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# DESIGN AND *IN-VIVO* EVALUATION OF TOPICALLY APPLIED CHLORPHENIRAMINE MALEATE GELS

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**Keywords:**

Chlorpheniramine maleate, Topical gel, Factorial design, Franz diffusion cell, Ratskin, Permeation

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**ABSTRACT:** This study was aimed at formulating topically applied Chlorpheniramine maleate gel (CPM gel). Combined effects of propylene glycol and polyethylene glycol as permeation enhancers were investigated using response surface methodology. The formulated gels were characterized for various formulation attributes including viscosity, homogeneity, pH, spreadability and accelerated stability studies (40 ± 0.5 °C / 75% RH). *In-vitro* studies were also conducted using silicone sheets and rat skin as model membranes. The permeation study revealed that an increase in the drug permeation across model membranes was due to an increasing concentration of enhancers. Based on formulation attributes and permeation parameters, FM6 was identified as optimized formulation. The drug release from optimized formulation followed the first order release kinetics. Draize's skin irritation test was conducted on healthy human volunteers to elucidate the safety profile of the formulations. Pharmacokinetic profiling of optimized gel was also conducted, and finally, the optimized gel was subjected to anti-allergenic challenge. Pharmacokinetic studies revealed that topical application produced comparable results with the oral delivery and the optimized gel was excellent in the management of allergy in rabbits. This study showed that the optimized CPM gel (FM6) containing a combination of propylene glycol and polyethylene glycol as permeation enhancers would be beneficial for addressing topical allergies and should be further tested in more clinically relevant settings.

**INTRODUCTION:** Chlorpheniramine maleate (CPM) belongs to alkylamines class of chemicals which structurally mimics histamine. CPM acts primarily by reversibly blocking histamine from reaching the receptor sites, thus minimizing the allergic reactions [1]. CPM is extensively metabolized by the liver, and about 25-45% of orally administered drug reaches the systemic circulation [2, 3].

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Antihistamines like CPM produce side effects such as drowsiness, dizziness, muscle weakness and gastrointestinal disturbances when given orally. Therefore, other delivery routes are sought for safe and effective use of antihistamines. In this regard, drug delivery into and through the skin is considered as an effective means of addressing the local and systemic diseases.

However, penetration of chemicals into and through the skin is often challenged by the impermeability of the stratum corneum [3, 4, 5, 6], which is considered as the primary barrier to skin permeation. The impermeability of the stratum corneum can be temporarily and reversibly altered by the judicious choice of the vehicle [7]. Various solvents and chemicals have been used to

overcome the skin's barrier properties, which lead to the enhanced penetration of drugs across the skin [8, 9, 10, 11]. The success of topical formulations is their ability to facilitate penetration of drugs into skin layers. The extent of absorption will then be dependent on the physicochemical properties of the penetrant and the vehicle. In addition to that, easiness of application and whether the patients accept the product contribute substantially toward the success of topical formulations [12, 13]. For example, products which are unpleasant to touch are unlikely to be accepted by the patients regardless of its potential benefits [14]. Among various delivery vehicles, the gels can prove to be efficient in topical or local drug delivery to the skin. Gels are semisolid preparations with excellent acceptability in cosmetic, pharmaceutical and food technologies [15]. The gels are typically formed from a liquid phase that has been thickened with a minor component that usually is a gelling agent [16, 17]. The continuous liquid phase allows free diffusion of molecules through the three-dimensional polymeric scaffolds of the gels, and hence drug release should be equivalent to that from a simple solution. Additionally, gels can hydrate the skin by retaining the water at the skin surface that could otherwise escape into the atmosphere [18].

Previously, we reported that a combination of propylene glycol (PG) and polyethylene glycol (PEG-1000) in a lotion formulation could enhance the nimesulide permeation across the skin [19]. Here we report the development and subsequent optimization of CPM gel by using a combination of PG and PEG as the permeation enhancers. Combination of chemicals often leads to an exhaustive number of formulations that are required to be tested before a decision is reached. Here we applied a more robust computer-aided approach, namely response surface design to study the effect of enhancer's combination on the performance of CPM gels. Various attributes of formulations including physical and chemical characterization, *in-vitro* drug release and skin permeation properties, pharmacokinetic parameters and anti-histaminic activity were assessed.

## EXPERIMENTAL:

**Materials:** Chlorpheniramine maleate was gifted by Hamaz Pharmaceuticals (Pvt.) Ltd., Propylene glycol and carbopol-934 was purchased from Merck (Germany) and polyethylene glycol-1000 from Fluka (Germany). All other chemicals used in this study were of analytical grade and were used without further purification.

**Assay of Chlorpheneramine Maleate:** Stock solution was prepared by dissolving 10mg of CPM in phosphate buffer saline (at pH 7.4) in 100 ml volumetric flask and made up final volume up to 100 ml. The calibration curve for Chlorpheneramine maleate was constructed at UV absorbance of 265nm in a concentration range of 0.5-5 µg/ml. The regression equation for calibration curve was Y= 0.023x + 0.0027 with regression coefficient ($R^2$) = 0.992, whereas; Y = Absorbance at 265 nm, m= Slope (0.023), b = Intercept (0.0027), and x = Concentration (µg/mL) of Chlorpheneramine maleate.

**Determination of CPM Solubility and Partition Coefficient:** Solubility of CPM in distilled water, methanol and phosphate buffer saline (at pH 7.4) was determined. An excess quantity of CPM was added to each of the solvent (10 mL) and kept under controlled stirring at a constant temperature of 37 °C ± 2 for 48 h. After that, each solvent was centrifuged at 13000 rpm for15 min to separate the undissolved drug. The supernatant aliquot from each of the solvent was analyzed after appropriate dilutions using a UV-spectrophotometer set at a wavelength of 265 nm. The solubility was determined in triplicate and reported as mean ± SD.

Partition coefficient was determined by adding a weighed quantity of CPM to pre-equilibrated PBS/octanol mixture (1:1 ratio) in a 50 ml separation funnel. The separating funnel was shaken vigorously for 30 min and then allowed to stand for 24 h vertically. The aqueous and organic layer was collected and then centrifuged for 20 min at 2000 rpm. Aliquots were taken and quantified for CPM concentration at 265 nm by UV spectrophotometer after appropriate dilutions with respective solvents. All this procedure was carried out in triplicate at room temperature (25 ± 0.2 °C).

**Experimental Design:** A central composite design (CCD) with $\alpha = 2$ was employed to prepare the gels as described previously [17, 19]. The factors, namely PG (X1) and PEG (X2) planned at 5 levels were selected based on the results of preliminary

experiments. It was found that the combination of enhancers (PG up to 35% and PEG up to 8%) could enhance the permeation (data not shown). Therefore, it was decided to optimize formulated gels within the studied range. The central point (0, 0) was studied in quintuplicate. All other CPM gel formulations and process variables were kept invariant throughout the study as given in **Table 1**.

**Preparation of CPM Gels:** 100 g of CPM gel having various concentrations of PG and PEG-1000 were prepared after carefully weighing and measuring all the ingredients **Table 1**. First of all, carbopol-934 was left overnight to dissolved in the required quantity of PG with the help of magnetic stirrer (polymeric solution). Then methanol was taken in another flask and dissolved PEG-1000 and menthol crystals in the required quantity by continuous stirring (PEG-mixture). A small amount of water was taken in a conical flask, and 1 g CPM was dissolved in it by stirring (drug solution).

The drug solution was then mixed into PEG-mixture, and the resultant mixture was slowly added into the polymer mixture with continuous stirring until all materials were mixed homogeneously. Then benzyl alcohol and ethylene glycol were added in it with continuous stirring. The mixture was neutralized using triethanolamine, and the final volume up to 100 g of gel was adjusted with the help of double distilled water [17].

**TABLE 1: COMPOSITION OF CPM GELS AS PER CCD**

| CPM gel Formulations | CPM % w/w | $X_1$=PG % w/w | $X_2$= PEG-1000 % w/w | Carbopol - 934 % w/w | Benzyl alcohol % w/w | Ethylene glycol % w/w | Methanol % w/w | Triethanol amine % w/w | Menthol % w/w | Distilled water (q.s) up to 100g |
|---|---|---|---|---|---|---|---|---|---|---|
| FMC | 1.0 | 0 | 0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 48.2 |
| FM1 | 1.0 | 20.0 | 3.5 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 24.7 |
| FM2 | 1.0 | 30.0 | 3.5 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 14.7 |
| FM3 | 1.0 | 20.0 | 6.5 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 21.7 |
| FM4 | 1.0 | 30.0 | 6.5 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 11.7 |
| FM5 | 1.0 | 15.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 28.2 |
| FM6 | 1.0 | 35.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 8.2 |
| FM7 | 1.0 | 25.0 | 2.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 21.2 |
| FM8 | 1.0 | 25.0 | 8.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 15.2 |
| FM9 | 1.0 | 25.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 18.2 |
| FM10 | 1.0 | 25.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 18.2 |
| FM11 | 1.0 | 25.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 18.2 |
| FM12 | 1.0 | 25.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 18.2 |
| FM13 | 1.0 | 25.0 | 5.0 | 2.5 | 20.0 | 0.55 | 25.0 | 2.5 | 0.25 | 18.2 |

***In-vitro* Characterization of CPM Gels:**

**Determination of pH:** The pH of CPM gels were determined by pH meter (Mettler & Toledo, Giessen, Germany) at room temperature (25 ± 0.2 °C).

**Rheological Studies:** Brookfield digital viscometer (Model RVTDV 11, Brookfield Engineering Laboratories, lnc, Stoughton, MA) was the used to measure the viscosity of CPM gels at room temp. (25 ± 0.2 °C). The spindle (S 63) was rotated at a rate of 0.6 rpm. Data were acquired in triplicate.

**Spreadability:** The spreadability of the optimized gel was determined by glass slide method. The amount of 0.1 mg of optimized FM6 CPM gel was put on glass plates in the circle mark and was pressed between glass plates with a weight of 100 gram for ~ 5 min. The diameter of spread gel circular area was measured in cm [20]. The spreadability was determined according to the formula:

$$S = M \times L / T$$

Where S is spreadability, M is weight/volume tide to upper slide, L is the length of the glass slide, t is the time taken to separate the slides from each other.

**Homogeneity:** The CPM gels were visually inspected with the naked eye for homogeneity to check any aggregates or lumps.

**Drug Content Analysis:** A weighed quantity of gels was dissolved in 10 ml of 0.1 N sulphuric acid and UV absorbance at 265 nm was recorded after suitable dilutions. A series of standard solutions were also prepared in 0.1N HCl, and a standard curve was constructed. The drug was quantified using the linear equation of the standard curve.

**Permeation across Silicone Membrane:** CPM diffusion from gels across silicone membrane was determined to elucidate the effects of enhancers on

the formulated gels performance. Sheets of silicone membrane (already soaked overnight in PBS) were cut to appropriate size in a circular disc form.Franz-type diffusion cells were used which had a diffusional area of ~0.788 $cm^2$ and receptor phase volume of ~5 mL. The diffusion cells were placed on a stirring bed immersed in a water bath at 37 ± 1°C to maintain a temperature of 35°C at the membrane surface. A sample of 200 µl of the sample from receptor solution was drawn using a micropipette at definite time intervals of 15, 30, 45, 60, 90, 120 and 180 min. After each withdrawal of sample, the receptor medium was replenished with 200 µl fresh pre-thermo stated receptor fluid to maintain sink condition. The drawn samples were analyzed spectrophotometrically in triplicate manner.

**Drug Release Studies:** *In-vitro* dissolution of optimized gel (FM6) was monitored by USP type-II apparatus. The studies were done in 500 ml of phosphate buffer (pH 7.4) with the temperature maintained at 37.0 ± 0.5 °C, while stirred at 75 rpm. Drug release kinetics was studied by fitting the drug release data to various models including zero-order, first order, and Higuchi.

**Draize's Skin Irritation Test:** For primary skin irritation test, three volunteers were selected, and then CPM gels were applied on an area of 2 square inches of the wrist for 2 h and observed the skin for any abrasion/lesion.

**Stability Studies:** The optimized CPM gel was selected for accelerated stability study in the stability chamber for six months at 40 ºC ± 1 and Relative humidity 75 ± 2%. The optimized gel was packed in the collapsible aluminum tubes. The physical appearance, pH value, and drug content, viscosity and spreadability were analyzed after 0, 1 week, 2 weeks, 1 month, 3 months and 6 months.

***Ex-vivo* Diffusion Studies through Rat Skin:** Diffusion studies of the optimized FM6 Chlor-pheniramine gel across rat skin were carried out using two chambered modified Franz-type diffusion cells having a receptor phase of ~5 mL and a diffusional area of ~0.788. Following approval (ref no. 86-2010/BZU.PHM) by the Board of Advance Studies and Research, Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan, this study was carried out according to international guidelines for animal use in laboratory experiments. Abdominal skin of rat was carefully excised after sacrificing the rat. Subcutaneous fats and other extraneous tissues adhering to the dermis were completely removed. The skin was cleaned with PBS (pH 7.4) and stored in a freezer at –20 °C until further use [21]. Before diffusion studies, the skin was thawed and bathed in PBS. Sheets of skin were cut to appropriate sizes (~ 1 $cm^2$) in round-shape and mounted between the two compartments of the diffusion cells with epidermis side facing the donor compartment.

***In-vivo* Analysis:**

***In-vivo* Pharmacokinetic Studies:** Pharmaco-kinetic study was conducted on male New Zealand rabbits to compare the oral and transdermal application of CPM. Animals were housed under controlled environmental conditions and were given food and water *ad libitum*. Various pharmacokinetic parameters were determined [22].

**Anti-allergenic Challenge:** The efficacy of CPM gel against managing allergy was challenged in anti-allergenic studies. Allergy was induced in healthy rabbits (n=3) by injecting 0.0001M histamine solution subcutaneously in the abdominal region. Once allergy was induced with the appearance of redness on the skin, the CPM gel was applied. Control group was also established, and no gel was applied to them to compare the effectiveness of the optimized formulation.

**Statistical Data Analysis:** The analysis of responses, namely lag time (t lag), and permeability coefficient (KP) were performed using Design Expert® software (Sigma XL trial version 8.0.4; State-Ease Inc., Minneapolis, MN, USA). Linear, quadratic and cubic mathematical models were employed. The best fit model was selected based on the comparison of several parameters including the multiple correlation coefficients ($R^2$), adjusted multiple correlation coefficients (adjusted $R^2$), predicted residual sum of square (PRESS), and the lack of fit (p-value).

ANOVA (one-way) was applied to estimate the significance of model ($p < 0.05$). All measured data has been expressed as mean ± SD of a minimum of 3 replicates.

## RESULTS AND DISCUSSION:

**Solubility and Partition Coefficient Studies:** It is important to establish solubility of the drug to select a suitable receptor medium for diffusion studies. Poor solubility can limit the diffusion process and often leads to discrepancies when a correlation is needed to develop between in vitro and *in-vivo* results [23]. The solubility of CPM in water, methanol, and PBS was found to be 687.58 mg/ml, 547.98 mg/ml and 732.3 mg/ml, respectively. The highest solubility was found to be in PBS. Therefore it was selected as receptor medium for the diffusion studies across silicone membrane and the rat skin. Partition coefficient was found to be 6 with logarithmic value equals to 0.778, indicating that the given drug consists of nearly sufficient lipophilicity value that is considered important for topical drug delivery.

**Characterization of Gels:** Various tests were applied to characterize the prepared gels. The amount of drug content for CPM gels was found in the range of required standards, *i.e*. 93-107% for CPM gel. Various physical parameters such as viscosity, pH, spreadability, clarity, precipitation, and homogeneity were determined. Rheological studies were carried out at room temperature (25 ± 0.5°C) using Brookfield viscometer and showed that all gel formulations have a viscosity in the range of 130-162 $\times 10^3$ centipoise. The pH value was in the range of 5.04-5.19. All CPM gel formulations were clear and had satisfactory homogeneity.

**Diffusion Studies:** CPM permeation across the silicone membrane was tested for each of the gel prepared as per CCD model. Various diffusion parameters were calculated and are presented in **Table 2**. The permeation parameters of interest were $t_{lag,}$ and ER, which were analyzed using response surface plots **Fig. 1** and **2**. The lag time showed a significant change with changing enhancer's concentrations **Fig. 1**.

**TABLE 2: CALCULATED VALUES OF DIFFERENT PERMEATION PARAMETERS FOR ALL FORMULATED CPM GELS ACCORDING TO EXPERIMENTAL DESIGN**

| Formulations | X1 (PG) (%) | X2 (PEG) (%) | $t_{lag}$ (min) | Flux (µg/cm$^2$.min) | D $\times 10^{-3}$ (cm$^2$/min) | Kp$\times 10^{-3}$ (cm/min) | ER |
|---|---|---|---|---|---|---|---|
| FM1 | 20.0 | 3.5 | 36.98 | 25.03 | 0.48 | 2.50 | 1.07 |
| FM2 | 30.0 | 3.5 | 41.44 | 28.72 | 0.53 | 2.87 | 1.23 |
| FM3 | 20.0 | 6.5 | 34.41 | 23.56 | 0.44 | 2.36 | 1.01 |
| FM4 | 30.0 | 6.5 | 50.48 | 27.83 | 0.65 | 2.78 | 1.20 |
| FM5 | 15.0 | 5.0 | 19.57 | 25.91 | 0.25 | 2.59 | 1.11 |
| FM6 | 35.0 | 5.0 | 24.47 | 31.40 | 0.32 | 3.14 | 1.34 |
| FM7 | 25.0 | 2.0 | 34.38 | 23.61 | 0.44 | 2.36 | 1.01 |
| FM8 | 25.0 | 8.0 | 43.83 | 28.88 | 0.57 | 2.89 | 1.24 |
| FM9 | 25.0 | 5.0 | 37.64 | 23.88 | 0.49 | 2.39 | 1.02 |
| FM10 | 25.0 | 5.0 | 37.55 | 23.89 | 0.49 | 2.39 | 1.02 |
| FM11 | 25.0 | 5.0 | 37.43 | 24.03 | 0.48 | 2.40 | 1.03 |
| Fm12 | 25.0 | 5.0 | 37.03 | 23.92 | 0.48 | 2.39 | 1.02 |
| FM13 | 25.0 | 5.0 | 34.84 | 24.32 | 0.45 | 2.43 | 1.04 |
| FMC | 0 | 0 | 24.11 | 23.36 | 0.31 | 2.33 | - |

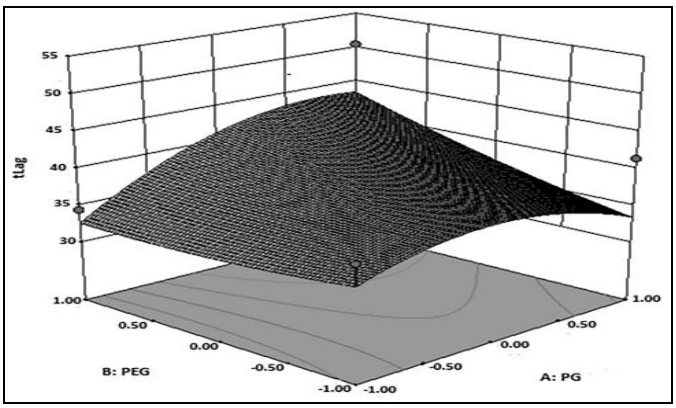


**FIG. 1: EFFECT OF PERMEATION ENHANCERS ON lag TIME**

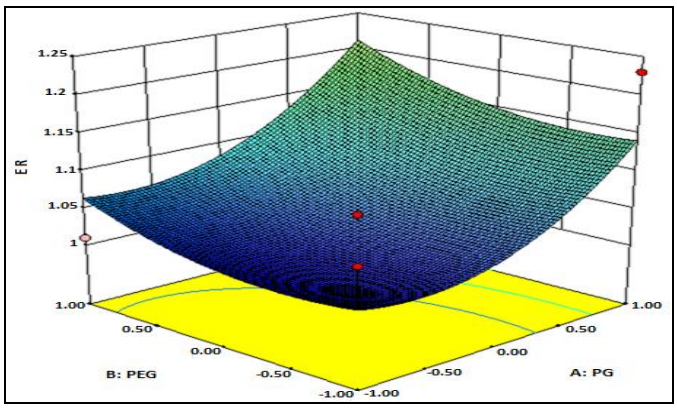


**FIG. 2: EFFECT OF PERMEATION ENHANCERS ON ENHANCEMENT RATIO OF FLUX**

In this case, PEG content played the key role in altering the lag time. It was noted that PEG content at medium level (5%) produced the desired results. It was also interesting to note that the lag time of CPM from control formulation (FMC) was same as that of the FM6. This also confirmed a minimum effect of the combination of enhancers on the CPM permeation across the silicone membrane. Among all the formulation, FM6 produced the highest flux, which was 1.34 times more than that from the control. Also, the lag time was about 24 min, therefore, it was decided to use this optimized formulation for further studies.

The flux values of all the gels were compared with the control gel, and then enhancement ratio (ER) was calculated for easy comparison **Fig. 2**. In most of the cases, there was a slight increase in the flux of CPM across the silicone membrane. Same is the case with the permeability coefficient values, where an insignificant difference was observed in the values. Silicone membranes are established skin mimics and are routinely used to study the permeation behavior of compounds of varying physicochemical properties [23].

In comparison to the skin, silicone membranes produce reproducible results and being structurally dissimilar to the skin; formulation attributes are rather easier to study with such membrane systems. Since skin is made of lipids, any alteration to the structure and arrangement of the skin lipids would lead to an enhanced permeation of the compounds. This enhancement would then be reflected by a significant change in the KP values. In this study, the slight change in the flux and KP values was attributed to an increase in the solubility of the drug inside the silicone membrane. CPM is sufficiently hydrophilic, and the presence of PG inside the membrane allowed more drug to penetrate the membrane and even cross it. However, this was only true when the highest content of PG was used in the formulation.

**Draize's Skin Irritation Test:** Primary test for irritation was performed on human volunteers. For this, three volunteers were selected, and a small amount of optimized CPM gel (FM6) was applied on an area of 2 square inches to the back of the hand. The volunteers were observed for lesions or irritation, and no irritation was reported by the volunteers, which confirmed the suitability of the gels [17].

**Stability Studies:** Stability study of FM6 formulation was performed at 25 ± 0.5 °C, and 40°C and various in vitro attributes were studied **Table 3**. The optimized gel was found to be stable over 6 months long accelerated stability period, and no significant change in pH, viscosity, spreadability, homogeneity and drug content was observed.

**TABLE 3: STABILITY STUDY OF OPTIMIZED CPM GEL (FM6) AT 40 °C**

| Time period | pH | Viscosity(cP) | Spreadability (cm) | Homogeneity | Drug content (%) |
|---|---|---|---|---|---|
| 1st day | 5.98 | 166 ± 0.02 | 3.61 ± 0.001 | Clear | 100.61 ± 0.01 |
| 7th day | 5.97 | 167 ± 0.05 | 3.63 ± 0.003 | Clear | 100.54 ± 0.01 |
| 2 weeks | 5.92 | 166 ± 0.01 | 3.64 ± 0.001 | Clear | 100.45 ± 0.02 |
| 1st month | 5.89 | 161 ± 0.04 | 3.7 ± 0.004 | Clear | 100.44 ± 0.02 |
| 3rd month | 5.88 | 160 ± 0.03 | 3.76 ± 0.002 | Slightly milky | 100.44 ± 0.01 |
| 6th month | 5.88 | 158 ± 0.01 | 3.81 ± 0.004 | Slightly milky | 100.43 ± 0.02 |

***Ex-vivo* Permeation Studies across Rat Skin:** Permeation of CPM across rat skin from the optimized gel (FM6) was studied. The cumulative amount permeated through rat skin from optimized gel FM6 was found to be 2864.69 ± 14.84 (μg/cm$^2$) within 3 hours. The flux of CPM across the rat skin was 13.388 (μg/cm$^2$/min), which is three times less than that produced from the silicone membrane and endorsed the structural dissimilarity between rat skin and silicone membrane.

**Drug Release Kinetics:** Drug release kinetics has shown many releasing mechanisms related to the controlled release matrix system. The most suitable method that superlative fits above release data were evaluated by Regression coefficient ($R^2$=1). The result showed that optimized gel formulation followed the first order kinetic release model with a regression coefficient value of 0.99.

***In-vivo* Pharmacokinetic Studies:** Pharmacokinetics studies were based on the plasma concentration variation of drugs as shown in **Fig. 3**. Different parameters were studied in healthy rabbits such as plasma half-life of drug (t ½), the area under the curve (AUC), the volume of

distribution (Vd), clearance (Cl), steady state concentration (Css). The pharmacokinetics parameters of topical optimized CPM gel formulation were compared **Table 4** with the oral CPM which showed that topical route for CPM gel was better than the oral route. The time to reach peak plasma concentration and peak plasma concentration by topical route was obtained much faster as compared to the oral route.

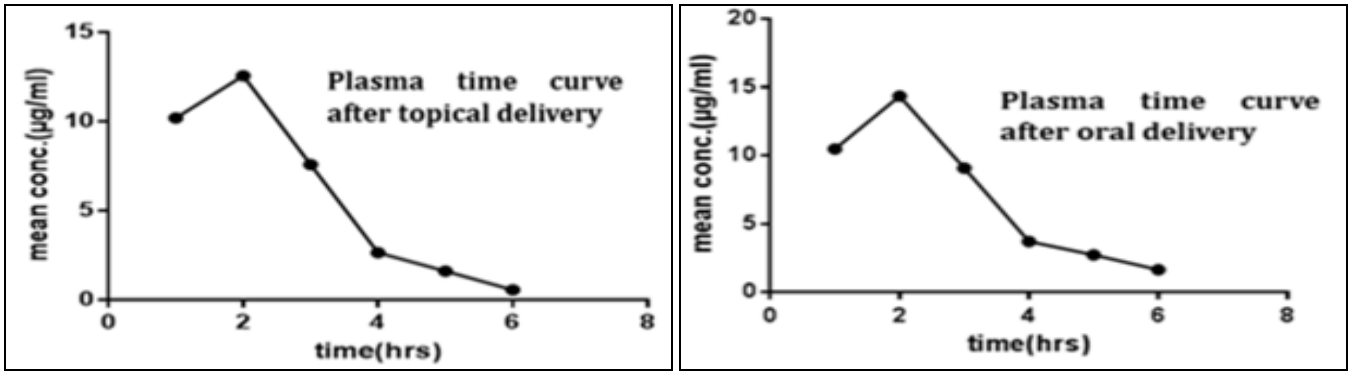


**FIG. 3: PLASMA TIME PROFILE OF CPM AFTER TOPICAL AND ORAL ADMINISTRATION**

**TABLE 4: PHARMACOKINETIC PARAMETERS COMPARISON BETWEEN ORAL AND TOPICAL CPM DELIVERY IN HEALTHY RABBITS**

| Pharmacokinetic parameters | Topical administration | Oral administration |
|---|---|---|
| A (µg/ml) | 356.3 ± 18.1 | 340.5 ± 0.5 |
| $K_a$ (1/h) | 18.1 ± 0.1 | 2.9 ± 0.1 |
| $K_{10}$(1/h) | 0.7 ± 0.1 | 3.1 ± 0.1 |
| $t_{1/2}$ $K_a$ (h) | 1.8 ± 0.1 | 2.1 ± 0.0 |
| $t_{1/2}K_{10}$ (h) | 1.9 ± 0.0 | 2.0 ± 0.0 |
| V/F(mg)/ (µg/ml) | 36.7 ± 1.1 | 30.9 ± 0.5 |
| Cl/F(mg)/ (µg/ml)h | 20.4 ± 0.4 | 23.7 ± 0.4 |
| $T_{max}$(h) | 1.2 ± 0.0 | 2 ± 0.0 |
| $C_{max}$(µg/ml) | 12.9 ± 0.5 | 11.4 ± 0.4 |
| $AUC_{0-t}$ (µg/ml×h) | 38.4 ± 1.0 | 35.7 ± 0.4 |
| $AUC_{0-\infty}$(µg/ml×h) | 40.4 ± 0.9 | 38.1 ± 0.4 |
| MRT (h) | 2.5 ± 0.1 | 2.3 ± 0.1 |

**Anti-allergenic Challenge:** This study was performed on the allergenic rabbits, and then plasma concentration of optimized gel was calculated. 0.1 ml histamine solution (0.0001M) was injected subcutaneously to healthy rabbits (weighing 1.5 kg) to induce allergenic symptoms such as redness of area (about 4 cm), swelling, small red warts appearance on the whole body (persists for 3 days), low grade fever (persist for 2 days), laziness and drowsiness. This was followed by the application of optimized CPM gel (dose equivalent to 1 mg) to the skin of the abdominal region. (1 mg dose). It was noteworthy that the recovery started within 10 min of application, while peak plasma concentration (23.29 ± 0.07) was achieved within 2 h post application. This suggested that the optimized formulation was effective in managing allergenic reactions in a short interval of time.

**CONCLUSION:** A series of CPM gels were formulated using response surface methodology to check the influence of PG and PEG as permeation enhancers. All the formulated gels showed desirable attributes regarding spreadability, homogeneity, pH and viscosity. The optimized gel (FM6) was selected by permeation across the silicone membrane and the gel with faster permeation rate and relatively shorter lag time. FM6 was further subjected to *ex-vivo* permeation, irritation to human volunteers, pharmacokinetic profiling and finally challenged for its anti-allergenic capability.

The optimized gel showed sufficient permeation across the rabbit skin, and the release of CPM from the gel followed first order release kinetics. Draize irritation test on healthy volunteers showed no signs of irritation to the skin while the optimized gel was stable over 6 months long testing period. The pharmacokinetic study revealed the superiority of gels over the conventional oral route and the gel managed allergic conditions in rabbits.

**APPROVAL BY ETHICS COMMITTEE:** The approval for *ex-vivo* studies in animals and human volunteers were taken from the "Ethical Committee" (ref no. 86-2010/BZU.PHM) of Faculty of Pharmacy, B. Z. University Multan.

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## CONFLICT OF INTEREST: Declared none.

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