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Formulation and Evaluation of Microemulsion Based Topical Hydrogel Containing Lornoxicam

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ABSTRACT

The objective of present study was to formulate hydrogel thickened Lornoxicam transdermal formulation. Eutectic mixture of camphor and menthol was chosen as oily phase (maximum 10%), solvent for Lornoxicam and powerful penetration enhancer. Tween 80, ethanol and Carbopol 934p, HPMC K-15M and Xanthan gum were selected as surfactant, co-surfactant and hydrogel thickening agent respectively. Ternary phase diagrams were constructed to obtain the concentration range of oil phase, surfactant and co-surfactant for microemulsion formulation. Hydrogel thickened microemulsions were characterized for pH, viscosity, spreadability**,** in vitro drug transport study with excised rat skins and invivo anti inflammatory activity. The average drug transport rate of optimized hydrogel thickened microemulsion containing 1 % w/w Lornoxicam, 10 % w/w oily phase of camphor and menthol, 30 % w/w tween 80, ethanol (2:1), 57 % w/w water, 1.5 % w/w Carbopol 934p and 0.5 % w/w Triethanolamine through rat skin was 2.02 µg/cm^2/h . The percentage in vitro drug release of optimized hydrogel thickened microemulsion was 78.91 %. pH, viscosity and spreadability of optimizes batch was 6.4, 5291 cps and 5.98 gcm/sec.

INTRODUCTION

Inflammation is a general, non-specific reaction to foreign particles and other noxious stimuli such as toxins and pathogens (Madigan *et al.,* 2002). Characteristics of the inflammatory response include redness, swelling, pain and heat which are localized at the site of infection (Fur *et al.,* 1992). Inflammation may occur due to burns, chemical irritants and infection by pathogens, physical injury, immune reactions due to hypersensitivity, ionizing radiation and foreign bodies (Gloster *et al.,* 1996). Lornoxicam acts by inhibiting the metabolites of COX branch of arachidonic acid pathway. It inhibits both isoform in the same proportion; perfectly balanced inhibition of COX-1 and COX-2 is achieved. As Prostaglandins play an important role in gastrointestinal mucosal protection by strengthening the mucosal barrier for acid and in inhibiting gastric acid secretion. Thus inhibition of prostaglandin synthesis leads to adverse effects (Prakash *et al.,* 2010). Lornoxicam is practically insoluble in water (Ammar *et al.,* 2012).

Its low solubility leads to low dissolution rate and thus poor therapeutic efficacy. The aim of the present research work was to formulate hydrogel thickened microemulsion with good stability, powerful permeation ability and suitable viscosity for the topical delivery of lornoxicam using eutectic mixture of camphor and menthol as oily phase, solvent for the lornoxicam, power penetration enhancer and imparts cooling effect to the skin. Carbopol 934p, HPMC K15M and Xanthan gum was used as a hydrogel thickening agent.

MATERIALS & METHODS

Lornoxicam was obtain as a gift sample from Alkem research Lab. Mumbai, HPMC K15M, Carbopol 934p and Xanthan gum from accurate pharma, Camphor and Menthol from chem. Dyes, Tween 80 from fine star industry and Ethanol from Triveni Chemicals.

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Determination of solubility of Lornoxicam

Solubility studies were conducted by placing an excess amount of lornoxicam (approximately 200mg) in a 2mL microtube containing 1mL of each vehicle (Table 1). Then, the mixture was vortexed and kept for 3 days at 37°C in a shaking water bath to facilitate the solubilisation. The samples were centrifuged at 10,000 rpm for 10min to remove the undissolved lornoxicam. The supernatant was taken and diluted with methanol for quantification of lornoxicam by UV Spectrophotometer.

Plotting of ternary phase diagrams

Ternary phase diagrams were constructed to obtain the components and their concentration ranges that can result in large existence area of microemulsion without the drug or containing 1% lornoxicam (Yun *et al.,* 2001). Eutectic mixture consisting of equal parts of camphor and menthol was selected as the oily phase. Tween 80 was selected as the surfactant in the study as it was readily miscible with the eutectic mixture. When co-surfactant (ethanol) was used, the ratio of surfactant to co-surfactant was 1:1, 1:2 and 2:1. The ternary phase diagrams (Figure 3) were constructed using water titration method at ambient temperature. For each phase diagram, the ratio of oil to surfactant or mixture of surfactant and co-surfactant was varied from 1:9 to 9:1. Water was added drop by drop, under gentle agitation, to each oily mixture until mixture become turbid. Transparent to translucent fluid systems were characterized as microemulsion (Sheikh *et al.,* 2007).

Formulation of microemulsion

Lornoxicam (1% w/w) was dissolved in oily phase consisting of equal amount of camphor and menthol. The lornoxicam solution was then mixed with mixture of surfactant and co-surfactant. Finally, an appropriate amount of water was added to the lornoxicam solution mixture drop by drop to get microemulsion (Yang *et al.,* 2004). The composition of the different formulated microemulsion (batches A1-A3) is shown in Table 2.

Formulation of hydrogel thickened microemulsion

Carbopol 934p, HPMC K15M and Xanthan gum was hydrated in fixed amount of water for at least 4 h and then previously formulated microemulsion was gradually added with continuous stirring till clear viscous solution was obtained (Chandra *et al.,* 2009). Finally, fixed amount of triethanolamine was added to get different hydrogel thickened microemulsions (batches F1-F9, Table 2).

Evaluation of Microemulsion Based Hydrogel

Globule Size Determination

The average droplet size of samples was measured at 25°C by Malvern zeta sizer. The microemulsion based hydrogel (2-2.5 ml) was transferred to a disposable polystyrene cuvette with the help of plastic syringe or micropipette and the droplet size of the microemulsion was determined via a combination of laser doppler velocimetry and phase analysis light scattering (PALS) at an angle of 90^0 at 25^0C. (Behera *et al.,* 2010)

Determination of viscosity

The viscosity microemulsion were measured at 25°C with a Brookfield viscometer. (Brookfield DV–E) Viscosity of the samples was determined using a Brookfield digital viscometer with spindle number 63. The sample temperature was controlled at 25±1°c before the each measurements (Tsai *et al.,* 2010).

Zeta potential determination

Zeta potential of samples was measured by Zeta sizer. Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with methanol and rinsed using the sample to be measured before each experiment (Mandal *et al.,* 2010)

Physical appearance and pH

The pH of hydrogel formulations was determined by using digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated, using a calibrated digital pH meter at 25°C. (Bazigha *et al.,* 2010)

Spreading Coefficient

An apparatus modified by suitably in the laboratory and was used for spreadability study. The apparatus was made of wooden block with scale and glass slide having a pan mounted on a pulley. Excess formulation was placed between glass slide and the smooth polish board. A 100g weight was placed on the upper glass slide for 5 min to compress the formulation to uniform thickness. Weight (100 g) was added to the pan. The time in seconds required to separate the slides was taken as a measure of spreadability (Margaret *et al.,* 1956). The spreadability was calculated by using the following formula:

$S = (m \times l)/t$

Where S is spreadability; m is weight tied to the upper slides; l is length of glass slide and; t is time taken in seconds.

Drug Content Determination

Weigh accurately 1 gm of hydrogel and it was dissolved in 100 ml of phosphate buffer pH 7.4. The volumetric flask was kept for 4hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. 1ml of the solution was taken in to 10ml volumetric flask and the final volume was made with 7.4 phosphate buffer (Khullar *et al.,* 2011). The absorbance was measured spectrophotometrically at 378 nm after appropriate dilution against corresponding phosphate buffer pH 7.4 as blank.

In Vitro Drug Release Study

The *in vitro* drug release studies were performed by using Franz diffusion cell with cellophane paper. The water jacketed recipient compartment had total capacity of 30 ml and it

had one arms for sampling and other side for water inlet and outlet. The donor compartment had internal diameter of 2.8 cm^2. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The receptor compartment contained phosphate buffer solution pH 7.4. That was maintained at 37°C ± 1°C (Mukhrjee *et al.,* 2005). The membrane was equilibrated before application of the microemulsion based Hydrogel equivalent to 8 mg of drug onto the donor side. 1ml of Samples were periodically withdrawn from the receptor compartment, replacing with the same amount of fresh PBS solution, and assayed by using a spectrophotometer at 378 nm. .

In vitro skin permeation and skin deposition studies

Ex vivo skin permeation study was performed by using Franz diffusion cells with an effective diffusion area of 2.8 cm^2. The excised skin samples of rat were clamped between the donor and the receptor compartment of Franz diffusion cells. Then, 1g of microemulsion based Hydrogel containing 1% (w/w) Lornoxicam was applied on the donor compartment. The receptor compartment was filled with PBS pH 7.4 and maintained at 37°C with stirring at 100 rpm. At predetermined time intervals (1hr), 1 ml receptor medium was withdrawn and the same volume of pure medium was immediately added into the receptor compartment. The procedure was repeated up to 8 hr.

All samples were filtered through Whatman filter paper and analyzed by UV spectrophotometer at 378 nm. The amount of the drug permeated per unit surface area (µg/cm^2) was plotted versus time (hours) and the flux (µg/cm^2 hr^{-1}) was calculated from the slope of the line. The permeability coefficient was then calculated according to the following equation (Kasliwal *et al.,* 2008).

$$P_m = J_{ss} / C_d$$

Where: P_m is permeability coefficient, J_{ss} is flux and C_d is concentration of the drug in the donor side.

After 8h of the in vitro skin permeation experiment, the surface of skin specimens was washed with methanol. The effective surface area of the skin (2.8 cm^2) was separated and minced with a surgical sterile scalpel then finally homogenized in a vial filled with methanol (1 mL/cm^2) by using ultra turrax homogenizer at 16,000 rpm for 5 min on ice bath (4^0C) (Lee *et al.,* 2010). The tissue suspension was centrifuged for 5 min, and then the supernatants were filtered and assayed for the lornoxicam content by UV at 378nm.

***In-vivo* Anti- Inflammatory Activity**

Edema was induced on the left hind paw of the rats by sub plantar injection of 0.1ml of 1 % (w/v) carrageenan. Formulations F1, F4 and standard were applied topically with gentle rubbing to the paw of each rat of respective group 30 min before carrageenan administration. The paw volume was measured at intervals of 60 min up to 8Hr by mercury displacement method using plethysmometer. The average paw edema volume of all the groups were calculated and compared with that of control. The % inhibition of paw edema in drug treated group was compared with carrageenan control group and calculated according to the formula (Gupta *et al.,* 2006). The animal care and handling procedure described above were performed in accordance with CPCSEA guidelines. The experimental protocols were approved by animal ethical committee of the B.Pharmacy college rampura, godhra, Gujarat.

$$\% \text{ inhibition of drug} = Vc\text{-}Vt / Vc \times 100$$

Vc = Inflammatory increase in paw volume control group, Vt = Inflammatory increase in paw volume in (drug+carrageenan) treated animals.

RESULTS AND DISCUSSION

A eutectic mixture is a mixture of two or more phases at a composition that has the lowest melting point, and where the phase simultaneously crystallizes from molten solution at a particular temperature. Camphor and menthol forms eutectic mixture.

Camphor is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol and acts as mild local anesthetic and antimicrobial substance. Menthol is widely used in pharmaceuticals, confectionery, and toiletry products as a flavouring agent or odour enhancer. The aim of the present study was to develop a hydrogel thickened microemulsion using eutectic mixture of menthol and camphor which is novel, industrial acceptable, functional yet technologically difficult to copy creating a high barrier to reverse engineering by counter feiters.

The eutectic mixture worked as an oily phase and solvent mixtures for the solubilisation of the lornoxicam. The solubility of lornoxicam in the oil phase (Eutectic mixture) was 147.22 ±2.46 mg/ml. Tween 80 and ethanol was 6.21 ±0.11 and 4.05 ±0.78.

Ternary phase diagrams

The construction of pseudo-phase diagram (CHEMIX Software) makes it easy to find out the concentration range of components for the existence range of microemulsions. The transparent to translucent microemulsion region is presented in phase diagrams (Figure 3). No distinct phase inversion of microemulsions was observed. The rest of the region on the phase diagram represents the turbid and conventional emulsions based on visual observation. Figure 3 shows that the incorporation of co-surfactant (ethanol) increased the maximum amount of incorporated water in the oil-surfactant system with the microemulsion zone being increased in all cases compared to the co-surfactant free system. As the ratio of surfactant to co-surfactant increases, the existence area of microemulsion becomes enlarged, reaching maximum at 2:1. Addition of surfactant co-surfactant mixture in 2:1 ratio increased the water incorporation to a maximum of 58% compared to 44% in the co-surfactant free system. Based on these results, microemulsions containing 1% Lornoxicam were prepared at surfactant to co-surfactant ratio of 2:1.

Table 1: Solubility of Lornoxicam in Various Solvents Saturated for 72 hours at 37°C

	Solvent	Solubility (mg/ml)
Water	Water	1.87 ± 0.71
Oil	Eutectic Mixture	147.22 ±2.46
Surfactant	Tween 80	6.21 ±0.11
Co Surfactant	Ethanol	4.05 ±0.78

Table 2: Formulation of Microemulsion

	Amount of each ingredient (wt. in gm)			
Batch code	**Lornoxicam**	**Oil Phase**	**S/C* (2:1)**	**Water**
A1	1	10	30	09
A2	1	10	25	14
A3	1	10	20	19

S/C * is the mixture of surfactant to co-surfactant (2:1)

Table 3: Formulation of Microemulsion Based Hydrogel

Batch code		**Ingredients (wt in gm)**		
Trial -1	**Carbopol-934p**	**Water**	**Microemulsion**	**Triethanolamine**
F1	1.5 g	48 g	50 g of batch A1	0.5 g
F2	1.5 g	48 g	50 g of batch A2	0.5 g
F3	1.5 g	48 g	50 g of batch A3	0.5 g
Trial -2	**HPMC K15M**	**Water**	**Microemulsion**	**Triethanolamine**
F4	1.5 g	48 g	50 g of batch A1	0.5 g
F5	1.5 g	48 g	50 g of batch A2	0.5 g
F6	1.5 g	48 g	50 g of batch A3	0.5g
Trial -3	**Xanthan gum**	**Water**	**Microemulsion**	**Triethanolamine**
F7	1.5 g	48 g	50 g of batch A1	0.5 g
F8	1.5 g	48 g	50 g of batch A2	0.5 g
F9	1.5 g	48 g	50 g of batch A3	0.5g

Table 4: Physicochemical Parameters of the Various Microemulsion Formulations

Code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Globule Size (nm)	175.7	241.01	271.3	228.8	257.1	284.6	268.5	294.1	305.1
Zeta Potential(mV)	-21.4	-17.6	-13.6	-11.2	-10.2	-9.4	-9.1	-8.7	-8.1
PDI	0.289	0.497	0.583	0.482	0.682	0.741	0.694	0.751	0.894

Table 5: Evaluation parameter of Microemulsion Based Hydrogel

Batch No.	pH	**Viscosity (cp)**	**Drug content**	**Spreadability (g.cm/sec)**
F1	6.4 ± 0.21	5291 ± 11.02	94.87 ± 2.8	5.89 ± 0.13
F2	6.9 ± 0.19	5841 ± 09.83	91.32 ± 2.3	5.45 ± 0.41
F3	7.4 ± 0.11	6382 ± 10.35	93.99 ± 1.9	5.18 ± 0.28
F4	5.1 ± 0.16	4756 ± 10.27	90.57 ± 1.5	6.79 ± 0.33
F5	5.9 ± 0.24	4812 ± 08.56	91.47 ± 1.3	6.11 ± 0.47
F6	6.5 ± 0.15	5151 ± 12.36	92.55 ± 2.6	5.25 ± 0.15
F7	5.2 ± 0.18	4146 ± 11.37	89.12 ± 2.1	7.29 ± 0.24
F8	6.1 ± 0.21	4254 ± 09.67	90.42 ± 2.6	6.14 ± 0.27
F9	6.8 ± 0.14	4460 ± 10.83	89.87 ± 1.5	5.93 ± 0.28

The values are expressed as mean±SD (N=3)

Table 6: *In vitro* Drug Release of Microemulsion Based Hydrogel.

Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	32.24	18.60	10.69	34.26	29.30	6.51	34.18	22.21	17.59
2	45.18	26.39	16.04	47.58	36.13	12.69	49.99	37.19	22.31
3	49.42	34.19	22.87	58.91	38.39	19.57	59.12	47.12	28.27
4	55.31	36.85	25.55	61.51	37.68	22.12	62.44	50.81	30.28
5	63.28	44.03	27.79	66.39	45.00	28.89	67.23	58.19	36.88
6	67.52	47.26	30.53	71.30	50.02	32.05	72.22	62.04	39.30
7	71.78	51.19	32.97	75.45	55.47	35.64	76.2	65.58	43.54
8	78.91	57.84	38.14	80.75	64.09	42.90	82.17	70.72	53.12

Table 7: Result of Model fitting for Different formulation.

Formulation	**Model**			
Code	**Zero-order**	**First-order**	**Higuchi**	**Hixon Crowell**
F1	0.963745833	0.858068432	0.980669944	0.941803428
F4	0.966766526	0.837739778	0.979023553	0.936095262
F7	0.879060752	0.879948071	0.955255694	0.911945396

Table 8: Permeation Parameters of Lornoxicam across Rat Skin.

Batch No.	**Flux J_{ss} (µg cm^{-2} h^{-1})**	**Permeation coefficient**	**Cumulative deposition on skin (µg cm^{-2})**
F1	2.02 ± 0.023	0.202	3.91 ± 0.061
F4	2.34 ± 0.057	0.234	4.31 ± 0.023

The values are expressed as mean±SD (N=3)

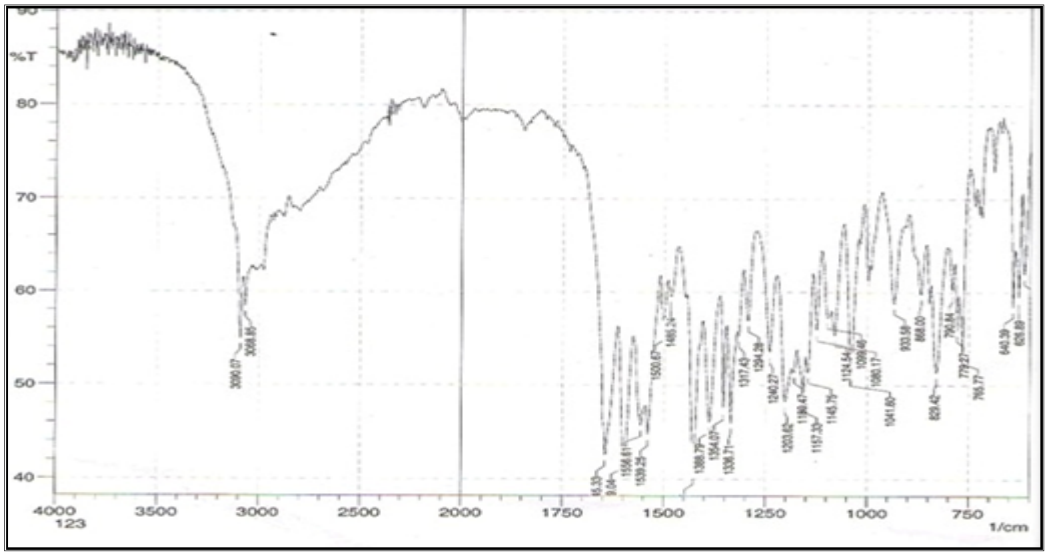

Fig. 1: IR graph of pure drug.

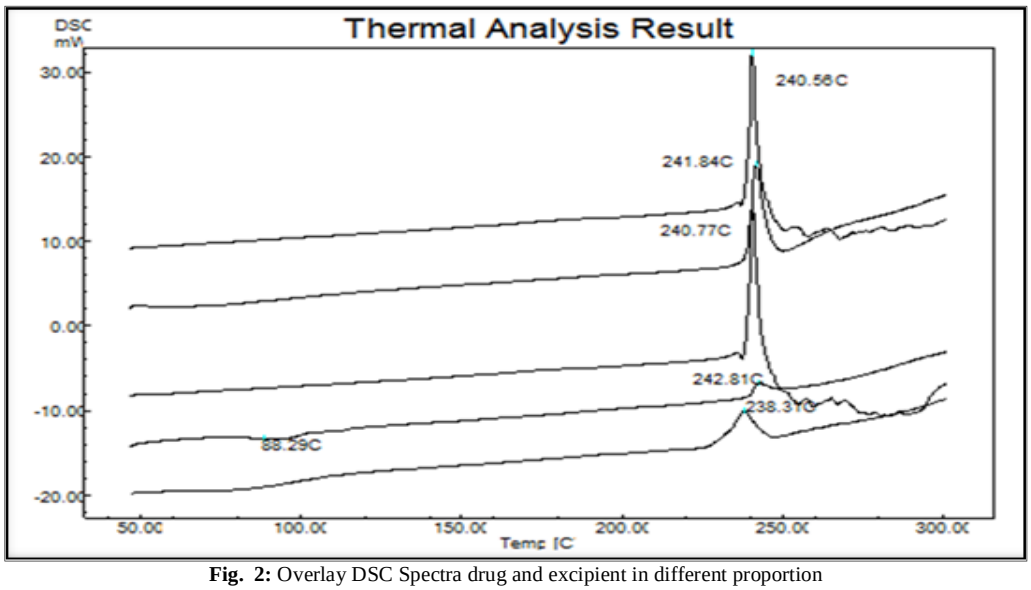

Fig. 2: Overlay DSC Spectra drug and excipient in different proportion

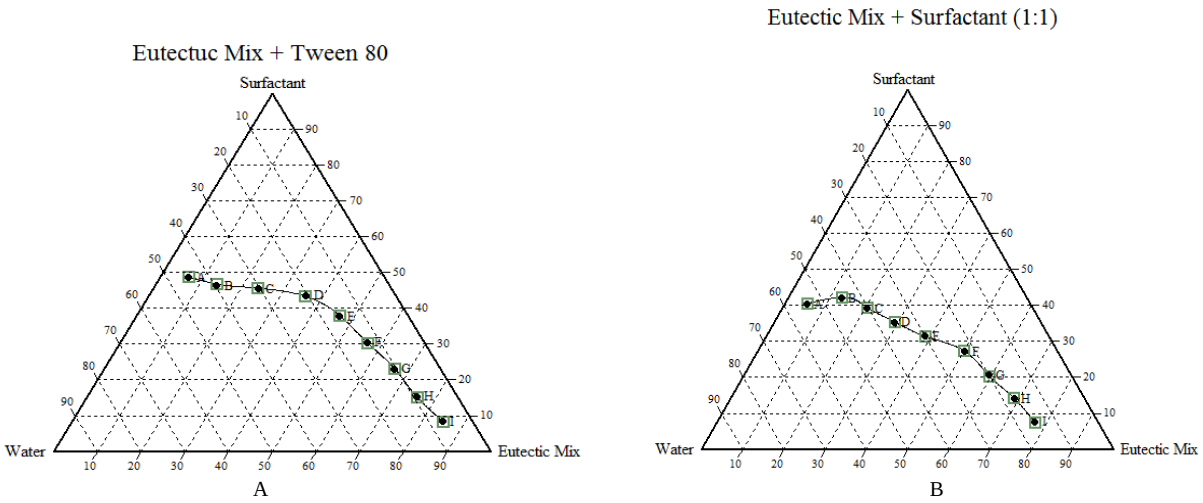

Fig. 3:….

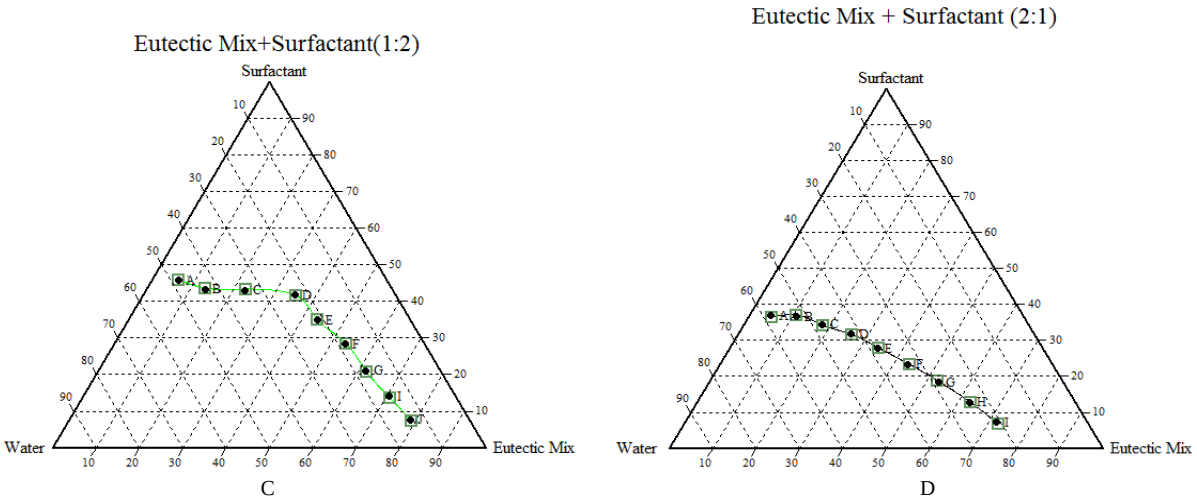

Fig. 3: The ternary phase diagrams of eutectic mixture, tween 80 and water in presence and absence of co-surfactant (ethanol); (a) co-surfactant free system (b) 1:1 ratio of tween 80 and ethanol (c) 1:2 ratio of tween 80 and ethanol (d) 2:1 ratio of tween 80 and ethanol.

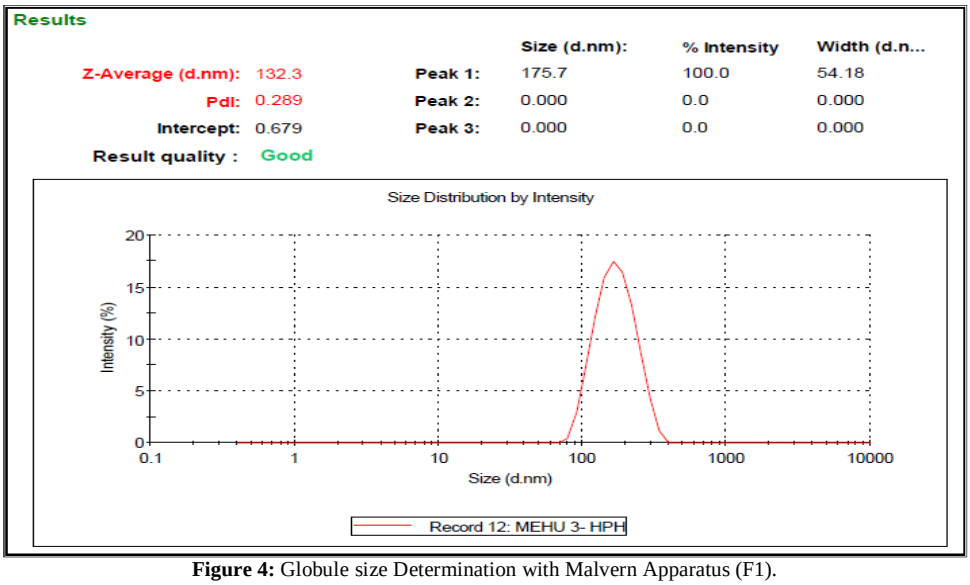

Figure 4: Globule size Determination with Malvern Apparatus (F1).

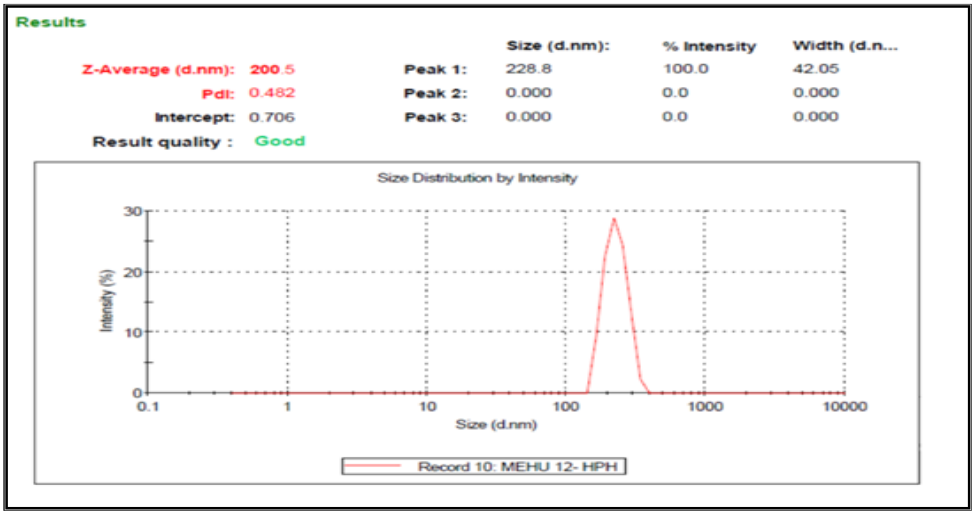

Fig. 5: Globule size Determination with Malvern Apparatus (F4).

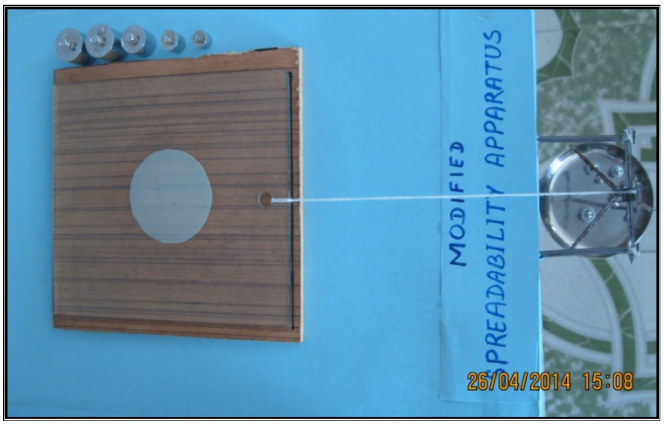

Fig. 5: Spreadability study with wooden block with scale and glass slides.

Fig. 6: Viscosity Determination of Hydrogel (Spindle No. 63).

Microemulsions

The microemulsions containing lornoxicam resulted in similar phase diagrams as for the microemulsions without the drug. In these formulations, the content of oil phase (eutectic mixture) was 10gm, while the content of surfactant co-surfactant mixture was varied from 30, 25 and 20gm each. The detailed composition of three different microemulsions is shown in Table 2.

Microemulsion Based Hydrogel

All these formulations existed inside the area of the microemulsion formation, thus, forming clear microemulsion at the additive concentrations examined. The droplet size ranged from 175.7-305.1nm. A higher concentration of surfactant result in finer droplet size however it also result in corresponding increasing viscosity of the formulation and zeta potential value lies between -21.4 to -8.1. Hydrogel thickened microemulsion were formulated using Carbopol 934p, HPMC K15M, and Xanthan gum (Table 3). Table 5 shows that the pH and viscosity of the hydrogel thickened microemulsion of batches F1-F9 ranged from 5.2-7.4 and 4146-6382 cPs respectively. The pH and viscosity of hydrogel thickened microemulsion gradually increased with decrease in concentration of surfactant co-surfactant mixture in the formulation. Spreadability test was carried out for all the formulations. Spreadability of the hydrogel was increases with the increases in the concentration of the surfactant and viscosity of the formulation. The spreadability is very much important as show the behaviour of hydrogel comes out from the tube. The release of lornoxicam from the hydrolgel was varied according to the viscosity of different polymer. The release of the drugs from its microemulsified gel formulation can be ranked in the following descending order: F7 > F4 > F1> F8 > F5 >F2 > F9 > F6>F3, Where the amounts of the drug released after 8 hr were 82.17%, 80.75%, 78.91%, 70.72%, 64.09%, 57.84%, 53.12%, 42.90%, 38.14% respectively. The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the viscosity of hydrogel. The cumulative % drug release profile of all the formulation batches has been shown in Table 6. Model fitting was done using an in-house program developed by the authors. Zero-order, first-order, Higuchi and Hixson- Crowell, models were tested. Table 7 depicts that the best fit was shown by Higuchi model. The mechanism of transport was by anomalous diffusion (diffusion coefficient, n=0.98). Ex vivo Release Study was carried out only on two best optimized formulations. The study showed the flux of the drugs from its microemulsified hydrogel formulation F1 and F4 were 2.02 and 2.34 respectively in 8 hr, The results are show in Tab 8. The anti inflammatory action of formulation F1 and F4 was calculated and it was compared with marketed preparation. The mean paw edema volume in rats after carrageenan induced shown in Fig 10. This showed that the formulations were as effective as marketed formulation.

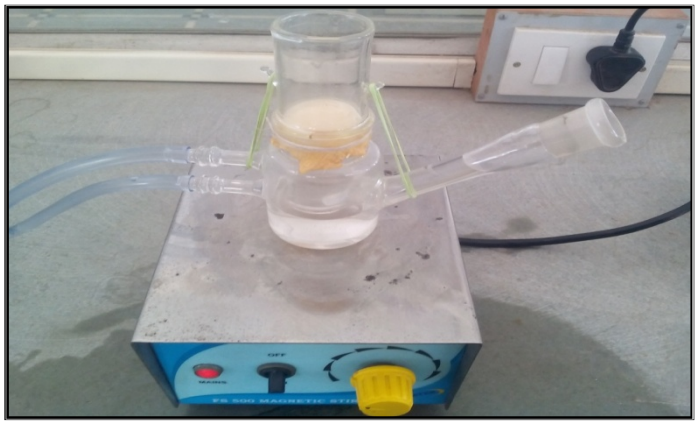

Fig. 7: *Ex vivo* skin permeation Through Franz Diffusion Cell.

Fig. 8: Carrageenan Induced Inflammation.

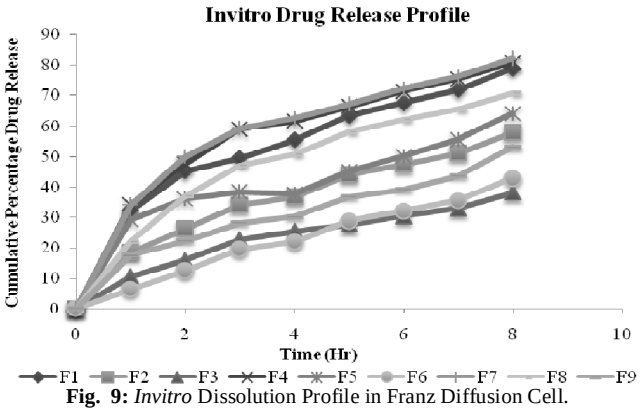

Fig. 9: *Invitro* Dissolution Profile in Franz Diffusion Cell.

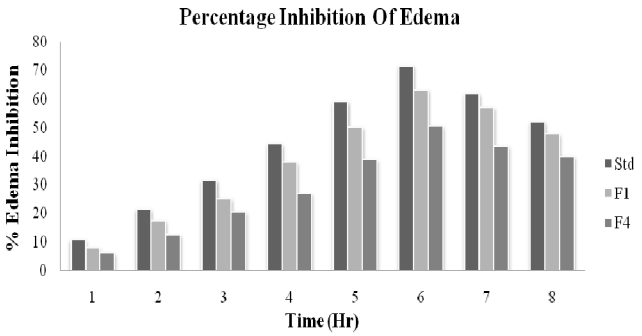

Fig. 10: Comparison of rat paws inhibition of edema of different formulation and standard.

CONCLUSION

In summary, in this research paper several microemulsion-based hydrogels were developed and evaluated for their potential as topical delivery systems for Lornoxicam, a hydrophobic drug presenting extensive first-pass metabolism and short elimination half-life after oral administration, and also poor aqueous solubility. The results showed that the content of microemulsion based hydrogels components (oil, Smix and water) had significant effect on their physical, rheological and *in vitro* drug release characteristics. It were considered as most desirable formulations the microemulsion-based hydrogels containing eutectic mixture [Camphor (5%) and menthol (5%) respectively] as oil phase, Smix (2:1) Tween 80 Ethanol (30%) as surfactant-cosurfactant, Carbopol 934p (1.5%) as gelling agent. since they exhibited high flux value (2.02 μg/cm^2/hr), highest release rate values (78.91%), good spreadability values (5.89 g.cm/sec). The formulations also possessed the globule size of 175.7 nm, the polidispersity index of 0.289 and zeta potential of -21.4 mV respectively. Carrageenan induced paw edema tests revealed anti inflammatory and analgesic activity. The formulations F1 and F4 were comparable with marketed topical gel. So lornoxicam hydrolgel can be used as an anti-inflammatory and analgesic agent for topical drug delivery.

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