

Research Article



Formulation and Evaluation of Meloxicam In-situ Gel Designed for Sustained Drug Release to Reduce Dosing Frequency in the Management of Arthritis

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ABSTRACT

Meloxicam has short biological half-life and is rapidly eliminated, frequent oral administration is necessary to maintain its therapeutic concentration, but this can increase chances of missing dose. This makes Meloxicam a good applicant for oral sustained release formulation. The objective of study was to develop in-situ gel formulations of Meloxicam for sustained release to reduce the dosing frequency in the treatment of rheumatoid arthritis. Method of Ion sensitive in-situ gelation was used in this study. Meloxicam In-situ gel formulations were prepared by varying concentrations of sodium alginate as a bio-degradable gel forming polymer, CaCl₂ as a cross-linking agent and Chitosan/ HPMCK4/HPMCK15/Guar gum/Gellan gum/ Xantha 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 was conducted for Meloxicam, excipients used and optimized formulation. Formulations showed an optimum viscosity that will allow ease of administration and swallowing. All formulations are shown pH between 4.7-4.9, floating lag time was 2-3sec and floated for >12 hrs. In vitro drug release studies reporting that commercially available product Meloxicam SR has showed 99.92% drug release in 8 hrs and out of eight formulations F11 showing in-vitro drug release of 99.52% over a 12hrs extended period. FTIR studies revealed no interaction between drug and excipients used. The results of In-vivo kinetic studies are approving the better performance of the optimized formulation in comparison to marketed formulation, The C_{max}, T_{max}, half-life AUC values are confirming the same thing. In conclusion, Formulation (F11) was selected as optimized formulations could be offered as shows optimum sustained drug release compared to commercial formulation. Hence Meloxicam containing Chitosan as drug release controlling polymer as promising approach for the treatment of rheumatoid arthritis treatment in a convenient dosage form with much patient compliance and better therapeutic response.

Keywords: Meloxicam, Arthritis, In-situ gels, sodium alginate, Chitosan.

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INTRODUCTION

Arthritis is an "autoimmune disease described by joint inflammation and pain/ache, with progressive bone erosions and cartilage damage, accompanied as a result of synovial hypertrophy"^{1,2}. The causing reason of disease is unidentified and above 1% of world population suffering from Rheumatoid arthritis, characteristically Arthritis disease commencement at the age of 30 to 50 years³. An expected 2.5 million individuals in India is pretentious by Rheumatoid arthritis and has economic impact in billions. About 0.5–0.75% of Asian people has been suffering from Arthritis with a woman to man ratio 3:1⁴. In addition RA promotes rate of premature death, patients with savage ischemic coronary illness or lymphoma which extraordinarily effects on monetary cost^{5,6}.

In spite of progressions in fundamental science and therapeutics, the present available treatments are partially effective because of several disadvantages like drug dosage, time of administration and related toxicities⁷. The perfect system should be easily administered, sustained drug release manner and optimum concentration of drug must be retaining without unpleasant negative activities. A variety of therapeutic agents are obtainable for the management of Arthritis consists 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 agents⁸.

Meloxicam is an exceptionally strong anti-inflammatory non-steroidal 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 (RA), ankylosing-spondylitis and osteoarthritis⁹.

The main aim of study was formulation and evaluation of Meloxicam 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.



MATERIALS AND METHODS

Meloxicam was acquired from Glenmark Pharma private Ltd, Mumbai, India. All the polymers received were of pharmaceutical grade (Chitosan/ HPMCK4/HPMCK15 are obtained from Lepid Life Sciences Pvt Ltd, Delhi, India and Guar gum/Gellan gum/ Xantha gum/pectins are obtained from Sigma-Aldrich Germany) were used as received. Sodium alginate, Sodium citrate and Calcium chloride were obtained from S.D Fine chemicals, Mumbai, India. All chemicals and solvents utilized were of HPLC grade. Throughout the study distilled water was used.

Determination of absorption maximum (λ_{max}) of Meloxicam¹⁰ and construction of calibration curve

The standard solution of drug was prepared in methanol and examined at 200 to 400 nm range using Elico UV spectrophotometer, to find out absorption maxima for analysis of samples. Meloxicam 10 mg of pure drug was dissolved in methanol and made upto 10ml with 0.1N HCl by slight shaking (1000 mcg/ml) and second stock solution was prepared by diluting 1ml of standard to 10 ml with addition of 0.1N HCl, which gives 100 mcg/ ml. As of concentrations like 10, 20, 30, 40 and 50 μ g/ml in 0.1N HCl were prepared and absorbance's were recorded. A standard graph was plotted and calculated the correlation coefficient of Meloxicam.

Preparation of Meloxicam in-situ gels formulation

Ion sensitive in-situ gelation method was employed for preparation of Meloxicam in-situ gels and charts of

formulation specified in table no 1. In preparation of insitu gels sodium alginate used as a Gelling agent, Sodium citrate as a sequestering agent and cross linking agent was Calcium chloride apart from these, polymers like Chitosan/ HPMCK4/HPMCK15/Guar gum/Gellan gum/ Xantha gum/pectins were utilized as rug release rate controlling polymer.

On addition of formulations (F1-F3) to 0.1 N HCl, F1 - sol to gel transformation occurred very slowly. Transparent, less compact and freely pourable gel was formed. In case of F2 - Sol to gel transformation is not very slow and formed transparent and nice matrix. F3 - Sol to gel transformation occurred immediately and formed opaque gel. Therefore Increasing concentration of Sodium Alginate resulted in producing an intact gel which could reside for longer period of time but further rise in concentration leads to further opaque gel which is not acceptable. So 3% Sodium Alginate is selected for further trials.

To know the effect of calcium chloride concentration, on gelling time and gel consistency, F4 to F7 preparations were designed by increasing concentration of calcium chloride.

There is no-detectable change in the gelling time and gel consistency; hence the least concentration is selected for further formulations preparation. Further trials were planned by adding drug and drug release controlling polymer at the concentration of 0.1%.

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
Calciumchloride(g)	0.05	0.05	0.05	0.1	0.1	0.15	0.15
Distilled water upto (ml)	100	100	100	100	100	100	100

Table 1: Preparation of Meloxicam In-situ gel formulation systems

Ingredient	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
Meloxicam (g)	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320	0.320
Sodium alginate (g)	3	3	3	3	3	3	3	2	2	2	2	-	-	-	-	-	-
Xanthan gum (g)	0.1	-	-	-	-	-	-	-	-	-	-	0.5	1	-	-	-	-
Gellan gum (g)	-	0.1	-	-	-	-	-	-	-	-	-	-	-	0.5	1	-	-
Pectin (g)	-	-	0.1	-	-	-	-	-	-	-	-	-	-	-	-	0.5	1
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
Distilled water	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

Formulation containing, xanthan gum(F8), Gellan gum (F9) and pectin(F10) have immediately formed gel without showing sol to gel conversions are not acceptable

formulations. The F11- F14 formulations formed thick opaque gel upon transformation. Hence F15 (SA 2%, Chitosan 0.1%) F16 (SA 2% guar gum 0.1%), F17 (SA2%



HPMC k4), F18 (SA 2%, HPMC K15) having declining concentration of Sodium alginate (2%) formed clear transparent gels upon transformation.

As F8, F9, F10 formulations were not shown sol to gel transformation instead directly formed gels, F19 to 24 formulations were prepared by polymers alone at concentrations of 0.5% and 1% without Sodium alginate incorporation.

Among F19 to 24, the formulations containing Xanthan gum alone (F19 & F22) showed sol to gel change upon experience to 0.1 N HCl but could not maintain the gel integrity for more than two hours of disintegration. The F23 & F24 formulations containing Pectin alone formed direct gel instead of solution formulation so not accepted. Therefore further studies hence dissolution studies were planned for F11 to F18 and marketed SR Tablet.

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 8400S¹¹. IR spectra's of lornoxicam and along with excipients are determined and scanning at range of 500 to 4000 Cm^{-1} results are given in the Fig no.2.

Differential scanning calorimeter (DSC) studies

The samples thermal behavior was investigated by using DSC Q100. Accurately weighed required number of samples were taken in an aluminum pans then precisely crimped. At the rate of 20 $^{\circ}\text{C}/\text{min}$ from -40 $^{\circ}\text{C}$ to 300 $^{\circ}\text{C}$ test samples were heated under stable nitrogen cleansing at a rate of 40 ml/min.

Evaluation of Meloxicam *in situ* gel

The general appearance, color and odor of formulation were physically visualized and recorded and the pH was determined by using digital pH meter¹².

In-vitro gelation studies

The formulations are subjected to know their *in-vitro* gelling capacity; accurately 10ml of measured each formulation was taken in a beaker and added 0.1N HCl 100ml, pH of 1.2 followed by gentle agitation. The formed gels were observed and gel formed patterns are recorded.

In vitro floating time

The *in-vitro* floating studies were performed by introducing about 10 ml of in-situ gel preparation was added to 100 ml of 0.1N HCl, pH of 1.2 at 37 $^{\circ}\text{C}$. The time taken by the formulation to float was recorded.

Drug content estimation

Gel equivalent to 10 mg of drug is transferred into a 100 ml volumetric flask and initially dissolved in 20 ml of 50% Methanol. Finally, the volume is fabricated to 100 mL with 50% Methanol. 1 ml of this supernatant is then transferred into 10ml measuring flask and makes volume to 10ml. Drug concentration was determined by using UV

spectrophotometer against blank solution at wavelength of 276 nm.

Viscosity studies

The viscosity of Meloxicam in-situ gels was measured for solution form and to gel form at 37 $^{\circ}\text{C}$ by viscometer Brookfield DV Pro-II, United States. The testing samples are equilibrated in water thermo-stated jacket for 10 min; measured at 50 rpm with spindle no.65.

In vitro drug release studies

The *In vitro* drug release study was carried in a triplicate using USP II [paddle apparatus method] dissolution apparatus. The medium for dissolution studies was 900 ml of 0.1N hydrochloric acid as dissolution at 37 $^{\circ}\text{C}$. The rate of stirring was 50 rpm. The maintained speed to be simulates in-vivo existing gentle agitation moreover be sluggish enough to avoid the infringement of gel formulation. At programmed time intermissions, accurately 5ml of sample was withdrawn and equivalent amount of fresh medium replaced at 37 $^{\circ}\text{C}$ and the absorbance of the samples were measured at 373 nm using UV-Visible Spectrophotometer.

Pharmacokinetic studies

Twelve rabbits weighing 2–2.5Kg, randomly divided into four groups, be used in this study as follows:

Group -1 - Control group, Group - 2 - Active Pharmaceutical Ingredient (Meloxicam), Group - 3 - Marketed formulation, Group - 4 - Optimized formulation.

Measurement of pharmacokinetic parameters of the treatments confirmed to guide lines of Institutional Animal Ethical committee having ID No. SVCP/IAE/2018. Each group consists of three rabbits. Each formulation was administered orally to the rabbits by oral feeding tube, and dose was followed considering the literature review. Animals were initially segregated based on their body mass and were divided into 4 groups of 3 each (groups were named as Blank, Marketed formulation, Pure drug and optimized formulation. Animals were maintained under standard laboratory conditions at 24 \pm 2 $^{\circ}\text{C}$, relative humidity 50 \pm 15% and maintained under normal photoperiod (12 h dark/ 12 h light cycles) throughout the experiment. Blood samples were collected in K₂ EDTA coated blood collection tubes from marginal ear vein as per the standard protocol. The sampling time intervals were 0.0, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0 and 24 hrs respectively for each animal of all the groups. The blood samples were collected centrifuged at 4000 rpm and the plasma was separated. Plasma samples were stored at -20 $^{\circ}\text{C}$ until analysis. Samples are examined for medicine concentrations by HPLC and PK parameters were studied. The PK parameters such as $t_{1/2}$, T_{max} , C_{max} , $\text{AUC}_{0-\infty}$, AUC_{12} are estimated for all the formulations and compared to that of API.



X-ray imaging studies for floating of the formulation

A protocol was designed for the x-ray studies to know floating time period of optimized In-situ gel formulation of Meloxicam. After getting authorization from Institutional Animal Ethical Committee, the studies were performed using White Newzeland Rabbits model. As per protocol the healthy rabbit weighing 2.5 kg which has housed for a minimum of 72 hours early to the study and had free access to water and food. Animals were kept for overnight fasting and prepared optimized Meloxicam *In situ* gel formulation along with radio opaque agent BaCl₂ at the concentration of 15%w/v to ensure visibility by X-ray was administered orally. Throughout the experiment animal was not allowable to eat, but have free access to water. X-

ray imaging studies were performed at programmed time intervals of 0, 1, 2, 4, 6, 8 and 12 hrs.

RESULTS AND DISCUSSION

λ_{\max} of Meloxicam

The λ_{\max} of Meloxicam: UV spectrum of Meloxicam showed maximum absorbance at 236 nm, 247nm, 256nm and 375nm wave-length shown in figure no.1&2. The calibration curve of Meloxicam by plotting concentration against absorbance results in a straight line and Better peak response and less placebo interference were observed at 375 nm. Therefore wavelength of 375 nm is preferred to estimate the drug.

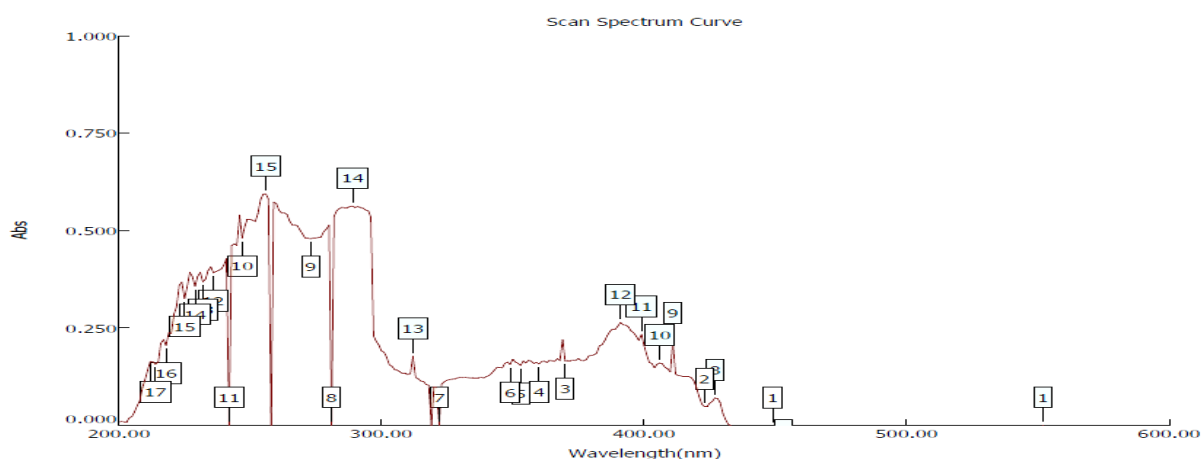


Figure 1: Meloxicam Absorption curve (λ_{\max} : 375nm)

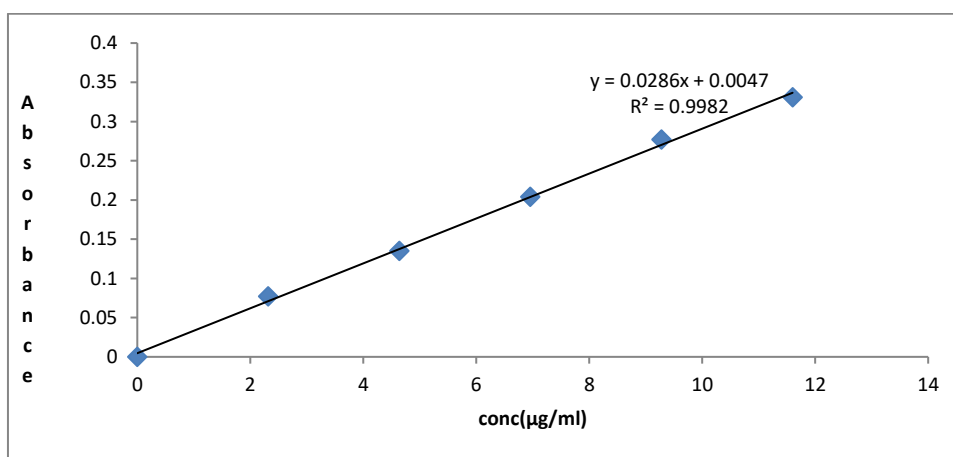


Figure 2: Calibration curve of Meloxicam

FTIR and DSC studies

The IR spectrum of Meloxicam pure, excipients of optimized formulation and Meloxicam optimized formulation illustrated that peaks characteristics of Meloxicam are not altered and with no changes in their spot, by this means representing no chemical drug interaction among drug and excipients. An IR spectral studies: confirmed that compatibility of Meloxicam with polymers utilized for in-situ gel preparations. The major peaks are obtained almost at the same wave numbers which belonging to drug functional

groups. On the other hand, in the physical mixtures additional peaks were obtained due to attendance of impurities however there is no influence in the drug peaks. The observation of spectral studies has indicating that there was no significant change in the peaks of drug polymer mixture. Therefore, no specific interaction among drug and polymers was observed, outcomes of IR studies were given in fig no.3. The DSC studies of Meloxicam indicate that the obtained sample was a hydrate form result was shown in fig no.3.

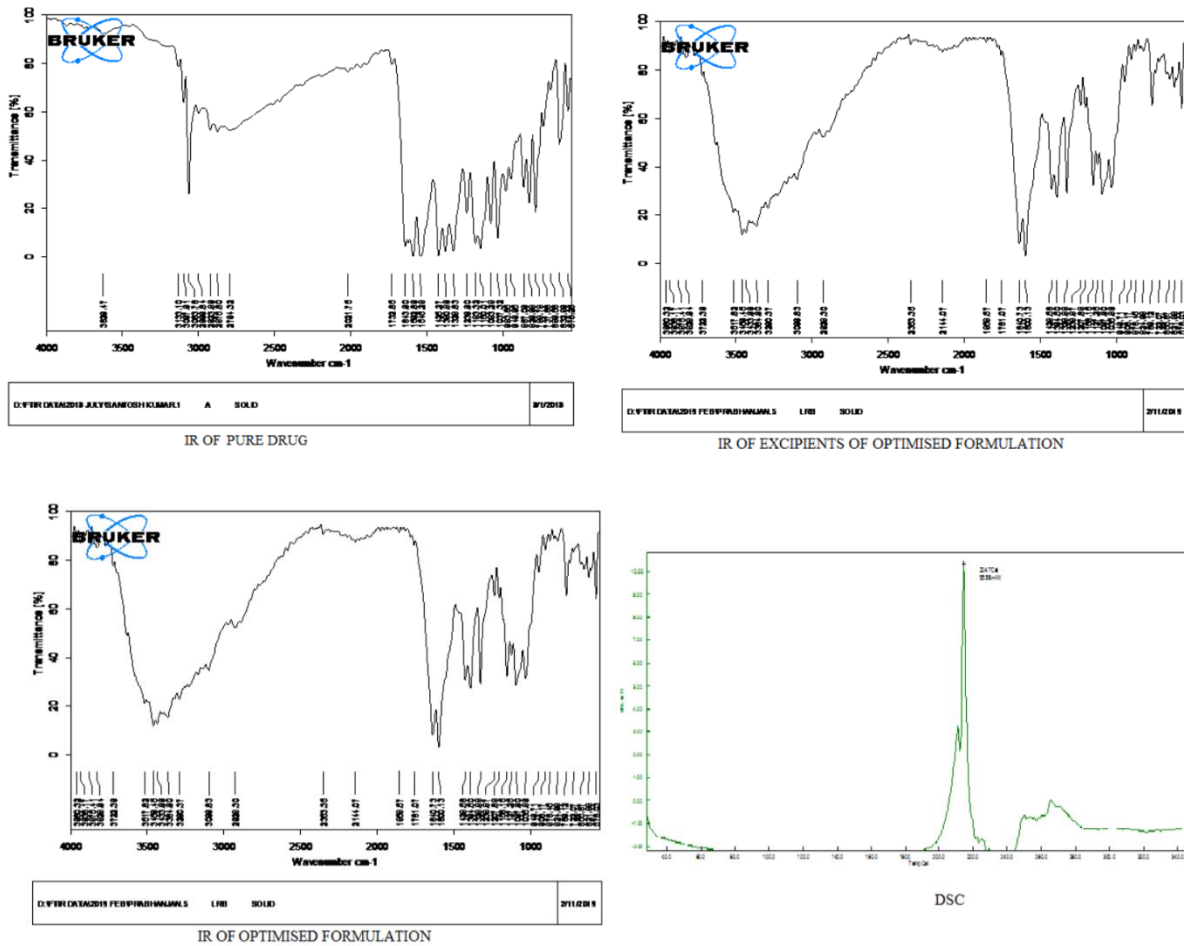


Figure 3: The IR spectra’s of the Meloxicam, excipients of optimized formulation and Meloxicam optimized formulation and DSC of the Meloxicam.

Physical appearance, pH and response of gelation

The pH measurement is very essential for oral preparations; or else, it leads to annoyance to the gullet. All prepared formulations have to some extent acidic pH. The formulations pH was founded in the range of 4.75-4.97

and physical appearance of formulations as shown in table no.2. Increasing concentration of Sodium Alginate resulted in producing an intact gel which could reside for longer period of time at concentration of 3% Sodium alginate and there is no much change in the gelling time and gel consistency by increasing concentration of calcium.

Table 2: Evaluation parameters (Gel appearance, pH, Gelation response and %Drug content) of *in-situ* gel formulations of Meloxicam

Formulations	Gel appearance	pH	Gelation response	%Drug content
F11(C)	Opaque	4.85	+++	99.99%
F12(G)	Opaque	4.97	+++	100.01%
F13(Hk4)	Opaque	4.77	+++	98.99%
F14(HK15)	Opaque	4.95	+++	99.01%
F15 (CS2%)	slightly opaque	4.83	+++	99.6%
F16(GS2%)	slightly opaque	4.93	+++	101.04%
F17 (HK4 S2%)	slightly opaque	4.75	+++	99.1%
F18 (HK15 SA2%)	slightly opaque	4.92	+++	99.5%

(+++): Immediate gelations remain for an extended period

Determination of drug content

Content of drug in all F11toF18 preparations were assessed and outcomes are in the acceptable range. The

ranges of drug content values of formulations are in between 90to 100% and the results were shown in the table no.2.



Viscosity and Floating studies

The viscosities of the all-prepared formulations were low, a considerable increase was reported at due to conversion of sol–gel. The Meloxicam in-situ gel (F11) viscosity was 1321cps, a prominent raise was observed after gelation was 42068cps. Taking into account all the results and findings of characterization, formulation F11 was considered for further studies results were shown in the table no.3.

Floating time and lag time were shown in table no. 3. As the concentration of crosslinking polymer resulted in change in viscosity, hence time taken from the sol to cohesive gelation and to appear on the surface of the medium was affected although significant difference is not observed. The *in vitro* floating test revealed the ability of all formulations to keep buoyancy for above 12 hr. All formulations exhibited total floating time of >12 h. Floating lag-time varied with formulation variables. Floating lag times of F11-F18 are in between 2-4sec.

Table 3: Evaluation parameters (Viscosity, floating lag time in sec and floating duration in hrs) of *in-situ* gel formulations of Meloxicam.

Formulation	Viscosity:(cps)		Floating : lag time (sec)	floating duration (hrs)
	Formulation	Gel		
F11(C)	1321 ± 50	42068 ± 25	3	>12
F12(G)	1283 ± 38	41870 ± 18	4	>12
F13(Hk4)	1015 ± 31	38077 ± 24	3	>12
F14(HK15)	953 ± 23	31010 ± 13	4	>12
F15(CS2%)	534 ± 16	25137 ± 14	2	>12
F16(GS2%)	572± 16	27245 ± 22	3	>12
F17(HK4 S2%)	710 ± 26	26503 ± 26	2	>12
F18(HK15 SA2%)	904± 36	31512 ± 15	3	>12

In vitro drug release studies

The *In vitro* drug release study results were graphically shown in Fig.no.4. F11, F12, F13 and F14 released 96.12%, 98.96%, 92.27% and 99.52% in 12, 8, 6 and 8 hrs of dissolution. Formulations F15 and F16 released 98.32%, 99.98% in 6 hrs and F17, F18 formulations released 99.78% and 96.71% in 4hrs of dissolution respectively.

Commercially available product SR, Meloxicam has showed 99.92% drug release in 8 hrs. Compare to all formulations based on the results of diffusion studies, F11 can be considered as optimized formulation as aim of study is sustained release of the drug. Hence formulation F11 showing *in vitro* drug release of 99.52% over a 12hrs extended period.

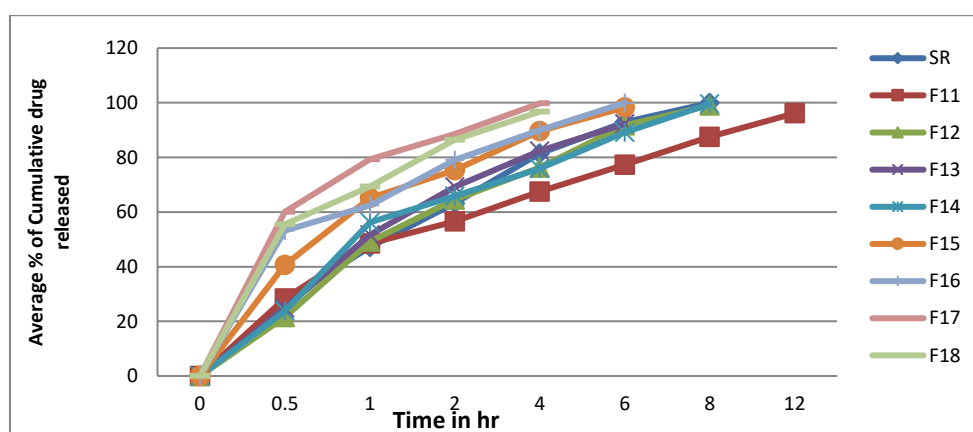


Figure 4: Comparative Summarization of *in vitro* dissolution studies of SR and F11 to F18

Pharmacokinetic studies

The percent of drug concentration in plasma was evaluated and plasma concentrations versus time curve for Meloxicam was shown in Fig.no.5. Pharmacokinetic parameters are presented in Table.no. 5. As compared to pure drug (168.3 ng/ml) F11 formulation showing C_{max} value of 1121ng/ml in blood and bioavailability and T_{max} of F11 was 10hrs, and pure drug was 8hrs. AUC is an

important parameter for evaluating bioavailability of drug from dosage form as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching. The F11 formulation and pure drug should have maximum variations in the case of AUC parameter.

Table 4: Pharmacokinetic studies of optimised formulation F11, pure drug and marketed formulation.

Pharmacokinetic Parameters for Meloxicam in Rabbits					
Formulation	AUC _{0→t}	AUC _{0→∞}	t _{1/2} (hrs)	C _{max} (ng/ml)	T _{max} (hrs)
Pure Drug	2767.15	389.563	6.69043	168.3	8
Marketed Formulation	3660.2	502.565	7.16482	265.74	8
F11	14524.2	2735.82	9.09548	1121.05	10

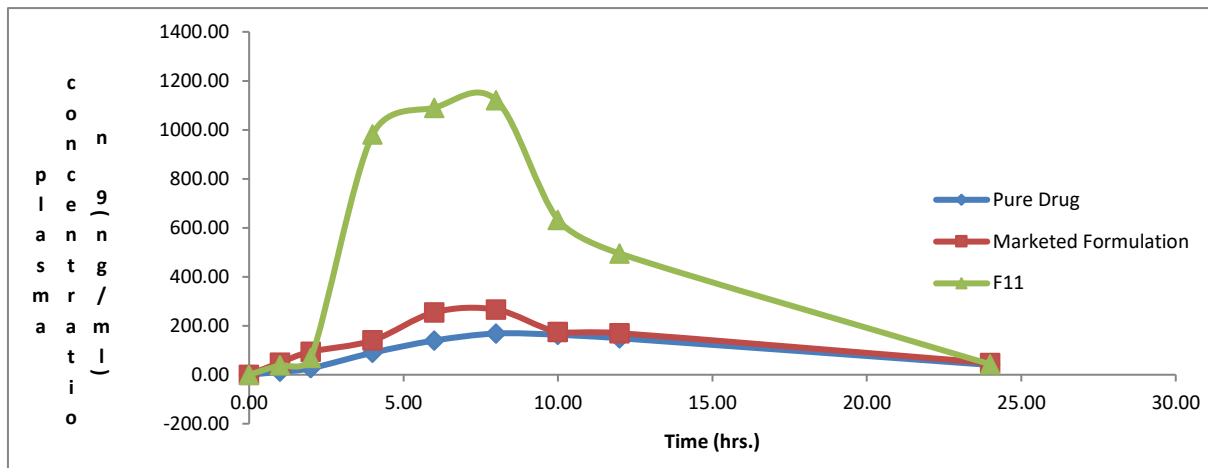
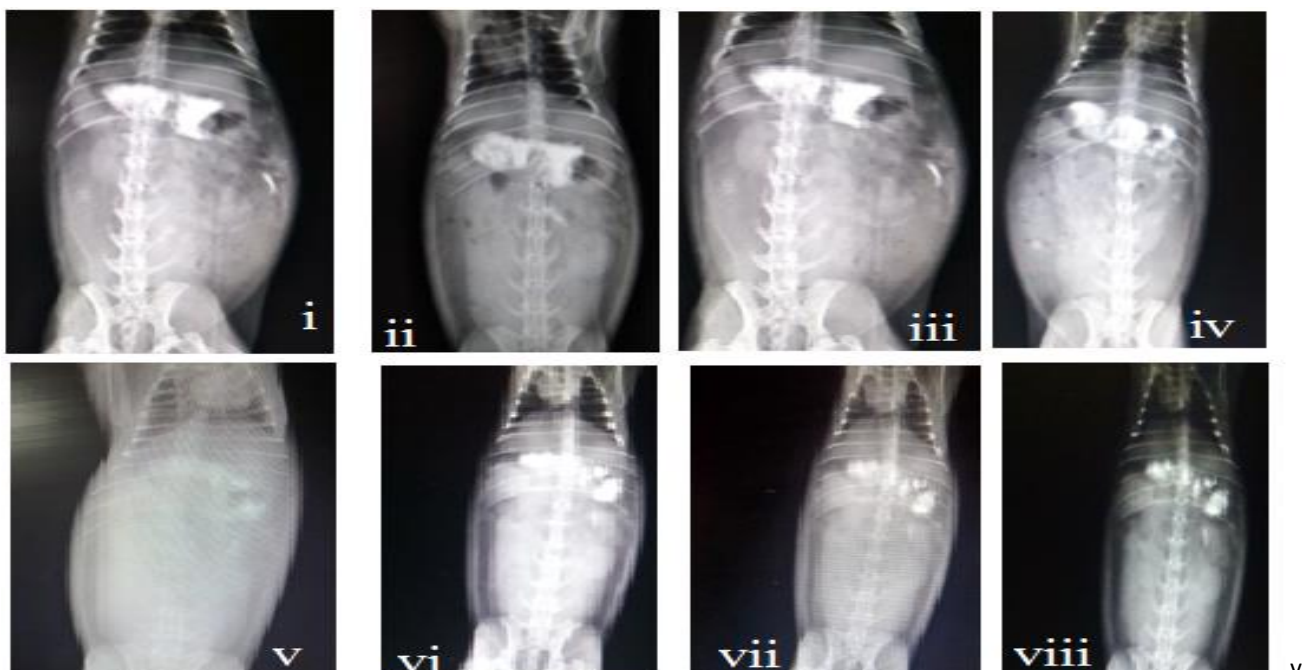


Figure 5: plasma concentrations verses time curve of formulations [F11], pure drug and marketed Formulation.

In-vivo x-ray imaging studies

An in-vivo Xray imaging study was performed in healthy Newzealand rabbit. The optimized formulation added with Barium Chloride at the concentration of 15%w/v was administered to rabbit through oral route and its abdomen X-ray images was taken to confirm the floating ability of optimized gel formulation (F11) of the Meloxicam. The X-ray imagings were taken as i) X-ray image of Immediately

after administration ii) X ray image After 1 hr after gel administration iii) X-ray image after 2 hr. of gel administration and iv, v, vi, vii & viii are X-ray images after 4,6,8,10 and12 hr of gel administration. It was found that oral floating in-situ gel was float immediately after feeding to rabbit and it was observed to be floating in the stomach more than 12hr and results of x-ray imaging’s are given in fig no.6.



i) x-ray image of Immediately after administration ii) x ray image After 1hr after gel administration iii) X-ray image after 2hr. of gel administration and iv, v, vi, vii & viii are x-ray images after 4,6,8,10 and12 hr of gel administration.

Figure 6: In-vivo x-ray imaging studies of the Meloxicam optimized formulation.

CONCLUSION

Commercial Meloxicam has short biological half-life and is rapidly eliminated, frequent oral administration is necessary to maintain its therapeutic concentration, the optimized formulation F11 having 3% concentration of sodium alginate along with chitosan and calcium chloride had sustained effect improved than the marketed formulation basing on in-vitro drug release over an extended period of above 12 hrs. The X- ray imaging studies are confirming the sustainability in 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 in comparison to marketed formulation, the Cmax, Tmax, half-life AUC values are confirming the same thing. Hence, the in-situ gel formulation of Meloxicam containing sodium alginate along with chitosan as drug release controlling polymer as promising approach for the treatment of rheumatoid arthritis in a convenient dosage form with much patient compliance and better therapeutic response.

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