Formulation and evaluation of gastroretentive mucoadhesive tablets containing Pioglitazone

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ABSTRACT

In this study, pioglitazone gastroretentive mucoadhesive tablets were designed to improve gastric residence time and overall bioavailability. Different mucoadhesive polymers such as HPMC K200 M, Na CMC, Carbopol 974P, gum karaya, chitosan and xanthan gum were selected for the production of tablets. Various formulations have been prepared using polymers at different concentrations. The repose angle, bulk density, tap speed, Carr index and Hausner ratio of the pioglitazone mucoadhesive tablet pre-compressed mixture were characterized and the results showed that the mixture had better flow and hence better performance. Swelling studies were performed on the formulations and the results showed a good swelling index for all formulations. Drug release studies show that the formulation releases the drug in a first-class sequence. Therefore, according to the results, the RF13 formula was seen to be an optimized formulation.

Keywords: Mucoadhesive tablets, Pioglitazone, Bioadhesive polymers

INTRODUCTION:

The oral route is considered the safest and easiest route of drug administration. According to patients, 90% of current medications are oral medications. When used orally, the drug remains in the absorption window for a short time, leading to low bioavailability. Oral administration is the most popular form of administration. This type of drug delivery releases the drug at a fixed or variable rate to match the dose.. [1-3]

The most popular oral administration method is gastric retention dosing (GRDDS), in which the dose is retained in the stomach for a long period of time, causing the temperature to rise over time (GRT). GRDDS can be defined as a system that stores the active part in the stomach for a sufficient period of time and releases it in a controlled manner. [4] Over the past two years, several GRDDS have been created to expand GRT. The main goal of the GRDDS program is to reduce problems with available verbal information and improve patients' medication intake. [5-7]

Therefore, this study developed anti-inflammatory drugs, different types of controlled-release pioglitazone, and different mucoadhesive polymers to improve the structure to help solve the above problems.

MATERIAL AND METHODS:

Pioglitazone is an antidiabetic drug with a purity certificate obtained from a pharmaceutical company. Residual polymers such as PMC K 200M, sodium carboxymethyl cellulose, Carbopol 974P, karaya gum, chitosan, xanthan gum and other pore-expanding aids such as sodium bicarbonate, magnesium stearate,

talc, lactose obtained from the human body are also allowed. All excipients and reagents used in the laboratory. the excipients and reagents used were of laboratory grade.

Pre-compressional evaluations [6-8]

Solubility Studies

The solubility of pioglitazone in 0.1 N HCl at pH 1.2 is determined by the phase balance method. Place the excess solution in a 20 mL vial containing 10 mL of 0.1 N HCL (pH 1.2). Cover the vial with a rubber cap and stir continuously for 24 hours at room temperature using a rotary shaker. After 24 hours, the solution was filtered through μm Whatmann filter paper. The amount of solution was estimated by measuring the absorbance at 248 nm using a UV spectrophotometer. Prepare a standard curve of pioglitazone in 0.1 N HCl and calculate the solubility of pioglitazone based on the slope. The study was repeated three times (n = 3) and the average value was calculated.

Drug-excipient compatibility studies

Fourier transform infra-red spectroscopic studies:

A Fourier transform – infra red spectrophotometer was used to study the non-thermal analysis of (drug: excipient 1:1 binary mixture) was examined using non-thermal compatibility analysis (Fourier transform infrared spectrophotometry). The spectrum of each sample was recorded in the range of 450-4000 cm-1. The relationship between pure pioglitazone and the body mixture (excipients) was investigated. (binary mixture of drug: excipient 1:1 ratio) compatibility.

Pre-compression Evaluation:

The polymer must be prepared chemically and physically before it is converted into drug dosage form. Preformulation studies provide the information needed to create a dosage form and form the basis for the combination of drugs and additives in pharmaceutical products.

Powder flow properties Angle of repose:

A method for determining the angle of residence using a funnel. Friction in powder can be measured by the angle of repose. The tangent of the angle of repose is equal to the coefficient.

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

Where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

Compressibility index:

Compression index is an important measure that can be obtained from the speed difference and speed level. Materials with values below 20% to 30% mean that water is insufficient. the percentage compressibility of the bulk drug was determined by using the following formula.

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$$I = (DT - Db / DT)100$$

Where, I is the Compressibility index, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density

$$H = Dt / Db$$

Where, H is the Hausner's ratio Dt is the tapped density of the powder and Db is the bulk density of the powder.

Preparation of Gastroretentive mucoadhesive tablets: [9]

Direct compression method was used in the preparation of gastroretentive mucoadhesive tablets containing pioglitazone. Different products were prepared from different amounts of HPMC K200 M, NaCMC, Carbopol 974P, gum karaya, chitosan, xanthan gum, NaHCO3, talc, magnesium stearate and lactose. The drug and polymer mixture was prepared by mixing the drug with HPMC K200 M, Na CMC, Carbopol 974P, gum karaya, chitosan, xanthan gum (gastroretentive   mucoadhesive polymer) and lactose in a glass mortar for 15 min. Lubricate the directly compressible powder with talc and magnesium stearate in a polyethylene bag for 2 minutes. The mixture (100 mg) is then compressed in a 9-station field press (Lab Press, India) using a 6 mm diameter die. Design details are included in the table. 1. After the compression parameters differ, continue analyzing the differences..

Table No. 1: The Composition of Gastroretentive Mucoadhesive Tablets Of Pioglitazone

Ingredients	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9	RF10	RF11	RF12	RF13	RF14	RF15	RF16	RF17	RF18
Pioglitazone	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
HPMC K200 M	4	8	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Na CMC	-	-	-	4	8	12	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 974P	-	-	-	-	-	-	4	8	12	-	-	-	-	-	-	-	-	-
Karaya gum	-	-	-	-	-	-	-	-	-	4	8	12	-	-	-	-	-	-
Chitosan	-	-	-	-	-	-	-	-	-	-	-	-	4	8	12	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	8	12
NaHCO3	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Magnesiiun stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Lactose	75	71	67	75	71	67	75	71	67	75	71	67	75	71	67	75	71	67
Total Weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Note: All quantity are mentioned in mg

Post- compression Evaluation: [10-12]

Physicochemical characterization of tablets:

The prepared Pioglitazone Gastroretentive mucoadhesive tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

A. Weight variation:

This 'weight variation' test is carried out by a random selection of 20 tablets and followed by weighed accurately. The mean weight of 20 tablets calculated and followed by compared with the weight of the tablet individually. If two or more than two tablets are coming outside the range (± 7.5 %) than it batch is failed or else pass. The same study was repeated to determine the mean (n=3). The percentage of deviation was calculated as follows:

% Deviation = (Individual weight – Mean weight / Mean weight) X 100

The average weight of tablets in each formulation was calculated and presented with standard deviation.

Table No. 2: Pharmacopoeia specifications for tabletweight variation

Average weight of tablets (mg)	Maximum % of difference allowed
80 or less	± 10
More than 80 but less than 250	± 7.5
250 or more	± 5

B. Tablet Thickness:

The thickness and diameter of the tablet are carefully controlled during the production process. Due to the difference between the granulation rate and the pressure applied to the tablet and the speed of the tablet press, the thickness will be different but the weight will not be different. Therefore, this indicator is important in terms of customer satisfaction, tablet compatibility and packaging. Tablet thickness and diameter were measured using a digital caliper. Ten tablets of each recipe were used and the average was calculated. The average thickness of the tablet was calculated and expressed as standard deviation..

C. Tablet Hardness:

Tablet hardness is measured as the force required to break a tablet in a diameter compression test. Tablets must have a certain strength or hardness and resistance to brittleness to prevent impact during handling, production, packaging and shipping. The ability of the tablet to prevent chipping, abrasion or breakage under storage, deformation and transportation conditions before use depends on its hardness. For the tablet taken from each sample, the average value is calculated by measuring the hardness with a Monsanto hardness tester. It is expressed in kg/cm2.

D. Friability:

Tablet hardness is not an accurate indicator of strength because some formulations lose their plasticity when compressed into very hard tablets. Therefore, another frequently measured indicator of tablet strength is friability. Tablet strength is measured using a Roche friability tester. The testing equipment uses a plastic chamber that rotates at 25 rpm for 4 minutes and a distance of 6 inches at a time to measure the tablet's impact on impact and wear. Place the pre-measured tablet sample into the Roche crusher and run it for 100 cycles. The tablets are then dusted and recycled.

Friability (%) = Initial weight of 10 tablets – final weight of 10 tablets X 100
$$\frac{\text{Initial weight of 10 tablets – final weight of 10 tablets} \times 100}{\text{Initial weight of 10 tablets}}$$

Where, Wo is the initial weight of the tablets before the test and W is the final weight of the

tablets after test.

D. Assay:

Take six tablets of each preparation and determine the content of medicine in each tablet. Take the powder equivalent to 1 tablet, add it to 100 mL pH 6.8 phosphate buffer and stir for another 10 minutes. The solution was filtered through a 0.45 μ filter, diluted appropriately, and the absorbance of the solution was measured by UV–visible spectrophotometer at 248 nm using pH 6.8 phosphate buffer.

In vitro Buoyancy studies:

In vitro buoyancy studies Buoyancy is determined by buoyancy delay time and total buoyancy time. The tablet was placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to float to the surface was determined as the gastroretentive time (GRT), and the time during which the tablet continued to float on the separation medium was divided as the total gastroretentive time (TGT), respectively).

In vitro release studies: [13-14]

Drug release rate from gastroretentive mucoadhesive tablets was examined using a USP Type II dissolution tester. The tablet needs to release the drug from one side only, so the film is pointlessly placed on the other side of the tablet. Tablets were mounted on 2×2 cm slides using cyanoacrylate adhesive. It is then placed in the melting device. The dissolution medium was 900 ml of 0.1N HCl at 50 rpm and 37 ± 0.5 °C. 5 mL samples were collected at different times up to 12 h and analyzed after appropriate dilution using a UV spectrophotometer at 237, 248, 227 nm.

In vitro bioadhesion strength:

Using a state-of-the-art dynamometer-based microprocessor equipped with a driver's seat (Ultra Test Tensile Strength Tester, Mecmesin, West Sussex, United Kingdom) equipped with a 25 kg weight as described on the sensor, in this test the pork membrane was formed into a circular It is held firmly on the stainless steel adapter and the gastroretentive mucoadhesive piece to be tested is adhered to another cylindrical stainless wire adapter of similar diameter using a cyanoacrylate bioadhesive. 100 µL of 1% w/v mucin solution is applied to the mucosal surface   and the lozenge immediately comes into contact with the mucosa. At the end of the contact period, the upper support is lifted at a speed of 0.5 mm/s until the tablet is completely removed from the mucosa. Adhesion performance is determined by the area under the force curve. The highest separation force is the maximum force that separates a tablet from the mucosa

$$\text{Force of adhesion} = \frac{\text{Bioadhesion strength x } 9.8}{1000}$$

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\text{Surface area}}$$

Moisture absorption:

Dissolve agar (5% m/V) in hot water. Transfer it to the Petri dish and wait for it to freeze. Before the study, 6 gastroretentive mucoadhesive tablets of each design were placed in vacuum overnight to remove moisture (if any) and laminated on one side with irreversible film. They are then placed on the agar surface and incubated for one hour at 37°C. The tablets are then taken out and weighed and the percent moisture absorption is calculated by the following formula:

%Moisture Absorption =Final weight – Initial weight x 100

Initial weight

Kinetic analysis of dissolution data: [15-21]

To analyze the in vitro release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.

In vivo studies - pharmacokinetic studies:

Pharmacokinetic studies were conducted to examine maximum plasma concentrations. In vivo studies were conducted on male Wistar rats weighing 250-300 g. They were in polypropylene cages with free food and water. Calculate the pioglitazone dose based on the animal's body weight and create a tablet formulation based on the calculated dose. The animal project was approved by the Animal Ethics Committee. Gastroretentive mucoadhesive matrix tablets optimized for oral administration. Blood samples were collected within 24 hours of the scheduled sample collection time. Various pharmacokinetic parameters such as Cmax, Tmax, AUC were determined.[22]

RESULT AND DICSUSSION:

Solubility Studies:

Table No. 3: Solubility studies

S.No	Medium	Amount present (µg/mL)
1	Water	30.87
2	Methanol	100.69
3	0.1 N HCL	48.88

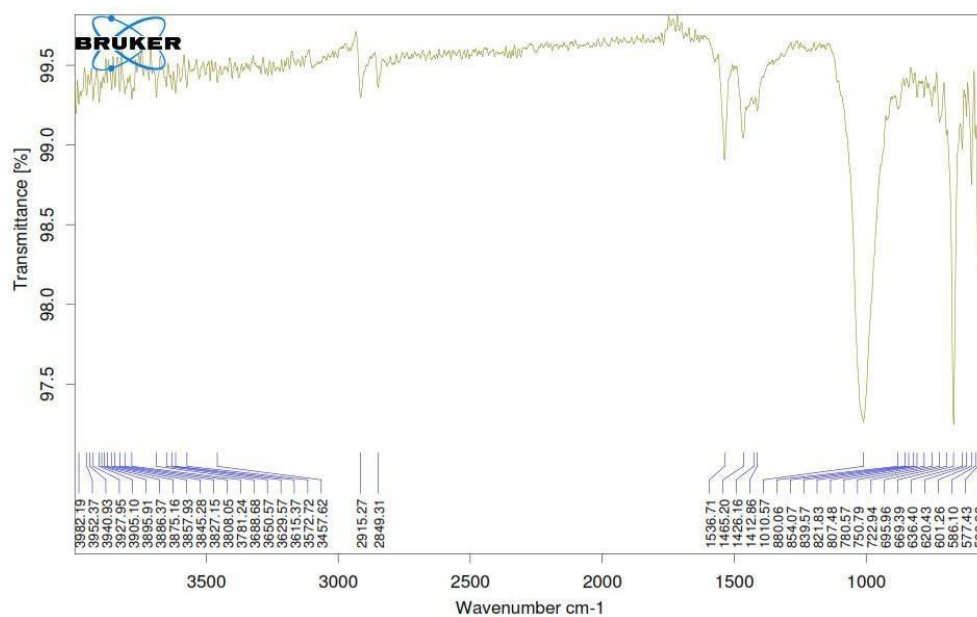## Drug –Polymer Compatibility Studies by FTIR

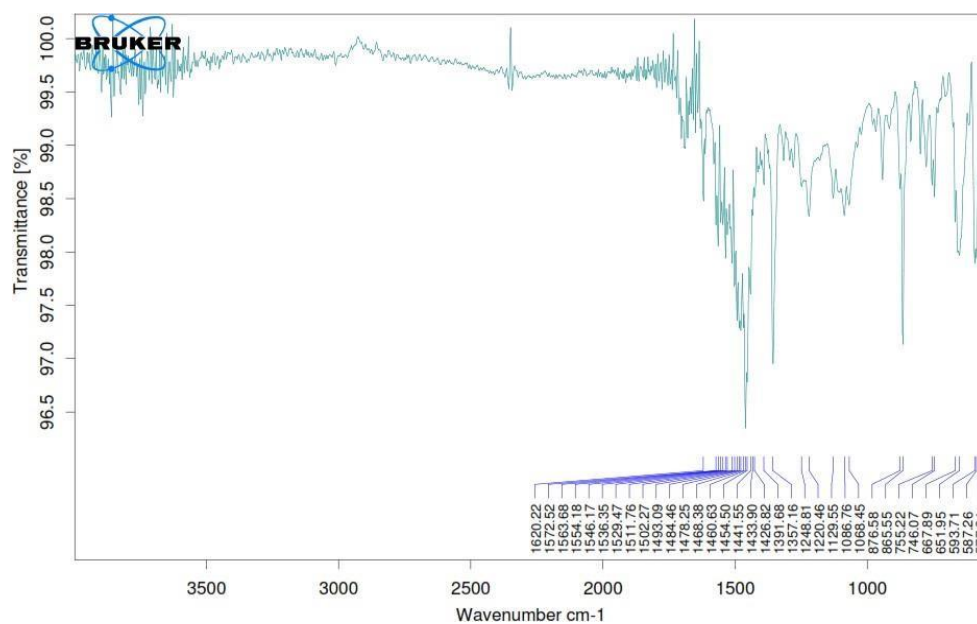**Figure No.1: FT-IR of Pioglitazone Pure Drug**

Figure No.2: FTIR Spectra of Optimised Formulation (RF13)

Pre-compression Evaluation:

Table No. 4: Pre-compression Evaluation

| Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
RF1	0.415±0.009	0.475± 0.008	25.7 ±0.47	12.50± 0.35	1.13± 0.34
RF2	0.383± 0.007	0.432± 0.006	26.0 ±0.34	11.53± 0.25	1.13± 0.28
RF3	0.555± 0.011	0.713± 0.013	26.6 ±0.22	22.22± 0.15	1.27± 0.36
RF4	0.383± 0.004	0.442± 0.006	25.98±0.40	13.46± 0.19	1.14± 0.27
RF5	0.265± 0.013	0.311± 0.017	26.32±0.87	14.66± 0.27	1.16± 0.39
RF6	0.306± 0.008	0.356± 0.006	25.94±0.56	12.84± 0.13	1.15± 0.34
RF7	0.306± 0.006	0.443± 0.009	25.05±0.65	12.46± 0.28	1.15± 0.38
RF8	0.383± 0.016	0.432± 0.013	24.94±0.56	16.85± 0.22	1.21± 0.24
RF9	0.265± 0.014	0.306± 0.011	25.02±0.61	12.33± 0.19	1.14± 0.29
RF10	0.345± 0.006	0.404± 0.008	26.21±0.93	14.35± 0.28	1.16± 0.36
RF11	0.322± 0.007	0.375± 0.002	25.28±0.33	13.09± 0.18	1.16± 0.31
RF12	0.391± 0.009	0.452± 0.011	24.81±0.61	14.24± 0.20	1.15± 0.35
RF13	0.319± 0.005	0.367± 0.004	25.10±0.53	12.58± 0.15	1.16± 0.21
RF14	0.311± 0.015	0.357± 0.010	25.21±0.32	12.84± 0.31	1.15± 0.25
RF15	0.32± 0.007	0.37± 0.005	25.31±0.79	13.15± 0.19	1.15± 0.29
RF16	0.306± 0.009	0.35± 0.13	26.69±0.59	12.3± 0.21	1.14± 0.31
RF17	0.376± 0.014	0.452± 0.009	26.82±0.23	13.2± 0.25	1.15± 0.28
RF18	0.231± 0.015	0.272± 0.010	26.31±0.57	15.52± 0.28	1.18± 0.24
Note: Each worth speaks to the mean ± SD (n=3)					
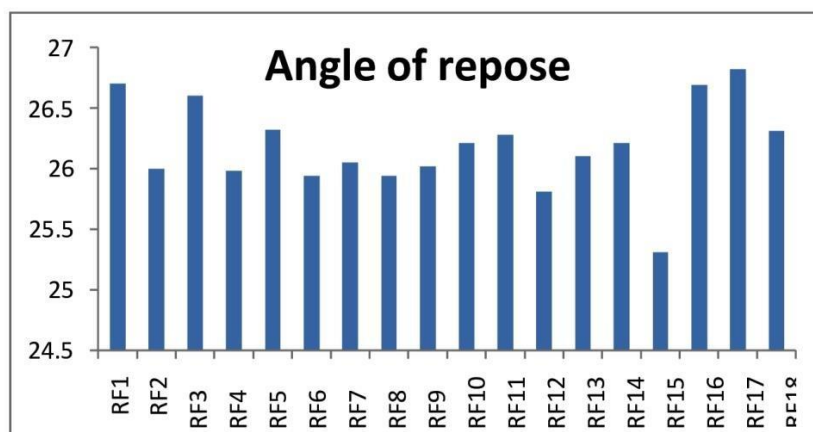
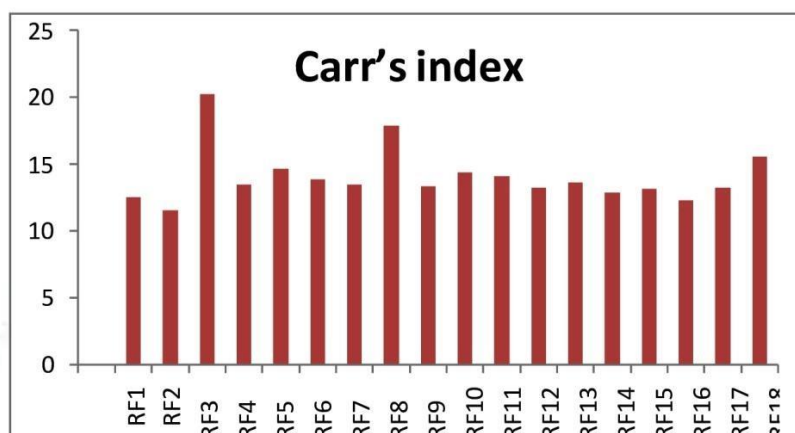**Figure No.3: Angle of Repose for the obtained formulations**

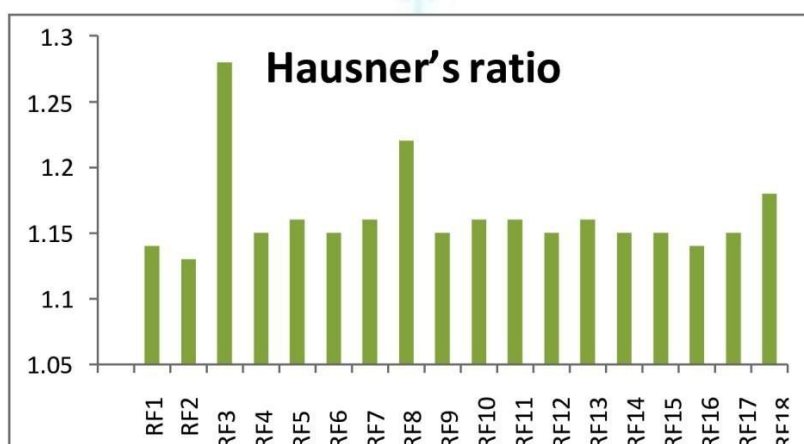**Figure No.4: Carr's Index for the obtained formulations**

Figure No.5: Hausner's Ratio Index for the obtained formulations
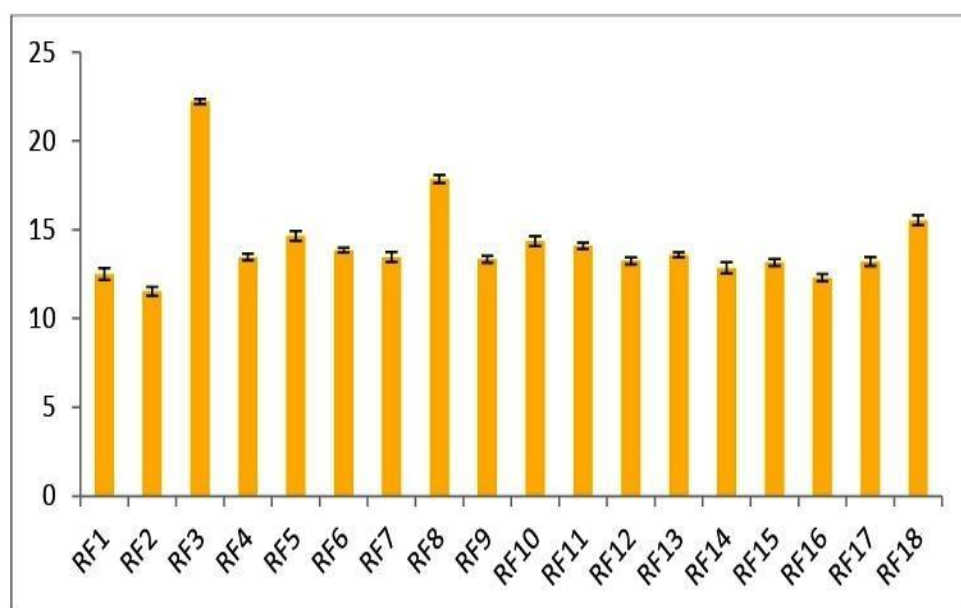
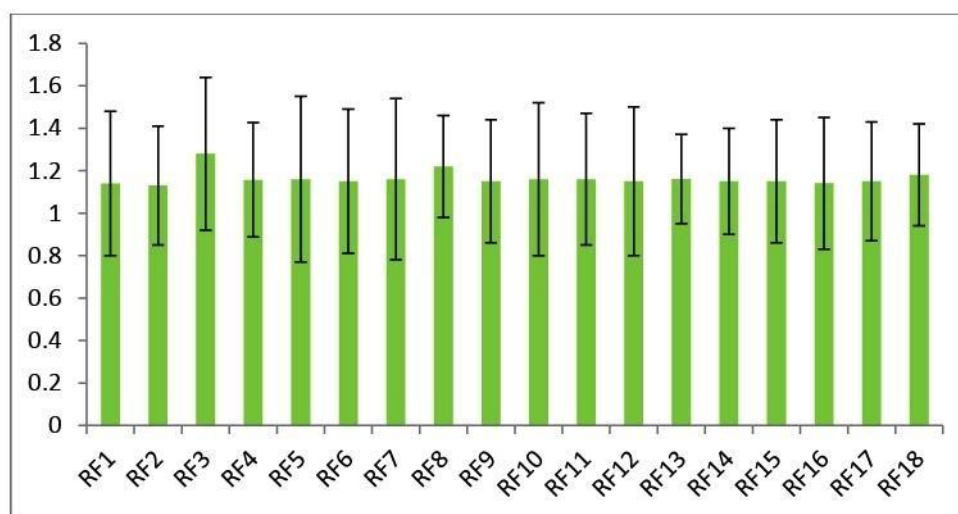Figure 6 Carr's Index for the obtained Pioglitazone formulations

Figure 7 Hausner's ratio for the obtained Pioglitazone formulations

Post-compression Evaluation:

Table No.5: Evaluation of gastroretentive mucoadhesive tablets of Pioglitazone

| Formulation Code	Thickness (mm) (mean±SD)	Average Weight (mg)(mean±SD)	Hardness (Kg/cm²) (mean±SD)	Friability (%) (mean±SD)	Content uniformity(%) (mean±SD)	Total Gastroretentive time (hrs) (mean±SD)	Gastroretentive Lag time (s) (mean±SD)
RF1	4.57±0.09	97.25±0.28	5.2±0.15	0.35±0.04	94.36±0.27	13±0.59	34.3±0.37
RF2	4.91±0.06	98.35±0.24	5.6±0.13	0.28±0.02	98.25±0.24	15.5±0.30	42.0±0.34
RF3	4.86±0.04	94.61±0.19	5.9±0.19	0.51±0.06	97.14±0.21	18±0.97	47.1±0.36
RF4	4.39±0.06	98.39±0.24	5.4±0.09	0.48±0.02	100.2±0.19	12.5±0.83	38.2±0.31
RF5	4.98±0.10	98.48±0.17	5.8±0.13	0.63±0.04	98.45±0.24	14±0.59	32.9±0.30
RF6	4.87±0.08	98.67±0.39	5.9±0.17	0.81±0.09	97.61±0.30	15±0.98	25.6±0.29
RF7	4.67±0.04	96.52±0.25	5.0±0.20	0.23±0.08	98.75±0.29	19±1.00	12.0±0.28
RF8	4.90±0.11	97.15±0.20	5.3±0.17	0.27±0.05	98.87±0.34	15±0.92	15.7±0.24
RF9	4.18±0.06	98.45±0.26	5.7±0.18	0.61±0.10	96.10±0.18	20±0.49	17.0±0.23
RF10	4.71±0.02	100.0±0.17	5.9±0.16	0.37±0.05	98.38±0.24	19±0.73	39.2±0.18
RF11	4.67±0.08	97.31±0.16	5.4±0.15	0.46±0.07	96.82±0.18	18.5±0.82	45.6±0.25
RF12	4.38±0.03	96.45±0.31	5.1±0.24	0.59±0.11	98.34±0.19	21±0.93	111±0.17
RF13	4.56±0.15	99.12±0.19	5.2±0.17	0.66±0.08	95.92±0.35	22±0.74	45.0±0.19
RF14	4.37±0.06	96.35±0.24	5.8±0.24	0.15±0.04	96.24±0.27	21±1.16	55.2±0.25
RF15	4.28±0.01	97.46±0.21	5.1±0.26	0.42±0.09	94.89±0.26	19±0.62	51.0±0.26
RF16	4.34±0.08	98.14±0.23	5.0±0.28	0.56±0.12	98.75±0.29	20±0.81	70.8±0.19
RF17	4.63±0.10	96.32±0.21	5.8±0.21	0.42±0.05	96.19±0.30	18±0.79	75.6±0.30
RF18	4.65±0.15	99.47±0.20	5.8±0.15	0.38±0.09	99.69±0.21	17.5±0.59	130±0.38
Note: Each worth speaks to the mean ± SD (n=3)							

In vitro drug release
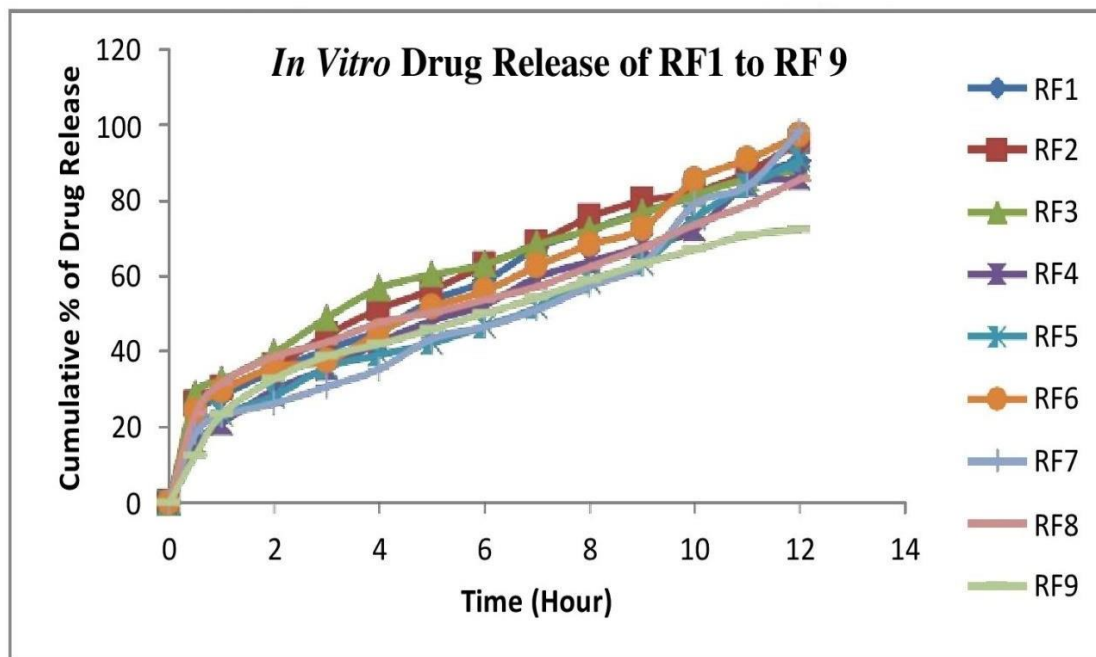
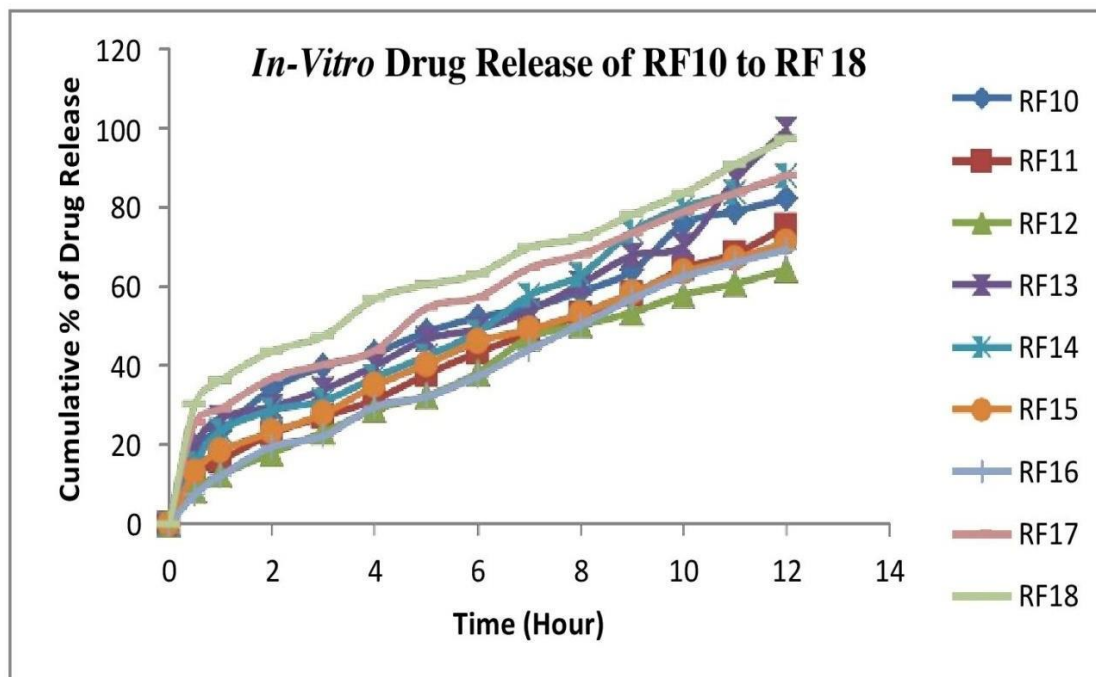**Figure No.8: In vitro Dissolution study of RF 1 to RF 9**

Figure No.9: In vitro Dissolution study of RF 10 to RF 18

Moisture absorption, bioadhesion strength values of selected formulations

Table No. 6: Moisture absorption, bioadhesion strength values of selected formulations.

Formulation Code	Moisture absorption (%)	Bioadhesion strength	
		Peak detachment force(N)	Work of adhesion(mJ)
RF1	62±0.29	3.4±0.19	13.54±0.59
RF2	47±0.21	3.6±0.14	14.9±0.83
RF3	52±0.19	3.6±0.11	14.01±0.67
RF4	49±0.14	3.5±0.16	13.51±0.59
RF5	59±0.25	3.6±0.21	12.56±0.53
RF6	53±0.16	3.4±0.09	11.76±0.39
RF7	58±0.23	3.8±0.13	13.72±0.51
RF8	51±0.31	3.6±0.18	11.89±0.48
RF9	43±0.26	3.4±0.14	12.43±0.62
RF10	65±0.24	3.7±0.17	14.67±0.46
RF11	61±0.33	3.5±0.14	15.4±0.72
RF12	53±0.21	3.5±0.17	15.9±0.66
RF13	66±0.33	4.8±0.12	15.89±0.61
RF14	60±0.27	3.9±0.14	13.82±0.52
RF15	61±0.25	4.1±0.18	11.43±0.68
RF16	57±0.18	3.5±0.14	15.04±0.48
RF17	59±0.24	3.7±0.12	14.56±0.57
RF18	63±0.21	3.7±0.19	15.43±0.63
Note: Each worth speaks to the mean ± SD (n=3)			

Formulation Code	Moisture absorption	Bioadhesion strength	
		Peak detachmentforce (N)	Work of adhesion (mJ)
RF13	66±0.33	4.8±0.12	23.41±6.18

Each value represents the mean±SD (n=3)

Release kinetics:

In vitro release data obtained from the model showed better drug release fit to multiple equations to describe the release kinetics of pioglitazone from mucoadhesives. The data were fitted to various kinetic models such as zero-order kinetics, first-order kinetics, higuchi and korsmeyer peppas mechanisms, and the results are shown in the table below.

Table No 7: Table of release kinetics and correlation factors

| CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2				100	4.642	4.642	0
18.17	0.5	0.707	1.26	-0.301	1.913	36.38	0.055	-0.74	81.81	4.642	4.341	0.3
23.45	1	1	1.37	0	1.884	23.46	0.0426	-0.63	76.54	4.642	4.246	0.396
31.35	2	1.414	1.497	0.301	1.837	15.685	0.0319	-0.503	68.63	4.642	4.094	0.547
37.31	3	1.732	1.572	0.477	1.797	12.437	0.0268	-0.428	62.69	4.642	3.973	0.669
44.13	4	2	1.645	0.602	1.747	11.048	0.0226	-0.355	55.81	4.642	3.822	0.82
52.82	5	2.236	1.723	0.699	1.674	10.568	0.0189	-0.277	47.16	4.642	3.613	1.029
60.53	6	2.449	1.782	0.778	1.596	10.095	0.0165	-0.218	39.43	4.642	3.404	1.238
66.72	7	2.646	1.824	0.845	1.522	9.531	0.015	-0.176	33.28	4.642	3.217	1.425
73.61	8	2.828	1.867	0.903	1.421	9.205	0.0136	-0.133	26.36	4.642	2.976	1.665
79.52	9	3	1.9	0.954	1.311	8.836	0.0126	-0.1	20.48	4.642	2.736	1.906
83.72	10	3.162	1.923	1	1.211	8.375	0.0119	-0.077	16.25	4.642	2.533	2.109
95.62	11	3.317	1.981	1.041	0.636	8.697	0.0105	-0.019	4.33	4.642	1.63	3.012
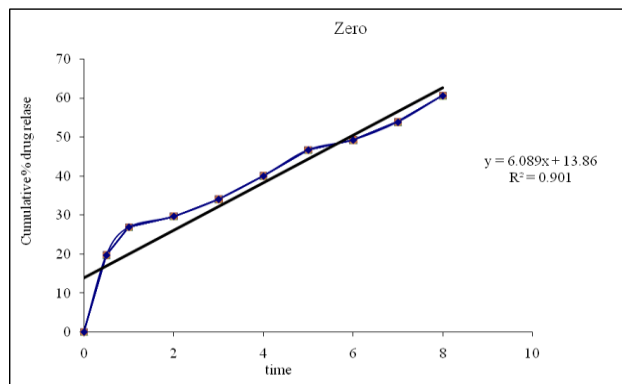
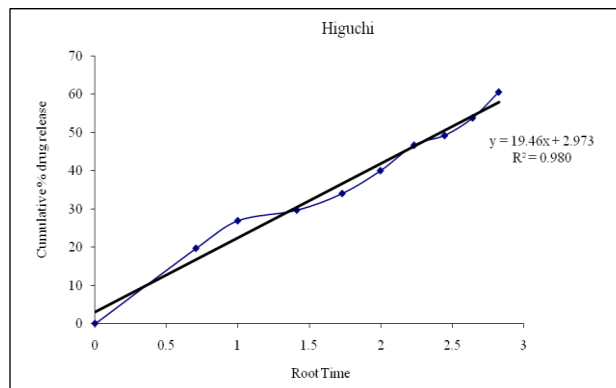**Figure No.10: Zero order plot of optimized formulation**

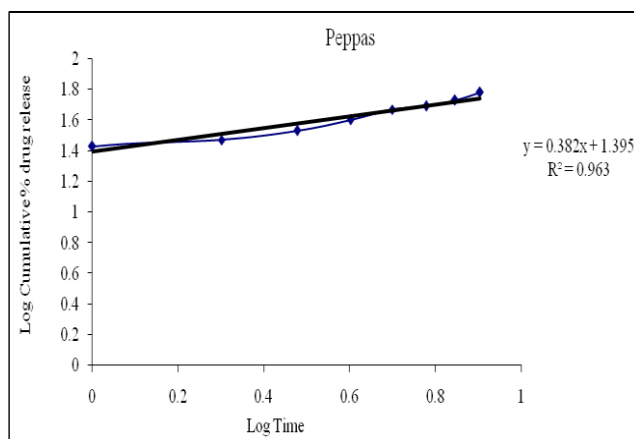**Figure No.11: Higuchi plot of optimized formulation**

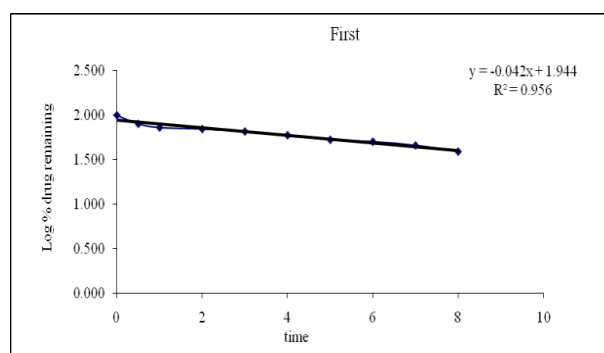**Figure No.12: Koresmeyer-peppas plot of optimizedformulation**

Figure No.13: First order plot of optimized formulation

Based on the all studies RF13 formulation was found to be better when compared with all other formulations. This formulation was following Higuchi mechanism with regression value of 0.980.

In vivo **Studies - Pharmacokinetic Studies:**

All the pharmacokinetics parameters displayed in Table. Mean time to reach peak drug concentration (Tmax) was 1.75 hours, while mean maximum drug concentration (Cmax) was 640 mg/mL. The values for Cmax, Tmax, AUC were found to be comparable indicating that their sustained release patterns were similar.

Table No 8: Pharmacokinetic parameters of optimized formulation

S.No	Parameter	Rosiglitazone
1	Cmax	640 mg/mL ($\pm$0.22)
2	T max (hr)	1.75 hours($\pm$ 0.56)
3	AUC	3.62 mg/L · h ($\pm$1.24)

Solubility studies show that the drug is less soluble in water compared to methanol and 0.1N HCl. Solubility data confirm that pioglitazone is one of the best drug models to be developed in GRDDS. FTIR studies show that there is no interaction between the drug and the polymer. There was no change in the drug base peak. The angle of repose of all formulations is below 30 degrees. So we can say that the powder mixture has good flow properties. The Carr's Index and Hausner ratio show that the powder blend has a good flow property. So direct compression method can be used to formulate the tablets. The

mean thickness of all the formulations ranges between 4.19 to 4.99 mm. It can be concluded that all the tablets have uniform size and shape. The weight of the tablets ranged between 95.61mg to 100mg. For tablets from 80 mg to 250 mg, the weight difference is limited to ± 7.5. Therefore, tablets are prepared as prescribed. Tablet hardness range is 5-6 Kg/cm2. Friability testing showed that all tablets had a friability index less than 1. This indicates that the prepared tablets have good mechanical strength and tolerance. All prescriptions have good drug content. The RF7 tablet has a swim time as low as 12 seconds, while the RF18 tablet has a swim time as high as 130 seconds. In vitro drug release was achieved for 12 hours using 0.1N HCl, pH 1.2. The results showed that the RF12 formulation containing a high concentration of karaya gum had the lowest drug release. The highest drug release was observed in the RF13 formulation containing chitosan. As the ratio of karaya gum increases, the release rate of the drug decreases significantly. Samples containing carbomer and chitosan showed inconsistent drug release. The bioadhesive power of RF13 has been shown to be the best choice for long-term mucoadhesion. Various kinetic studies have been conducted and it has been seen that the RF13 model is superior to   other models. The formula follows the Higuchi mechanism with a regression value of 0.980. In vivo pharmacokinetic studies showed that the drug reached its maximum at 1.75 hours. Cmax and AUC data predict oral bioavailability of drugs

CONCLUSION

From the results obtained, it was concluded that drugs can be easily produced in GRDDS by using different rate control polymers such as chitosan, NaCMC, HPMC K200 and Carbopol 934. Chitosan has been found to be a promising polymer in terms of cost and control. The drug is released from the dosage form & Additional work can be done to create more GRDDS.

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