RESEARCH ARTICLE

Preparation, Characterization and *In-Vitro* Diffusion Study of Different Topical Flurbiprofen Semisolids

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ABSTRACT

Flurbiprofen (FLB) is chemically 2-(3- fluoro-4-phenyl phenyl) propanoic acid. It is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis and osteoarthritis. Oral administration of this drug is associated with severe gastrointestinal side effects like ulceration and gastrointestinal bleeding. The solution to this problem lies in the fact that topically applied NSAIDs are safer than orally. This study aims to prepare different topical semisolid formulation of FLB as cream base (o/w), (w/o) and gel base using different gel-forming agents in different concentrations. Comparing characterization properties in addition to release and diffusion study for all the prepared formulas to select the best one.

Method: Topical semisolid FLB preparations were formulated using different semisolid formulation starting from emulsion bases w/o and o/w comparing with different gelling agents in different concentrations which include carbopol 934, sodium carboxy methylcellulose (SCMC) and combination of both polymer in different concentration to get 1% gelling agents. All the gel formulations were evaluated for physical appearance, pH, spreadability, rheological studies, drug content, *in vitro* release and diffusion studies.

Results: All gel formulations which contain gelling agent exhibit better *in vitro* drug release and permeation compared with the emulsion bases, especially 1% polymer combination. Ethanol exerts a significant effect ($p < 0.05$) on the *in vitro* drug release and diffusion for 2% carpbopol 934 compared with SCMC. Drug content was found to be uniform in all the formulations. The pH ranges of formulated gels were found to be suitable for topical application.

Conclusion: Based on overall results, FLB can be successfully prepared as topical semisolid preparation with accepted properties.

Keywords: Carbopol 934, Flurbiprofen, SCMC, Topical gel.

INTRODUCTION

A promising concept for a long time is drug delivery through the skin because skin has a large surface area with vast exposure to the circulatory and lymphatic networks. It is easy to access and not invasive.[1] One of the most popular and important pharmaceutical dosage forms is topical gel preparation. This route of drug delivery has gained popularity because it avoids first-pass effects, gastrointestinal irritation, and metabolic degradation associated with oral administration.[2] Only 25–45% of the orally administered dose reaches the blood circulation due to the first past effect. The gel formulations have been proposed as a topical application to bypass these disadvantages.[3] Gels have better potential as a vehicle to administer drug topically in comparison to ointment because they are not sticky, requires low energy during formulation.[4] Percutaneous absorption of drugs from topical formulations involves the release of the drug from the formulation and permeation through the skin to reach the target tissue.[5]

FLB is chemically 2-(3- fluoro-4-phenyl phenyl) propanoic acid; it possesses antipyretic and analgesic activity. FLB' s anti-inflammatory effect occurs via reversible inhibition of the enzyme responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin synthesis pathway. This effectively decreases the concentration of prostaglandin involved in inflammation, pain, swelling, and fever. FLB a non-selective Cyclooxygenase (COX) inhibitor and inhibits the activity of both COX-1 and COX-2. It is also one of the most potent NSAID in terms of prostaglandin inhibitory activity.[6,7]

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AIM OF THE STUDY

The present research has been undertaken with the aim to develop a topical semisolid formulation of FLB, which would attenuate the gastrointestinal related toxicities associated with oral administration. It is established which one of the prepared semisolid formulations are superior over any other topical formulations. In this research, different semisolid formulations were prepared to start from o/w, w/o cream bases and gel bases, which were prepared using SCMC and carbopol 934 as gel-forming polymers either alone or in a combination of both. All the formulated topical semisolid bases were evaluated for physical appearance, rheological behavior, *in vitro* drug release and diffusion study.

MATERIALS AND METHODS

FLB was purchased from Hangzhou Hyper Chemicals Limited, Zhejiang, China. Carbopol 943 and SCMC were received as a gift sample from Samarra Drug Industry (SDI). Methyl paraben, propyl paraben, ethanol, and triethanolamine were purchased from Fluka Chemical AG, Switzerland. All other chemicals and solvents were of analytical reagent grade, and deionized water also was used in this study.

Calibration Curve of FLB

The calibration curve of FLB was constructed by taking 0.01g of FLB, which is dissolved in 5 mL of ethanol then the volume was completed to 100ml using phosphate buffer 7.4. From this stock solution different standard solutions were prepared such as 2 Mg/mL, 3 Mg/mL, 4 Mg/mL, 6 Mg/mL, 8 Mg/mL, 9 Mg/mL,10 Mg/mL and 12 Mg/mL. These solutions were analyzed for drug absorbance using UV Visible spectrophotometer at 247 nm, as shown in Figure 1.[8]
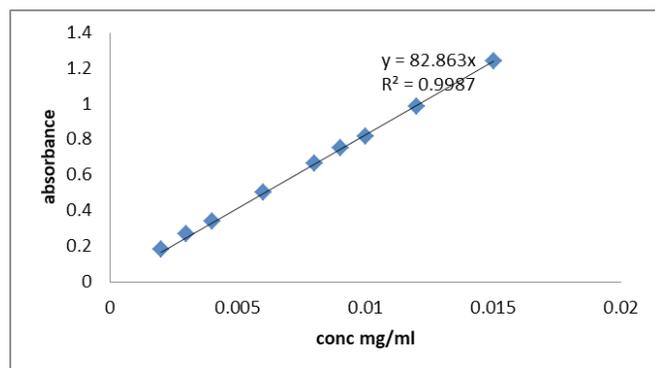
Preparation of the Phosphate Buffer Solution

Two stock solutions were prepared:

Solution **A** (1/15 molar Potassium dihydrogen phosphate KH2PO4):

It was prepared by dissolving 9.08 g of KH2PO4 in sufficient D.W to make one liter.

Solution **B** (1/15 molar Disodium hydrogen phosphate Na2 HPO4.2H2O):

This solution was prepared by dissolving 11.87 g of Na2 HPO4.2H2O in sufficient D.W to make 1-liter solution.

Figure 1: Calibration curve of FLB, concentration versus absorbance

The buffer solution of pH 7.4 was then prepared by mixing 19.7 ml of solution A with 80.3 ml of solution B.[9]

Preparation of the Cream Bases

The general method employed for the preparation of the cream bases was the fusion method, then incorporation of FLB using spatula and slab. The following bases were used:

Water in Oil Cream Base (w/o)

Wool fat	70 g
Water	30 g

The wool fat was melted in a beaker on a water bath; the water was heated to 75 °C in a separate container. The aqueous phase was then added to the oil phase with continuous stirring until congealed. Then 5gm of FLB was incorporated in the prepared base using a spatula.[10]

Oil in Water Cream Base (o/w)

White beeswax	1 g
Cetyl alcohol	15 g
Propylene glycol	10 g
Sodium lauryl sulfate	2 g
Water	72 g

The white bees wax and cetyl alcohol were heated on a water bath to about 75°C, the water temperature was raised to 75°C in a separate beaker, sodium lauryl sulfate and propylene glycol were added to water. The aqueous phase was then added to the oil phase with continuous stirring until congealing. Then 5 gm of FLB was incorporated in the prepared base using a spatula.[10]

Preparation of the Gel Base Using Carbopol 934 and SCMC Gel Either Alone or In-combination

The specified quantity of polymer was weighed and sprinkled slowly on the surface of three quarter distilled water (D.W) required then leaving for hydration overnight in the refrigerator. Stirring at 500 rpm using mechanical stirrer for about 30 minutes than the specified amount of drug (5g) was sprinkled slowly with continuous stirring for 30 minutes. Finally, the required quantity of methylparaben and propylparaben as a preservative were added to the gel formula, and then the volume was completed to 100 mL using D.W with continuous stirring till drug get dispersed completely. 0.1 mL of triethanolamine was added to the gel formula containing carbopol as shown in Table 1.

All the prepared semisolid formulas, which include o/w, w/o cream, and gel formulas from F1 to F11, were considered for further physical and *in vitro* diffusion studies except formula F6 containing 0.5 gm of SCMC as gelling agent due to precipitation.

Evaluation of FLB Semisolid

The above-prepared cream and gel formulas were evaluated for their physical appearance, pH determination, spreadability, viscosity, drug content, and *in vitro* diffusion studies.

Physical Appearance

The prepared gel formulations were inspected visually for their color, homogeneity, consistency, grittiness.[11]

Table 1: Formulation of FLB gels using different gelling agents.

Ingradients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Flurbiprofen	5	5	5	5	5	5	5	5	5	5	5
SCMC	-	2	-	1	-	0.5	-	2	0.25	0.5	0.75
Carbopol 934	2	-	1	-	0.5	-	2	-	0.75	0.5	0.25
Ethanol (mL)	-	-	-	-	-	-	20	20	-	-	-
Methyl paraben	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Propyl paraben	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Triethanolamine (mL)	0.1	-	0.1	-	0.1	-	0.1	-	0.1	0.1	0.1
D.W (mL) ad to	100	100	100	100	100	100	100	100	100	100	100

Spreadability

The spreadability of formulations was determined 48 hours after preparation by parallel plate method.[12]

A sample (1g) of the formulation was transferred to the center of the glass plate (20 x 20 cm) placed over a paper on which concentrically divided squares of 1 mm sides were drawn, and spread over an area of 1 cm^2. Another glass plate having a mass of 100 g was placed gently on the formulation, and 2 kg weight was placed at the center of the plate with care to avoid sliding of the glass plate. The spread diameter in cm was measured after 3 minutes, where no more spreading was expected. Results obtained are the average of three determinations.[13]

pH Determination

The pH of the prepared cream and gel formulas was determined by using a digital pH meter (CG 820, Schott Geräte GmbH, Hofheim, Germany). One gram of the prepared formula was dissolved in 100 ml of D.W (1% solution) then pH measurement was performed. The measurement of pH of each formulation was done in triplicate, and average values were calculated. [14]

Viscosity Study

Viscosity measurements were done on Brookfield digital viscometer (NDJ–5S) at 30 rpm after selecting a suitable spindle number depending on the sample viscosity (spindle no. 4) and at room temperature. Fifty g of preparation was kept in 50 mL wide glass tube, which was set till the spindle groove was dipped, and rpm was set at 30, and dial reading was measured after 3 minutes. The average of three readings was used to calculate the viscosity and obtained values were recorded as milliPascals per second (mPa. s).[15]

Drug Content

To ensure uniform formulation, it was sampled from the different locations and assayed for the drug content. Drug content was determined by dissolving an accurately weighed quantity of each prepared formulas (about 1 g, which contains 0.05 g of FLB) in about 100 ml of pH 7.4 phosphate buffer. These solutions were quantitatively transferred to volumetric flasks, and appropriate dilutions were made with the same buffer solution. The resulting solutions were then filtered through a 0.45μm membrane filter before analysis for FLB spectrophotometrically at 247 nm .[16]

In vitro Release Study

The *in vitro* release study was performed using the USP dissolution apparatus II (paddle type). It was carried out with a small beaker 2.5cm in diameter modified to be overturned (inverted)and filled with 0.25 g of the semisolid bases, each containing 5%(w/w) of FLB. The mouth of the beaker was covered with filter paper 0.45μm, which was secured in place with a rubber band. Each beaker was immersed from the top only in 500ml phosphate buffer of pH 7.4 at 37°C stirred at 25 rpm during 4h of the study.5ml samples were pipetted from the dissolution media at 30,60,120,180, and 240minutes then replaced with an equal volume of fresh buffer solution. The samples then analyzed spectrophotometrically at 247nm.[17]

In vitro Diffusion Studies

The diffusion of the drug from all the prepared formulas were determined by using vertical modified Franz diffusion cells (heat block with 10ml modified plastic syringe) as shown in Figure.2. The diffusion medium was phosphate buffer pH 7.4, maintained at 32°C. The dialysis membrane (0.08 μm pore size) which was previously soaked in phosphate buffer pH 7.4 for 1hr and then air-dried. It was mounted between the donor and receptor compartment, which were clamped together. The phosphate buffer pH 7.4 was filled in the receptor compartment (13ml capacity) and stirred using magnetic stirrer continuously at 600 rpm. 0.2g of each prepared formula was placed in the receptor compartment fitted with plastic plug as shown in the figure below. The diffusion cell area was 2 cm.^{2} At different time intervals samples were withdrawn and replaced with an equal volume of buffer. The samples were analyzed spectrophotometrically after appropriate dilution at 247 nm.[18]
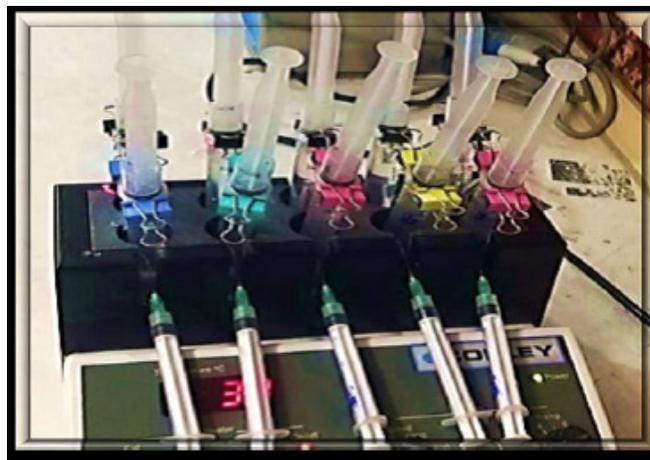
Figure 2: Modified Franz diffusion cell

Data Analysis

The amounts of FLB contained in the receptor samples (drug permeated) were quantified in order to calculate the cumulative amount (Q) of FLB in the receptor compartment as a function of time. The individual permeation profile of each formulation was obtained by plotting the cumulative amounts of FLB permeated per unit of semipermeable membrane area versus time. The flux (J) was determined from the slope of the linear portion of the plot. The lag time represents the x-axis intercept of the extrapolated linear portion of the permeation profile. Permeability coefficient P is calculated using Equation 1.[19]

$$P = J/C \tag{1}$$

Where C is the concentration of FLB in the donor (initial drug concentration), and J is the flux.

The permeation parameters obtained for the different formulations were compared using ANOVA. Differences among the treatments were assumed to be significant at $p < 0.05$.

RESULTS AND DISCUSSION

All formulas showed good homogeneity with an absence of lumps, showing no phase separation. Variable consistency of gel ranging from liquid to thick preparations. The formulated preparations containing carbopol as a gelling agent was white as compared to the preparation containing SCMC as a gelling agent was much clear and translucent. Results are shown in Table 2.

The pH values of all developed formulas were between 4 to 5.69, as shown in Table 2, which lie in the normal pH range of the skin. This is considered acceptable to avoid the risk of irritation upon application to the skin.[20]

The values of spreadability indicate that the gel is easily spreadable by small amount of shear. Table 2 showed that the spreadability of the formulated gels containing carbopol or SCMC alone as gelling agents was in range of 5.93–6.8 g.cm/s, while the spreadability of the formulated cream base was higher than 6 .8 g.cm/s. Medium value of spreadability was gained upon mixing different ratio of the two polymer as shown in formulas F9, F10 and F 11.[21]

An important requirement for a topical preparation use it's viscosity. It should be in a range which will allow ease of application and permit the formulation to stay at site of application. Table 2 shows that cream bases o/w and w/o exhibit higher viscosity value 8038.1 and 14402, respectively.

The obtained viscosity values of FLB gel formulations were in the range of 1129–13549 mPa.s, as shown in Table 2. The viscosity of the formulations was found to be affected by the type of polymer used. Higher viscosity value for the gel formulated with carbopol 934 compared to those formulated with SCMC. A significant increase ($p < 0.05$) in viscosity was observed with increasing polymer concentrations, so the viscosity value increase in the rank F1 > F3 > F5 also F2 > F8. Furthermore, the viscosity of the formulations was found to be influenced by the type and concentration of polymers used, which exerts a higher degree of cross-linking at higher concentrations of polymers. This is in accordance with results reported by Lakshmi et al. on their study on Ibuprofen topical gel evaluation.[20]

Formulations containing 1% combinations of polymers (F9, F10, and F11), exhibit an acceptable and higher viscosity value 15344,11051 and 4188 mPa.s respectively than those containing only one polymer in the same ratio 1%. This may be due to the viscous and hydrophilic nature of SCMC and Carbopol 934, the combination might have expanded more in water than the individual polymers would in water and hence the increase in solution viscosity.[22] Significant decrease($p < 0.05$) in the viscosity were obtained upon addition of 20 mL ethanol, so F1 containing 2% of cabopol 934 exerts 13 549 mPa.s compared to F7 containing ethanol which exerts 3710 mPa.s.[23]

The percentage drug content of all prepared formulations i.e., F1 to F11 gel and (o/w), (w/o) cream bases, were found to be in the range of 99.18 ± 0.2 **to** $101.03 \pm 0.04\%$. The percentage drug content of formulations was found to be within the I.P limits. Hence methods adopted for gels and creams formulations were found suitable.[23] The results are shown in Table 2.

Effect of Different Bases on the *in vitro* Release and Diffusion (Permeation) Studies of FLB

In vitro release of the drug from the topical dosage form gives an idea about the amount of free active drug available for partitioning into the stratum corneum. *In vitro* release

Table 2: Evaluation parameters of formulated gels and cream bases

Formulas no.	Homogeneity	Spreadabiliy (g.cm/sec)	pH	Viscosity (mPa.s)	Drug content (%)
F1	Good	6.0 ± 0.08	4.07 ± 0.15	13549 ± 120	100.22 ± 0.01
F2	Good	6.27 ± 0.2	5.86 ± 0.02	7748.6 ± 100	99.18 ± 0.21
F3	Excellent	5.93 ± 0.31	4.47 ± 0.12	9487.4 ± 111	99.8 ± 0.11
F4	Good	6.83 ± 0.05	5.19 ± 0.01	1129.5 ± 122	99.11 ± 0.81
F5	Satisfactory	6.43 ± 0.09	5.21 ± 0.03	4320 ± 100	101.03 ± 0.04
F7	Satisfactory	5.93 ± 0.2	4.0 ± 0.22	3710 ± 121	100.2 ± 0.12
F8	Satisfactory	5.97 ± 0.4	4.84 ± 0.12	6848.2 ± 100	99.2 ± 0.54
F9	Excellent	5.87 ± 0.08	4.78 ± 0.02	15344 ± 111	$100,.04 \pm 0.01$
F10	Good	6.07 ± 0.1	4.7 ± 0.04	11051 ± 130	99.98 ± 0.11
F11	Excellent	6.53 ± 0.01	5.42 ± 0.02	4188 ± 112	100.01 ± 0.01
o/w	Good	6.9 ± 0.21	5.69 ± 0.01	8038.1 ± 150	99.86 ± 0.02
w/o	Good	6.97 ± 0.07	5.6 ± 0.03	14402 ± 111	99.91 ± 0.04

All values were calculated as mean $\pm$ SD, n = 3

of FLB from different semisolid bases containing 5%(w/w) of the drug can be illustrated in the bellow Figure 3 which demonstrates the cumulative percentage of FLB released from the prepared formulas by the following order F2 > F4 > F5 > F3 > F1 > o/w > w/o bases. This could be explained as the drug is poorly soluble in water (0.012 mg/ml) so partitioning of drug is decreased according to the nature of the bases. Although the drug is highly partitioning in the internal oil phase, it's released from w/o cream base was insignificantly ($p > 0.05$) higher than o/w cream base.

Figure 4 shows the in-vitro diffusion of FLB from different semisolid bases. The data listed in Table 3 indicates that **J** value calculated from the slope of linear portion of the plots for all the gel formulas is significantly higher ($p < 0.05$) than cream bases whether it's (o/w) or (w/o), as well as the p-value which is directly proportional to the value of flux (J).

The Lag time value calculated from the intercept of the extrapolated line with x-axis gives an indication about the time required for the diffusion or permeation to be started and increased that was(o/w) cream base exerts higher value(longer time = 0.552 hour) compared with(w/o) cream base(0.168 hour) this can be explained related to the higher solubility of FLB in the oil phase and lower solubility in water 8mg/L.[24]

Effect of Different Polymer Concentration on the *in vitro* Release And Diffusion (Permeation) Studies of FLB

Figure 5 shows the effect of different concentrations of polymer on the release of FLB from the prepared gel formulas, so the cumulative percentage of drug released increased in the following order F1 < F3 < F5, so as the carbopol concentration increased the cumulative percentage of drug released decreased.

For the formula prepared with SCMC due to the lower viscosity value (7748.6 mPa.s) it exhibits a higher cumulative percentage of drug released than carbopol (13549 mPa.s), as shown in Figure 5 below.

Figure 6 also clarifies the effect of polymer concentration on the diffusion rate (flux value), so as the concentration increases the J value decreases as well as p-value.

Polymer type at a ratio of 1% significantly ($p < 0.05$) effect on the J and p-values. So the formulas prepared with carbopol
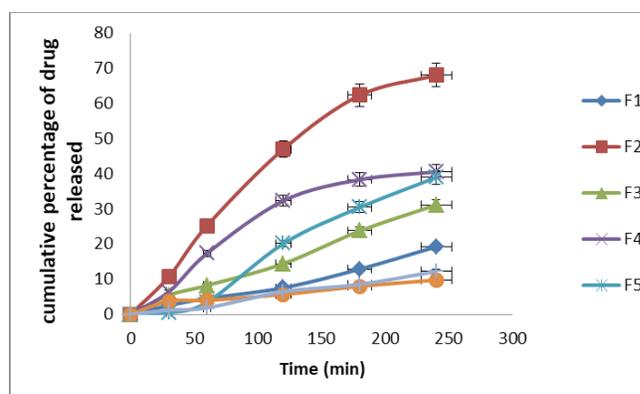

Figure 3: Effect of different semisolid base on the *in vitro* release of FLB, (mean ± SD, n = 3).
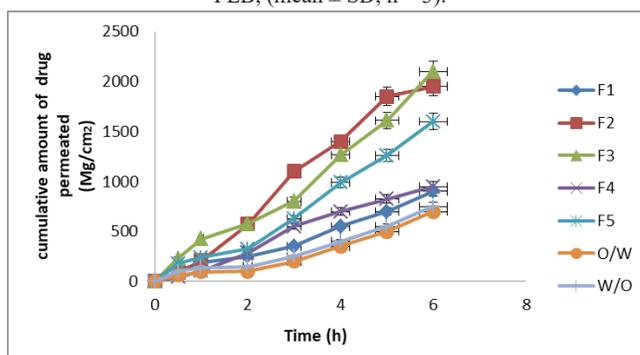

Figure 4: Effect of different semisolid base on the *in vitro* diffusion of FLB (mean ± SD, n = 3).
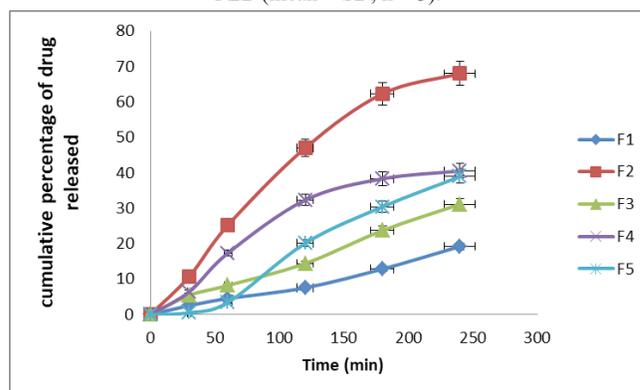

Figure 5: Effect of different polymers concentration on the *in vitro* release studies of FLB (mean ± SD, n = 3).

Table 3: Effect of different polymer type, concentration and ratio on the permeation parameters of FLB

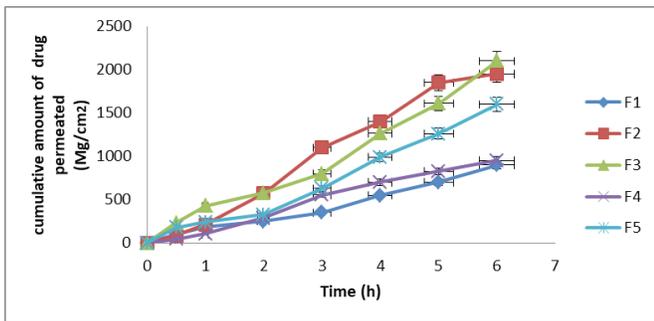| Formula type	Flux (Mg/cm^2) (J) value	Lag time (h)	Permeability coefficient (P x 10^{-2})
F1	1.41 x10^2	3.36	2.8
F2	3.72 x10^2	0.296	7.44
F3	3.29 x10^2	2.5x10^{-2}	6.6
F4	1.66 x10^2	0.1	3.3
F5	2.65 x10^2	0.255	5.3
F7	3.46 x10^2	0.105	6.9
F8	3.64 x10^2	0.54	7.3
F9	2.03 x10^2	4.7x10^{-3}	4.1
F10	3.29 x10^2	2.5x10^{-2}	6.6
F11	3.9 x10^2	4.1x 10^{-2}	7.8
O/W cream	1.14 x10^2	0.552	2.274
W/O cream	1.15 x10^2	0.168	2.3

Figure 6: Effect of different polymers concentration on the *in vitro* diffusion (permeation) studies of FLB, (mean ± SD, n = 3)
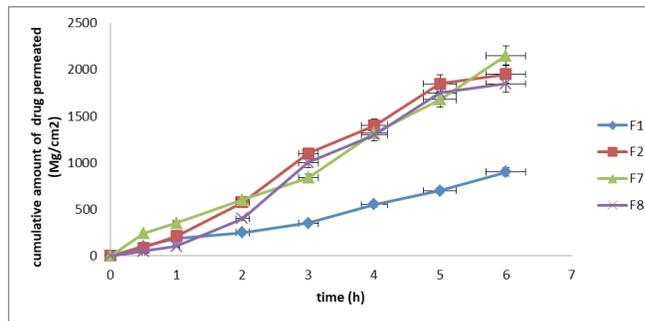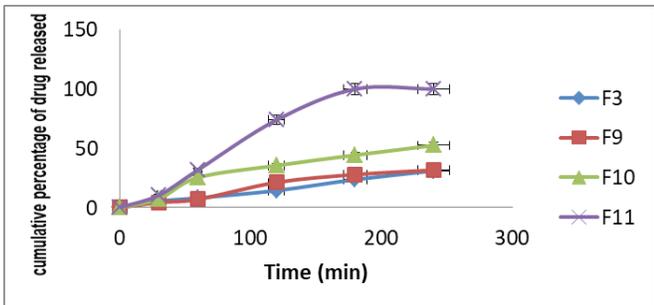

Figure 7: Effect of different polymer-combination ratio on the *in vitro* release studies of FLB, (mean ± SD, n = 3).
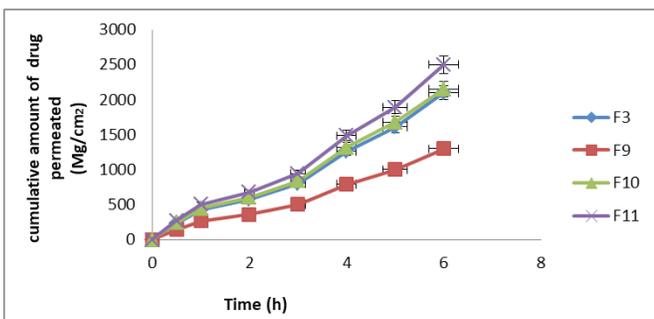

Figure 8: Effect of different polymer-combination ratio on the *in vitro* diffusion (permeation) studies of FLB, (mean ± SD, n = 3)
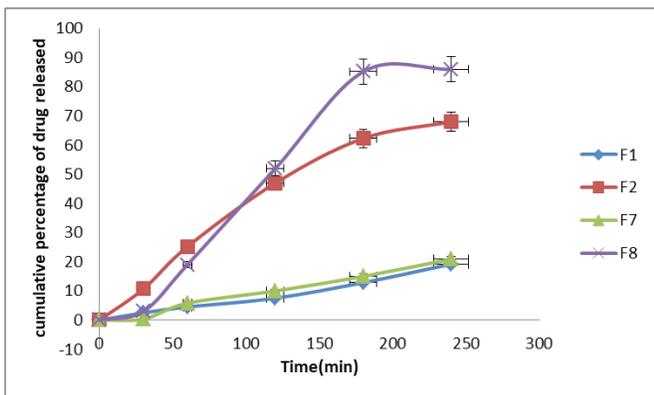

Figure 9: Effect of ethanol on the *in vitro* release studies of FLB, (mean ± SD, n = 3)

943 (F3) exerts better diffusion compared with those prepared with SCMC(F4), as shown previously in Table 3.

This result is consistent with the reported results which stated that the release rate of a drug depends on the physical

Figure 10: Effect of ethanol on the *in vitro* diffusion (permeation) studies of FLB (mean ± SD, n = 3).

structure of the polymer network if the gel is highly hydrated (low polymer concentration), the diffusion occurs through the pores while in case of low hydration (high polymer concentration) the drug dissolves or stays in the polymer and is transported between the chains so cross-linking increases hydrophobicity of gel and diminishes the diffusion rate of the drug.[5]

Effect of Different Polymer Combination Ratio on the *in vitro* Release And Diffusion (Permeation) Studies of FLB.

From the above figure it's clear that 1% is the best polymer ratio that exerts better diffusion rate compared with the other ratio so we decided to make three combination ratio of carbopol 934 and SCMC to achieve 1% , F9, F10 and F11, which represent the combination ratio of the two polymers (carbopol 934: SCMC) as below:

(0.75: 0.25), (0.5: 0.5) and (0.25: 0.75) respectively as shown in Figures 7 and 8 which indicate that the best combination ratio is 0.25 carbopol 934 and 0.75 SCMC due to the higher release and diffusion rate appear, so 100% cumulative drug released for F11 > F10 > F9 > F3, as well as the flux (J) and Permeability coefficient (P) values are significantly increase($P<0.05$) compared with F9 but the difference are insignificantly ($p > 0.05\%$) compared with F8 and F10 as shown in Table 3 listed above.[26]

Effect of Ethanol on the *in vitro* Release And Diffusion (Permeation) Studies of FLB

Figures 9 and 10 show that the cumulative percentage released and diffusion rate of FLB from F1 (carbopol 934 2%) is significantly increased ($p < 0.05$) upon addition of 20 ml ethanol while SCMC shows no significant effect on diffusion rate after addition of 20 ml ethanol.

As well as the permeation parameters listed previously in Table 3 show no significant change in J and P values for F2 and F8, while the formula containing ethanol with carbopol 934 shows significantly increased in the permeation parameters compared with those containing carbopol 934only.[27]

CONCLUSION

From the above results we can conclude that semisolid formulation prepared with different gelling agents (carbopol 934 and SCMC) exert better physical properties and *in vitro* release and diffusion compared with the cream bases whether its o/w or w/o. Also can conclude that FLB gel formulations

prepared by combination of different gelling agents such as carbopol 934 and SCMC to achieve 1% showed acceptable physical properties and in -vitro diffusion study (permeation). All prepared gels showed acceptable physical properties, homogeneity, consistency, spreadability and pH value. Among all gel formulations, gel containing (0.25:0.75) ratio of carbopol 934 and SCMC respectively, shows superior *in vitro* diffusion results with higher permeation parameters also it exerts higher percentage of drug released compared with other ratios and gels containing carbopol 934 or SCMC alone as gelling agent. The gel formulation that contains 20 ml of ethanol with carbopol 934 shows better permeation parameters (J and P values) compared with the formula that contains 20ml of ethanol with SCMC.

ACKNOWLEDGMENT

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