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Formulation and Evaluation of Floating Oral *In Situ* Gel of Empagliflozin

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Abstract: The objective of the study was to develop the floating *in situ* gel of Empagliflozin for the management of Type 2 diabetes mellitus. The preformulation studies were carried out. FTIR analysis results revealed that there was no chemical interaction between the drug and the polymers. The *in situ* gel of the Empagliflozin formulations were fabricated by using various concentrations of sodium alginate as a biodegradable polymer, HPMC, and calcium carbonate as a cross-linking agent along with other supportive excipients. Totally 7 formulations were prepared and were evaluated for pH, viscocity, *in vitro* buoyancy, and *in vitro* drug release. All the results obtained were good and reliable. From the results of drug content and % CDR, formulation (F7) was selected and optimized. The *in vitro* data obtained from formulation 7 (F7) was fitted with various release kinetics which follow the zero-order kinetics, The Korsmeyerpeppas equation showed the n value between 0.45-0.85 indicating that the formulation followed a non-fiction diffusion release mechanism. The stability study results showed that there was no marked change in drug content and % CDR, during the stability studies. However, it was concluded that the gastro retentive *in situ* gel system prolonged the gastric residence time and targeted size-specific drug release at upper GIT. The results of the study ensure that the fabricated *in situ* gel of Empagliflozin is of promising use for the management of type 2 diabetes mellitus and thus an alternative drug delivery to conventional drug delivery and enhances patient compliance and improves bioavailability.

Keywords: Oral *in situ* gel, Gastroretentive, Empagliflozin, Diabetes mellitus

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Introduction

Oral drug administration remains the preferred route for a majority of clinical applications due to its convenience and patient compliance (Remya *et al*., 2007). *In situ* gel forming systems have garnered significant attention as effective vehicles for controlled drug delivery (Chaturvedi and Manigauha, 2022). These systems are designed to transition from a liquid drug-polymer formulation to a gel state at the targeted site, facilitating drug retention and enhanced bioavailability (Shetty and

Sheeba, 2024). The gel formed by *in situ* gelling systems is lighter than gastric fluids, allowing it to float on top of the stomach contents (Baghwan *et al*., 2021). This buoyancy effect leads to gastric retention of the dosage form and increases gastric residence time, thereby enabling prolonged drug delivery within the gastrointestinal tract (Patel *et al*., 2012).

Empagliflozin is a widely used anti-diabetic medication belonging to the class of sodium-glucose co-transporter 2 (SGLT2) inhibitors. It acts by inhibiting SGLT2 in the proximal tubules of the kidneys, thereby reducing the reabsorption of glucose and promoting its excretion in the urine (Framptonf 2018). Empagliflozin has unique pharmacological properties. It functions as a competitive antagonist of SGLT2, exerting its effects primarily in the renal tubules. Empagliflozin's selectivity for SGLT2 leads to decreased glucose reabsorption, resulting in improved glycaemic control in patients with type 2 diabetes mellitus (Dwivedi and Darwhekar, 2019).

Empagliflozin has a relatively short elimination half-life, typically around 12 to 14 h. Its efficacy is dose-dependent, with recommended doses ranging from 10 to 25 mg once daily. Unlike some medications, Empagliflozin's oral absorption is not significantly affected by food (Anas *et al*., 2021).

Based on these reasons, in this study Empagliflozin is formulated as *in situ* gel, a new controlled-release system for the management of type 2 diabetes mellitus.

Materials and Methods

Materials

Empagliflozin was obtained as a gift sample from Teva API India Pvt. Ltd. The other chemicals and ingredients were used in analytical grade.

Drug excipient compatibility studies:

FTIR spectroscopy was conducted employing a Shimadzu FTIR 8400 Spectrophotometer within the range of 4000 to 400 cm^{-1}, and the resulting spectrum was documented (Chatwal and Anand, 2014).

Preparation of calibration curve for Empagliflozin:

A standard solution for Empagliflozin was prepared by dissolving precisely 100 mg of bulk Empagliflozin in 5 ml of methanol and adjusting the volume with 0.1N HCl. Subsequently, 10 ml of the stock solution was pipetted into a separate 100 ml standard flask, and the volume was adjusted with 0.1N HCl. Sequentially, aliquots of 2, 4, 6, 8, and 10 µg/ml were pipetted from the resulting solution into separate 100 ml standard flasks, and each was made up to volume using 0.1N HCl.

Preparation of oral in situ gel of Empagliflozin:

Various concentrations of gelling polymers, sodium alginate, and xanthan gum were dissolved in deionized water with a weighed amount of sodium citrate at 70ºC on a magnetic stirrer. Simultaneously, the Empagliflozin solution was prepared by dissolving it in deionized water. In another container, the required quantity of the release-retardant polymer HPMC K4M was soaked in deionized water until fully dissolved. Subsequently, the solutions of sodium alginate, xanthan gum, Empagliflozin, and HPMC were combined with continuous stirring. After cooling to 40ºC, calcium carbonate, previously dissolved in water, was added, followed by sodium citrate, methyl paraben, and propylparaben, ensuring thorough mixing. The resulting solution was cooled to 40ºC, and water was added to attain the desired consistency before being stirred well and stored in bottles.

Composition of in situ gel formulation:

Seven formulations (F1-F7) were prepared by mixing various ingredients with Empagliflozin (Table 1).

Characterization of in-situ gel:

Visual appearance

Appearance and consistency of formulations were visually noted (Sharmila and Srilakshmi, 2013).

Table 1: Composition of formulation

INGREDIENTS	FI	F2	F3	F4	F5	F6	F7
Empagliflozin (mg)	25	25	25	25	25	25	25
Sodium Alginate (% w/v)	5	5	5	15	15	15	15
Xanthan Gum (% w/v)	25	65	75	40	55	25	50
HPMC (% w/v)	75	25	25	50	35	65	50
Calcium Carbonate (% w/v)	1	1	1	1	1	1	1
Sodium Citrate (% w/v)	2	2	2	2	2	2	2
Methyl Paraben (% w/v)	1	1	1	1	1	1	1
Propyl paraben (% w/v)	1	1	1	1	1	1	1
Deionized water (ml)	qs	qs	qs	Qs	qs	qs	qs

Measurement of pH

The pH determination of the formulations was conducted using a pH meter (Sindhoor *et al*., 2018).

In vitro gelation study

A 10 ml test tube was filled with 5 ml of simulated gastric fluid (0.1N HCl, pH 1.2) and maintained at 37ºC. After that, 1 ml of the formulation was added to the test tube (Zahraa *et al*., 2021).The pipette was directed toward the fluid's surface, and the formulation was gradually released (Singh *et al*., 2019). In contact with the gelation medium, the formulation transformed into a gel-like consistency. The assessment of *in vitro* gelling capacity was based on the gel's stiffness and the duration it retained its gel-like state (Ali *et al*., 2010).

Determination of viscosity

The viscosity of the formulations was assessed using Brookfield's Digital Viscometer (DV-II) (Khan *et al*., 2022).

Measurement of gel strength

10 g of the gel was taken in a 50 ml beaker and a 5 g weight wa splaced on the center of the surface of the gel and allowed to penetrate through the gel (Solunke *et al*., 2020). The time taken by the 5 g weight to penetrate 5 cm down through the gel was noted for all the formulations (Madan *et al*., 2009).

Determination of the drug content

In a 100 ml standard flask, 5 ml of the formulation, equivalent to 50 mg of the drug, was introduced and mixed with 100 ml of 0.1N HCl (pH 1.2), followed by thorough stirring (Rathi *et al*., 2021). Following a 1 h interval, the solution underwent filtration, and the drug concentration was subsequently assessed using a UV-Vis spectro-photometer at 223 nm against an appropriate blank solution (Khan *et al*., 2022).

In vitro buoyancy study

The study was carried out using a USP Type II dissolution apparatus, employing simulated gastric fluid (pH 1.2) as the medium, maintained at 37±0.5°C. Approximately 10 ml of the *in situ* gel formulation was introduced into the medium (Mayur and Niranjan, 2015). The duration for the *in situ* gel formulation to float on the surface of the medium (floating lag time) and the time during which the formulation remained buoyant (duration off loating) were noted (Gopa *et al*., 2022).

In vitro drug release study of the in-situ gel

An *in vitro* dissolution study was conducted using a USP apparatus with 900 ml of 0.1N HCl (pH 1.2) maintaining the temperature at 37ºC. At predetermined time intervals, 10 ml of samples were withdrawn and replaced the sample with

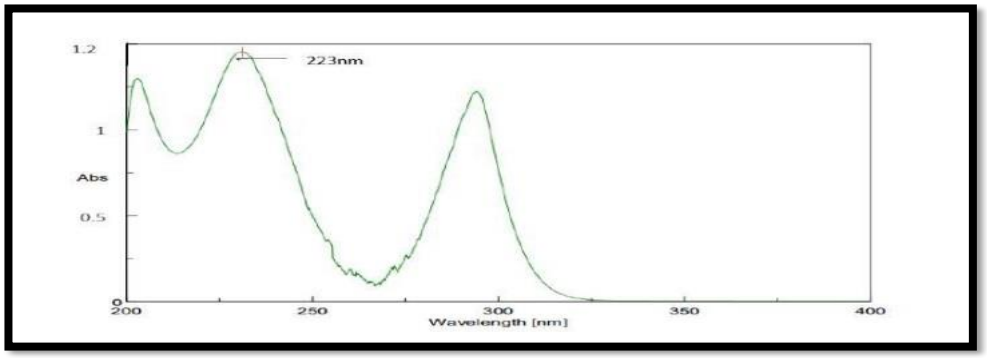


Fig. 1: UV Spectrum of Empagliflozin.

Table 2: Concentration and absorbance values for the calibration curve of Empagliflozin at 223 nm

S. No.	Concentration (µg/ml)	Absorbance at 223 nm
1	2	0.1891
2	4	0.3726
3	6	0.5783
4	8	0.7762
5	10	0.9971

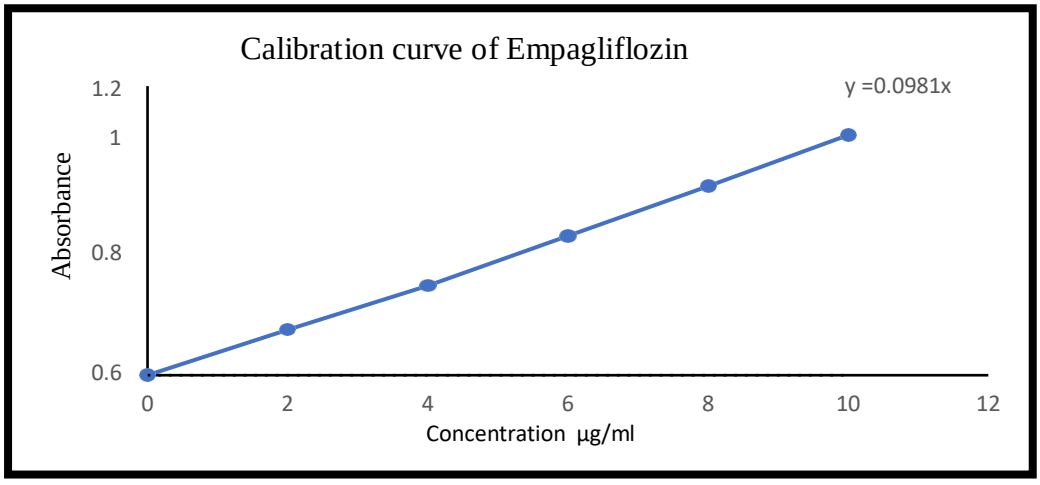


Fig. 2: Calibration curve of Empagliflozin.

fresh dissolution medium and analyzed using a UV spectrophotometer at 223 nm (Prannoy and Lakshmi, 2020).

Release kinetics of the optimized formulation

The optimized formulation (F7) was fitted with various kinetic equations like zero order, first order, Higuchi's, and Korsmeyer-peppas models (Dash *et al*., 2010).

Stability Studies

The optimized formulation (F7) was stored in an amber-colored bottle and the stability study was carried out by ICH guidelines, and was evaluated for visual appearance, drug content, as well as *in vitro* drug release (WHO-GMP, 2003).

Results and Discussion

Preformulation Studies

Construction of the Calibration curve of Empagliflozin

The UV/Vis spectrophotometric method was used to analyze Empagliflozin (Fig. 1). The absorbance of the drug in 0.1N HCl (pH 1.2), was measured at a wave length of 223 nm. The results are given in

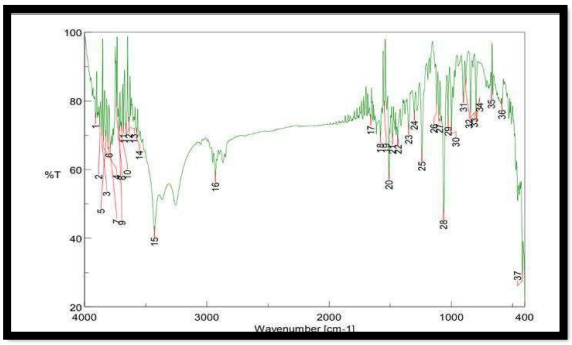


Fig. 3: FTIR spectrum of Empagliflozin.

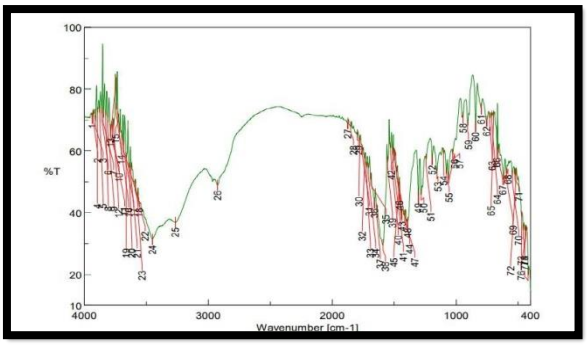


Fig. 4: FTIR spectrum of Optimized formulation.

Table 3: Physical appearance of prepared oral *in situ* gel

S. No.	Formulation code	Appearance	Pourability
1	F1	Dull white	Pourable
2	F2	Dull white	Pourable
3	F3	Dull white	Pourable
4	F4	Dull white	Easily pourable
5	F5	Dull white	Easily pourable
6	F6	Dull white	Pourable
7	F7	Dull white	Easily Pourable

Table 2 and Figure 2. The calibration curves were linear and the correlation coefficient values were 0.999 indicating excellent linearity of data.

Chemical compatibility study:

From the FTIR Figures 3 and 4, various functional groups of pure drug and optimized formulation of Empagliflozin were identified. FTIR spectrum of optimized formulation exhibited characteristics bands at 3567.10 cm^{-1} represents CH_2-OH (str), 1483.34 cm^{-1} (C-H) bending, 673.546 cm^{-1} represents C-Cl (str) and showed that the characteristics peak of Empagliflozin were not altered by the addition of excipients and after formulated into *in-situ* gel. From the spectra it was cleare that there was no interaction between drug and excipients.

Physical appearance of the prepared Empagliflozin in situ gel:

All the formulations are visually inspected for their appearance, clarity and consistency. The results are illustrated in Table 3.

All the prepared formulations were dull white in appearance. The optimized Formulation F7 is easily pourable.

pH of Empagliflozin oral in situ gel:

The pH of all formulations was measured and the results are shown in Table 4.

The pH of all the formulations was within the orally acceptable range (i.e., salivary pH range 6.6. Therefore, it will not cause any irritation on administration of the formulations.

In vitro gelation study of Empagliflozin oral in situ gel:

The gelation study of the all formulations was done in 0.1N HCl (pH1.2) ranging between + and +++ as shown in Table 5.

Viscosity of Empagliflozin oral in situ gel:

The viscosity of all the *in situ* gelling formulations was determined at 50 rpm at 25º C using Brookfield Viscometer. The results of viscosity measurement of all the formulations are shown in Table 6.

In vitro buoyancy of Empagliflozin oral in situ gel:

The results of buoyancy studies are given in

Table 4: pH of prepared oral *in situ g*el

S. No.	Formulation code	pH
1	F1	6.428
2	F2	7.345
3	F3	7.294
4	F4	6.634
5	F5	7.462
6	F6	6.347
7	F7	6.875

Table 5: Gelling capacity of formulated *in situ* gel

S. No.	Formulation Code	Gelling capacity
1	F1	+++
2	F2	+
3	F3	+++
4	F4	++
5	F5	+++
6	F6	+++
7	F7	+++

(+)-- Gelation in a few seconds, disperses rapidly; (++)-- Gelation immediately, remains for 12 h; (+++) – Gelation after a few minutes, remains for more than 12 h.

Table 6: Viscosity of formulated *in situ* gel

S. No.	Formulation code	Viscosity (Centipoise)
1	F1	184.1
2	F2	166.41
3	F3	104.13
4	F4	168.11
5	F5	233.13
6	F6	201.44
7	F7	239.61

Table 7: *In vitro* buoyancy of formulated *in situ* gel

S. No.	Formulation code	Floating Lagtime (min)	Floating duration (h)
1	F1	<1	>12
2	F2	<1	>12
3	F3	<1	>12
4	F4	<1	>12
5	F5	<1	>12
6	F6	<1	>12
7	F7	<1	>12

Fig. 5: *In vitro* buoyancy of Empagliflozin *in situ* gel.

Table 8: Density of formulated *in situ* gel

S. No.	Formulation code	Density of oral *in situ* gel (g/cm^3)
1	F1	0.631
2	F2	0.647
3	F3	0.593
4	F4	0.621
5	F5	0.688
6	F6	0.704
7	F7	0.753

Table 9: Gel strength of formulated *in situ* gel

S. No.	Formulation code	Average gel strength (sec)
1	F1	27.3
2	F2	17.6
3	F3	15.7
4	F4	20.4
5	F5	35.8
6	F6	32.3
7	F7	40.9

Table 7.

Density of Empagliflozin oral In situ gel:

Density of *in situ* gel is important evaluation parameter for buoyancy ability of the gastro-retentive dosage form and it should have a density less than or equal to that of the gastric contents. The density of all the formulations are less than that of the gastric fluid (~1.004 gcm¯3) (Table 8).

Measurement of gel strength of Empagliflozin oral in situ gel:

All the formulations showed good gel strength (Table 9). When the gel strength is more, the formulation may retain its consistency for a prolonged period of time. Thus the release of the drug is also prolonged.

Percentage water uptake by Empagliflozin oral in situ gel:

The percentage water uptake of all the formulations are given in Table 10**.**

Drug content of Empagliflozin oral in situ gel:

The percentage drug content of the formulations are given in Table 11.

In vitro dissolution study of Empagliflozin oral in situ gel:

The results of *in vitro* drug release study of the *in situ* gel formulations are given in Figure 6.

From the *in vitro* drug release studies of the *in situ* gel formulations, it was observed that the formulation F7 containing the combination of both the polymers in equal concentration (Xanthan

Table 10: Percentage water uptake of *in situ* gel formulations

Time (min)	Percentage Water Uptake by the Formulation						
	F1	F2	F3	F4	F5	F6	F7
30	4.36	2.25	2.94	5.73	5.86	4.79	6.45
60	6.79	6.71	6.68	8.92	8.47	13.26	11.93
90	9.23	9.93	9.43	9.74	10.94	14.58	16.82
120	14.38	12.91	14.26	14.23	13.56	21.67	26.42

Table 11: Percentage drug content of formulated *in situ* gel

S. No.	Formulation code	Drug content
1	F1	90.30
2	F2	92.45
3	F3	95.65
4	F4	89.34
5	F5	94.87
6	F6	97.31
7	F7	98.26

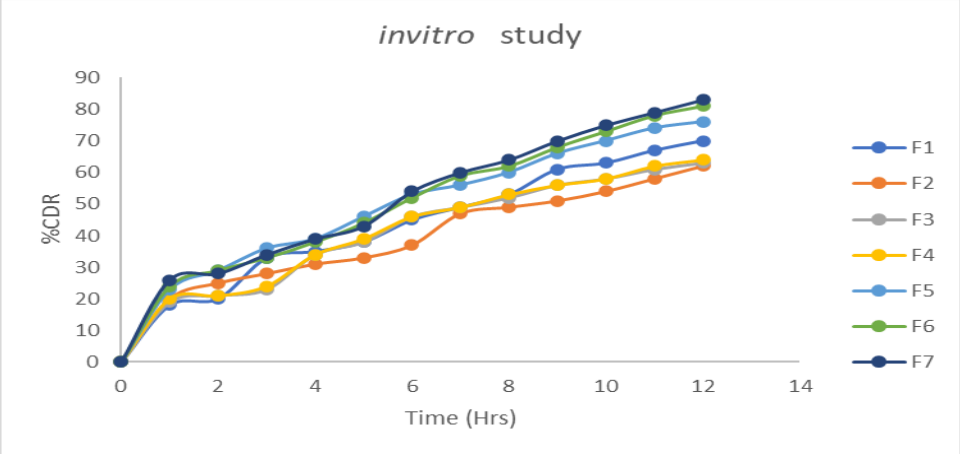


Fig. 6: *In vitro* drug release study of *in situ* gel formulations (F1–F7) of Empagliflozin.

gum and HPMC) provided prolonged release of the drug up to12 h. Formulation F7 containing both Xanthan gum (50%w/v) and HPMC (50%w/v) showed 83.54% of drug release at the end of 12 h.

The release data of the optimized formulation was fitted with various kinetic equations. From the graphical representation it can be understood that is best in zero order kinetics which has shown are gression coefficient (R^2=0.951) and Higuchi model (R^2=0.823), Peppas equation was used to analyze the release pattern of the drug from the polymeric system. The value of "n" was found to be 0.45 < n < 0.89, indicating the drug release follows non-fickian diffusion.

Stability Studies:

The optimized formulations (F7) was subjected to stability study as per ICH guidelines and the results are given in Table 12.

The results revealed that there is no significant change during stability testing for physical appearance, gelling capacity, floating duration,

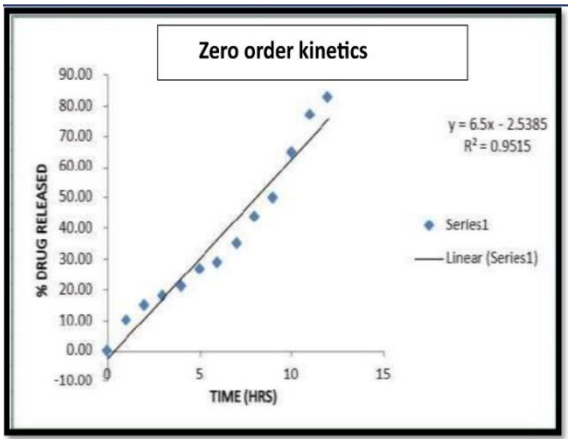


Fig. 7: Zero order kinetics of optimized formulation (F7).

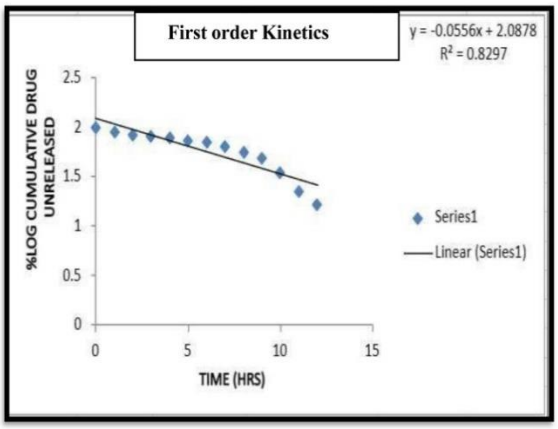
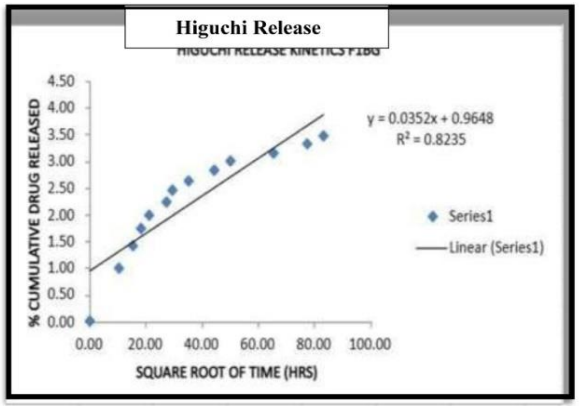


Fig. 8 :First order kinetics of optimized formulation (F7).



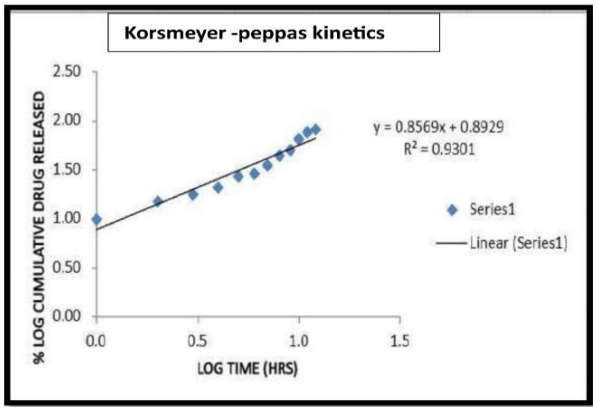


Fig. 9: Higuchi release kinetics of optimized formulation (F7). Fig. 10: Korsmeyer kinetics of optimized formulation (F7).

Table 12: Stability study of Empagliflozin (F7) *in situ* gel formulation

Parameter	Before stability testing	Duration of the study		
		Day 30	Day 60	Day 90
Physical appearance	Dull white	Dull white	Dull white	Dull white
Gelling capacity	+++	+++	+++	+++
Floating duration (h)	>12	>12	>12	>12
Drug content (%)	98.26	97.54	97.36	96.21
% CDR	83.54	81.96	80.21	79.98

% drug content and % CDR.

Conclusion

From the study, it was concluded that the formulation of Empagliflozin as oral floating in situ gel provides a controlled release of the drug. This may improve patient compliance due to ease of administration and reduction in dosing frequency. Hence, the developed formulation can be used as an alternative to the conventional dosage form for the management of type 2 diabetes mellitus.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

Author Contributions

Each author has contributed equally in designing

the research, conducting thorough analysis, drafting the manuscript, and refining its content. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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