RESEARCH ARTICLE

Formulation, Development, and Evaluation of Indomethacin Emulgel Using Pregelatinized Starch from *Ipomoea batata* Tubers

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Abstract

Aim: The purpose of the present study was to develop and optimize the emulgel system for indomethacin (IND), using four types of gelling agents: Carbopol 934, HPMC K4M, xanthum gum, and pregelatinized *Ipomoea batata* starch (PGIBS), which are dispersed in purified water with constant stirring at a moderate speed, then the pH was adjusted to 6-6.5 using triethanolamine. **Materials and Methods:** The prepared emulgels were evaluated in terms of physical appearance, pH, spreadability, rheological study, viscosity, drug content determination, *in vitro* drug release, accelerated stability studies, and fitting of results into different kinetic equations was also carried out. **Statistical Analysis Used:** The Fourier transform infrared spectra of the IND and different polymers alone and in combination show the compatibility of the drug and excipients. **Results:** *In vitro* release study demonstrated diffusion controlled release of IND from formulation up to 8 h. The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics a. The accelerated stability studies were performed according to ICH guidelines for 3 months, and the results were found to be stable in varying temperature. All the prepared emulgels showed acceptable physical properties concerning color, homogeneity, consistency, spreadability, pH value, and with higher drug release than conventional gel. **Conclusion:** The optimized formulations were found to be C4, H4, G4, and I4 containing a lower concentration of light castor oil and a higher concentration of emulsifiers. In the case of all evaluation parameters PGIBS and castor oil-based formulation, i.e., I4 showed better properties. So, as a general conclusion, it was suggested that the IND emulgel formulation prepared with PGIBS having the oil phase concentration in its low level and emulsifying agent concentration in its high level was the formula of choice. The results demonstrate that the release of the drug is dependent on the viscosity of the polymer used.

Key words: Carbopol 934, castor oil, indomethacin, optimization, pregelatinized *Ipomoea batata* starch, Xanthum Gum

INTRODUCTION

Topical drug delivery systems have been used for centuries for the treatment of local skin disorders and relieve the pain. One side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and delivering the drug for an extended period of time at the effected site that mainly acts at related regions. On the other hand, the topical delivery system increases the contact time and mean resident time of the drug.

Indomethacin (IND) is a potent non-steroidal anti-inflammatory drug (NSAID) with analgesic and anti-pyretic properties. Like other NSAIDs, the most common side effect

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of IND in oral dosage forms is a gastrointestinal irritation. The long-term use of NSAIDs is associated with severe gastropathy.[1] Thus, alternative routes of administration for these drugs are being currently investigated. Recently, more attention has been focused on emugels for topical drug delivery.[2,3]

When gels and emulsions are used in a combined form, the dosage forms are referred to as emugels.[4] Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and as vehicles to deliver various drugs to the skin.[5] Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin.

In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase.[6] Natural polymers, such as Xanthan Gum, have many advantages over synthetic gelling agent like Carbopol 934.[7] The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Emugels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, and transparent with long shelf life and pleasing appearance.[8]

In the development of emugel dosage form, an important issue is to design and optimized formulation with an appropriate drug diffusion rate in a short period of time and a minimum number of trials. For this purpose, a computer-based optimization technique with a 2-level factorial design utilizing a polynomial equation has been widely used. This technique requires minimum experimentation and time, thus is far more effective and cost-effective than the conventional methods of formulating emugel dosage forms.[9]

The aim of this work was to develop and optimize the emugel formulation of IND with four types of gelling agents such as Carbopol 934, HPMC K4M, Xanthan Gum, and pregelatinized *Ipomoea batata* starch (PGIBS) separately, using 22 factorial design. Optimized formulations evaluated for anti-inflammatory activity and *ex vivo* skin permeation study. The influence of the type of the gelling agent was also investigated.[10]

MATERIALS AND METHODS

Materials

IND was received as a gift sample from Hetero Labs Ltd., Hyderabad, Telangana, India. Carbopol 934 was purchased from Manish Pharmaceuticals, Mumbai, Maharashtra, India. Xanthan Gum was received as a gift sample from CP Kielce, Mumbai, Maharashtra, India. Light liquid paraffin, Span-80, Tween-80, methylparaben, and propylparaben were purchased from Loba Chemie, Mumbai, Maharashtra, India. All other chemicals and reagents used were of analytical grade. Deionizer distilled water was used throughout the study.

Preparation of emulgel[18,19]

The composition of emulgel formulations is shown in Table 1. First, the gel was prepared by dispersing Carbopol 934 in heated purified water (80°C), and the dispersion was cooled and left overnight. The oil phase of the emulsion was prepared by dissolving Span-80 in liquid paraffin while the aqueous phase was prepared by dissolving Tween-80 in purified water. Methyl and propylparabens were dissolved in propylene glycol, whereas IND was dissolved in ethanol, and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70-80°C then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel. Finally, pH of emulgel was adjusted using triethanolamine.[11] The same procedure was followed for HPMC K4M, Xanthan Gum, PGIBS as gelling agents instead of using Carbopol 934.[13]

Characterization of the IND emulgel[14,15]

Physical appearance

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, grittiness, and phase separation.[12]

pH determination

pH of all formulations was determined by a pH meter (Digital pH meter MK VI). The pH meter was calibrated with a standard buffer solution having pH 4 and 7 before use. 1 g of the formulation was dissolved in distilled water and stirred until it forms a uniform suspension, kept it aside for 2 h. The volume made up to 100 ml and pH of the suspension was measured with the help of calibrated pH meter.

UV-spectrum: (Determination of λ Max)

IND was examined in the range 230-360 nm a 10 ppm solution of IND in methanol shows absorption maxima at about 256 nm. Absorbance at 256 nm shows 0.5887.

Preparation of calibration curve of IND

Calibration curve of IND in methanol: The absorbance values of IND solutions in methanol are shown in Figure 1 and in a buffer having pH 7.4 shown in Figures 1 and 2.

Table 1: Composition of various indomethacin emulgel formulations

Ingredients (%w/w)	C1	C2	C3	C4	H1	H2	H3	H4	G1	G2	G3	G4	I1	I2	I3	I4
Indomethacin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carpool 934	2.5	5	2.5	5	-	-	-	-	-	-	-	-	0.25	0.5		
HPMCK4M	-	-	-	-	2.5	5	2.5	5	-	-	-	-	-	-	-	-
Xanthum Gum	-	-	-	-	-	-	-	-	2.5	5	2.5	5	-	-	-	-
PGIBS	-	-	-	-	-	-	-	-	-	-	-	2.5	5	2.5	5	
Light liquid paraffin	0.25	0.5	-	-	0.25	0.5	-	-	0.25	0.5	-	-	0.25	0.5	-	-
Castor oil	-	-	0.25	0.5	-	-	0.25	0.5	-	-	0.25	0.5	-	-	0.25	0.5
Tween-80	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5	0.25	0.5
Span-80	0.6	0.9	0.6	0.9	0.6	0.9	0.6	0.9	0.6	0.9	0.6	0.9	0.6	0.9	0.6	0.9
Propylene glycol	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Ethanol	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Methylparaben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propylparaben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Purified water q.s.	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Triethanolamine q.s	Adjust pH 6-6.5															

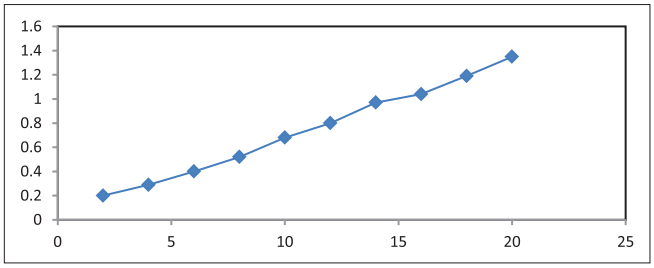

Figure 1: Calibration curve of indomethacin in methanol

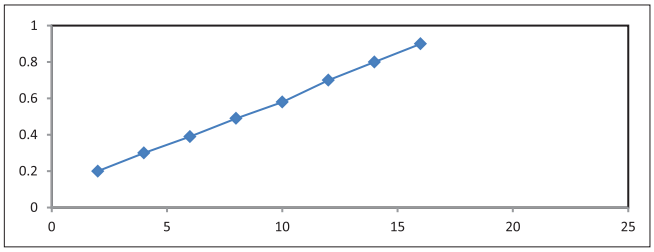

Figure 2: Calibration curve of indomethacin in buffer (7.4)

Characterization of drug by infrared spectrophotometer (Fourier transform infrared [FTIR])

The IR spectrum of IND was recorded using FTIR spectrophotometer (Shimadzu, Japan) with diffuse reflectance principle. Sample preparation involved mixing the sample with potassium bromide, triturating in a glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000-400/cm.

Spreadability

One of the criteria for an emulgel to meet the ideal quantities is that it should possess good spreadability. It is term expressed to denote the extent of the area to which gel readily spread on application to the skin or affected part. The therapeutic efficacy of a formulation also depends on its spreading value. It is performed by "slip and drag method" by modified spreadability apparatus. It consists of a wooden block over which a glass slide of 10 × 10 cm is fixed. An excess 2 g of emugel is placed on the fixed slide over which another slide is placed to which a pan is attached to add weights. A weight of 1 kg is placed over both the slides to expel air for 5 min. Then, the weight is removed over the two slides. Weight of 80 g is added to the pan and time required for the slide to slip is noted. Lesser the time taken for separation of two slides, better the spreadability. It is calculated using the formula.[3]

$$S = M. L/T$$

Where, M = wt. tied to the upper slide
L = length of glass slides
T = time taken to separate the slides

Rheological study

The viscosity of different emulgel formulations was determined at 37°C using a brook field viscometer.

Extrudability study

In conducting the test, a closed collapsible tube containing 20 g of gel was pressed firmly at the crimped end, and a clam was applied to prevent any rollback. The cap was removed, and the microencapsulated gel was extruded until the pressure was dissipated.

Drug content determination

The drug content in emulgels was determined by a spectrophotometer. IND content was measured by dissolving known quantity of emulgel formulation in methanol by sonication. Absorbance was measured after suitable dilution at 260 nm using UV-VIS spectrophotometer.[4,5]

In vitro diffusion study

In vitro diffusion was carried out by modified Franz diffusion cell. A glass cylinder with both ends open, 10 cm height, 3.7 cm outer diameter, and 3.1 cm inner diameter was used as permeation cell. An egg membrane (soaked in phosphate buffer 24 h before use) was fixed to one end of the cylinder with the aid of an adhesive to result as a permeation cell. 1 g of medicated emulgel was taken in the cell (donor compartment), and the cell was immersed in a beaker containing 200 ml of 7.4 pH phosphate buffer as receptor compartment. The entire surface of the cell was in contact with the receptor compartment which was agitated using magnetic stirrer and a temperature of 37±1°C was maintained. 10 ml sample from the receptor compartment were taken after an interval of 1 h. Over a time period of 8 h with the same amount replaced. The sample was analyzed for IND at 260 nm against blank using UV spectroscopy. The amount of IND released at various time intervals was calculated with the help of calibration curve with phosphate buffer pH 7.4 and plotted against time.[8] When gel concentration at a higher level, it affects the release of drug and shows decrease in % drug release.

Data treatment with kinetic models[16]

To study the kinetics of *in vitro* drug release, data were applied to kinetic models such as zero order, first order, Higuchi, and Korsmeyer–Peppas. Equations for models are as follows.

The equation for zero order release is

$$Qt = Q0 + K0\ t.$$

The first order release equation is Log Qt = Log Q0 + Kt /2.303.
The Hixson - Crowell release equation is WO 1/3 – Wt 1/3 = kt.
Korsmeyer–Peppas equation is (Mt/M) = Kmtn.

Stability studies[17]

Stability study was performed on various prepared emulgel formulations. The preparations were packed in collapsible aluminum tubes (5 g) and subjected to stability studies at 25°C/60% RH and 30°C/65% RH, for a period of 3 months. Samples were withdrawn at an interval of 45 days and were evaluated for physical appearance, rheological properties, and drug content. All the test results were found to be in limits. Hence, the formulations were stable understated storage condition.[20]

RESULT AND DISCUSSION

UV-spectrum (Determination of λ Max)

IND was examined in the range 230-360 nm a 10 ppm solution of IND in methanol shows absorption maxima at about 256 nm. Absorbance at 256 nm shows 0.5887.

FTIR study

Interactions were studied by comparing obtained spectra of drug and excipients. The results of FTIR spectra of the drug, Castor oil, Span-80, Tween-80, and combination were observed, and different functional groups were reported. From this FTIR spectral analysis indicates that there were no significant physicochemical interactions between drug and excipients (Figures 3-5).

Physical appearance

Emulgel formulations were white viscous creamy preparation with a smooth, homogeneous texture, and glossy appearance. Results have been discussed in Table 2.

Spreadability

Spreadability is one of the essential criteria for an emulgel. Spreadability is depending on its viscosity of the formulation. The high viscosity of formulation would have poor spreadability. Spreadability is term expressed to denote the extent of the area on which the gel readily spreads on application to the skin. From above spreadability results, emulgel have the capacity to spread easily on the skin. Spreadability of emulgel shown in Figure 6.

Rheological study

The emulgel was rotated at 50 rpm for 10 min with spindle 07. The corresponding reading was noted. The viscosity of the emulgel was obtained (Figure 7). The viscosity of the formulations increases as the concentration of polymer increases.

Drug content determination

The drug content in emulgels was determined by spectrophotometer. IND content was measured by dissolving known quantity of emulgel formulation in methanol by sonication. Absorbance was measured after suitable dilution at 260 nm using the UV-VIS spectrophotometer as shown

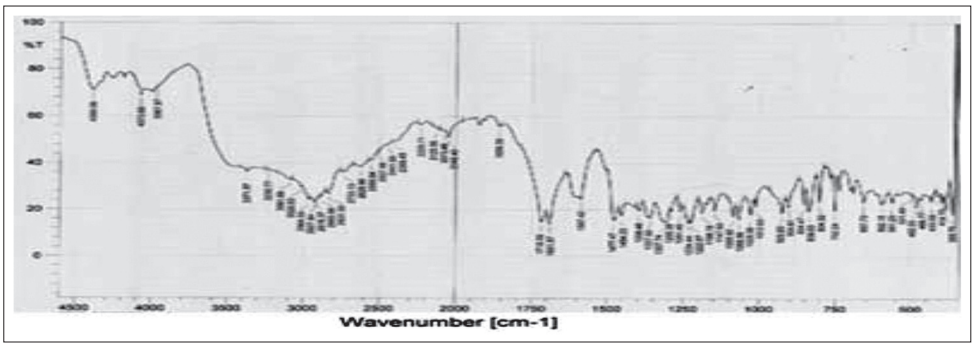

Figure 3: Fourier transform infrared spectra of indomethacin

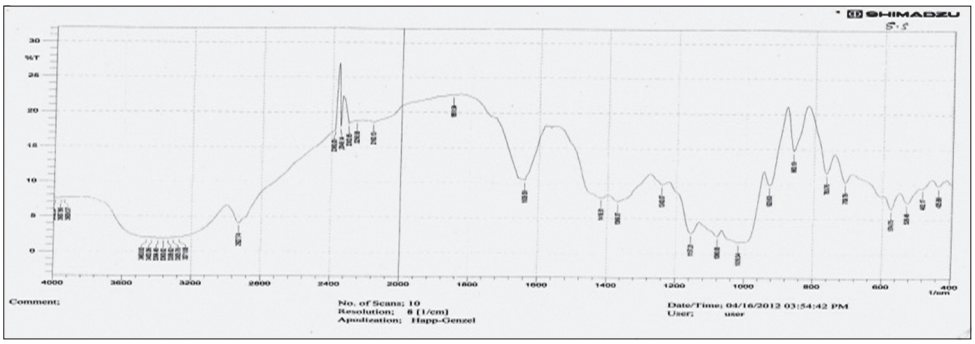

Figure 4: Fourier transform infrared spectra of pregelatinized *Ipomoea batata* starch

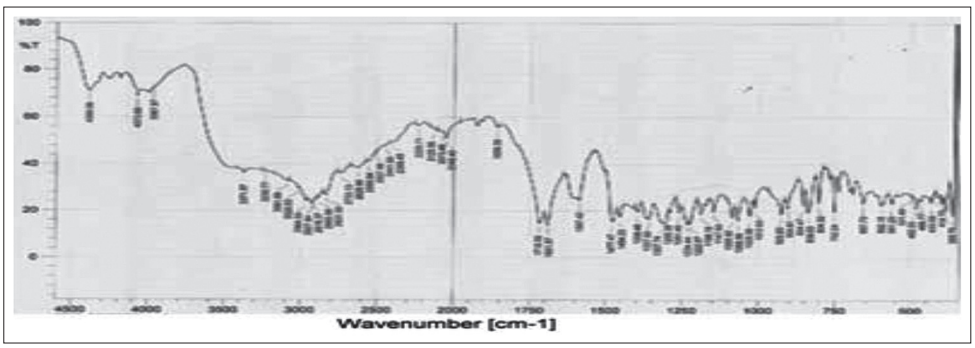

Figure 5: Fourier transform infrared spectra of physical mixture of indomethacin and pregelatinized *ipomoea batata* starch, Tween-80, and Span-80

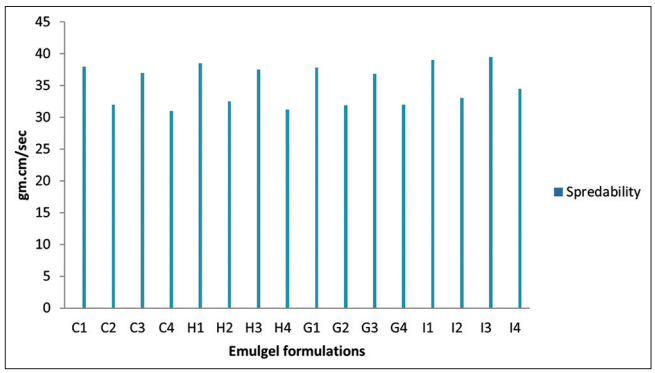

Figure 6: Spreadability of emulgel formulations

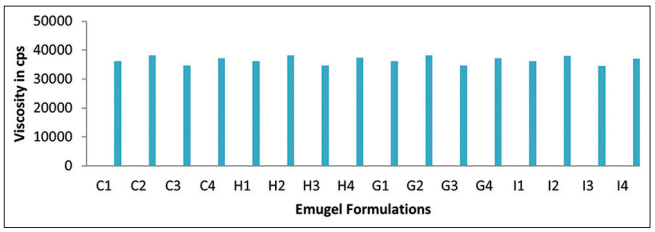

Figure 7: Viscosity of emulgel formulation

in Table 3. It was observed that the drug content of emulgel from C1 to I4 batches is between the range of 98.1-99.92% which was found to be satisfactory.

In vitro diffusion test

The *in vitro* release profiles of IND from its various Gellified Emulsion formulations are represented in Figure 8. It was observed that all the formulation had become liquefied and diluted at the end of the experiments, indicating water diffusion through the membrane. In general, it can be observed from

Table 2: Physicochemical characteristics of indomethacin emulgel formulations

Batch number	Appearance and color	Homogeneity	Consistency	pH	Viscosity (c.p)
C1	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.2	36200
C2	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.3	38240
C3	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.25	34750
C4	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.45	37242
H1	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.21	36202
H2	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.31	38241
H3	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.26	34751
H4	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.45	37291
G1	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.23	36168
G2	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.33	38248
G3	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.28	34738
G4	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.46	37221
I1	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.21	36145
I2	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.34	38110
I3	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.29	34455
I4	Yellowish, creamy	Homogenous with no grittiness	Cream like semisolid	6.49	37012

Table 3: Drug content of different gellified formulations

Formulation	Drug content (%)
C1	98.15
C2	99.89
C3	98.7
C4	99.71
H1	97.9
H2	99.72
H3	98.2
H4	99.6
G1	98.1
G2	99.75
G3	98.23
G4	99.91
I1	98.5
I2	99.88
I3	98.21
I4	99.87

figures that the better release of the drug from all Gellified Emulsion formulation. From results of *in vitro* diffusion studies using Franz diffusion cell, it can be concluded that I4 had better-sustained release than the other formulations. To understand the complex mechanism of drug release from the emulgel, the *in vitro* ciprofloxacin release data were fitted to Korsmeyer–Peppa's release model and interpretation of release exponent values (n) enlighten us in understanding the release mechanism from the dosage form. The release exponent values thus obtained were from 0.50 to 0.79. Based on these values, we can

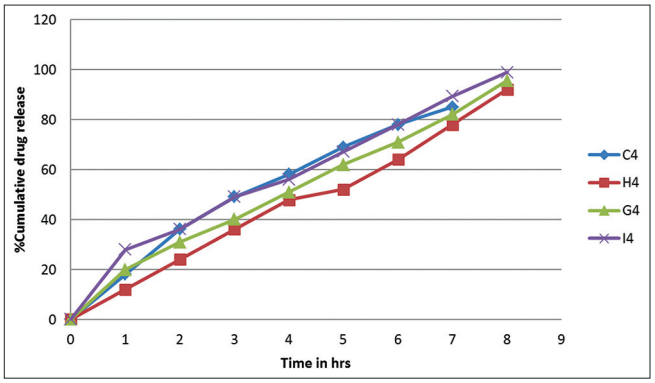

Figure 8: *In vitro* diffusion profile of various emulgel formulations

say that the formulation exhibited non-Fickian transport. The drug release was diffusion controlled as the plot of Higuchi's model was found to be linear ($r > 0.9291$). The formulations showed higher R^2 values for zero order plots indicating that drug release followed zero order kinetics, and drug release from these emulgels were by both diffusion and erosion.

Kinetics of drug release

The results obtained in *in vitro* release studies were plotted in different kinetic models. Regression coefficient (R^2) values of different kinetic models are shown in Table 4. This indicated that the release data of best formulation (I4) follows zero order kinetics because the value of R^2 is greater than 0.9. The mechanism of drug release is determined by zero order s where "*n*" is the release exponent. Hence, the mechanism of drug release is non-Fickian diffusion for I4 formulations given in Table 4.

Table 4: Kinetic profile of various formulations

F code	Zero-order		First-order		Higuchi		Korse-Meyer Peppa's		Possible mechanism of drug release
	n	R^2	n	R^2	n	R^2	n	R^2	Zero-order, non-Fickian
C1	11.52	0.995	0.19	0.764	34.32	0.890	0.9	0.950	Zero-order, non-Fickian
C2	12.09	0.992	0.19	0.755	35.77	0.900	0.992	0.959	Zero-order, non-Fickian
C3	12.29	0.993	0.198	0.731	35.74	0.925	1.004	0.979	Zero-order, non-Fickian
C4	12.46	0.991	0.199	0.746	36.77	0.904	1.022	0.963	Zero-order, non-Fickian
H1	10.98	0.975	0.205	0.815	33.94	0.842	0.917	0.918	Zero-order, non-Fickian
H2	11.16	0.961	0.208	0.833	34.89	0.826	0.936	0.903	Zero-order, non-Fickian
H3	11.11	0.975	0.207	0.826	34.50	0.847	0.932	0.925	Zero-order, non-Fickian
H4	11.16	0.986	0.206	0.821	34.62	0.833	0.932	0.907	Zero-order, non-Fickian
X1	11.31	0.990	0.196	0.747	33.25	0.896	0.924	0.954	Zero-order, non-Fickian
X2	11.48	0.995	0.195	0.744	33.74	0.901	0.937	0.955	Zero-order, non-Fickian
X3	10.37	0.956	0.202	0.745	12.92	0.117	0.623	0.390	Zero-order, non-Fickian
X4	12.07	0.993	0.197	0.746	16.75	0.245	0.747	0.509	Zero-order, non-Fickian
I1	11.29	0.989	0.196	0.761	14.82	0.199	0.984	0.455	Zero-order, non-Fickian
I2	10.68	0.934	0.195	0.791	13.59	0.157	0.638	0.390	Zero-order, non-Fickian
I3	12.36	0.986	0.193	0.717	17.18	0.262	0.762	0.525	Zero-order, non-Fickian
I4	10.86	0.939	0.195	0.785	33.15	0.800	0.892	0.870	Zero-order, non-Fickian

Comparative *in vitro* diffusion study

Release of optimized emulgel formulation up to 8 h compared with the marketed Indo methacin gel. Graph was plotted as cumulative percent drug release of IND emulgel and marketed IND gel versus time in hours (Figure 9).

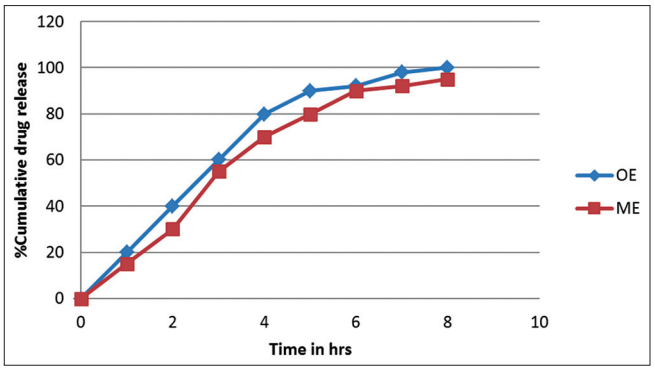

Figure 9: Comparison of *in vitro* diffusion of optimized and marketed emulgel

Stability studies

All the prepared emulgels were found to be stable on storage for 3 months; no change was observed in their physical appearance, pH, rheological properties, and drug content.

CONCLUSION

FTIR study revealed no interaction between the drug and excipients. The sixteen preliminary trial batches arranged/prepared by different concentrations of excipients lead to the final optimized concentration of the gel. *In vitro* diffusion and viscosity were taken as the responses for study, which were found to be within the expected range. Final formulation was prepared by the optimized concentration of the clove oil, Smix (Span-80 + Tween-80) and gelling agent (PGIBS), and general parameters were evaluated. The % release for the optimized batch (I4) was found to be 98.92% after 8 h of release study and viscosity was found to be 37012 cps. The formulations follow zero order kinetic model of drug release which involves the diffusion and erosion mechanism. The physical appearance was yellowish creamy, pH was 6.49. Thus, results of the current study clearly indicate, a promising potential of the IND emulgel as an alternative to the conventional dosage form using of natural excipient. Hence, emulgel is novel approach to decrease the dosing frequency and increase patient compliance.

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