ORIGINAL ARTICLE

Design, Fabrication, *In Vitro* and *In Vivo* Assessment of *Aloe vera* Containing Transgel for Delivery of Meloxicam

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Abstract

Aim: Aim of the present investigation is to develop meloxicam incorporated *Aloe vera* gel (MAG) and to study its pharmacodynamics and *in vitro* evaluation studies. **Materials and Methods:** 2^3 factorial design was used to optimize the independent variables as amount of hydroxy propyl methyl cellulose (HPMC) (X1), amount of carboxy methyl cellulose (CMC) (X2), and amount of Carbopol 934 (X3) as gelling agent at varying concentration, i.e. 1% and 2%. Total 8 batches (F1-F8) were prepared and evaluated for gel consistency, spreadability, drug content, physicochemical parameters such as pH, viscosity, and *in vitro* diffusion assessment. Pharmacodynamic activity of MAG (batch F8) was evaluated in Wistar albino rats and compared with commercially available marketed cream (MC) against the same parameters. **Results:** Batch F8 containing a higher concentration of Carbopol 934, HPMC, and CMC shows improved gel consistency, with good spreadability, viscosity, and drug content. These results indicate the suitability of 2^3 factorial design for fabrication of MAG. Noteworthy, batch F8 showed significant ($P < 0.05$) *in vitro* drug release (76.72%) compared to marketed formulation (70.56%) at 150 min. Percentage inhibition of edema was greater for the batch F8 (26.48%) compared to MC (20.32%) after 60 min. This improved efficacy might be due to direct stimulation of the activity of macrophages and fibroblasts by *A. vera* gel and binding of mannose 6-phosphate to the growth factor receptors on the surface of the fibroblasts, thereby promoting tissue repair. **Conclusion:** Hence, decisively *A. vera* gel serves as an effective gel base to incorporate meloxicam with high drug loading capacity.

Key words: *Aloe vera*, Carbopol 934, edema, gelling consistency, meloxicam, percentage inhibition

INTRODUCTION

Meloxicam (4-hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) belonging to class of non-steroidal anti-inflammatory drug (NSAID) is extensively used to offer effective therapy in patients suffering with many inflammatory conditions including rheumatoid arthritis and osteoarthritis.[1] Nonetheless, their oral administration leads to number of gastrointestinal (GI) disorders which can reduce patient compliance. It gives anti-inflammatory, analgesic, and antipyretic effect due to inhibition of prostaglandin synthetase (cyclooxygenase), followed by inhibition of prostaglandin synthesis. Meloxicam is practically insoluble in water and has a larger onset of action. Oral use of the meloxicam is challenging as approximately 30% of patients receiving daily doses of 15 mg of it experiences side effects such as GI perforations, ulceration of the GI mucosa, even bleeding, and upper abdominal pain.[2,3] Transdermal delivery of NSAIDs is an effective strategy for avoiding their adverse effects on the GI tract, while improving patient compliance by transcellular passive diffusion of drug.[4,5] It has been also reported that NSAIDs promote local analgesia when applied topically.[6] Meloxicam is a lipophilic drug with a logP of 3.4 having good transdermal penetration.[7] In addition, literature revealed that

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Received: 24-05-2016
Revised: 18-06-2016
Accepted: 25-06-2016

topical application of cyclooxygenase inhibitors suppresses ultraviolet B (UVB)-mediated cutaneous inflammation. Therefore, topical application of meloxicam seems to have another important role inhibiting UVB-mediated inflammation as well as its systemic anti-inflammatory effects without major GI side effects.[8] Hence, in the present investigation, an attempt has been made to incorporate meloxicam into a transdermal gel base of *Aloe vera*.

A. vera (*Aloe barbadensis* Miller) is a tropical and subtropical plant of the Liliaceae family, which is a perennial succulent plant. Since ancient time, it has been used for bountiful traditional medical purposes in several cultures for millennia.[6,8-10] It has been demonstrated that *A. vera* has UV protective, growth promoting activities, immunomodulatory, antimicrobial, anti-inflammatory, antifungal, wound healing properties, and many more.[8,9] In the present research work, the central parenchymal portion of *A. vera* was formulated into a gel using hydroxy propyl methyl cellulose (HPMC), carboxy methyl cellulose (CMC), and Carbopol 934 as a gelling agent. Meloxicam was incorporated into the prepared *A. vera* gel and evaluated for viscosity, pH, drug content, *in vitro* drug release, and *in vivo* studies. Its anti-inflammatory effect was evaluated in rats to assess the synergistic effect of meloxicam with *A. vera*. The results were compared with that of a commercial meloxicam cream.[10]

MATERIALS AND METHODS

Meloxicam was obtained as a gift sample from Cipla Ltd., Goa; India. Carbopol 934 was procured from S.D. Lab, Mumbai. HPMC was obtained from Colorcon as a gift sample and CMC was obtained from Molychem, Mumbai. Propylparaben and methylparaben were obtained from ACME Chemicals, Mumbai. Carrageenan was obtained from Hi Media Labs Pvt. Ltd., Mumbai. All other chemicals were of analytical grade and were used without any chemical modifications.

A. vera (*A. barbadensis*) plant was obtained from Herbal Garden, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India.

Extraction of *A. vera* juice

Thick, mature, succulent leaves of *A. vera* (A. barbadensis) plant were used to prepare hydrogel. The *Aloe* leaf can be divided into two major parts, namely, the outer green rind including the vascular bundles and the inner colorless parenchyma containing the *Aloe* gel. From the cutted leaf bases, the yellow juice was allowed to drain into a container to remove the exudates. The central parenchymatous pulp of *Aloe* leaves was scooped out with a spatula and was washed repeatedly with water and finally washed with 0.1 N sodium hydroxide (NaOH) solution to elevate the pH of *Aloe* pulp since it is highly acidic due to the presence of acemannan.[11,12] Further, the treated pulp was placed in a blender to obtain the juice which was consequently centrifuged at 3000 rpm for 30 min to separate the fibers. The supernatant (*A. vera* juice) obtained was prefiltered using a cotton bed to remove the leftover rind particles. Then, the juice was subjected to repeated vacuum filtration until a clear liquid was obtained which is used further for gel preparation.[13]

Optimization of formulation using 2^3 factorial design

The *Aloe* incorporated meloxicam gel was prepared using 2^3 factorial designs. A 2^3 factorial design for three factors at two levels each was selected to optimize the response of the variables. 2^3 factorial design is one of the tools used to study the effect of different variables on the quality determinant parameters of any formulation. Based on the principle of design of experiments, this design was employed to investigate the effect of three independent factors. The three factors amount of HPMC (X1), amount of CMC (X2), and amount of Carbopol 934 (X3) were varied, and the factor levels were suitably coded [Table 1]. The spreadability, viscosity, and percentage of drug content were taken as the response variables. Experimental trials were performed at all 8 possible combinations [Table 2]. In this design, three factors were evaluated, each at two levels, and experimental trials were performed for all possible combinations. All other formulation variables and processing variables were kept invariant throughout the study.[14]

As shown in Equation (1), a statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = bo + b1X1 + b2X2 + b3X3 + b12X1X2 + b23X2X3 + b13X1X3 \quad (1)$$

The responses in the above equation Y are the quantitative effect of the formulation components or independent variables X1, X2, and X3; b is the coefficient of the term X. Seven coefficients (b1-b7) were calculated representing b0 as the intercept, and b1-b7, various quadratic and interaction terms. Various response surface methodology computations for the current optimization study were performed

Table 1: Variable level of 2^3 factorial design for meloxicam-*Aloe vera* gel

Variable level	+1 (high)	–1 (low)
Amount of HPMC (X1) (%w/v)	2	1
Amount of CMC (X2) (%w/v)	2	1
Amount of Carbopol 934 (X3) (%w/v)	2	1

HPMC: Hydroxyl propyl methyl cellulose, CMC: Carboxy methyl cellulose

Table 2: Formulation of meloxicam *Aloe vera* gel using 2^3 factorial designs

Batches	*Aloe* extract (ml)	MX (g)	HPMC (g)	CMC (g)	Carbopol 934 (g)	Triethanolamine (ml)	Methylparaben (g)	Propylparaben (g)	Purified water (ml)
F1	75	0.500	1	1	1	1.8	0.020	0.002	Qs to 100
F2	75	0.500	2	1	1	1.8	0.020	0.002	Qs to 100
F3	75	0.500	1	2	1	1.8	0.020	0.002	Qs to 100
F4	75	0.500	2	2	1	1.8	0.020	0.002	Qs to 100
F5	75	0.500	1	1	2	1.8	0.020	0.002	Qs to 100
F6	75	0.500	2	1	2	1.8	0.020	0.002	Qs to 100
F7	75	0.500	1	2	2	1.8	0.020	0.002	Qs to 100
F8	75	0.500	2	2	2	1.8	0.020	0.002	Qs to 100
Plane *Aloe* gel	75	-	-	-	3	1.8	0.020	0.002	Qs to 100

HPMC: Hydroxyl propyl methyl cellulose, CMC: Carboxy methyl cellulose, MX: Meloxicam

employing Design-Expert software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN, USA). Polynomial models including quadratic terms were generated for all the response variables. In addition, two-dimensional contour plots and three-dimensional (3D) graphs were constructed using the output files generated by the Design-Expert software. The significance of these parameters on the variables was assessed by analysis of variance (ANOVA, 2-way).

Preparation of meloxicam incorporated *A. vera* gel (MAG)

To prepare meloxicam *A. vera* gel, first, methylparaben sodium and propylparaben sodium were dissolved in water on water bath. Then to this solution, *A. vera* juice was added. Further gelling agent with above-mentioned concentrations was added and dispersed uniformly ensuring that no lumps had formed and stirred continuously till it got swollen completely. Triethanolamine was slowly added to the dispersion with continuous stirring which resulted in a stiff gel. Volume was made with water and stirred continuously till a uniform gel was formed. Prepared *A. vera* gel was weighed and stored in airtight containers in a dark room to prevent photooxidation. These gels were evaluated for spreadability and viscosity studies to optimize the gelling agent and its concentration.[15] Medicated *Aloe* gel was prepared by dispersing the concentration of gelling agents such as Carbopol 934, HPMC, and CMC in *Aloe* juice to form a lump-free mixture, which is allowed to stand to free entrapped air. Meloxicam (0.5%) was also dispersed along with the gelling agent. A small portion of triethanolamine was added using moderate agitation to form the gel.

Evaluation studies

All the batches were evaluated for following tests.

Physical appearance

The prepared gel formulation was evaluated for color, appearance, and consistence visually.[16]

Weight of the gel

The obtained juice was weighed to measure the amount of gel formed from the volume of juice. The prepared gel juice was also weighed.

Percentage practical yield

Percentage yield was calculated by knowing the practical yield and theoretical yield. Moreover, it was calculated using the formula:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100 \quad (2)$$

Measurement of pH

The pH of the gels was determined by a digital pH meter (Elico LI 120). The pH meter was first calibrated using distilled water. Then, 1 g of the sample was placed on a watch glass, and the surface pH was noted. The pH of each formulation was measured thrice and the average values used for the data.[16]

Viscosity

Viscosity of the formulations was tested at room temperature using a Brookfield DV II viscometer (Germany) equipped with TF Helipath spindle at the 1st day after production date. Measurements were made at 100 rpm in three replicates, and viscosity values were recorded as centipoise (cP).

Drug content

Meloxicam content in gel and commercial cream was measured by dissolving known quantity of both the formulations in phosphate buffer at pH 7.4. Absorbance was

measured after suitable dissolutions at 362 nm in UV-visible spectrophotometer (Shimadzu, UV-1700), and % drug content was calculated from the obtained absorbance values.[17]

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container for their appearance and presence of any aggregate.

Spreadability

It was determined by wooden block and glass slide apparatus.

For the determination of spreadability excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 1000 g weight for 5 min.[18]

Weight (50 g) was added to the pan. The time required to separate the two slides, i.e. the time in which the upper glass slide moves over the lower plate till detachment of both plates was taken as measure of spreadability.[19] Spreadability was calculated using the formula:

$$S = \frac{ML}{T} \quad (3)$$

S = Spreadability
M = Weight tied to upper slide
L = Length moved on the glass slide
T = Time taken to separate the slide completely from each other.

In vitro diffusion studies

Diffusion studies were performed in a vertical Franz diffusion cell using egg membrane as a barrier layer. The formulation was applied on the membrane placed between donor and acceptor compartment. Phosphate buffer pH 7.4 was used as dissolution media. Constant stirring and temperature control were maintained by keeping the whole set up on a magnetic stirrer with temperature control. The temperature was maintained at 37°C ± 1°C. The samples were withdrawn at 0, 15, 30, 45, 60, 120, and 150 min. The receptor compartment was replaced with phosphate buffer pH 7.4 at each time interval to maintain sink conditions. The results were compared with the marketed cream (MC).[20]

Determination of flux

The flux (J) was determined as the angular coefficient of a curve obtained by plotting the cumulative amount of the permeated drug versus time.[21] The permeability coefficient (Kp) was calculated using the following equation:

$$K_P = \frac{J}{C} \quad (4)$$

Where, C is the initial concentration of drug in the vehicle applied to the donor phase.

Pharmacodynamic evaluation

Experimental animals

Male albino rats of Wistar strain weighing 180-230 g were used for the study. They were housed in polypropylene cages and maintained under standard laboratory conditions with a 12-12 h light-dark cycle as well as free access to standard rat pellet diet (Lipton, India Ltd.) and drinking water. They were acclimatized to laboratory conditions for 10 days before starting the experiment. The experimental protocol was approved by the Institutional Animal Ethical Committee (Reg. No. 988/c/PO/06/CPCSEA).

Left hind paw method

Anti-inflammatory activity was evaluated by carrageenan-induced hind paw edema in animals. Group I, control group received carrageenan (1%). Group II received *A. vera* gel and carrageenan. Group III served as standard group and received MC formulation followed by carrageenan. Group IV received (F8) optimized batch of MAG followed by carrageenan. Edema was induced on the left hind paw of the rats by injecting 0.1 ml of 1% (w/v) of carrageenan. *A. vera* gel, (F8) MAG, and MC were applied 30 min before carrageenan administration. To measure paw volume, animals were marked with a permanent marker at left hind paw ankle. The paw volume was measured at intervals of 0 min, 1 h, 3 h, and 5 h by Vernier caliper.[21] The percent inhibition of paw edema in drug-treated group was compared with carrageenan control group and calculated using the formula:

$$\% \text{ inhibition} = \frac{V - V_c}{V_c} \times 100 \quad (5)$$

Where, V_c is the inflammatory increase in paw volume in the control group, and V_t is the inflammatory increase in paw volume in standard or test group.

Statistical analysis

The data were expressed as mean ± standard deviation. Statistical analysis was performed by one-way ANOVA (two-way) test for multiple comparisons formed by Design expert software. Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Experimental data analysis

The experiment was design using 2^3 factorial design by considering three factors at two levels with −1 and +1 equivalent. To estimate the influence of individual variables, i.e., main effects and their second-order effects, this is an effective second-order experimental design associated with a minimum number of experiments. Further, this design has

an added advantage of determining the quadratic response surface, which is not estimable using a factorial design at three levels. The factors are systematically investigated using a full factorial design.

The spreadability of gels (Y1) was observed significant by ANOVA and the polynomial equation was found as follows:

$$Y = 22.60 + 1.15X1 + 0.34X2 + 2.19X3 - 0.18X1X2 + 1.44X2X3 + 7.500X1X3 \quad (6)$$

The positive sign for coefficient of X1, X2, and X3 indicates that as the concentration of gelling agent increases, spreadability increases. 3D plots [Figure 1] show that the spreadability is toward upper level at higher concentration of gelling agents. Spreadability was increased with increase amount of all gelling agents (HPMC, CMC, and Carbopol), results in easy spreading by small amount of shear. All the gelling agents are used in higher concentration, attributed to the soft and less viscous nature of gels, hence higher spreadability value which is acceptable. Optimum concentration of gelling agent was found to be 2%.

The effect on viscosity (Y2) was observed to be significant by ANOVA, and the polynomial equation was found as follows:

$$Y = 93.75 + 1.75X1 + 0.75X2 + 2.25X3 + 1.25X1X2 + 2.75X2X3 + 1.25X1X3 \quad (7)$$

The positive sign for the coefficient of X1, X2, and X3 indicates that as the concentration of gelling agent increases, the viscosity (Y2) also increases. 3D figures as shown in Figure 1 show nearly linear ascending pattern for the values of viscosity with increasing concentration of the gelling agent. At higher gelling concentration, the viscosity of gel was toward a higher level. This may be due to their high concentration, with slightly rigid nature. Viscosity indicated that the sol-gel behavior was due to the incorporation of meloxicam as base moiety in the gel formulation.

Similarly, the effect on percentage drug content (Y3) was observed to be significant by ANOVA, and the polynomial equation was found as follows:

$$Y = 98.75 + 0.51X1 - 0.19X2 - 0.40X3 + 0.34X1X2 - 0.43X2X3 + 0.60X1X3 \quad (8)$$

The positive sign of X1 indicates that increase in concentration of HPMC leads to increase in loading capacity of gel for drug, thus increased drug content in gel shown in Figure 1. Drug content determines the loading capacity of *Aloe* gel formulation. This also increases the homogeneity of drug in the gel base.

Physical appearance and homogeneity

All developed gels (F1-F8) showed good homogeneity with absence of lumps [Table 2]. Prepared gels were yellowish-white viscous transparent preparation with a smooth homogeneous texture and glossy appearance.

Weight of the gel

The collection of *A. vera* leaflets was carried out, and leaflets were thoroughly washed. The mucilage isolated showed a weight of 150.5 g out of which 98.7 ml of juice was obtained after serial filtrations.

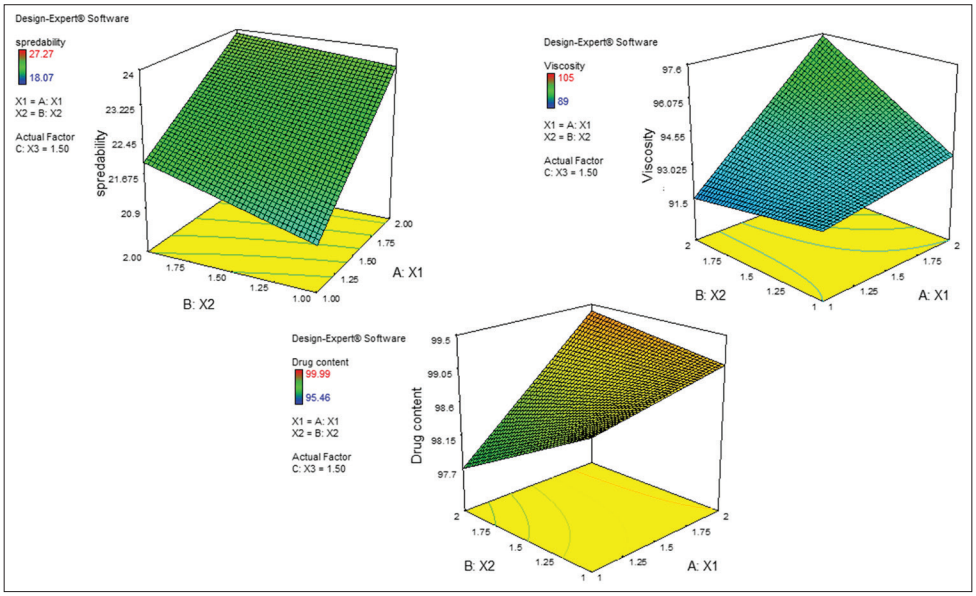

Figure 1: Response surface three-dimensional plots showing effect of independent variables on the dependent variables viz., spreadability, viscosity and percentage drug content by design expert on *Aloe vera* gel based formulations

Percent practical yield

Composition of all batches from F1-F8 is shown in Table 2. The prepared gel was weighed. Practical yield was obtained as 74.89-79.65 g, and theoretical yield was 80.5 g, thereby showing percentage yield as 93.03-98.94%.

Measurement of pH

As *A. vera* is highly acidic, it may induce irritation on application to the skin. Hence, it was treated with alkali. As meloxicam is basic moiety, it also caused the elevation in pH value of all developed formulations (F1-F8), and the pH of all batches was in the range of 6.2-7.3, which is compatible to normal pH range of the skin [Table 3]. Surface pH of the *Aloe* gel and MC gel was found to be 5.8 and 6.16, respectively.

Physicochemical parameters of gel formulations

Viscosity studies

The viscosity of various MAG gels was measured using a Brookfield viscometer and are given in Table 3. The rheological behavior of all formulated gels systems was studied. Viscosity of various formulated MAG gels was found to be in the range of 85-105 cPs. Batch F8 showed high viscosity due to their high concentration, with slightly rigid nature. Viscosity of the *A. vera* gel, (F8) MAG, and MC was observed as 105, 95, and 124 cps, respectively. Viscosity of MAG indicated that the sol-gel behavior was due to the incorporation of meloxicam as base moiety in the gel formulation. The viscosity of *A. vera* gel was higher than MAG.

Drug content

The percentage drug content of all prepared gel formulations was found to be in the range of 91-98.5%. The percentage drug content of formulations confirmed that the drug contents were in specified limits [Table 3]. Drug content determines the loading capacity of *Aloe* gel formulation. From the results, it was observed that the percentage drug content was highest for the MCA (F8) compared to MC implying more loading capacity of *Aloe* gel.

Diffusion studies

The study was conducted for 2.5 h, and the samples were analyzed at 362 nm. Figure 2 shows the cumulative amount of meloxicam released versus time profile for all eight formulations. It was observed that the drug was released immediately within an hour to about 13-52%, and thereafter, the drug release continued gradually. All the formulations showed sustained release effect. F1 and F2 show drug release of 70.17% and 71.57% after 2.5 h. However, F3, F4, and F5 show slightly less sustained release of 66.56%, 68.72%, and 65.82% as compared to CMC and Carbopol, which might be due high viscosity of HPMC. Formulations (F6, F7, and F8) show the highest drug release of 73.28%, 74.59%, and 76.72% due to the higher concentration of Carbopol 934 and due to its good drug loading capacity as compared to CMC and HPMC. F5 showed the lowest drug release (65.82%), whereas F8 showed the highest drug release of 76.72%. The release of meloxicam from all the formulations (F1-F8) followed zero-order kinetics ($r^2 > 0.988$). The release of optimized batch F8 was compared to marketed formulation MC. These imply that the amount of drug permeating through the membrane was more than 76.72% and nearly 70.56% for MC implying that the drug release was effective from the test formulation compared to MC due to the presence of *Aloe,* which provides an aqueous base for hydrating tissues of the skin [Figure 3].

Determination of flux

The flux (J) and permeability coefficients (Kp) of the F8 batch and marketed gel are shown in Table 4 and Figure 4. A plot of the cumulative amounts of meloxicam versus time was plotted to calculate flux [Figure 4]. The flux and permeability coefficient values of F8 were found be higher than that of MC, which may due to the effect of acemannan present in *A. vera* and has been reported as an effective penetration enhancer.

Table 3: Values of evaluation parameters of developed meloxicam-*Aloe vera* gel batches

Batches	pH	Homogeneity	Spreadability (g/cm/s)	Viscosity (cPs)	Drug content (%)
F1	6.4±0.324	Good	20.45±0.986	93±0.682	98.53±3.50
F2	6.4±0.154	Good	22.56±0.457	94±0.789	99.30±3.29
F3	6.8±0.245	Good	18.07±0.879	89±0.782	99.95±2.86
F4	6.7±0.478	Good	20.55±0.987	90±0.896	98.82±3.43
F5	6.8±0.542	Good	21.39±0.545	92±0.863	99.02±3.54
F6	7.0±0.321	Good	24.63±0.879	93±0.875	98.92±5.44
F7	7.2±0.546	Good	25.86±0.896	94±0.895	95.46±3.12
F8	7.3±0.781	Good	27.27±0.879	105±0.789	98.92±3.32
MC	6.16±0.562	Good	24.56±0.564	124±0.784	99.99±2.56
Aloe gel	5.8±0.425	Good	26.56±0.524	105±0.895	-

n=3. MC: Marketed cream, SD: Standard deviation, cPs: Centipoises

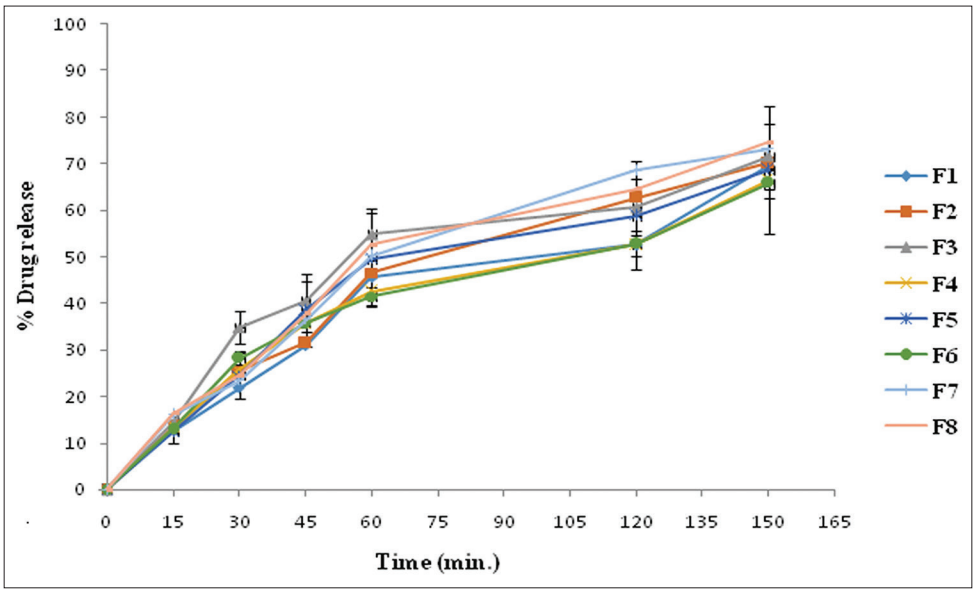

Figure 2: % drug release of meloxicam from all batches of gels values are presented as mean ($n = 3$) ± standard deviation

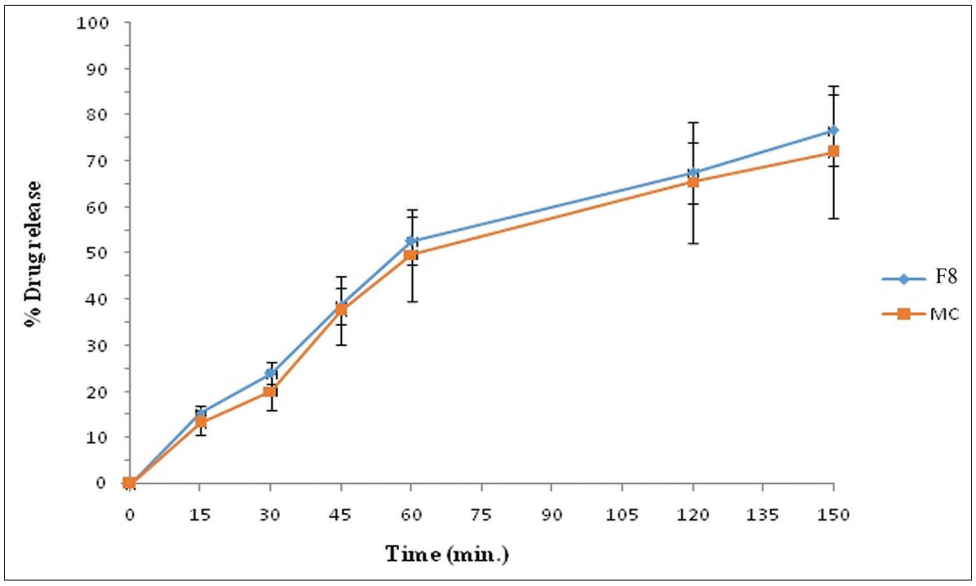

Figure 3: % Drug release of meloxicam from F8 batch and commercial transgels. Values are presented as mean ($n = 3$) ± standard deviation

Table 4: Physicochemical parameters of gel formulations

Formulations	Flux (μg/cm²/h)	Permeability coefficient (cm/h)
Aloe vera gel	-	-
MAG (F8)	0.0732	3.1×10^{-4}
MC	0.0637	2.7×10^{-4}

MAG: Meloxicam incorporated *Aloe vera* gel, MC: Meloxicam cream

Pharmacodynamic evaluation

Meloxicam is NSAID used in the treatment of osteoarthritis and rheumatoid arthritis. It is an oxicam derivative, in which 4-hydroxy-1,2-benzothiazine-1,1 dioxide moiety is responsible for its COX inhibition. Inhibition of COX alone does not account for its anti-inflammatory action. It also acts on oxidative stress which is dependent on the reduction of nitric oxide levels in osteoarthritis. The anti-inflammatory activity of all formulated gels was assessed by carrageenan-induced left hind paw method. The results of *in vivo* anti-inflammatory activity of MAG on carrageenan-induced paw edema in rats were measured as mean paw edema volumes in Table 5. Anti-inflammatory effect of MAG was evaluated after application of gel and subplantar injection of carrageenan in rats. The presence of meloxicam in deeper skin was highest in F8 compared to MC. In this study, the percent inhibition was observed as highest for the MAG with $P < 0.001$ at all-time intervals compared to MC as shown in

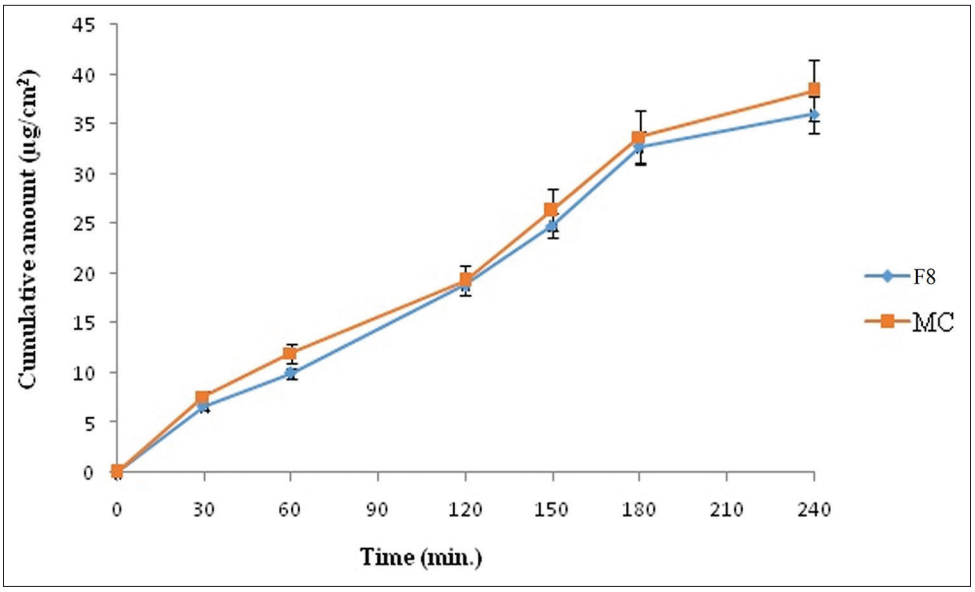

Figure 4: Cumulative amount of drug versus time plot, each value represents mean (n = 3) ± standard deviation

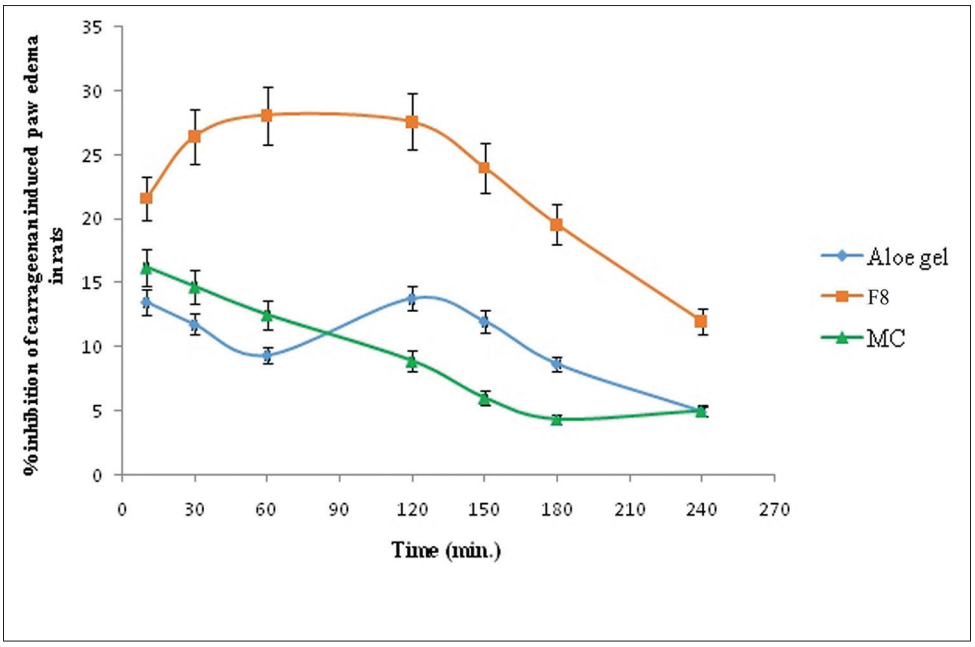

Figure 5: Percent inhibition plot of carrageenan-induced rat paw edema in all the groups. Values are expressed as mean (n = 3) ± standard deviation

Figure 5. The percentage inhibition of edema was assessed to measure the therapeutic efficiency of MAG. The inhibition of edema was observed to be less for plain *Aloe* gel compared to commercial meloxicam gel (considered as reference) and MAG. Test formulation had shown better inhibition of edema due to enhanced permeability of the meloxicam. Better inhibition shown by MAG is due the synergistic effect of *A. vera* on meloxicam, which has mild anti-inflammatory activity. This synergism might be due to direct stimulation of the activity of macrophages and fibroblasts by *A. vera* gel leading to increased collagen and proteoglycan synthesis, thereby promoting tissue repair. Remarkably, mannose 6-phosphate, the principal sugar component of *A. vera* gel, can bind to the growth factor receptors on the surface of the fibroblasts and thereby enhance their activity.

CONCLUSION

From the above study, one can predict that, in the coming years, topical drug delivery would be used extensively to ensure better patient compliance. Since gels are helpful in enhancing spreadability, adhesion, viscosity, and extrusion; this novel drug delivery has become popular. Moreover, these gels are suitable for loading hydrophobic drugs in water soluble gel bases for better drug diffusion profiles. The MAG

Table 5: Effect of transgel formulations on carrageenan-induced paw edema in rats

Time after carrageenan administration (min)	Paw volume (ml)			
	Group I (Control)	Group II (*Aloe vera* gel)	Group III (MAG)	Group IV (MC)
0	0.37±0.003	0.32±0.025	0.29±0.026***	0.31±0.022*
30	0.34±0.025	0.30±0.019*	0.25±0.007***	0.29±0.008**
60	0.32±0.31	0.29±0.006*	0.23±0.029***	0.28±0.013**
120	0.29±0.005	0.25±0.003**	0.21±0.034***	0.27±0.028***
150	0.25±0.029	0.22±0.006	0.19±0.009***	0.23±0.029**
180	0.23±0.031	0.21±0.026*	0.185±0.025***	0.22±0.022
240	0.20±0.011	0.19±0.022	0.175±0.025***	0.19±0.026*

*Values are presented as mean±SD (n=3); *P<0.05; **P<0.01; ***P<0.001 compared to control (Group I). MAG: Meloxicam incorporated *Aloe vera* gel, MC: Meloxicam cream. SD: Standard deviation

showed promising results using higher ratio of Carbopol, HPMC, and CMC as gelling agent. MAG was formulated in *A. vera* gel base and subjected to physicochemical studies, that is, rheological studies, pH measurement, *in vitro* release studies, and *in vivo* release studies through rat skin. *In vivo* release of the test formulations was performed to determine drug release rate from the gel. From the *in vitro* studies, MAG showed significantly better release than the MC. *In vivo* study was also performed by carrageenan-induced paw edema model to reveal the anti-inflammatory potentials of MAG. *A. vera* have a synergistic anti-inflammatory effect in the preparation. It is concluded that *A. vera* gel is an effective gel base to prepare MAG with an enhanced anti-inflammatory profile compared to transdermal gels.

ACKNOWLEDGMENT

The authors are thankful to Cipla Ltd. Goa, for providing meloxicam as gift samples for their search work. They are also thankful to Dr. H. N. More, Principal and Dr. A. A. Hajare, H. O. D. Pharmaceutical Technology, Bharati Vidyapeeth College of Pharmacy, Kolhapur, for providing required facilities to carry out this research work.

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Source of Support: Nil. **Conflict of Interest:** None declared.