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Reducing Topical Mometasone Furoate Doses by Applying Hyaluronic Acid as a Skin Penetration Enhancer

Khaled Aly Khaled [α], Usama Farghaly Aly [σ] & Doaa Amal Tawfik [ρ]

Abstract- The objective of the present study was to investigate the possibility to add hyaluronic acid (HA) as skin penetration enhancer to mometasone furoate (MF) to enhance its skin absorption, and so decrease the dose and side effects in different types of topical formulations including absorption ointment base, oil in water emulsion base and water in oil emulsion base in addition to alcoholic gel base. MF was introduced into the bases with and without the addition of 0.1% HA. The prepared formulations were evaluated for physical appearance, rheological behavior, drug release through a standard cellophane membrane and anti-inflammatory effects in carrageenan-induced oedema in male albino rats. Results showed that all formulations showed good and acceptable physical properties. The in-vitro release rate of each base and its corresponding one, with 0.1% HA, showed no statistical differences. The data obtained revealed that the total amount of drug released was affected by the nature and the composition of bases. Animal studies showed that the differences in decrease in oedema diameter between the full dose of MF 0.1% and the half and the quarter dose of MF with hyaluronic acid sodium salt 0.1% added were unnoticed and the statistical analysis showed that the difference was insignificant ($p>0.05$).

Keywords: hyaluronic acid, mometasone furoate, topical, rheology, release, anti-inflammatory, dose.

I. Introduction

Corticosteroids are derivatives of the natural corticosteroid hormones that are produced by the adrenal glands. These have many important functions in the body, including control of inflammatory responses. Corticosteroid medicines are mainly used for their effect in controlling inflammation, and topical corticosteroids are applied to the skin for the localized treatment of various inflammatory skin disorders (***warner et al, 2001***). While topical steroids have tremendous benefit in reducing inflammation, they also have significant side effects. Most of these side effects are seen with long-term use, but some may be noticed within days of starting therapy (***Wolverton 2001a, Wolverton 2001b, Maibach et al, 1962***). Local steroid use may induce a typical or extensive crusted scabies. Hypertrichosis, hypopigmentation from high- and super-potency steroids is a possible consequence when used on a dark skinned person. Repeated use of topical steroids in the same area can cause thinning of the epidermis and changes in the connective tissue of the dermis, and topical steroid allergy (***Wester et al, 1991***).

Mometasone furoate (9α, 21-dichloro-11β, 17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate)) is a synthetic corticosteroid which is non-fluorinated and containing a furoate moiety. Mometasone furoate is used topically to reduce inflammation of the skin or in the airways. It is a prodrug of the free mometasone. It is used in the treatment of inflammatory skin disorders such as eczema and psoriasis. It is also used in the treatment of allergic rhinitis and asthma (***Bousquet, 2009***). It reduces inflammation by causing several effects such as reversing the activation of inflammatory proteins, activating the secretion of anti-inflammatory proteins, stabilizing cell membranes and decreasing the influx of inflammatory cells.

Of the various skin layers, it is the stratum corneum that is the rate-limiting barrier to percutaneous drug transport. In fact, the stratum corneum is a remarkably more formidable barrier to drug transport than the epithelial barriers of gastrointestinal, nasal, buccal, vaginal, or rectal delivery routes. Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells (***Hoogstrate et al, 1991***). Some of the more desirable properties for penetration enhancers have been given such as, being non-toxic, non-irritating and non-allergenic. They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible. They should have no pharmacological activity within the body.

Hyaluronic acid (HA) has been introduced as a vehicle for topical application of drugs to the skin (***Tracey et al, 1999***). It is a naturally occurring polyanionic, polysaccharide that consist of N-acetyl glucosamine and glucoronic acid. It is present in the intercellular matrix of most vertebrate connective tissues especially skin.It is most frequently referred to as hyaluronic acid due to the fact that exists in vivo as a polyanion and not in protonated acid form. Commercially produced hyaluronic acid is isolated either from animal sources, within the synovial fluid, umbilical cord, skin, and rooster comb or from bacteria

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through a process of fermentation or direct isolation. (*Brown et al, 2005*).

The objective of the present study was to investigate the possibility to add hyaluronic acid to mometasone furoate to enhance its skin absorption, and so decrease the dose and its side effects in different types of pharmaceutical topical formulations including ointment bases such as absorption ointment base, oil in water emulsion base and water in oil emulsion base in addition to alcoholic gel base It was also introduced into the same bases with addition of 0.1% HA. The prepared formulations were evaluated for physical appearance, rheological behavior, drug release through a standard cellophane membrane and anti-inflammatory effects in carrageenan induced oedema in male albino rats.

II. Material and Methods

a) Materials

Mometasone furoate was kindly supplied by Sigma Pharmaceutical Industries, Egypt. Hyaluronic acid sodium salt from streptococcus, Sigma Aldrich, USA. Dialysis sacks, Sigma Aldrich, USA. Hydroxy propylmethylcellulose, winlab, UK. Carbopol 941, Sigma-Aldrich, USA. Stearyl alcohol, Fisher scientific, UK. Anhydrous lanolin, Elnasr pharmaceutical chemicals, Egypt, Tween 40, Columbus chemicals industries, USA. Span 60, Oxford laboratory reagents, Mumbai, India. All other ingredients were of analytical grade.

b) Preparation of Topical Formulations

Mometasone furoate (0.1%w/w) was introduced into various topical formulations including ointment bases such as absorption base, water in oil emulsion base and oil in water emulsion base in addition to alcoholic gel base. It was also introduced into the same bases with addition of 0.1% HA.

c) Absorption Base

Hard paraffine was added to anhydrous wool fat and the white soft paraffine, the all were heated up to 70±2°c in a water bath then added to liquid paraffin in which 0.1% MF was levigated at the same temperature then water was added with stirring and cooled down at room temperature (F1). The same base was prepared by the same manner with the addition of 0.1% HA that was previously dissolved in the water portion of the base (F2).

d) Oil in Water Emulsion Base

Stearyl alcohol and white soft paraffine were heated up to 70±2°c in a water bath then tween 40, propylene glycol and 0.1% MF previously dissolved in ethyl alcohol were added. Water was added with stirring and left to cool down at room temperature (F3). The same base was prepared by the same manner with the addition of 0.1% HA that was previously dissolved in the water portion of the base (F4).

e) Water in Oil Emulsion Base

Cetostearyl alcohol and white soft paraffine heated up to 70 ±2°c in a water bath, span 60 and 0.1% MF previously dissolved in ethyl alcohol were added. Water was added with stirring and left to cool down at room temperature (F5). The same base was prepared by the same manner with the addition of 0.1% HA that was previously dissolved in the water portion of the base (F6).

f) Alcoholic Gel Base

Hydroxypropylmethyl cellulose (HPMC) was soaked in distilled water till the polymer was fully hydrated. Then ethyl alcohol with 0.1% MF was added. Carbomer 941 and glycerin was added to the mixture and kept under magnetic stirrer for 5 hours (F7). The same base was prepared by the same manner with the addition of 0.1% HA that was previously dissolved in the water portion of the base (F8). The compositions of the prepared formulations were illustrated in table (1).

g) Physical Examination

The prepared formulations were inspected visually for their color and homogeneity. The spreadability of the formulations was determined by measuring the spreading diameter of 1 g of each formula between two horizontal plates (20 cm × 20 cm) after one min. The standardized weight tied on the upper plate was 125 g. The results obtained were average of three determinations. The pH of all formulations was checked by using a digital pH meter at constant temperature. The electrode was directly dipped into 1 gram of each formulation previously dissolved in appropriate volume of distilled water to produce concentration 10% w/v and readings were taken.

h) Rheological Studies

For the rheological measurements, the samples of all the 8 formulations , in addition to the commercial product, were examined using cole-parmer 98936 series viscosity centipoise (Vernon Hillss, IL 60061, USA), at 0.5, 1, 2.5, 5, 10, 20, 50 and100 rpm. Each reading was taken after equilibration of the sample, for 1 minute and temperature 25°C using 20 gram sample. The flow curves of all formulations were obtained by directly reading the viscosity (cps) and shear stress (rpm) from the viscometer.

i) In Vitro Drug Release

The release studies were carried out in a modified franz-diffusion cell. A sample of 2 grams of each formula was accurately weighed and placed on a semipermeable standard cellophane membrane previously immersed in distilled water for 24 hours. The loaded membrane was stretched over the lower open end of a glass tube of 3 cm diameter and sealed with a rubber band. The glass cylinder was then immersed in 250 ml beaker containing 150 ml of phosphate buffer (pH 7.4) in such a manner that the membrane was

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located just below the surface of the sink solution. The whole dialysis unit was placed in a thermostatically controlled shaker water bath adjusted at 37±0.1°c with a constant stirring at 30 rpm to avoid development of concentration gradient. Each 15 minutes an aliquot, 2 ml, was collected and replaced by equal volume of the buffer at the same temperature to make the volume of the sink solution constant during the 2 hours of the experiment. Samples were then assayed spectrophotometrically. Concentration of MF in each sample was determined from the standard curve previously constructed. Blank samples were carried out to check any interference simultaneously.

j) Kinetic Studies

To analyze the mechanism of MF release from the prepared formulations, the following plots were made: cumulative % drug release vs. time (zero order kinetic model: $C = k_0t$, where k_0 is the zero-order rate constant expressed in units of concentration/time and t is the time); log of cumulative % drug remaining vs. time (first order kinetic model, as log cumulative percent drug remaining versus time $\text{Log } C = \text{Log } C_0 - kt/2.303$, where C_0 is the initial concentration of drug and k is the first-order constant; and cumulative % drug release per surface area of membrane vs. square root of time (Higuchi model $Q = kt$, where k is the constant reflecting the design variables of the system).

k) Animal study

The in-vivo experimental protocol was approved by the ethical committee of faculty of pharmacy, El-Minia university. Male albino rats (120-170 g) were purchased from the animal house of faculty of medicine (Assuit University, Egypt). The animals were maintained under standard environmental conditions and had free access to standard diet and water. Anti-inflammatory activity was measured using carrageenan induced rat paw edema assay.

The animals were maintained under standard environmental conditions and had free access to standard diet and water. Anti-inflammatory activity was measured using carrageenan induced rat paw edema assay.

Rats were randomly classified into 14 groups. Each group contains 5 rats.

- Group 1: the rats were served as untreated group.
- Group 2: the rats were treated topically with absorption ointment base of 0.1% mometasone furoate (**F1**).
- Group 3: the rats were treated topically with absorption ointment base of 0.05% mometasone furoate (the half dose) combined with 0.1% hyaluronic acid sodium salt (**F2b**[1]).
- Group 4: the rats were treated topically with absorption ointment base of 0.025% mometasone furoate (the quarter dose) combined with 0.1% hyaluronic acid sodium salt (**F2c**[2]).
- Group 5: the rats were treated topically with oil in water emulsion base of 0.1% mometasone furoate (**F3**).
- Group 6: the rats were treated topically with oil in water emulsion base of 0.05% mometasone furoate (the half dose) combined with 0.1% hyaluronic acid sodium salt (**F4b**).
- Group 7: the rats were treated topically with oil in water emulsion base of 0.025% mometasone furoate (the quarter dose) combined with 0.1% hyaluronic acid sodium salt (**F4c**).
- Group 8: the rats were treated topically with water in oil emulsion base of 0.1% mometasone furoate (**F5**).
- Group 9: the rats were treated topically with water in oil emulsion base of 0.05% mometasone furoate (the half dose) combined with 0.1% hyaluronic acid sodium salt (**F6b**).
- Group 10: the rats were treated topically with water in oil emulsion base of 0.025% mometasone furoate (the quarter dose) combined with 0.1% hyaluronic acid sodium salt (**F6c**).
- Group 11: the rats were treated topically with alcoholic gel base of 0.1% mometasone furoate (**F7**).
- Group 12: the rats were treated topically with alcoholic gel base of 0.05% mometasone furoate (the half dose) combined with 0.1% hyaluronic acid sodium salt (**F8b**).
- Group 13: the rats were treated topically with alcoholic gel base of 0.025% mometasone furoate (the quarter dose) combined with 0.1% hyaluronic acid sodium salt (**F8c**).
- Group 14: the rats were treated topically with commercial product of mometasone furoate (Elcon, Schering-plough) of 0.1% mometasone furoate.

[1] Fb: the half dose of MF (0.05%) combined with HA (0.1%)

[2] Fc: the quarter dose of MF (0.025%) combined with HA (0.1%)

After 1 hour, 0.1 ml, 1% carrageenan suspension in 0.9% NaCl solution was injected into the sub-plantar tissue of the right hind paw. The linear paw circumference was measured at hourly interval for 5 hours using paw edema meter (vernier caliper). Anti-inflammatory activity was measured as the reduction in edema diameter when drug was present in full dose or fraction dose combined with hyaluronic acid sodium salt relative to the control group.

l) Statistical analysis

All values were expressed as Mean ± SEM. The statistical analysis was performed using one way analysis of variance (ANOVA). The value of p less than 5% ($p < 0.05$) was considered statistically significant.

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III. Results and Discussion

a) Physical Examination

The physical properties of all formulations are shown in Table 2. All formulations showed good homogeneity and spreadability. The physical appearance of most formulations was white to off white except the alcoholic gel base was transparent. The viscosities of all formulations have shown shear thinning/pseudoplastic behavior at ambient temperature where there is decrease in viscosity by increasing shear rate this shear thinning behavior is a desirable property for topical preparations as they should be thin during application and thick otherwise. The viscosity data obtained has been shown graphically in figures 1-4. The rheological properties of topical pharmaceutical formulations, and hence the patient's compliance, would be accepted. Being a shear-thinning polymer, (HA) can be easily spread on the surface of the skin. It could be also observed that the presence of HA did not affect the rheological behaviors of the prepared bases. The pH of all formulations was in range (5.9±0.159 to 7.8±0.057) with lowest pH value with oil in water emulsion base and the highest value was observed with alcoholic gel base that contains 0.1% HA. This pH range was expected not to produce any skin irritation.

b) Release of mometasone furoate from the prepared topical formulations

The release data of MF from the all formulations were obtained and displayed in table 3. The release of MF from the different formulations could be ranked in a descending order as: F1>commercial>F7>F3>F5. It could be noticed that the absorption ointment base showed the highest release pattern as compared to the other selected formulations. This could be due to the hydrophilic or water absorbing property of the absorption base and, this base is known to take up several times their own weight of water due to the effect of anhydrous lanolin (***sandhu, 2012***). The statistical analysis showed that the absorption ointment base has a significant higher release of MF than both oil in water and water in oil emulsion base ($p<0.001$), but also showed a statistically insignificant higher release rate than both the alcoholic gel base and the commercial mometasone furoate ($p>0.05$).

The table also demonstrated that the release of MF oil in water emulsion base was higher than its release from water in oil emulsion base but the statistical studies showed that the difference was insignificant ($p>0.05$). The stearyl alcohol present in oil in water emulsion base caused greater potentiating effect on water number of petrolatum over cetostearyl alcohol. Accordingly, the presence of stearyl alcohol increased the hydrophilic properties of this formulation over the one that contain cetostearyl alcohol. This increased the affinity of the base to absorb water from the release medium and subsequently increased the drug diffusion and release, this explanation was previously discussed by (***Aml et al, 2013***).

It could be observed also that the release of MF from alcoholic gel base which exhibited a higher release rate than the oil in water and water in oil emulsion base. Statistical studies showed that the difference was insignificant ($p>0.05$), this higher release rate could be attributed to the effect of excessive amount of alcohol that may facilitate the partitioning of drug into the receptor solution and decreasing the viscosity of the gel. These effects were previously suggested by (***Chi et al, 1991***). The commercial product containing 0.1% MF was in the second after the absorption ointment base in the order of the amount released but also the statistical studies showed that the difference was insignificant ($p>0.05$). Statistical analysis showed also a significant higher release of commercial product than both the oil in water emulsion base ($p<0.05$) and the water in oil emulsion base ($p<0.01$), while the release rate was insignificant as compared to the alcoholic gel base ($p>0.05$).

Table 3 demonstrated that the release of MF from all formulations that contains HA as skin penetration enhancer (F2, F4, F6, F8) was slightly higher than its release from the same bases but without HA (F1, F3, F5, F7). The statistical analysis showed that the difference was insignificant ($P>0.05$). This means, the drug release through synthetic membrane was mainly influenced by the rheological properties of the vehicles and diffusion ability through cellulose acetate membrane and HA had no penetration enhancing effect through the membrane.

c) Kinetic analysis of the release data

The kinetic analysis of the in vitro release data of MF from all the prepared formulations is presented in table 4 which listed the correlation coefficients (r^2) of the release profiles when different mathematical models for the analysis of the release kinetics were applied. The preference between the release mechanisms was dependent on the correlation coefficients. As shown in the table, r^2 indicated that the release of MF from w/o emulsion bases (F5 and F6) and the alcoholic gel base (F8) followed zero order kinetics. While the drug release from the other bases followed the Higuchi model.

d) Anti-inflammatory effect of 0.1% MF and (0.05% and 0.025% MF) combined with 0.1% HA formulated in all selected formulations on carrageenan induced paw oedema in rats

Figures 1-8 showed that after 3 and 5 hours, the reduction in oedema thickness produced by the formulations contain 0.1% of MF (the full dose), was

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nearly the same as the formulations that contain 0.05% of MF (the half dose) combined with 0.1% HA and those contain 0.025% MF (the quarter dose) combined with 0.1% HA. The statistical analysis showed that no significant difference was produced ($P>0.05$), between the formulations with full dose of MF and the others with half and the quarter dose of MF combined with HA. While the reduction in oedema diameter produced with all formulations was statistically significant when compared to the control group ($p<0.05$). Results also showed that no significant difference was observed between those formulations and the commercial one.

IV. Conclusion

In conclusion, the diffusion of mometasone furoate from different topical bases through a synthetic cellophane membrane depends on the nature and the composition of the bases. So, the release rate can be altered by changing the nature and the composition in addition to the viscosity of the bases and also by adding the HA. The rheology of all bases were affected by the addition of HA due to the viscoelastic nature of hyaluronic acid that when binds to water gives it a stiff viscous quality similar to "Jello and being a shear-thining polymer the hyaluronic acid also improves the spreadability of the different topical bases. From the in-vivo anti-inflammatory studies, it could be included that the difference in decrease in the oedema diameter in case of using formulation with(full dose) of MF and the same formulation of (half dose) and (quarter dose) MF combined with the skin penetration enhancer 0.1% HA was statistically insignificant (P>0.05). These results explain the effect of HA when absorbed from the surface of the skin and passes rapidly through epidermis, which may allow associated drugs to be carried in relatively high concentration at least as far as the deeper layers of the dermis. This effect was previously suggested by (*Tracey et al, 1999*).

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Table 1 : Composition of the prepared topical bases

Component	F1	F2	F3	F4	F5	F6	F7	F8
MF (%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HA (%)	-	0.1	-	0.1	-	0.1	-	0.1
Hard paraffin(g)	22	22	-	-	-	-	-	-
Anhydrous wool fat(g)	10	10	-	-	-	-	-	-
White soft paraffin(g)	8	8	25	25	18.5	18.5	-	-
Liquid paraffin(ml)	50	50	-	-	-	-	-	-
Stearyl alcohol(g)	-	-	25	25	-	-	-	-
Tween 40(ml)	-	-	2	2	-	-	-	-
Propylene glycol (ml)	-	-	12	12	-	-	-	-
Cetostearyl alcohol(g)	-	-	-	-	25	25	-	-
Span 60(g)	-	-	-	-	2	2	-	-
HPMC(g)	-	-	-	-	-	-	0.75	0.75
Carbomer 941(g)	-	-	-	-	-	-	0.1	0.1
Glycerin(ml)	-	-	-	-	-	-	2	2
Ethyl alcohol(ml)	-	-	10	10	10	10	70	70
Distilled water to(g)	100	100	100	100	100	100	100	100

Table 2 : Physical properties of the prepared formulations

Formulation	pH	Spreading diameter after 1 min (cm)	Color	Transparency	Grittiness
F1	7.7±0.1	3.2±0.2	Yellowish white	Opaque	Smooth
F2	7.2±0.2	2.2±0.057	Yellowish white	Opaque	Smooth
F3	5.9±0.15	3.4±0.1	White	Opaque	Smooth
F4	6.4±0.1	2.7±0.1	White	Opaque	Smooth
F5	6.7±0.12	3±0.1	White	Opaque	Smooth
F6	6.1±0.15	2.5±0.15	White	Opaque	Smooth
F7	7.5±0.15	6.7±0.15	Colorless	Transparent	Smooth
F8	7.8±0.06	5.8±0.15	Colorless	Transparent	Smooth
Commercial	7.4±0.00	4.6±0.15	White	Opaque	Smooth

Table 3 : Mean cumulative amount released

Time (minute)	Mean cumulative amount released (μg) ± standard deviation								
	F1	F2	F3	F4	F5	F6	F7	F8	Com-mercial
15	485.26 ±0.012	485.25 ±0.006	73.54 ±0.001	196.96 ±0.006	38.24 ±0.001	44.12 ±0.001	205.81 ±0.02	205.81 ±0.02	323.54 ±0.011
30	497.59 ±0.02	502.42 ±0.002	103.93 ±0.001	205.59 ±0.006	44.63 ±0.002	56.47 ±0.001	237.94 ±0.001	223.24 ±0.001	379.31 ±0.001
45	507.12 ±0.001	524.97 ±0.002	128.84 ±0.001	225.95 ±0.001	77.58 ±0.001	60.16 ±0.001	246.94 ±0.005	235.03 ±0.001	397.54 ±0.001
60	519.56 ±0.001	531.82 ±0.015	159.94 ±0.002	240.65 ±0.002	110.95 ±0.001	105.07 ±0.001	273.69 ±0.001	258.64 ±0.001	407.13 ±0.001
75	532.07 ±0.001	537.60 ±0.015	191.43 ±0.001	249.57 ±0.001	135.93 ±0.001	141.74 ±0.001	291.97 ±0.04	288.52 ±0.001	419.71 ±0.001
90	541.82 ±0.002	560.23 ±0.002	211.55 ±0.001	263.11 ±0.001	149.47 ±0.001	149.47 ±0.001	351.59 ±0.001	433.37 ±0.006	438.28 ±0.001
105	563.28 ±0.015	581.95 ±0.001	223.08 ±0.02	284.07 ±0.001	166.09 ±0.001	163.13 ±0.05	361.92 ±0.001	565.38 ±0.001	448.20 ±0.001
120	584.97 ±0.005	598.01 ±0.001	252.32 ±0.001	290.56 ±0.001	177.03 ±0.001	176.99 ±0.001	537.01 ±0.005	579.68 ±0.001	461.12 ±0.001

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Table 4 : Kinetic data of the release studies

Formula	Zero Order		First Order		Diffusion Model (Higuchi)	
	r^2	K *µg/min*	r^2	K *min^{-1}*	r^2	K *µg. $t^{0.5}$*
F1	-0.41	16.01	-0.85	-0.02	**0.57**	22.2
F2	-0.35	16.41	-0.85	-0.02	**0.6**	22.7
F3	0.91	5.8	-0.85	-0.02	**0.98**	7.6
F4	0.12	7.66	-0.85	-0.02	**0.82**	10.5
F5	**0.97**	4.04	-0.3	-0.02	0.91	5.23
F6	**0.95**	4.01	-0.85	-0.02	0.92	5.2
F7	0.73	10.53	-0.85	-0.02	**0.88**	13.9
F8	**0.88**	12.3	-0.85	-0.02	0.85	15.9
Commercial	-0.12	12.6	-0.85	-0.02	**0.72**	17.4

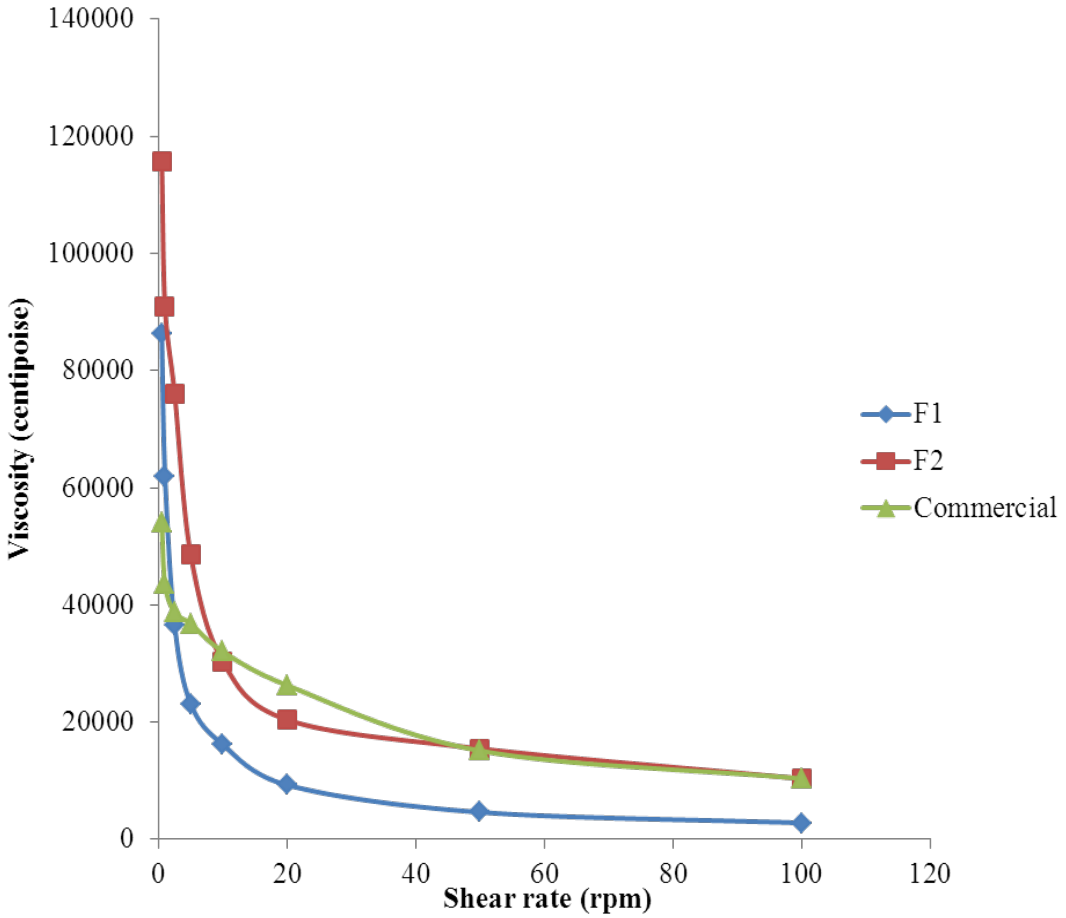

Figure 1 : Rheogram of absorption ointment base

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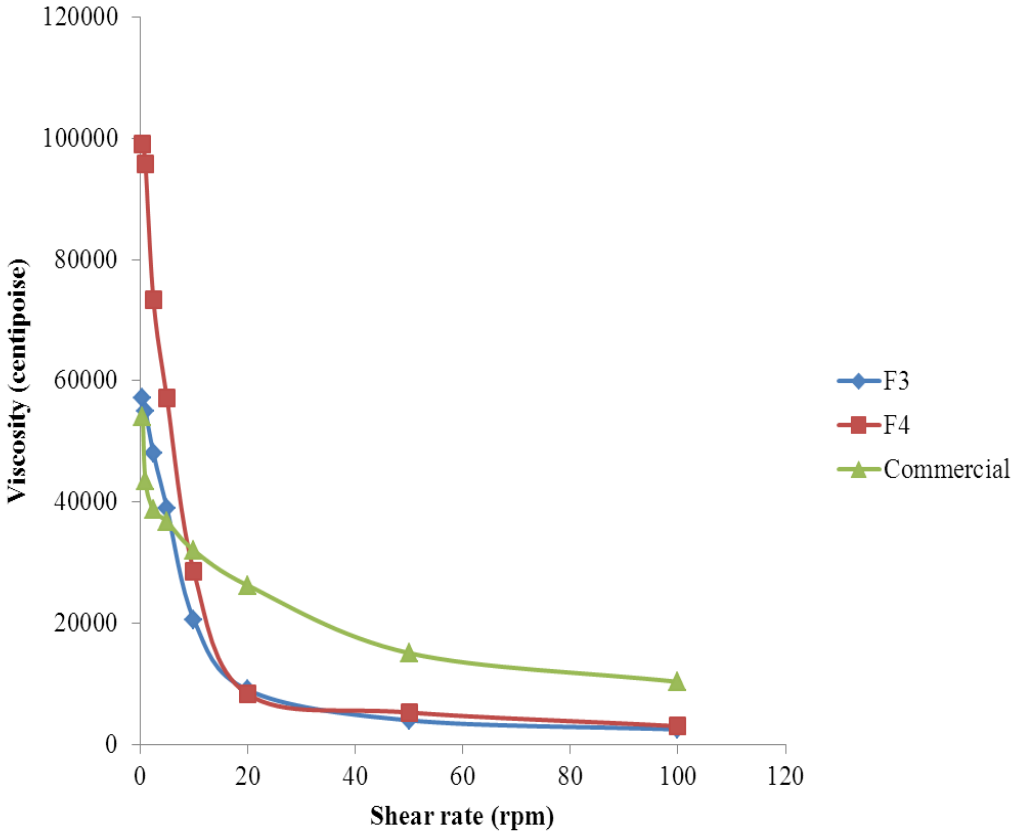

Figure 2 : Rheogram of oil in water emulsion base

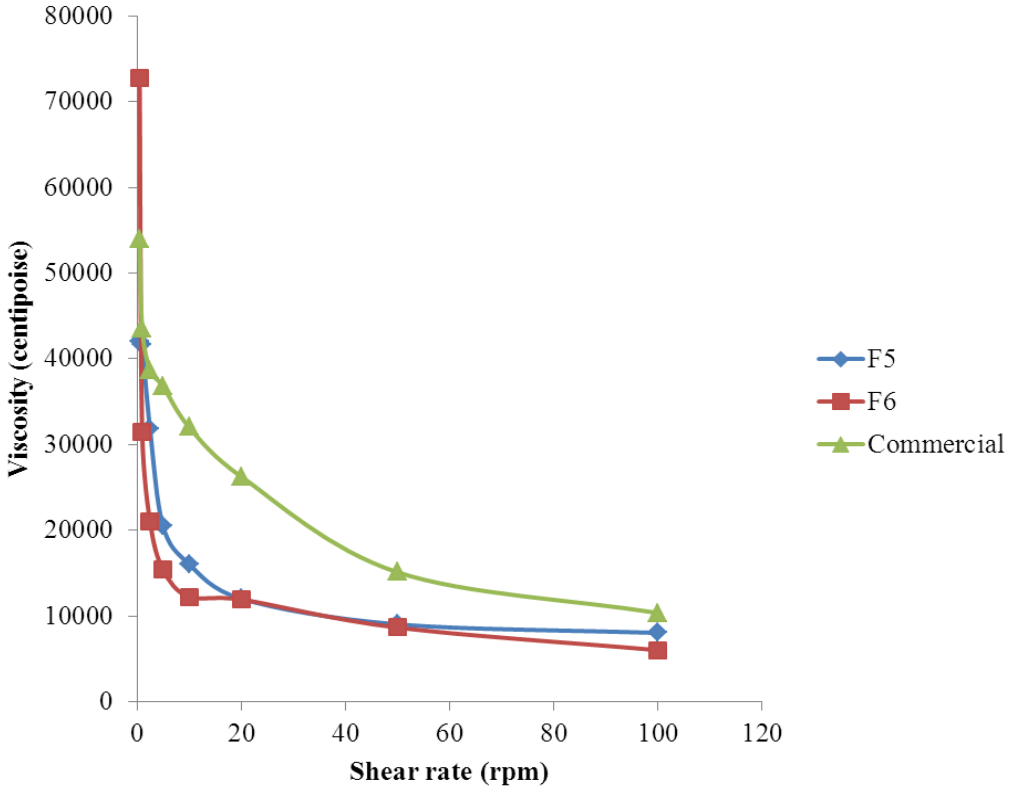

Figure 3 : Rheogram of water in oil emulsion base

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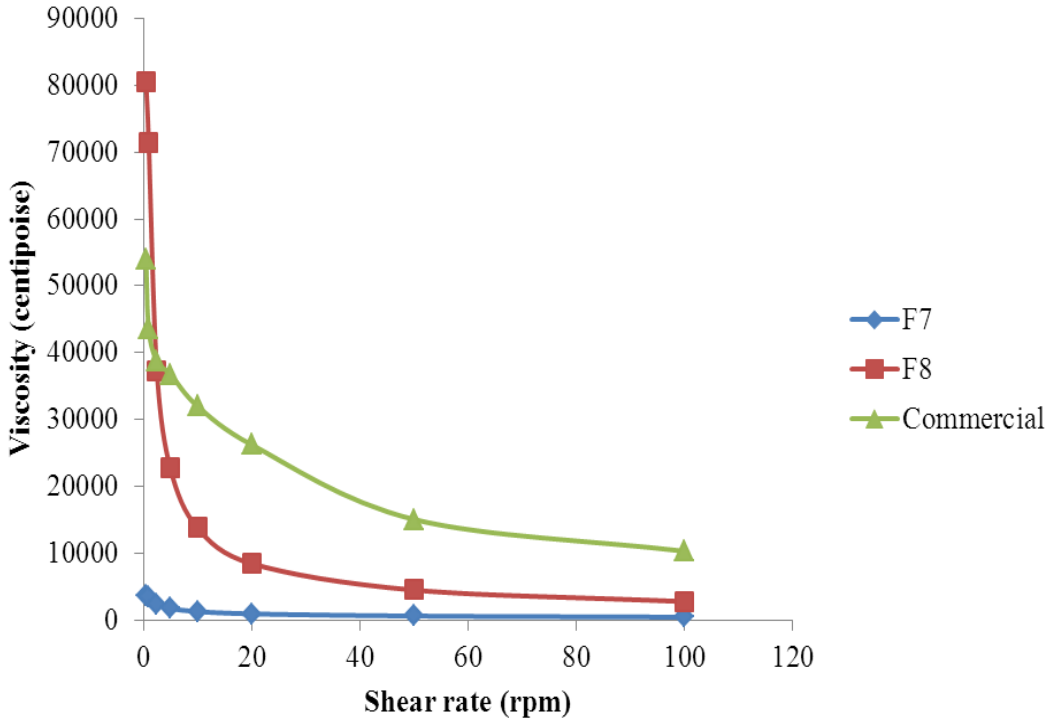

Figure 4 : Rheogram of alcoholic gel base

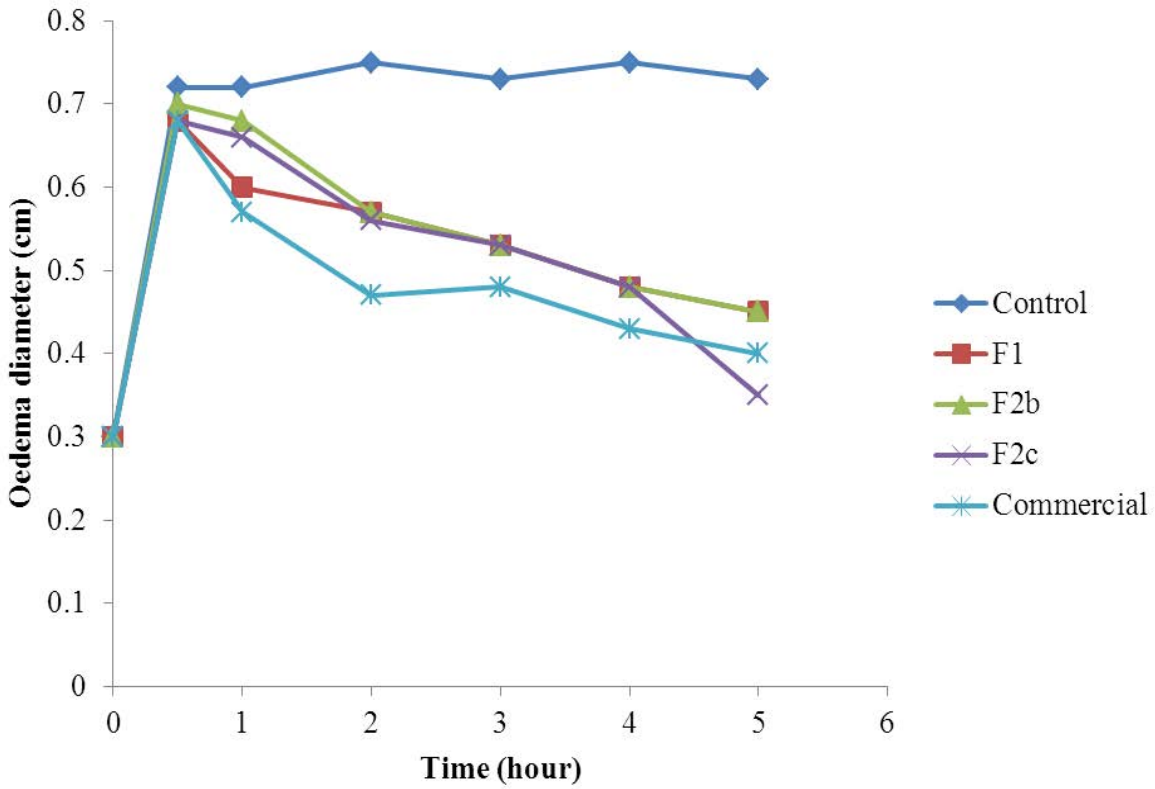

Figure 5 : Anti-inflammatory effect MF using absorption ointment base (F1, F2b and F2c)

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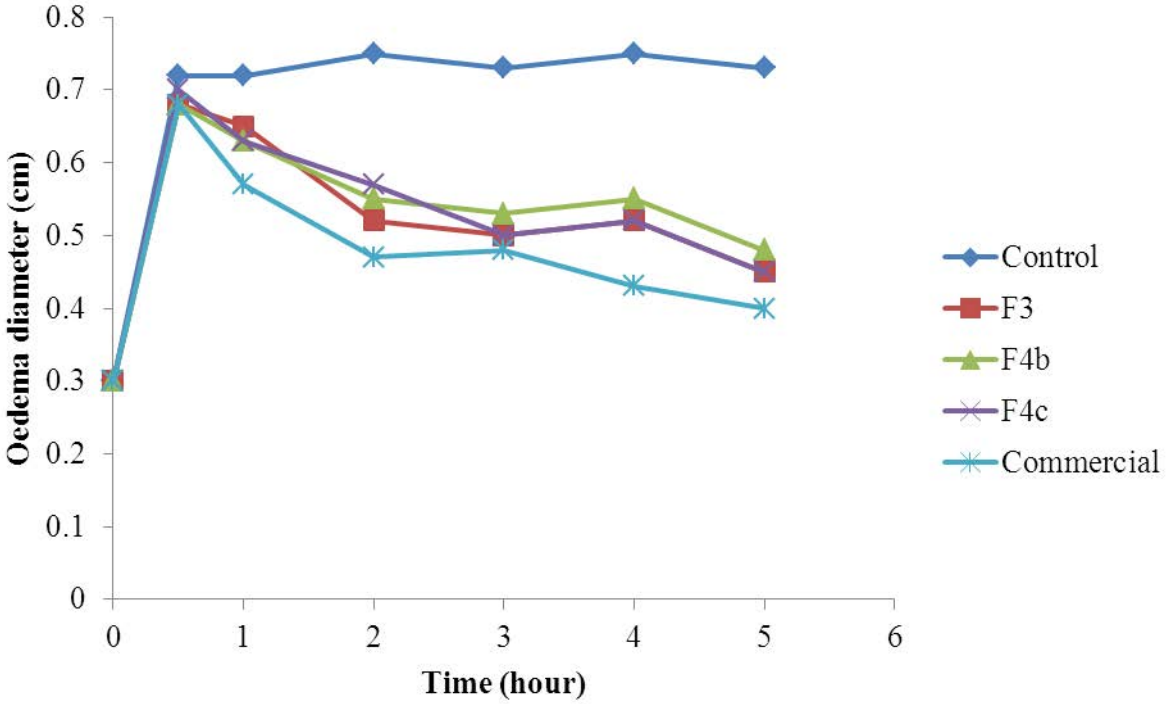

Figure 6 : Anti-inflammatory effect of MF oil in water emulsion base (F3, F4b and F4c)

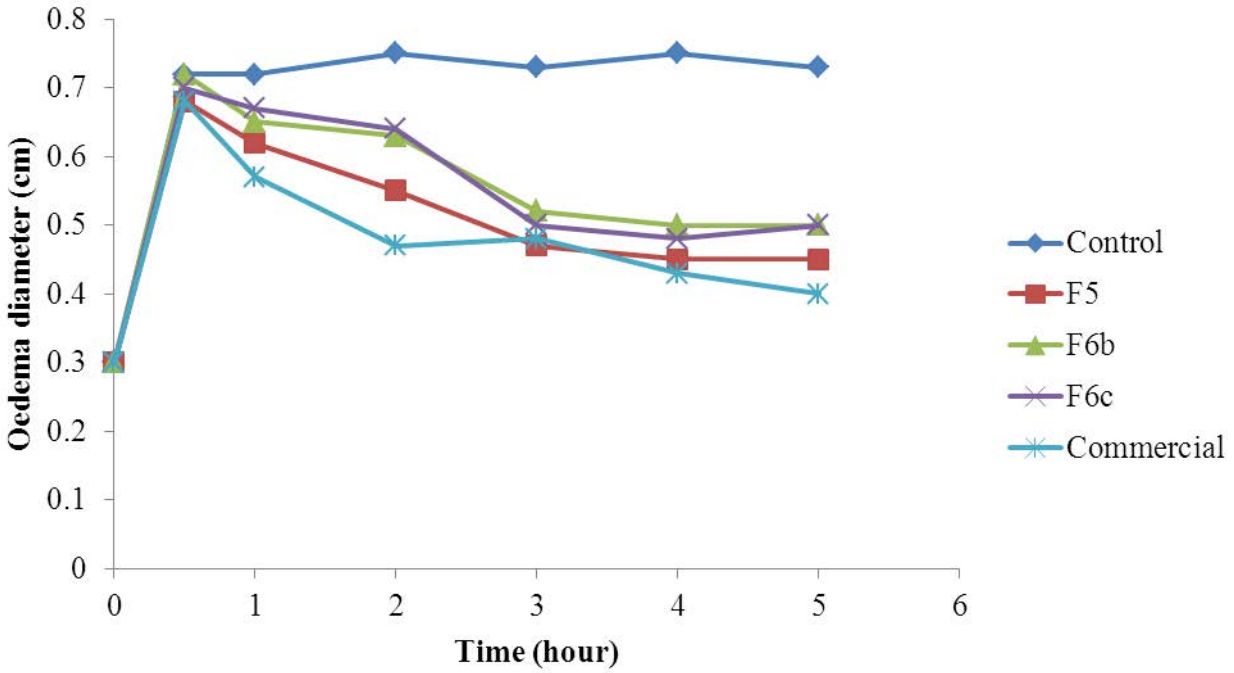

Figure 7 : Anti-inflammatory effect of MF using water in oil emulsion (F5, F6b and F6c)

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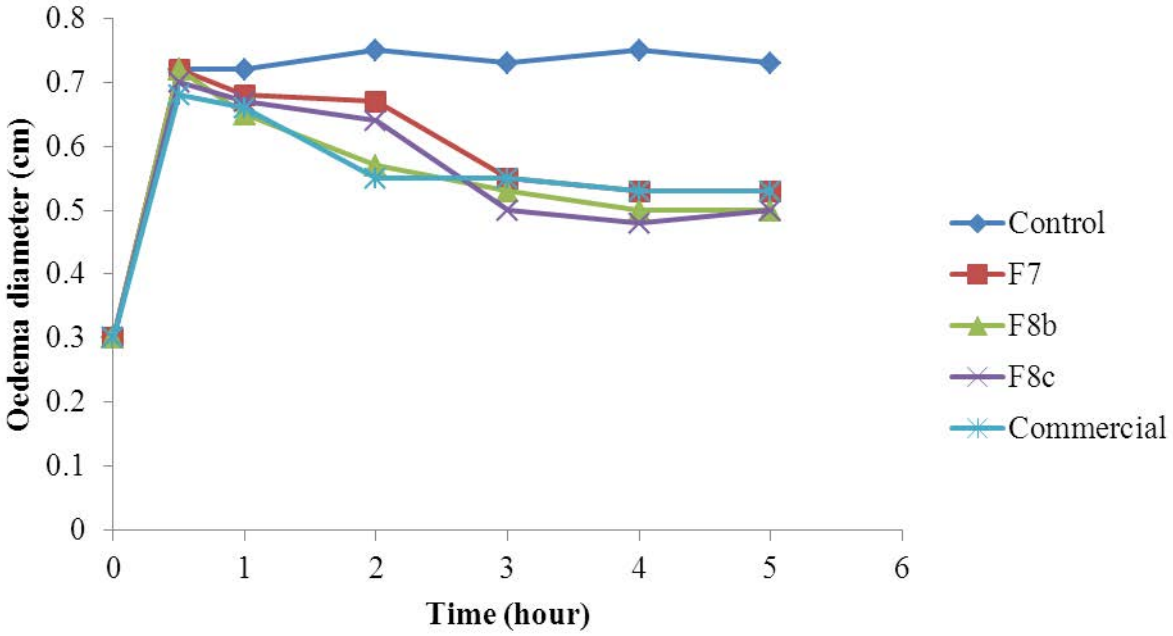

Figure 8 : Anti-inflammatory effect of MF using alcoholic gel base (F7, F8b and F8c)

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