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FORMULATION AND EVALUATION OF ORAL ANTI-DIABETIC IN-SITU GEL SYSTEM OF PIOGLITAZONE

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Pioglitazone, Diabetes mellitus, *In-situ* gels, Sodium alginate, Guar gum, Xanthan gum, Carbopol-934

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ABSTRACT: Pioglitazone is an oral anti-diabetic agent used in treating class – II diabetes mellitus. $T_{1/2}$of pioglitazone was 3-6 hrs and is eliminated rapidly. Hence sustained release is needed to prolong its duration of action and to increase its oral bioavailability. The study's main aim was formulation and evaluation of *an in-situ* gel system of pioglitazone to increase its bioavailability as a convenient dosage form. Method of Ion-sensitive *in-situ* gelation was used in this study. Total 15 formulations were prepared with Guar gum, Xanthan gum, and Carbopol-934 in various combinations and assessed for physical appearance, pH, viscosity, *in-vitro* gelling capacity, drug content, and *in-vitro* drug release. FTIR, DSC for Pioglitazone, excipients, and optimized formulation were conducted. *In-vivo* drug kinetic studies were conducted for optimized formulation. Formulations showed an optimum viscosity allowing ease of administration and swallowing. All formulations have shown pH between 6.9-7.3, floating lag time was 2-3sec and floated for >12 hrs. The x-ray image studies are also confirming the same thing. *In vitro, drug release studies report that F15 shows drug release of 99.52% over 12 hours*. FTIR studies revealed no interaction between drugs and excipients used. The results of In-vivo kinetic studies approve the better performance of the optimized formulation. In conclusion, the optimized formulation F15 showed maximum drug retardation for above 12 h. Hence, it is concluding that the study's main objective to increase its bioavailability as a convenient dosage form in the treatment of diabetes mellitus had been achieved.

INTRODUCTION: Controlled drug delivery system (CDDS) is currently forefront position in drug delivery compared to the developed systems; it consists of various technical approaches to help in individual care.

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The strategy of this system having bountiful favorable circumstances than existing conventional types involves improved efficiency, diminished toxic effect, and improved consumer conformity in addition ease.

In a controlled drug delivery system, systemically or locally, the drug delivers at a predetermined rate for a predefined period. The oral controlled release system entails drug delivery at knowable and consistent kinetics used for predetermined time intervals throughout the gastrointestinal (GI) tract [1].

A perfect and progressed oral drug delivery method precisely regulates velocity, time, and the site of the arrival of medicament independently of regular physiological factors like pH and digestive conditions of the gastrointestinal tract, peristaltic movement, and circadian cadence [2].

The healing capability of a remedy depends on the bioavailability of the drug. The solubility is an essential precondition to attain preferred drug concentration in the systemic bloodstream, absorption, and response. Drug oral administration is the easiest and uncomplicated medication path as it offers great patient compliance, comfort, precise dosing, and improved stability.

In-situ gel framing polymer systems have gained importance among NDDS novel drug delivery systems in modern days because of their benefits, such as sustained and delayed drug activity, better patient compliance, and diminished dosage drug frequency in contrast with regular conventional delivery systems [3, 4].

Pioglitazone is an oral anti-diabetic agent used in treating class – II diabetes mellitus. The biological half-life of pioglitazone was a maximum 3-6 h and is eliminated rapidly [5, 6]. Hence sustained-release formulations are needed for pioglitazone to prolong its duration of action and to increase its oral bioavailability. Practically insoluble in water and alkaline buffer solutions majorly absorbed from the stomach, so suitable for gastro retentive formulation development.

The study's main aim was formulation and evaluation of an in-situ gel system of pioglitazone using different release rate controlling polymers to increase its bioavailability as a convenient dosage form in the treatment of diabetes mellitus.

MATERIALS AND METHODS: Pioglitazone was acquired from Brundavan Laboratories private Ltd, Hyderabad, India. All the polymers received were of pharmaceutical grade (Guar gum/ Xanthan gum/ Carbopol-934 are obtained from Sigma-Aldrich, Germany) were used as received. Sodium alginate, Sodium citrate, and Calcium carbonate were obtained from S.D Fine chemicals, Mumbai, India. All chemicals and solvents utilized were of HPLC grade. Throughout the study, distilled water as used.

Determination of Absorption Maximum (λ_{max}) of Pioglitazone: Solution of the drug were prepared in methanol and scanned in the range of 200 to 400 nm using Elico UV spectrophotometer order to determine the absorption maxima for analysis of dissolution samples [7].

Preparation of Calibration Curve of Pioglitazone: 10 mg of pioglitazone was dissolved in the required amount of methanol and made upto10 ml of 0.1N HCl by slight shaking (1000 mcg/ml). 1 ml of this solution was taken and made up to 10 ml with 0.1N HCl, which gives 100 mcg/ ml concentration (second stock solution). From the second stock solution, concentrations of 10, 20, 30, 40, and 50 µg/ml in 0.1N HCl were prepared. The absorbance of diluted solutions was measured at 264 nm, and a standard plot was drawn using the data obtained. The correlation coefficient was calculated [8].

Preparation of Pioglitazone Oral *In-situ* Gel: Ion-sensitive in-situ gelation method was employed for the preparation of Pioglitazone in-situ gels. In preparation of *in-situ* gels, sodium alginate was used as a gelling agent, Sodium citrate as a sequestering agent, and the cross-linking agent was Calcium carbonate apart from polymers like Guar gum/ Xanthan gum/carbopol- 934 were utilized as drug release rate controlling polymer. Different formulations are prepared with various proportions of polymers such as Guar gum, Xanthan gum, and carbopol-934; several trials were performed varying the concentration of individual polymer to distinguish the ideal concentration needed for preparation.

Accurately weighed pioglitazone was solubilized in 10ml of warm de-ionized water with continuous stirring until a uniform solution was obtained. Diverse concentrations of Guar gum, Xanthan gum, and carbopol- 934 were taken, added 70ml of de-ionized water, and gently stirred and heated to 60°C to obtain a uniform solution.

The required quantity of calcium carbonate and sodium citrate were dissolved in 20ml of distilled water Heated to 60oc and added to polymer solution at 60 °C. Then the resultant solution was cooled to 40°C, and added with the drug solution. The chart of formulations is specified in **Table 1**.

TABLE 1: PREPARATION OF PIOGLITAZONE *IN-SITU* GEL FORMULATION SYSTEMS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Pioglitazone (mg)	600	600	600	600	600	600	600	600	600	600	600	600	600	600	600
Sodium Alginate (g)	2	2	2	2	2	2	2	2	2	2	2	2	1.5	1.5	1.5
Calcium Carbonate (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium Citrate (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Xanthan GUM (mg)	75	100	125	150	--	--	--	--	--	--	--	--	50	-	50
Guar Gum (mg)	--	--	--	--	75	100	125	150	--	--	--	--	50	50	
Carbopol 934 (mg)	--	--	--	--	--	--	--	--	75	100	125	150	-	50	50
Water upto 100ml	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Drug and Excipients Compatibility Study by FTIR Spectroscopy: The compatibility and interaction between drug and excipients utilized in the preparation of in situ gels are assessed by using FTIR-spectrophotometer 8400S [9]. IR spectra of pioglitazone and excipients were determined by scanning at a range of 400 to 4000 cm^{-1}.

Differential Scanning Calorimeter (DSC) Studies: The sample's thermal behavior was investigated using DSC Q100. Accurately weighed, the required samples were taken in aluminum pans then precisely crimped. At the rate of 20°C/min from- 40°C to 300°C, test samples were heated under stable nitrogen cleansing at a rate of 40 ml/min.

Visual Appearance, Clarity, and pH Measurement: The general appearance, color, and odor of formulation were physically observed and recorded, and the pH was determined by using digital pH meter [10].

Drug Content Estimation: Gel equivalent to 10 mg of drug is transferred into a 100 ml volumetric flask and initially dissolved in 20 ml of 50% Methanol. Finally, the volume is fabricated to 100 mL with 50% Methanol. 1 ml of this supernatant is then transferred into a 10ml measuring flask and makes volume to 10ml. Drug concentration was determined by using UV spectrophotometer against a blank solution at a wavelength of 264 nm.

***In-vitro* Floating Time:** The *in-vitro* floating studies were performed by introducing about 10 ml of *in-situ* gel preparation to 100ml of 0.1N HCl, pH of 1.2 at 37°C. The time taken by the formulation to float was recorded.

***In-vitro* Gelation Studies:** The formulations are subjected to know their *in-vitro* gelling capacity; accurately 10ml of measured each formulation was taken in a beaker and added 0.1N HCl 100ml, pH of 1.2 followed by gentle agitation. The formed gels were observed, and gel formed patterns are recorded.

Viscosity Studies: The viscosity of pioglitazone in-situ gels was measured for solution form and to gel form at 37°C by viscometer Brookfield DV Pro-II, United States. The testing samples are equilibrated in a water thermo-stated jacket for 10 min; measured at 50 rpm with spindle no 65.

***In-vitro* Release Studies:** The *in-vitro* drug release study was carried in a triplicate using USP II [paddle apparatus method] dissolution apparatus. The medium for dissolution studies was 900 ml of 0.1N hydrochloric acid as dissolution at 37 ºC. The rate of stirring was 50 rpm. The maintained speed to simulate *in-vivo* existing gentle agitation moreover be sluggish enough to avoid the infringement of gel formulation. At programmed time intermissions, accurately 5ml of the sample was withdrawn, and an equivalent amount of fresh medium replaced at 37°C, and the absorbance of the samples was measured at 264 nm using a UV-Visible spectrophotometer.

***In-vitro* Kinetic Studies:** To know the mechanism of drug release, kinetic models are used. In order to study the definite mechanism of drug release from the formulation, drug release data were analyzed by Zero-order, first-order, Korsmeyer/Peppas, and Higuchi square root plot.

The obtained data were processed for regression analysis by MS EXCEL statistical function. It is known that the Peppas model is broadly used to affirm whether the release mechanism is Fickian diffusion and non- Fickian diffusion. The release exponent of the Korsmeyer/ Peppas model 'n' value could be used to explain different release mechanisms. The interpretation of the n value was done in the following manner, shown in **Table 2.**

TABLE 2: DIFFUSION COEFFICIENT AND MECHANISM OF DRUG TRANSPORT

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.45<n=0.89	Non-Fickian transport
0.89	case II transport
Higher than 0.89	Super case II transport

X-Ray Imaging Studies for Floating of The Formulation: A protocol was designed for the x-ray studies to know the floating time period of an optimized *in-situ* gel formulation of pioglitazone. After getting authorization from the Institutional Animal Ethical committee having approval no. 1962/PO/Re/S/17/CPCSEA, the studies were performed using White Newzealand Rabbits. As per protocol, the healthy rabbit weighing 2.5 kg which has housed for a minimum of 72 h early to the study and had free access to water and food. Animals were kept for overnight fasting and prepared optimized Pioglitazone *in-situ* gel formulation along with radio-opaque agent $BaCl_2$ at the concentration of 15% w/v to ensure visibility by X-ray was administered orally. The animal was not allowable to eat throughout the experiment but have free access to water. X-ray imaging studies were performed at programmed time intervals of 0, 0.5, 1, 2, 4, 6, 8, 10, and 12 h.

***In-vivo* Pharmacokinetic Studies for the Optimized Formulation:** Measurement of pharmacokinetic parameters of the treatments confirmed the Institutional Animal Ethical committee guidelines having Approval No. 1962/PO/ Re/S/17/CPCSEA. Each group consists of three white albino rats. Pure drug suspension and the optimized formulation were administered orally to the rabbits by oral feeding tube, and the dose was followed considering the literature review. Animals weighing 180-200 g were divided into three groups of 3 each. Groups were named as Blank, Pure drug, and optimized formulation. Animals were maintained under standard laboratory conditions at 24 ± 2°C, relative humidity 50 ± 15%, and maintained under normal photoperiod (12 h dark / 12 h light cycles) throughout the experiment.

Blood samples were collected in K_2 EDTA coated blood collection tubes from marginal ear vein as per the standard protocol. The sampling time intervals were 0.0, 0.5, 1.0, 2.0, 4.0, 6.0, 12.0, and 24 h, respectively, for each animal of all the groups. The blood samples were collected, centrifuged at 4000 rpm, and separated the plasma. Plasma samples were stored at -20°C until analysis. Samples are examined for medicine concentrations by HPLC, and PK parameters were studied. The PK parameters such as $t_{1/2}$, T_{max}, C_{max}, AUC_{0-t} are estimated for the formulation and compared to API.

RESULTS AND DISCUSSION:

Determination of Absorption Maximum (Λ_{max}) Of Pioglitazone: UV spectrum of pioglitazone: UV-Scan Spectrum Performed at Range 200.00 to 350.00 nm showed maximum absorbance at 270nm wavelength are shown in figure no1. The calibration curve of pioglitazone by plotting concentration against absorbance results in a straight line, and Better peak response and less placebo interference were observed at 264 nm. Therefore, the wavelength of 264 nm, as shown in **Fig. 2,** was preferred to estimate the drug.

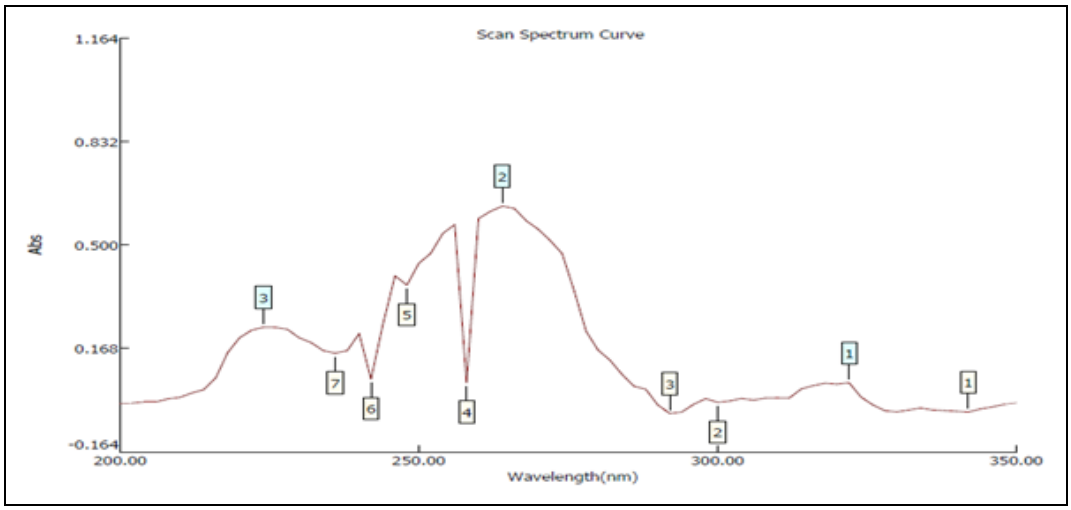

FIG. 1: PIOGLITAZONE ABSORPTION CURVE (Λ_{MAX}: 264 nm)

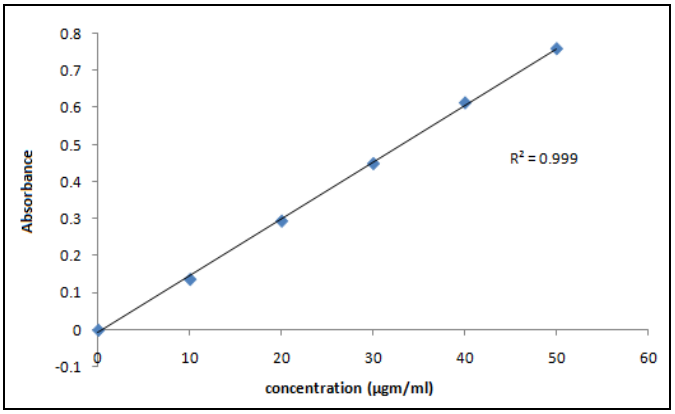

FIG. 2: CALIBRATION CURVE OF PIOGLITAZONE WITH REGRESSION VALUE

FTIR and DSC Studies: The IR spectrum of pioglitazone pure, excipients of optimized formulation, and pioglitazone optimized formulation illustrated that peak characteristics of pioglitazone are not-altered and with no changes in their spot, by this means representing no chemical drug interaction among drug and excipients. IR spectral studies confirmed the compatibility of pioglitazone with polymers utilized for *in-situ* gel preparations. The major peaks are obtained almost at the same wavenumbers belonging to drug functional groups. On the other hand, in the physical mixtures, additional peaks were obtained due to the attendance of impurities; however, there is no influence on the drug peaks. The observation of spectral studies indicates no significant change in the peaks of the drug-polymer mixture. Therefore, no specific interaction among drugs and polymers was observed, outcomes of IR studies were given in **Fig. 3**. The DSC studies of pioglitazone indicate that the obtained sample was a hydrate form result was shown in **Fig. 3.**

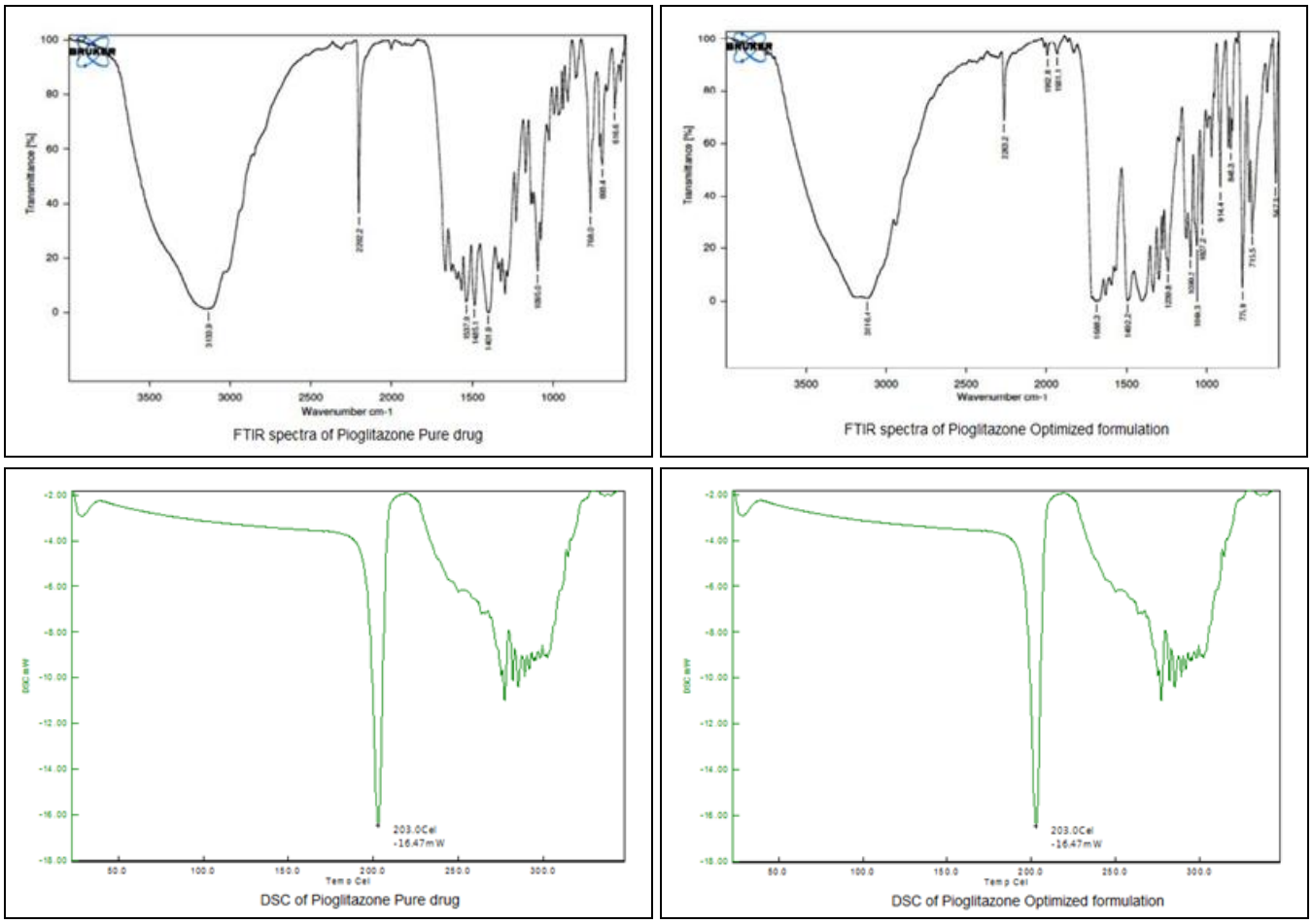

FIG. 3: THE IR SPECTRUMS OF THE PIOGLITAZONE, EXCIPIENTS OF OPTIMIZED FORMULATION, AND DSC OF THE PIOGLITAZONE

Physical Appearance, pH and Response of Gelation: The pH measurement is essential for oral preparations; or else, it leads to annoyance to the gullet. All prepared formulations pH was found in the range of 6.9-7.3 and physical appearance of formulations as shown in **Table 3**.

TABLE 3: EVALUATION PARAMETERS (GEL APPEARANCE, pH, GELATION RESPONSE, %DRUG CONTENT, VISCOSITY, FLOATING LAG TIME IN SEC AND FLOATING DURATION IN HRS) OF *IN-SITU* GEL FORMULATIONS OF PIOGLITAZONE

Code	Formulation appearance	pH	Gelation response	% Drug content	Floating: lag time	Floating duration	Viscosity: (cps)	
							Formulation	Gel
F1	Pourable and pleasing	6.9	+++	94.21	2sec	>12 hrs	312± 31	1456
F2	Pourable and pleasing	7.1	+++	94.73	3sec	>12 hrs	325± 26	1478± 23
F3	Pourable and pleasing	7.1	+++	95.78	2sec	>12 hrs	348± 16	1512± 26
F4	Pourable and pleasing	7.0	+++	94.94	2sec	>12 hrs	356± 68	1536± 31
F5	Pourable and pleasing	6.9	+++	94.89	3sec	>12 hrs	332± 23	1414± 13
F6	Pourable and pleasing	7.0	+++	95.10	2sec	>12 hrs	356± 26	1486± 16
F7	Pourable and pleasing	7.1	+++	95.68	4sec	>12 hrs	369± 38	1526± 22
F8	Pourable and pleasing	7.3	+++	95.52	2sec	>12 hrs	374± 25	1598± 50
F9	Pourable and pleasing	7.2	+++	95.26	2sec	>12 hrs	368± 13	1468± 18
F10	Pourable and pleasing	7.3	+++	95.89	3sec	>12 hrs	388± 50	1518± 26
F11	Pourable and pleasing	7.0	+++	96.42	3sec	>12 hrs	396± 24	1548± 15
F12	Pourable and pleasing	6.9	+++	96.05	4sec	>12 hrs	408± 22	1592± 36
F13	Pourable and pleasing	7.1	+++	96.17	5sec	>12 hrs	438± 15	2556± 25
F14	Pourable and pleasing	7.3	+++	97.52	2sec	>12 hrs	468± 18	2594± 38
F15	Pourable and pleasing	7.3	+++	97.69	2sec	>12 hrs	483± 36	2608± 24

(+++): Immediate gelations remain for an extended period

Determination of Drug Content: Content of drugs in all F1 to F15 preparations were assessed, and outcomes are in the acceptable range. The ranges of drug content values of formulations are between 94 to 97.6%; hence, it clearly indicated that the drug was steady throughout its shelf life and the results were shown in **Table 3.**

Floating Studies: Floating time and lag time are shown in **Table 3**. As the concentration of polymer results in an increase in viscosity, hence the time taken from the sol to cohesive gelation and to appear on the surface of the medium was lowered. The *floating in-vitro* test revealed the ability of all formulations to keep buoyancy for above 12 h. All formulations exhibited a total floating time of>12 h. Floating lag-time varied with formulation variables. Floating lag times of F1-F15 are in between 2-5sec.

Viscosity Studies: The viscosities of the all-prepared formulations were low; a considerable increase was reported at due to the conversion of sol-gel. The pioglitazone *in-situ* gel (F15) viscosity was 483±36cps; a prominent raise was observed after gelation was 2608±24cps. Taking into account all the results and findings of characterization, formulation F15 was considered for further studies results were shown in **Table 3.**

***In-vitro* Drug Release Studies:** The *in-vitro* drug release study results were shown in **Fig. 4.** Formulations (F1-F4) containing the composition of pioglitazone with various concentrations of Xanthan gum showed 92.36%, 94.26%, 98.05%, and 97.10% drug release in 6 hrs of dissolution. Drug along with Guar gum (F5-F8) and Carbopol 934 (F9-F12) composite formulations showed drug release range in-between 84.31%-99.47% within 8hrs of dissolution.

Formulations (F13-F15) having compositions of pioglitazone with a combination of Xanthan gum, Guar gum, and Carbopol showed an extended period of drug release, as compared to all formulations based on the results of dissolution studies and other evaluation parameter values F15 can be considered as optimized formulation as it showing drug release of around 98.11% over 10 h extended period.

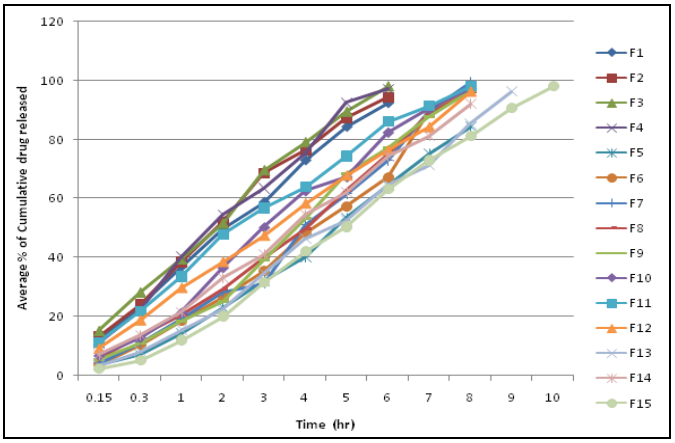

FIG. 4: COMPARATIVE SUMMARIZATION OF *IN-VITRO* DISSOLUTION STUDIES OF (F1 TO F15) PIOGLITAZONE

Kinetic Analysis of *in-vitro Drug* Release Studies: Zero-order analyzed the cumulative drug release data of optimized formulation (F15), first-order, Kores Mayer Peppas and Higuchi square root to find out drug release mechanism. The correlation coefficient (r^2) values of F15 were specified in **Table 4**. Hence it can be assessed that the optimized formulation (F15) follows zero-order and diffusion mechanisms for drug release. Kinetic model plots were shown in **Fig. 4.**

TABLE 4: KINETIC MODELS AND THEIR SLOPE VALUES AND R² VALUES

S. no.	Model	R^2 and Slope values
1	zero order kinetic	y = 10.01x + 0.921 R² = 0.998
2	First order kinetic	y = -0.098x + 2.082 R² = 0.519
3	Higuchi kinetic	y = 33.18x - 16.56 R² = 0.946
4	Koresmayer\peppas kinetic	y = 1.319x + 1.835 R² = 0.031

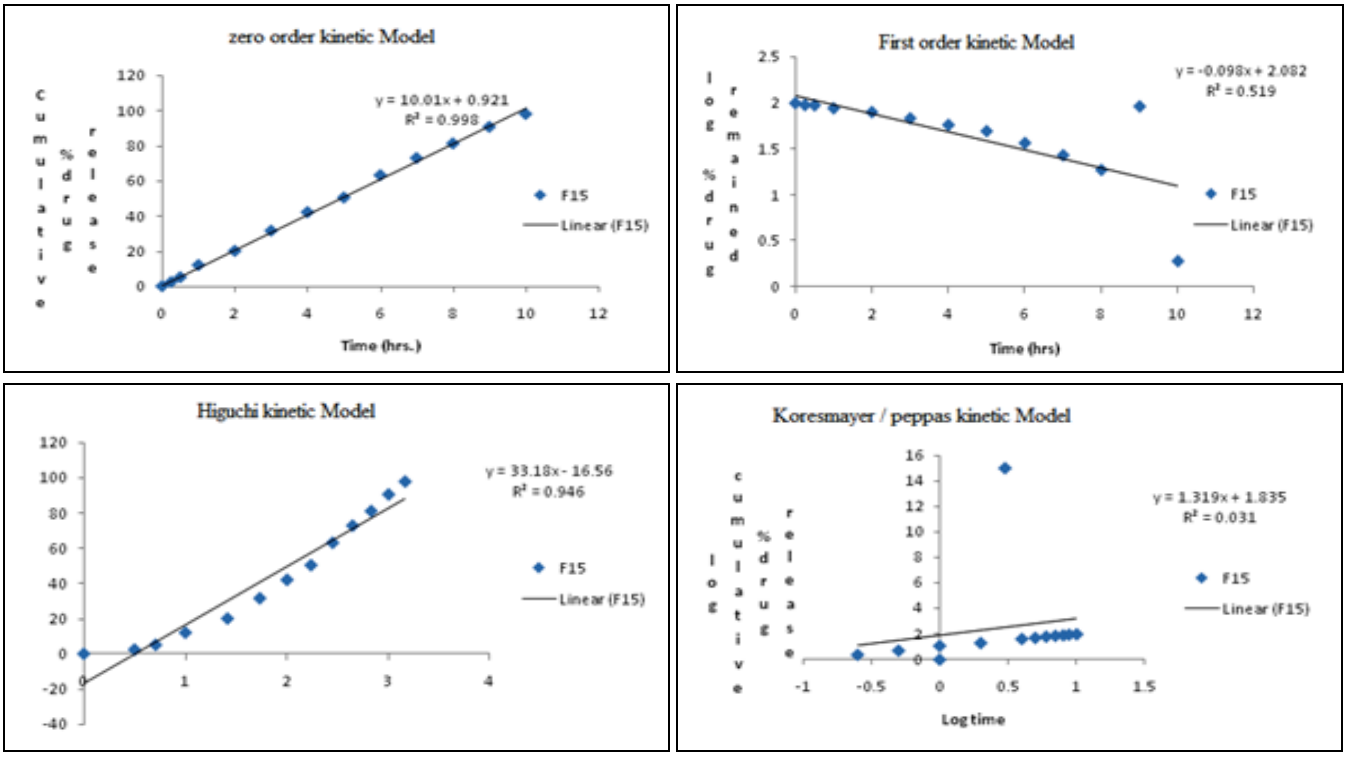

FIG. 5: KINETIC MODELS AND THEIR GRAPHS OF THE PIOGLITAZONE OPTIMIZED FORMULATION

***In-vivo* X-ray Imaging Studies:** An *in-vivo* X-ray imaging study was performed on a healthy New Zealand rabbit. The optimized formulation added with Barium Chloride at the concentration of 15% w/v was administered to the rabbit through the oral route. Its abdomen X-ray images were taken to confirm the floating ability of optimized gel formulation (F15) the pioglitazone. The X-ray imaging was taken as i) X-ray image of Immediately after administration ii) X-ray image After 0.5 hr after gel administration iii) X-ray image after 1 hr. of gel administration and iv, v, vi, vii-viii & ix are X-ray images after 2, 4, 6, 8, 10 and 12 h of gel administration. It was found that oral floating in-situ gel was floating immediately after feeding to the rabbit, and it was observed to be floating in the stomach for more than 12 h, and results of x-ray imaging's are given in **Fig. 6**.

***In-vivo* Pharmacokinetic Studies for the Optimised Formulation:** The percent of drug concentration in plasma was evaluated, and plasma concentrations versus time curve for pioglitazone was shown in **Fig. 5**. Pharmacokinetic parameters are presented in **Table 5**. Compared to the pure drug (4.945ng/ml) F15 formulation showing C_{max} value of 6.886 ng/ml in blood and bioavailability and T_{max} of F15 was 4hrs, and the pure drug was 1 h.

AUC is an important parameter for evaluating the bioavailability of a drug from a dosage form as it represents the total integrated area under the blood concentration-time profile and represents the total amount of drug reaching. The F15 formulation and pure drug have had maximum variations in the case of AUC parameter.

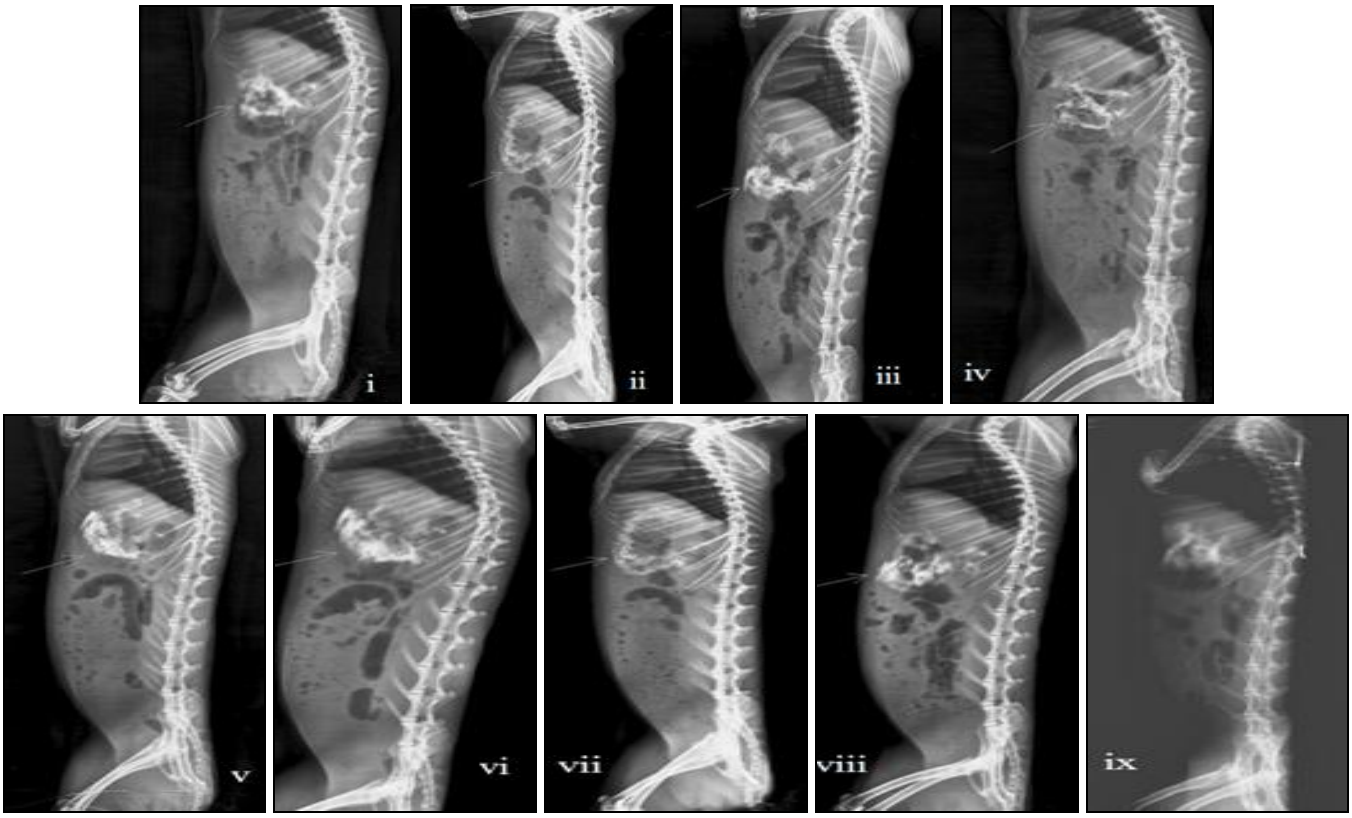

FIG. 6: *IN-VIVO* X-RAY IMAGING STUDIES OF THE PIOGLITAZONE OPTIMIZED FORMULATION. i) x-ray image of Immediately after administration ii) x-ray image After 0.5 hr after gel administration iii) X-ray image after 1 h of gel administration and iv, v, vi, vii-viii & ix are X-ray images after 2, 4, 6, 8, 10 and 12 h of gel administration.

TABLE 5: PHARMACOKINETIC STUDIES OF OPTIMIZED FORMULATION F15, AND PURE DRUG

Pharmacokinetic Parameters for pioglitazone in Rabbits				
Formulation	AUC $_{0\rightarrow24}$	$t_{1/2}$ (hrs)	C_{max}(ng/ml)	T_{max} (hrs)
Pure Drug	33409.6	4.4955	4945	1
F15	107269	5.7155	6886	4

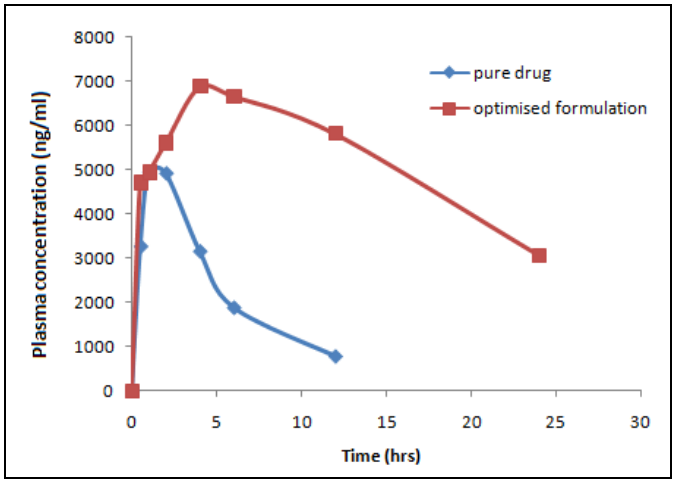

FIG. 7: PLASMA CONCENTRATIONS VERSUS TIME CURVE OF FORMULATIONS [F15], PURE DRUG

CONCLUSION: Diabetes is the most common disorder; for the management of diabetes, many anti-diabetic drugs are available in the market in solid dosage forms. Pioglitazone is an oral anti-diabetic agent, which is used in treating type – II diabetes mellitus. The biological half-life of pioglitazone was a maximum 3 h and is eliminated rapidly. The optimized formulation F15 Thereby, the 1.5% concentration of sodium alginate along with Xanthan gum and Carbopol-934 had shown an extended period of drug release for above 12 hours. The *in-vivo* drug release studies and x-ray studies confirmed that the optimized formulation showed extended bioavailability above 12 h. Hence, it is concluded that the study's main objective was to increase the bioavailability of pioglitazone as a convenient dosage form in the treatment of diabetes mellitus.

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CONFLICTS OF INTEREST: All the authors declare that they have no conflict of interest.

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