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Design Development and Preparation of Rosiglitazone microcapsules for control release drug delivery

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ABSTRACT: Background: Rosiglitazone is thiazolidinediones group of drug which decreases blood sugar by activation of the peroxisome proliferator-activated receptors. **Aim:** The study aimed to design and prepare rosiglitazone microcapsule. **Methods:** The rosiglitazone microcapsule formulations (F1 to F8) were prepares by ionic gelation technique using carbopol – 934, hydroxy propyl methyl cellulose and sodium carboxy methyl cellulose as rate controlling polymer in different ratios of 1:1, 1:2 and 1:2.5 (Drug: polymer). The drug polymer compatibility was studied using FTIR and DSC techniques. The prepared microcapsule 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 & discussions:** The microcapsules size was small and spherical shape, with good flow properties. No such significant physical or chemical interaction was occurred between drug and polymer. The drug content was found to be satisfactory. Highest drug content (84%) was obtained with F8. All microcapsule formulations released drug in control manner. The microcapsule formulation F8 (0.8%) Hydroxy propyl cellulose) was found to release the drug only 15.003 % even after 8 h in constant manner with regular fashion for longer period of time when compared to other microcapsules formulations. **Conclusion:** It could be concluded that the microcapsule formulation F8 is the best optimized formulation, which could be use for safe management of type II diabetes.

KEY WORDS: -*Diabetes, Rosiglitazone, microcapsules, mucoadhesive*.

I. INTRODUCTION

Controlled release drug delivery systems are aimed at controlling the rate of drug delivery, sustaining the duration of the activity and targeting the delivery of the drug to a tissue. One of the essential factors of controlled drug release is the residence time of drug at absorption site [**1**]. The development of efficient orally delivered mucoadhesive drug delivery system includes advantages like, enhanced bioavailability, targeted specific delivery to specific region of the GI tract, maximized absorption rate due to intimate contact with the absorbing membrane, improved drug protection by polymer encapsulation and longer gut transit time resulting in extended periods for absorption [**1,2]**. The microcapsule is defined as spherical particle with size varying from 50 nm – 2 mm, containing a core substance coated by a polymeric material**.** Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules with many useful properties. Rosiglitazone is thiazolidinediones group of drug which decreases blood sugar by activation of the peroxisome proliferator-activated receptors [**3**]. With the objectives to minimize the side effects of rosiglitazone by maintaining steady plasma concentration and to minimize frequency of dosing, study was aimed to design, formulate and prepare rosiglitazone microcapsule using various mucoadhesive release rate controlling polymers.

II. MATERIALS AND METHOD

The drug Rosiglitazone was obtained as gift sample from Dr. Reddy Lab., Hyderabad. The polymers such are Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC) were obtained from Universal Chemical Ltd., Mumbai. All other chemicals and reagents of analytical grade were procured from authorized dealer.

2.1 Formulation design and preparation of micorcapsules

Rosiglitazone microcapsules were prepared by ionic gelation method employing carbopol, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC) 1:1 and 1:2 drug polymer ratios and Sodium Carboxy Methyl Cellulose (SCMC), in 1:1, 1:2 and 1:2.5 ratios. Sodium alginate (500 mg) and the mucoadhesive polymer (500 mg) were dissolved in purified water (32 ml) to form a homogeneous polymer solution. Core material, rosiglitazone (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

(gage 20) in to 100 ml of (4 %) aqueous calcium chloride solution and stirred 100 rpm. After stirring for 15 min microcapsules were separated, washed with water and dried at 70°C for 6 h in an oven [**4,5**].

2.2 Percentage yield estimation

The yield was calculated as the weight of the microcapsules recovered from each batch divided by total weight of drug and polymer used to prepare that batch by 100 [**5**].

2.3 Drug polymer interaction study by FTIR

The Fourier Transform Infrared Radiation measurement (FTIR) spectral measurements were taken at ambient temperature using IR spectrophotometer (Shimadzu, model 840, Japan). Two mg of pure drug, empty microcapsules and drug loaded microcapsules were selected and measured in the range of 4000-400 cm^{-1} for 100 scans using KBr pressed pellet technique [**6**].

2.4 Surface morphology study by scanning electron microscopy (SEM)

Scanning electron microscopy (Stereo scan S250 MK III, Cambridge, UK) was carried out to study the morphological characteristics of rosiglitazone microcapsule. The dried microcapsules were coated with gold (100 A°) under an argon atmosphere in a gold coating unit. Scanning electron micrographs of microcapsules were observed at resolutions of 5 KV X 4000 [**7,8**].

2.5 Particle size measurement

The microcapsules size distribution was determined by the optical microscopy method using a calibrated stage micrometer (µm) was calculated by using equation[10], $Xg = 10 \times [(n_i \times \log X_i) / N]$. Xg is geometric mean diameter, n_i is number of particle in range, xi is the midpoint of range and N is the total number of particles [**9].**

2.6 Determination of Wall Thickness

Theoretical mean wall thicknesses of the microcapsules were determined by the method as suggested by Luu et al. using the equation[10], $h = r (1- P) d_1 / 3 [P d_2 + (1-P) d_1]$, Where, h is the wall thickness in µm, r is the arithmetic mean radius in µm of the microcapsules, d_1 is the density in g/cc of the drug material, d_2 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 [**10**].

2.7 Micromeritic study [11-13]

2.7.1 Determination of angle of repose

The Angle of repose was determined using funnel method. The microcapsules were poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius (r) of the heap was measured and the angle of repose (Q) was calculated using the formula, $\theta = \tan^{-1} (h/r)$.

2.7.2 Bulk Density

The product was tapped using bulk density apparatus for 1000 taps in a cylinder and the change in volume was measured. The Carr's index and Hausner's ratio were calculated by formula, Carr's index (%) = $[(D_f - D_o) / D_f] \times 100$ and Hausner's ratio = D_f / D_o, Where, D_o is the poured density in g/cc and D_f is the tapped density in g/cc.

2.8 Drug content estimation

Drug loaded microcapsules (100 mg) were powdered and suspended in 100 ml 0.1N HCl solution and kept for 24 h. It was stirred for 5 min and filtered [**10**]. Rosiglitazone content in the filtrate was determined spectrophotometrically (UV-visible-1700, spectrophotometer Shimadzu, Japan) at 203 nm.

2.9 Drug Entrapment Study

The drug entrapment efficiency (DEE) was calculated by the equation[10], $EE = (Pc / Tc) \times 100$, Where, Pc is practical content, Tc is the theoretical content. The entire test was performed in triplicate [**14,15**].

2.10 Loose surface crystals study

The rosiglitazone loaded microcapsules prepared by various techniques were evaluated by loose surface crystal study to observe the excess drug present on the surface of microcapsules. From each batch, 500 mg of microcapsules was shaken in 20 ml of double distilled water for 5 minute and then filtered through whatman filter paper 41. The amount of drug lost in filtrate was determined spectroscopically and calculated as a percentage of total drug content [**14-17**].

2.11 Determination of swelling properties

Microcapsules of known weight were placed in dissolution solution for 6 h and the swollen microcapsules were collected by a centrifuge and the wet weight of the swollen microcapsules was determined. The percentage of swelling of microcapsules in the dissolution media was then calculated by using equation, $S_w = [(W_t - W_{o)} / W_o] \times 100$**,** Where S_w = percentage of swelling of microcapsules, Wt = weight of the microcapsules at time t, W_O = initial weight of the microcapsules [**14-17**].

2.12 Determination of Percentage of moisture loss

To evaluate the hydrophilic nature of polymers, the microcapsules weighed initially kept in desiccator containing calcium chloride at 37°C for 24 h. The final weight was noted when no further change in weight of sample[13]. % of moisture loss = [(Initial weight- final weight/ Final weight] ×100 [**17,18**].

2.13 *In vitro* drug release study

In vitro drug release study was carried out in USP XXI peddle type dissolution test apparatus using 0.1 N HCl as dissolution medium of volume 900 ml and bath temperature was maintained at (37±1)°C throughout study[14]. Peddle speed was adjusted to 50 rpm. An interval of 1 h, five ml of sample was withdrawn with replacement of five ml fresh medium and analyzed for Rosiglitazone content by UV-Visible spectrophotometer at 203 nm. The entire release tests were performed in triplicate [**17,18**].

2.14 In vitro drug release kinetic study

In order to study the exact mechanism of drug release from microcapsules, drug release data was analyzed according to zero order [**19**], first order [**20**], Higuchi square root [**17**] and Korsemeyer-Peppas model [**21**]. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

2.15 Accelerated stability studies

Stability studies were performed according to ICH guidelines. The optimized best formulation was stored in room temperature at (25±1)°C, in oven at (37±1)°C, and at (60±1)°C for a period of 8 weeks. The samples were analyzed for drug content every week by spectrophotometer at 203 nm [**22**].

2.16 Mucoadhesion testing by in vitro Wash-off test

A piece of stomach mucosa (5 × 2cm) 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 a USP tablet disintegrating test machine. By operating the disintegrating test machine the tissue specimen was given a slow regular up and down movement in the test fluid at 37^oC 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 [**23,24**].

2.17 Statistical studies

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) [**25**].

III. RESULTS AND DISCUSSIONS

The yields of all the formulations were good (35.02±0.021 to 89.33±0.061 % as given in Table 1), suggesting that the processing parameters did not affect the yield from the ionotropic gelation method, as given in Table 1. 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 (rosiglitazone), polymers HPC) and selected microcapsule formulation (F8) is represented in Fig 18. From figure it is concluded that no such drug polymer interaction is taking place in physical mixture of rosiglitazone and HPC. The optical microscopy revealed that all microcapsules thus obtained, were opaque, small and discrete with smooth surfaces as shown in Fig 2. The size (Average diameter) various microcapsule formulation was the ranges from 74.1±0.02 to 467.9±0.02 µm. The minimum size was obtained with microcapsule formulation F1 where as maximum size was obtained with microcapsule formulation F5 as represented in Table 2 and Fig 3. The wall thickness values of the prepared microcapsule formulations lied in the ranges of 0.843±0.27 to 3.888±0.25 mm (Table 2). The bulk density was found in the range of 1.123±0.5 to 1.76±0.2. 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 3.630. The good flowability of the microcapsules was also evidenced with angle of repose within range of 15.6±0.08 to 27.9±0.05°, which is below 30° indicating excellent flowability

except microcapsule formulations F5 and F6 with good flowabilty. Relatively high drug content and encapsulation efficiency was observed for each formulation. The encapsulation efficiency was in the ranges from 43.66±0.035 (F1) to 84.17±0.049 % (F8) as given in Table 3. The surface drug content was in the ranges from 8.01±0.23 to 26.7±0.3 as presented in Table 3. The result showed that less mount of drug being present in surface of microcapsules. The swelling indexes of microcapsules were found satisfactory. The minimum swelling index (44±0.23 %) was obtained with microcapsule formulation F3 where as maximum selling index (78±0.13 %) was obtained with microcapsule formulation F1. The percentage of moisture loss was found in a ranges from 2.24 to 13.26 % ensures the presence of diminutive water content. The *in vitro* drug release data of various microcapsule formulations is given in Table 3 and Fig 4. The release of drug from the microcapsules exhibited a sustained pattern, in controlled manner (except formulation F1 and F2) over extended period of time. The microcapsule formulation F8 was found to release the drug only 21.98±0.79 % even after 12 h with zero order release kinetic fashion as evident from in vitro drug release kinetic data given in Table 4. The optimized microcapsules were found to be stable at different storage condition as all physicochemical parameters of optimized formulation (F8) was unchanged. All the rosiglitazone loaded microcapsules are showing good mucoadhesion. The mucoadhesion wash-off test showed that the microcapsule formulation F8 and F7 exhibited highest and lowest mucoadhesion as evident from Fig 5.

IV. CONCLUSION

It could be concluded that the microcapsule formulation F8 containing 0.8% hydroxyl propyl cellulose, is the best optimized formulation as it possess maximum encapsulation efficiency and it releases drug in more control manner, thus this Rosigltazone microcapsule formulation could be use for safe management of type II diabetes.

V. ACKNOWLEDGEMENT

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Table 1. Formulation design and yield of rosiglitazone loaded microcapsule formulations.

Formulation	$CaCl_2$ (%)	Sodium Alginate (%)	HPMC (%)	Carbopol- 934 (%)	SCMC (%)	HPC (%)	Yield (%) (X±S.D.)
F1	4	2	1	-	-	-	35.02±0.021
F2	4	2	2	-	-	-	45.16±0.052
F3	4	2	-	0.66	-	-	44.66±0.061
F4	4	2	-	1.32	-	-	81.17±0.062
F5	4	2	-	-	1	-	52.66±0.025
F6	4	2	-	-	2	-	51.72±0.044
F7	4	2	-	-	-	0.4	89.33±0.061
F8	4	2	-	-	-	0.8	85.33±0.075

HPMC – Hydroxy propyl methyl cellulose, SCMC – Sodium carboxy methyl cellulose, HPC – Hydroxy propyl cellulose. Each value represent mean ± standard deviation (n – 3). Standard error mean < 0.043.

Table 2. Average Size, flow properties and wall thickness data of rosiglitazone loaded microcapsule formulations.

Formulation	d_{avg} (µm) (X±S.D.)	Bulk Density (g/cc) (X±S.D.)	Carr's index (%)	Hausner's ratio	Angle of Repose (°) (X±S.D)	Wall Thickness (mm) (X±S.D.)
F1	74.1±0.02	1.38±0.4	8.6	1.093	24.8±0.11	2.512±0.21
F2	148.4±0.03	1.22±0.74	10.8	1.107	21.6±0.09	3.567±0.18
F3	145.8±0.02	1.17±0.3	7.5	1.081	20.0±0.12	3.888±0.25
F4	114.3±0.01	1.12±0.5	7.9	1.085	15.6±0.08	1.848±0.14
F5	467.9±0.02	1.65±0.8	12.9	1.148	26.4±0.14	0.843±0.27
F6	278.3±0.02	1.76±0.2	13.6	1.158	27.9±0.05	1.052±0.11
F7	442.9±0.01	1.72±0.3	11.2	1.131	21.9±0.13	2.167±0.14
F8	457.3±0.03	1.43±0.6	9.5	1.135	25.6±0.17	3.008±0.15

Each value is represented as mean ± standard deviation (n = 3). Standard error mean < 0.461.

Table 3. Encapsulation efficiency, loose surface crystal study, swelling index and moisture loss data of rosiglitazone loaded microcapsule formulations.

Formulation	Encapsulation Efficiency (%) (X±S.D.)	Surface drug content (%) (X±S.D.)	Swelling Index (%) (X±S.D.)	Moisture Loss (%) (X±S.D.)	Cumulative % drug release (12 h) (X±S.D.)
F1	43.66±0.035	8.01±0.23	78±0.13	4.11±0.014	43.21±1.12
F2	59.07±0.051	15.91±0.31	80±0.33	5.19±0.060	61.26±0.92
F3	55.34±0.041	8.25±0.12	44±0.23	7.36±0.054	105.29±0.88
F4	56.76±0.039	18.26±0.32	55±0.13	9.88±0.029	101.19±1.06
F5	52.18±0.041	26.70±0.13	48±0.43	8.81±0.018	50.14±1.11
F6	49.65±0.039	23.65±0.14	60±0.09	2.24±0.017	95.1±1.03*
F7	79.26±0.051	9.53±0.23	59±0.11	13.26±0.025	25.11±0.84
F8	84.17±0.049	14.38±0.42	66±0.18	3.19±0.032	21.98±0.79

Each value is represented as mean ± standard deviation (n = 3). Standard error mean < 0.635.* 5 h study.

Table 4. *In vitro* drug release kinetic studies of rosiglitazone microcapsule formulations.

Formulations	Zero order kinetics	First order kinetics	Higuchi square root equation	Korsmeyer - Peppas model	
	Regression co-efficient (r)				n
F1	0.9802	0.9130	0.9999	0.9872	0.1694
F2	0.9818	0.9131	0.9997	0.9543	0.4050
F3	0.9943	0.9256	0.9971	0.9234	0.9220
F4	0.9957	0.9351	0.9949	0.9675	0.1875
F5	0.9650	0.8700	0.9889	0.9788	0.4830
F6	0.9921	0.8497	0.9626	0.9342	0.5204
F7	0.9901	0.8903	0.9923	0.9132	0.2230
F8	0.9723	0.9257	0.9923	0.9426	0.7203

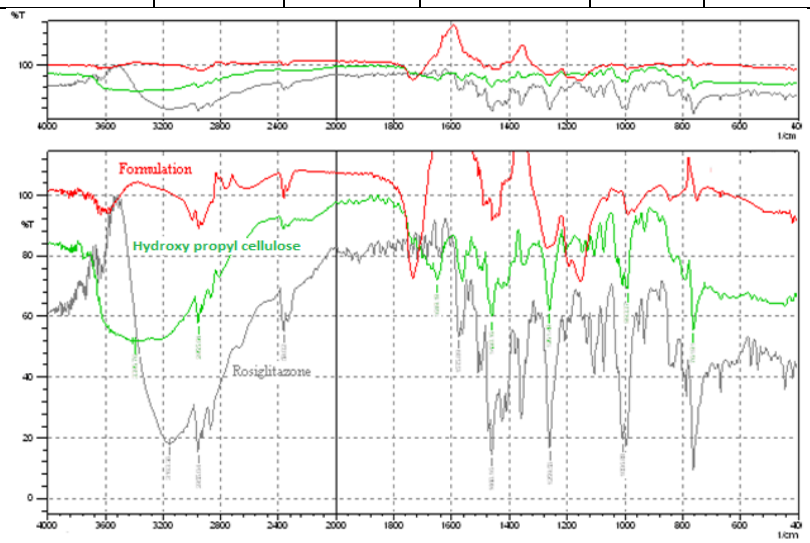

Fig 1. Drug polymer interaction study by FT-IR (Drug – rosiglitazone + HPC + formulation, F8). HPC – Hydroxy propyl cellulose.

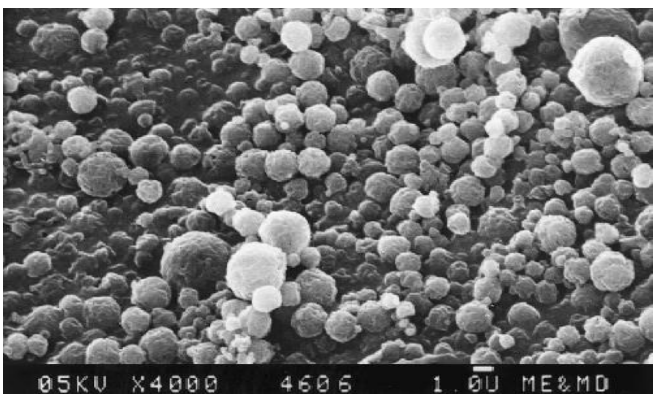

Fig 2. Scanning electron photomicrograph of prepared microcapsules (F8) under resolution of 5 KV X 4000.

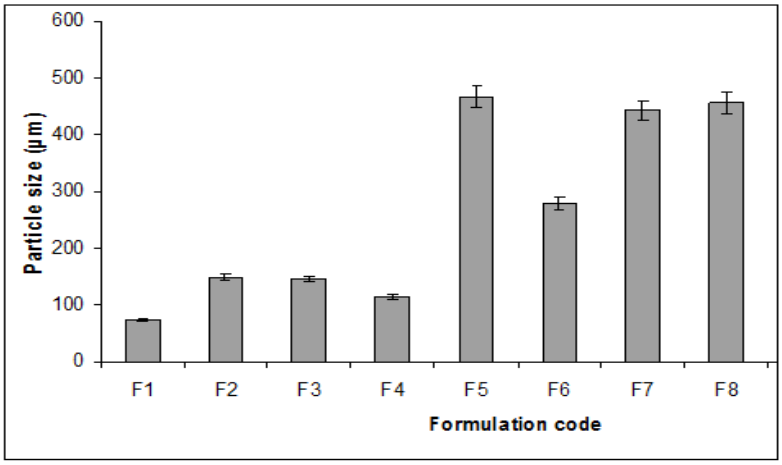

Fig 3. Particle size distribution data of rosiglitazone microcapsule formulation by optical microscopy.

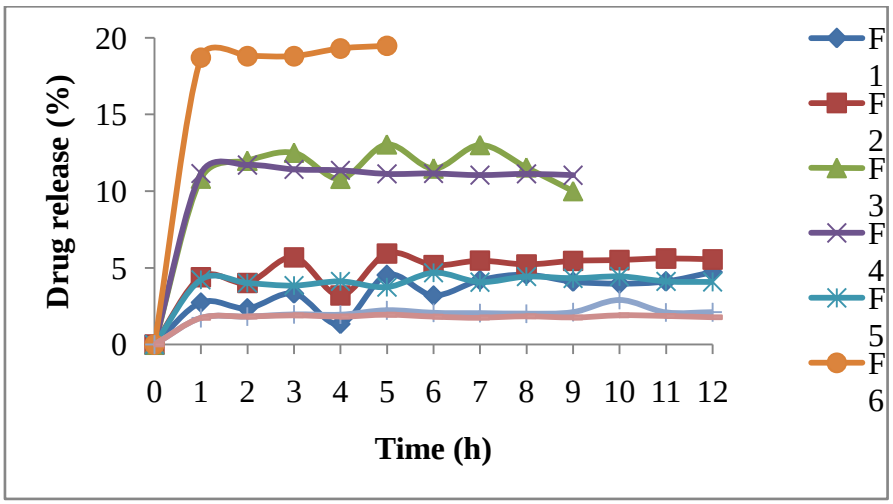

Fig 4. In vitro drug release profile of Rosiglitazone loaded microcapsule formulations.

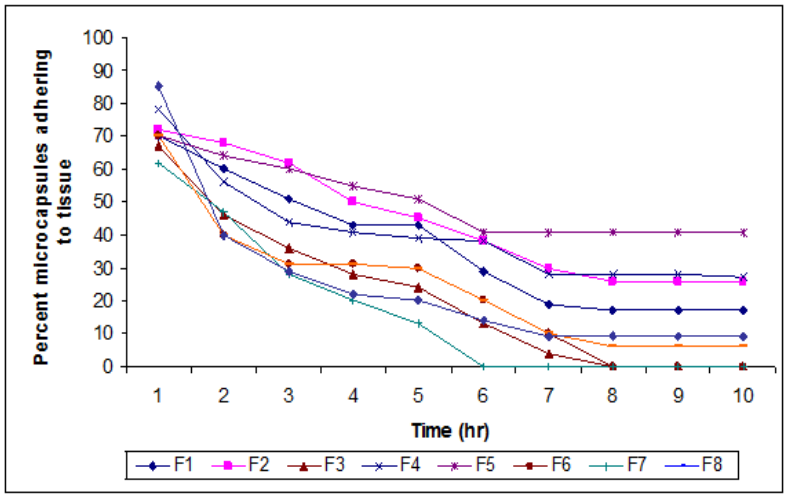

Fig 5. Mucoadhesion measurement of various rosiglitazone microcapsules by *in vitro* wash-off test.