Available online on 15.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Formulation design, development and characterization of dexibuprofen emulgel for topical delivery: *In-vitro and In-vivo* evaluation

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ABSTRACT

Emulgels have emerged as a promising drug delivery system for the delivery of hydrophobic drugs. The objective of the study was to prepare emulgel of Dexibuprofen, a NSAID, using Carbapol 940 as a gelling agent. Clove oil and Mentha oil were used as penetration enhancers. The emulsion was prepared and it was added in gel base. The formulations were evaluated for rheological studies, spreading coefficient studies, bioadhesion strength, skin irritation studies, in vitro release, ex vivo release studies, anti-inflammatory activity and analgesic activity. Formulation showed comparable analgesic and anti-inflammatory activity when they compared with marketed diclofenac sodium gel. So, it can be concluded that topical emulgel of Dexibuprofen possess an effective anti-inflammatory and analgesic activity.

Keywords: Emulgel, Dexibuprofen, Topical Drug Delivery, bioavailability, NSAIDs

Article Info: Received 03 March 2019; Review Completed 07 April 2019; Accepted 09 April 2019; Available online 15 April 2019

Cite this article as:

Mahajan VR, Basarkar GD, Formulation design, development and characterization of dexibuprofen emulgel for topical delivery: *In-vitro and In-vivo* evaluation, Journal of Drug Delivery and Therapeutics. 2019; 9(2-s):330-342

http://dx.doi.org/10.22270/jddt.v9i2-s.2711

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INTRODUCTION

Several analgesic agents are available in the market in different topical preparations (e.g. creams, ointments, and powders for the purpose of local dermatological therapy. It is applied locally in mild uncomplicated dermatophyte and other cutaneous infections.[1,2] 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. 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 addition, the formulator can control the viscosity, appearance, and degree of greasiness of cosmetic or dermatological emulsions. Oil-in-water emulsions are most useful as water washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications.[3] Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients, and water-soluble or miscible. Emulgels are emulsions, either of the oil-in-water or water in- oil type, which are gelled by mixing with a gelling agent. They have a high patient acceptability since they possess the previously mentioned advantages of both emulsions and gels. Therefore, they have been recently used as vehicles to deliver various drugs to the skin.[4,5]

MATERIALS AND METHODS

Materials

Dexibuprofen was obtained as a gift sample from Glenmark Pharmaceuticals Pvt. Ltd. Sinnar (Maharashtra). Carbopol 940 was obtained from Loba chemicals Mumbai. Dialysis membrane was procured from Hi media, Mumbai. All other chemicals used were of analytical grade and were used without any further chemical modification.

Solubility study

Screening of excipients can be done by determining the equilibrium solubility of Dexibuprofen in different oils, surfactants and co-surfactants. The solubility of Dexibuprofen in different oils, surfactants and co-surfactants was determined using shake flask method. An excess amount of Dexibuprofen was added to each vial containing 2ml of each excipient, and mixed by vortexing in order to facilitate proper mixing of Dexibuprofen with the vehicles. Vials were then shaken for 48 hrs in a Thermostatically controlled shaking water bath at 37 ± 1°C followed by equilibrium for 24 h. In order to separate the undissolved drug, the supersaturated sample was centrifuged at 3000

rpm for 10 min. The supernatant was then filtered using a membrane filter (0.45 µm, Whatman) and suitably diluted with methanol. The drug concentration was obtained via UV validated method at 221 nm.

Preliminary screening of oils, surfactants

The oil and surfactant having good solubilizing capacity for Dexibuprofen were selected for the studying there emulsifying properties. Briefly, 3ml of the surfactants were added to 3 ml of the oily phase. The mixture were gently heated at 40-50°C for homogenization of the components. Each mixture, 0.1 ml was then diluted with distilled water to 10 ml in a stopper conical flask. Ease of emulsification was judged by time required to yield homogeneous emulsion when it diluted 100 times with distilled water with continuous stirring on magnetic stirrer. Emulsifying ability of the mixture was categorized in five classes on the basis of time required to form homogeneous emulsion (shown in Table 2). Emulsions were allowed to stand for 2 hr and emulsions were furthermore observed visually for any turbidity or phase separation.

Preliminary screening of co-surfactant

The selected oily phase and surfactant were used for further screening of the different co-surfactants for their emulsification ability. Mixtures of 3 ml of co-surfactant, 3 ml of surfactant and 3 ml of oil were prepared and evaluated in similar fashion as described in screening of surfactants.

Drug-Excipient Compatibility Study

After selection and screening of the oil, surfactant and co-surfactant, next step is the physicochemical compatibility study of Dexibuprofen with excipients. The drug and excipient were equally distributed in glass ampoules. They were kept at room temperature 25°C and at 40°C/75% RH. The samples were drawn at intervals of 0, 2 and 4 weeks and analyzed for its physical appearance and drug stability by FT-IR.

Preparation of emulgel

Different formulations were prepared using varying amount of gelling agent and penetration enhancers. The method only differed in process of making gel in different formulation. The preparation of emulsion was same in all the formulations. The gel phase in the formulations was prepared by dispersing Carbopol 940 in purified water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5 using triethanolamine (TEA). The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propyl paraben were dissolved in propylene glycol whereas Dexibuprofen was dissolved in ethanol, and both solutions were mixed with the aqueous phase. Clove oil and mentha oil were mixed in oil 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 it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel[5]. The composition of different formulations has been discussed in Table 11.

Preformulation Study

Organoleptic Characterization of Drug

Melting Point: Melting point of the drug was found to be 52°C - 54°C by using Capillary tube method. The readings were taken in triplicate and average was taken. The Reference melting point is in the range 49 °C - 53°C.

Solubility: The solubility of Dexibuprofen in different solvents was determined using shake flask method. The results obtained were noted below in table 2.

Table 1: Organoleptic Properties of Drug

S. N.	Parameter	Observation
1	Colour	White to off white or Colorless
2	Odor	Odorless
3	Appearance	Solid crystalline powder

Table 2: Solubility of Dexibuprofen in different solvent

Sr. No.	Solvent	Solubility (mg/mL) at 25°C
1	Distilled Water	0.020± 0.0023
2	Cotton seed oil	0.027± 0.0054
4	Oleic acid	0.043± 0.0046
5	Sesame oil	0.050 ± 0.0006
6	Castor oil	0.039 ± 0.0061
7	Capryol-90	0.048± 0.0003
8	Tween 20	0.045 ± 0.0033
9	Tween 40	0.038± 0.0049
10	Tween 60	0.046± 0.0036
11	Tween 80	0.042± 0.0043
12	Span 20	0.045±0.0021
13	Span 80	0.042±0.0069
14	Labrasol	0.042±0.0002
15	Arachis oil	0.031±0.0010
16	sunflower oil	0.049 ±0.0020
17	Soybean oil	0.035±0.0012
18	Polyethylene glycol 400	0.047±0.0064
19	Polyethylene glycol 600	0.053 ±0.0009
20	Transcutol P	0.042±0.0002

FT-IR Spectroscopy:

FTIR spectrum (shown in Figure 1) of the drug sample showed all the characteristic IR peaks as reported in indicating the presence of functional groups of Dexibuprofen shown in table 3.

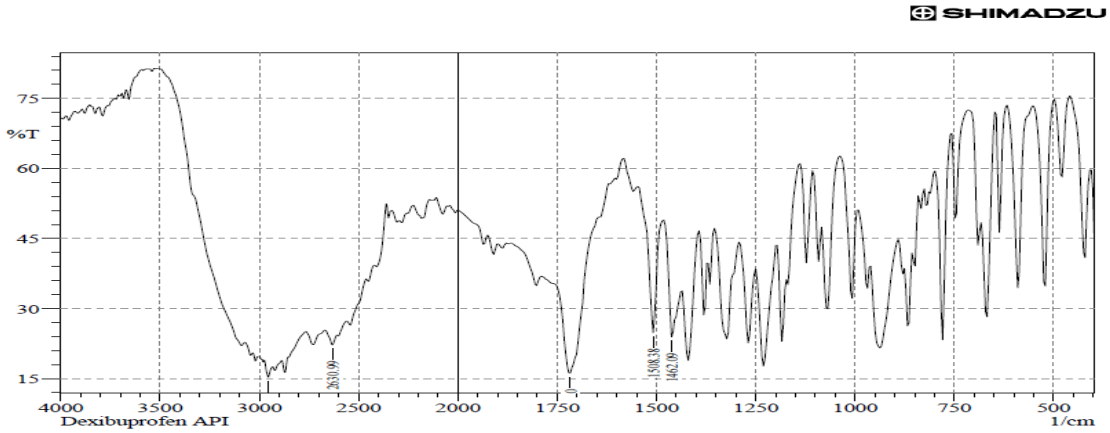


Figure 1: FT-IR of Dexibuprofen

Table 3: IR Interpretation of dexibuprofen

Sr. No.	Typical IR bands (cm^{-1})		Interpretation
	Reference range	Observed	
1	2960-2850	2955.04	C-H stretching vibration
2	2700-2500	2630.99	C=C stretching vibration
3	1600-1450	1508.38	COOH stretching vibration

UV Spectroscopy:

Maximum absorbance of Dexibuprofen in methanol is shown in table 4 and figure 2. The λmax of Dexibuprofen in methanol was found to be at 221 nm this is characteristic property of Dexibuprofen in its pure form, hence it can be confirmed that obtained sample was authentic.

Calibration curve of Dexibuprofen in methanol

The calibration curve of the Dexibuprofen was prepared in methanol. Table 5 shows the absorbance at λ_{max} 221 nm for different concentrations of Dexibuprofen and figure 3 shows calibration curve. The regression coefficient was found to be 0.999 with slope value 0.052 and the Y intercept value 0.

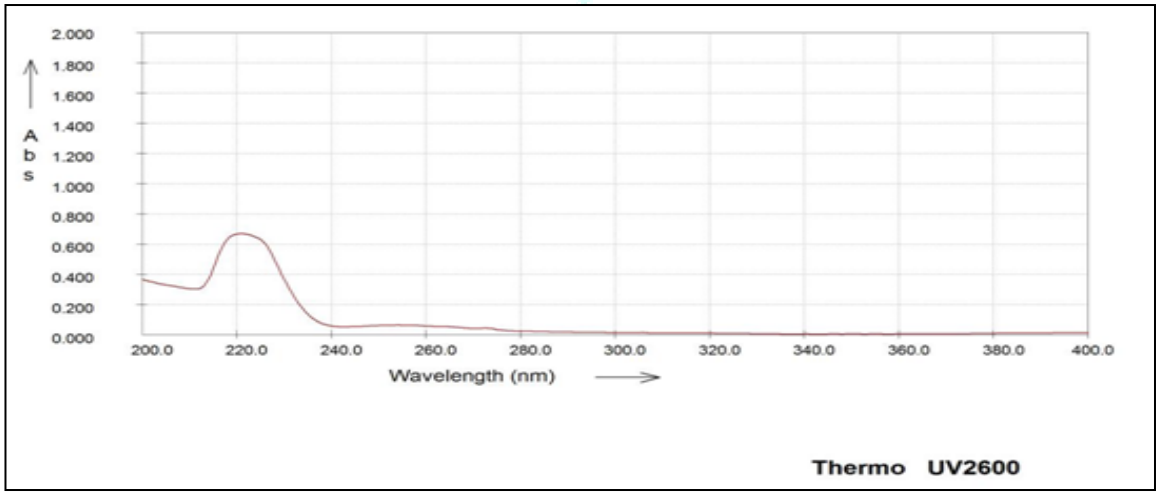


Figure 2: UV- Spectra of Dexibuprofen in Methanol

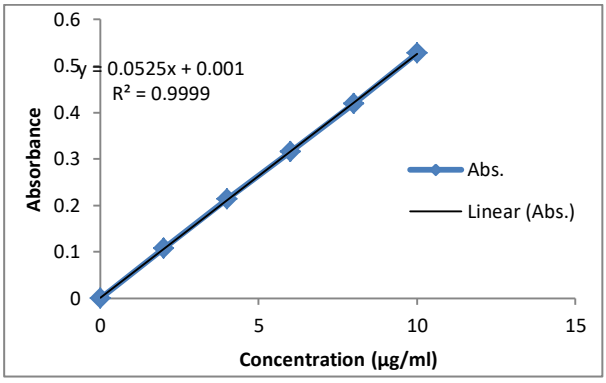


Figure 3: Calibration curve of Dexibuprofen in Methanol

Table 4: Maximum wavelength (λmax) of Dexibuprofen in Methanol.

Solvent	Wavelengths of maximum absorbance λmax (nm)	
	Observed	Reference
Methanol	221	220

Table 5: Calibration curve data of Dexibuprofen in Methanol

Sr. No.	Concentration (µg/ml)	Absorbance
1	2	0.107
2	4	0.214
3	6	0.315
4	8	0.419
5	10	0.530

Table 6: Preliminary selected components from solubility study

Preliminary selected Components for SMEDDS		
Oils	Surfactants	Co-surfactants
Sesame oil	Tween 60	PEG 600
Sunflower oil	Tween 20	PEG 400
Oleic acid	Tween 80	Span 20

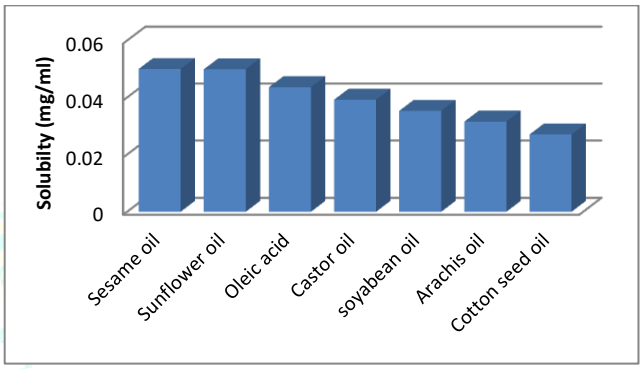


Figure 4: Solubility of Dexibuprofen in OILS

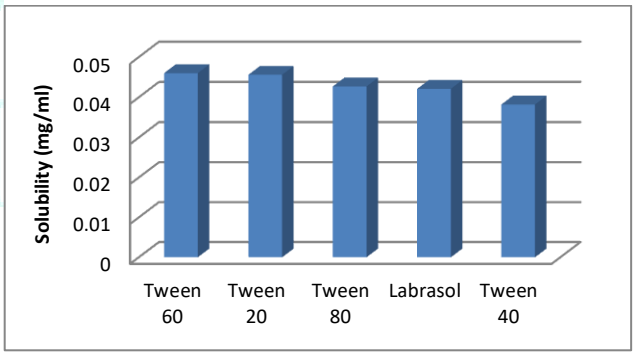


Figure 5: Solubility of Dexibuprofen in SURFACTANTS

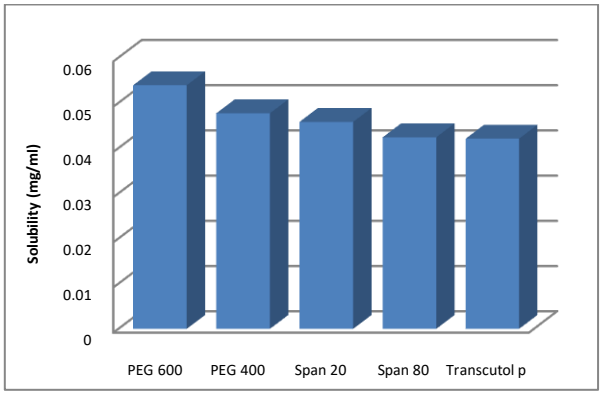


Figure 6: Solubility of Dexibuprofen in CO-SURFACTANTS

Excipients Screening

Solubility study

SMEDDS, an emulsion based formulation is a blend of oils and surfactants in suitable proportion that rapidly forms an oil in water (o/w) microemulsion with moderate gastric motility when exposed to the aqueous media present in the GIT. Co-surfactant and organic solvent can also be added sometime to improve the emulsification and solubility respectively. In order to select a best combination of oils, surfactants, and co-surfactants for SMEDDS formulation, component which shown a maximum solubility for Dexibuprofen was selected.

The solubility of Dexibuprofen in different oils and surfactant and co-surfactant are shown in figure 4, 5 and 6. The solubility study of the Dexibuprofen in different oils reveals that Sesame oil, Sunflower oil and oleic acid shows very good solubility for Dexibuprofen as compared with other oils as shown in figure 4. The surfactants such as Tween 60, Tween 20 and Tween 80 shows very good solubility for Dexibuprofen as compared with other surfactants as shown in figure 5. The co-surfactant PEG 600, PEG 400 and Span 20 shows good solubility than other co-surfactants as shown in figure 6.

Preliminary screening of oils, surfactants:

Oil (Sesame oil, Sunflower oil, Oleic acid) and Surfactant (Tween 60, Tween 20, Tween 80) having good solubilizing capacity for Dexibuprofen were selected for the studying there micro emulsifying properties. Micro emulsifying ability of oils such as Sesame oil, Sunflower oil, and Oleic acid in combination with different surfactants such as Tween 60, Tween 20 and Tween 80 was determined.

The micro emulsifying property of Sesame oil in combination with Tween 60 rapidly forms micro emulsion but it was slightly less clear and forms bluish white appearance and forms gel like appearance after 24 hr. Therefore combination with Tween 60 will be rejected. While Sesame oil in combination with Tween 20 forms rapid micro-emulsification having clear and slightly bluish appearance within 1 min. but it was shows two separate layers after 24 hr. Therefore combination with Tween 20 will be rejected. The micro emulsifying property of Sesame oil in combination with Tween 80 rapidly forms microemulsion but it was slightly less clear and forms bluish white appearance and forms gel like appearance after 24 hr. Therefore combination with Tween 80 will be rejected. The micro emulsifying property of Sunflower oil in combination with Tween 60,Tween 20 and Tween 80 rapidly forms microemulsion but it was slightly less clear and forms bluish white appearance ,all these combination shows two separate layer after 24 hr. Therefore all combination with Sunflower oil will be rejected. While Oleic acid in combination with Tween 60 and Tween 20 forms rapid micro-emulsification having clear and slightly bluish appearance within 1 min. In comparison of both the combinations of Oleic acid with Tween 60 and Tween 20, the second combination i.e. combination with Tween 20 observed less clear than combination with Tween 60. Therefore combination of Oleic acid and surfactant Tween 60 was selected. The micro emulsifying property of Olive oil in combination with Tween 80 rapidly forms microemulsion but it was slightly less clear and forms bluish white appearance, also the Tween 80 combination gives gel like appearance after 24 hr. Therefore combination of Oleic acid and surfactant Tween 80 was rejected.

From the above study for preliminary screening of oil and surfactant the two combinations were found better involving first combination of oleic acid and Tween 60 and second combination of oleic acid and Tween 20. As per the solubility study of drug in Surfactant the Tween 60 has more solubility than the Tween 20, therefore first combination of oil Oleic acid and surfactant Tween 60 were selected for further study.

Preliminary screening of co-surfactant:

The selected oil phase (Oleic acid) and surfactant (Tween 60) are used for screening of the different co-surfactants (PEG 600, PEG 400, Span 20) for their emulsification ability. The emulsifying ability of different combination is shown in table 8.

Oleic acid and Tween 60 mixture combination with the selected three excipients were studied for their emulsification ability and found that the combinations with Co-surfactant PEG 600 and PEG 400 shows better micro emulsion formation within 1 min. But the combination of the co-surfactant Span 20 shows rapidly forming but slightly less clear micro emulsion, having a bluish white and PEG 400 with the oil and surfactant mixture shows phase separation after 24 hrs so PEG 400 will be rejected. Further study will concluded that the combination of the co-surfactants i.e. PEG 600 were selected for further study, and it will be used in the co-surfactant for the self micro emulsifying system.

Conclusion from all the above study that finally selected components for the SMEDDS formulation of Dexibuprofen was given in table 9.

Table 7: Emulsifying properties of oils in combination with different surfactants.

Oil	Surfactant	Observation	Grade
Sesame oil	Tween 60	Rapidly forming, slightly less clear microemulsion, having a bluish white.	B
	Tween 20	Rapidly forming microemulsion, having a clear or slightly bluish appearance.	A
	Tween 80	Rapidly forming, slightly less clear microemulsion, having a bluish white.	B
Sunflower oil	Tween 60	Rapidly forming, slightly less clear microemulsion, having a bluish white.	B
	Tween 20	Rapidly forming, slightly less clear microemulsion, having a bluish white.	B
	Tween 80	Rapidly forming, slightly less clear microemulsion, having a bluish white	B

Table 8: Emulsifying property of different Co-surfactant with selected oil and surfactant

Oil and Surfactant mixture	Co-surfactant	Observation Grade
Oleic acid + Tween 60	PEG 600	A
	PEG 400	A
	Span 20	B

Table 9: Finally selected components for the SMEDDS formulation

Drug	Oil	Surfactant	Co-surfactant
Dexibuprofen	Oleic acid	Tween 60	PEG 600

Drug-Excipient Compatibility Study

Visual method

Drug-excipient compatibility study was done for four week at 25°C (RT) and 40°C and samples are visually observed initially, after 2 weeks, after 4 weeks for any color change and results are shown in table 10.The visual observation shows that there is no color change observed during storage for four week.

Table 10: Visual observation of the drug and excipient

S. N.	Drug + Excipient	Temp.	Observation		
			Initially	After 2 Week	After 4 Week
1	Drug + Oleic acid	25°C	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid
		40°C	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid
2	Drug + Tween 60	25°C	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid
		40°C	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid
3	Drug + PEG 600	25°C	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid
		40°C	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid	Clear, Transparent, Yellowish liquid

FT-IR Spectroscopic method

After four week FT-IR of L-SMEDDS samples were taken to determine the any functional group change during the storage and result are shown in figure 7. The L-SMEDDS FT-IR of sample placed for compatibility shows the functional peaks of Dexibuprofen (drug) at 2924.18,1708.99,1552.24 cm^{-1} and no change in functional peaks of drug observed after 4 week.

Visual observation and FT-IR study shows that there is no interaction between the drug and excipients selected for the formulation of self micro emulsifying system of Dexibuprofen.

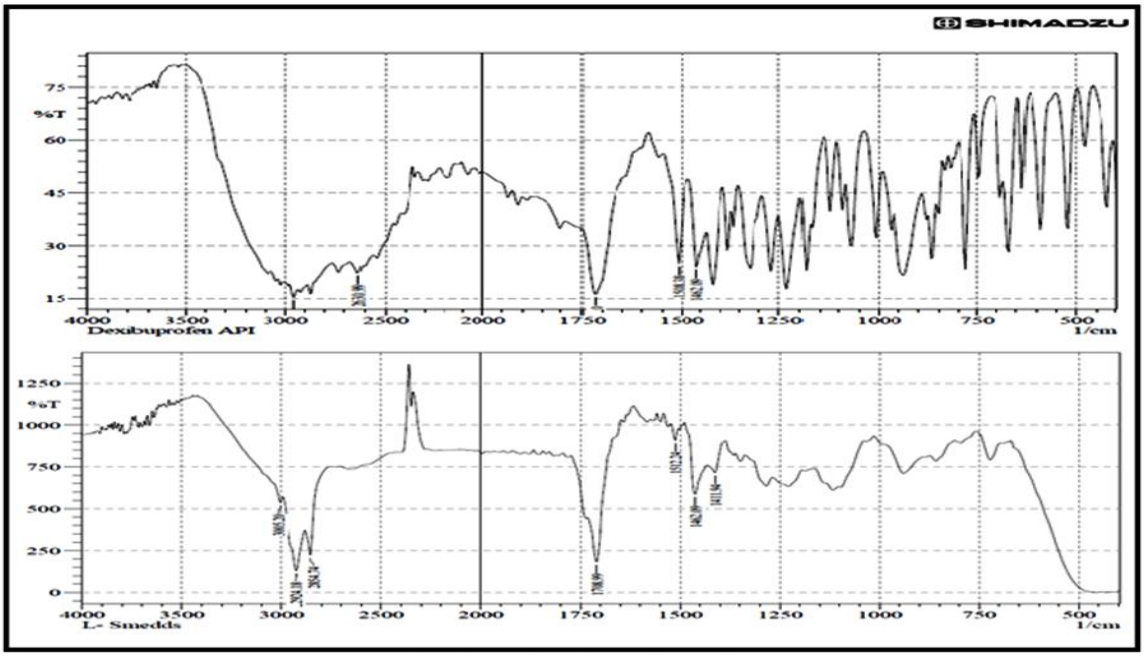


Figure 7: Drug excipient compatibility study by FT-IR

Evaluation of emulgel

Physical examination

The prepared emulgel formulations were inspected visually for their color, appearance and consistency.[6]

Table 11: Composition of different formulation batches (%w/w).

Ingredient	F1	F2	F3	F4
Dexibuprofen	1	1	1	1
Carbapol 940	1	1	1	1
Oleic Acid	7.5	7.5	7.5	7.5
Tween 60	0.5	0.5	0.5	0.5
Span 20	1	1	1	1
PEG 600	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5
Methyl paraben	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01
Sesame Oil	-	-	8	10
Clove oil	4	6	-	-
Water	q.s.	q.s.	q.s.	q.s.

Rheological study

The viscosity of the formulated batches was determined using a cone and plate viscometer with spindle 7 (Brookfield Engineering Laboratories). The assembly was connected to a thermostatically controlled circulating water bath maintained at 25°C. The formulation whose viscosity was to be determined was added to a beaker covered with thermostatic jacket. Spindle was allowed to move freely into the emulgel and the reading was noted.[7]

Spreading coefficient

Spreading coefficient was determined by apparatus. It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide was fixed on the wooden block. An excess of emulgel (about 2 g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. Weight of 500 mg was placed on the top of the two

slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in s) required by the top slide to cover a distance of 5 cm was noted. A shorter interval indicates better spreading coefficient.[8]

Skin irritation test (patch test)

A set of 8 rats were used in the study. The emulgel was applied on the properly shaven skin of rat. Undesirable skin changes, i.e., change in color, change in skin morphology were checked for a period of 24 hr.[9]

Table 12: Physical parameters of formulation batches.

Formulation	Color	Homogeneity	Consistency	Phase separation
F1	White	Excellent	Excellent	None
F2	White	Excellent	Excellent	None
F3	Pale Yellow	Excellent	Excellent	None
F4	Yellow	Excellent	Excellent	None

Bioadhesive strength measurement

The modified method was used for the measurement of bioadhesive strength. The apparatus consist of two arm balance. Both the ends are tied to glass plates using strings. One side contains two glass plates. Other side contains single glass plate for keeping weight. The right and left pans were balanced by adding extra weight on the left hand pan. The balance was kept in this position for 5 min. Accurately weighed 1 g of emulgel was placed between these two slides containing hairless fresh rat skin pieces, and extra weight from the left pan was removed to sandwich the two pieces of glass and some pressure was applied to remove the presence of air. The balance was kept in this position for 5 min. Weight was added slowly at 200 mg/min to the left hand pan until the two glass slides got detached from each other. The weight (gram force) required to detach the emulgel from the glass surface gave the measure of bioadhesive strength.[10] The bioadhesive strength is calculated by using following:

Biodhesive strength = Weight required (gm) /Area (cm^2)

In vitro release studies

The in vitro drug release studies were carried out using a modified Franz diffusion (FD) cell. The formulation was applied on dialysis membrane which was placed between donor and receptor compartment of the FD cell. Phosphate buffer pH 7.4 was used as a dissolution media. The temperature of the cell was maintained at 37°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (5 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 221 nm and the cumulative % drug release was calculated. The difference between the readings of drug release and control was used as the actual reading in each case.[11]

Ex vivo drug release study

The ex vivo drug release study of selected formulations (F2 and F4) was carried out in a modified Franz diffusion cell, using wistar male rat skin. A section of skin was cut and placed in the space between the donor and receptor compartment of the FD cell, keeping the dorsal side upward. Phosphate buffer pH 7.4 was used as dissolution media. The temperature of the cell was maintained constant at 32 °C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously. The samples were withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media.[12] Samples were analyzed spectrophotometrically at 221 nm.

In vivo anti-inflammatory activity

Experimental design

Edema was induced on the left hind paw of the rats by subplantar injection of 1% (w/v) carrageenan. Formulations, i.e., F2, F4 and standard (diclofenac sodium gel) were applied 30 min before carrageenan administration. The paw volume was measured at intervals of 30, 60, 90, 120 min by mercury displacement method using plethysmometer.[13]

Group 1 (Control group): Carrageenan (1%) was administered in the plantar surface of rat.

Group 2 (Standard group): Topical marketed diclofenac gel + Carrageenan.

Group 3 (Test): Formulations F2 and F4 + Carrageenan.

The % inhibition of paw edema in drug treated group was compared with carrageenan control group and calculated according to the formula:

% Inhibition of drug = (Vc –Vt) /Vc x 100

Where,

Vc = inflammatory increase in paw volume control group

Vt = inflammatory increase in paw volume in (drug +carrageenan) treated animals.

In vivo analgesic activity

The analgesic activity was carried out using hot plate method. Following groups were made and latency period in which rat responded to hot plate was calculated **Group 1 (Control Group):** No topical treatment was given and latency period was calculated.

Group 2 (Standard Group): The rats were treated with diclofenac gel and its latency period was calculated.

Group 3 (Test Group): The rats were treated with test formulations, i.e., F2 and F4 and latency period was calculated.

Stability studies

The prepared emulgels were packed in aluminum collapsible tubes (5 g) and subjected to stability studies at 5 °C, 25 °C / 60% RH, 30 °C /65% RH, and 40 °C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties and drug content.[14]

RESULTS AND DISCUSSION

Physical appearance

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

Spreading coefficient

The spreading coefficient of various emulgel formulations are given in Fig. 8.

Rheological studies

The tests were performed at 100 rpm for 10 min. Results are given in Fig. 9.

Skin Irritation test

No allergic symptoms like inflammation, redness, irritation appeared on rats up to 24 h.

Biodhesive strength measurement

The bioadhesive strength of various emulgel formulations have been shown in Fig. 10.

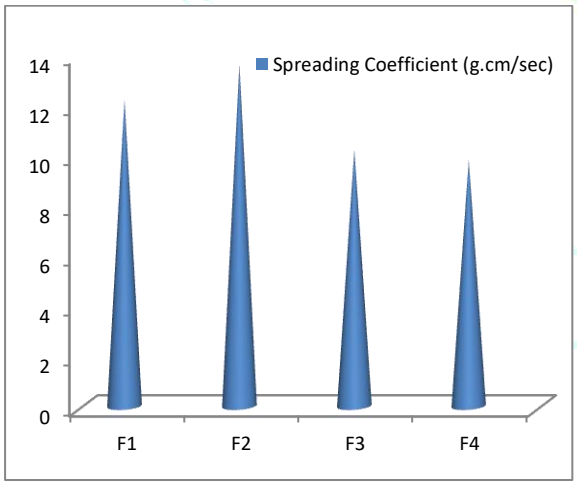


Figure 8: Spreading coefficient of the formulation F1–F4 (mean± SD).

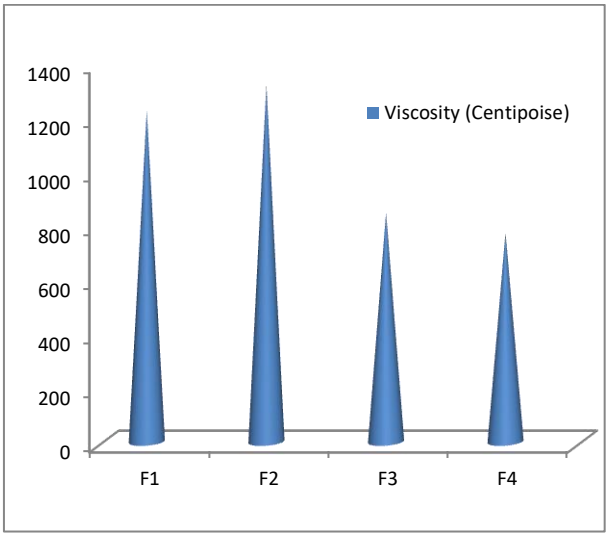


Figure 9: Viscosity of the formulations F1–F4 (mean± SD).

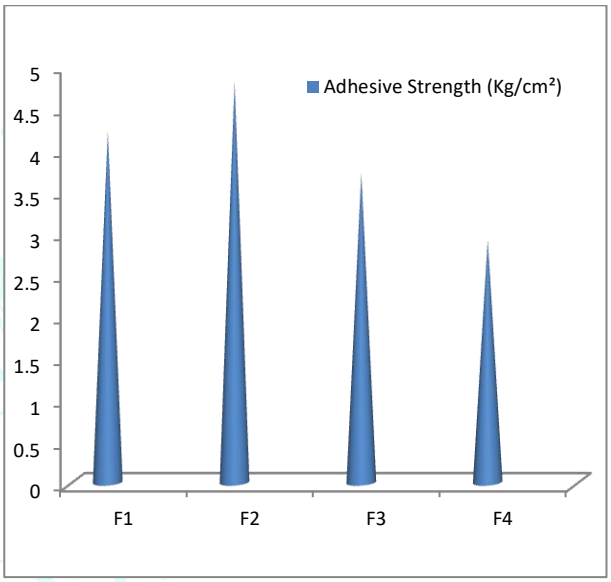


Figure 10: Bioadhesive strength of formulations F1–F4 (mean ± SD).

In vitro release study

The study showed the release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F4 > F1 > F2 >F3 where the amounts of the drug release of the drug released after 150 min were 61.08%, 59.48%, 57.21%, 55.91%, respectively (Fig. 11, Table 15).

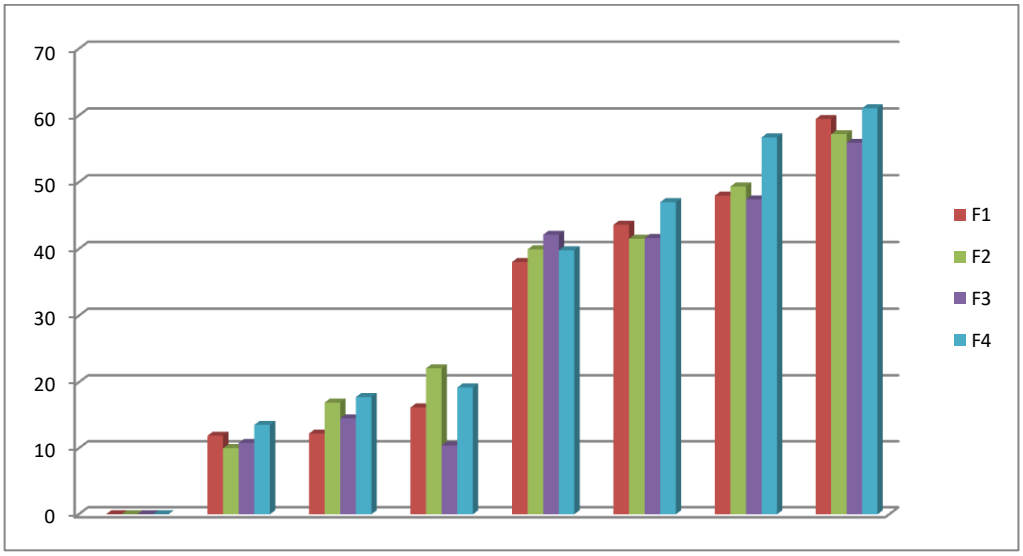


Figure 11: In vitro cumulative % drug release of formulation F1– F4.

Ex vivo release study

This study was carried out only on two best optimized formulations. The study showed the release of the drugs from its emulsified gel formulation F2 and F4 were 59.45% and 61.68%, respectively in 150 min. The results are show in Fig. 12.

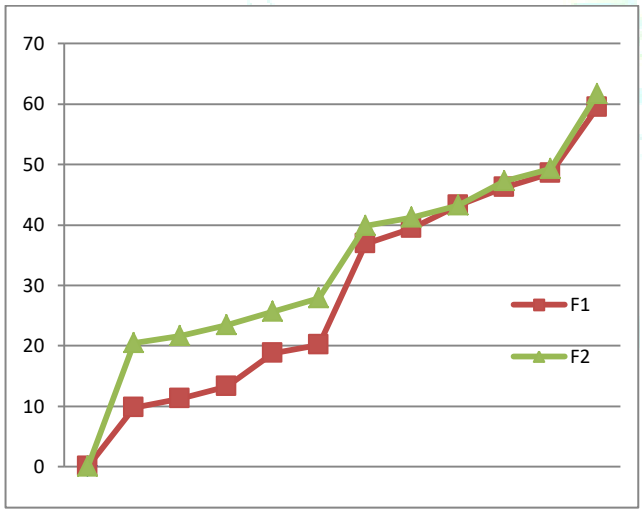


Figure 12: Ex vivo cumulative % release of formulations F2 and F4.

Anti-inflammatory activity

The anti-inflammatory action of formulation F2 and F4 was calculated and it was compared with diclofenac sodium (marketed preparation). The % inhibition of diclofenac sodium, F2 and F4 were found to be 64.81%, 58.28% and 59.62%, respectively. This showed that the formulations were as effective as marketed formulation.

Analgesic activity

The formulations showed hike in lapse time. They were compared with diclofenac sodium gel (marketed preparation).

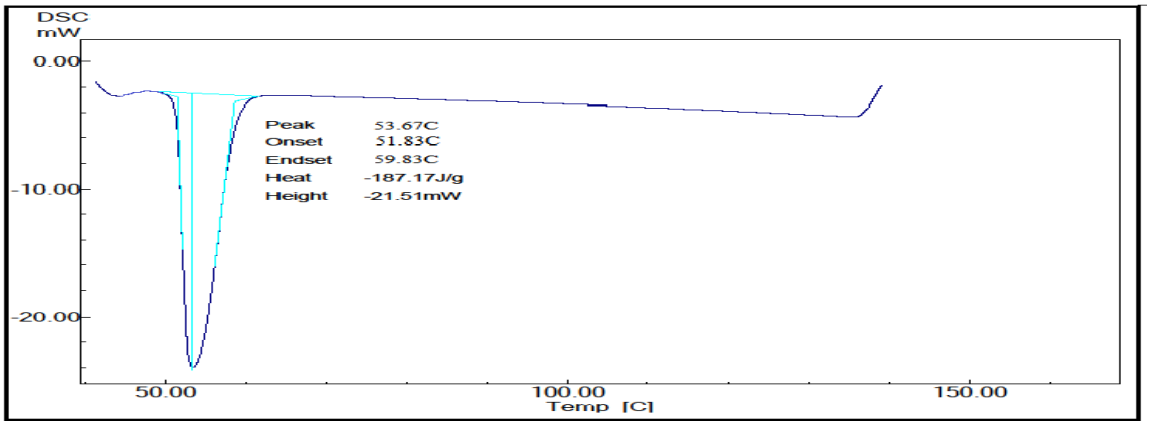
The lapse time of diclofenac sodium gel, F2 and F4 were found to be 6.8 s, 5 s and 5.1 s.

Stability study

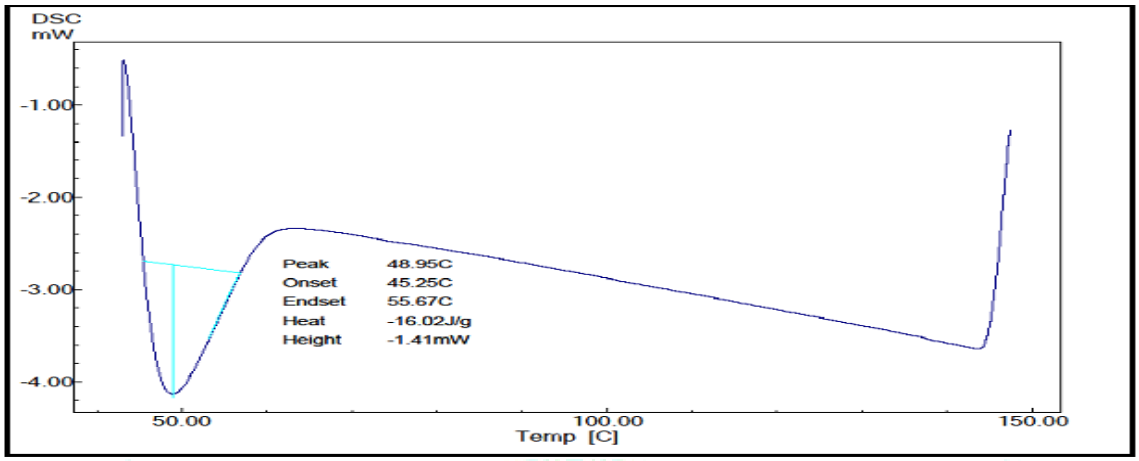
All the prepared emulgel formulations were found to be stable upon storage for 3 months, no change was observed in their physical appearance, pH, rheological properties and drug content.

Differential Scanning Calorimetry

The DSC thermogram of pure Dexibuprofen exhibited a sharp endothermic peak at 53.67°C. The DSC of optimized formulation not shows any sharp melting peak of Dexibuprofen. The absence of sharp melting peak of Dexibuprofen at 48.95°C in the DSC of optimized formulation indicate that the lipids and aerosil 200 inhibited the crystallization of Dexibuprofen i.e. Dexibuprofen is in amorphous form or in solubilized form in optimized formulation.



(A)



(B)

Figure 13: Differential Scanning Calorimetry of (A) Dexibuprofen (B) Optimized Formulation.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used to determine the particle morphology of pure drug and optimized formulation. The SEM of Dexibuprofen and optimized formulation were done and results are shown in figure 14.

Figure 14 revealed that Dexibuprofen present as crystalline powder with cylindrical shaped crystals. The optimized formulation shows irregular shaped granular particle. SEM of the optimized formulation does not show any cylindrical crystals of drug (Dexibuprofen) on the surface of aerosil 200, the shape of formulation is spherical and somewhat smooth. It indicates that drug is present in the soluble form in lipid (SMEDDS formulation), which is adsorbed on the surface of aerosil 200.

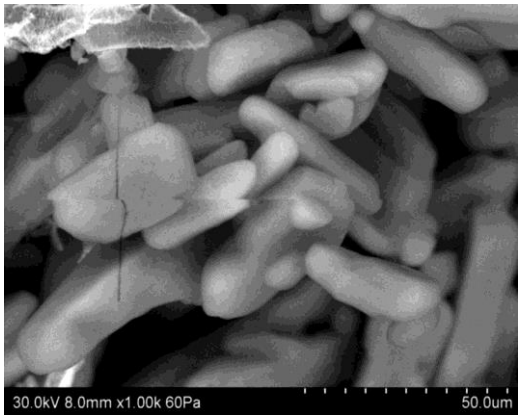


Figure (A)

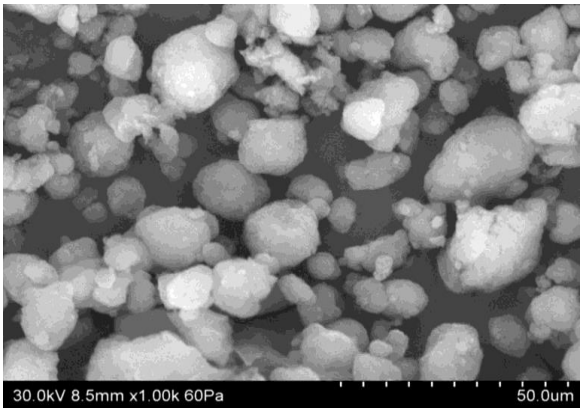


Figure (B)

Figure 14: Scanning electron microscopy of (A) Dexibuprofen (B) Optimized Formulation

Powder X-ray Diffraction

The X-ray diffraction pattern of Dexibuprofen and Optimized formulation was done and shown in figure 15.

In the X-ray diffraction pattern of Dexibuprofen the sharp peaks at a diffraction angle 2θ of 12.46°, 14.12°,14.86°, 16.83, 17.74°, 19.42°, 20.22°, 22.51, 24.40°, 25.12°, 27.90, 28.64°,29.56, 31.10°, 32.10°, 34.10°, 35.76°, 36.96°, 37.72°, 38.68°, 41.16°, 43.94° and 45.22° are present. The presence of sharp X-ray diffraction peaks of Dexibuprofen is absence in the optimized formulation reveals that drug (Dexibuprofen) either present in the amorphous form or present in solubilized form in optimized formulation.

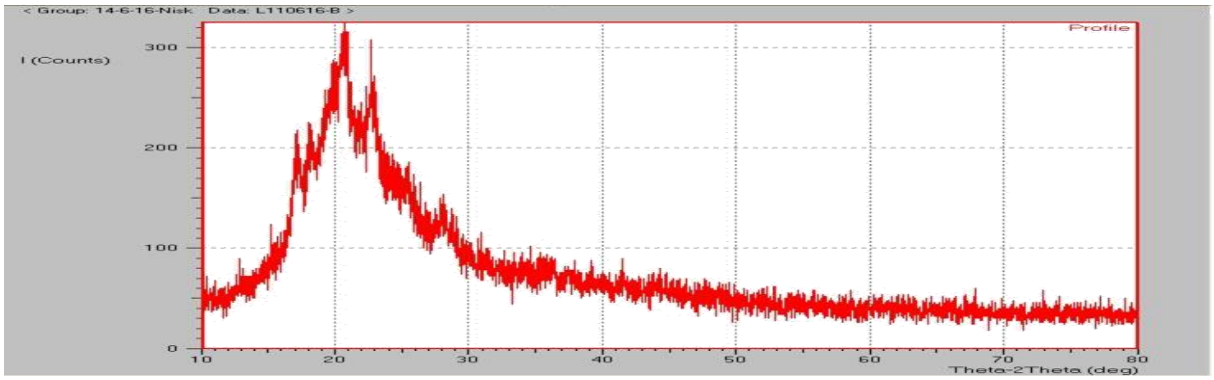


Figure (A)

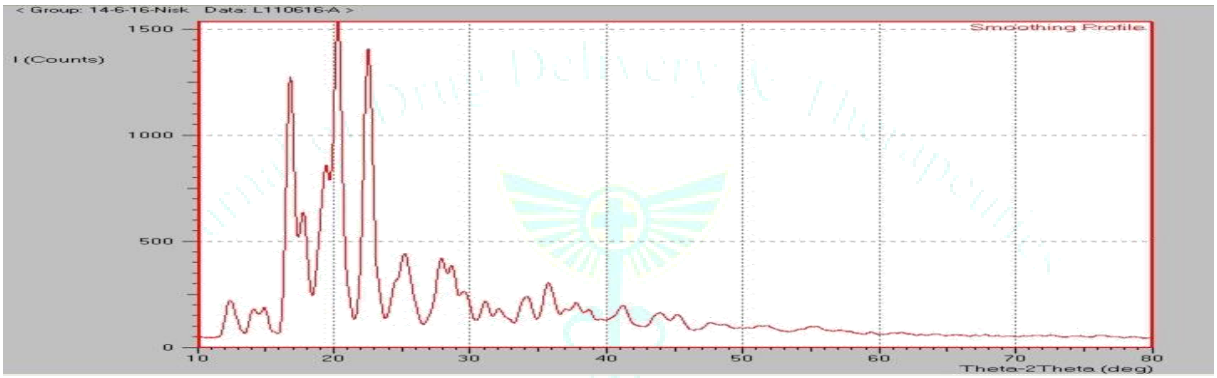


Figure (B)

Figure 15: X- ray Powder Diffraction of (A) Dexibuprofen (B) Optimized Formulation

Stability Study

Liquid SMEDDS

The thermodynamic stability study was carried out for Liquid-SMEDDS formulation.

Heating cooling cycle: The liquid SMEDDS was subjected to the six cycles between refrigerator temperatures 4ºC and 45ºC with storage at each temperature for not less than 48 hours was studied. There is no change found in the formulation that means the formulation found stable.

Centrifugation test: Passed SMEDDS was centrifuged at 3500 rpm for 30 min using centrifuge (Remi motors Ltd.), there was no phase separation found.

Freeze thaw cycle: Three freeze thaw cycles between -21ºC and +25ºC with storage at each temperature for not less than 48 hours was done for SMEDDS, and it was found stable.

Solid SMEDDS

Stability study of optimized formulation at Freeze temperature (-20°C), Room temperature (25°C) and High temperature (40°C) was done for three month and evaluated for following parameters.

Visual Observation

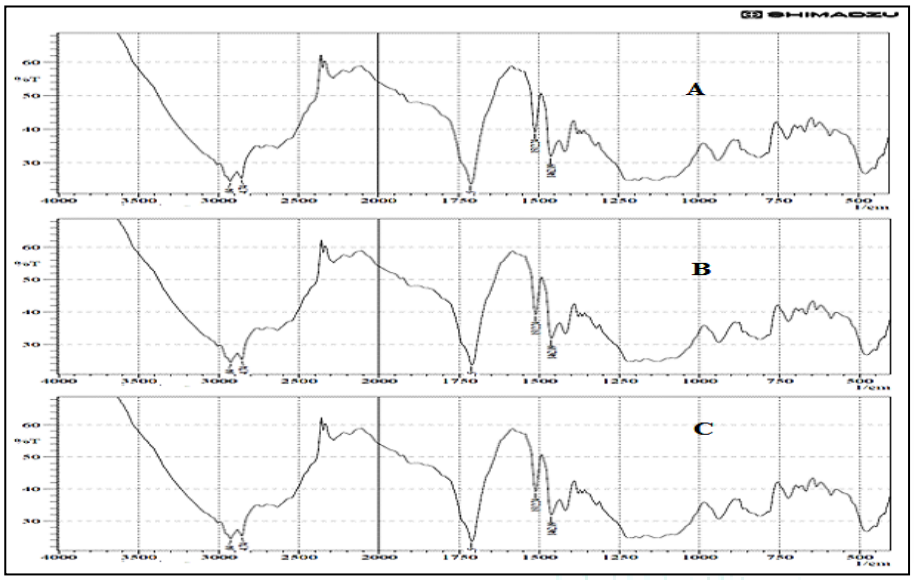
Visual observation study (shown in table 13) reveals that there is no change in color observed during stability study for 3 month.

Table 13: Visual observation data of Optimized formulation for 3 month

Formulation	Temp.	Initially	Time (months)		
			1 month	2 month	3 month
Optimized Formulation	-20°C	White color, Odorless powder	White color, Odorless powder	White color, Odorless powder	White color, Odorless powder
	25°C	White color, Odorless powder	White color, Odorless powder	White color, Odorless powder	White color, Odorless powder
	40°C	White color, Odorless powder	White color, Odorless powder	White color, Odorless powder	White color, Odorless powder

FT-IR

FT-IR of optimized formulation sample placed at different temperature (-20°C, 25°C, 40°C) was done after 3 month to determine any change in drug and result is shown in figure 16. The FT-IR of optimized formulation shows that there is no change in the functional peaks of drug (Dexibuprofen) at all temperature after 3 months.



(Where, A, B and C are FT-IR of optimized formulation sample placed at different temperature -20°C, 25°C, 40°C respectively)

Figure 16: FT-IR of optimized formulation sample placed at different temperature (A 20°C, B -25°C, C - 40°C)

Drug Content and Emulsifying Property

Drug content and emulsifying property of optimized formulation was done after each month for 3 months and results were shown in table 14. The drug content data shows that there is no change in drug content of optimized formulation. Also no change in emulsifying property of optimized formulation was found.

In-vitro drug release study

In vitro drug release study of optimized formulation was done after 3 month in pH 6.8 phosphate buffer solution.

Table 14: Drug content and emulsifying property of optimized formulation for 3 months

Parameter	Temp.	Time (Month)		
		1 Month	2 Month	3 Month
Drug Content	-20°C	98.23	98.43	98.43
	25°C	98.82	98.82	98.62
	40°C	98.43	98.62	97.84
Emulsifying Property	-20°C	Disperse uniformly to form micro emulsion instantly	Disperse uniformly to form micro emulsion instantly	Disperse uniformly to form micro emulsion instantly
	25°C	Disperse uniformly to form micro emulsion instantly	Disperse uniformly to form micro emulsion instantly	Disperse uniformly to form micro emulsion instantly
	40°C	Disperse uniformly to form micro emulsion instantly	Disperse uniformly to form micro emulsion instantly	Disperse uniformly to form micro emulsion instantly

Table 15: Data for in vitro cumulative % drug release data of formulations F1–F4.

Time (Min)	F1	F2	F3	F4
0	00.00 ± 0.00	00.00 ± 00.00	00.00 ± 00.00	00.00 ± 00.00
5	11.91 ± 00.01	10.02 ± 08.65	10.82 ± 06.83	13.55 ± 30.44
15	12.23 ± 00.05	16.93 ± 09.24	14.54 ± 13.30	17.76 ± 10.21
30	16.19 ± 01.30	22.13 ± 06.83	10.44 ± 10.2	19.22 ± 15.72
60	38.05 ± 31.70	39.95 ± 24.70	42.14 ± 00.38	39.82 ± 00.03
90	43.63 ± 31.70	41.56 ± 03.10	41.64 ± 07.55	47.02 ± 03.12
120	48.01 ± 07.55	49.38 ± 02.80	47.44 ± 03.10	56.72 ± 13.34
150	59.48 ± 02.85	57.21 ± 02.21	55.91 ± 00.49	61.08 ± 02.34

CONCLUSION

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel is helpful in enhancing spreadability, adhesion, viscosity and extrusion, this novel drug delivery become popular. Moreover, they will become a solution for loading hydrophobic drugs in water soluble gel bases for the long term stability. Similarly in the study, topical emulgels of Dexibuprofen were formulated and subjected to physicochemical studies i.e. rheological studies, spreading coefficient studies and bioadhesion strength, in vitro release studies and ex vivo release studies through rat skin. In vitro release of the tests formulations were performed to determine drug release from emulgel rate and duration of drug release. From the in vitro studies, formulation F4 showed maximum release of 61.08% in 150 min. Ex vivo drug release was also performed in which formulation F4 showed best release of 61.68% in 150 min. Carrageenan induced paw edema and hot plate tests revealed anti-inflammatory and analgesic activity. The formulations F2 and F4 were comparable with marketed diclofenac topical gel. So Dexibuprofen emulgel can be used as an anti-inflammatory analgesic agent for topical drug delivery.

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