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Research article

Formulation of Chlorpheniramine maleate in span 60/ tween20 based organogels for transdermal delivery

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Key words: organogel, chlorpheniramine maleate, tween 20, span 60, sunflower oil.

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Abstract

Objectives: Transdermal drug delivery is an attractive alternative to the oral route of drug administration due to avoidance of the first pass effect, reduced adverse reactions and better patient compliance. The aim of the study was to formulate chlorpheniramine maleate in anorganogel base in order to overcome the problems related with oral route. **Materials and methods:** Different organogels were prepared using a mixture of span60 and tween 20 in sunflower oil at 60˚C. The formulated organogels were evaluated for physical appearance, emulsion type, drug content, pH, viscosity, gel-sol transition temperature, spreadability and in vitro drug release through cellophane membrane. The permeation of the optimum formulation through rat skin was compared with organogels containing different concentrations of menthol. Finally, the efficiency of organogel formulation with the highest skin permeation was studied in vivo and compared with oral Chlorpheniramine maleate. **Results:** All the prepared organogels exhibited acceptable physical properties. Surfactant mixture / water ratio and viscosity had significant effects ($P < 0.05$) on % drug release. Incorporation of 5% menthol significantly improved chlorpheniramine maleate permeation through rat skin. Skin irritancy testing showed no allergic manifestation. Promising edema inhibition within one hour was observed for 2% and 5% Chlorpheniramine maleate organogel rather than oral route. **Conclusion:** Transdermal application of chlorpheniramine maleate in organogels may be a promising alternative to the oral route.

Introduction

Transdermal drug delivery can be defined as drug delivery through the skin to achieve a systemic effect of a drug. It is considered as a leading edge over other routes by elimination of first-pass effect, controlled drug release with maintenance of steady drug plasma level, avoidance of undesirable effects and better patient compliance [1].
Organogels have emerged as a promising vehicle for enhancing transdermal permeability of many drugs [2]. Organogel sarevisco-elasticbi-continuous systems consisting of gelators and apolar phase, which may or may not contain water-molecules entrapped within the network structure of the gelator [3]. The gelators undergo physical or chemical interactions to form self-assembled fibrous structures which get entangled with each other resulting in the formation of a three-dimensional networked structure which prevents the flow of external apolar phase [4, 5]. Common examples of organogelators include lecithin, spans and tweens and the a polar phase may be mineral oil, organic solvent or vegetable oil [6, 7]. Literature reported many advantages for organogels that include: nonirritant, biocompatible, simple preparation method with low production cost, ease of administration, capable of solubilizing various guest molecules and possess long term stability [8]. The thermodynamic stable nature of the organogels can be ascribed to the spontaneous formation of fibrous structure by virtue of which the organogels reside in a low energy state [9]. Since organogels can efficiently partition with the skin, they enhance skin permeation and transport of both hydrophilic and lipophilic drugs [10].
Chlorpheniramine maleate is an antihistamine that is used for acute inflammatory and allergic conditions such as

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sunburn, urticaria, angioedema, pruritus, insect bites, cough and runny nose [11]. It is marketed in the form of tablets, capsules and syrups with no availability of topical formulations. After oral administration, it causes sedation, dizziness, muscular weakness and gastrointestinal disturbances [12]. In order to improve patient incompliance, the organogel formulation was proposed as a transdermal delivery system for chlorpheniramine maleate.

So, the present work was designed to formulate chlorpheniramine maleate in aspan60/tween20 based organogel as an alternative dosage to the oral delivery in order to overcome the problems associated with the oral route.

Experimental

Chlorpheniramine maleate (CPM) was a gift sample from *Al Gomhoria Co., Cairo, Egypt.* Polyoxyethylene sorbitanmono laurate (Tween 20) and sorbitanmono stearate (span 60) were purchased from *S. D. Fine Chem. Pvt. Ltd, Mumbai, India*. Edible sunflower oil was purchased from*t he local market in Makkah, Saudi Arabia*. Menthol was purchased from *Rajesh chemicals Co., Mumbai,* India. HPLC grade acetonitrile and methanol, trimethylamine, Hexansulfonic acid sodium salt and cellophanemembrane (MW cut-off - 60 kDa) were purchased from *Himedia,Mumbai, India.*All other Chemicals were used for study are of analytical grade.

Preparation of organogel formulations

Span 60 in different amounts was mixed with 3% tween 20 to obtain different surfactant mixtures which considered as gelator. Surfactant mixtures were added to different amounts of sunflower oil at 60°C and kept on stirring on a magnetic stirrer (Raypa AG-2, R. Espinar, S.L., Barcelona) for 20 min. Subsequently, water was added dropwise and the systems either formed gelled structures or remained as a liquid mixture.The samples were regarded as organogels, if the mixture did not flow when the bottles were inverted.A ternary phase diagram was plotted (tri-plot software) to find out the area of organogel formation [13].

According to the constructed ternary phase diagram, proper amounts of surfactant mixture, oil and water were selected and samples containing CPM were prepared by dissolving 2% CPM in the aqueous phase and complete the procedure as described before (Table 1). Furthermore, different concentrations (1, 2.5 and 5% w/w) of menthol were added to the optimized organogel formulation to investigate its effect on the permeation of CPM through rat skin.

Characterization of organogels

Physical examination

The formulated organogels were inspected visually for color, homogeneity, consistency and presence of any clog [14].

Determination of emulsion type

In order to determine whether the prepared oragogels were w/o or o/w type, a simple dye test was performed [15]. The oil soluble dye (SudanIII) was used. The dye was added to an organogel sample and thoroughly mixed. The formulation was directly observed under the Trinocular light microscopy (Olympus CH 20i) at magnification of 200X.

Chromatographic analysis for the determination of CPM

A high performance liquid chromatographic system (Agilent Technologies, Santa Clara, CA, USA) with UV/VIS detector using Inertsil C18 (250mm x 4.6mm, 5µn) analytical column. Analysis of CPM was carried out at 261 nm by injecting 10 uL injection volume at 25°C using a mixture of Acetonitrile: water : methanol (15:75:10 v/v/v) and buffer solution (pH=2.8) containing 0.3 ml triethylamine and 4 ml of Hexansulfonic acid sodium salt as ion pair (14mmol/l) as the mobile phase [16].

Drug content

A sample of 0.5 g was taken in a 50 ml volumetric flask and diluted with phosphate buffer (pH 5.4) up to mark. The content was shaken to dissolve the drug in the buffer. The solution was filtered through Whatman filter paper (No.1). The above filtrate (1 ml) was pipetted out, diluted to 10 ml with phosphate buffer and analyzed by HPLC chromatographic method. The test was performed in triplicate and the mean was calculated [17].

Table 1. Formulation of span 60/tween 20 based organogels of chlorpheniramine maleate

Contents (%w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
CPM	2	2	2	2	2	2	2	2	2	2	2
Span 60	17	18	19	20	21	22	17	22	21	21	21
Tween 20	3	3	3	3	3	3	3	3	3	3	3
Water	40	34	28	22	16	10	20	25	16	16	16
Sunflower oil	40	45	50	55	60	65	60	50	59	57.5	55
Menthol	-	-	-	-	-	-	-	-	1	2.5	5

pH Determination

The pH of various organogel formulations was determined using digital pH meter. About 1 g of each formulation was dissolved in 100 ml of distilled water, left aside for 2 hours and the pH of each formulation was measured. The experiment was done in triplicate and average values were calculated [18].

Viscosity determination

Viscosity was determined using Brookfield Viscometer (Model: RV-DV-E 230, Brookfield Engineering Lab., Inc., Middleboro, USA). Spindle no. 6 at 2 rpm was used. Three measurements were taken and the average was calculated.

Gel-sol transition study

Gel-sol transition temperature (Tgs) was determined by incubating the organogels in a water bath (LSB-030S, Daihan Lab Tech Co., LTD, Indonesia), whose temperature was varied from 30-70 ºC. An increment of 5ºC was made after 5 min of incubation at the previous temperature. The temperature, at which the gels started to flow, when the glass vials were inverted, was noted as the gel-sol transition [19].

Spreadability study

The spreadability was measured on the basis of 'slip and drag' characteristics of the organogels. An excess amount of each formulation (2 g) was sandwiched between two glass slides in which the lower one was fixed on a table and the upper one was movable and tied to a thread which passed over a pulley carrying a weight. A 500 gm weight was placed on the top of the two slides for 5 minutes, to expel air and to provide a uniform film of the organogel between the slides. The top slide was then subjected to a pull with 50 g of weight. The time (sec) required to separate the two slides was noted and the spreadability was calculated from the following formula [20]:

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

where S is the spreadability (g.cm/sec), M represents the weight tied to the upper slide (50 g), L represents length of the glass slide (11cm), and T stands for the time taken to separate the slides completely from each other (sec).

In vitro drug release

To test the pattern of CPM release from different formulations, *in vitro* release studies were carried out through cellophane dialysis membrane, MW cut-off-60 k Da. Dialysis membrane was soaked in medium used for release study for 24 hr before mounting on a dialysis cell. About 1.5 gram of organogel formulation was spread uniformly on a dialysis membrane which was then stretched over the lower open end of a dialysis tube (locally fabricated glass cylinder, length 15 cm and internal diameter of 2.9 cm) with the aid of rubber band. The tubes were attached to the dissolution apparatus (Dissolution tester, rotating basket SP6-400, G.B. CALEVA Ltd., Dorset, England) and allowed to stir at 50 rpm. The release medium was 150 mL phosphate buffer (pH 7). The whole assembly was maintained at 37±1°C. Aliquots (3 ml) were withdrawn at regular interval of 1 h for a period of 8 h and replaced with equal volume of fresh medium equilibrated at 37±1°C, analyzed by HPLC chromatographic method and the concentration of CPM in each sample was determined from a previously calculated, standard curve [17]. Each experiment was carried out in triplicate.

In order to investigate the mechanism of drug release from the different formulations, the following plots were made: % drug release vs. time (zero order kinetic model); log % drug remaining vs. time (first order kinetic model) and % drug release per surface area of membrane vs. square root of time (Higuchi model). The correlation was used as an indicator of goodness-of-fit [21].

In vitro skin permeation Studies

The permeation of the optimal organogel formula (selected in terms of acceptable viscosity, gel-sol transition point, spreadability and % CPM release) was studied using rat skin and compared with organogel formulations containing different concentrations of menthol as a penetration enhancer.

Male rats weighing 180 - 200 g, were shaved at abdominal region, anesthetized and their skin was carefully excised. The skin samples were cleaned, soaked in normal saline and kept frozen until used. The skin samples were mounted with the stratum corneum side facing upward and the dermal side facing downward into the medium and complete the procedure as described before in in vitro release study [17].

The average cumulative amount of drug permeated per unit surface area of the skin was plotted versus time. The slope of the linear portion of the plot was calculated as flux J_{ss} (µg /cm^2/h), and the permeability coefficient was calculated using the following formula: [12]

$$KP = J_{SS} / C_U$$

Where; KP is the permeability coefficient and C_U is the total amount of drug.

The enhancement of drug permeation due to presence of menthol compared with plain organogel was noted as enhancement factor (EF) which was calculated using the following formula:

$$EF = KP \text{ (organogel with menthol)} / KP \text{ (plain organogel)}.$$

In vivo study

The optimum formulation F11 (21% span60, 3% tween 20, 16% water, 5% menthol and sunflower oil to 100g) that exhibited both acceptable physical properties and skin permeation parameters was further investigated in vivo for its skin compatibility and anti-inflammatory activity.

Skin irritation study

In the present study 5 rabbits weighing between (400-500g) were used. Hairs were depleted from the back of rabbits with the help of depilatories and an area of 2.5 x 2.5 cm was marked on both sides. After 24 hrs from hair depletion, the animals were used in which one side served ascontrol(non-medicated organogel base) and the other one as test (the medicated organogel containing 5% CPM). The test formula was applied (500mg /rabbit) once a day for 3 days and site was covered with cotton bandage and observed for any sensitivity and the reaction (if any) was graded as 0-No reaction, 0.5-Slight patchy erythema, 1-Slight but confluent or moderate patchy erythema, 2-Moderate erythema and 3-Severe erythema with or without edema [22].

In vivo Anti-inflammatory study

In vivo anti-inflammatory study was conducted using 25 albino rats of either sex weighing (100-150g) and divided into 5 groups. Rats of group II, III and IV were anaesthetized by inhalation of diethyl ether and the back hairs of the animals were depilated by shaving an area of 2 x 2cm which was marked on the right side for topical application of medicated or non-medicated organogel base. Group I animals (negative oral control) received 1 mL/rat distilled water (by oral gavage). Group II animals (negative topical control) received non-medicated organogel base. Group III animals topically received the medicated organogel containing 2% CPM. Group IV animals topically received the medicated organogel containing 5% CPM. Group V animals received 1mL/rat of raw CPM (3 mg/kg) in distilled water (by oral gavage) [23]. The experiment was conducted according to the Guidelines for Animal Care and Treatment of the European Community and was approved by the Institutional Animal Ethical Committee, Faculty of Pharmacy, Umm Al Qura University.

Acute inflammation was induced by sub-planter injection of 0.1 ml freshly prepared 1% w/v solution of histamine in normal saline in the left hind paw of rats [24]. For groups II, III & IV: non-medicated organogel base or medicated organogels (2% or 5% CPM), 0.25 g was applied topically with gentle rubbing to the paw of each rat of respective group 1 hour before histamine injection. For groups I& V: 1 ml of either distilled water or CPM aqueous solution was administered orally, 1 hour before histamine injection. The extent of paw edema was evaluated by measuring dorsal – planter paw thickness by dial micrometer (Cole-Parmer Instrument Co., Japan) just before, 0.5, 1, 2 and 3 h after histamine injection. Increase in paw thickness (mm) after histamine injection relative to pre-injection value for each animal was taken as an indication of paw edema. The percentage inhibition of edema was calculated according to the following equation [25]:

$$\% \text{ inhibition} = \frac{Mean\ paw\ edema\ of\ control - Mean\ paw\ edema\ of\ test}{Mean\ paw\ edema\ of\ control} \times 100$$

Statistical Analysis

Data from *in vitro* drug release and *in vivo* anti-inflammatory studies were analyzed statistically using one way analysis of variance (ANOVA) using SPSS version 16.0, SPSS Inc., Chicago, USA. The level of significance was considered at $P<0.05$.

Results

Preparation& characterization of CPM organogels

The area of organogel formation is shown in the ternary phase diagram (Figure 1) and the results of organogels characterization are presented in Table 2. All the prepared organogels were pale yellow, translucent in nature, oily to touch, with a smooth and homogeneous appearance.

Table 2. Characterization of span 60/tween 20 based organogels of chlorpheniramine maleate

Formulation	Surfactants/ water ratio	CPM content (%)	pH	Viscosity (centipoise)	Tg (˚C)	Spreadability (g. cm/sec)
F1	0.5:1	95.6±0.64	6.4±0.17	3930±0.2	35±0.0	35.5±0.05
F2	0.6:1	85.5±0.34	6.2±0.14	4962±0.1	37±0.11	36.5±0.2
F3	0.8:1	90.4±1.2	5.9±0.10	5205±2.1	37±0.2	40.2±0.1
F4	1:1	92.3±1.4	6.6±0.11	5612±1.1	45±0.3	40.7±0.03
F5	1.5:1	98.9±0.33	6.2±0.09	6300±1.9	45.5±0.2	42.5±0.3
F6	2.5:1	98.3±0.52	6.3±0.06	7520±1.6	55±0.2	35.1±0.5
F7	1:1	87.8±0.36	6.3±0.08	6830±2.2	42±0.3	39.1±0.2
F8	1:1	93.4±0.82	6.4±0.09	6800±0.15	45±0.5	39±0.1
F9	1:1	93.4±1.43	6.4±0.11	6120±2.14	45±0.5	42.6±0.7
F10	1:1	90.8±1.52	6.4±0.08	5980±1.2	43.1±0.2	44.2±0.7
F11	1:1	90.2±1.62	6.4±0.07	5760±1.5	42.3±0.1	46.2±0.6

Note: Data are presented as mean ± standard deviation

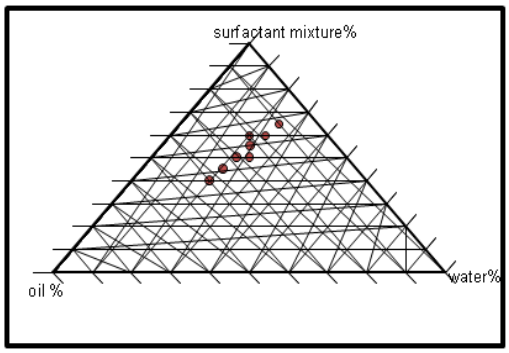


Figure 1. Ternary phase diagram of organogels



Figure 2. Span 60/Tween 20 based organogel containing 2% chlorpheniramine maleate.

Determination of emulsion type

The photomicrographs (Figure 3) indicated that the formulated organogels were w/o type of emulsion as the oil soluble dye showed the coloured background (continuous phase) and the water globules (dispersed phase) remained uncoloured.

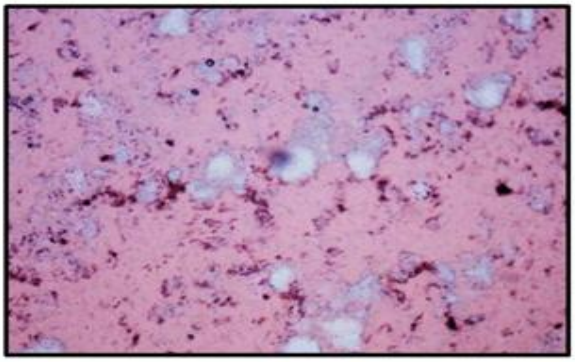


Figure 3. Trinocular light microscopy of chlorpheniramine maleate organogel indicating the type of emulsion. (200X)

Drug content

The drug content fororganogel formulations (F1-F8) was found to be in the range of 85.5 to 98.3%.

pH determination

The pH values of all organogelslies in the range of5.9 to 6.6.

Viscosity determination

The prepared organogels showed viscosity in the range of 3930 – 7520 cps.

Gel-sol transition study

The gel-to-sol transition temperature of the organogels varied from 35˚ C to 55˚ C, depending on the composition of the organogels.

Spreadability study

The values of the spreadability study were in the range of 35.5 – 44.2 g.cm/sec. Formulation F11 gave the highest value for spreadability, while F6 showed poor spreadability.

In vitro drug release

The *in vitro* release profiles of CPM from its various organogel formulations (F1–F8) are represented in Figure 4. It was evident that the higher the surfactant mixture/water ratio in the formulation, the lower the release rate of CPM. The formulation F1 (surfactant mixture/water ratio = 0.5:1) exhibited about 80.3% of drug release at the end of 8 hours compared to only 40.8% of CPM release from the formulation F6 (surfactant/water ratio = 2.5:1).

Correlation analysis of the effect of surfactant mixture/water ratio and viscosity on the % of CPM release revealed that both factors had significant ($P < 0.05$) negative effect (Pearson correlation > -0.9) on the % CPM release.

In order to elucidate the release mechanism for CPM organogels through cellophane membrane, the data was fitted into the models representing zero order, first order and Higuchi equations. The kinetic values obtained from different plots are listed in Table 3. It was observed that the release was in accordance to Higuchi model indicating the mechanism of release was diffusion controlled.

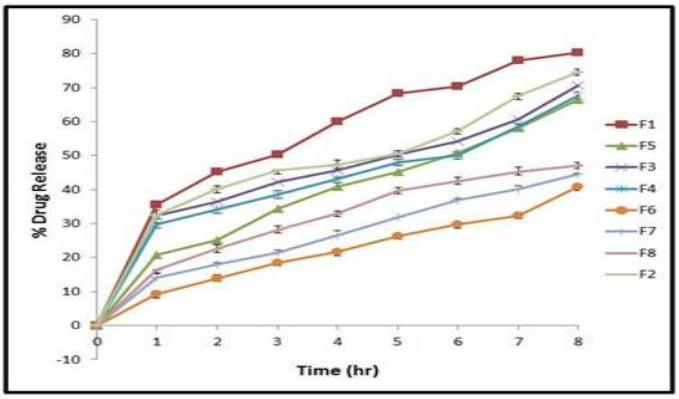


Figure 4. *In vitro* release profile of chlorpheniramine maleate from different organogels through cellophane membrane in phosphate buffer pH 7.
(Error bars were omitted for clarification)

In vitro skin permeation studies

The formulation F5 (exhibited acceptable physical properties and % drug release through the cellophane membrane) was further studied for the drug permeation through rat skin.

The plain organogel formulation F5 exhibited a flux and permeability coefficient of 138.2±0.6 ug/cm^2/hr and 0.0046 ±0.6 cm/hr, respectively. Incorporation of different concentrations of menthol resulted in adirect proportionate increase in CPM flux and permeability coefficient (Table 4).

In vivo study

Skin irritation test

The Primary Irritation Index of the test article was calculated and found to be 0.00.

In vivo Anti-inflammatory study

Sub-plantar injection of histamine evoked a local edema with maximal rate detected within 1 h after injection and thereafter declined to the end of the experiment. All CPM treated groups showed a significant decrease ($P < 0.05$) in paw thickness as function of time; however the maximum inhibition percentage was after 0.5 and 1 h indicating anti-inflammatory activity of both oral and transdermal CPM treated groups (Table 5). The organogel containing 2% CPM showed % inhibition of edema after 0.5 and 1 h of 35.5% and 47.01% , respectively, and that containing 5% showed 42.2 % and 53.8% of edema inhibition, respectively when compared with control ($P <0.05$) (Table 5 and Figure 5). On the other hand, oral administration of CPM (3 mg/kg) 1 hour before induction of the inflammation showed maximum percent inhibition of edema after 1 and 2 hours (32.9% and 24.3% respectively). The results confirmed that transdermal application of CPM (2& 5%) as organogel showed rapid onset of inhibition in comparison with oral administration of CPM ($P <0.05$).

Table 3. Kinetic parameters of organogels of chlorpheniramine maleate through cellophane membrane at pH 7.

Formulation	Zero-order		1st-order		Higuchi	
	r^2	K_0	r^2	K_1	r^2	K_H
F1	0.8685	8.6	0.9882	-0.17	0.9907	28.5
F2	0.8678	7.3	0.91	-0.13	0.9653	24.1
F3	0.8636	6.8	0.9246	-0.11	0.9697	22.5
F4	0.8783	6.6	0.9261	-0.1	0.9702	21.6
F5	0.9597	7.2	0.9784	-0.11	0.9825	22.7
F6	0.9591	4.5	0.9738	-0.052	0.9741	13.9
F7	0.966	5.1	0.9723	-0.07	0.9874	15.8
F8	0.9216	5.4	0.9766	-0.09	0.9939	17.5

Table 4. Permeation study of chlorpheniramine maleate organogels in presence and absence of menthol as a permeation enhancer.

Formulation	Flux ug/cm2/hr	Permeability coefficient (cm/hr)	EF
F5	138.2±0.6	0.0046±0.16	-
F9	180.9±0.12	0.006±0.34	1.3
F10	199.85±0.45	0.0066±0.38	1.4
F11	249.6±0.17	0.008±0.25	1.7

Note: Data are presented as mean ± standard deviation

Table 5. Mean paw edema thickness shown by chlorpheniramine maleate organogels versus its oral route.

Group treatment	Mean paw edema thickness (mm) ± SEM			
	0.5 hr	1 hr	2 hr	3 hr
Oral Control	3.5 ± 0.2	4.1 ± 0.3	3.51 ± 0.01	3.1 ± 0.02
Topical Control	3.67 ± 0.016	4.36 ± 0.009	3.11± 0.01	2. 73 ± 0.011
F11 containing 2% CPM	2.38 ± 0.017*×	2.31± 0.038*×	2.35 ± 0.007*×	2.4 ± 0.014*
F11 containing 5% CPM	2.12 ± 0.09*×	2.01± 0.05*×	2.14 ± 0.01*×	2.11 ± 0.006*×
Oral CPM	2.79 ± 0.012@	2.7 ± 0.014@	2.65 ± 0.016@	2.75 ± 0.003@

Note: Data are presented as mean ± standard deviation

***: Significantly different from topical control at $P^< 0.05$**

@: Significantly different from oral control at $P^< 0.05$

× : Significantly different from oral CPM at $P^< 0.05$

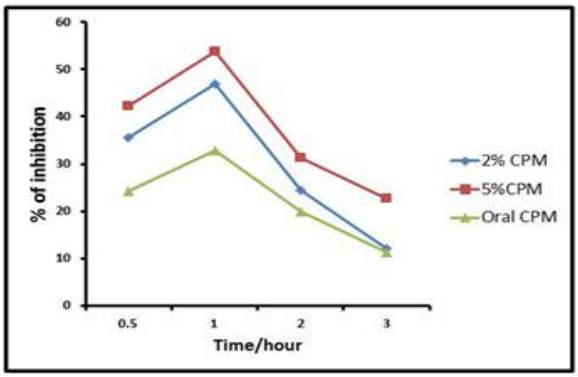


Figure 5. Time-dependent inhibitory effect of topically applied 2 and 5% chlorpheniramine maleate organogels versus its oral route against histamine-induced paw edema in rats.

Discussion

Mechanism of organogel formation

In the present study, two surfactants namely Span 60 (lipophilic, HLB = 4.7) and Tween 20 (hydrophilic, HLB =16.7) were used in combination for the preparation of organogels. Span 60 was chosen as it is considered as a good gelator for organogel formation due to its ideal geometry to form bilayers which constitute rod like aggregates in organogels [26]. Addition of Tween 20 is important for the preparation of a stable organogel as it was reported that mixtures of a low HLB and a high HLB surfactant give better coverage at the oil/water interface and hence the resulting organogel does not synerese upon storage [27]. Water was added to promote gelation and as a solvent for incorporating the hydrophilic drug, CPM [28].

In this study, the organogels were prepared according to the fluid-fiber mechanism, in which sorbitanmono-stearate (span60) molecules arranged themselves as toroidal inverse vesicles, which on further cooling led to the development of rod-shaped tubules which undergo non-covalent cross-linking and mechanical entanglement among each other forming a three-dimensional network structure with subsequent immobilization of the oil [29, 30].

Characterization of organogels

Determination of emulsion type

The water in oil nature of the prepared organogels confirmed the theoretical calculation of theirHLB value which was 6.5.

HLB value was calculated from the following equation: [31]

$$HLB_{mixture} = f HLB_A + (1-f) HLB_B$$

Where *f* is weight fraction of emulsifier A and (1-f) is weight fraction of emulsifier B.

Drug content

The results of drug content indicated uniform dispersion of CPM in the prepared organogels.

pH determination

The pH of all the prepared organogels were within the normal pH range of the skin indicating no signs of skin irritation during application.

Viscosity determination

The results revealed that the viscosity was directly proportional to the surfactant mixture / water ratio. This is may be due to more extensive entanglement of long reverse cylindrical polymer like micelles at higher surfactant mixture / water ratios resulting in formation of a network like structure with very high viscosity. [15]Jibry and co-workers reported that, with increasing gelator concentration, numerous gelator tubules will exist with increase in viscosity [32].

Decrease in viscosity was observed with subsequent increase in the concentration of menthol. This result may be ascribed to the penetration of menthol into the palisade layer of micelles with reduction in micellar curvature and hence changes the network structure and reduces the organogel viscosity [33].

Gel-sol transition study

Generally, the gel-sol transition temperature increased as the surfactant mixture/water ratio increased from 0.5 to 2.5 reflecting the more cohesive network of gelator aggregates which immobilize the fluid phase. Previous literature reported the presence of a positive correlation between the degree of interaction amongst the self-assembled structures formed by gelator molecules and the amount of energy required to cause disruption of this network structure and hence flowing of the gelled system [32, 34].

Spreadability study

Pawar and co-workers defines spreadability as the extent of area to which gel readily spreads on application to the skin which determines its therapeutic efficacy [35]. The results demonstrated that the spreadability of different organogels was dependant on the concentration of gelator molecules and hence the viscosity of the prepared organogels. This result was in agreement with the findings reported by Singh *et al.,* who reported that organogels containing a higher sorbitanmonostearate concentration showed a lower spreadability due to the higher elastic component of the organogels [30].

In vitro drug release

It was evident that the release of CPM was inversely proportional to the surfactant mixture/water ratio which could be ascribed to increased number of cylindrical

micelles that transforms into long tubular with ability to entangle into a three dimensional network with a high viscosity. This network is responsible for the entrapment and unavailability of drug molecules [15]. The results also indicated that CPM release from different organogel preparations was dependent on the presence of balanced proportions of surfactants and oil.

In vitro skin permeation studies

The improved CPM flux and permeability coefficient by incorporation of menthol as a penetration enhancer was in agreement with Raut and coworkers who mentioned that hydrophilic terpenes containing functional moieties with hydrogen bonding ability such as menthol are effective in skin transport of hydrophilic drugs [15]. Generally, menthol improves skin permeation by a dual mechanism: 1) formation of a eutectic mixture with the drug, thereby lowering its melting point and hence increasing its solubility, 2) distribution into the intercellular spaces of stratum corneum and possibly reversible disruption of lipid domains of the stratum corneum [36].

In vivo study

Skin irritation test

Since the skin compatibility studies demonstrated the absence of any allergic manifestations like erythema and edema, the prepared organogels proved to be skin friendly.

In vivo Anti-inflammatory study

Previous literature reported the validity of histamine-induced inflammation as a model to study paw edema and neutrophil infiltration in paw tissue after inflammatory states [24, 25 37]. Subcutaneous injection of histamine in the ventral aspect of rat hind paw produced paw edema while pretreatment with CPM either transdermally or orally suppressed this histamine-induced inflammatory response, so the percent inhibition of paw edema was taken as a measure of the anti-inflammatory and antiphlogestic activity of CPM. Histamine H1 receptors are involved in mediating the inflammation induced by various inflammatory agents. Previous literature revealed that oral administration of CPM suppressed histamine-induced paw edema in rats [38]. Moreover, intravenous injection of CPM inhibited the edema response induced by subcutaneous injection of substance P, a mediator of inflammation [39].

The results of the anti-inflammatory study was parallel to that reported by Sahoo and coworkers who found that the organogel based sorbitanmonostearate (span 60) showed higher cumulative amount of drug release and higher anti-fungal activity as compared to conventional ointments and creams [40]. The significantly pronounced anti-inflammatory activity of CPM organogels (2 & 5%) when compared with oral CPM suggested that the organogel application to the skin may not only facilitate but also potentiate the antiedematous effect of CPM by: 1) avoidance of the 1st pass metabolic effect that results in only 25-45% of CPM orally administered dose reaches the blood circulation [17], 2) presence of sorbitanmono stearate (span 60) that increases the partition of CPM into the skin and 3) presence of menthol, a penetration enhancer, which increases the skin permeation of hydrophilic drugs as mentioned earlier.

Conclusion

An organogel based drug delivery system can be designed for the transdermal delivery of chlorpheniramine maleate using sunflower oil, a mixture of span 60 and tween 20 and menthol as a penetration enhancer. From the developed formulations the release of chlorpheniramine maleate was best in the formulation F11 (containing 2% CPM, 21% span 60, 3% tween 20, 16% water, 5% menthol and sunflower oil to 100g). Transdermal application of CPM incorporated organogel exhibited higher anti-inflammatory activity as compared to its oral administration. Thus some side effects of oral CPM may be easily eliminated and desired therapeutic concentration at the application site can be achieved.

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