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Optimization of Chlorphenesin Emulgel Formulation

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ABSTRACT

This study was conducted to develop an emulgel formulation of chlorphenesin (CHL) using 2 types of gelling agents: hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The influence of the type of the gelling agent and the concentration of both the oil phase and emulsifying agent on the drug release from the prepared emulgels was investigated using a 2^3 factorial design. The prepared emulgels were evaluated for their physical appearance, rheological behavior, drug release, antifungal activity, and stability. Commercially available CHL topical powder was used for comparison. All the prepared emulgels showed acceptable physical properties concerning color, homogeneity, consistency, spreadability, and pH value. They also exhibited higher drug release and antifungal activity than the CHL powder. It was found that the emulsifying agent concentration had the most pronounced effect on the drug release from the emulgels followed by the oil phase concentration and finally the type of the gelling agent. The drug release from all the emulgels was found to follow diffusion-controlled mechanism. Rheological studies revealed that the CHL emulgels exhibited a shear-thinning behavior with thixotropy. Stability studies showed that the physical appearance, rheological properties, drug release, and antifungal activity in all the prepared emulgels remained unchanged upon storage for 3 months. As a general conclusion, it was suggested that the CHL emulgel formulation prepared with HPMC with the oil phase concentration in its low level and emulsifying agent concentration in its high level was the formula of choice since it showed the highest drug release and antifungal activity.

KEYWORDS: chlorphenesin, emulgel, factorial design.

INTRODUCTION

Several antifungal agents are available on the market in different topical preparations (eg, creams, ointments, and powders for the purpose of local dermatological therapy). One of these antifungal agents is chlorphenesin (CHL), which has both antifungal and antibacterial properties. It is applied locally in mild uncomplicated dermatophyte and other cutaneous infections.[1,2]

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Both oil-in-water and water-in-oil emulsions are extensively used for their therapeutic properties and as vehicles to deliver various drugs to the skin.[3] Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. In addition, the formulator can control the viscosity, appearance, and degree of greasiness of cosmetic or dermatological emulsions. Oil-in-water emulsions are most useful as water-washable drug bases and for general cosmetic purposes, while water-in-oil emulsions are employed more widely for the treatment of dry skin and emollient applications.[4]

Gels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, compatible with several excipients, and water-soluble or miscible.[5]

Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. They have a high patient acceptability since they possess the previously mentioned advantages of both emulsions and gels. Therefore, they have been recently used as vehicles to deliver various drugs to the skin.[6-8] In the local Egyptian market, 2 emulgels are available: Voltaren emulgel (Novartis Pharma, Basle, Switzerland), containing diclofenac diethylamine, and Miconaz-H emulgel (Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt), containing miconazole nitrate and hydrocortisone.

The aim of this work was to develop an emulgel formulation of CHL using 2 types of gelling agents: Carbopol 934 and HPMC. The influence of the type of the gelling agent and the concentration of both the oil phase and the emulsifying agent on the release of the drug from the prepared emulgels was investigated using 2^3 factorial design. The rheological properties and antifungal activity of the prepared emulgels were also evaluated.

MATERIALS AND METHODS

Materials

The following materials were used in this study: CHL (Chemical Industries Development, Cairo, Egypt); Carbopol 934 (Goodrich Chemical Co, Cleveland, Ohio); HPMC 2910, 4000 cps (Tama, Tokyo, Japan); Tween 20 and Span 20 (Union Carbide, Houston, TX); methyl and propyl parabens (Mallinckrodt Specialty Chemicals Co, Paris, KY); light liquid paraffin, propylene glycol, triethanolamine (TEA), and ethyl alcohol (El-Nasr Co for Chemicals and Pharmaceuticals,

Table 1. Factors and Levels for the 2^3 Factorial Design

Factors	Levels
(A) Gelling agent type	+ HPMC - Carbopol
(B) Liquid paraffin concentration	+ 7.5% - 5%
(C) Emulsifying agent concentration	+ 2.5% - 1.5%

Cairo, Egypt); cellulose membrane with a molecular weight cutoff point of 10 000 (Spectrum Medical Industries Inc, CA); and *Candida albicans* NCTC 3179 (clinical isolate grown at 25°C for 24 hours on Sabouraud's agar).

Experimental Design

Eight CHL emulgel formulations were prepared according to a 2^3 factorial design employing the qualitative factors and levels shown in Tables 1 and 2.

Preparation of CHL Emulgel Formulations

The composition of CHL emulgel formulations is shown in Table 3. The gel in formulations F_1, F_3, F_5, and F_7 was prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed; then the pH was adjusted to 6 to 6.5 using TEA. In formulations F_2, F_4, F_6, and F_8, the gel was prepared by dispersing HPMC in heated purified water (80°C), and the dispersion was cooled and left overnight. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and propyl parabens were dissolved in propylene glycol whereas CHL was dissolved in ethanol, and both solutions were mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel.

Table 2. Qualitative Composition of Chlorphenesin Emulgel Formulations

		Composition†		
Combination*	Formulation	A	B	C
(1)	F1	-	-	-
A	F2	+	-	-
B	F3	-	+	-
AB	F4	+	+	-
C	F5	-	-	+
AC	F6	+	-	+
BC	F7	-	+	+
ABC	F8	+	+	+

*A, Gelling agent type, B, liquid paraffin concentration, C, emulsifying agent concentration

†Factor at low level, +, factor at high level.

Physical Examination

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency, spreadability, and phase separation. The pH values of 1% aqueous solutions of the prepared emulgels were measured by a pH meter (CG 820, Schott Gerate GmbH, Hofheim, Germany).

Rheological Studies

The viscosity of the different emulgel formulations was determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories, model HADV-II, Middleboro, MA) and connected to a thermostatically controlled circulating water bath (Polyscience, model 9101, Niles, IL). The recorded viscosities are collected in Table 4, and the entire rheograms are shown in Figures 1 and 2.

Table 3. Quantitative Composition of Chlorphenesin Emulgel Formulations (% wt/wt)

Ingredient	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Chlorphenesin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 934	1		1		1		1	
HPMC*		2.5		2.5		2.5		2.5
Liquid paraffin	5	5	7.5	7.5	5	5	7.5	7.5
Tween 20	0.6	0.6	0.6	0.6	1	1	1	1
Span 20	0.9	0.9	0.9	0.9	1.5	1.5	1.5	1.5
Propylene glycol	5	5	5	5	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Purified water to	100	100	100	100	100	100	100	100

*HPMC indicates hydroxypropylmethyl cellulose.

Table 4. Viscosities (in Poise) of Chlorphenesin Emulgel Formulations at Low and High Rates of Shear

Formulation	η min*	η max†	Formulation	η min*	η max†
F_1	6410	1200	F_2	66.84	27.55
F_3	6330	1060	F_4	96.73	27.95
F_5	7610	1220	F_6	54.26	19.97
F_7	6680	1090	F_8	57.41	17.44

*Viscosity at low rate of shear.
†Viscosity at high rate of shear.

In Vitro Release Studies

A glass cup with a cross-sectional area of 7.5 cm^2 was filled with 3 g of the emulgel, covered with a cellulose membrane, sealed with a rubber band, and inverted under the surface of 500 mL of phosphate buffer of pH 5.5 at 37°C ± 0.5°C in a *United States Pharmacopeia (USP)* dissolution tester (Pharma Test, PTW, Type II, Hainburg, Germany) with a paddle speed of 50 rpm. Such assembly has been validated in a previous study.[9] Aliquots were withdrawn at specified time intervals over a 3-hour period and immediately replaced with fresh dissolution medium. The drug content in the withdrawn samples was determined spectrophotometrically at 226 nm using a UV spectrophotometer (Shimadzu UV 240, Kyoto, Japan). The CHL topical powder commercially available in the local market was used for comparison. The in vitro release profiles of CHL from its emulgel formulations are represented in Figure 3. Statistical and kinetic treatments of the release data of the drug from the different emulgel formulations were performed, and the results are compiled in Tables 5 and 6, respectively.

Microbiological Assay

Ditch plate technique was used. It is a technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations.[10] Previously prepared Sabouraud's agar dried plates were used. Three grams of the emulgel were placed in a ditch cut in the plate. Freshly prepared culture loops were streaked across the agar at a right angle from the ditch to the edge of the plate. The commercial CHL powder was used for comparison. Control plates containing plain emulgel bases were also prepared. After incubation for 18 to 24 hours at 25°C, the fungal growth was observed and the percentage inhibition was measured as follows:

$$\% \text{ inhibition} = L_2 / L_1 \times 100 \quad (1)$$

where L_1 = total length of the streaked culture, and L_2 = length of inhibition. The results of this experiment are compiled in Table 7.

Stability Studies

The prepared CHL emulgel formulations were stored away from light in high-density polyethylene bottles at 40°C and 4°C for 3 months. After storage, the samples were tested for their physical appearance, pH, rheological behavior, drug release, and antifungal activity.

Results and Discussion

Physical Examination

The prepared CHL emulgel formulations were white viscous creamy preparations with a smooth and homogeneous appearance. They were easily spreadable with acceptable bioadhesion and fair mechanical properties. The pH values of all the prepared formulations ranged from 6.3 to 6.5, which is considered acceptable to avoid the risk of irritation upon application to the skin.[11,12]

Rheological Studies

Figures 1 and 2 show the entire rheograms (shear stress vs shear rate) of CHL emulgel formulations. As seen in the figures, all the prepared emulgel formulations exhibited a shear-thinning behavior since the viscosity (the slope of the curve) decreased with increasing the shear rate. As the shear stress is increased, the normally disarranged molecules of the gelling material are caused to align their long axes in the direction of flow. Such orientation reduces the internal resistance of the material and hence decreases the viscosity. The figures also show that all CHL emulgel formulations possessed thixotropic behavior, where the down curve was displaced with regard to the up curve, showing at any rate of shear on the down curve a lower shear stress than it had on the up curve; a hysteresis loop was formed between the 2 curves. Thixotropy, or time-dependent flow, occurs because the gel requires a finite time to rebuild its original structure that breaks down during continuous shear measurements.[5] It is noteworthy that thixotropy is a desirable characteristic in pharmaceutical preparations, both in engineering design and consumer application, in order to deliver an initially thick product as a thinner, easily spreadable material. These findings are in agreement with Abd El-Bary et al, who had prepared chloramphenicol emulgel using Carbopol 940 as the gel-forming material.[6] The recorded viscosities of the different CHL emulgel formulations at both low and high shear rates are collected in Table 4, which showed that the Carbopol-based formulations (F_1, F_3, F_5, and F_7) possessed considerably higher viscosities than the HPMC-based formulations (F_2, F_4, F_6, and F_8).

In Vitro Release Studies

The in vitro release profiles of CHL from its various emulgel formulations are represented in Figure 3. It was observed that

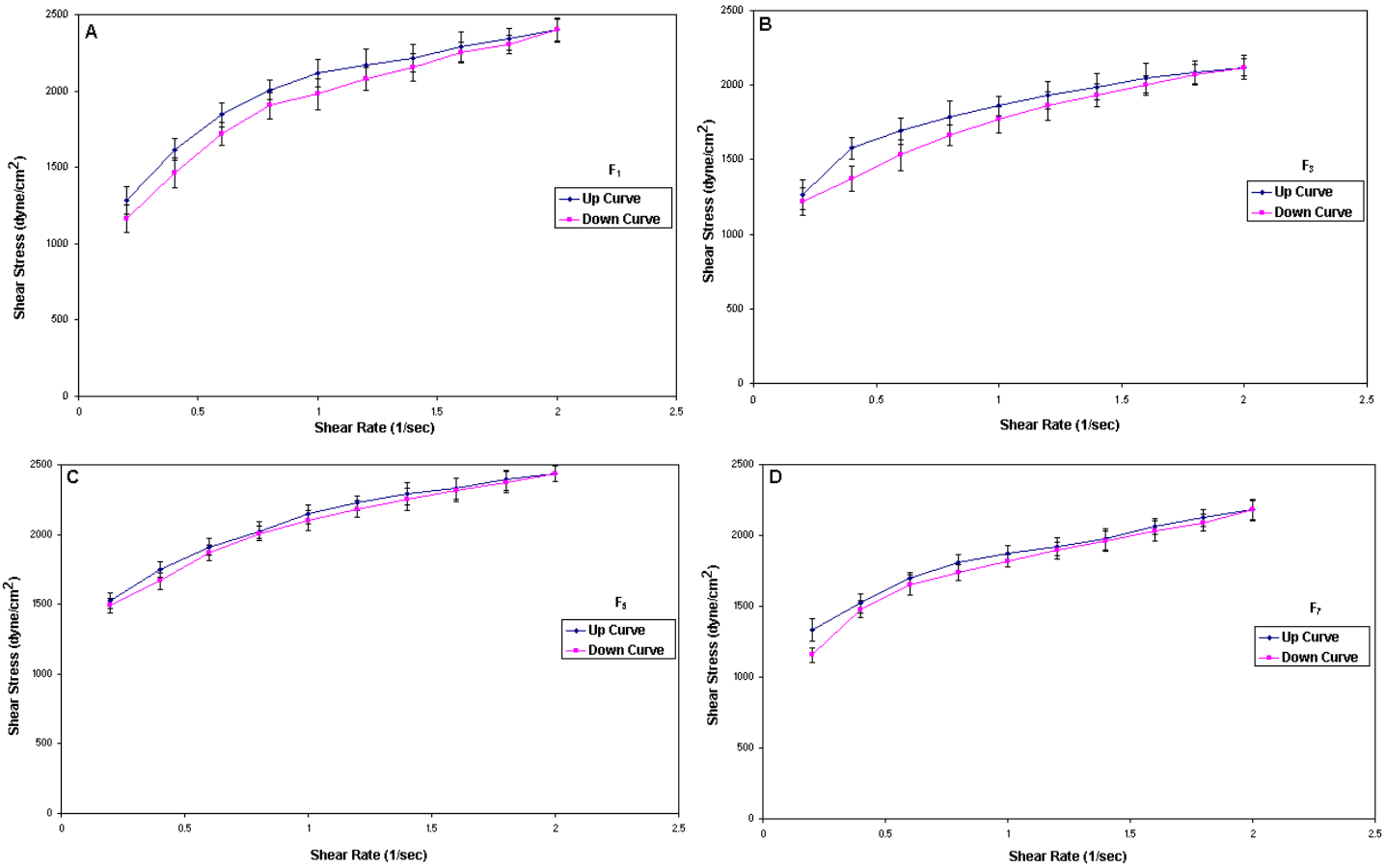

Figure 1. Rheograms of carbopol-based chlorphenesin emulgel formulations (mean ± SD, n = 3): (A) formulation F_1, (B) formulation F_3, (C) formulation F_5, and (D) formulation F_7.

all the formulations had become liquefied and diluted at the end of the experiment, indicating water diffusion through the membrane. In general, it can be observed from Figure 3 that the release of the drug from its all emulgel formulations was higher than its release from its commercial powder. The release of the drug from its emulgel formulations can be ranked in the following descending order: $F_6 > F_5 > F_8 > F_2 > F_7 > F_1 > F_4 > F_3$, where the amounts of the drug released after 3 hours were 39.44%, 31.32%, 28.91%, 27.28%, 26.64%, 25.08%, 24.33%, and 23.1%, respectively. However, only 18.1% of the drug was released from the commercially available powder after the same period of time. Thus, the greatest drug release was observed with formulations F_6 and F_5. This finding may be due to the presence of liquid paraffin in its low level and the emulsifying agent in its high level in both such formulations, which leads to an increase in the hydrophilicity of the emulgel, which, in turn, facilitates penetration of the release medium into the emulgel and diffusion of the drug from the emulgel. This finding was in agreement with Abd El-Bary et al,[6] who proved that the presence of liquid paraffin led to retardation of chloramphenicol release from its emulgel formulation. The lower drug release from formula F_5, which is Carbopol-based, than the drug release from formula F_6, which is HPMC-based, may be due to the higher viscosity of Carbopol emulgel formulations as observed in Table 4. It may also be due to the entrapment of the drug in the network structure of Carbopol 934.[13] Contrary to F_6 and F_5 formulations, F_4 and F_3 showed the lowest drug release. In formulations F_4 and F_3, liquid paraffin is present in its high level, while the emulsifying agent is in its low level. Formula F_8, containing both liquid paraffin and the emulsifying agent in their high levels, exhibited greater drug release than formula F_2, containing both liquid paraffin and the emulsifying agent in their low levels. This finding indicated that the enhancing effect of the emulsifying agent on the drug release was more pronounced than the lowering effect of liquid paraffin on the drug release. The same observation was found in F_7 and F_1 formulations. Although F_5 is Carbopol based, it showed a greater drug release than F_8, which is HPMC based. This finding is due to the lower liquid paraffin content in formula F_5 than in formula F_8. The same is true for F_1 and F_4. This finding proved that the effect of liquid paraffin in decreasing the drug release from the emulgel was more predominant than the enhancing effect of HPMC on the drug release. Thus the 3 studied factors can be arranged according to their effect on the drug release from the emulgel formulations as follows: the emulsifying agent concentration > liquid paraffin concentration > the gelling agent type.

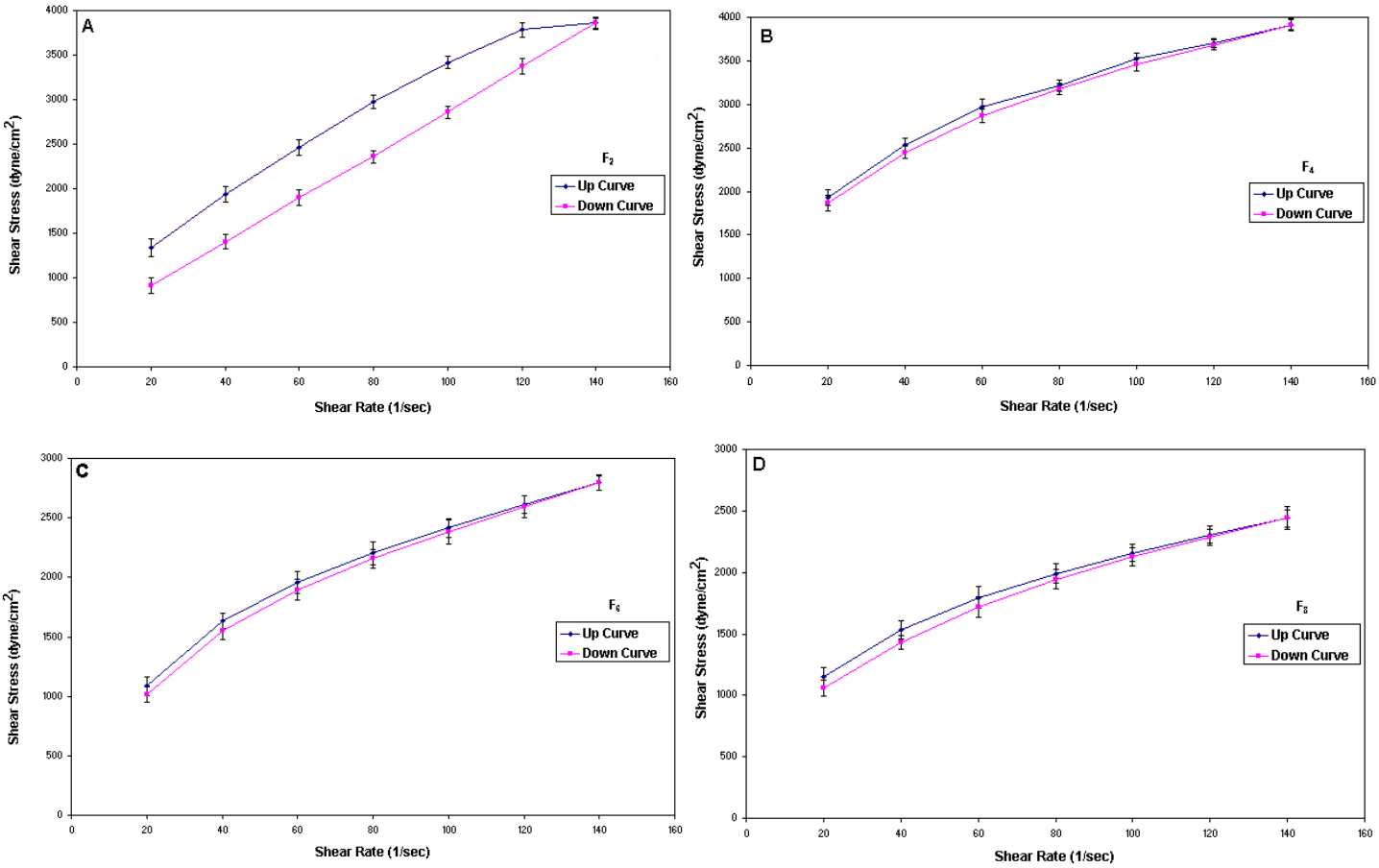

Figure 2. Rheograms of HPMC-based chlorphenesin emulgel formulations (mean ± SD, n = 3): (A) formulation F_2, (B) formulation F_4, (C) formulation F_6, and (D) formulation F_8.

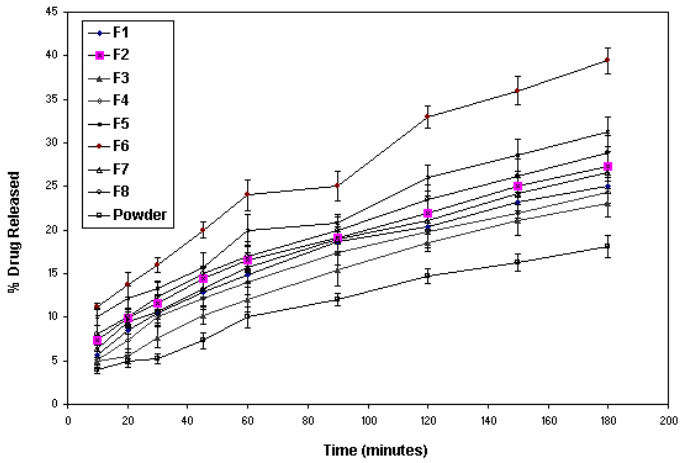

Figure 3. Release profiles of chlorphenesin from its emulgel formulations (mean ± SD, n = 3).

Table 5 shows the results of evaluation of the factorial design using Yates analysis of variance.[14] These results demonstrated that the 3 main effects (EA, EB, and EC) were statistically significant at $P \leq .05$. The most important factor for enhancing the drug release was the emulsifying agent concentration followed by liquid paraffin concentration and then the gelling agent type. This was in accordance with the previous finding. Regarding the primary interactions (IAB, IAC, and IBC), it is obvious from Table 5 that the most important interaction took place between liquid paraffin concentration and the emulsifying agent concentration (IBC), and such interaction was significant at $P \leq .25$.

The drug release data were analyzed according to zero- and first-order kinetics as well as diffusion- controlled mechanism using linear regression analysis. The results, as shown in Table 6, revealed that the drug release from the CHL emulgel formulations followed Higuchi diffusion model[15] with a correlation coefficient ranging from 0.9924 to 0.9992, which means an excellent model fit. This finding indicates that the rate-controlling stage in the release process was diffusion of the dissolved drug through the gel network to the external medium, which, in turn, explains why the amount of the drug released did not exceed 39.44%.

Microbiological Assay

The use of control plates showed that the plain emulgel bases were microbiologically inert toward the tested *Candida albicans* strain. The antifungal activity of CHL in its different emulgel formulations as well as in its commercially available powder form are shown in Table 7. Percentage inhibition was taken as a measure of the drug antifungal activity. The emul-

Table 5. Statistical Analysis of the Main Effects (E) and Interactions (I) on the Percentage Chlorphenesin Released After 3 Hours (Q) From Its Emulgel Formulations

E or I	Response (Q)	Effect	Mean Square	*df*	F
E A	25.28	3.455	23.87	1	4.82†
E B	21.1	-5.035	50.7	1	10.24†
E C	29.32	6.63	87.91	1	17.76†
I AB	22.33	-1.705	5.81	1	1.17
I AC	37.44	1.74	6.06	1	1.22
I BC	24.64	-2.57	13.21	1	2.67
I ABC	26.91	-1.22	2.98	1	0.6
			Error* = 4.95	3	

*Error mean square based on AB, AC, and ABC interactions.
† $P \leq .05$

Table 6. Kinetic Treatment of the Release Data of Chlorphenesin From Its Emulgel Formulations

	Correlation Coefficient				
Formulation	Zero Order	First Order	Diffusion	Mechanism of Release	Release Rate Constant ($mg.min^{-1/2}$)*
F_1	0.9787	0.9845	0.9986	Diffusion	1.8854
F_2	0.9863	0.9911	0.9992	Diffusion	1.9263
F_3	0.9914	0.9945	0.9965	Diffusion	1.8746
F_4	0.9804	0.9861	0.9992	Diffusion	1.8652
F_5	0.9883	0.9918	0.9927	Diffusion	2.1168
F_6	0.9873	0.9917	0.9924	Diffusion	2.8013
F_7	0.9859	0.9907	0.9987	Diffusion	1.9407

*Release rate constant of the diffusion mechanism.

gel formulations were found to have the same rank order in their antifungal activities as in the in vitro release studies. Thus, the greatest activity was observed with formula F_6, where the percentage inhibition reached up to 25.3%, while the lowest activity was found with F_3 and F_4, where the percentage inhibition was ~9%.

Stability Studies

All the prepared CHL emulgel formulations were found to be stable upon storage for 3 months, where no change was observed in their physical appearance, pH, rheological properties, drug release, or antifungal activity.

CONCLUSION

From the above results we can conclude that CHL emulgel formulations prepared with either Carbopol 934 or HPMC showed acceptable physical properties, drug release, and antifungal activity, which remained unchanged upon storage for 3 months. However, the HPMC-based emulgel with the liquid paraffin in its low level and the emulsifying agent in its high level proved to be the formula of choice, since it showed the highest drug release and antifungal activity.

Table 7. Percentage Inhibition as a Criterion for the Antifungal Activity of Chlorphenesin in Its Different Emulgel Formulations

Formulation	% Inhibition	Formulation	% Inhibition
CHL powder*	8.4	F_5	20.2
F_1	11.1	F_6	25.3
F_2	16.2	F_7	13.4
F_3	9.4	F_8	19.3
F_4	9.1		

*CHL indicates chlorphenesin

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