 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. (Table 5).

Table 7. Microspheres adherence capacity

Percentage of Microspheres adhering to tissue at pH7.4					
Formulation code	1 hour	2 hour	4 hour	6 hour	8 hour
MC1	72.66± 2.08	70.66 ±1.52	54.00 ±1.73	32.00 ±1.2	22.33 ± 3.05
MC2	74.66±1.527	63.57 ±1.3	41.66 ±3.51	25.33 ±1.52	16.00 ± 3.4
MC3	72.33 ±1.52	69.33 ±1.15	45.33±3.05	29.66±1.527	15.00 ± 1.7
MC4	72.33 ±2.08	61.66 ±2.52	49.66 ±1.27	21.66 ±2.08	11.33 ±1.527
MC5	63.66 ± 3.21	56.66±0.57	40.00 ±1.4	11.66 ±2.7	06.70 ± 2.1
MC6	68.52 ± 1.3	54.07 ±2.08	39.72 ± 1.3	29.00±1.52	11.00 ±1.4
MC7	67.22 ±1.8	41.57 ±1.73	35.84±1.15	10.77± 3.4	02.33±1.15
MC8	57.97 ±1.6	33.50 ±1.4	25.36 ±1.02	04.37 ± 1.84	------

4.8. Mucoadhesive Testing

The mucoadhesive property of the microcapsules was evaluated by wash-off [15] In vitro method. Freshly excised pieces of intestinal mucosa (2 × 2cm) from sheep were mounted onto glass slides (3 × 1inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support. About 50 microcapsules were spread onto each wet rinsed tissue specimen, and immediately the slides were hung on to the arm of USP tablet disintegrating test apparatus. The tissue specimen was given a slow, regular up-and-down movement in the test fluid at 37°C contained in a 1L vessel. After definite time interval, the apparatus was stopped and the number of microcapsules still adhering to the tissue was counted. Phosphate buffer (pH 7.4) was used as test fluid. (Table 7).

5. Results and Discussion

5.1. Solubility Studies of Pioglitazone

The Solubility of Pioglitazone HCl in distilled water at 27°C was found to be 5.32µg/mL. The influence of polyvinyl pyrrolidone K30 and polyethylene glycol 6000

upon the solubility of Pioglitazone HCl is presented in Figure 3 and shows the solubility of Pioglitazone HCl increases with increase the concentration of both carriers. PVP K30 has the better solubility enhancing capacity than PEG 6000. (Figure 2).

5.2. Physical Characterization

The solid dispersion of pioglitazone prepared by solvent evaporation method were found to be discrete and free flowing. The final formulation solid dispersion incorporated microcapsules of pioglitazone prepared by the orifice-ionic gelatin method were found to be discrete, spherical, free flowing, and the monolithic matrix type. The SEM photographs indicated that internal structure of solid dispersion of sample B13 show the amorphous and A13 show the crystalline stage. (Figure 6 E, F) and the solid dispersion incorporated microcapsules were uniform in size, with size range of 300µm. The SEM photographs indicated that microcapsules were spherical and completely covered the coat polymer (Figure 6-A, B, C, and D).

5.3. Practical yield of Solid Dispersion

The percentage practical yield was found to be in the range of 81.37 to 89.39 %. The maximum percentage practical yield was found to be 89.39% for B13. (Table 4).

5.4. Practical Yield of Solid Dispersion Incorporated Microcapsules

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 6).

5.5. Percentage Drug Content of Solid Dispersion

The actual drug content of all formulations are given in Table .the percentage drug content ranges from 83.37% to 98.02% for formulation B15 to B11. The maximum percentage drug content was found to be 98.02% IN B11. (Table 4).

5.6. Percentage Drug Content and Encapsulation Efficiency of Solid Dispersion Incorporated Microcapsules

The actual drug content and encapsulation efficiency of all nine formulations are given in Table 6. 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.

5.7. Particle Size Distribution of Solid Dispersion Incorporated Microcapsules

The average size of microcapsules in various batches was found to be 350µm, 347µm, and 389µm, 410µm 387µm, 341µm, 354µm, 372µm and 345µm for MC1, MC2, MC3, MC4, MC5, MC6, MC7, MC8 and MC9 respectively.(Table 6).

5.8. In-Vitro Drug Release

5.8.1. In-Vitro Drug Release Study of Solid Dispersion

Pioglitazone HCl release from the solid dispersion and alone was studied in phosphate buffer (pH 7.4) up to 2 hours. The average percentage release of the pure Pioglitazone HCL was found to be 46% in 2 hours. (Figure 3A, and Figure 3B) In the solid dispersion formulation using polyvinyl pyrrolidone K30 and polyethylene glycol 6000 as carriers, the dissolution rate increased with increased amount of carriers. The best results among solid dispersions with Polyvinyl pyrrolidone K30 were obtained from the formulation A13 (Figure 3C). The increased dissolution rate may be due to the higher solubility of PVP K30 in dissolution medium and better wettability of Pioglitazone hydrochloride in the formulation. The regression coefficient (r) values for formulations A11 to B15 are tabulated in Table 5.

5.8.2. Drug Release Kinetics Studies of Solid Dispersion

The regression coefficient ‘r’ values were found to be higher in the Korsmeyer-peppas models, Hill equation model, Michaelis menten model and Weibull model respectively, indicating that the dissolution of pioglitazone from all formulations followed following above model.(Table 5).

5.8.3. In-Vitro Drug Release Study of Solid Dispersion Incorporated Microcapsules

The *in vitro* release profiles of nine formulations MC1 to MC9 are shown in Figure 8. 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 5.

5.8.4. Drug Release Kinetics Studies of Solid Dispersion Incorporated Microcapsules

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.(Table 5).

5.9. Muco-Adhesive Testing

Microspheres with a coat consisting of alginate and a mucoadhesive polymer exhibited good muco-adhesive properties in the in vitro wash-off test. From the in vitro wash-off test it was observed that, the drug adherance the microcapsules from tissue was increase with an increase in muco-adhesive material in the microcapsules. The maximum adherence resulted in MC1, MC2 and MC3

respectively and minimum found in MC9 and MC8. (Table 7).

5.10. Analytical Testing

5.10.1. Fourier Transforms Infrared Spectroscopy

FT-IR studies were done to detect the possible interactions between the Pioglitazone hydrochloride and carriers (polyvinyl pyrrolidone K30 and polyethylene glycol 6000). The characteristic peaks of Pioglitazone hydrochloride, polyvinyl pyrrolidone K30, polyethylene glycol 6000, physical mixtures and their formulations are given in Figure 4. Comparing the spectra of physical mixtures with those of solid dispersions 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 Polyvinyl pyrrolidone K30 with Pioglitazone HCl under investigation. The absence of any significant change in the IR spectral pattern of drug-polymer physical mixture indicated the absence of any interaction between the drug and the polymer.

5.10.2. Powder X-Ray Diffraction Study

The diffraction spectra of Pioglitazone HCl and polyethylene glycol 6000 show numerous distinct peaks indicating that both are present in a highly crystalline state (Figure 5A, C) and the broad peaks of Polyvinyl pyrrolidone K30 indicating a amorphous state. The PXRD pattern of solid dispersion of sample A13 (Figure 5F) exhibits the characteristic broad peaks of polyvinyl pyrrolidone K30 and crystalline pioglitazone HCl, represent the amorphous state of sample A13. B13 represent the numerous distinct peaks indicating that sample B13 is present in a highly crystalline state (Figure 5G).

5.10.3. Compatibility Studies of Solid Dispersion Incorporated Microcapsules

FTIR studies were done to detect the possible interactions between the drug and the polymers in the microcapsules. Figure 7 Show the IR spectrum's 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 7).

6. Conclusion

The study clearly shows that addition of polyvinyl pyrrolidone K30 to Pioglitazone HCl improved its dissolution rate. Mechanisms involved are solubilization and improved wetting of the drug in the polyvinyl pyrrolidone K30 rich micro-environment formed at the surface of drug crystals after dissolution rate compared with physical mixtures. No solid solution formation and no hydrogen bonding interaction between polyvinyl pyrrolidone K30 with pioglitazone HCl could be detected. The crystallinity of the drug was reduced in solid dispersion formulation with polymers i.e. polyvinyl pyrrolidone K30.

The study also indicated that the solid dispersion incorporated muco-adhesive microcapsules could be formulated by using cell forming polymer sodium alginate and muco-adhesive polymers (Carbopol, Sodium CMC and HPMC) by orifice ion gelation method. Increasing the concentration of cell forming polymer (sodium alginate) in microcapsule formulation decreases the rate of drug release dramatically and the mucoadhesive property increase with increasing the muco-adhesive polymer. The solid dispersion incorporated muco-adhesive microcapsules of all the formulated batches were spherical, discrete and free flowing. FTIR studies indicate that there were not any possible interactions between the solid dispersion (drug) and the polymers in the microcapsules. 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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