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Research Article

Formulation, Optimization and Evaluation: Piroxicam Emulgel for Topical Drug Delivery Systems

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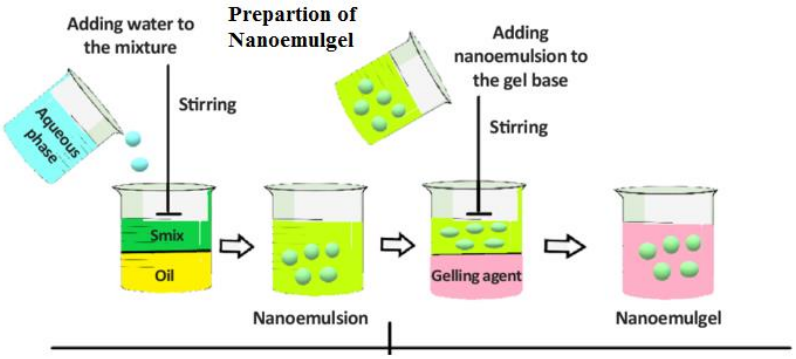
Graphical Abstract



ABSTRACT
Piroxicam is nonsteroidal anti-inflammatory drug that is classified as BCS class II drug (low solubility and high permeability). In the present study preparation of piroxicam loaded emulgel for the topical drug delivery is optimized by the central composite experimental design. The effect of different concentrations of surfactants i.e., span-80 & tween-80 was investigated on zeta potential (mv), polydispersity index (PDI), particle size (nm) & entrapment efficiency. The optimized batch of formulation suggested by the central composite design (CCD) was characterized by Fourier transform infrared spectroscopy (FT-IR) & Transmission electron microscopy analysis and also the mechanical and rheological properties were studied. The optimized batch of the formulation possess adequate spreadibility and viscosity. Results of in-vitro release studies revealed that the drug loaded emulgel showed (91.10 %) release in 12 hours dissolution study whereas in-vitro antiinflammatory study determined by egg albumin denaturation method exhibited 98.88% inhibition. However, ex-vivo bioadhesion study displayed the comparable results between piroxicam loaded emulgel (0.036 ± 0.4 N) and marketed Pirox® gel (0.037 ± 0.15). Hence, piroxicam when loaded in emulgel can be administered topically with improved properties.

Keywords: Piroxicam, Emulgel, *In-vitro* anti-inflammatory Activity, *In-vitro* release, Ex-vivo bioadhesion study.

INTRODUCTION

Piroxicam is nonsteroidal anti-inflammatory drug that is classified as BCS class II drug (low solubility and high permeability). It is highly effective in the treatment of fever, pain and inflammatory conditions including chronic pain, osteoarthritis, rheumatoid arthritis, postoperative surgical conditions and menstrual cramps[1,2] etc. NSAIDs inhibit cyclooxygenase (COX) enzymes which are responsible for the production of prostaglandins which play major role in the production of inflammation. Prostaglandins (PGs) are by products of fatty acid metabolism produced via the COX pathway. Piroxicam inhibits the COX enzymes, disrupted prostaglandin production thus inhibiting the inflammatory responses[3]. Conventional dosage forms available of

piroxicam such as tablet, capsule, injection causes many side effects such as nausea, vomiting, diarrhoea, gastric ulceration or bleeding and due to such side effects on the gastrointestinal system and some undesirable physicochemical properties such as its poor solubility it has limited use in therapeutic regimens. Therefore, to overcome limitations associated with oral drug delivery of piroxicam topical drug delivery system has been explored by various researchers. Piroxicam has been explored in various formulations in literature as topical drug delivery such as microemulsion[4], solid lipid nanoparticles[2], cocrystals[5], emulgel[6], transdermal patch[7], liposomes[8], niosomal gel[9], nano emulsion[10], oil-in-water cream[11], nanocream[12] and liquisolid compacts[13], etc till date.

Emulgels have emerged as a newer promising topical drug delivery system for the delivery of both hydrophilic as well as lipophilic drugs[14]. The advantages attributed to emulgel as a delivery system includes the feasibility of controlled drug release, improvement in drug bioavailability, targeted drug delivery, minimum systemic toxicity and exposure of drugs to non-infectious tissues/sites, ease of application, patient compliance, facility to easy termination of medication whenever required, delivery of drugs with short half-life and narrow therapeutic index and better loading efficiency[15]. Emulgels are emulsions, either of the oil-in-water or water in-oil type which are gelled by mixing with a gelling agent[16]. Direct (oil-in-water) systems are used to entrap lipophilic drugs, whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) systems[17], Mefenamic acid[18], calcipotriol[19], clotrimazole[20], ketoprofen[21, 22], chlorphenesin[16], meloxicam[17], clarithromycin[23], diclofenac[24], clindamycin[25], resveratrol[26], ofloxacin[27], fluconazole[28], cyclosporine[29], ketoconazole[30], diphenhydramine[31] etc. are the drugs investigated as emulgel delivery system.

The present research work is designed to evaluate the potential of emulgel as a topical delivery of hydrophobic drug piroxicam in the treatment of inflammation. Development of piroxicam emulgel was accomplished as per central composite experimental design (CCD) by standard experimental design protocol selecting 2-factors at 3 levels (Design Expert software version 11). The optimized batch was characterized by FTIR, TEM and texture analysis studies and evaluated for ex-vivo bioadhesion, invitro anti-inflammatory and in-vitro drug release studies.

METHODOLOGY

Materials: The drug Piroxicam, Carbopol-940, Cetostearyl alcohol, Disodium hydrogen phosphate and Potassium dihydrogen phosphate all were obtained from Hi-media laboratories Pvt. Ltd. Mumbai, India. Oleic acid, Triethanolamine, Propyl paraben and Propylene glycol were obtained from Sigma Aldrich, USA. Span-80, Tween-80 and Methanol were purchased from Fisher Scientific (Mumbai, India). Sodium chloride was obtained from Central drug house (New Delhi, India). All chemicals used were of reagent grade and used as such.

Preparation of Piroxicam Emulgel

The piroxicam loaded emulgel was fabricated with the method detailed by Khullar et al; 2012 with slight modification. On scanning the literature, it was found that piroxicam was soluble in optimum concentration of oleic acid, therefore, oleic acid was selected as solvent for solubilizing the drug in the study. The oil phase of the emulsion is prepared by dispersing the Span-80 (0.6-0.9%) in oleic acid containing cetostearyl alcohol (2.5%) as stabilizer. The aqueous phase of the emulsion is prepared by dispersing the Tween-80 (0.7-1.5%) in distilled water. Propyl paraben (0.03%) as preservative after dilution in (propylene glycol 4%) was mixed in the aqueous phase with continuous stirring. Drug (0.5 % w/w) was directly incorporated with oil phase. Both the phases of emulsion are heated to 60 - 70 °C separately for 15 minutes. After heating, oil phase is introduced into the aqueous phase drop wise with slow and continuous stirring till the emulsion is formed. Carbopol-940 (1 % w/v) as a gelling agent was added to the distilled water and left overnight to ensure complete humectation of the polymer chains followed by stirring at 1000 rpm until no lumps of carbopol remained or a homogeneous gel is formed[32]. The prepared emulsion was dispersed in the Carbopol gel in ratio (1:1) with continuous stirring at 1000 rpm to obtain an emulgel. At last, triethanolamine (TEA) was introduced in the formulation which adjust pH to 5- 6.5.

Experimental Design

A central composite experimental design (Design Expert Software, version 11) was used to optimize preparation of piroxicam loaded emulgel. On the basis of preliminary trials, two independent variables i.e., concentration of Span 80 (oil soluble surfactant) & tween 80 (aqueous surfactant) were selected to study

their effect on dependent variables i.e., Particle size, PDI, Zeta potential & Entrapment efficiency[33, 34]. The independent variables were studied at three (-1, 0, +1) different levels (Table 1).

Particle Size, Polydispersity Index (PDI) and Zeta Potential

The average particle size, particle size distribution (PDI) and zeta potential of emulgel was determined using dynamic light scattering technique by Malvern Zeta Sizer[35].

Entrapment Efficiency (%)

The entrapment of piroxicam in emulgel was determined by centrifugation at 4000 rpm for 30 minutes by separating free drug from emulgel. The clear supernatant was analysed for content of unentrapped piroxicam by measuring absorbance at 240nm in a uv-vis spectrophotometer[35]. The % entrapment efficiency was calculated by using equation (1).

Entrapment Efficiency (%) = Theoretical drug−Free drug Theoretical drug×100 (1)

Characterization

Fourier Transform Infrared Spectroscopy (FT-IR)

Piroxicam, Carbopol-940 and optimized batch of piroxicam were subjected to FT-IR spectroscopy) to study the compatibility of drug and excipients[36,37]. The KBr method was used to record the infrared spectra of pure drug and a mixture of drug and excipients using a Fourier transform infrared spectrophotometer (PerkinElmer Spectrum Version 10.03.08) in wavelength numbers ranging from 4000 to 400 cm-1.

Transmission Electron Microscope (TEM)

Transmission electron microscope was used to examine the morphology of the particles in the formulation. A drop of emulgel was put onto a 200 mesh carbon coated copper grid and air dried. Thereafter, sample was negatively stained at room temperature with 2% phosphotungstic acid and TEM micrograph was captured[35].

Texture Analysis

Texture analysis gives significant information about adhesiveness, hardness and cohesiveness of pharmaceutical gels. Texture profile analysis was performed by the TAXT2i texture analyzer equipped with, 5 kg load cell. The experiment is based on the penetration of probe into the sample to a predetermined depth. The experiment was performed by placing the gel below the probe. The texture analyzer was calibrated with the predetermined parameters before performing the experiment[38]. Cylindrical probe with diameter (10 mm) was used for determination of mechanical properties the emulgel. The texture analyzer was set to compression mode with velocity 3mm/s. The pre and post-test speed were kept 1mm/s with compression force of 0.05N, the penetration depth of probe was 4mm for 2 cycles whereas time interval between two compression cycles was kept 5 sec. Data acquisition rate was set to 200 pps.

Evaluation of Optimized Batch

Physical Appearance

The prepared formulation was visually assessed for colour, homogenicity, consistency and phase separation[39].

PH Determination

The pH of the prepared formulation was determined using digital pH meter. The pH meter was calibrated with distilled water before determining the pH of the formulation. Then the pH was measured[28].

Spreadability

Spreadibility is defined as the ease of application of formulation. The spreadability of emulgel was measured using glass plate method. 1g of emulgel was weighed and put on the pre marked 1cm diameter circle on glass plate. Another glass plate of equal size is placed above the previous glass plate. Combing a weight of 100 gm is placed on upper glass plate for 5 minutes. The diameter of the circle after 5 minutes of spreading of the emulgel was noted[40]. The spreading diameter of the formulation is considered as the spreadability (cm) of the formulation.

Viscosity

The viscosity of optimized batch was determined[41] by using Brookefield Viscometer (Brookefield DV-E Viscometer) with spindle 07 at 100 rpm for 10 minute.

Ex-Vivo and In-Vitro Evaluation

Ex-vivo bioadhesion strength measurement

Modified balance method was used for determination of bioadhesive strength of emulgel. For determination of bioadhesive strength of emulgel freshly cut hairless pig ear skin was used. The skin was cut into two pieces and washed with 0.1 N NaOH. The two individual pieces were adhered with two glass

plates. One glass plate was stick under the right pan and another glass plate was stick on the base blow the right pan of the balance. The left pan of the balance was balanced against right pan of the balance by putting some extra weight. Now the 1 ml of emulgel was sandwiched between these two glass plates containing hairless pig skin by keeping the weight of 100 gm for 5 minutes. After 5 minutes, the weight (5g/min) is added slowely to the left pan and continuously increased until both the pieces of skin get detached from each other. The weight required to detach the emulgel from the skin give the measurement of bioadhesive strength of emulgel[42, 43]. The following formula (equation-2) is used for the measurement of the emulgel

Bioadhesive Strength = $Weight\ required\ (in\ gram)\ Area\ (in\ cm2)$ (2)

Drug Content

The formulation containing drug equivalent to 0.5 % was weighed and dissolved in 100 ml freshly prepared phosphate buffer (pH 7.4). After sonication for 2 hours, the sample was analysed using uvvisible spectrophotometer at 240 nm. The drug content was calculated by the following formula (equation-3):-

Drug content (%) = $\frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$ (3)

In-Vitro Anti-Inflammatory Activity

Protein (egg albumin) denaturation method was used for the determination of in-vitro anti-inflammatory activity of piroxicam pure drug and piroxicam loaded emulgel formulation. The reaction mixture (5ml) contains fresh egg albumin (0.2ml), phosphate buffer saline (pH 7.4) (2.8ml) and formulation (2 ml) having different concentration (125, 250, 500, 650, 1000 µg/ml) of piroxicam emulgel formulation in solvent methanol. Similar concentrations with same procedure were made up of model drug piroxicam as a reference. After mixing and proper incubation (15 minutes at 37 °C) the mixture was cooled to room temperature and turbidity was checked using a uv-visible spectrophotometer at λmax 660 nm. Phosphate buffer saline (pH7.4) was used as control for this study[44,45,46]. The percentage inhibition of protein denaturation was calculated using the following formula (equation4):

% Inhibition = $\frac{Absorbance\ of\ control - Absorbance\ of\ sample\ Absorbance\ of\ control}{} \times 100$ (4)

In-Vitro Drug Release Study

Franz diffusion (FD) cell was used for the determination of in-vitro drug release studies of the optimized formulation. The emulgel formulation (1 g) was kept over dialysis membrane that was placed between the FD cell's donor and receptor compartments. As a dissolution medium, phosphate buffer (pH 7.4) was used. The entire assembly was placed on a magnetic stirrer (50 rpm), and the solution was continuously stirred with a magnetic bead with maintained temprature at 37±0.5 °C. The sample (5 ml) was withdrawn at different time intervals for 12 hours, and replaced with equal amounts of freshly prepared dissolution media. Samples were analysed spectrophotometrically at 240 nm and the cumulative drug release (%) was calculated[18, 40,47,48].

RESULTS AND DISCUSSION

The preparation of emulgel using piroxicam was optimized using 2-factor, 3 level central composite experimental design (CCD). The concentration of span-80 (X1) and concentration of tween-80 (X2) were designated as independent variables whereas zeta potential (mV, X1), polydispersity index (PDI, X2), particle size (nm,Y1) and entrapment efficiency (Y2) were specified as dependent (response) variables. Formulation parameters and responses for experimental design for different batches of piroxicam emulgel are displayed in (Table 1). The particle size of different batches of piroxicam emulgel was observed in nanometer (nm) range (271.7 - 375.2). The polydispersity index (PDI) of all batches of piroxicam emulgel was found < 1 which indicates monodispersity in the formulation. Piroxicam emulgel has shown that a handsome amount of drug (99.81% to 99.93 %) is entrapped in all the batches. The total drug content of optimized formulation was observed (99.89±0.0008 %). The uniform drug content indicates that piroxicam was distributed uniformly in the emulgel. No physical changes were observed in the formulation even after 5 months.

Table 1 Formulation parameters with observed responses for experimental design

Batch No	Concentrations	Zeta Potential (mV)	PDI	PSA (nm)	EE (%)

Span 80 (ml)		Tween 80 (ml)				
	X_1	X_2	Y_1	Y_2	Y_3	Y_4
1	0.6	0.7	-30.8	0.279	274	99.87
2	0.9	0.7	-35.8	0.402	315.4	99.84
3	0.6	1.5	-39.9	0.299	301.9	99.80
4	0.9	1.5	-38.4	0.278	315.3	99.82
5	0.6	1.1	-36.9	0.2	311.4	99.85
6	0.9	1.1	-38.7	0.235	271.7	99.92
7	0.75	0.7	-36.6	0.268	267.8	99.85
8	0.75	1.5	-40.08	0.335	294	99.81
9	0.75	1.1	-39.1	0.333	365	99.87
10	0.75	1.1	-40.7	0.328	325.6	99.91
11	0.75	1.1	-38.5	0.302	299.8	99.92
12	0.75	1.1	-41.8	0.358	375.2	99.93
13	0.75	1.1	-41	0.725	370	99. 87

Zeta Potential

The result of zeta potential (Y1) of the piroxicam emulgel, formulated in accordance with the experimental design expert protocol is displayed in (Table 1). The generated responses were fitted into different polynomial models using the experimental design. It was observed that response zeta potential (Y1) was found best fit into quadratic response surface model with none transformation of the data. The polynomial models for the responses Y1 can be explained by the given equation:

$$Y1 = -40.18-0.8833X1-2.53X2+1.62\ X1X2 +2.27\ X12+1.73X22 \quad (5)$$

Table 2 summarizes the results of analysis of variance on the response surface model. The polynomial model was found to be significant ($P < 0.0500$) with non-significant ($P > 0.05$) lack of fit. A greater value of R2 (0.9) indicated good correlation among the observed and predicted responses. Adequate precision more than 4 is adequate signal and model fit to navigate the design space.

Table 2 Model statistics summary.

Response factors	**Model F-value**	**Prob. > F**	**R^2**	**Adeq. Prec.**	**C.V. (%)**	**Lack of fit F-value**	**Prob. > F**
Y_1 (z-avg)	13.24	0.0019	0.9044	12.44	3.04	0.34	0.07975

Fig. 1 displays the combined effect of concentration of span-80 & Tween-80 on the response zeta potential. It can be inferred from the surface plots that independent & dependent variables exists in a curvilinear relationship.

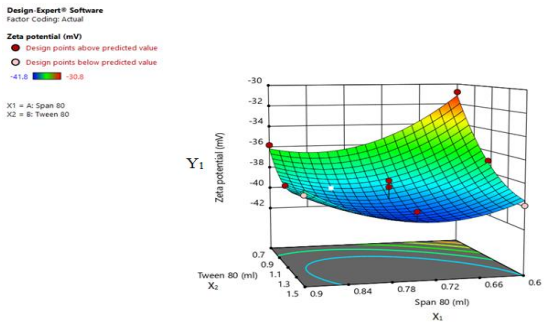


Fig. 1 3D response surface plots for the combined effect of span 80 & tween 80 on zeta potential (Y1)

Optimization

Design Expert Software with numerical optimization tool using desirability function was used to prepare piroxicam loaded emulgel with desirable zeta potential. Independent variables optimization was done by keeping zeta potential constraints in range. The suggested parameters through optimization tool were employed for preparing optimized batch of piroxicam loaded emulgel. The distinct set of solutions were provided by the numerical optimization tool in design expert software. The

suggested parameters by the CCD were concentration of span-80 (0.834ml) & concentration of tween- 80 (1.38 ml) that provide piroxicam emulgel with zeta potential value -30.8 mV (predicted value -40.2 mV) The closer relationship between obtained and predicted values confirm high predictive ability of the model.

Characterization of Optimized Emulgel Fourier Transform Infrared Spectroscopy (FT-IR)

The spectra of piroxicam (Fig. 2) reported major peak at 1637.03 cm^{-1} (-C=O amide). The spectra of piroxicam also exhibited other characteristic peaks at 1531.74 cm^{-1} due to -C=C stretching of aromatic ring, at 1298.39 cm^{-1} due to -C-O stretch, 1180.89 cm^{-1} due to (S-O) stretch and at 1150.42cm^{-1} due to S(-O)2 stretching. The spectra of Carbopol-940 exhibit characteristics peaks at 3453.26 cm^{-1} due to NH stretch, 2958.79cm^{-1} due to -C-H (alkanes stretch) and 1713.84 cm^{-1} due to -CO ketone (Figure 2). In the spectra of piroxicam emulgel formulation the peak due to N-H stretching of piroxicam is shifted from 3453.26 cm-1 to 3446.05 cm-1 and the peak due to S-O stretch at 1180.89 cm^{-1} of piroxicam and 1249.20 cm^{-1} of carbopol-940 shifted to 1287.00 cm^{-1}. The spectra of the piroxicam emulgel exhibited same characteristics peaks except for a slight shift in the intensity of the peaks due to slight overlapping between the drug and the polymer characteristic peaks. Hence, there was no interaction between the drug and the excipients used in the study.

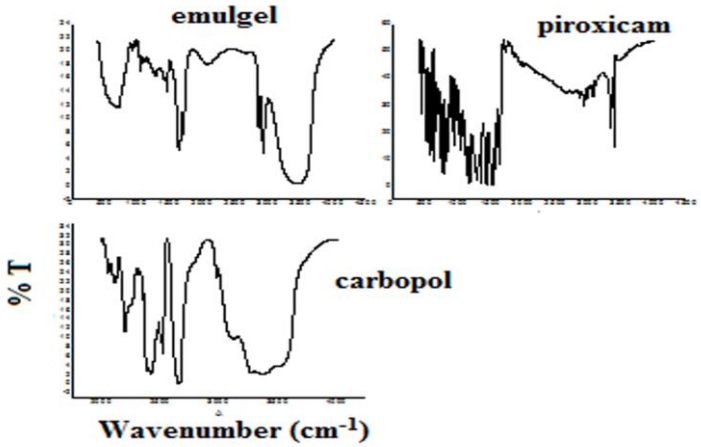


Fig. 2 FTIR Spectrum Piroxicam Emulgel, Pure Drug Piroxicam & Carbopol 940

Transmission Electron Microscope (TEM)

TEM images are depicted in the (Fig. 3). TEM images reveals that particles have spherical morphology and particles size was found in nanometres range which was later confirmed by zetasizer. No aggregation of particles was reported and particles have shown good dispersity. The drug was seen uniformly distributed in particles.

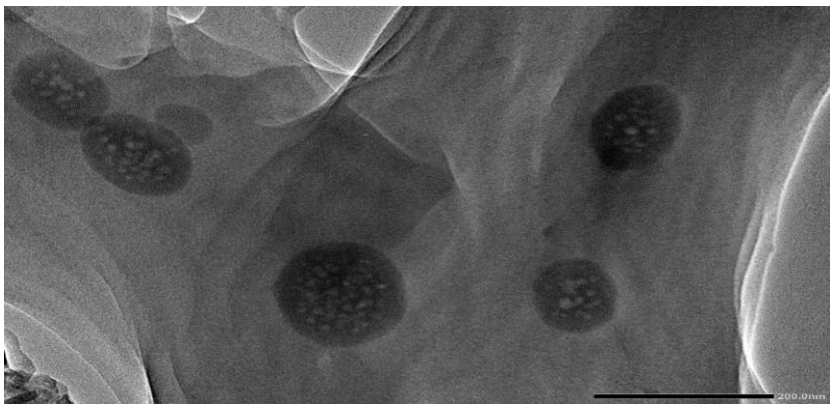


Fig. 3 Transmission electron microscopy (TEM) images of piroxicam emulgel

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Texture Analysis

The piroxicam loaded emulgel was characterized mechanically for their hardness, adhesiveness and cohesiveness (Fig. 4). The height of the first positive peak on the force time curve gives the hardness (0.06 N) of the formulation. It indicates the resistance to compression indicating the ease by which product can be removed from the container. Adhesiveness (-0.008 N.s) is expressed as area of first negative peak in force-time curve after first compression cycle which measures the work required to overcome the force of attraction between probe and surface of gel. Cohessivness (0.125 N.s) is calculated as the ratio of area of second positive peak to first positive peak. It indicates the structural recovery of gel formulation after compression. Fig. 4 depicts the results of mechanical parameters of piroxicam loaded emulgel.

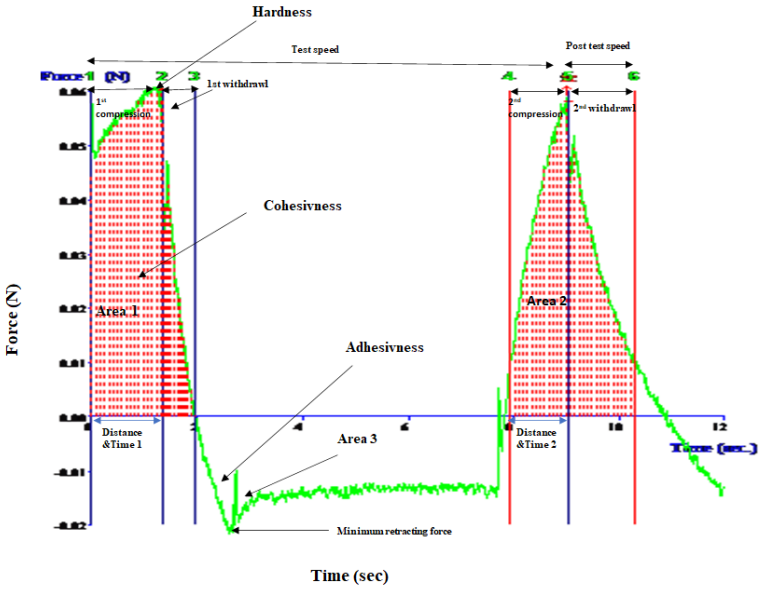

Fig. 4 Mechanical parameters of optimized batch of emulgel

Evaluation of Optimized Emulgel Physical Evaluation

The colour, homogeneity, consistency and phase separation of the prepared formulation all were visually examined. The pH of the prepared emulgel was found in between normal range of skin pH 5-6.5 which means that formulation will not cause skin irritation when applied topically. The optimized formulation has shown adequate rheological characteristics for topical application. The formulation showed good homogeneity with no phase separation having viscosity of 5.323±185 (Pascal-second) with a good spreadibility (5.13 ± 0.15 cm).

Evaluation of Optimized Emulgel Ex-Vivo Bioadhesive Strength Measurement

Modified physical balance method was used to determine the ex-vivo bioadhesive strength of optimized emulgel formulation. The results of ex-vivo bioadhesive strength of the optimized formulation (0.036±0.4 N) were found comparable with Pirox® gel (0.037±0.15 N) a marketed formulation.

In-Vitro Anti-Inflammatory Activity

Anti-inflammatory activity was determined by egg albumin denaturation method. It was measured by measuring the absorbance of samples and converting it into total inhibition of protein denaturation. Fig. 5 depicts the comparison plot of % protection from protein denaturation at different concentration of optimized formulation and pure drug. The egg albumin method has revealed the significant concentration-dependent anti-inflammatory activity by protection of protein. Pure drug and optimized emulgel formulation at different concentrations have shown significant % protection. It is concluded from the results that piroxicam loaded emulgel is more effective in producing anti-inflammatory response in comparison to pure drug.

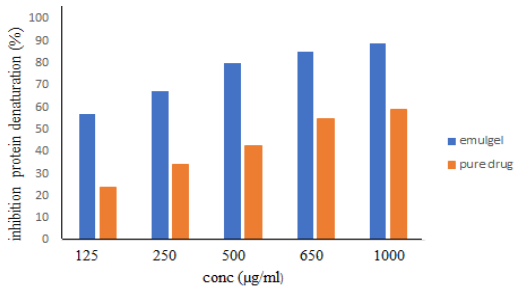

Fig. 5 % Inhibition of drug and optimized formulation emulgel.

In-Vitro Drug Release Studies

Franz diffusion cell was used to determine the cumulative drug release (%) of piroxicam from optimized emulgel formulation. Piroxicam has shown controlled release of (91.10 %) from the optimized emulgel formulation in 12 hours of study (Fig. 6).

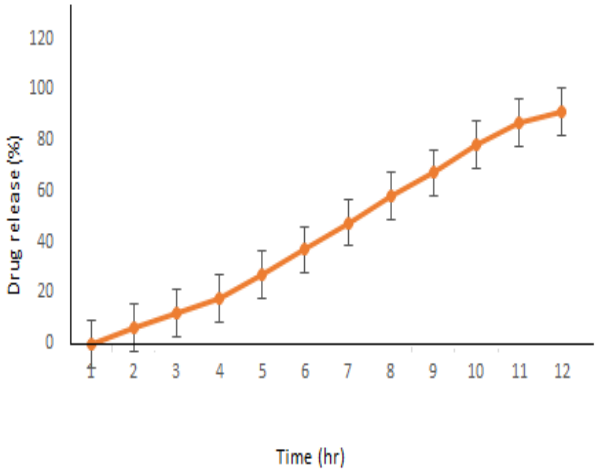

Fig. 6 In-vitro drug release of piroxicam from emulgel

For determining the kinetics of release the data of cumulative percentage release was put in various kinetics model and it found to be best fit into zero order model (R^2 = 0.9922). Further, the value of 'n' >1.0 (n=1.2) the release exponent of Korsemeyer -Peppas equation indicated that the release of piroxicam from emulgel occurs by super-case-2 transport

CONCLUSION

In the present research, piroxicam loaded emulgel was successfully prepared, characterized and evaluated for topical delivery of drug. The central Composite Design (CCD) was employed to investigate the effect of independent variables (span80 & tween80) on the dependent variables zeta potential (mV), polydispersity index (PDI), particle size (nm) and entrapment efficiency (%). The optimized batch of piroxicam after characterization by FT-IR, TEM & TPA studies was further evaluated for in-vitro drug release, in-vitro anti-inflammatory & ex-vivo bioadhesion studies. It was observed that all batches of optimization have shown that handsome amount of drug is entrapped (99.80–99.93 %) with particle size (271.7-375.2 nm) in nanometer range and a good monodispersity index (0.2- 0.725). Zeta potential of all batches of optimization is found in between (-30.8 to -41mV) which shows good stability of all the batches. Mechanical properties such as hardness (0.06 N), adhesiveness (-0.008 N. s) & cohessivness (0.125 N. s) were determined by texture analyzer. The invitro release of piroxicam from piroxicam loaded emulgel by Franz diffusion cell was observed (91.10 %) controlled release in 12 hours study. The in-vitro anti-inflammatory study of piroxicam loaded emulgel by egg albumin protein denaturation method showed (88.88±3.70 %) inhibition as compared to pure drug piroxicam (59.13±2.17 %) as the concentration increases. The ex-vivo bioadhesion studies (0.036±0.4 N) of piroxicam loaded emulgel exhibited comparative results with market Pirox® gel (0.037±0.15 N). So, it is concluded from the results that topical delivery of piroxicam will be a good approach in

reducing associated side effects and to overcome it's solubility problems.

Consent for Publication
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Conflict of Interest
The authors declare that there is no conflict of interest.

Author Contributions
Dr. Sunita Devi- Conceptualization, Writing – Original Draft Preparation; Prof. Meenakshi Bhatia- Conceptualization, Supervision; Pooja Rani- Review & Editing, Software; Dr. Kavita Bahmani- Writing – Review & Editing, Data Curation; Samiksha Grewal- Review & Editing, Data Curation and Neelam Sihag - Review & Editing, Data Curation.

Abbreviations
FD- Franz diffusion cell
FT-IR – Fourier transform infrared spectrophotometer
TEM- Transmission electron microscopy
TPA- Texture profile analysis
ANOVA- Analysis of variance
CCD- Central composite design
PDI- polydispersity index
NSAIDs- Non-steroidal anti-inflammatory drugs

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List of Figures

Fig. 1 3D response surface plots for the combined effect of span 80 & tween 80 on zeta potential (Y1)

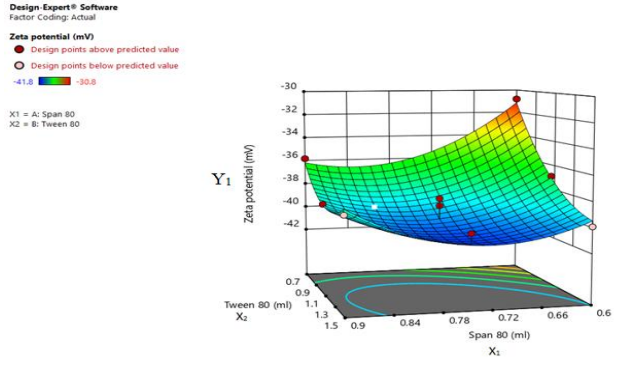

Fig. 2 FTIR Spectrum Piroxicam Emulgel, Pure Drug Piroxicam & Carbopol 940

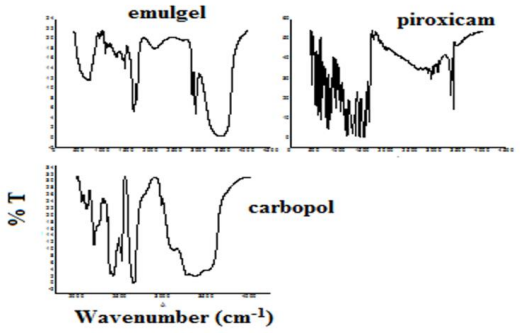

Fig. 3 Transmission electron microscopy (TEM) images of piroxicam emulgel

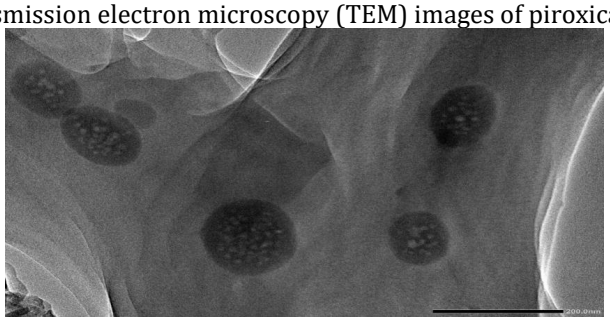

Fig. 4 Mechanical parameters of optimized batch of emulgel

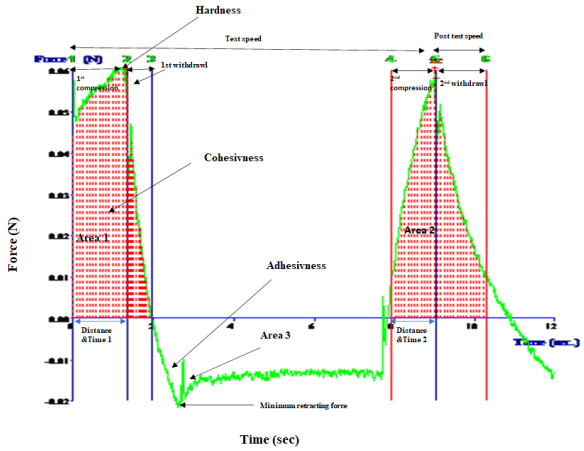

Fig. 5 % Inhibition of drug and optimized formulation emulgel.

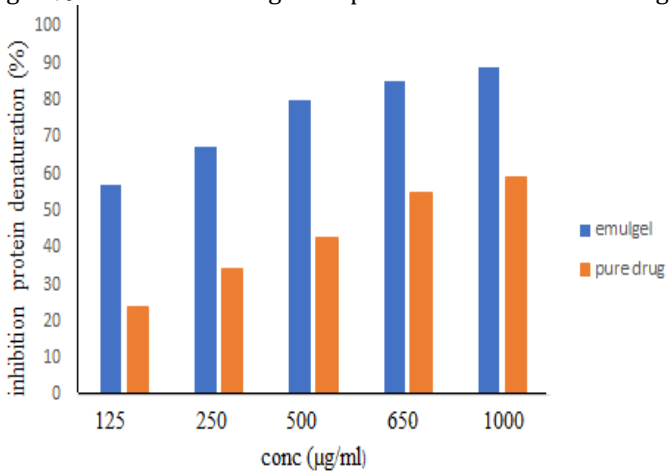

Fig. 6 In-vitro drug release of piroxicam from emulgel

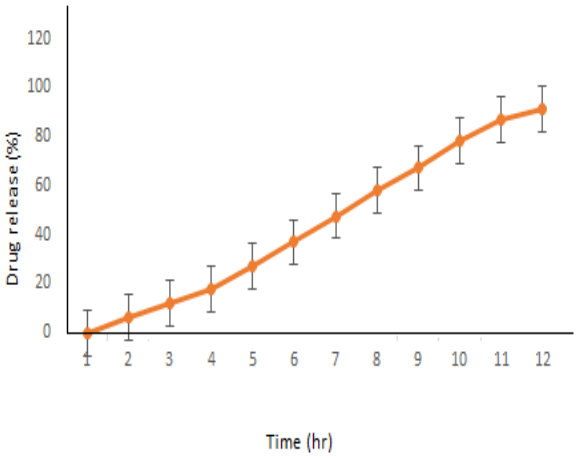

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Table 1 Formulation parameters with observed responses for experimental design

Batch No	**Concentrations potential (mV)**		**Zeta**	**PDI**	**PSA (nm)**	**EE (%)**
Span 80 (ml)		Tween 80 (ml)				
	X_1	X_2	Y_1	Y_2	Y_3	Y_4
1	0.6	0.7	-30.8	0.279	274	99.87
2	0.9	0.7	-35.8	0.402	315.4	99.84
3	0.6	1.5	-39.9	0.299	301.9	99.80
4	0.9	1.5	-38.4	0.278	315.3	99.82
5	0.6	1.1	-36.9	0.2	311.4	99.85
6	0.9	1.1	-38.7	0.235	271.7	99.92
7	0.75	0.7	-36.6	0.268	267.8	99.85
8	0.75	1.5	-40.08	0.335	294	99.81
9	0.75	1.1	-39.1	0.333	365	99.87
10	0.75	1.1	-40.7	0.328	325.6	99.91
11	0.75	1.1	-38.5	0.302	299.8	99.92
12	0.75	1.1	-41.8	0.358	375.2	99.93
13	0.75	1.1	-41	0.725	370	99. 87

Table 2 Model statistics summary.

Response factors	Model F-value	Prob. > F	R^2	Adeq. Prec.	C.V. (%)	Lack of fit F-value	Prob. > F
Y_1 (z-avg)	13.24	0.0019	0.9044	12.44	3.04	0.34	0.07975