International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 5, 2022

Original Article

FORMULATION AND EVALUATION OF NOVEL INSITU GEL SYSTEM IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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Received: 07 Dec 2021, Revised and Accepted: 18 Jul 2022

ABSTRACT

Objective: To develop *in-situ* gel formulations of Lornoxicam for sustained release to reduce the dosing frequency in the treatment of rheumatoid arthritis.

Methods: The method of ion-sensitive *in-situ* gel formation was used in this study. Lornoxicam in situ gel formulations were prepared by varying concentrations of sodium alginate as a bio-degradable gel-forming polymer, $CaCl_2$ as a cross-linking agent, and chitosan, $HPMCK_4$, $HPMCK_{15}$, guar gum, gellan gum, xanthan gum, pectin were used as drug release rate controlling polymers. The formulations F11-F18 were assessed for physical appearance, pH, *in vitro* drug release, viscosity, *in vitro* gelling capacity, and drug content. FTIR, DSC, and *in vivo* drug kinetics studies were conducted for lornoxicam pure drug and optimized formulation.

R**esults:** Formulations showed an optimum viscosity that will allow ease of administration and swallowing. All formulations were shown pH between 6.7 to 7.3, floating lag time was 2-3 sec and floated for 12 h. *In vitro*, drug release studies were reporting that commercial sustained release formulation of lornoxicam released 99.92% drug in 8 h, and optimized formulation F11 released 99.52% of the drug over a 12 h extended period. FTIR studies revealed no interaction between drugs and excipients used. The results of *in vivo* kinetic studies are approving the better performance of the optimized formulation. The C_{max}, T_{max}, $t_{1/2,}$ and AUC values are confirming the same thing.

Conclusion: Lornoxicam oral *in situ* gel containing chitosan as a drug release controlling polymer is a promising approach for the treatment of rheumatoid arthritis in a convenient dosage form with better patient compliance and therapeutic response.

Keywords: Lornoxicam, Rheumatoid arthritis, *In situ* gels, Sodium alginate, Chitosan

DOI: https://dx.doi.org/10.22159/ijap.2022v14i5.43792. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Rheumatoid arthritis is an ''autoimmune disorder described by joint inflammation and ache, with progressive bone erosions and cartilage damage, accompanied as a result of synovial hypertrophy" [1, 2]. The causing reason for the disease is unidentified and above 1% of the world population suffers from rheumatoid arthritis; characteristically, the disease commences at the age of 30 to 50 y [3]. An expected 2.5 million individuals in India are pretentious by rheumatoid arthritis, which has an economic impact of billions. About 0.5–0.75% of Asian people have been suffering from rheumatoid arthritis, with a women-to-men ratio of 3:1 [4]. In addition, this promotes the rate of premature death of patients with savage ischemic coronary illness or lymphoma, which extraordinarily affects monetary cost [5, 6].

Despite progressions in fundamental science and therapeutics, the presently available treatments are partially effective because of several disadvantages like drug dosage, time of administration, and related toxicities [7]. The perfect system should be easily administered, release the drug in a sustained manner and optimum concentration of drug must be retained without unpleasant negative activities. A variety of therapeutic agents are obtainable for the management of rheumatoid arthritis consisting of (i) NSAIDs (non-steroidal anti-inflammatory drugs)/selective cyclo oxygenase-2 (COX-2) inhibitors, (ii) Disease-modifying anti-rheumatic drugs (DMARDs), (iii) Glucocorticoids, (iv) Natural origin compounds and (v) Biological agents [8].

Lornoxicam is an exceptionally strong anti-inflammatory nonsteroidal drug; it has been utilized efficaciously in the therapeutic management of an extensive range of inflammatory and painful conditions, for example, moderate to chronic rheumatoid joint inflammation ankylosing spondylitis, and osteoarthritis [9].

The main aim of the study was formulation and evaluation of lornoxicam *in-situ* gel preparation for sustained drug release to reduce dosing frequency in a convenient dosage form for geriatric patients in the treatment of rheumatoid arthritis. Elderly patients with dysphagia are between a rock and a hard place because they require a large number of prescriptions like other geriatric patients [10, 11], but difficulties with swallowing or dysphagia limit or preclude the administration of solid oral dosage forms, which are by the far the most common formulations on the market. The problem could easily be bypassed if all the active pharmaceutical ingredients (APIs) contained in marketed products were available in formulations other than solid oral dosage forms. Unfortunately, this is not the case, and in clinics, compounding is a daily practice as caregivers dispense crushed tablets or opened capsules to facilitate the administration of solid oral dosage forms to dysphagic patients [12]. Hence it is highly needful.

MATERIALS AND METHODS

Lornoxicam was acquired from Glenmark Pharma Private Ltd, Mumbai, India. All the polymers were of pharmaceutical grade. Chitosan, $HPMCK_4$, and $HPMCK_{15}$ were obtained from Lepid Life Sciences Pvt Ltd, Delhi, India, and guar gum, gellan gum, xanthan gum, and pectin were obtained from Sigma-Aldrich, Germany was used as received. Sodium alginate, sodium citrate, and calcium chloride were obtained from SD Fine chemicals, Mumbai, India. All solvents utilized were of HPLC grade. Throughout the study, distilled water was used.

Preparation of lornoxicam *in situ* gels formulation

Ion sensitive *in-situ* gel formation method was employed for the preparation of lornoxicam *in-situ* gels and the formulations were specified in table 1. In the preparation of in situ gels, sodium alginate was used as a gelling agent, sucralose as a sweetening agent, sodium citrate as a sequestering agent and cross-linking agent was calcium chloride; apart from these, polymers like chitosan $HPMCK_4$, $HPMCK_{15}$, guar gum, gellan gum, xanthan gum, pectin were utilized

as drug release rate controlling polymers. Clear sodium alginate solution was prepared, added with rate-controlling polymer, and heated to 60 ° C until a clear solution was formed. Then allowed to reduce the temperature to 40 °C and added with lornoxicam and the separately prepared sodium citrate and calcium chloride solution.

F1-sol to gel transformation occurred very slowly. The transparent, less compact, and freely pourable gel was formed. In the case of F2-sol to gel transformation was slow and formed a transparent and good matrix. F3-sol to gel transformation occurred immediately and formed an opaque gel. Therefore increasing the concentration of sodium alginate resulted in producing an intact gel that could reside for a longer period but a further rise in concentration leads to further opaque gel, which is not acceptable. So 3% w/v sodium alginate is selected for further trials. To know the effect of calcium chloride concentration on gelling time and a gel consistency, F4 to F7 preparations were prepared by increasing the concentration of calcium chloride. There is no detectable change in the gelling time and gel consistency; hence the least concentration is selected for further formulation preparation. Further trials were planned by adding drug and drug release controlling polymer at the concentration of 0.1%w/v.

Table 1: Formulation tables of lornoxicam in situ gel preparations F1 to F7

Ingredient	F1	F2	F3	F4	F5	F6	F7
Sodium alginate (g)	1	2	3	2	3	2	3
Sodium citrate(g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Calcium chloride(g)	0.05	0.05	0.05	0.1	0.1	0.15	0.15
Distilled water up to (ml)	100	100	100	100	100	100	100

Table 2: Formulation tables of lornoxicam *in situ* gel preparations F8 to F24

Ingredient	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
Lornoxicam (g)	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0	0.32 0
Sodium alginate (g)	3	3	3	3	3	3	3	2	2	2	2	3	2	3	2	3	2
Xanthan gum (g)	0.1	-	-	-	-	-	-	-	-	-	-	0.05	0.05	-	-	-	-
Gellan gum (g)	-	0.1	-	-	-	-	-	-	-	-	-	-	-	0.05	0.05	-	-
Pectin (g)	-	-	0.1	-	-	-	-	-	-	-	-	-	-	-	-	0.05	0.05
Chitosan (g)	-	-	-	0.1	-	-	-	0.1	-	-	-	-	-	-	-	-	-
Guar gum(g)	-	-	-	-	0.1	-	-	-	0.1	-	-	-	-	-	-	-	-
HPMC K4M (g)	-	-	-	-	-	0.1	-	-	-	0.1	-	-	-	-	-	-	-
HPMC K15M (g)	-	-	-	-	-	-	0.1	-	-	-	0.1	-	-	-	-	-	-
Sodium citrate (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Calcium chloride (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sucralose (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium benzoate (g)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled water up to	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Formulations containing xanthan gum (F8), gellan gum (F9), and pectin(F10) have resulted in gel formulation during preparation instead of liquid form hence considered not acceptable formulations. The F11-F14 formulations formed thick opaque gel upon transformation. Hence F15 (SA 2%w/v, Chitosan 0.1%w/v) F16 (SA 2%w/v guar gum 0.1%w/v), F17 (SA2%w/v HPMC k4 0.1%w/v), F18 (SA 2% w/v, HPMC K15 0.1%w/v) having declining concentration of sodium alginate (2%) formed clear transparent gels upon transformation. F19 to 21 prepared by decreasing the concentration of polymers xanthan gum, gellan gum and pectin to 0.05% along with 3% w/v sodium alginate. F22-F24 formulations were prepared by decreasing the concentration of polymers xanthan gum, gellan gum and pectin to 0.05% and also decreasing the conc. of SA also to 2%w/v. The formulations F19, F20, F23 and F24, formed direct gel instead of solution, although concentrations are decreased. The direct gelation instead of solution form is may be due to the nature of the polymers used, as they hydrocolloid polymers. So not accepted. The formulations F21andF22 containing xanthan gum showed sol to gel change upon exposure to 0.1 N HCl but couldn't maintain the gel integrity for more than two hours of disintegration. Hence not considered for further studies. Therefore further evaluation studies were planned for F11 to F18.

Fourier transform infrared (FTIR) spectroscopy

The compatibility and interaction between drug and excipients utilized in the preparation of *in situ* gels are assessed by using FTIR-spectrophotometer. IR spectra of lornoxicam and excipients are determined and scanned at the range of 500 to 4000 Cm-1 [13]. Results are given in fig. 2.

Differential scanning calorimeter (DSC) studies

The sample's thermal behavior was investigated by using DSC studies. Accurately weighed samples were placed on the sample pan in hermetically sealed condition. At the rate of 20 °C/min from-40 °C to 300 °C test samples were heated under stable nitrogen cleansing at a rate of 40 ml/min.

Evaluation of lornoxicam *in situ* gel

The general appearance, color, and odor of the formulation were physically visualized and recorded. The pH was determined by using a digital pH meter.

***In vitro* gelation studies**

To test the *in vitro* gelling behavior of the formulations prepared, 10 ml of the formulation was added slowly on to the surface of 100 ml 0.1N HCl. The formed gels were observed and their patterns were recorded.

***In vitro* floating studies**

To test the floating characterstics of the prepared formulations, 10 ml of *in situ* gel formulation was added to 100 ml of 0.1N HCl and the time taken by the formulation to float was recorded.

Drug content estimation

5 ml of the formulation was added to 100 ml of 0.1N HCl and stirred for 1hr using a mechanical stirrer. The solution was filtered and suitably diluted with 0.1N HCl and the drug concentration was determined by using a UV-visible spectrophotometer against a blank solution at a wavelength of 373 nm [14].

Viscosity studies

The viscosity of Lornoxicam *in situ* gel formulations was measured at a physiological temperature 37 °C by Brookfield viscometer DVE-LV model at 100 rpm with spindle no. 65.

***In vitro* drug release studies**

The *In vitro* drug release study was carried out in triplicate using the USP dissolution apparatus II. The medium for dissolution studies was 900 ml of 0.1N hydrochloric acid and dissolution was carried out at 37 °C. The rate of stirring was 50 rpm. The maintained speed was to simulate *in vivo* existing gentle agitation and moreover be sluggish enough to avoid the infringement of gel formulation. At programmed time intermissions, accurately 5 ml of the sample was withdrawn and an equivalent amount of fresh medium was replaced and the absorbance of the samples was measured at 373 nm using UV-Visible Spectrophotometer.

Pharmacokinetic studies

After getting approval from the Institutional Animal Ethical committee having approval no. 1962/PO/Re/S/17/CPCSEA, six rabbits weighing 2–2.5Kg were randomly divided into two groups having 3 animals in each group. Animals were maintained under standard laboratory conditions at 24 ± 2 °C, relative humidity 50 ± 15%, and maintained under normal photoperiod (12 h dark/12 h light cycles) throughout the experiment. Group-1 received lornoxicam pure drug suspension, and Group-2 received an optimized formulation of lornoxicam at a dose of 0.75 mg/kg [15]. Blood samples were collected into K_2 EDTA-coated blood collection tubes from the marginal ear vein as per the standard protocol. The sampling time intervals were 0, 1, 2, 4, 6, 8, 12, and 24 h. The blood samples collected were centrifuged at 4000 rpm and the plasma was separated. Plasma samples were stored at-20 °C until analysis. Samples were examined for drug concentration by HPLC and Pharmacokinetic parameters such as $t_{1/2}$, T_{max}, C_{max}, $AUC_{0-\infty}$, and AUC_{0-24} were calculated.

X-ray imaging studies for floating of the formulation [16, 21]

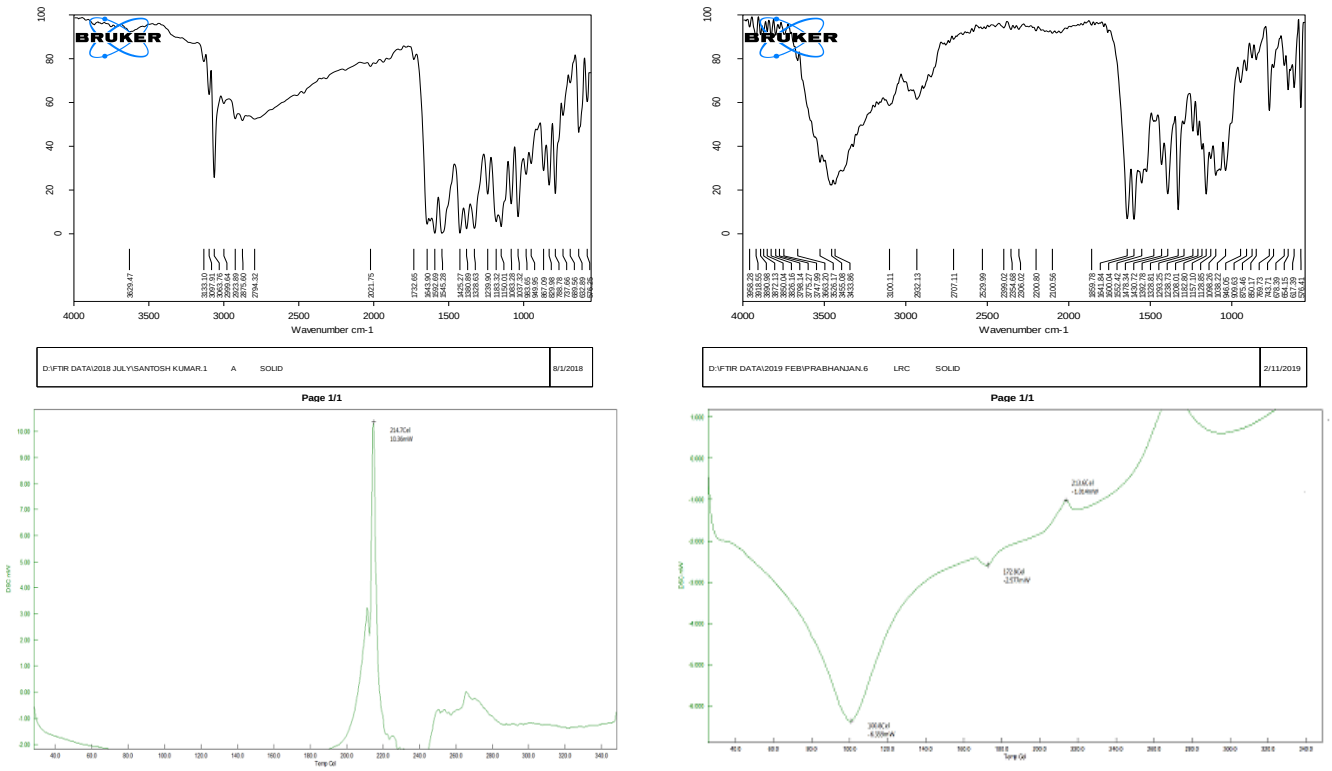
A The study was employed using 2.5 kg healthy rabbit which was housed for 72 h, had free access to water and food and fasted for 12h prior to the study, but the water was allowed. The optimized lornoxicam *in-situ* gel formulation prepared by loading 15%w/v $BaSO_4$ as a radio-opaque agent in place of the drug was administered orally using the animal oral feeding tube. Throughout the experiment, the animals fasted with free access to water, and X-ray images of the rabbit abdomen were taken at pre-programmed time intervals of 0, 1, 2, 4, 6, 8, and 12 h [16, 20, 21].

RESULTS AND DISCUSSION

FTIR and DSC studies

The IR spectrum of Lornoxicam pure shown significant bands at 3100 cm^{-1} NH stretch, 2808 cm^{-1} CH2 stretch, 1640 cm^{-1}>C=O 1380 cm^{-1} 0=S=0 stretch, and 788 cm^{-1} Cl stretch, which resemble the structure of lornoxicam and existence of the same peaks in the IR spectrum of the optimized formulation illustrated no chemical interaction among drug and excipients and confirmed the compatibility of lornoxicam with polymers used for in-situ gel preparation. Outcomes of IR studies were given in fig. 3. Similar observations were noted by Soad Ali Yehia *et al.*, during the formulation of Lornoxicam microparticles [17-19].

The DSC studies of lornoxicam exhibit a sharp peak at 214.7 °C in the thermogram of lornoxicam pure drug as shown in fig 2, indicating the crystalline nature of the drug. Similar results were observed by Vaibhav Mhasal *et al.*, during a drug excipient study of lornoxicam with polymers [19]. The presence of the same peak at 213.6 °C in the thermogram of the optimized formulation indicates the existence of lornoxicam in its crystalline structure without any interactions with the excipients of the formulation, which is desired.



DSC of pure drug **DSC of optimised formulation**

Fig. 1: The IR spectra and DSC spectra of the lornoxicam pure drug and optimized formulation

Evaluation of various physical parameters evaluated for various formulations of lornoxicam

The results of the evaluation of the physical parameters of formulations were shown in table 2. F11 to F18 formulations resulted in formulations having a slightly opaque to opaque appearance and all of them showed immediate gelation upon contact with 0.1N HCl that remained for an extended period of more than 12hr. The pH is very essential for oral preparations or else it leads to annoyance to the gullet. The formulation's pH was found in the range of 6.7 to 7.3, indicating that excipients used in the formulations are yielding formulations of suitable pH for oral delivery. This was also evident by S. Prasanthi *et al.*, during the formulation and optimization of buoyant *in-situ* gel system of valsartan using natural polymer in which guar gum is also used as one of the excipients [20], also by Jyotsna R Madan *et al.*, during formulation and evaluation of *in-situ* gel formulation of pregabalin using Sodium alginate and HPMC [21] and also by Anuja T Kadam during the design and evaluation of chitosan-based ocular in situ gel drug delivery [22].

Table 2: Results of various physical parameters evaluated for various formulations of lornoxicam

Formulations	Gel appearance	pH	Gelation response	%Drug content
F11	Opaque	6.8±0.56	+++	99.99±1.78
F12	Opaque	6.7±0.19	+++	100.01±0.56
F13	Opaque	7.3±0.67	+++	98.99±0.89
F14	Opaque	7.5±0.45	+++	99.01±0.78
F15	slightly opaque	6.8±0.34	+++	99.6±2.14
F16	slightly opaque	6.9±0.23	+++	101.04±1.67
F17	slightly opaque	7.2±0.98	+++	99.1±0.61
F18	slightly opaque	7.3±0.12	+++	99.5±1.89

(Values represent mean±SD, n=3), (+++): Immediate gelation remained for an extended period

Determination of drug content

The drug content estimation results were shown in table 2. The range of drug content values of formulations was between 90 to 100%. The outcomes were in the acceptable range indicating all the selected polymers and the method of preparation is very suitable for the uniform distribution of the drug.

Viscosity and floating studies

The viscosities of all prepared formulations were low, a considerable increase was reported due to the conversion of sol-gel. The optimized lornoxicam *in-situ* gel formulation (F11) viscosity was 1211cps, which is superior to all formulations prepared. This may be due to the contributions of sodium alginate and chitosan as viscosity contributors. The floating lag time, floating duration, and viscosity results were shown in table 3. As the concentration of crosslinking polymer resulted in a change in viscosity, the time taken for conversion from the sol to cohesive gelation and to appear on the surface of the medium was affected, although a significant difference was not observed. The *in vitro* floating test revealed the ability of all formulations to keep buoyancy above 12 h. All formulations exhibited a total floating time of>12 h. Floating lag-time varied with formulation variables. Floating lag times of F11-F18 are between 2-4 sec.

Table 3: Results of various evaluation parameters of various *in situ* gel formulations of lornoxicam

Formulation	Viscosity(cps)	Floating lag time (sec)	Floating duration (h)
F11	1211±.0.50	3±0.5	>12
F12	1183±0.3	4±0.5	>12
F13	953±0.3	3±0.5	>12
F14	1015±3.1	4±0.5	>12
F15	904±3.6	2±0.5	>12
F16	710±2.6	3±0.5	>12
F17	534±0.16	2±.05	>12
F18	572±0.16	3±0.5	>12

(Values represent mean±SD, n=3)

***In vitro* drug release studies**

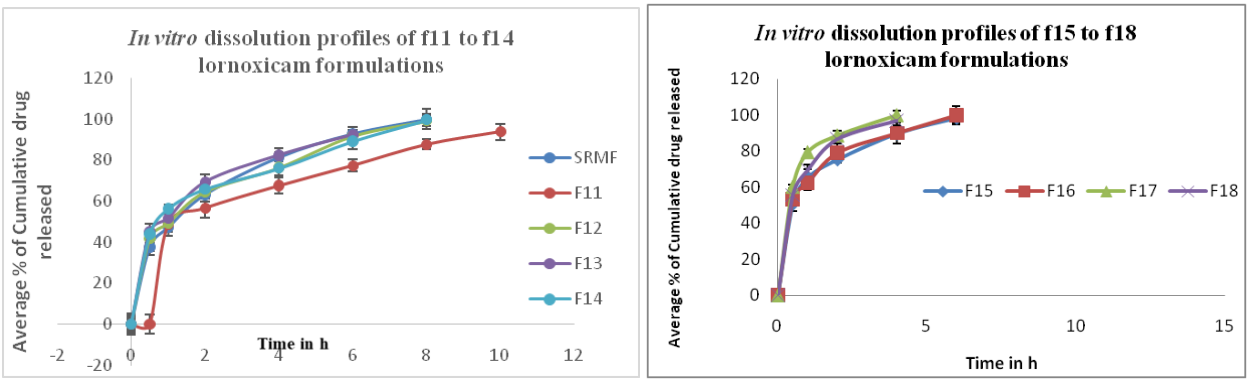


Fig. 2: Comparative *in vitro* dissolution studies of F11 to F18 and marketed formulation

The *in vitro* drug release study results are graphically shown in fig. 3. F11, F12, F13 and F14 released 96.12%, 98.96%, 92.27% and 99.52% in 12, 8, 6 and 8 h of dissolution respectively. Formulations F15 and F16 released 98.32%, and 99.98% in 6 h, and F17, and F18 formulations released 99.78% and 96.71% in 4h of dissolution, respectively. As the rate-controlling polymer and its concentration vary, the drug release rate was also affected. The change in the concentration of sodium alginate from 3%w/v to 2%w/v affected the viscosity as well as the release rate significantly. The marketed product has shown 99.92% drug release in 8 h only. The formulation F11 showed *in vitro* drug release of 99.52% over an extended period of 12 h. Based on all evaluation test results, formulation F11 can be considered as an optimized formulation as it was showing better results and sustained release in comparison to remaining prepared formulations and marketed formulations. Similar observations were noted by A. Maheswaran *et al.*, during the preparation of floating *in situ* gel of diltiazem HCl [23].

Pharmacokinetic studies

The percent of drug concentration in plasma was evaluated and plasma concentrations versus the time curve for lornoxicam were shown in fig. 4. Pharmacokinetic parameters are presented in the table 4. In the case of pure drug, the blood plasma concentration was decreased within 12h, whereas in the case of optimized *in situ* gel formulation, the blood plasma drug concentration was maintained up to 24 h. The pure drug showed a Cmax value of 880±10.89 ng/ml and the optimized formulation showed a C_{max} value of 705ng/ml in blood and the T_{max} of F11 was 6 h, and that of the pure drug was 3h. AUC is an important parameter for evaluating the bioavailability of a drug from a dosage form as it represents the total integrated area under the blood concentration-time profile and represents the total amount of drug reaching the systemic circulation. The F11 formulation and pure drug should have maximum variations in the case of the AUC parameter.

Table 4: Pharmacokinetic parameters of pure drug and optimized formulation (F11)

Pharmacokinetic parameters for lornoxicam in rabbits					
Formulation	**AUC $_{0\rightarrow t}$**	**AUC $_{0\rightarrow\infty}$**	**$t_{1/2}$ (h)**	**C_{max}(ng/ml)**	**T_{max} (h)**
Pure Drug*	3387.6±72.8	3521.487±280.1	1.26±0.01	880±10.89	3±0.15
F11*	9947.6±67.9	11206.737±435.9	7.5±0.05	705±12.68	6±.15

*Each value is represented as a mean±SD of observations (n=3)

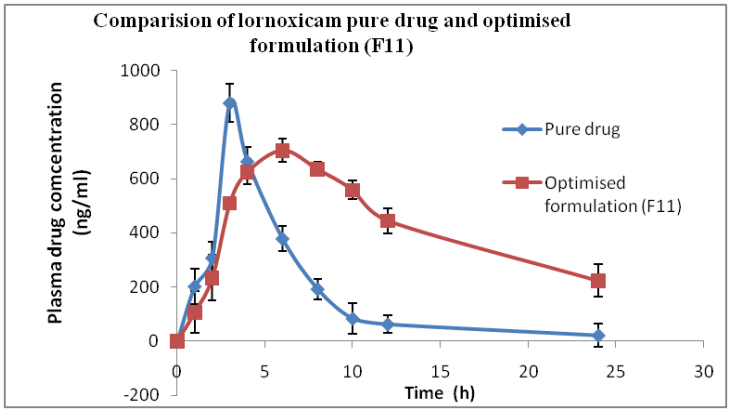


Fig. 3: Plasma concentrations versus time curve of pure drug and optimized formulation

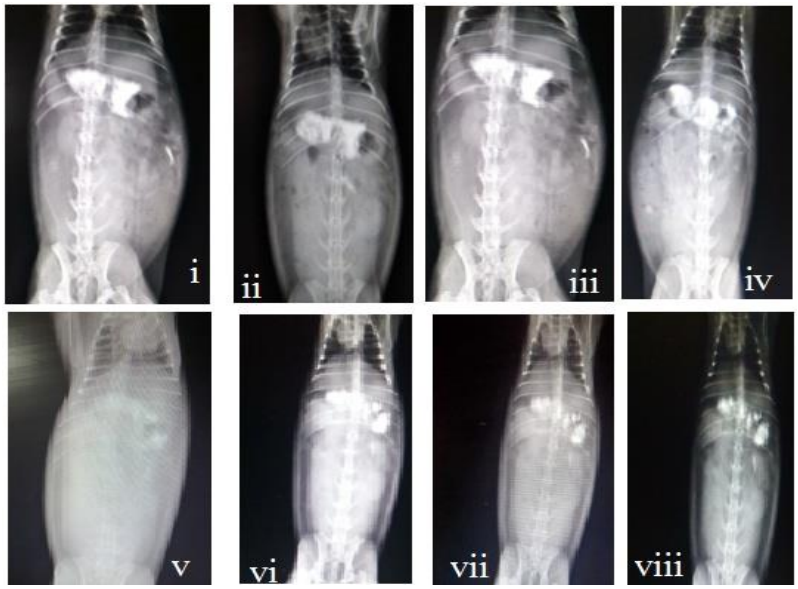


Fig. 4: *In vivo* X-ray images showing the presence of optimized formulation in the stomach region of the rabbit at i) 0h ii) 1h iii) 2h iv) 4h, v) 6h, vi) 8h, vii) 10h viii) 12 h

***In vivo* x-ray imaging studies**

The X-ray imaging study was performed on the rabbit to check the floating behavior of the optimized formulation. The X-ray images were taken immediately after administration, after 1 h 2 h, 4 h, 6 h, 8 h, 10 h and 12 h of gel administration. It was found that oral floating *in situ* gel was floated immediately after administring to the rabbit and it was observed to be floating in the stomach for 12h. Results of the X-ray imaging study are given in fig. 6.

CONCLUSION

The optimized formulation F11 having a 3% w/v concentration of sodium alginate along with chitosan and calcium chloride, had shown better-sustained release of drug in comparison to the marketed formulation in *in vitro* dissolution studies. The X-ray imaging studies confirmed the sustained gel integrity maintenance, which facilitates the continuous, sustained release of the drug instead of burst release. The *in vivo* kinetic studies are approving the better performance of the optimized formulation. The C_{max}, T_{max}, half-life, and AUC values are confirming the same thing. Hence, the *in-situ* gel formulation of Lornoxicam containing 3%w/v of sodium alginate along with chitosan as a drug-release-controlling polymer is a promising approach for the treatment of rheumatoid arthritis in a convenient dosage form with better patient compliance and therapeutic response.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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