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Original Article

Design and Development of Deflazacort pH Transition Injectable *in-situ* Implant for Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis is a chronic inflammatory disorder causing painful swelling and damaging various body systems. Deflazacort is a drug of choice for treatment, but it exhibits lower mineral corticoid activity and lower bioavailability when administered orally. The novel formulation is required to achieve a successful release rate in a well-controlled manner and facilitate the drug's uptake. **Materials and Methods:** The *in situ* injectable implants are developed as a solution using a cold technique and the ingredients carbopol 934P, hydroxypropyl methyl cellulose K4M, and hydroxypropyl methyl cellulose K15M were utilized. When exposed to external stimuli, like as pH, the solution begins to shift into a gel state. The developed formulations was subjected to pH, rheology, drug content, gelling ability, *in vitro* permeability, and release kinetics studies. **Results:** Among all the batch formulations, F14, F17, and F18 exhibited good gelling properties and optimum viscosity. *In vitro* permeation studies of F14 showed drug release of 95.45% in 24 hr. Further, the drug diffusion data of F14 revealed that it followed the Higuchi model, which suggests that the drug release occurred followed Non-Fickian diffusion kinetics which is ideal for injectable *in situ* implant formulations. **Conclusion:** The present study concluded that deflazacort injectable *in situ* implant formulations inhibit the initial burst release and sustain the drug delivery for 24 hr when administered intramuscularly or subcutaneously.

Keywords: Anti-inflammatory drugs, Sustained drug delivery, Gel- sol transition, pH, Sustained release.

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INTRODUCTION

Deflazacort is a synthetic oxazoline derivative of prednisolone, used in treating diseases such as rheumatoid arthritis because of its anti-inflammatory and immunosuppressive properties.[1] USFDA approved deflazacort in 2017 to treat patients suffering Duchenne Muscular Dystrophy (DMD) who are at least 2 years old. They exhibit suboptimal concentration when administered orally, resulting in lower mineral corticoid activity in the body, ensuring low bioavailability.[2] Two drawbacks concerned to these drugs are, low bioavailability attributed to the limited dissolution and the shorter drug's in-body retention time. Another drawback include, dosing of drug when targeted to benign chronic diseases.

However, some patients consistently show treatment and support followed by resistance to follow-up therapies, which led to recurrence.[3] Hence, maintaining the therapeutic level in plasma is unfeasible, resulting in repeated drug administration. Therefore, A novel formulation is required to achieve a successful release rate in a well-controlled manner and facilitate the drug's uptake. The present work utilizes carbopol as a pH-triggered *in situ* gel-forming polymer to deliver deflazacort intramuscular or subcutaneously. A polyacrylic acid polymer called carbopol that has a carboxylic acid group, will exhibit an ionized state in alkaline pH. A conformational shift and a reduction in the polymer's solubility result from the electrostatically repelling interaction between polymer chains. Due to the irritant effect of acidic carbopol solution, it was combined with HPMC, a viscosity-inducing agent, which improves the consistency of a gel and also increases the pH of the formulation, thereby reducing the concentration of carbopol in *in-situ* gelling systems. Overall, carbopol has the ability to be an efficient pH-dependent *in-situ* depot-forming gel and bears the property like good solubility, chemical compatibility, biocompatibility, and stability. Most importantly, the initial burst of drug release was eliminated.[4] This study aimed to develop injectable *in-situ* implants of deflazacort,

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causing the drug release for 12 hr or longer when administered intramuscularly or subcutaneously.

MATERIALS AND METHODS

Drug Deflazacort was purchased from Athene Chemicals, Ahmedabad (India), Carbopol 940 was purchased from Balaji Chemicals, Ankleshwar, Gujarat, Hydroxy Propyl Methyl Cellulose Balaji Chemicals, Ankleshwar, Gujarat. The part of the chemicals and solvents were all procured from local vendors and were of analytical quality. UV–visible spectra were recorded on Shimadzu UV spectrophotometer.

Preformulation Studies

Saturated shake-flask Solubility Studies

This study was carried out using various solvents such as phosphate buffer solution pH 7.4, pH 7.0, water, N-methyl 2-pyrrolidone, and ethanol. Here excess quantity of the drug taken in a conical flask is made to dissolve in a fixed volume(10ml) of solvents until the formation of a saturated solution. The saturated solution is then shaken for 24 hr with an orbital Shaker at 50 rpm. The temperature was held at 37 ±0.5°C through the whole of the study period until steady state is reached. After the stated time, the solution is filtered using Whatman paper 41mm followed by suitable dilution of filtrate. A small amount of aliquot is analyzed using UV Visible spectrophotometer (UV–1601PC, Shimadzu Corporation, Japan) at 243nm.[5,6]

Fourier Transform Infrared Spectroscopy studies

Using an FTIR spectrophotometer (Agilent Cary 630), the infrared (IR) spectra were collected in the 400–4000 cm^{-1} range of frequency using the KBr pellet technique. To examine if the drug is compatible with excipients, the spectra of deflazacort in its pure form and those of physical mixture comprising *in situ* implants were compared.[5]

Development of Deflazacort *in-situ* Implants

Method of preparation of implants

In situ gelling solution containing deflazacort was prepared using the cold method. The composition of the formulation is shown in Table 2. Accurately weighed Carbopol 940 was transferred into a beaker containing N-Methyl 2-Pyrrolidone solution and stirred using a vortex stirrer. The resultant solution is placed overnight for hydration. To the above mixture, HPMC K4M and HPMC K15M solutions are added with continuous stirring until it forms a clear solution. Deflazacort is then dissolved in the required amount of ethanol, followed by the addition of remaining additives. The preparation was stirred until a clear solution was obtained.[7,8]

Evaluation of Deflazacort containing *in situ* Injectable Implant

The prepared formulations with varying concentrations of polymer were investigated for pH, gelling time, viscosity, *in vitro* permeation studies, release kinetics, and stability studies.

pH and Physical Characteristics

The physical appearance of all the formulations was visually inspected to check their clarity. The pH determination was made using a digital pH meter (Lab Matrix).[7]

Determination of *in-vitro* Gelling time

The ability to gel *in vitro* of prepared formulations was measured by injecting 1ml of the formulation into 5ml of the phosphate buffer 7.4 contained in a glass test tube. The temperature of phosphate buffer 7.4 is maintained at 37±1°C depicting the body temperature. The solution turns to gel form. The rate at which the gel is formed and the extent of gelling capacity is observed and graded.[8]

Determination of formulation viscosity both at the solution and gel state

The rheological properties of the *in situ* injectable implant, both in solution and in the gel were determined using the Brookfield Viscometer model (Remi Electrotechnics) at 100 rpm utilizing a spindle number 62. Viscosity determination started with a liquid solution at 25°C further, placing it in a water bath maintained at 37±1°C, the solution slowly starts gelling. Later viscosity of the *in-situ* gel is determined.[9]

Estimation of drug content

The stock solution was prepared by weighing *in situ* gelling solution equivalent to 1mg of deflazacort in ethanolic phosphate buffer in a standard volumetric flask. Then, 1ml was subsequently diluted with PBS (pH 7.4) to 100ml. Spectrophotometric analysis was applied to determine the absorbance at 243 nm and reported in Table 4.

In vitro permeation study

Using a modified Franz diffusion cell with a 60 ml capacity, an *in-vitro* drug release study was carried out. An artificial

Table 1: Saturated solubility studies of drug luliconazole using various solvents.

Sl. No.	Solvents	Solubility (mg/ml)
1	Water	0.0175±0.01
2	N-methyl 2- pyrrolidone	10.45±0.03
3	Phosphate buffer 7.0	09.08±0.13
4	Phosphate buffer 7.4	10.36±0.08
5	Ethanol	11.92±0.17

Table 2: Composition of a drug-loaded formulation containing varying concentrations of Carbopol, HPMC KM4, and HPMC K15M.

FC	Deflazacort (mg)	Carbopol 940 (g)	NMP (ml)	HPMC K4M (g)	HPMC K15M(g)	Ethanol(ml)
F1	1	0.1	100	-	-	1
F2	1	0.2	100	-	-	1
F3	1	0.3	100	-	-	1
F4	1	0.4	100	-	-	1
F5	1	0.5	100	-	-	1
F6	1	0.6	100	-	-	1
F7	1	0.7	100	-	-	1
F8	1	0.8	100	-	-	1
F9	1	0.9	100	-	-	1
F10	1	1	100	-	-	1
F11	1	0.5	100	0.5	0.5	1
F12	1	0.5	100	0.5	1	1
F13	1	0.5	100	0.5	1.5	1
F14	1	0.5	100	0.5	2	1
F15	1	0.5	100	1	0.5	1
F16	1	0.5	100	1	1	1
F17	1	0.5	100	1	1.5	1
F18	1	0.5	100	1	2.0	1

Note FC-formulation code, NMP- N-Methyl 2-Pyrrolidone, HPMC- Hydroxypropyl methylcellulose

membrane like cellophane membrane was placed between receptor and donor compartments that acts as a barrier. One gram of *in situ* gel was placed in the donor compartment and thereby brought in contact with the cellophane membrane and the receptor compartment below it was filled with phosphate buffer (pH 7.4). The diffusion cells were maintained at 37°C with magnetic stirring at 100rpm throughout the experiment. One milliliter of aliquots was withdrawn at each periodic interval and to maintain sink condition same amount of fresh phosphate buffer 7.4 (PBS) was replaced. The studies extended for 24hr to get information on sustained release pattern of the formulation. The samples were analyzed using a UV spectrophotometer at a wavelength of 243nm.[8,10]

Release kinetics

Several mathematical models such as Korsmeyer-Peppas, Higuchi, zero-order, and first-order models were used to analyze the drug release kinetics of the final optimized formulations. The best fit model, was obtained by calculating the correlation coefficient (R^2) and root mean square error (RMSE), and the model that has the highest regression coefficient is considered.[8]

Statistical Analysis

Statistical analysis was carried out using two-way Annova and *p*-values less than 0.05 were considered statistically significant.

Stability studies

Optimized formulation was preserved at 40± 2°C and 75 ± 5 % RH for thirty days. At the end of stability studies, the formulation is measured for physical characteristics, pH, gelling capacity, and drug content. The results were compared with the initial pH and physical characteristics, *in vitro* gelling capacity, drug content, and *in vitro* permeation study.[11]

RESULTS

Saturated Solubility Studies

The data for the saturated solubility study is given in Table 2.

Fourier Transform Infrared Spectroscopy

To investigate the possible interaction between drug and polymer FTIR studies were carried out for drug and mixture of drug and polymer. Results were depicted in Figure 1(a),1(b).

FT-IR spectrum of pure drug Deflazacort 2931.60 cm^{-1}(Aliphatic CH_3 C-H stretching), 1658.67cm^{-1} (C=O stretching), 1442.66 cm^{-1} (C=N stretching), and 2871.81cm^{-1} (Aliphatic CH2.C-H stretching). FT-IR spectrum of a final mixture containing deflazacort and other excipients showed characteristic peaks at 2931 cm^{-1} (aliphatic CH_3 C-H stretching), 1651 cm^{-1} (C=O stretching), 1443.72 cm^{-1} (C=N stretching), 1733.37 cm^{-1} (C-O-C stretching). After spectral comparison, it was confirmed that all characteristic peaks of Deflazacort were observed in the

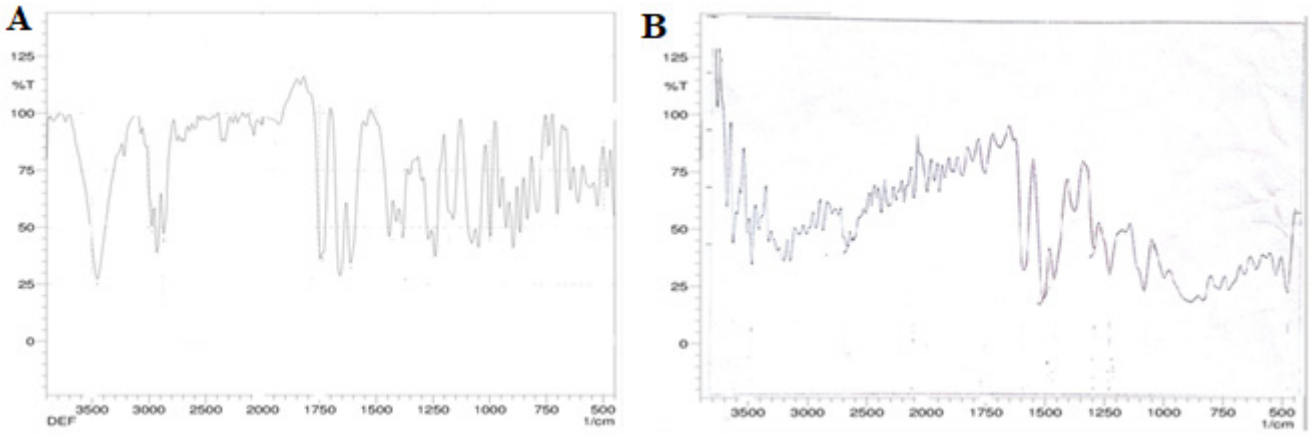

Figure 1: FTIR Spectrum of a) Pure drug Clomphene Citrate b) *In situ* gel final mixture.

physical mixture of the formulation. Neither new peaks nor the elimination of distinctive peaks occurred. This concludes that there is no incompatibility between drugs and other excipients.

Evaluation of Gel

Physical Appearance and pH

The physical appearance of formulations was observed to be transparent and clear. Ideally, the pH of the formulation containing Carbopol is slightly acidic. Therefore, pH of the formulation was found within the range of 6 – 6.8 and was confirmed found to be satisfactory.[12]

In-vitro Gelling capacity

The ability to gel *in vitro* of prepared formulations was evaluated every 6 hr and reported in Table 2. All prepared formulations were able to turn to gel state upon injecting *in vitro* into phosphate buffer 7.4.

Viscosity of the gelling solution and *in situ* implant

Viscosity and the ability to gel *in vitro* are the key rheological properties of gelling dosage forms. At 25°C and 37°C, the viscosity of the gelling solution and the *in-situ* gel were assessed using a Brookefield viscometer. Results are reported in Table 3.

Estimation of drug content

The drug content was analyzed using a UV spectrophotometer, and results were found to be within the permissible limits for each formulation, indicating the preparation's accuracy. The percentage drug content of formulations varies from 93-98%. The drug content of the optimized formulation was reported in Table 4.

In vitro drug permeation study

In vitro permeation study helped to determine the concentration of polymer Carbopol and HPMC K4M and HPMC K15 M that could sustain the drug release from the drug reservoir. From the series of permeation studies (F1-F10) assessed by varying the concentration of Carbopol, the optimum concentration was found to be 0.5%w/v. Further increase in carbopol concentration could not achieve sustainability in drug permeation. Nevertheless, to attain the drug release for 24 hr, rate-controlling polymer HPMC K4M and HPMC K15 M were incorporated. Among the batches only F14, F17 and F18 showed a gelling capacity of up to 24 hr. The drug diffusion from *in-situ* implants was affected by the concentration of different grades of rate-controlling polymer. Batch F14 with polymer ratio 0.5:2 (HPMC K4M: HPMC K15 M) showed a maximum drug diffusion of 95.45% at 24 hr. Formulations F17 and F18 showed a drug release of 92.40% and 90.49% with a polymer ratio of 1:1.5 and 1:2, respectively. The drug diffusion studies, as shown in Figure 2, concluded that all three formulations showed almost complete drug diffusion for 24 hr.[14] The results, which are displayed in Figure 2, revealed statistically significant values ($P< 0.01$) that suggest the injectable implant's *in vitro* release from *in situ* gel was sustained for 24 hr.

The *in vitro* permeation profile of formulation F14, F17, and F18 subjected to release kinetics helped to determine the pattern of drug deliver. The drug deliver information of the above three batches was applied to various models to determine the regression coefficient. The R^2 value of these three batches showed that all batches best fit with the zero-order kinetic model. This is evident from the regression coefficient R^2 given in Table 6. F14 batch with a regression coefficient value of 0.980 in zero-order model was considered to possess the ideal release characteristics.

Release kinetics

The drug diffusion data of the F14 formulation has been found to best fit with the Higuchi model having an R^2 value of 0.980, which confirms that the drug release is occurred by diffusion. This concludes that it is not the drug concentration but the presence of

Table 2: Evaluation of Appearance, pH, gelling capacity.

Formulation code	Appearance	pH	Gelling capacity
F11	Clear	6.2	+++
F12	Clear	6.1	+++
F13	Clear	6.3	+++
F14	Clear	6.3	++++
F15	Clear	6.8	+++
F16	Clear	6.5	++
F17	Clear	6.4	++++
F18	Clear	6.6	++++

+ - immediate gelation and gel remain for 6 hrs.++ - immediate gelation and gel remain for 12 hrs.+++ - immediate gelation and gel remain for 18 hrs.++++ - immediate gelation and gel remain for 24 hrs.

Table 3: Viscosity of optimized formulation both in gelling solution and *in situ* implant.

Formulation code	Viscosity of gelling solution (cps)	Viscosity of *in situ* implant(cps)
F14	148	1455
F17	154	1506
F18	177	469

Table 4: Estimation of drug content of optimized formulation F14, F17, and F18.

Formulation code	Drug content
F14	97.26±0.21
F17	97.04±0.36
F18	96.85±0.41

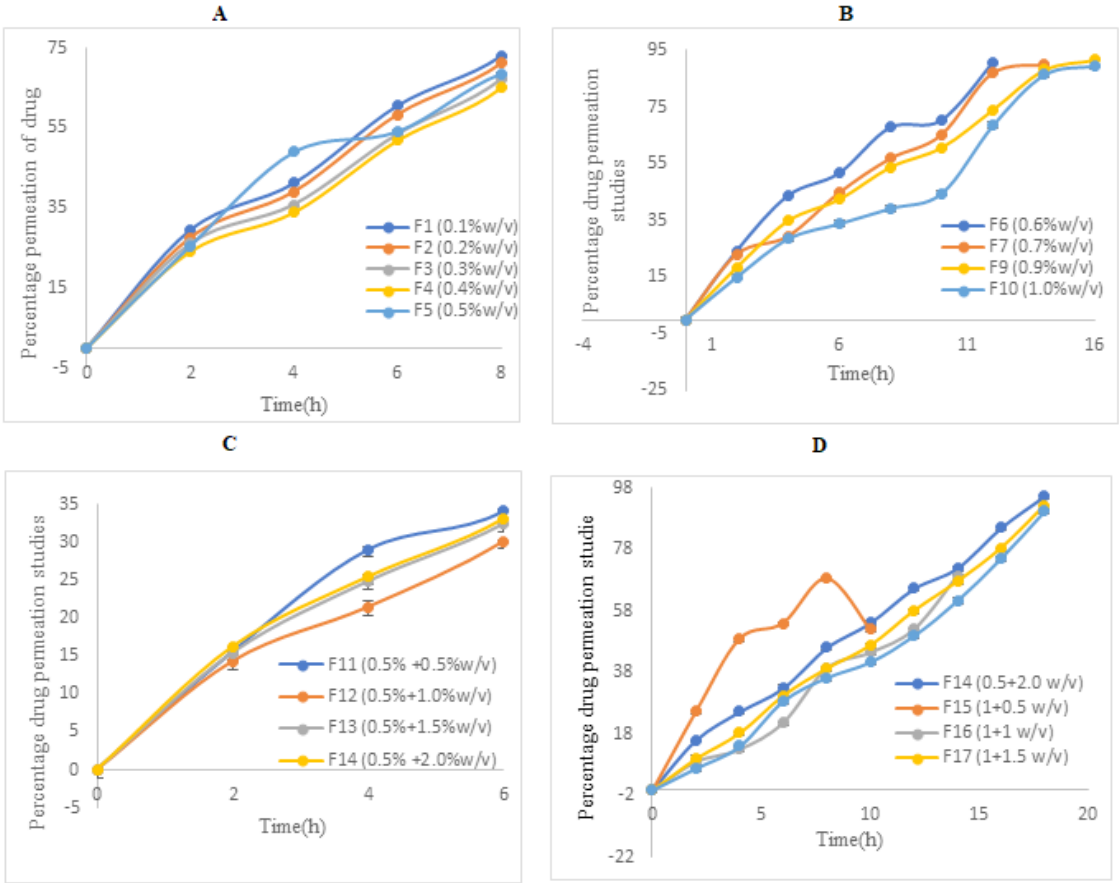

Figure 2: *In vitro* drug permeation studies. A) F1-F5 Carbopo (0.1-0.5%w/v) B) F6-F10 Carbopol (0.1-0.6%w/v) C) F11-F14 Carbopol (0.5%w/v)+HPMC and HPMC KM15 D) F14-F18 Carbopol (0.1-0.5%w/v) +HPMC and HPMC KM15 (*n*=3). The data were statistically evaluated through a one-way analysis of variance an all data represents mean+ standard deviation.

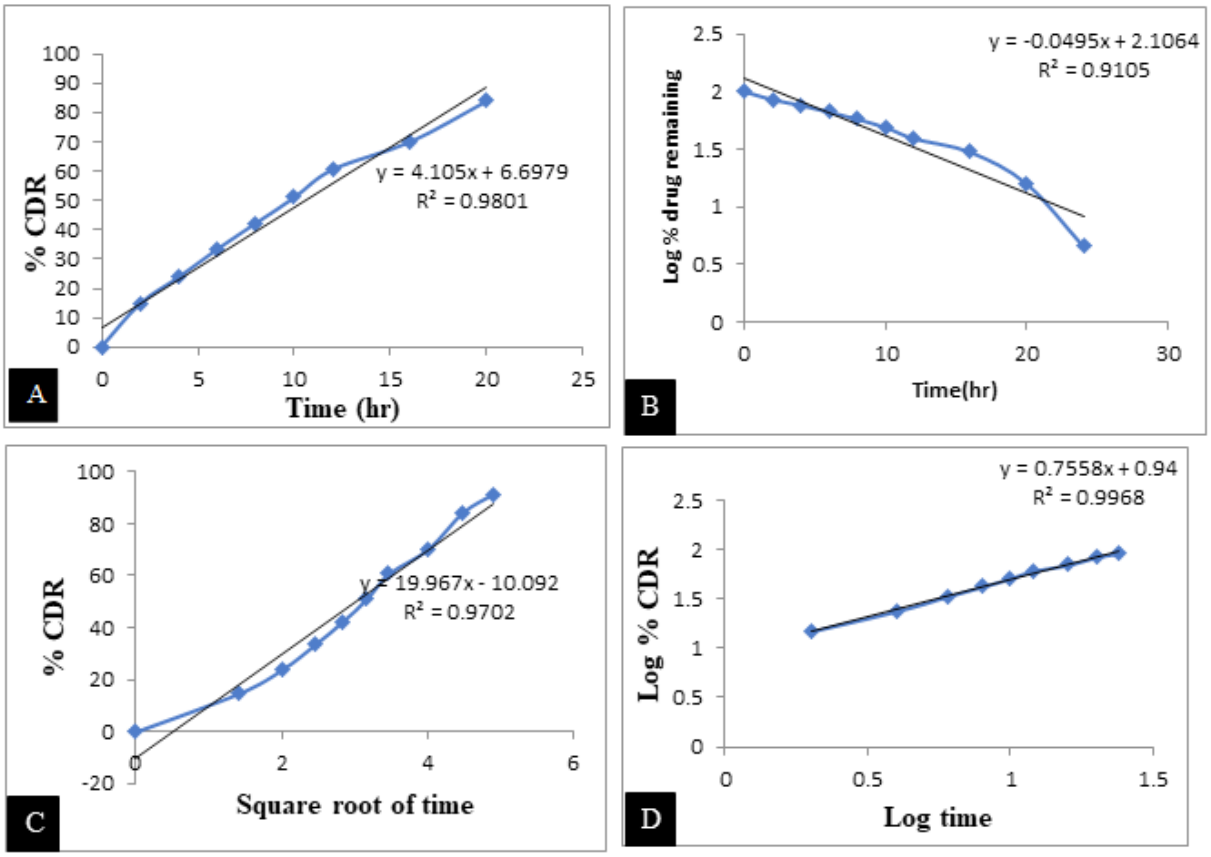

Figure 3: Kinetic relese profile of formation F1 following (FigA) zero order, (Fig C) Higuchi model and (Fig D) Korsmeyer peppas midel.

Table 5: Regression coefficient values.

Formulation	Zero-order, R^2	First-order, R^2
F14	0.980	0.910
F17	0.901	0.874
F18	0.947	0.890

Table 6: Best fit models for drug diffusion studies, optimized formulation F14.

Formulation code	Zero-order R^2	First-order R^2	Higuchi model R^2	Peppas Model $R2$
F14	0.970	0.910	0.980	0.996

excipients like gel-forming polymer and rate-controlling polymer that influences the control drug release.

Stability studies

Accelerated stability tests were conducted on the optimized formulation of F14. as per the ICH guidelines for one month. After the stipulated time, the gel was evaluated for gel properties such as physical characteristics, pH, ability to gel *in vitro*, viscosity, drug content, and *in vitro* drug permeation study**.** The results are reported in Table 7.

Table 7: Stability studies of optimized formulation F14.

Formulation	Physical Appearance	
F14	Initial	After stability
	clear	Clear
	Ph	
	Initial	After stability
	6.3	6.3
	The viscosity of *in-situ* implant(cps)	
	Initial	After stability
	48690	48230
	Gelling capacity	
	Initial	After stability
	++++	++++
	Drug content (%)	
	Initial	After stability
	97.26±0.56	97.18±0.23
	In vitro drug permeation study	
	95.45±0.41	93.38±0.81

The evaluation of formulations after stability charging showed no significant changes concerning the physical characteristics, pH, ability to gel *in vitro*, viscosity, drug content, and *ex vivo* permeation study concerning findings received before stability charging. As a result, it was proven that the formulations met the ICH guidelines' requirements for stability compliance.

DISCUSSION

This study aimed to treat rheumatoid arthritis, a painful swelling, inflammatory disorder using deflazacort as a model drug to treat the disorder. However, the drug is poorly soluble in an aqueous environment limiting its therapeutic effect. Hence preliminary Studies were performed to select the solvents suitable for the drug to make it a clear solution. The study utilized the saturated solubility studies by shake flask method performed by Biju *et al.* (2021), was utilized in the study. From the studies, the solubility of the drug in distilled water (0.0175±0.01) was low, which indicates that the drug remains in the unionized form in water. Solubility in higher pH phosphate buffer was observed to be rate-limited and it was found that the drug underwent decomposition in solution after 6 hrs. According to Ismail *et al.* (2011), the drug solubilizing solvent diffuses out to the external environment from the formulation upon penetration of body fluid into the system resulting in the precipitation of the polymeric network. By considering this finding, the solvent with the same solubility parameter as the drug was chosen. A minimal quantity of ethanol is sufficient for the dissolution of the drug hence less quantities of ethanol are required for formulation, thus reducing the chance of tissue irritation. Another problem in these delivery systems is the use of solvent DMSO and NMP in the preparation of implants, which are highly controversial solvents. Studies revealed extensive toxicity for oral, intraperitoneal, and intravenous administration, but not for subcutaneous or intramuscular use Tang, Y *et al.* (2009).

Carbopol is a macromolecule that ionizes at low pH and tends to lose the protons and gradually precipitates to yield a gel that is hydrated at physiological pH. This formation is due to an increase in pH, the carbopol 934 P remains in a unionized state. This capability is often used to develop effective polymers that gel naturally at physiological pH. Since the *in situ* injectable implant formulation in the present study is pH triggered, analysis of pH forms primary importance and was found to be optimum. Gel state occurs with swelling of carbopol, thereby releasing two protons since carbopol contains carboxylic acid. The prepared formulations F12, F13, F14, F16, F17, and F18, underwent immediate gelation and decreased the burst effect. The experiment was continued using the same formulation wherein the injected solution is observed physically to determine the time required to retain in gel state. Formulations F14, F17, and F18 showed the best results when the concentration of HPMC K5M was amplified from 0.5%w/v to 2%w/v. Hence it was confirmed that as the concentration of polymer HPMC is increased, the gelling strength also increases. More importantly, the volume of ethanol used was negligible that as a capability to reduce the gelling strength.[13] Since F14, F17, and F18 formulation exhibited immediate gelation, the viscosity of the same was determined, also considering it as critical rheological parameters viscosity of solution and gel state was determined. In the solution state, as the concentration of HPMC K5M was increased from 0.5%w/v to 2%w/v, the viscosity was increased. This change was observed because of the increased HPMC KM5 in all consecutive batches, reducing the formulation's drug release. A unique biodegradable implant method for the delivery of medications is represented by injectable implants. Agarwal P *et al.* (2013), suggested that carbopol alone produces weak gels with a fast disintegrating structure that are unfit for continued administration. This drawback in the present research is overcome by improving the structural durability of carbopol in fusion with HPMC K4M and HPMC K15M. Carbopol blended with HPMC KM4, and HPMC KM15 gets crosslinked entangled to establish a polymer arrangement that is semi-interpenetrating and has naturally gelled at physiological pH.[15]

Consequently, incorporating HPMC K4M and HPMC K 15M can reduce the high concentrations of carbopol used in the formulation. The same was observed in the present studies that Carbopol, when used up to 0.5%w/v concentration and 0.5 HPMC K4M:2 HPMC K15M (F14), showed a drastic drug release, but on a further increase of carbopol concentration, the drug release studies showed no change. Thus, HPMC K4M and HPMC K15M benefited the formulation to gain an elastic behavior and helped in depot formation and sustain the drug release for 24h.[16] The drug release kinetics studies confirm that drug release occurs for 24h through diffusion.

CONCLUSION

The deflazacort *in situ* gelling solution was successfully formulated using 0.5%w/v concentration of carbopol and varying concentrations of HPMCK4M and HPMC K15M as viscosity-enhancing agents. carbopol, a biodegradable polymer used in the formulation, bears an efficient temperature-dependent *in-situ* depot-formation in plasma, good soluility, chemical compatibility, biocompatibility, and overall stability. Therefore, the developed formulation with its sustained release characteristics can be a safe and cost-efficient alternative to the conventional immediate release dosage forms.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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