AAPS PharmSciTech, Vol. 11, No. 1, March 2010 (© 2010)
DOI: 10.1208/s12249-009-9369-0

Research Article

Design, Characterization, and Evaluation of Meloxicam Gel Prepared by Suspension and Solution Polymerization Using Solubility Parameter as the Basis for Development

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Received 18 May 2009; accepted 16 December 2009; published online 15 January 2010

Abstract. Meloxicam gel was designed based on the matching of the solubility parameter (δ) of the drug with that of the polymer and subsequently with skin for improved dermal delivery of meloxicam. The δ of meloxicam (11.48 $(cal/cm^3)^{0.5}$) determined by solubility measurement was matched statistically to the solubility parameter of monomers, *n*-vinyl-2-pyrrolidone, polyvinyl alcohol (PVA), hydroxyl ethyl methacrylate, ethylene glycol methacrylate (EGMA) determined by intrinsic viscosity measurement. Consequently gels were formulated by polymerization in selected solvent blend of water/ethyl acetate (20:80) in which the drug showed maximum solubility. Thus, F1–F16 formulations designed were evaluated for physicochemical properties, textural analysis, and *in vitro* drug release. On the basis of optimum characteristics, F2 (PVA, δ=16.96 $(cal/cm^3)^{0.5}$) and F8 (EGMA, δ=18.35 $(cal/cm^3)^{0.5}$) formulated by suspension polymerization were selected and subjected to skin irritation and topical anti-inflammatory studies. The formulation F8 demonstrated significant ($p<0.05$) of anti-inflammatory activity in comparison to marketed piroxicam gel and was free from irritation.

KEY WORDS: anti-inflammatory activity; hydrogel; meloxicam; physicochemical evaluation; solubility parameter.

INTRODUCTION

Meloxicam (4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1, 1-dioxide) a selective cox-2 inhibitor is used orally to relieve the symptoms of arthritis, primary dysmenorrheal pain, fever, and as analgesic (1).The topical anti-inflammatory effects have been researched, but it is commercially available as tablets and to the best of our knowledge, no topical formulation of meloxicam is available commercially. However, various research reports on formulative approaches for meloxicam gel find place in literature. These include the effect of permeation enhancer on the formulated meloxicam gel (2), effect of mixed-solvent system of pH 7.4 buffer and ethanol for preparing meloxicam gel (3), and hybrid thermosensitive chitosan gel for sustained release of meloxicam (4); all focused on transdermal delivery with the aim to overcome the drawbacks of oral delivery. Investigation reports for topical delivery are fewer. Tsai *et al.* have investigated *in vitro* permeation for meloxicam gel and reported it to be suitable for dermal and topical administration with excellent tissue tolerability (5). Nevertheless, the consideration of solubility parameter for designing the topical delivery of meloxicam has not been made.

The use of solubility parameters of drugs and vehicles to describe the transport of drugs through skin is based on the efforts of Hildebrand equation, in a rational way, for solvent–solvent and solute–solvent interaction in the process of dissolution. The results of these efforts to develop a theoretical basis for solubility is represented in simplified form by the equation $-\log X_i^{v} = (\Delta H_f/2.3RT)[(T_m - T)/T_m] + \log \gamma_i^{v}$, where X_i^{v} is the mole fraction solubility of drug in the solvent or vehicle, ΔH_f is the heat of fusion of drug at its melting point, T_m is the melting point of drug, T is the temperature at which the solubility is being measured, and γ_i^{v} is the activity coefficient of the drug in the vehicle (6).

The rational design of pharmaceutical dosage forms result from a clear understanding of (a) the chemical and physical properties of the dosage form components and (b) their potential to interact with each other and the environments to which they are exposed. Such material properties and subsequent interaction can be readily estimated from knowledge of cohesive energy. Cohesive energies are especially important to the pharmaceutical materials because they determine many of the critical physicochemical properties of drug and excipients and also increase awareness of as to how the pharmaceutical materials will behave when processed or when dosed into the human body. The most common approach to quantify the cohesive energy of a material is to use solubility parameter (δ) that can be obtained by solubility measurements in a variety of solvents. Different methods are available for determination of solubility parameter: (a) theoretical methods that contains Fedor's group substitution

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method, molar volume method, from molar attraction constant, group additive method, and Lin and Nash method and (b) experimental methods that contains solubility/miscibility measurement, surface free energy measurement, swelling measurement, viscosity measurement, mechanical measurements, inverse gas chromatography, and partial least square regression method (7).

The transport through the skin is a diffusion process that depends on a concentration gradient; hence, the application of solubilities, derived in part from solubility parameter to predict concentration gradient and hence the diffusion, (8) is a logical approach. Thus, the present work is aimed at determination of solubility parameter of drug and polymer(s), statistically matching the solubility parameter of polymer with that of drug and consequently with the skin for designing the gel of meloxicam and subsequently formulating and identifying the gel with best physical and rheological characteristics that permitted the most rapid release of active principle and assessment of its pharmacodynamic activity against marketed formulation.

MATERIALS AND METHODS

Materials

Meloxicam was supplied by Zydus Cadila, Ahemdabad, Gujarat; *n*-hydroxy ethyl methacrylate and *n*-ethylene glycol methacrylate were procured from Sigma-Aldrich, USA; *n*-vinyl-2-pyrrolidone was supplied by Thomas Baker Chemical Ltd., USA; polyvinyl alcohol (PVA) was from Qualikems Fine Chemical Pvt. Ltd.; HIMEDIA dialysis membrane 50 was purchased from Himedia Lab Pvt. Ltd., Mumbai, India. The binary mixtures were prepared (by volume) with ethanol, glycerol, propylene glycol, ethyl acetate (EA; Ranbaxy Fine Chemicals Ltd., New Delhi, India).

Methods

Equilibrium Solubility Study

Sealed flasks containing an excess of meloxicam in the pure solvents and solvent blends (100:0, 80:20, 60:40, 40:60, 20:80, 0:100) each of water/ethanol, water/propylene glycol, water/glycerol, and water/EA were shaken at 37±0.5°C in a temperature-controlled water bath. When the saturation concentration was attained (after 72 h), the solid phase was removed by filtration through nylon filter disk (0.45 μ), and the clear solutions were diluted with double distilled water assayed at 363 nm. The densities of the solutions were determined at 37±0.5°C in 10 ml pycnometer (Jindal Scientific Instruments, Ambala, India) to convert molar solubilities into mole fraction units. All the experimental results are the average of at least three replicated experiments. The coefficient of variation (SD/mean×100) was within 2% among replicated samples for the solubility.

Determination of Solubility Parameter of Meloxicam

The solubility parameter was calculated by solubility measurement (9), molar volume method (10), and by method of Lin and Nash (11). In solubility measurement method, the solubility parameter of drug is assumed to be equal to that of the solubility parameter of the solvent blend (δ_1) in which the drug exhibits maximum solubility. Hence, the solubility data obtained by the method described in preceding section (equilibrium solubility study) was used to determine δ_2. A plot was made between the solubility parameter(s) of solvent blends and solubility (X_2) of meloxicam in each blend, and the solubility parameter of the solvent blend (δ_1) corresponding to peak solubility was identified as solubility parameter of meloxicam (δ_2).

By using molar volume method, the solubility parameter of meloxicam was determined by calculating the mole fraction solubility (X_2^i) of meloxicam in solvent blends containing water with ethanol and ethyl acetate in different ratios. The mole fraction solubility was calculated by using the following equation:

$$X_2^i = n_2/n_1 + n_2 \quad (1)$$

where n_1 = number of moles of solvent and n_2 = number of moles of solute. A plot of mole fraction solubility of meloxicam in the various ratios of the binary mixtures was made against $\Delta\delta$ ($\delta_1 - \delta_2$). The solubility parameter of the solvent blend (δ_1) in which meloxicam showed peak mole fraction solubility represented the solubility parameter of meloxicam (δ_2).

Lin and Nash method is based on the use of experimental mole fraction solubility of drug in given solvent blends. Thus, δ_2 can be determined by use of the following equation:

$$\delta_2 = \frac{\sum X_2^i \delta_1}{\sum X_2^i} \quad (2)$$

in which δ_2 is the solubility parameter of meloxicam, X_2^i is the mole fraction solubility of the solute in a given solvent, and δ_1 is the solubility parameter of the solvent.

Determination of Solubility Parameter of Monomers/Polymer

The solubility parameters of monomers/polymer (δ_{3-6}) were determined by intrinsic viscosity measurement method. From the stock solution(s) of monomers/polymer (50/100 ml) in pure solvent(s) and in different solvent blends, dilutions ranging from 0.05 to 0.25 g/ml were prepared and the viscosity determined by Brookfield viscometer (model DV-II + Pro, Brookfield Engineering Laboratories, Inc., USA) attached with T-bar spindle (spindle-C, S-93, 50 rpm) at 25± 0.5°C. Intrinsic viscosity (η) was determined by extrapolating the graph between concentration and viscosity to zero on *y*-axis. The intrinsic viscosities of the polymer in different solvent blend were plotted against of δ_1, and the peak value was interpreted as solubility parameter of the polymer (12,13). Thus, solubility parameters of *n*-vinyl-2-pyrrolidone (δ_3), polyvinyl alcohol (δ_4), *n*-hydroxy ethyl methacrylate (δ_5), and *n*-ethylene glycol methacrylate (δ_6) were determined.

Formulation of Gel

Chain polymerization was accomplished by two methods, namely suspension polymerization and solution polymeriza-

tion (14). In suspension polymerization method, continuous phase comprising of 25 ml *n*-hexane and 0.02 to 1.5% (*w*/*w*) stabilizer (PVA/Span 60) was heated to 70°C. The disperse phase comprising of monomer/polymer (25%, *w*/*w*) in selected solvent blend of water/EA $\left(\delta_1 = 11.48\left(\text{cal}/\text{cm}^3\right)^{0.5}\right)$ was mixed with initiator H_2O_2 (0.2–0.5%, *w*/*w*), and meloxicam (0.4%, *w*/*w*) was incorporated gradually into the continuous phase and the reaction mixture was heated to 70°C with agitation to accomplish polymerization for 1–4 h. Polymerization was stopped by heat termination, and the dispersion was allowed to cool at room temperature to get the gel.

In solution polymerization, the monomer/polymer (5–25%, *w*/*w*) was dissolved in selected solvent blend mixed with initiator H_2O_2 (0.2–0.5%, *w*/*w*) and drug (0.4%, *w*/*w*). The reaction mixture was heated to 80°C with agitation to initiate polymerization and stirred for 1 to 4 h. The reaction was terminated at the start of gelling by removing from heat and letting the contents cool down at room temperature to obtain the gel. The gels formed were stored in vacuum for 6 h to ensure removal of *n*-hexane.

The gels containing distilled water instead of the selected solvent blend were also made by suspension and solution polymerization that served as controls in their respective groups. The formulation design is listed in Table I. For both the methods, two groups were designated as A and B where group A (aqueous solvent) always referred to control formulation(s) and group B to formulations made using water/EA (20:80; $\delta_1 = 11.48\ (\text{cal}/\text{cm}^3)^{0.5}$). All the formulations were evaluated for physicochemical properties and *in vitro* drug release.

Evaluation of Gel

Physicochemical Properties: Viscosity Measurement. The viscosity of gel was measured by using a programmable viscometer (model DV-II + Pro, Brookfield Engineering Laboratories, Inc., USA). T-bar spindle (spindle-C, S-96) was lowered perpendicularly into the gel placed in a beaker taking care that the spindle does not touch the bottom of the beaker. The spindle was rotated at a speed 50 rpm, and the readings were recorded after 30 s when the gel level stabilized (15).

Physicochemical Properties: Measurement of pH. One gram of gel was dispersed in 100 ml of distilled water and stored at room temperature for 2 h, and the pH was recorded by digital pH meter (DB—1011, HICON, India). All the measurements were made in triplicate.

Physicochemical Properties: Equilibrium Swelling Study. The 0.5-g gel was filled in emptied and previously weighed tea bag. The experiment was carried out by measuring the weight gain as a function of immersion time in 10 ml of buffer solution, pH 7.4. Measurements were made until equilibrium hydration degree was reached, when three consecutive determinations gave the same weight. Before the final weight measurement, the tea bag was hung up to 15 min in order to remove the excess immersion fluid. The equilibrium swelling was calculated by dividing the difference in weight of swollen gel to that of dried gel by weight of dried gel (16).

Physicochemical Properties: Textural Analysis. Texture analysis of the gel was done on Texture Analyser (TA-XT plus, Stable Micro Systems, Haslemere, Surrey, UK) in compression mode using P/0.5R probe (1/2″ Dia Cylinder Delrin Radiused) with pretest speed of probe 1.0 mm/s, test speed of 1.0 mm/s, and posttest speed of 10.0 mm/s. The probe was depressed a distance of 5.0 mm, with load cell capacity 50,000 g.

In Vitro Release Study

Meloxicam release from the gels was measured across Himedia dialysis membrane 50 using Franz diffusion cells, with a diffusional area of 2.26 cm^2 and receptor volume of 11 ml. The membrane soaked in receptor medium for 8 h was mounted between the donor and the receptor compartment. One-gram gel was placed on the membrane surface in the

Table I. Formulation Design of the Meloxicam Gels Prepared by Suspension and Solution Polymerization

	Formulation															
	Suspension polymerization								Solution polymerization							
	Group 1A (aqueous solvent)				Group 1B (water/EA, 20:80)				Group 2A (aqueous solvent)				Group 2B (water/EA, 20:80)			
Component (%, *w*/*v*)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Meloxicam	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
PVA (stabilizer)	–	–	3.6	3.6	–	–	3.6	3.6	–	–	–	–	–	–	–	–
Span 60	3.6	3.6	–	–	3.6	3.6	–	–	–	–	–	–	–	–	–	–
H_2O_2	2.5	2.0	1.5	1.0	2.5	2.0	1.5	1.0	2.5	2.0	1.5	1.0	2.5	2.0	1.5	1.0
n-Vinyl-2-pyrrolidone	25	–	–	–	25	–	–	–	25	–	–	–	25	–	–	–
PVA	–	25	–	–	–	25	–	–	–	25	–	–	–	25	–	–
HEMA	–	–	25	–	–	–	25	–	–	–	25	–	–	–	25	–
EGMA	–	–	–	25	–	–	–	25	–	–	–	25	–	–	–	25

EA ethyl acetate, *PVA* polyvinyl alcohol, *HEMA* hydroxyl ethyl methacrylate, *EGMA* ethylene glycol methacrylate

donor compartment that was sealed from the atmosphere with aluminum foil. The receptor compartment of cell was filled with 11 ml of phosphate buffer(s), pH 6.5 (pH of skin), 7.4 (physiological pH), and 8.0 (inflamed skin pH) solution separately for three different set of experiments. During the experiments, the solution of receptor side was kept at 32± 0.5°C and was stirred with Teflon-coated magnetic stirring bar. One-milliliter aliquots were collected from the receptor side at designated time intervals of 0, 5, 10, 15, 30, 60, 120, 240, 480, and 720 min and replaced by the same volume of fresh receptor solution to maintain sink condition and constant volume. The samples were analyzed spectrophotometrically (Pharmaspec1700, Shimadzu, Japan) at 363 nm. Cumulative percentage drug released and amount permeated were determined from the calibration curves. Predicted flux was calculated by using following equation $J_{SS}=V/A\times dc/dt$ where V is receptor volume, A is surface area, c is meloxicam concentration in receptor phase, and t is time.

Spectral Characterization

SEM. Scanning electron micrograph (SEM) of pure drug and xerogel of F2 and F8 formulation was done at magnification ×4.0 (KX BP SE1, Japan) at an accelerating voltage of 15 kV. The samples were mounted on a double-faced adhesive tape and sputtered with gold before microscopy.

TGA. Thermogravimetric analysis studies were carried out using differential scanning calorimeter (DSC; Perkin Elmer, Pyris Diamond). Alumina powder standards were used to calibrate the temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min over a temperature range of 25–600°C; inert atmosphere was maintained by purging nitrogen gas at a flow rate of 200 ml/min.

Skin Irritation Study

The experimental protocol was approved by Institutional Animal Ethics Committee of the Rajiv Academy for Pharmacy, Mathura vide letter no. IAEC/RAP/2082/2008, and the care and handling of the animals were in accordance with the National Institute of Health guidelines. The required number of rabbits was acclimatized to the experimental condition at least 1 day prior to initiation of application of gel and fasted over night. The back of rabbit measuring 1.76 cm^2 was shaved. Selected gel (F2 and F8) was applied on the shaved area by rubbing it for 15 s. The rabbits involved in the study observed for 48 h after application of gel. The signs of irritation were observed after 0.5, 2, 24, and 48 h, respectively, and scored on the basis of Draize scale.

Topical Anti-inflammatory Activity

The rat of either sex was used in the experiment. Subplanar injection of 0.1 ml of a 1% (*w*/*v*) solution of carrageenan in water was given in both rear foot pads of the rat, and the paw volume at zero time was recorded. Half an hour after carrageenan injection, meloxicam gel (equivalent to a dose 200 mg) was applied topically by rubbing it to the right hind paw for 15 s and the other paw used as a vehicle control. Paw volume of both hind paws was quantitated at 0, 1, 2, 3, 4, 6, and 8 h, respectively, after carrageenan injection using a mercury plethysmograph (17).

RESULTS AND DISCUSSION

Equilibrium Solubility Study

The equilibrium solubility curves (Fig. 1a) clearly indicated improved solubility of meloxicam with increased percentage of cosolvent in all the solvents blends except water/glycerol blend in which a decrease in solubility of meloxicam was recorded. Maximum increase in solubility was observed with water/EA blend due to preferential interaction of drug with EA, and the highest solvent action of water/EA suggests that ethyl acetate is more effective than other cosolvents in breaking the highly ordered water structure. On the other hand, glycerol due to its high viscosity was unable to disrupt the crystal structure of drug to allow its molecular dispersion in the solvent (18). Thus, a peak solubility (X_2) of 10.16 mg/ml for meloxicam (Fig. 1b) was observed in a solvent blend of water/EA (80:20) with δ_1 of 11.48 $(cal/cm^3)^{0.5}$. Thus, the solubility parameter for meloxicam can be defined as 11.48 $(cal/cm^3)^{0.5}$, as according to the solubility measurement method, δ_2 is that value δ_1 at which the drug exhibits maximum solubility.

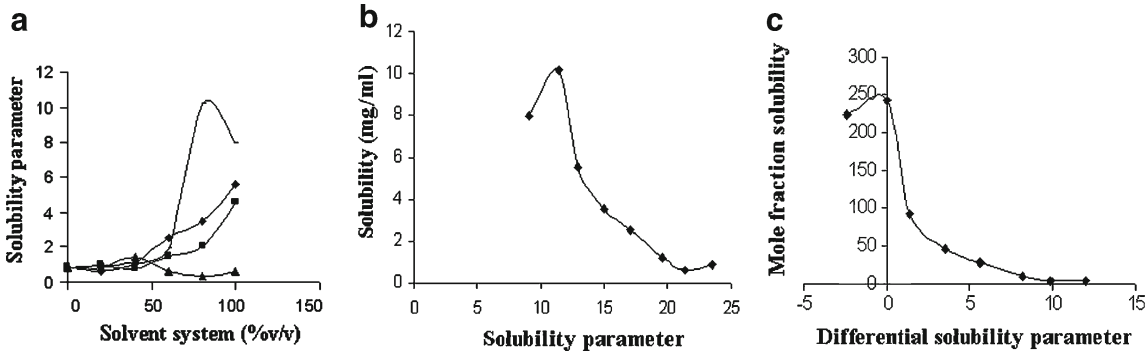

Fig. 1. **a** Equilibrium solubility curves of meloxicam in solvent blends containing of varying solubility in water with ethanol (*diamond*), propylene glycol (*square*), glycerol (*triangle*), ethyl acetate (*circle*). **b** Solubility *vs* solubility parameter (δ) curve of meloxicam for determination of δ by solubility measurement method and (**c**) mole fraction solubility *vs* $\Delta\delta$ for determination of δ of meloxicam by molar volume method

The determination of δ_2 by solubility measurements was corroborated with theoretical methods of solubility parameter determinations, namely molar volume method and Lin and Nash method. In molar volume method, the mole fraction solubility (X_2^i) of meloxicam in solvent blends of varying solubility parameters was plotted against $\Delta\delta = (\delta_1 - \delta_2)$ and the peak mole fraction solubility (Fig. 1c) corresponding to δ_2 was identified as 11.48 $(cal/cm^3)^{0.5}$. The method of Lin and Nash also resulted in δ_2 as 11.48 $(cal/cm^3)^{0.5}$. Conclusively, the solubility parameter of meloxicam was determined as 11.48 $(cal/cm^3)^{0.5}$ that formed the basis of selection of polymer for gel formulation. Additionally, the determined solubility parameter of meloxicam was close to the solubility parameter skin (10.0 $(cal/cm^3)^{0.5}$) which is presumed to facilitate its permeation into the skin (8). The solubility parameter, in addition to other physicochemical considerations that make meloxicam suitable for topical delivery, includes a molecular weight of 351.4 (desirable is <400) and log P=1.904 (desirable −1 to 4) that substantiate meloxicam as a potential candidate for topical drug delivery (19).

Solubility Parameter of Monomers

In order to formulate meloxicam, topical formulation gel system was selected, as gels have numerous advantages over the other topical delivery systems. The selection of polymers for gel was based on determination of solubility parameter of polymers so that a topical drug delivery system could be designed wherein the solubility parameter of drug matches the solubility parameter of skin and consequently the polymer in order to obtain a formulation that can effectively transport the drug through the skin. Of the various methods for determination, solubility parameter of monomer/polymer the intrinsic viscosity method was selected. The intrinsic viscosity is said to be maximum when the solubility parameter of the monomer/polymer equals to the solubility parameter of the solvent (20). Based on this principle, the plots of (η) *vs* δ_1 were made (Fig. 2a–d), and the solubility parameters were determined as δ_3=20.02 $(cal/cm^3)^{0.5}$ for *n*-vinyl-2-pyrrolidone, δ_4=16.96 $(cal/cm^3)^{0.5}$ for PVA, δ_5=14.78 $(cal/cm^3)^{0.5}$ for cross-linked hydroxyl ethyl methacrylate (HEMA), and δ_6=18.36 $(cal/cm^3)^{0.5}$ for cross-linked ethylene glycol methacrylate (EGMA).

The test for significance of difference was applied on the solubility parameter(s) of the polymers with that of meloxicam at 95% level of significance and on the solubility parameter of meloxicam determined by three different methods. No significant difference was observed between the solubility parameter determinations of drug and polymers with that of skin at $p<0.05$; thus, the selected polymers could rationally be used for gel formulation of meloxicam. The gels were prepared by chain polymerization using free radical initiator by two different methods, namely suspension polymerization (F1–F8) and solution polymerization (F8–F16).

Evaluation of Gel

Physicochemical Properties

Viscosity Measurement and pH. The viscosity values ranged between 1,800 to 7,000 cps depending upon the polymer, the processing conditions, and the method of gel formation. Thus, F11 and F12 composed of polyHEMA and polyEGMA made by solution polymerization exhibited least viscosity values while F9 displayed maximum viscosity (all group 2A formulations). Thus, a very vast range of viscosity variation was observed in formulations made with water whereas the viscosity variation was narrower in group 2B formulations made with selected solvent blend of water/EA (20:80). A similar pattern of viscosity variation was observed among

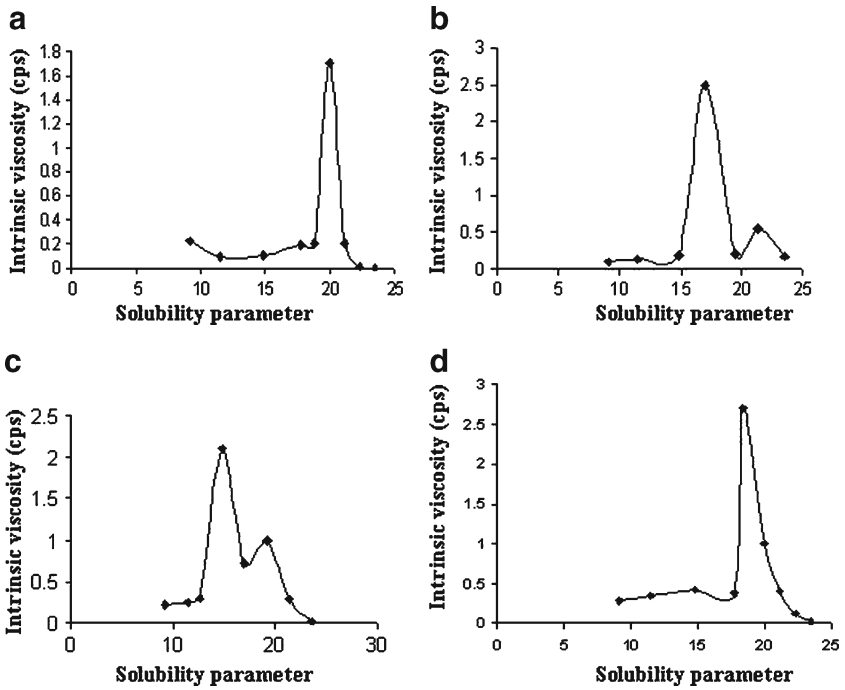

Fig. 2. Solubility parameter of monomers by intrinsic viscosity measurement method for **a** *n*-vinyl-2-pyrrolidone, **b** PVA, **c** HEMA, and **d** EGMA

group 1A and group 1B formulations; nevertheless, the viscosity ranged from 2,800 to 6,000 cps. Thus, the effect of solvent and the method of preparation on the viscosity of gel was clearly documented (Table II). In free radical polymerization reactions, as the polymer molecules react and grow, larger macromolecular groups can be formed. These groups become entangled within one another quickly as the polymer chains become larger. This development of macromolecules causes an increase in the viscosity of the system. The formation of these macromolecules is often desired in polymer materials due to higher mechanical strengths and other properties. The viscosity change that is apparent in high-conversion free radical polymerization often occurs over a relatively short time period. The *in situ* polymerization of EGMA and HEMA, in the sol state leading to formation of polyEGMA and polyHEMA, respectively, increased the steric hindrance due to formation of long polymeric changes that got entangled and consequently increased the viscosity.

Malkin and Kulichikin (21) describe the viscosity increase as determined by the increase of the molecular weight of the polymer, the amount of high molecular weight polymer in the system, and the initial concentration of initiator in the system and determine how that affects the viscosity of the polymerization. It was also suggested by Cioffi *et al.* (22) that the initial concentration of initiator might play a role in the increase of the viscosity. Perhaps a greater amount of initiator would cause a greater increase in viscosity at a shorter reaction time that was actually observed while optimizing the processing conditions for preparation of gels. The difference in viscosities is also evidently related to the type of polymer and is also a function of aging (23). Thus, viscosity analysis of gels stored for 30 days at 25°C showed slight changes in viscosity in all the formulations, and the formulations made with cross linked HEMA (F3, F7, F11, F15) showed phase separation. On the contrary, gels stored at 5°C recorded unchanged viscosity. Thus, storage of gel at refrigerated conditions is indicated. The pH of all gels was found between 4.80 and 6.5, which lie in the normal pH range of skin, 4.0 and 6.5 (24); hence, the formulations shall not irritate the skin upon application.

Equilibrium Swelling Study. Swelling behavior of the gels was determined at the pH of normal skin (6.8) and inflamed skin pH (8.0) and was reported in Table II. Equilibrium swelling ranged between 0.712 and 0.944 g/g at pH 6.8 and 0.744 and 0.985 g/g at pH 8.0 for all the formulations, and F8 exhibited maximum equilibrium swelling after 4 h at both pH values closely followed by F2. EGMA that constituted F8 is an acrylic monomer that displays increased degree of hydration up to 40 times (25) while PVA constituting F2 has been reported to affect a volume expansion to the tune of 500% at 37°C (26). Least swelling was documented for F11 made of polyHEMA at both pH values and rest of the formulation displayed intermediate values.

Textural Analysis. Texture can be regarded as a manifestation of the rheological properties of a product. In texture analysis, an analytical probe is depressed into the sample at a defined rate to a desired depth. From the resultant force–distance curve, the mechanical parameters of firmness and adhesiveness (27) may be derived. Force necessary to attain a given deformation is called firmness, and in texturograms, firmness is correlated with positive area (maximum force) whereas adhesiveness is correlated to the negative area. Adhesiveness is regarded as the work necessary to overcome the attractive forces between the surface of sample and surface of the probe with which the sample comes into contact. Of all the formulations tested, F2 and F8 exhibited textural characteristics of low firmness and high adhesiveness (Table III) desirable for a topical delivery system (28). In the entire force distance curves of selected formulations in each subgroup, as the time increased positive or negative, force was increased and reached to a peak value of force on both side of curve .Thus, firmness and adhesiveness were recorded as 0.765 and −2.185 for F2 and 0.874 and −2.076 for F8. A

Table II. Comparative Results of Physicochemical Properties of Meloxicam Gels Formulated by Suspension Polymerization (Groups 1A and 1B) and Solution Polymerization (Groups 2A and 2B)

Formulation code	Formulation group	Drug content (%)	Surface pH	Viscosity (cps; spindle no. 96, 50 rpm)	Equilibrium swelling (g/g; after 4 h)	
					pH 6.80	pH 8.00
F1	1A	98.41±0.51	4.87	3,800±0.10	0.894	0.912
F2		98.85±0.45	5.59	4,200±0.56	0.915	0.976
F3		96.25±0.35	4.92	6,000±0.45	0.756	0.852
F4		95.04±0.21	5.30	3,600±0.67	0.934	0.982
F5	1B	92.03±0.16	5.20	2,800±0.32	0.823	0.908
F6		95.00±0.23	5.50	4,200±0.28	0.905	0.943
F7		97.46±0.56	5.01	3,400±0.37	0.789	0.889
F8		99.50±0.78	5.84	4,400±0.12	0.944	0.985
F9	2A	97.81±0.13	4.96	7,000±0.59	0.845	0.899
F10		90.90±0.56	5.70	3,600±0.05	0.932	0.977
F11		97.87±0.48	4.91	1,800±0.53	0.712	0.789
F12		98.10±0.76	4.82	1,800±0.51	0.913	0.957
F13	2B	97.44±0.29	5.01	4,200±0.23	0.903	0.937
F14		96.39±0.78	5.51	4,600±0.64	0.812	0.886
F15		96.99±0.51	5.40	3,200±0.45	0.763	0.842
F16		95.41±0.15	5.30	4,400±0.59	0.910	0.934

Table III. Firmness and Adhesiveness Force (Grams) of Meloxicam Gel as Determined by Textural Analysis Using P/0.5R Probe (1/2″ Dia Cylinder Delrin Radiused) with Load Cell Capacity 50,000 g

Formulation code	Firmness force 1 (g)	Adhesiveness force 2 (g)
F1	1.202	−1.529
F2	0.765	−2.185
F3	1.202	−2.622
F4	1.202	−1.966
F5	0.655	−1.857
F6	0.874	−2.403
F7	2.294	−4.698
F8	0.874	−2.076
F9	0.982	−1.857
F10	0.765	−2.185
F11	0.756	−1.857
F12	0.546	−1.966
F13	0.874	−1.639
F14	1.857	−1.311
F15	1.202	−1.529
F16	2.076	−4.916

topical application must exhibit acceptable mechanical characteristics as low firmness (firmness is related to the ease of product removal from the container and ease of application onto substrate) and high adhesiveness (property related with bioadhesion describes the relative adhesive properties of a formulation). Such a gel will adhere firmly yet gently to the healthy surface and will not adhere to the wet wound surface resulting in painless dressing (29).

In Vitro Drug Release Studies of Meloxicam in Phosphate Buffer (pH 6.8, 7.4, and 8.0)

In both the groups (1,2) classified on the basis of method of polymerization, the formulations prepared using solvent blend exhibited higher drug release when compared to their respective control formulations made with aqueous solvent (Fig. 3a–f). Thus, F8 displayed highest release (86.35% ±0.00 at pH 6.5, 95.25% ±0.09 at pH 7.4, 98.58% ±0.02 at pH 8.0) in group 1 followed by F2 (78.31% ±0.44 at pH 6.5, 87.04% ±

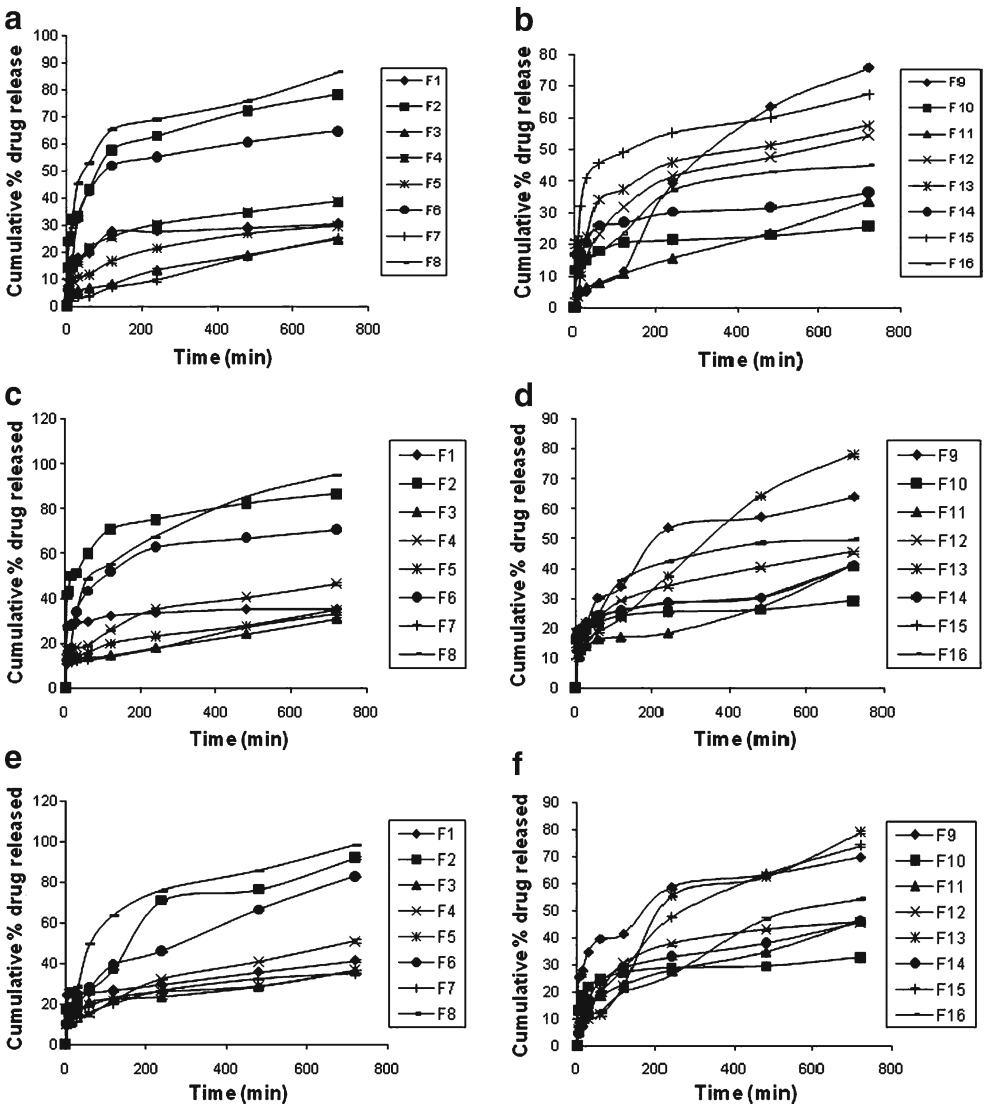

Fig. 3. Drug release profile of meloxicam hydrogel by suspension polymerization (**a**, **c**, and **e**) at pH 7.4, 6.8, and 8.0, respectively, and by solution polymerization (**b**, **d**, and **f**) at pH 7.4, 6.8, and 8.0, respectively

0.03 at pH 7.4, 92.3% ±0.45 at pH 8.0),while in group 2, F15 (67.65% ±0.41 at pH 6.5, 68.50% ±0.04 at pH 7.4, 74.17% ± 0.43 at pH 8.0) gave maximum release at all three pH values followed by F9 (57.68% ±0.50 at pH 6.5, 64.11% ±0.26 at pH 7.4, 69.98% ±0.22 at pH 8.0). The highest *in vitro* release of meloxicam from F8 may be attributed to thermosensitive properties of EGMA (30) that facilitates the drug to release from 3D network of gel whereas for F2, the hydrophilic polymer PVA facilitated drug diffusion (23). The order of release was F8>F2>F15>F9, and all the formulations exhibited higher release at the inflamed skin, i.e., at pH 8 than in 7.4 and 6.5 as meloxicam being an acidic drug will exhibit higher solubility in alkaline pH.

The *in vitro* release profile could also be correlated to the solubility parameter of polymers. Poly(EGMA) with a solubility parameter of 18.36 $(cal/cm^3)^{0.5}$ allowed higher release in comparison to the gel of PVA with solubility parameter of 16.96 $(cal/cm^3)^{0.5}$ that was much closer to the δ value of the meloxicam 11.48 $(cal/cm^3)^{0.5}$. Thus, the drug could be slowly released from a system that preferentially favored its partitioning to the polymeric gel rather than the release media. The same release analysis could be accounted for gels F15 (poly HEMA, δ_6=18.36 $(cal/cm^3)^{0.5}$) and F9 (poly (*n*-vinyl-2-pyrrolidone), δ_4=16.96 $(cal/cm^3)^{0.5}$). For the calculations of release parameters, the *in vitro* release profiles were subjected to PCP Disso software 2.0, Pune, India. The flux rate from all the formulations was found to be higher than the predicted flux rate of 3.98 μg/cm^2 h, and formulation F8 showed highest percent enhancement with a zero-order release profile closely followed by F5 (Peppas modeled release) in group 1 (Table IV). In group 2 though formulations F14 and F15 showed enhancement of 41.33% and 40.04%, respectively, these obeyed Peppas and matrix release orders; thus, formulation F8 was selected for further studies. Additionally, F2 was also selected that was a prototype of the formulation made using water with best physicochemical properties, as reference control that could clearly express the effect of using a solvent blend for gel formulation. Thus, F2 and F8 were subjected to spectral characterization, skin irritation, and topical anti-inflammatory activity (AIA) study.

Spectral Characterization

Scanning electron micrograph of pure meloxicam, F2, and F8 are shown in Fig. 4a–c. Pure meloxicam consisted of a mixture of a some large crystals with microparticles, Micro-photograph of F2 showed the crystals of drug partially embedded in the folds of xerogel that was made with PVA in aqueous solvent (δ_1=23.5 $(cal/cm^3)^{0.5}$) in which drug (δ_2= 11.48 $(cal/cm^3)^{0.5}$) is less soluble whereas the micrograph of F8 showed 3D cross linked structure made with EGMA in solvent blend of water/EA (20:80, δ_1=11.48 $(cal/cm^3)^{0.5}$) in which the drug exhibited maximum solubility and hence was not seen as separate entity.

Thermogravimetry curve (Fig. 5) of meloxicam indicated T_g at 251°C corresponding to a weight of 97.35% that got reduced to 37.45% at 295°C indicating weight loss that was compared with T_G curve of F2 with and without drug. The weight loss in F2 with drug was found to be 93.4% at 200°C that dropped to 45.18% at 350°C. The quantum of weight loss was comparable to F2 without drug (reference) that recorded weight loss of 84.25% at 250°C to 21.57% at 383°C. This indicated the stability of drug during the formulation process as weight loss in drug-loaded formulation was closely same as in the formulation without drug. In F8, weight loss was found to be 85.27% at 275°C to 3.80% at 424°C, and the weight loss in reference formulation (F8 without drug) was found to be 91.75% at 200°C to 4.91% at 425°C. Again the results confirmed stability of drug remained unaffected during processing. When thermal changes between pure drug and gel were compared, high melting temperature and higher crystallinity was observed. According to the modern theory of gelation (31), polymer segments are allowed to interact with each other in two ways: one is by van der Waals interaction and the other is by a directional interaction which leads to the

Table IV. *In Vitro* Model-Dependent and Model-Independent Drug Release Parameters of Formulated Meloxicam Gel

Formulation code	t_{20}% (min)	% Enhancement	Flux rate (μg/cm^2 h)			Order of release	*R*
			pH 6.8	pH 7.4	pH 8.0		
F_1	15±0.00	–	1.69±0.51	1.99±0.73	2.33±0.69	Peppas	0.9963
F_2	08±0.01	–	4.00±0.44	4.42±0.03	4.72±0.45	Zero order	0.8727
F_3	240±0.00	–	1.42±0.55	1.76±0.04	2.11±0.67	Peppas	0.9918
F_4	60±0.03	–	1.40±0.89	1.66±0.17	1.81±0.05	Peppas	0.9955
F_5	120±0.04	30.49	2.30±0.22	2.70±0.13	2.86±0.05	Peppas	0.9975
F_6	20±0.08	5.23	5.70±0.13	4.27±0.02	7.60±0.35	Zero order	0.7256
F_7	120±0.00	2.27	1.53±0.13	2.08±0.30	2.19±0.32	Peppas	0.9908
F_8	05±0.00	31.81	5.72±0.00	6.32±0.09	6.54±0.02	Zero order	0.9976
F_9	60±0.06	–	3.84±0.41	3.95±0.04	4.07±0.09	Zero order	0.8824
F_{10}	05±0.08	–	3.06±0.11	3.46±0.00	3.90±0.17	Matrix	0.7718
F_{11}	27±0.12	–	1.74±0.52	2.09±0.25	2.35±0.07	Peppas	0.9834
F_{12}	60±0.00	–	3.13±0.46	2.61±0.07	3.13±0.28	Peppas	0.9956
F_{13}	07±0.021	13.27	3.43±0.50	3.78±0.26	4.13±0.22	Peppas	0.9971
F_{14}	16±0.04	41.33	1.77±0.24	2.01±0.34	2.24±0.45	Matrix	0.8654
F_{15}	10±0.02	40.04	5.07±0.41	4.87±0.04	5.55±0.42	First order	0.7512
F_{16}	20±0.45	20.59	4.18±0.29	4.62±0.28	4.23±0.18	Matrix	0.7634

Percent enhancement was calculated for gel made with solvent blend (water/EA, 20:80) against the formulation made with same polymer and method using water. The calculations done pairwise are F_1 F_5, F_2 F_6, F_3 F_7, F_4 F_8, F_9 $_{13}$, F_{10} F_{14}, F_{11} F_{15}, and F_{12} F_{16}

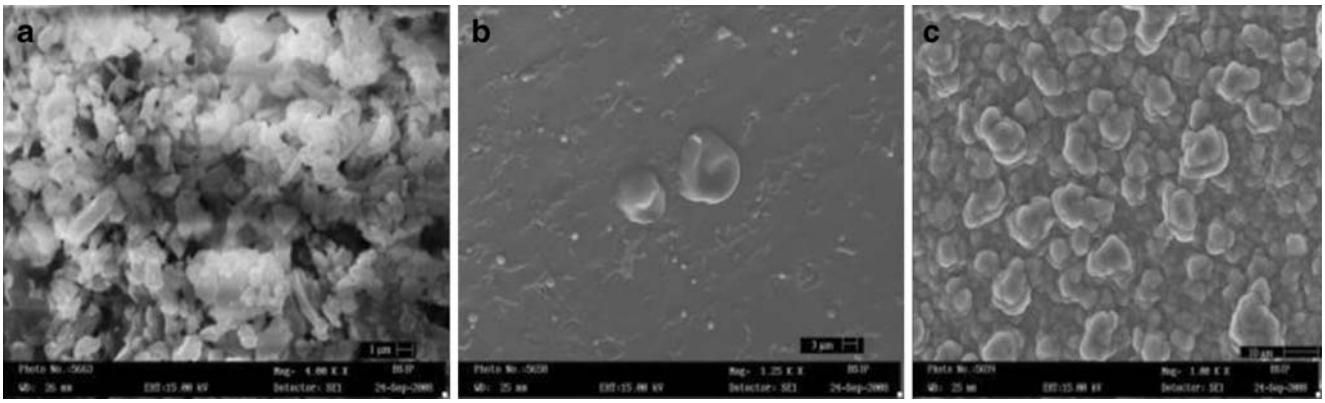

Fig. 4. Scanning electron micrograph of **a** pure drug, **b** F2 xerogel, and **c** F8 xerogel

tie point in the gel. When an infinite network is formed by a directional interaction, the system is a gel and assumed to be hydrogen-bonded. Thus, higher melting temperature and higher crystallinity recorded for gels are suggestive of the contribution of van der Waals interactions and hydrogen bonding in gel formation.

Skin Irritation Study

No sign of irritation could be observed for F8; however, for F2 formulation, half an hour after application of the gel, very slight erythema was observed that disappeared after 24 h. The signs of erythema shown by F2 may be attributed to PVA that is reported in literature to cause slight irritation on rabbit skin (32). No sign of edema was observed in either case.

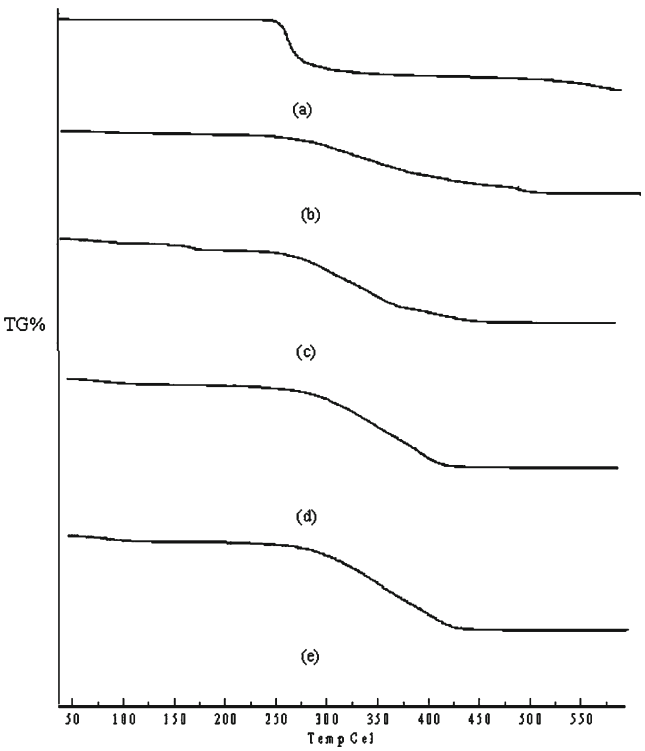

Fig. 5. Thermograph of *a* meloxicam, *b* F2, *c* PVA, *d* F8, and *e* EGMA

Topical Anti-inflammatory Activity

F8 showed extremely significant AIA at fourth hour (Fig. 6) that was maintained till sixth hour, in contrast to extremely significant ($p<0.001$) effect observed at sixth hour with marketed piroxicam gel; thus, the onset of action of F8 (designed on the basis of solubility parameter) was faster than marketed formulation. The formulation F2 (aqueous vehicle) formulation did not exhibit extremely significant AIA effect at any time point but displayed a significant effect ($p<0.01$) at fourth hour that got reduced in sixth hour .Thus, the rank order for anti-inflammatory activity was F8 > marketed formulation > F2. All the three tested formulations inhibited edema after 3 h as both meloxicam and piroxicam are known to inhibit prostaglandin synthesis by decreasing the activity of the enzyme cyclooxygenase that is corroborative with the experimental results.

CONCLUSION

The studies based on designing topical gel of meloxicam by use of solubility parameter were conclusive in selecting a formulation made by a solvent blend that had a solubility parameter close to meloxicam and consequently to the skin exhibited superior physical, textural, *in vitro* drug release properties, and faster onset of anti-inflammatory action without irritation when compared to marketed anti-inflammatory gel.

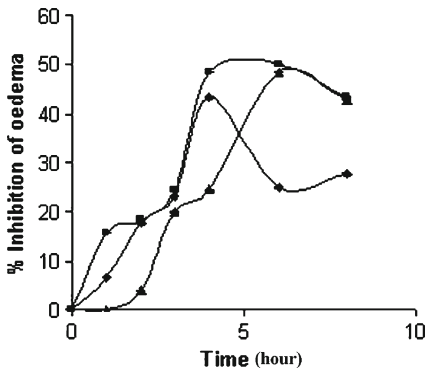

Fig. 6. Topical anti-inflammatory effect of selected of meloxicam hydrogel formulation F2 (*diamond*), F8 (*square*), and marketed piroxicam gel (*triangle*)

ACKNOWLEDGMENT

The authors would like to thank Indian Institute of Technology, Roorkee for providing the facilities for SEM and DSC analysis of the samples.

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