

Formulation and evaluation of a thermosensitive mucoadhesive rectal in situ gel of pioglitazone hydrochloride for localized treatment of ulcerative colitis

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Abstract—The present study was aimed at the development of a thermosensitive mucoadhesive in situ gel for rectal delivery of pioglitazone hydrochloride as a localized and sustained release alternative to oral thiazolidinedione therapy for ulcerative colitis. Nine thermosensitive mucoadhesive gels (F1-F9) were prepared using cold method using Poloxamer 407 and HPMC K4M. Poloxamer 407 at 16, 18 and 20% w/w was mixed with HPMC K4M at 0.5, 1.0 and 1.5% w/w at a fixed drug loading of 300 mg per 100 g. The prepared gels were evaluated for appearance, gelation temperature, gelation time, gel strength, pH, viscosity, syringeability, spreadability, swelling index, drug content, and in vitro release along with FTIR drug-excipient compatibility and SEM morphology studies. The gelation temperature of the nine batches ranged from 32 to 49 °C and the gelation time from 120 to 480 s, with both decreasing with increasing Poloxamer 407 concentration. The formulation F7 (20% w/v Poloxamer 407, 0.5% w/v HPMC K4M) was found to have a gelation temperature of 36 ± 1 °C, a gelation time of 120 s, the highest drug content among the fast-gelling batches (99.08%), favorable spreadability (12.26 cm), and gel strength > 300 s and was selected as the optimized formulation. In vitro drug release study using a Franz diffusion cell showed that F7 exhibited a cumulative release of 78.4% at 420 min, which followed the Higuchi diffusion model ($R^2 = 0.9888$) with a Korsmeyer–Peppas exponent $n = 0.6625$, indicating an anomalous (non-Fickian) transport mechanism involving diffusion and polymer relaxation/erosion. The optimized formulation F7 showed a more sustained drug release (78.4% vs. 87.8% at 420 min) as compared to plain (non-thermosensitive) mucoadhesive gel of pioglitazone. To summarize, pioglitazone

thermosensitive mucoadhesive rectal in-situ gel is a promising localized and sustained release platform for ulcerative colitis management.

Index Terms—Pioglitazone, ulcerative colitis, thermosensitive gel, mucoadhesive, rectal drug delivery, poloxamer 407, cold method technique

I. INTRODUCTION

The chronic, relapsing-remitting inflammatory bowel illness known as ulcerative colitis (UC) is characterized by persistent mucosal and submucosal inflammation that usually starts in the rectum and moves proximally across the colon [1-3]. In contrast to Crohn's disease, UC is characterized by a continuous rather than discontinuous pattern of involvement and is caused by a dysregulated mucosal immune response that includes decreased epithelial barrier function and elevated pro-inflammatory cytokines including TNF- α , IL-6, and IL-13[4]. Clinically, patients exhibit urgency, tenesmus, bloody diarrhea, and abdominal pain. Prolonged illness is associated with a higher risk of colorectal dysplasia [5]. Local, site-specific medication administration to the rectum and distal colon is a pharmacologically sound and clinically significant therapy approach because these areas are the main sites of inflammation in most UC cases, especially proctitis and proctosigmoiditis. Aminosaliclates, corticosteroids, and immunomodulators are among the conventional oral treatments for UC that are limited in this situation by

extensive first-pass hepatic metabolism, systemic absorption that results in off-target adverse effects, delayed onset of action because of upper gastrointestinal transit, and unpredictable release influenced by luminal pH and gastric emptying [6, 7]. Rectal injection allows for greater local drug concentrations at the inflammatory mucosa with less systemic exposure because it avoids most of the upper gastrointestinal tract [8]. However, early ejection, poor mucosal retention, limited proximal spread, and low patient compliance due to leakage and administration discomfort limit the use of traditional rectal dose forms, such as liquid enemas, suppositories, and foams [9]. Due to these drawbacks, there is increasing interest in innovative rectal delivery systems that can increase patient tolerability while extending mucosal contact time.

These restrictions are addressed by in situ gel-forming systems, which are free-flowing liquids during administration and undergo a sol-to-gel phase shift in response to a physiological stimulus at the application site, such as temperature, pH, or ionic strength [10]. Because they can be administered as a low-viscosity solution that evenly covers the mucosal surface and then changes into a viscoelastic gel upon contact with the rectal mucosal temperature ($\sim 37^{\circ}\text{C}$) to prevent premature expulsion, thermosensitive systems—which gel in response to body temperature—are especially well suited for rectal delivery [11-13].

One of the most popular thermogelling agents for this purpose is Poloxamer 407, a polyoxyethylene–polyoxypropylene–polyoxyethylene triblock copolymer, because of its temperature-dependent micellization behavior and adjustable gelation temperature [14-17]. By encouraging sticky contacts with the mucosal mucin layer, combining Poloxamer 407 with a mucoadhesive polymer like hydroxypropyl methylcellulose (HPMC K4M) improves formulation effectiveness and extends residence time beyond what is possible with thermogelation alone [18].

Peroxisome proliferator-activated receptor-gamma (PPAR- γ), a receptor that is extensively expressed in colonic epithelial cells [19], is selectively activated by pioglitazone hydrochloride, a thiazolidinedione that is typically employed as an insulin-sensitizing drug in type 2 diabetes mellitus. In addition to its metabolic function, PPAR- γ activation has local anti-inflammatory effects related to UC, including as NF- κB signaling inhibition, pro-inflammatory cytokine

downregulation, and epithelial barrier integrity repair. Pioglitazone's anti-inflammatory potential can be utilized locally while reducing systemic exposure by formulating it into a rectally administered, mucosa-retentive in situ gel [22, 23]. Delivering pioglitazone systemically for this purpose would expose patients to metabolic effects unrelated to its intended colonic action.

The present study was therefore undertaken to design, develop, and characterize thermosensitive mucoadhesive rectal in situ gel formulations of pioglitazone HCl, using Poloxamer 407 as the thermogelling agent and HPMC K4M as the mucoadhesive polymer, and to evaluate their gelation behavior, mucoadhesive strength, in vitro drug release, and release kinetics, with the aim of identifying an optimized formulation for the localized management of ulcerative colitis.

II. MATERIALS AND METHODS

2.1. Materials

Pioglitazone hydrochloride was procured from Prim Drugs and Pharmaceuticals Pvt. Ltd. Poloxamer 407 was obtained from SM Pharma and Chemicals. Polyethylene glycol 400 (PEG 400), used as a drug-solubilizing co-solvent, was supplied by Mohini Organics Pvt. Ltd. Hydroxypropyl methylcellulose (HPMC K4M) and sodium chloride were obtained from G.S. Scientific Services, Madurai. Distilled water was used throughout as the vehicle. All other chemicals and reagents used were of analytical grade.

2.2. Methodology

2.2.1. Pre-formulation studies

Pioglitazone hydrochloride was the subject of pre-formulation research to verify the drug's identity and describe its physicochemical behavior before formulation. Through direct visual and sensory analysis, organoleptic characteristics (color, odor, taste, and appearance) were noted. In order to determine solubility in distilled water, methanol, ethanol, and acetic acid, an excess of drug was equilibrated with 10 mL of each solvent at $25 \pm 2^{\circ}\text{C}$ with constant mechanical shaking until equilibrium was reached. This was followed by filtration, the proper dilution, and spectrophotometric estimation at 269 nm (λ_{max} of pioglitazone). A mutually saturated biphasic system was used to calculate the n-

octanol/water partition coefficient, and a capillary melting-point device was used to estimate the melting point, which was then compared to the value described in the literature.

2.2.2. Preparation of calibration curve

A standard stock solution of pioglitazone hydrochloride (1000 µg/mL) was prepared in 0.1 N hydrochloric acid and serially diluted to obtain working solutions of 10–50 µg/mL. Absorbance was measured at 269 nm against 0.1 N hydrochloric acid as blank using a Shimadzu UV-1700 (Japan) spectrophotometer, and a calibration curve of absorbance versus concentration was constructed.

2.2.3. Drug–excipient compatibility (FTIR)

Fourier Transform Infrared (FTIR) spectroscopy (Shimadzu RXI, Japan) was performed on the pure drug, PEG 400, Poloxamer 407, HPMC K4M, a physical mixture of all components, and the final thermosensitive gel formulation. Samples were scanned over 4000–400 cm⁻¹ to detect any shift, disappearance or emergence of characteristic absorption bands indicative of drug–excipient interaction.

2.2.4. Preparation of pioglitazone-loaded thermosensitive mucoadhesive rectal in-situ gel

Nine formulations (F1–F9) were prepared by the cold method [10,17], varying Poloxamer 407 at 16, 18 and

20% w/w in combination with HPMC K4M at 0.5, 1.0 and 1.5% w/w, with the drug (300 mg), PEG 400 (10 mL) and sodium chloride (0.5 g) held constant and the batch made up to 100 g with purified water (Table 1). Pioglitazone was first dissolved in PEG 400 under stirring at room temperature (warmed to a maximum of 40 °C only if required for complete dissolution). Separately, HPMC K4M was dispersed in hot purified water (80–90 °C), cooled to room temperature, and sodium chloride was dissolved into this solution. Poloxamer 407 was hydrated in cold purified water (4–5 °C) with gentle stirring on an ice bath and stored overnight at 4 °C to achieve complete dissolution, since warm water addition causes premature, incomplete gelation. The HPMC–NaCl solution and the drug–PEG 400 solution were then combined sequentially with the poloxamer base under continued ice-bath conditions, the volume was adjusted with cold water, and the pH was corrected to 6.8–7.4 with 0.02 g sodium bicarbonate per 10 mL where required. The finished gel was stored in amber glass vials at 4 ± 1 °C and allowed to equilibrate for 24 h before evaluation. Based on a total drug load of 300 mg per 100 g of gel, each gram of gel contained 3 mg of pioglitazone hydrochloride (0.3% w/w), corresponding to a 15 mg dose per 5 mL unit.

Table 1. Composition of pioglitazone-loaded thermosensitive mucoadhesive rectal in-situ gel formulations (per 100 g).

Formulation	Pioglitazone HCl (mg)	Poloxamer 407 (g)	HPMC K4M (g)	NaCl (g)	PEG 400 (mL)	Water
F1	300	16.0	0.5	0.5	10	q.s.
F2	300	16.0	1.0	0.5	10	q.s.
F3	300	16.0	1.5	0.5	10	q.s.
F4	300	18.0	0.5	0.5	10	q.s.
F5	300	18.0	1.0	0.5	10	q.s.
F6	300	18.0	1.5	0.5	10	q.s.
F7	300	20.0	0.5	0.5	10	q.s.
F8	300	20.0	1.0	0.5	10	q.s.
F9	300	20.0	1.5	0.5	10	q.s.

*HPMC K4M and sodium chloride were varied/added as indicated above; all other batch parameters were held constant



Fig .1 Plain gel



Fig .2 Thermosensitive gel formulation (F1-F9)

2.2.5. Physicochemical characterization

Appearance and clarity were assessed visually against black and white backgrounds. Surface morphology of the optimized formulation was examined by scanning electron microscopy (ZEISS) after drying and gold-sputter coating. Gelation temperature was determined by immersing the sol-state sample in a water bath, increasing the temperature at $1\text{ }^{\circ}\text{C}/2\text{ min}$ and identifying the temperature at which the sample no longer flowed upon tube inversion. Gelation time was recorded as the time for a sample immersed at $37\text{ }^{\circ}\text{C}$ to stop flowing on inversion. pH was measured in triplicate with a calibrated digital pH meter, with pH adjusted using sodium bicarbonate where necessary to fall within 6.8–7.4. Viscosity was measured using a Brookfield viscometer (AMETEK). Gel strength was determined as the time (or minimum weight, up to 200 g) required for a weighted probe to sink 5 cm through the gelled sample at $36 \pm 1\text{ }^{\circ}\text{C}$. Spreadability was measured using the glass-slide slip method and calculated as $S = M \times L / T$, where M is the applied weight, L the distance moved, and T the time taken. Syringeability was tested by dispensing formulations through 5 mL syringes fitted with 18-gauge needles. Swelling index was determined in phosphate buffer (pH 6.8) at 1, 2, 4, 8, 12 and 24 h as $(W_t - W_0)/W_0 \times 100$. Drug content was determined by UV spectrophotometric estimation at 269 nm after appropriate dilution of the gel in phosphate buffer pH 6.8.

2.2.6. In-vitro drug release and kinetic modelling

In-vitro release studies were conducted using a Franz diffusion cell at $37 \pm 1\text{ }^{\circ}\text{C}$ and 100 rpm, with a $0.45\text{ }\mu\text{m}$ mixed cellulose ester membrane separating the donor compartment from a receptor compartment containing phosphate buffer pH 7.4. Samples were withdrawn at 30, 60, 120, 180, 240, 300, 360 and 420 min, with immediate replacement of an equal volume of fresh, pre-warmed buffer to maintain sink conditions, and analyzed spectrophotometrically at 269 nm. The resulting release data for all nine batches were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell models,[24,30] and the correlation coefficient (R^2) of each model was compared to identify the best-fit release model; the Korsmeyer–Peppas exponent (n) was used to interpret the release mechanism ($n < 0.45$, Fickian diffusion; $0.45 < n < 0.89$, anomalous/non-Fickian transport; $n \geq 0.89$, case-II/super case-II transport) [25,26].

2.2.8. Data analysis

All measurements were performed in triplicate ($n = 3$) and results are expressed as mean $\pm$ standard deviation. Data were analyzed using one-way analysis of variance (ANOVA), with $p < 0.05$ considered statistically significant.

III. RESULTS AND DISCUSSION

3.1. Pre-formulation studies

Pioglitazone hydrochloride was obtained as a white, odourless powder with a bitter taste, consistent with its

Certificate of Analysis. The drug was practically insoluble in distilled water (0.047 mg/mL) but freely soluble in methanol (83.65 mg/mL), soluble in acetic acid (13.72 mg/mL) and slightly soluble in ethanol (6.84 mg/mL) (Table 2), confirming its classification as a poorly water-soluble (BCS Class II) drug and supporting the use of PEG 400 as a solubilizing co-solvent in the gel base. The n-octanol/water partition coefficient was approximately 2.4, indicating a moderately lipophilic character favourable for

diffusion across the rectal mucosa while retaining sufficient aqueous-phase solubility for release from the hydrophilic gel matrix. The λ_{max} of pioglitazone was confirmed at 269 nm, and the calibration curve (10–50 $\mu\text{g/mL}$) showed excellent linearity ($R^2 = 0.9979$), confirming adherence to Beer's law over the working concentration range and validating the UV method for subsequent drug content and release estimations.

Table 2. Solubility profile of pioglitazone hydrochloride in different solvents.

Solvent	Mean absorbance	Solubility (mg/mL)	USP description
Distilled water	0.052	0.047	Practically insoluble
Methanol	1.842	83.65	Freely soluble
Acetic acid	0.318	13.72	Soluble
Ethanol	0.241	6.84	Slightly soluble

3.2. Drug–excipient compatibility (FTIR)

The FTIR spectra of the physical mixture and optimized formulation were analyzed to assess the compatibility of pioglitazone HCl with the selected excipients. The physical mixture showed characteristic peaks at 3368.07, 2872.45, 1663.30, 1455.03, 1348.96, 1251.58 and 1098.58 cm^{-1} , corresponding to O–H/N–H, C–H, C=O, C–H/C–N and C–O/C–O–C vibrations. The optimized formulation exhibited peaks at 3365.17, 1639.20, 1350.89 and 1084.76 cm^{-1} . The slight shifts in the

absorption bands may be attributed to hydrogen bonding and interactions among the polymeric components. Since no major new peaks or disappearance of characteristic drug peaks was observed, the FTIR results confirmed the compatibility of pioglitazone HCl with Poloxamer 407, HPMC K4M, PEG 400 and sodium chloride, indicating the absence of significant chemical interaction and suitability of the selected excipients for formulation development.

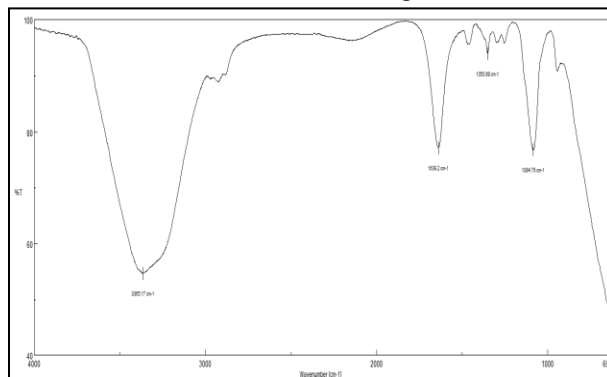


Fig.3 Physical mixture

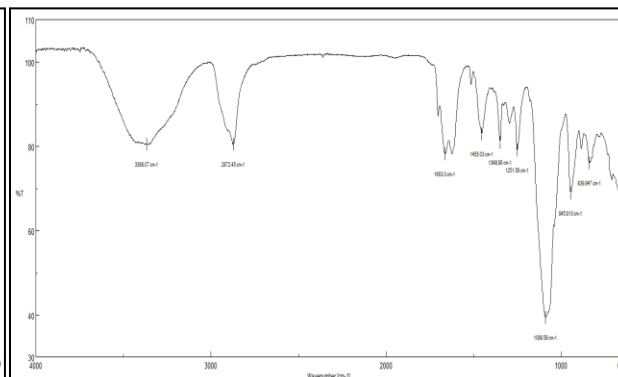


Fig.4 Thermosensitive gel formulation

3.3. Morphology (SEM)

Scanning electron microscopy of the optimized formulation (F7) revealed a predominantly smooth, continuous surface with no prominent cracks, pores or large aggregates. This homogeneous morphology is

consistent with uniform interpenetration of Poloxamer 407 and HPMC within the gel matrix, in which Poloxamer 407 forms the continuous thermogelling network while HPMC contributes to matrix cohesion

and viscosity, together supporting good physical stability of the formulation

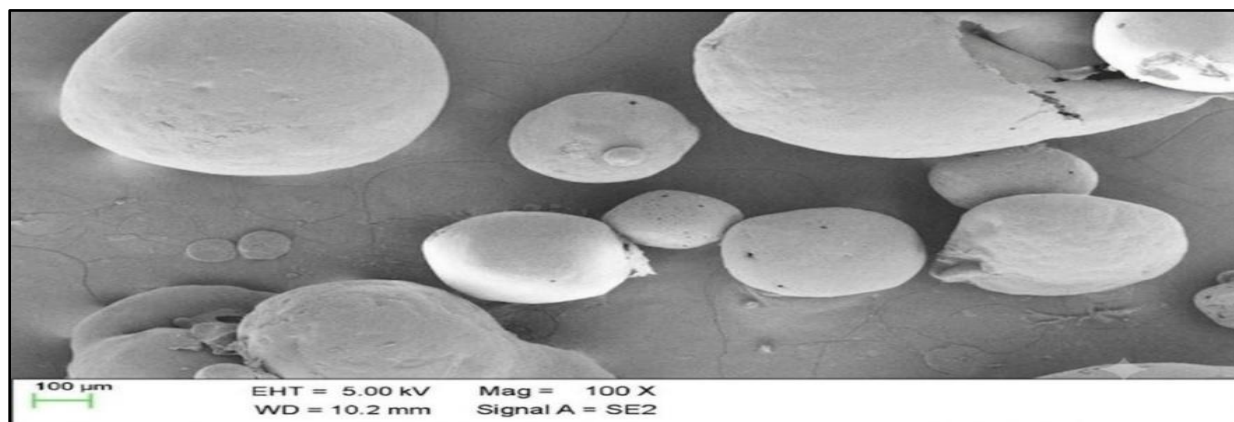


Fig.5 SEM image of best formulation

3.4. Preparation and physicochemical characterization of formulations F1–F9

All nine formulations were translucent, white, homogeneous sols at room temperature that transformed into non-flowing gels upon warming, with no visible particulate matter or phase separation, indicating good homogeneity across the entire polymer concentration range studied.

Gelation time and gelation temperature

Gelation time and gelation temperature were strongly influenced by Poloxamer 407 concentration, decreasing progressively as the polymer level increased from 16% to 20% w/w (Table 3, Fig. 1).

Gelation time fell from 480 s in F1 (16% P407, 0.5% HPMC) to 120–135 s in F7–F9 (20% P407), while gelation temperature fell from 49 °C in F1 to 32–36 °C in F7–F9. This trend reflects the greater number of poloxamer micelles available to entangle into a three-dimensional gel network at higher P407 concentration, consistent with the known reverse thermal gelation behaviour of Poloxamer 407. Among the nine batches, F7–F9 showed gelation behaviour closest to the physiologically ideal range for rectal in-situ gelling systems, avoiding both premature gelation before administration and excessive delay that would risk drug leakage[14,15,17]

Table 3. Physicochemical characterization of pioglitazone thermosensitive mucoadhesive gel formulations (F1–F9).

Formula	P407 (%)	HPMC K4M (%)	Gelation temp. (°C)	Gelation time (s)	pH	Gel strength (s)	Viscosity (cps)	Drug content (%)
F1	16	0.5	49	480	7.1	320	575	95.48 ± 0.42
F2	16	1.0	45	460	7.3	300	675	93.86 ± 0.51
F3	16	1.5	42	400	7.2	315	750	97.21 ± 0.36
F4	18	0.5	40	200	6.7	320	775	94.75 ± 0.47
F5	18	1.0	39	190	7.1	325	850	98.13 ± 0.29
F6	18	1.5	38	180	6.9	330	950	96.54 ± 0.34
F7	20	0.5	36	120	6.9	335	1050	99.08 ± 0.25
F8	20	1.0	34	130	6.8	345	1120	99.94 ± 0.18
F9	20	1.5	32	135	6.9	350	1175	97.82 ± 0.31



Fig. 6: Gelation time and temperature

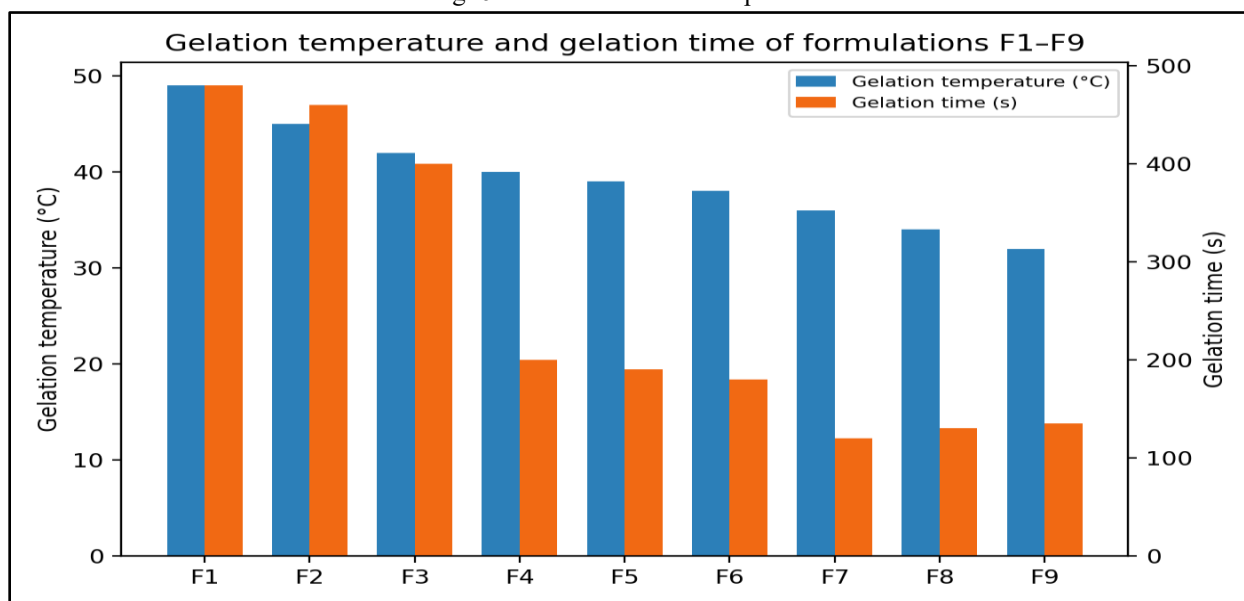


Fig. 7: Graphical representation of gelation time and temperature

pH of the formulations

pH of the sol-state formulations ranged from 6.7 to 7.3, close to the physiologically acceptable range for rectal administration; minor formulation-to-formulation variation was attributed to the concentration-dependent influence of Poloxamer 407 on the polymer–water microenvironment rather than any intrinsic acidity of the non-ionic surfactant, and pH was corrected with sodium bicarbonate where required to ensure the target range of 6.8–7.4.



Fig. 8 pH of the formulations

Gel strength

Gel strength exceeded 300 s for every formulation, well above the 15 s minimum generally considered necessary for adequate retention and ease of insertion, and increased slightly with rising polymer concentration (320 s in F1 to 350 s in F9), consistent with greater hydrogen bonding and cohesion between Poloxamer 407 and HPMC at higher polymer loads.

Viscosity

Viscosity increased progressively and consistently with increasing polymer concentration, from 575 cps in F1 to 1175 cps in F9, reflecting greater micelle formation by Poloxamer 407 and increased polymer chain entanglement contributed by HPMC K4M, both of which strengthen the three-dimensional gel network and support sustained drug release. All nine formulations passed the syringeability test through 18-gauge needles, confirming ease of administration despite the increase in viscosity at higher polymer concentrations. [16, 17]



Fig .9 Brookfield viscometer

Syringeability

Based on the results of the syringe-ability test using gauge 18 needles, all formulations (F1-F9) passed the test, indicating that they could be easily extruded through the needles and ease the administration of the gel.



Fig.10 syringeability

Swelling index

The swelling index of F1–F9 increased gradually with time, indicating progressive hydration of the polymeric matrix. The swelling behavior was mainly influenced by the HPMC concentration, as HPMC absorbs water and forms a hydrated gel network. Formulations containing higher HPMC concentrations generally showed greater swelling. At 24 h, the swelling index ranged from $61 \pm 3\%$ to $86 \pm 4\%$, with F9 showing the highest swelling.[18] F7 showed $76 \pm 4\%$ swelling, indicating controlled swelling and good matrix hydration. This controlled swelling may contribute to gel integrity, prolonged residence, and sustained drug release at the rectal site.

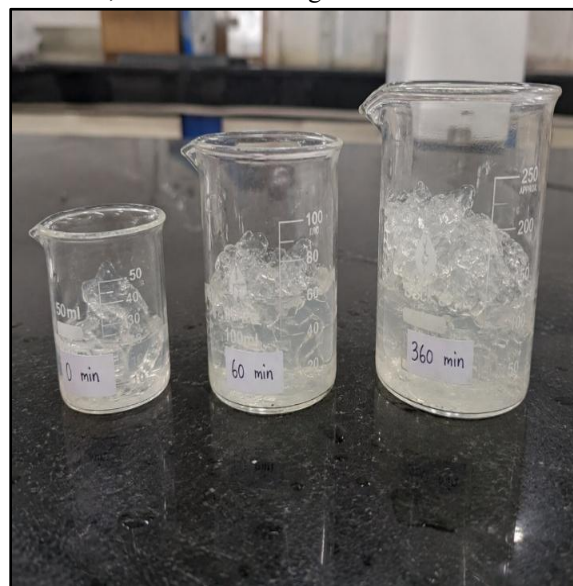


Fig .11 Swelling index

Drug content

Drug content across the nine formulations ranged from $93.86 \pm 0.51\%$ (F2) to $99.94 \pm 0.18\%$ (F8), all within the acceptable 90–110% range and indicating satisfactory and uniform drug incorporation during the

cold-method preparation. Among the fast-gelling, physiologically favourable batches (F7–F9), F7 and F8 showed the highest drug content (99.08% and 99.94%, respectively).

Table 4. Spreadability and swelling index of formulations F1–F9.

Formula	Spreadability (cm)	SI – 1 h (%)	SI – 2 h (%)	SI – 4 h (%)	SI – 8 h (%)	SI – 12 h (%)	SI – 24 h (%)
F1	5.21 ± 0.12	42 ± 2	48 ± 2	53 ± 3	57 ± 3	59 ± 3	61 ± 3
F2	5.54 ± 0.15	46 ± 2	53 ± 2	59 ± 3	64 ± 3	67 ± 3	70 ± 3
F3	4.79 ± 0.18	50 ± 2	58 ± 3	65 ± 3	71 ± 3	74 ± 3	78 ± 4
F4	6.08 ± 0.14	46 ± 2	52 ± 2	57 ± 3	61 ± 3	63 ± 3	65 ± 3
F5	6.26 ± 0.17	50 ± 2	57 ± 3	63 ± 3	68 ± 3	71 ± 3	74 ± 3
F6	5.42 ± 0.16	54 ± 3	62 ± 3	69 ± 3	75 ± 3	78 ± 4	82 ± 4
F7	12.26 ± 0.15	55 ± 3	63 ± 3	68 ± 3	72 ± 3	74 ± 3	76 ± 4
F8	12.11 ± 0.18	53 ± 3	61 ± 3	67 ± 3	72 ± 3	75 ± 3	78 ± 4
F9	10.85 ± 0.15	58 ± 3	66 ± 3	73 ± 3	79 ± 4	82 ± 4	86 ± 4

Spreadability ranged from 4.79 ± 0.18 cm (F3) to 12.26 ± 0.15 cm (F7), with F7–F9 showing markedly higher spreadability than F1–F6, favouring uniform distribution over the rectal mucosal surface on administration. The swelling index increased progressively with time for all formulations and was 3.5. In-vitro drug release

In vitro release from all nine formulations, evaluated over 420 min using a Franz diffusion cell, showed a mild initial burst (14.8–20.5% at 30 min) followed by a sustained release phase (Table 5, Fig. 2). Cumulative release at 420 min ranged from 71.6% (F9) to 89.5% (F1), with an inverse relationship generally observed between polymer concentration and the extent of release, reflecting the greater diffusional resistance

strongly influenced by HPMC K4M concentration, with 24 h values ranging from $61 \pm 3\%$ (F1) to $86 \pm 4\%$ (F9); F7 showed a controlled 24 h swelling of $76 \pm 4\%$, suggesting adequate matrix hydration without excessive erosion, consistent with sustained gel integrity and prolonged rectal retention.

imposed by denser gel networks at higher Poloxamer 407 and HPMC K4M content. Among the physiologically favourable fast-gelling batches (F7–F9), F7 (20% P407, 0.5% HPMC) gave the highest cumulative release (78.4% at 420 min), combining rapid, physiologically appropriate gelation with a comparatively open, less densely cross-linked matrix that still provided controlled, sustained drug liberation rather than a rapid burst

Table 5. In-vitro cumulative % drug release of pioglitazone from thermosensitive mucoadhesive gel formulations (F1–F9).

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
30	20.5	19.2	17.8	18.8	17.5	16.3	17.2	16.0	14.8
60	34.8	32.7	30.5	32.1	30.0	27.8	29.3	27.2	25.1
120	52.6	49.8	46.7	48.9	45.9	42.8	44.7	41.9	39.0
180	66.4	63.1	59.5	61.8	58.1	54.3	56.7	53.4	49.8
240	76.8	73.3	69.5	71.9	67.8	63.6	66.0	62.2	58.3
300	83.2	79.8	75.9	78.3	74.1	69.9	72.4	68.5	64.3
360	87.0	83.7	80.0	82.1	77.9	73.8	76.2	72.4	68.3
420	89.5	86.2	82.7	84.8	81.0	75.0	78.4	75.5	71.6

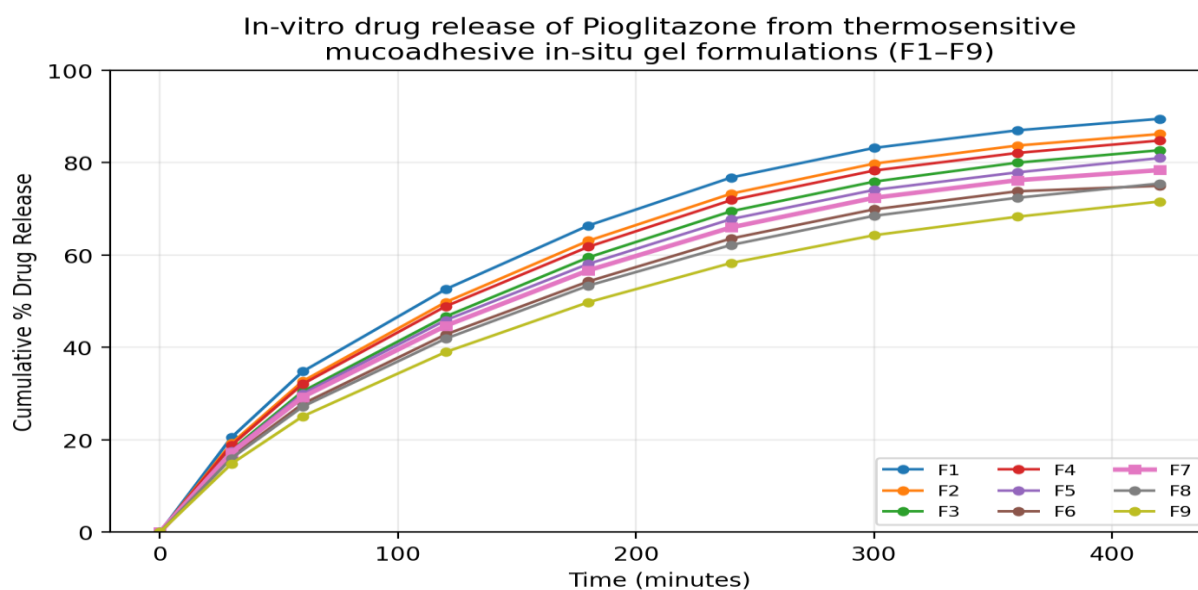


Fig. 12. In-vitro cumulative % drug release of pioglitazone from formulations F1–F9 (Franz diffusion cell, phosphate buffer pH 7.4, 37 ± 1 °C).

3.6. Release kinetics modelling

Across all nine batches, the Higuchi model consistently gave the highest correlation coefficients ($R^2 = 0.9985$ – 0.9998), indicating that drug release from the polymeric gel matrix was predominantly diffusion-controlled, as expected for a hydrophilic thermosensitive gel system [24, 27]. The Korsmeyer–Peppas diffusional exponent (n) ranged from 0.663 to 0.725 across formulations, falling within the $0.45 < n < 0.89$ range characteristic of anomalous (non-Fickian) transport [25, 26, 28], in which drug release proceeds through a combination of diffusion through

the swollen gel matrix and polymer chain relaxation/erosion.

For the optimized formulation F7, release increased progressively from 17.2% at 30 min to 78.4% at 420 min. The Higuchi model gave the best fit ($R^2 = 0.9888$), closely followed by the Korsmeyer–Peppas model ($R^2 = 0.9887$, $n = 0.6625$), confirming diffusion-controlled release with an anomalous transport mechanism combining diffusion and polymer relaxation[29,30] (Table 6).

Table 6. Release kinetics modelling parameters for the optimized formulation F7.

Kinetic model	X-axis	Y-axis	Slope	R ²
Zero-order	Time (min)	Cumulative % drug release	0.2293	0.7823
First-order	Time (min)	Log % drug remaining	0.00446	0.9805
Higuchi	$\sqrt{\text{Time}}$ (min)	Cumulative % drug release	4.0354	0.9888
Hixson–Crowell	Time (min)	$W_0^{1/3} - W_t^{1/3}$	0.00122	0.9473
Korsmeyer–Peppas (n = 0.6625)	Log time	Log cumulative drug release	3.8276	0.9887

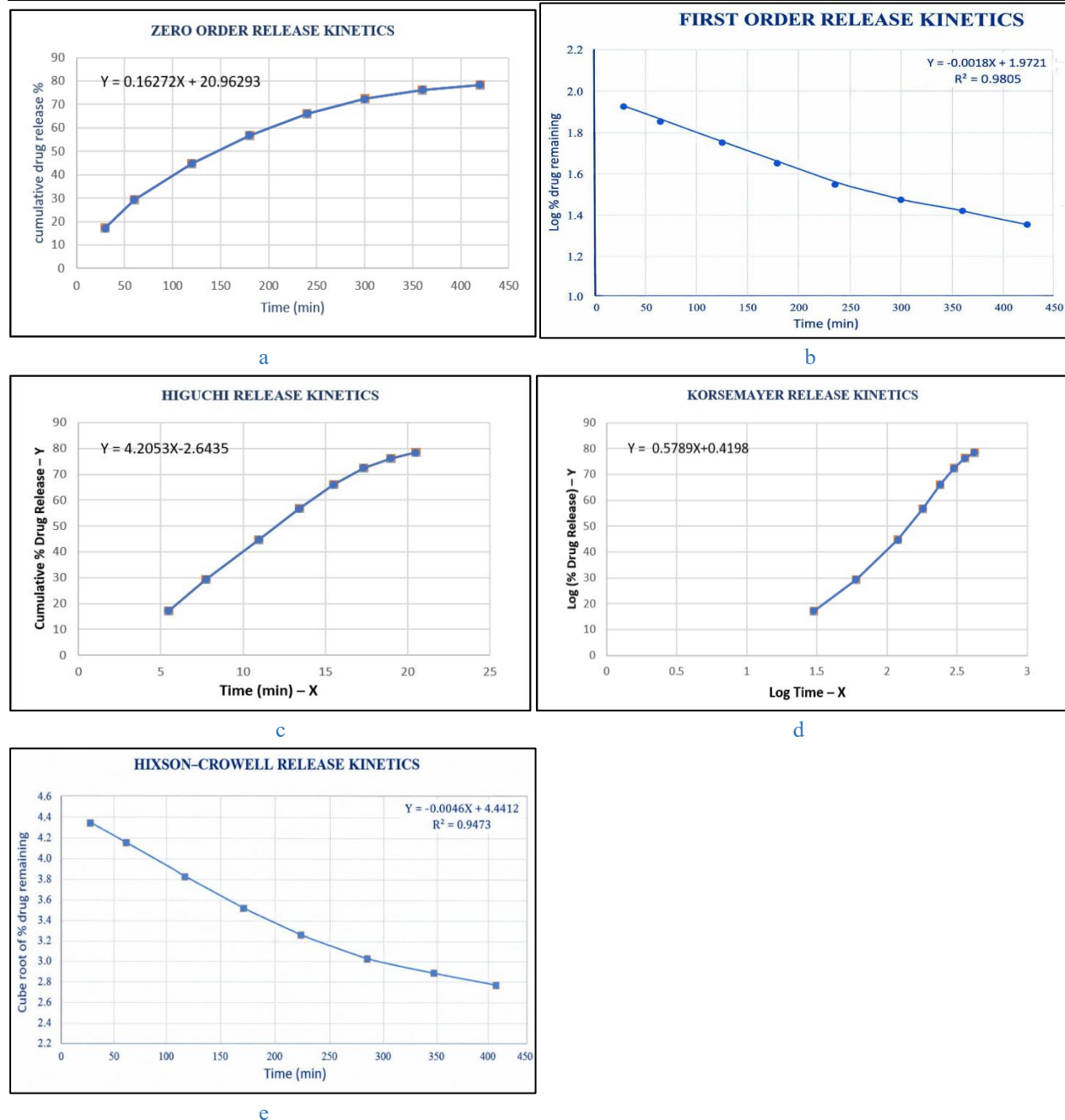


Fig .13 a) zero order b) first order c) Higuchi release kinetics d)korsmeyer release kinetics e) Hixon release kinetic

3.8. Selection of the optimized formulation

Considered together, gelation temperature and time closest to the physiological range, gel strength above 300 s, high and uniform drug content, favourable spreadability, controlled swelling, and the highest cumulative in-vitro release among the fast-gelling batches identified F7 (20% w/v Poloxamer 407, 0.5% w/v HPMC K4M) as the optimized pioglitazone

IV. CONCLUSION

A thermosensitive mucoadhesive rectal in-situ gel of pioglitazone hydrochloride was successfully developed using Poloxamer 407 and HPMC K4M by the cold method, and FTIR studies confirmed the absence of major drug–excipient incompatibility. Across nine formulations (F1–F9), increasing Poloxamer 407 concentration progressively lowered gelation temperature and gelation time while increasing viscosity and gel strength, and formulation F7 (20% w/v Poloxamer 407, 0.5% w/v HPMC K4M) emerged as the optimized batch on the basis of gelation behaviour, gel strength, drug content, spreadability and in-vitro release performance. In-vitro release from F7 followed the Higuchi diffusion model with a Korsmeyer–Peppas exponent of 0.6625, indicating anomalous (non-Fickian) transport, and F7 sustained drug release more effectively than a plain mucoadhesive gel lacking the thermogelling polymer. Overall, this thermosensitive mucoadhesive in situ gel of pioglitazone offers a patient-compliant, localized, and sustained-release rectal delivery platform with promise as an alternative, steroid-sparing local therapeutic approach for ulcerative colitis, warranting further ex vivo permeation, mucoadhesive strength, and in vivo evaluation.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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thermosensitive mucoadhesive rectal in-situ gel formulation. Its release profile, best described by the Higuchi model with a Korsmeyer–Peppas exponent indicative of anomalous (non-Fickian) transport, and its markedly slower release relative to a plain mucoadhesive gel, together support its suitability as a sustained, localized rectal delivery system for pioglitazone in the management of ulcerative colitis. technical and facilitation support provided during this work

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