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8**Pioglitazone Microcapsules: Formulation and *In vitro* - *Ex vivo* Characterization**Debabrata Sahoo¹, Bhabani Shankar Nayak*¹, Sruti Ranjan Mishra², P. Ellaiah²¹Department of Pharmaceutics, Institute of Pharmacy and Technology, Salipur, Cuttack-754202, Odisha, India.²Department of Pharmaceutical Technology, Jeypore College of Pharmacy, Rondapalli, Jeypore -764002, Koraput, Odisha, India.

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ABSTRACT: Background: Pioglitazone is a thiazolidinedione class drug with hypoglycemic action to treat type 2 diabetes. **Aim:** The study aimed to design, prepare and evaluate the Pioglitazone microcapsules. **Methods:** The Pioglitazone microcapsule formulations (F1 to F6) were prepared by ionic gelation technique using hydroxy propyl methyl cellulose (HPMC-E5LV), sodium carboxy methyl cellulose (CMC-LV) and Hydroxy Propyl Cellulose (HPC-SSL) as rate controlling polymer in two different ratios of 1:1 and 1:2 (Drug: polymer). The drug polymer compatibility was studied using FTIR and DSC techniques. The prepared microcapsules were evaluated for yield, particle size, shape (SEM study), wall thickness, flow property, drug content, loose surface crystal study, swelling index, percentage moisture loss, *in vitro* drug release and kinetic studies, stability study and mucoadhesion property. **Results:** The microcapsules size was small and spherical shape, with good flow properties. The FTIR and DSC study showed no such significant physical or chemical interaction was occurred between drug and polymers. All microcapsule formulations possessed good physicochemical properties. The maximum drug content was obtained with F6 (84 %). All microcapsule formulations released drug in control manner. The microcapsule formulation F6 (0.8 % Hydroxy propyl cellulose) was found to release the drug only 26 % even after 12 h in constant manner with regular fashion with good mucoadhesion, when compared to other microcapsules formulations. The optimized microcapsules were found to be stable at different storage condition. **Conclusion:** It could be concluded that the microcapsule formulation F6 is the best optimized formulation, which could be used for safe management of type II diabetes orally.

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INTRODUCTIONS:

The performance of a drug can often be optimized by controlling the rate and extent of its release in the body. The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate in predetermined rate for certain period of time. Microcapsule is one of the novel dosage form with various advantages like sustained release of the

drug, masking the unpleasant taste and odor of many drugs, improves patient compliance, converts liquid drugs to free flowing powder, protect light, oxygen and moisture sensitive drugs, prevent the incompatibility between drugs, protect volatile drug from volatilization, reduce toxicity and GI irritation of drugs, enable the drug to change the site of absorption, enhances stability of drug, increases bioavailability of drugs, reduces frequency of administration of drugs, reduces side effects of drugs and also can be design as intrauterine devices [1-3]. The controlled release polymers like HPMC, CMC and HPC are hydrophilic, nontoxic and biodegradable polymers extensively used in manufacturing of microcapsules [4].

Thiazolidinediones, such as pioglitazone, are synthetic ligands for peroxisome proliferator-activated receptors (PPARs). They alter the transcription of genes influencing carbohydrate and lipid metabolism, resulting in changed amounts of protein synthesis and, therefore, metabolic changes. Pioglitazone improves glycaemic control in people with Type 2 diabetes by improving insulin sensitivity. The Pioglitazone and its conventional tablet, due to sudden increase in blood concentration or fluctuation in blood concentration, possesses following side effects like fluid retention, peripheral edema, congestive heart failure, anemia, weight gain, upper respiratory tract infection, sinusitis, headache, myalgia, cholestatic hepatitis [5-7]. Thus present investigation is aimed to prepare and evaluate Pioglitazone microcapsules which might be successful in overcoming above mentioned side effects.

MATERIALS AND METHODS:

The drug Pioglitazone was obtained as gift sample from Macleod Pharma, Gangtok, Sikkim. The polymers such as Hydroxy Propyl Methyl Cellulose (HPMC), sodium carboxy methyl cellulose and Hydroxy Propyl Cellulose (HPC) were obtained from Universal Chemical Ltd., Mumbai. All other chemicals and reagents of analytical grade were procured from authorized dealer.

Formulation and Preparation of Microcapsules:

Pioglitazone Microcapsules were prepared by ionic gelation technique using hydrophilic, drug control release polymers HPMC E5LV, CMC-LV and HPC-SSL in the drug polymer ratios of 1:1 and 1:2. Sodium alginate (500 mg) and the mucoadhesive polymer (500 mg) were weighed individually using electronic digital balance (Shimadzu, ELB 120) and were dissolved in

purified water (32 ml) to form a homogeneous polymer solution. Core material, Pioglitazone (500 mg) was added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resultant solution was extruded drop wise with the help of syringe and needle (Optimized gage 20) at optimized injection rate and height, in to 100 ml of (4 %) aqueous calcium chloride solution and stirred 100 rpm using magnetic stirrer (Remi ML Series 1266). After stirring for 15 min, microcapsules were separated, washed with water and dried using Hot air oven (Universal Lab 110S) at 50°C for 6 h [8,9]. The different batches of microcapsules were prepared and were stored for further investigations.

Table 1. Formulation design of Pioglitazone loaded microcapsules.

FC	SA (%)	HPMC (%)	SCMC (%)	HPC (%)
F1	2	1	-	-
F2	2	2	-	-
F3	2	-	1	-
F4	2	-	2	-
F5	2	-	-	1
F6	2	-	-	2

FC - Formulation code, CaCl₂ = 4 %. SA - Sodium alginate, HPMC - Hydroxy propyl methyl cellulose, CMC - Carboxy methyl cellulose, HPC - Hydroxy propyl cellulose.

Drug polymer interaction study by FTIR:

The compatibility between drug and polymers was evaluated using Fourier Transform Infrared Radiation measurement (FTIR) at ambient temperature using IR spectrophotometer (Shimadzu, model 840, Japan). The pellets of about 2 mg of pure drug, empty microcapsules and drug loaded microcapsules were selected and measured separately in the range of 4000-400 cm⁻¹ for 100 scans by Potassium bromide pressed pellet technique [10].

Surface morphology study by Scanning Electron Microscopy (SEM):

The morphological characteristics of Pioglitazone microcapsule was studied by using Scanning electron microscopy (Stereo scan S250 MK III, Cambridge, UK). At first the microcapsules were dried and coated with gold (100 Å) in a gold coating unit under the controlled environment of argon atmosphere. The resolution of SEM study was 5 KV×4000 [11].

Particle size measurement:

The microcapsules size distribution was determined by the optical microscopy method [12] using microscope (Olympus DSX 510) with a calibrated stage and eye piece micrometer (µm) was calculated by using equation, $X_g = 10 \times [(n_i \times \log Xi) / N]$ (1)

Where, X_g is geometric mean diameter, n_i is number of particle in range, X_i is the midpoint of range and N is the total number of particles.

Table 2. Yield, diameter and wall thickness data of various Pioglitazone loaded microcapsule formulations.

FC	Yield (%) (X±S.D.)	d _{avg} (µm) (X±S.D.)	WT (µm) (X±S.D.)
F1	49.7±0.11	164±0.28	3.9±0.35
F2	85.3±0.12	132±0.18	1.85±0.11
F3	53.6±0.25	478±0.19	3.18±0.25
F4	54.7±0.14	281±0.22	2.17±0.17
F5	90.3±0.13	114±0.14	1.52±0.13
F6	88.4±0.17	128±0.28	0.89±0.29

Each value is represented as mean ± standard deviation, n = 3. Standard error mean < 0.202. FC – Formulation code. WT – Wall thickness.

Determination of Wall Thickness:

The method such as suggested by Luu *et al.* was used to determine Theoretical mean wall thicknesses of the microcapsules by using the equation [12,13],

$$h = r (1 - P) d1 / 3 [P d2 + (1-P) d1] \dots\dots\dots (2)$$

Where, h is the wall thickness in µm, r is the arithmetic mean radius in µm of the microcapsules, d1 is the density in g/cc of the drug material, d2 is the density in g/cc of the polymer material and P is the proportion of the medicament in the microcapsules. The wall thickness of each formulation was done for three times and the mean values with standard deviation are presented.

Flow Properties study:

Determination of angle of repose:

The Angle of repose was determined using falling funnel method. The microcapsules were poured through a vertically placed of height (h). Radius (r) of the heap was measured and the angle of repose (Q) was calculated by using the formula [14],

$$= \tan^{-1} (h/r) \dots\dots\dots (3)$$

Bulk Density:

The product was tapped using digital bulk density apparatus (HAMCO 124-A, Hamko India) for 1000 taps in a cylinder and the changes in volume were measured. The Carr’s index (CI) and Hausner’s ratio were calculated by using the following formula [14],

$$CI (\%) = [(D_f - D_o) / D_f] \times 100 \dots\dots\dots (4)$$

$$\text{Hausner’s ratio} = D_f / D_o \dots\dots\dots (5)$$

Where, D_o is the poured density in g/cc and D_f is the tapped density in g/cc.

Drug content estimation:

By the help of mortar and pestle, drug loaded microcapsules (100 mg) were powdered and suspended in 100 ml 0.1N HCl solution and was kept over Rotary shaker (Rotary Scientific RSW 137). Then the solution was double filtered using Whatman Filter paper 4. Pioglitazone content in the filtrate was determined spectrophotometrically (UV-visible-1700, spectrophotometer Shimadzu, Japan) at 270 nm [15].

Drug Encapsulation Study:

The drug encapsulation efficiency (DEE) was calculated by using the equation,

$$DEE (\%) = (Pc / Tc) \times 100 \dots\dots\dots (6)$$

Where, Pc is practical content, Tc is the theoretical content. The entire test was performed in triplicate [15].

Table 3. Flow properties data of various Pioglitazone loaded microcapsule formulations.

FC	Bulk Density (g/cc)	Carr’s index (%)	Hausner’ ratio	AOR (°) (X±S.D.)
F1	1.171	7.58	1.09	20.8±0.15
F2	1.121	8.21	1.11	16.8±0.09
F3	1.652	12.91	1.151	25.88±0.12
F4	1.759	13.55	1.162	27.25±0.08
F5	1.723	11.76	1.129	22.15 ±0.11
F6	1.433	9.45	1.138	21.32 ±0.17

Each value is represented as mean ± standard deviation, n = 3. Standard error mean < 0.202. FC – Formulation code. AOR – Angle of repose.

Loose surface crystals study:

This parameter was evaluated to observe the excess drug present on the surface of microcapsules. About 500 mg of microcapsules from each batch was shaken in 20 ml

of double distilled water for 5 min and then filtered through whatman filter paper 22. The amount of drug lost in filtrate was determined Spectroscopically and calculated as a percentage of total drug content [16].

Table 4. Drug content, encapsulation efficiency, moisture loss, surface drug content and swelling index data of Pioglitazone microcapsules.

FC	TDC (mg)	PDC (mg) (X±S.D.)	EE (%) (X±S.D.)
F1	74	40.95±0.24	57.23±0.44
F2	53.76	30.51±0.13	59.66±0.29
F3	31.64	16.50±0.17	53.8±0.34
F4	58.76	29.17±0.25	51.51±0.33
F5	45.45	36.02±0.13	80.23±0.51
F6	36.76	30.94±0.19	84.11±0.42

Each value is represented as mean ± standard deviation, n = 3. Standard error mean < 0.266. TDC – Theoretical drug content. PDC – Practical drug content. EE – Encapsulation efficiency.

Table 5. Drug content, encapsulation efficiency, moisture loss, surface drug content and swelling index data of Pioglitazone microcapsules.

FC	Moisture Loss (%) (X±S.D.)	Surface drug content (%) (X±S.D.)	Swelling Index (%) (X±S.D.)
F1	8.26±0.044	9.22±0.18	41±0.22
F2	9.25±0.034	17.29±0.22	53±0.16
F3	8.18±0.019	24.71±0.23	46±0.43
F4	7.24±0.022	22.66±0.24	61±0.11
F5	11.22±0.029	10.44±0.27	58±0.16
F6	3.23±0.042	10.08±0.46	67±0.19

Each value is represented as mean ± standard deviation, n = 3. Standard error mean < 0.266.

Swelling Index:

The pre weighed microcapsules were placed in dissolution medium for 6 h. The swelled microcapsules were filtered and kept in room temperature for few minutes. The wet microcapsules were weighed using digital balance. The percentage of swelling of microcapsules in the dissolution media was then calculated by using the equation [17],

$$S_w = [(W_t - W_0) / W_0] \times 100 \dots\dots\dots (7)$$

Where, S_w is percentage of swelling of microcapsules, W_t is weight of the microcapsules at time t, W₀ is initial weight of the microcapsules.

Table 6. In vitro drug release kinetic studies of microcapsule formulations.

FC	ZOK	FOK	HSRE	KMPM	
	Regression co-efficient (r)			n	
F1	0.943	0.916	0.997	0.934	0.910
F2	0.958	0.931	0.995	0.975	0.175
F3	0.952	0.869	0.989	0.9788	0.831
F4	0.991	0.874	0.963	0.942	0.254
F5	0.982	0.889	0.993	0.922	0.332
F6	0.983	0.956	0.993	0.961	0.732

FC – Formulation code, ZOK – Zero order kinetic, FOK – First order kinetic, HSRE - Higuchi square root equation and KMPM - Korsmeyer-Peppas model

Moisture loss (ML) study:

This parameter was studied to evaluate the hydrophilic nature of polymers. The microcapsules were weighed initially and kept in desiccator containing calcium chloride at 37°C for 24 h. The final weight was noted, until unless no further change in weight of sample was observed [17].

$$ML (\%) = [(IW - FW) / FW] \times 100 \dots\dots\dots (8)$$

Where, IW and FW are initial and final weight.

In vitro drug release study:

In vitro drug release study was carried out in USP XXXI paddle type dissolution test apparatus (Dissolution Test Apparatus VDA-1D, Universe Surgical, Chennai) using 0.1 N HCl as dissolution medium of volume 900 ml and bath temperature was maintained at (37±1)°C throughout study. Peddle speed was adjusted to 50 rpm. An interval of 1 h, 5 ml of sample was withdrawn with replacement of 5 ml fresh medium and analyzed for Pioglitazone content by using UV-Visible spectrophotometer at 270 nm. The entire release tests were performed in triplicate [18,19].

In vitro drug release kinetic study:

This study shall give an idea on the exact mechanism of drug release from microcapsules. The drug release data was analyzed according to zero order [20], first order [21], Higuchi square root [22] and Korsmeyer-Peppas model

[23]. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Table 7. Accelerated stability study of optimized Pioglitazone microcapsule formulations (F6) according to ICH guide lines.

Temp (°C)	Potency of various Formulations (%)				
	Weeks				
	Initial	2	4	6	8
25 ± 2	99.42	99.42	99.38	99.24	99.11
37 ± 2	99.42	99.37	99.13	99.08	99.01
45 ± 2	99.42	99.28	98.91	98.82	98.78

Accelerated stability studies:

Stability studies were performed according to ICH guidelines. The optimized microcapsules formulation was stored in room temperature at (25±1)°C, oven at (37±1)°C, and at (45±1)°C for a period of 8 weeks in a stability chamber (Thermo Lab BD LX150). The samples were analyzed for drug content every week by spectrophotometer at 270 nm [24,25].

Mucoadhesion test (Ex Vivo study):

The *ex vivo* wash off method was adopted to determine mucoadhesion property of microcapsule formulations. A piece of stomach mucosa (Dimension was 5×2 cm) was taken from local slaughter house. It was mounted on to glass slides with adhesive. About 100 microcapsules were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on the arm of USP grade digital tablet disintegration Test apparatus (Veego Instrument Corporation) with little modification. By operating the disintegrating test machine the tissue specimen was given a slow regular up and down movement in the test fluid at 37 °C taken in the vessel of the machine. At the end of every one hour up to 10 h the machine was stopped and number of microcapsules still adhering onto the tissue was counted [26-28].

Statistical studies:

To make the study statistical significant, all the values obtained during observation were verified with different statistical methods including one way ANOVA at 5 % level of significance, standard deviation (SD), standard error mean (SEM) and coefficient of variance (CV) [29].

RESULTS AND DISCUSSIONS:

The preliminary plan of the work was to formulate, prepare and evaluate the Pioglitazone microcapsule. The formulation design is given in Table 1. Pioglitazone loaded microcapsule could successfully be prepared by

using ionotropic gelation technique. The generalized microparticulation protocol being regulated by choice of ingredient, successful preparation of microcapsules and optimization at every preparative steps. The resulting microcapsules prepared by ionotropic gelation method were found to be discrete, spherical and with good physical characteristics. Thus the ionotropic gelation method was found to be simple and reproducible. The yields of all the formulations were good, whose values varied from 53.6±0.25 to 90.3±0.13 % as shown in Table 2. The yields suggesting that the processing parameters did not affect the yield from the ionotropic gelation method. The yield was highest in formulation F6.

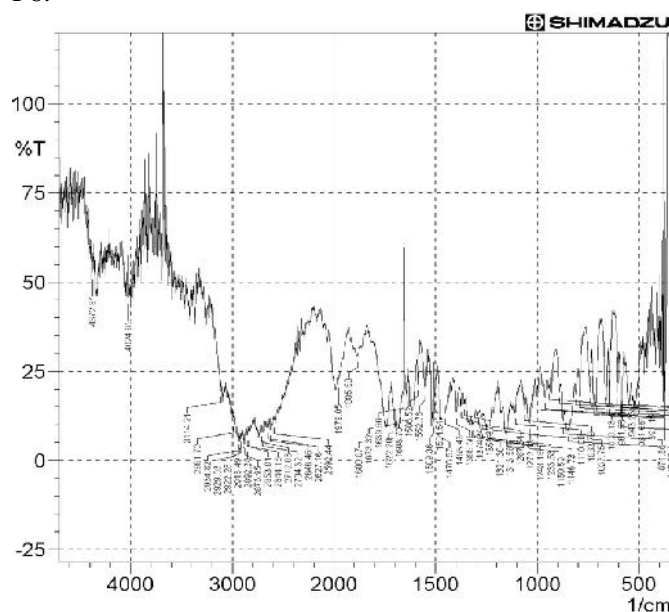


Fig 1. The FTIR data of pure drug, Pioglitazone.

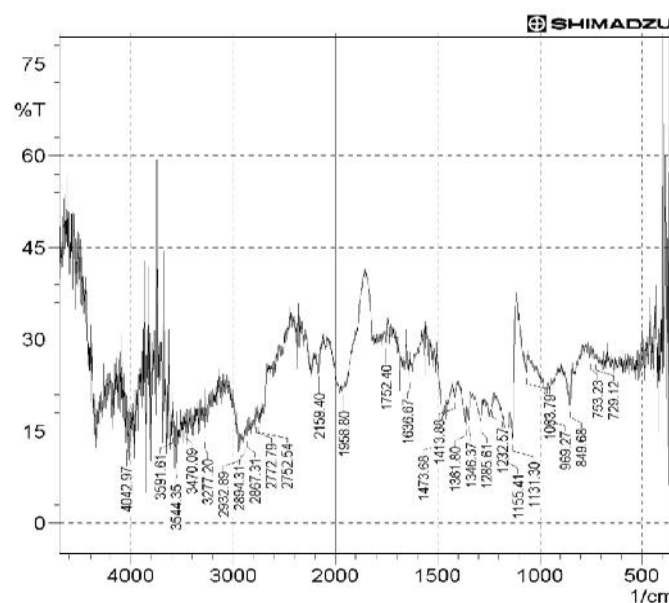


Fig 2. The FTIR data of optimized Pioglitazone microcapsule formulation (F6).

The interaction study between the drug and polymers in microcapsule formulation was performed using FTIR spectrophotometer. The pellets were prepared on KBr press. The spectra were recorded over the wave number range of 3600 to 400 cm^{-1} . The drug shows different peaks at C-H = 3008, C=C = 1605, 1495, 1466, O-H = 3231, N=N = 1576 and Cl = 1200-1400 cm^{-1} of benzene which confirms the purity of the drug. FT-IR spectrum of pure drug (Pioglitazone) and selected microcapsule formulation (F6 containing HPC) is represented in Fig 1 and 2. From figure it is concluded that no such significant drug polymer interaction was taking place in physical mixture of Pioglitazone and HPC^{28,29}. From figure it is concluded that no such drug polymer interaction is taking place in physical mixture of Pioglitazone and HPC.

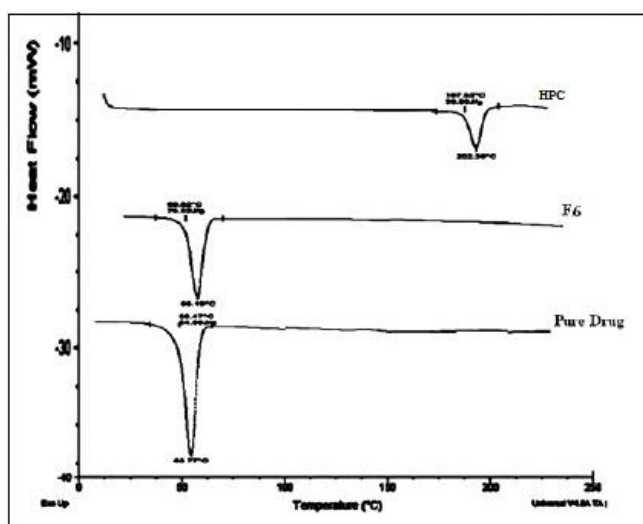


Fig 3. DSC chromatogram of pure pioglitazone, polymer (HPC) and optimized microcapsule formulation (F6).

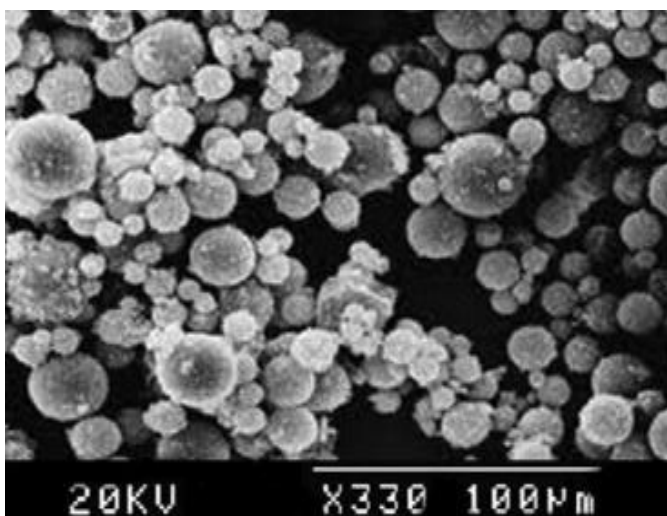


Fig 4. SEM micrograph of optimized Pioglitazone microcapsule formulation (F6).

The DSC study (Fig 3) revealed that no such changes in melting point of optimized microcapsule formulation F6 was observed in comparison to melting point of pure Pioglitazone, signifies that Pioglitazone was compatible with hydroxyl propyl cellulose.

The optical microscopy revealed that all microcapsules thus obtained, were opaque, small and discrete with smooth surfaces. It was further confirmed from the microcapsules picture obtained from SEM study as shown in Fig 4. The size (Average diameter) various microcapsule formulation was the ranges from 128 ± 0.28 to 478 ± 0.19 μm . The minimum size was obtained with microcapsule formulation F6 where as maximum size was obtained with microcapsule formulation F3 as represented in Table 2. The wall thickness values of the prepared microcapsule formulations lied in the ranges of 0.89 ± 0.29 to 3.9 ± 0.35 mm (Table 2). The wall thickness was minimum in microcapsule formulation F6. The flow properties data is given in Table 3. The bulk density was found in the range of 1.171 to 1.759. The microcapsules of all formulations had Hausner's ratio of 1.5 or less indicating good flowability. The Carr's index was found between 7.527 to 13.55 %, demonstrated no such flow properties problem being associated with all microcapsule formulations. The good flowability of the microcapsules was also evidenced with angle of repose within range of 16.8 ± 0.09 to $27.25 \pm 0.08^\circ$, which is below 30° indicating excellent flowability except microcapsule formulations F3 and F4 with good flowability. Relatively high drug content and encapsulation efficiency was observed for each formulation. The encapsulation efficiency was in the ranges from 51.51 ± 0.33 (F4) to 84.11 ± 0.42 % (F6) as given in Table 4. The surface drug content was in the ranges from 9.22 ± 0.18 to 24.71 ± 0.23 %, as presented in Table 5. The result showed that less amount of drug being present in surface of microcapsules. The swelling indexes of microcapsules were found satisfactory. The minimum swelling index (41 ± 0.22 %) was obtained with microcapsule formulation F1 where as maximum swelling index (67 ± 0.19 %) was obtained with microcapsule formulation F6 (Table 5). The percentage of moisture loss was found in a ranges from 3.23 ± 0.042 to 11.22 ± 0.029 % ensures the presence of diminutive water content (Table 5). The release of drug from the microcapsules exhibited a sustained pattern, in controlled manner over extended period of time. The microcapsule formulation F6 was released the drug 26 %

only even after 12 h as evident from Fig 5. The *in vitro* drug release kinetic data revealed that the microcapsule formulation F6 followed zero order release kinetic fashion as evident from Table 6. The optimized microcapsules (F6) were found to be stable at different storage conditions as the drug content (Potency in %) was found to be significantly unchanged up to two months (Table 7).

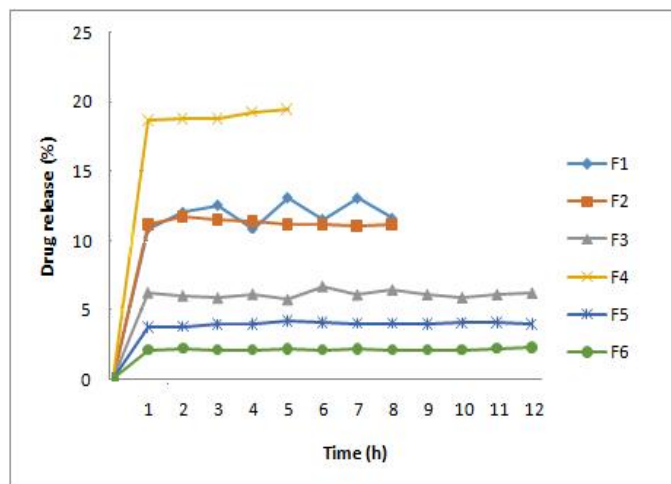


Fig 5. In vitro drug release study of various Pioglitazone microcapsule formulations.

All Pioglitazone loaded microcapsule formulations showed good mucoadhesion. The order of mucoadhesion property found as F6 > F3 > F2 > F4 > F1 > F5. The mucoadhesion wash-off test showed that the microcapsule formulation F6 and F5 exhibited highest and lowest mucoadhesion as evident from Fig 6. The microcapsules prepared from hydroxyl propyl cellulose exhibited highest mucoadhesion which might be due to more hydrophilic nature.

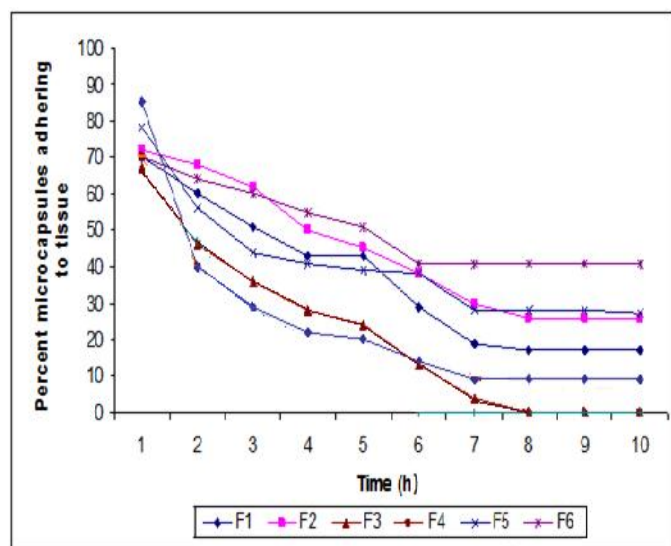


Fig 6. Mucoadhesion measurement data of various Pioglitazone microcapsules by *in vitro* wash-off test.

CONCLUSION:

From the research work findings, it could be concluded that the microcapsules formulation F6 containing 2 % hydroxyl propyl cellulose, is the best optimized formulation as it possess maximum encapsulation efficiency, good control drug release profile with satisfactory mucoadhesion property thus this microcapsule formulation of Pioglitazone could be use for safe management of type II diabetes. Further research to be extended over its *in vivo* study and *in vitro* – *in vivo* correlation.

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