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Original Research Article

Development of Floating In Situ Gel of Baclofen for Targeted Delivery in Gastroesophageal Reflux Disease

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Abstract: The present study was undertaken to develop and evaluate a floating in situ baclofen gel for targeted gastric delivery in the management of gastroesophageal reflux disease (GERD). Baclofen-loaded floating in situ gels (F1–F9) were formulated using sodium alginate (1.5–2.5% w/v) as a gelling polymer, calcium bicarbonate (0.5–1.5% w/v) as a gas-generating agent, and sodium citrate as a complexing agent. The prepared formulations were evaluated for clarity, pH, gelling time, viscosity, drug content, in vitro buoyancy, and in vitro drug release. All formulations showed acceptable clarity and an acidic pH range of 1.2–1.5, suitable for gastric conditions. Gelling time ranged from 55 ± 0.13 to 80 ± 0.58 s, while viscosity values varied between 148 ± 5.5 and 357 ± 7.3 cps. All formulations exhibited prolonged floating behavior for 12 h, with lag times of 50-82 s. Drug content uniformity was 98.18 ± 1.0%. Based on overall performance, formulation F7 was selected as the optimized formulation, showing a gelling time of 70 ± 0.43 s, viscosity of 282 ± 7 cps, and floating lag time of 51 s. The optimized formulation exhibited sustained drug release of 96.24 ± 0.132% over 24 h. Release kinetic analysis revealed that the drug release followed the Korsmeyer–Peppas model (R^2 = 0.993), indicating a diffusion-controlled release mechanism. The developed floating in situ baclofen gel shows promise as an effective gastroretentive drug delivery system for GERD management.

Keywords: Baclofen; Floating in situ gel; Gastroretentive drug delivery system; Sodium alginate; Gastroesophageal reflux disease; Sustained release.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic and recurrent gastrointestinal disorder characterized by the retrograde flow of gastric contents into the esophagus, leading to symptoms such as heartburn, regurgitation, and esophageal irritation [1,2]. The condition arises primarily due to transient lower esophageal sphincter relaxations (TLOSRs), impaired esophageal clearance, and delayed gastric emptying [3–5]. GERD significantly affects quality of life and, if left untreated, may result in complications including erosive esophagitis, Barrett's esophagus, and esophageal strictures. Conventional pharmacotherapy for GERD often requires frequent dosing and prolonged treatment, which can reduce patient compliance and therapeutic effectiveness.

Baclofen, a γ-aminobutyric acid type B ($GABA_B$) receptor agonist, has been reported to inhibit TLOSRs and reduce gastroesophageal reflux episodes [6–8] Unlike acid-suppressive therapies, baclofen acts on the central nervous system to modulate lower esophageal sphincter function, thereby addressing a key pathophysiological mechanism of GERD. However, oral administration of baclofen in conventional dosage forms is associated with rapid gastric emptying, short gastric residence time, and fluctuations in plasma drug levels, which may limit its clinical efficacy and increase the risk of systemic side effects [9]. **Fig. 1** shows the chemical structure of baclofen.

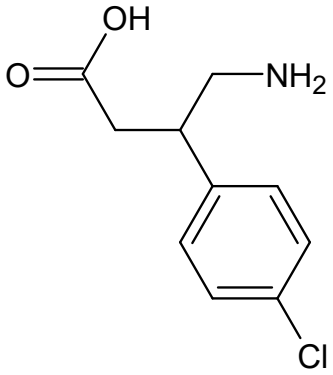

Fig. 1. Chemical structure of baclofen.

Gastroretentive drug delivery systems have emerged as a promising approach to enhance the therapeutic performance of drugs that are preferentially absorbed in the upper gastrointestinal tract or require prolonged gastric residence [10,11] Among these, floating drug delivery systems are designed to remain buoyant in gastric fluid for extended periods, thereby improving gastric retention time and ensuring sustained drug release. In situ gelling systems represent an advanced gastroretentive strategy, in which the formulation is administered as a low-viscosity liquid and undergoes a sol-to-gel transition upon exposure to gastric conditions [12]. This approach offers advantages such as ease of administration, improved patient compliance, and prolonged drug release. Sodium alginate is a widely used natural polymer for in situ gel formulations due to its biocompatibility, biodegradability, and ability to undergo ionic cross-linking in the presence of divalent cations such as calcium ions [13]. The incorporation of gas-generating agents, such as calcium bicarbonate, enables carbon dioxide formation in acidic gastric media, thereby imparting buoyancy to the gel system. Sodium citrate acts as a chelating agent, controlling premature gelation and ensuring formulation stability before administration [14]. The combined use of these excipients facilitates the development of a floating in situ gel capable of rapid gelation, sustained buoyancy, and controlled drug release.

In this context, the present study was undertaken to develop and evaluate a floating in situ baclofen gel for targeted gastric delivery in the management of GERD. The objective was to formulate a system that exhibits rapid gelation in acidic conditions, prolonged floating behavior, and sustained drug release, thereby enhancing gastric residence time and improving therapeutic efficacy. The developed formulations were systematically evaluated for physicochemical properties, in vitro buoyancy, drug content uniformity, drug release behavior, and release kinetics to establish their potential as an effective gastroretentive drug delivery system.

MATERIAL AND METHODS

2.1 Materials

The materials used in the present study included baclofen, which was procured from Sun Pharmaceutical Ltd., India. Sodium alginate was obtained from Shital Chemicals Ltd., India, and calcium bicarbonate was purchased from S.D. Fine Chemicals Ltd., India. Lesar Chemicals Ltd., India, supplied sodium citrate. All materials were of analytical grade and used as received, without further purification, for formulation and evaluation studies.

2.2 Pre-formulation studies

Pre-formulation represents an essential stage in the drug development process, during which the physical, chemical, and mechanical properties of the drug are systematically evaluated to enable the design of a safe, stable, and effective dosage form. These studies are critical for the rational development of a drug delivery system, as they provide fundamental insights into the characteristics of the active compound. In the present project, preformulation investigations on Baclofen were carried out across a range of parameters to establish its suitability for formulation

2.2.1 Organoleptic properties

The organoleptic properties of the drug were systematically observed and noted.

2.2.2 Melting point

The digital melting point apparatus determined the melting point of Baclofen.

2.2.3 FTIR spectroscopy

The pure drug sample was analyzed by infrared spectroscopy for identification. The baclofen was compressed at 5.5 metric tonnes of pressure in a KBr press using IR-grade potassium bromide to create a pellet. After that, the pellet was placed in the infrared chamber and scanned between 4000 and 450 cm^{-1} using an FTIR spectrophotometer (Model 8400S, Shimadzu, Japan)**.** The obtained spectrum was compared with the reference data (B.P., 2009) to confirm the characteristic peaks corresponding to the functional groups of Baclofen.

2.2.4 Solubility study

Solubility was assessed using the pharmacopeial method. Based on the results obtained in different

solvents, suitable diffusible and dispersible media were selected for drug release and pharmaceutical investigations. For the study, one part of Baclofen was added to varying volumes of solvents, including with water, methanol, ethanol, 0.1 N HCl, N-Octanoic acid, and Ethyl acetate. The mixtures were shaken reciprocally at 37 °C for 5 minutes to facilitate dissolution.

2.2.5 Ultraviolet/Visible spectrophotometric method development

A standard plot for Baclofen was constructed in 0.1 N HCl to enable its determination and quantification during different stages of preparation of drug designing.

2.2.5.1 Determination of Absorption Maximum (λmax)

A standard stock mixture of Baclofen (100 µg/ml) was set using 0.1 N Hcl. To determine the analytical wavelength, a 30 µg/ml solution was obtained by diluting the stock solution appropriately with the same solution. The solution was scanned over the wavelength range of 200–400 nm using a UV-Visible spectrophotometer. From the overlain spectrum, the wavelength of maximum absorbance (λmax) was identified and subsequently employed for all analytical determinations [15].

2.2.5.2 Construction of the Standard Calibration Curve for Baclofen

Baclofen (1000 µg/mL) was made as a main stock solution by precisely weighing 100 mg of the medication and dissolving it in 100 mL of 0.1 N hydrochloric acid. From this solution, 10 mL of the main stock was transferred into a 100 mL volumetric flask and diluted to volume with 0.1 N HCl to create a secondary stock solution (100 µg/mL). A series of working solutions with concentrations ranging from 10 to 60 µg/mL were obtained by further diluting aliquots of the secondary stock solution with 0.1 N HCl. A UV-visible spectrophotometer was used to measure the absorbance of each produced solution at 220 nm, and a calibration curve was created by charting absorbance against concentration.

2.3 Formulation of Floating Baclofen In-Situ Gel

Different amounts of sodium alginate solutions were made in deionised water with 0.25% sodium citrate. Low cation concentrations were enough to restrict hydration and stabilise molecular chains. The alginate solution was heated to 70°C with constant stirring, cooled to less than 40°C, and then mixed with various calcium bicarbonate and Baclofen concentrations. The in-situ gelling sodium alginate solution was obtained by fully dispersing the mixture while stirring, and it was then kept in amber bottles until needed [16] **(Table 1).**

Table 1 Composition of F1 to F9 Floating Baclofen In-Situ Gel.

Ingredients	Formulation codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Baclofen (mg)	20	20	20	20	20	20	20	20	20
Sodium alginate	1.5%	2%	2.5%	1.5%	1.5%	2.5%	2%	2%	2.5%
Calcium bicarbonate	0.5%	1%	0.5%	1%	1.5%	0.5%	1.5%	1%	1.5%

2.4 Characterization of floating Baclofen-loaded in situ gel

2.4.1 Clarity

The in situ gel solutions were made and visually assessed for clarity in light against white and black backgrounds.

2.4.2 pH measurement

The pH of the in-situ gel was measured with a digital pH meter [17]

2.4.3 Gelation time

At 25°C, the formulation temperature was maintained. The temperature of gelation was examined using a modified Miller and Donovan approach. Two-millilitre portions of the gel were placed in parafilm-sealed test tubes and incubated in a water bath at 4 degrees Celsius. 1 °C was added to the bath's temperature at a time, and each new setting was given 15 minutes to acclimatise. When the meniscus stopped moving at 90 °C, the samples were considered to have gelled.

2.4.4 Drug content

The amount of drug in the in situ gel formulations was analyzed by transferring 1 mL of the formulation into a 10 mL volumetric flask. A small volume of methanol was added, and the mixture was shaken continuously until the gel was fully dispersed, yielding a clear solution. The final volume was adjusted to 10 mL with 0.1 N HCl, and the solution was filtered. The drug concentration in the filtrate was quantified by UV spectroscopy, and the corresponding peak area was recorded.

2.4.5 Viscosity measurement

The viscosity of the sols was measured using a Brookfield digital viscometer (Model LVDV 2P230) with spindle number 1. Each 2 mL sample was kept at 25 ± 1 °C for 30 seconds [17]

2.4.6 In-vitro buoyancy

Using USP dissolving equipment II with 500 mL of simulated stomach fluid (pH 1.2) kept at 37 °C, in vitro buoyancy was measured. Using a disposable syringe, a 10 mL aliquot of the in situ gelling

formulation was extracted, moved to a Petri dish, and cautiously inserted into the dissolving vessel to prevent turbulence. Both the overall floating duration (the time the gel remained buoyant) and the floating lag time (the time required for the gel to reach the surface) were recorded [18].

2.4.7 In-vitro drug release

The in vitro release profile of baclofen from the in situ gel formulation was assessed using a modified dissolution technique. A USP type II dissolution apparatus fitted with a paddle was employed, operating at 50 rpm to ensure gentle hydrodynamic conditions without disturbing the formed gel matrix. The release study was performed in 500 mL of 0.1 N hydrochloric acid (pH 1.2), maintained at 37 ± 0.5 °C. At specific time intervals, 10 mL of the dissolution medium was withdrawn using a disposable syringe, carefully transferred into a Petri dish, and reintroduced into the dissolution vessel to minimize mechanical disturbance. To preserve sink conditions, the removed volume was promptly replaced with an equivalent volume of freshly made, heated dissolving medium. The amount of drug released was determined spectrophotometrically at 267 nm using a Shimadzu UV-1601 spectrophotometer. All release studies were conducted in triplicate over 12 hours. [74]

2.5 *In-vitro* drug release kinetics studies

Drug release from the in-situ gel was investigated by fitting the release data to the Higuchi, zero-order, and first-order kinetic models. Further analysis using the Korsmeyer–Peppas model provided insight into the underlying release mechanism.

RESULTS AND DISCUSSION

3.1 Pre-formulation studies

3.1.1 Organoleptic properties

Organoleptic evaluation revealed that the baclofen was a white to off-white crystalline powder with a slightly bitter taste and no distinctive odor.

3.1.2 Melting point analysis

The melting point of Baclofen was analyzed by Stuart's SMP30 digital melting point apparatus. The sample was analyzed in triplicate, and the mean was 207 °C (**Table 5.2**). The mean was almost the similar as that of the reported melting point i.e., 206-208°C (Indian Pharmacopoeia).

3.1.3 Solubility study

The solubility of Baclofen was determined with water, methanol, ethanol, 0.1 N HCl, N-Octanoic acid, and Ethyl acetate **(Table 2).**

Table 2: Solubility of Baclofen in different solvents.

Solvent	Solubility (Approx. Value, mg/mL)
Water	25–30 mg/mL
Ethanol	20–25 mg/mL
Methanol	5–8 mg/mL
0.1 N HCl	45–50 mg/mL
Ethyl acetate	2–4 mg/mL
n-Octanol	1–3 mg/mL

3.1.4 Preparation of calibration curve and Determination of λ_{max}

The UV absorption spectrum of baclofen was recorded, and the maximum absorbance (λ_max) was observed at 220 nm, consistent with reported values (Fig. 5.2). This wavelength was therefore selected for all subsequent analytical studies. A series of standard solutions was prepared within the concentration range of 10–60 µg/mL. The calibration curve demonstrated excellent linearity over the studied range, with a correlation coefficient (R^2) of 0.9974 (**Table 3, Fig. 2**).

Table 3: Calibration curve data of Baclofen in PBS in PH 7.4 at 220 nm.

Concentration (µg/ml)	Absorbance
10	0.134
20	0.287
30	0.421
40	0.587
50	0.78
60	0.921

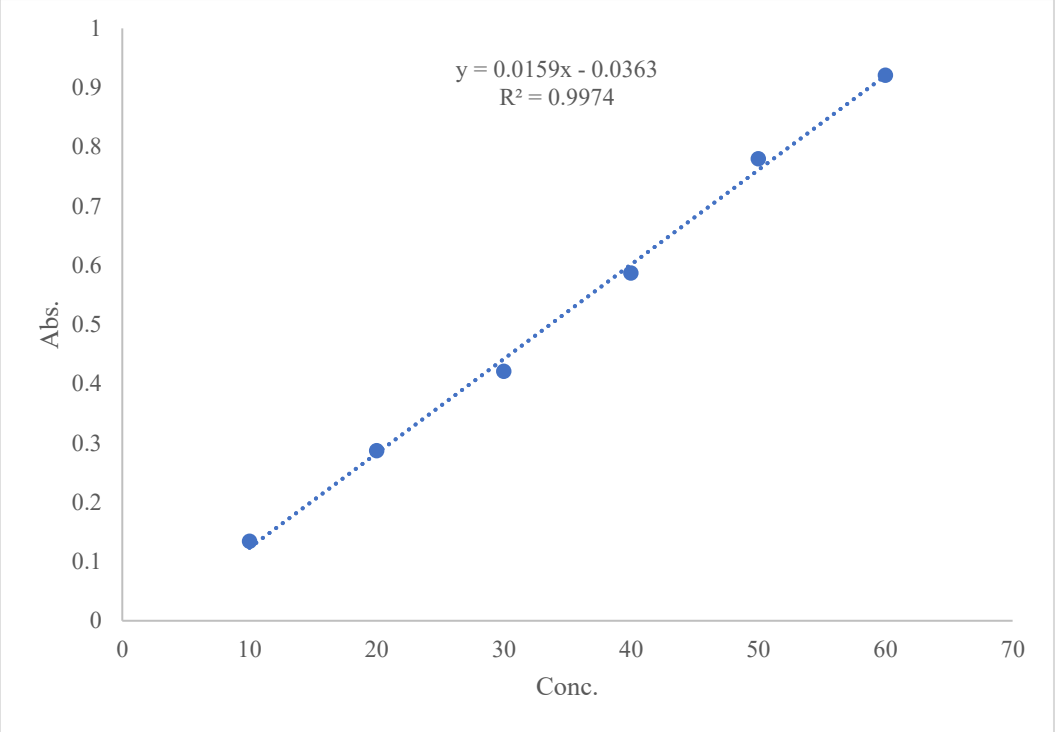

Fig. 2: Linearity curve of Baclofen in 0.1 N HCl at 220 nm.

3.1.5. FT-IR spectrum of Baclofen

The IR spectrum of pure Baclofen, where major absorption peaks corresponding to its functional groups are observed at 1100 cm^{-1} (C–Cl stretching), 1530 cm^{-1} (C=O vibrations of the carboxyl group), and 1610 cm^{-1} (N–H bending of the primary amine). The IR spectrum of the combination formulation, in which these characteristic peaks of Baclofen are retained. The persistence of these bands confirms that no significant chemical interaction occurred between Baclofen and the excipients, thereby establishing the drug's compatibility with the formulation components**.**

3.2 Characterization of Baclofen floating *in situ* gel

3.2.1 Clarity

The Formulation (F1 to F9) baclofen-loaded in situ gel formulations were white.

3.2.2 pH

The pH of Baclofen floating in situ gel formulations is around the F1-F9 range, 1.2–1.5, which corresponds to the acidic environment of simulated gastric fluid, indicating that the formulations were suitable and better**.**

3.2.3 Gelling Time

The gelling time of the prepared formulation is detailed in **Table 4** and **Fig. 3.**

Table 5.5. Results of the gelling time of the F1 to F9 formulation.

Formulation	Results (Sec)
F1	60±0.56
F2	67±0.45
F3	70±0.54
F4	55±0.13
F5	69±0.60
F6	78±0.34
F7	70±0.43
F8	74±0.38
F9	80±0.58

(Mean n=3)

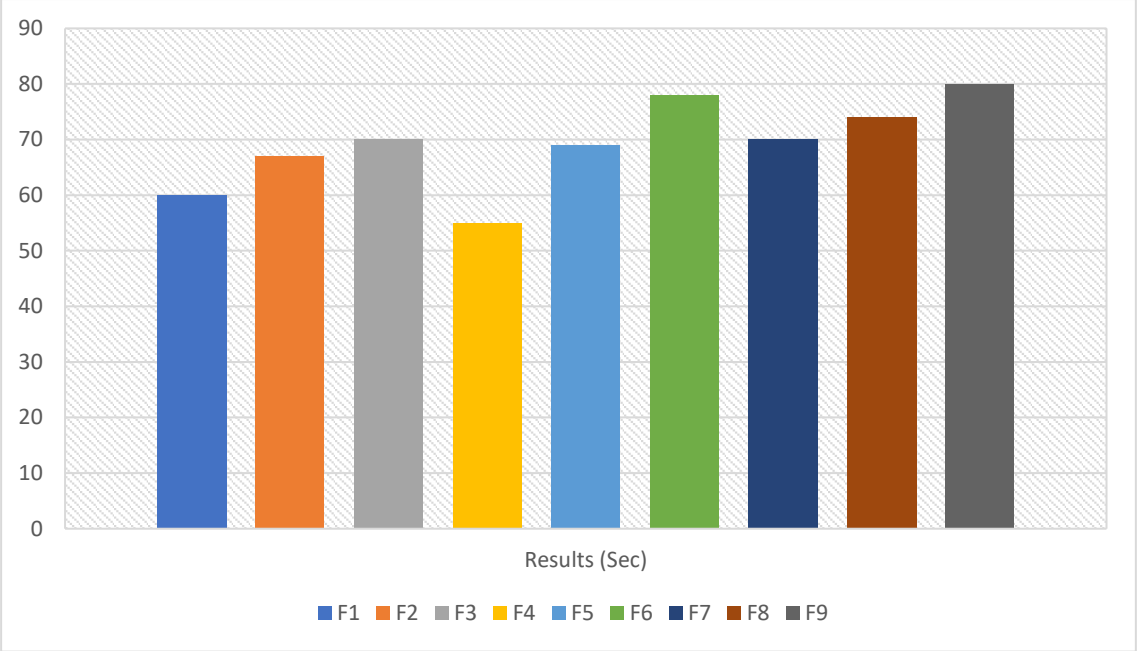

Fig. 3: Graph represents the gelling time of the F1 to F9 formulation.

3.2.4 Viscosity

The viscosity values of the in-situ gel formulations are presented in **Table 5 and Fig. 4,** highlighting the influence of both the polymer and calcium carbonate concentrations. The results indicate that calcium carbonate concentration exerted a pronounced effect on viscosity. An increase in calcium carbonate levels consistently led to higher viscosity across all polymer concentrations studied.

Table 5.6 Results of the viscosity of the F1 to F9 formulation.

Formulation	Results
F1	150± 6.2
F2	258± 3.5
F3	322 ± 9.5
F4	160± 7.5
F5	148± 5.5
F6	343 ± 11
F7	282± 7
F8	252± 10
F9	357 ± 7.3

(Mean n=3)

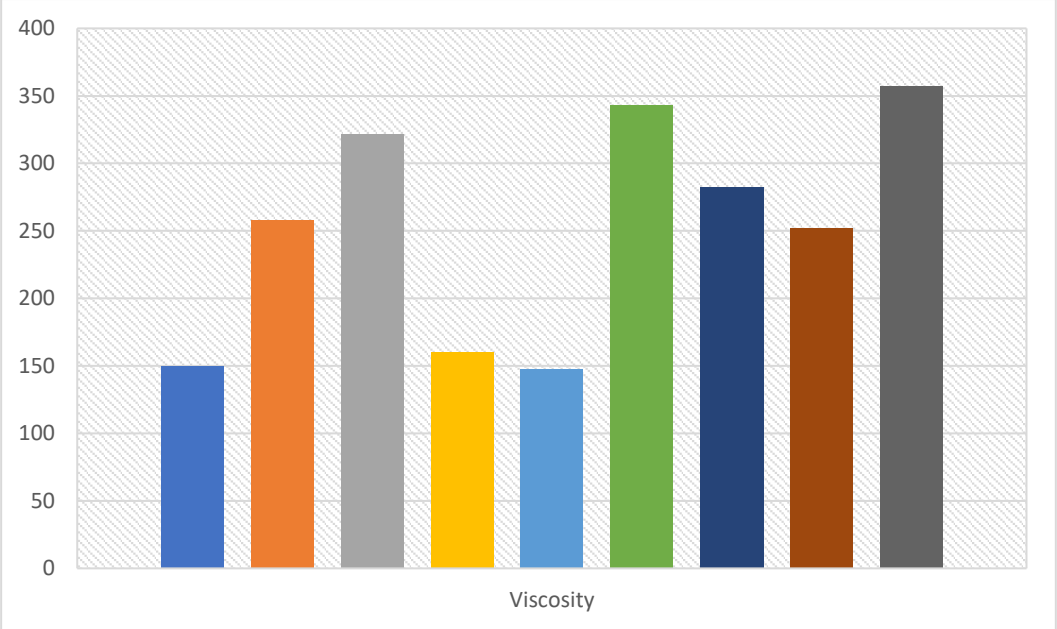

Fig. 4: Graph represents the viscosity of the F1 to F9 formulation.

3.2.4 Drug content

The drug content of the prepared formulations F1-F9 was found to be 98.18±1.0 %.

3.2.5 In-vitro buoyancy

All formulations were tested for floating behaviour in simulated gastric fluid by measuring floating lag time and duration of buoyancy **(Table 6).**

Table 6. Results of *in-vitro* buoyancy of F1 to F9 formulation.

Formulation	Floating time (h)	Floating lag time (sec.)
F1	12	80
F2	12	62
F3	12	81
F4	12	60
F5	12	53
F6	12	82
F7	12	51
F8	12	63
F9	12	50

5.2.6 In-vitro drug release

Among all the formulations, F7 was selected as the optimized formulation based on its acceptable gelling time, optimal viscosity to ensure ease of administration, minimum floating lag time, prolonged buoyancy of 12 h, and uniform drug content. These characteristics indicate that formulation F7 possesses the most desirable properties for a floating in situ gel system intended for gastric retention. The optimized F7 in-situ gel of drug released at different time intervals was depicted in **Fig. 5.** The *in-vitro* drug release profile data for the Baclofen-floated in-situ gel are presented in **Table 7.** Analysis of the in vitro release data revealed that the *in-situ* gel formulation exhibited the highest drug release, with 96.24 ± 0.132% at 24 hours.

3.3 *In-vitro* drug release kinetics studies

The drug release rate was determined from the slope of the respective plots, and the coefficient of determination (R^2) was calculated for each kinetic model. The release kinetics data for optimized (F7) Baclofen in the floating in situ gel formulation (**Table 8**; **Fig. 6–9)** revealed that the Korsmeyer–Peppas model provided the best fit, as indicated by the highest R^2 value. This finding was further supported by cumulative drug release-time plots, which showed R^2 values approaching 0.993, confirming the suitability of the Peppas model for describing the release mechanism.

Table 7: *In-vitro* drug diffusion study of Optimized formulation of (F7) baclofen loaded *in situ* gel membrane.

Sr No.	Time (hours)	%CDR
1.	0	0 ± 0.000
2.	0.25	3.03 ± 0.039
3.	0.5	5.35 ± 0.011
4.	1	8.21 ± 0.023
5.	2	15.78 ± 0.034
6.	4	35.17 ± 0.310
7.	6	47.5 ± 0.324
8.	8	67.12 ± 0.412
9.	12	86.09 ± 0.124
10.	16	92.65 ± 0.156
11.	24	96.24 ± 0.132

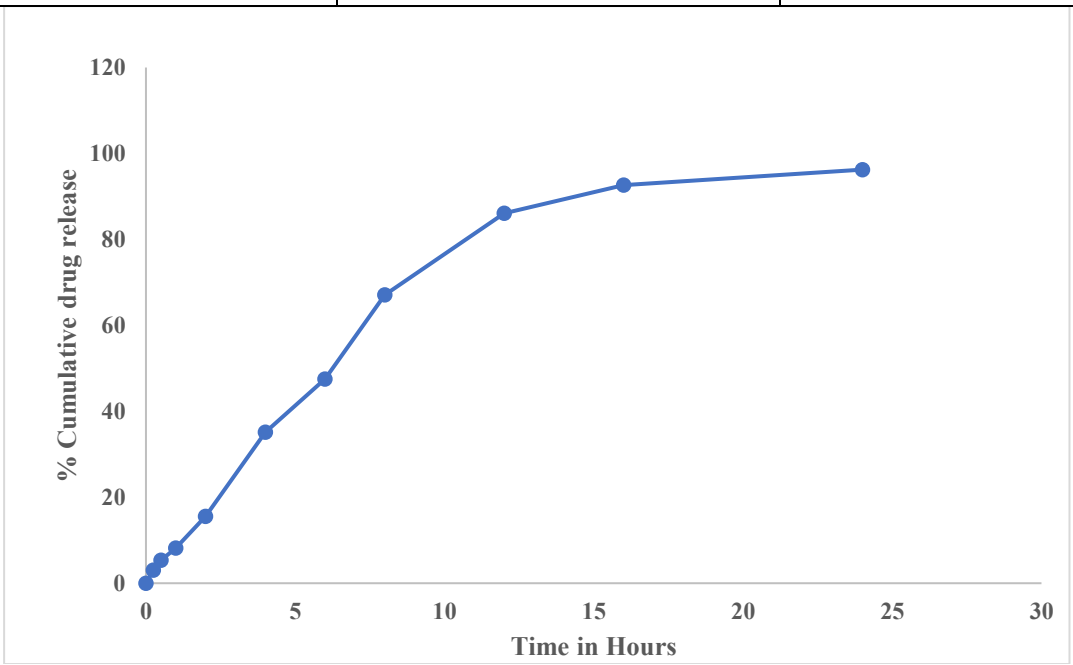

Fig. 5: Cumulative percent release of Baclofen from *in situ* gel.

Table 8: Model fitting to analyse the kinetics of drug release of the optimized in-situ gel.

Formulation	**Zero Order (R^2)**	**First Order (R^2)**	**Higuchi's (R^2)**	**Peppa's (R^2)**	**Best fitted model**
Baclofen in situ gel	0.9607	0.9837	0.98	0.993	Peppa's model

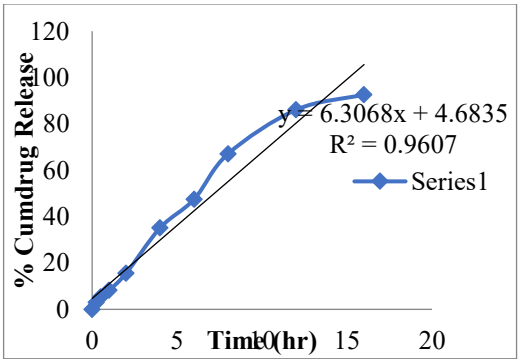

Fig. 6: Zero order plot for release kinetics of Baclofen from *in situ* gel.

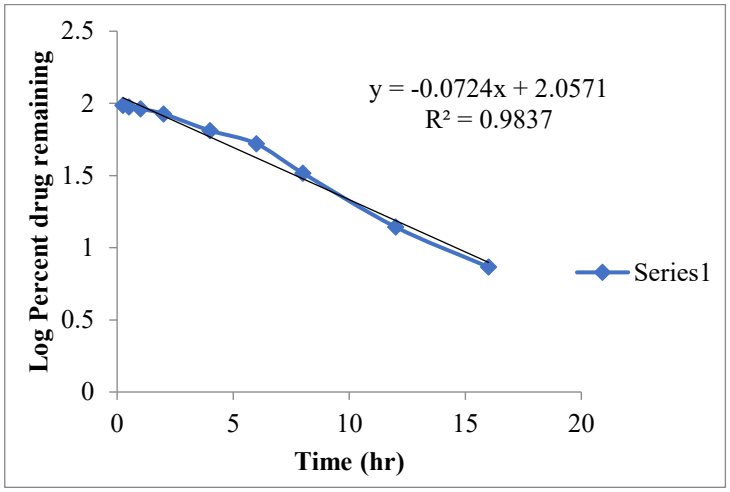

Fig. 7: First order plot for release kinetics of Baclofen from *in situ* gel.

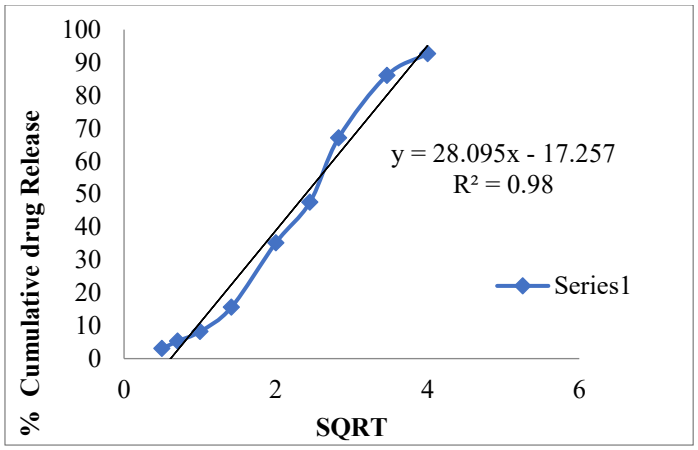

Fig. 8: Higuchi plot for release kinetics of Baclofen from *in situ* gel

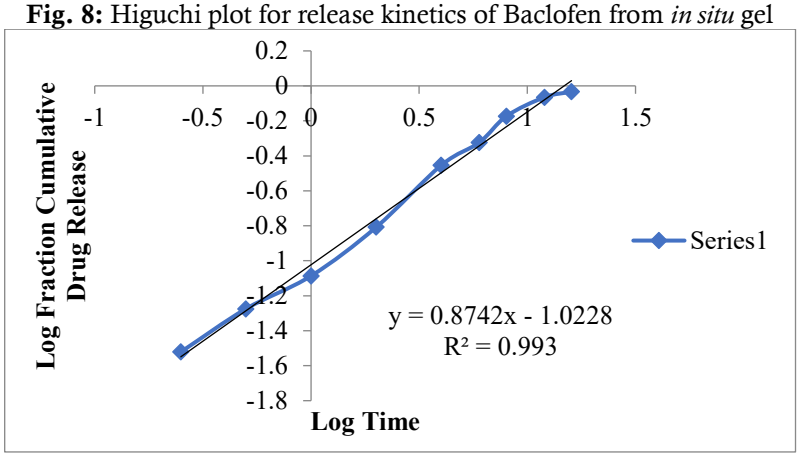

Fig. 9: Peppa's plot for release Baclofen from *in situ* gel.

CONCLUSION

The present study successfully developed a floating in situ gel of baclofen for gastroretentive drug delivery using sodium alginate as the primary polymer. All formulated batches demonstrated satisfactory physicochemical properties, including suitable gastric pH (1.2–1.5), rapid gelation (55–80 s), acceptable viscosity (148–357 cps), and high drug content uniformity (98.18 ± 1.0%). In vitro buoyancy studies confirmed prolonged floating behavior for up to 12 h with floating lag times ranging from 50 to 82 s. Among the evaluated formulations, F7 was identified as the optimized formulation due to its optimal gelling time (70 ± 0.43 s), balanced viscosity (282 ± 7 cps), minimal floating lag time (51 s), and consistent buoyancy for 12 h. The optimized formulation provided sustained, controlled drug release, achieving 96.24 ± 0.132% cumulative release over 24 h. Drug release kinetics followed the Korsmeyer–Peppas model with a high correlation

coefficient (R^2 = 0.993), indicating a diffusion-controlled release mechanism. These findings suggest that the developed floating in situ baclofen gel has strong potential to enhance gastric residence time, improve therapeutic efficacy, and reduce dosing frequency in the treatment of gastroesophageal reflux disease.

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