***Original Research Article***

# FORMULATION and EVALUATION of OPTIMIZED CLOTRIMAZOLE EMULGEL FORMULATIONS


***ABSTRACT***

**Aims**: The aim of this present study to develop an emulgel formulation of Clotrimazole using carbopol 934 or hydroxyl propyl methyl cellulose2910 as a gelling agent. The influence of the type of gelling agent and the concentration of both the oil phase and the emulsifying agent on the release of the drug and its microbial activity were investigated using $2^3$ factorial designs. In addition, rheological properties were also evaluated.

**Methodology:**Within the major group of semisolid preparations, emulgel has emerged as a promising drug delivery system for the delivery of hydrophobic drugs. Different emulgel formulations were optimized using a $2^3$ factorial design considering three independent factors at two levels; gelling agent (carbopol 934 and hydroxyl propyl methyl cellulose, liquid paraffin (2.5% and 5%) and emulsifying agent (1.5 and 2.5%). The amount of drug released ($Y_1$) and the antifungal activity ($Y_2$)were chosen as two dependent responses. The prepared emulgel were also evaluated for their physical properties,pH, drug content and rheological properties.

**Results:** The prepared emulgel exhibited higher release when compared with canestin cream as a market product. Rheological study revealed that the emulgel exhibited a thixotropic behavior. Candida albicans was used as a model fungus to evaluate the antifungal activity of the prepared formulations achieved using canestin cream as a control. Stability studies revealed no significant differences before and after storage for the selected formula.

**Conclusion:** It was suggested that Clotrimazole emulgel formulation (F6) prepared using HPMC 2910as gelling agent, emulsifying agent in its high level and liquid paraffin in its low level was the formula of choice since it showed the highest drug release and the highest antifungal activity.


***Keywords: Clotrimazole, Emulgel,multifactorial design, Antifungal activity***

## 1. INTRODUCTION

Topical formulations apply a wide spectrum of preparations both cosmetic and dermatological, to healthy or diseased skin [1]. These formulations range in consistency from solid through semisolid to liquids.

When gels and emulsions are used in a combined form, the dosage forms are referred to emulgel [2][3]. As the name suggests they are the combination of emulsion/ microemulsion and gel.

Novel polymers with complex functions as emulsifiers and thickeners have been used with great interest due to their gelling capacity which allows the formulation of stable emulsionby decreasing surface and interfacial tension and also by increasing the viscosity of the aqueous phase. Oil / water and water / oil emulsions are used as vehiclesto deliver various drugs to the skin [4]. Emulsion gels are gaining importance due to many reasons; they have better application property in comparison to classical formulation as creams and ointment, they have faster and more complete release of the drug from the vehicle to the skin, also they are convenient to apply on hairy skin due to the absence of greasiness and lack of residue upon application. They permit the incorporation of both aqueous and oleaginous ingredients, so hydrophobic or poorly water soluble drugs as antifungal agents are easily incorporated in such type of vehicles through the proper choice of the oily phase [5].

Clotrimazole is an antifungal agent which inhibits the growth of pathogenic dermatophytes. It shareswith econazole, miconazole, first choice status for topical treatment of tineapedis, tineacruris and tineacorporis due to candida albicans. It is effective for topical treatment of vulvovaginal and oropharyngeal candidiasis [6][7][8].

## 2. MATERIALS AND METHODOLOGY

### 2.1 Materials

Clotrimazole was kindly provided by Alexandria Co. for pharmaceutical and chemical industries(Alexandria, Egypt), carbpol 934 (Goodrich Chemicals Co., Cleveland, Ohio).Hydroxyl propyl methyl cellulose, (HPMC) 2910 was kindly supplied by Sedico for pharmaceuticals (Giza, Egypt). Tween 20, span20, methyl and propyl parabens, light liquid paraffin, propylene glycol, dimethyl formamide (DMF), hydrochloric acid and ethyl alcohol were purchased from Al – Nasr pharmaceutical chemicals (Cairo, Egypt). Triethanolamine (TEA) was supplied from Morgan Chemicals Ind.Co. (Cairo, Egypt). Canesten cream B.N.211030 is purchased from an Egyptian community pharmacy(Manufactured by Memfis for pharmaceuticals. Cellulose membrane (M.Wt. cutoff 10-000-14-1000) was supplied from Sigma Chemical Company(Saint Louis, MO). C. albicans ATCC No 10231was kindly provided by the Department of Microbiology, October University for Science and Modern Arts (MSA)(clinical isolate growth at 25°C for 24 hours on Sabouraud's agar.

### 2.2 Methodology

#### 2.2.1. *Preparation of Emulgel*

The detailed composition for the prepared emulgel formulations are given in Table 2.The gel in formulations F1, F3, F5 and F7 was prepared by dispersing cabopol 934 in purified water with continuous stirring using overhead stirrer for 5min at 2000 rpm. The gel in formulations F2, F4, F6 and F8 was prepared by dispersing HPMC in hot purified water (70˚C); the gel 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 while Clotrimazole was dissolved in ethanol; both were then mixed with the aqueous phase. Heat separately the aqueous and the oily phase to70˚C, and then the oily phase was added to the aqueous phase with continuous stirring till cooled to room temperature. The emulsion and the gel both mixed together in equal ratio with gentle stirring till obtaining the emulgel [9] [10].

#### 2.2.2 Experimental Design and Statistical analysis

A 3-factor, 2- level factorial design was used to explore response surfaces and constructing second- order polynomial models with Statgraphic plus software (Version 4.1). The 2-level factorial design was specifically selected since it requires fewer runs than other experimental designs. The nonlinear computer, generated quadratic model is given as:

$$Y=\beta0+\beta1\ X1+\beta2\ X2+\beta3\ X3+\beta12\ X1X2+\beta13\ X1X3$$

$$+\beta23\ X2X3+\beta1\ X12$$

Where Y is the predicted response; β0 is the model constant;X1, X2, and X3 are the independent variables; β1, β2, and β3 are the linear coefficients; β12, β13, and β23 are the cross-product coefficients; and β11, β22, and β33 are the quadratic coefficients. 2-level design, where selected each variable is tested at a low (-1) and high (+1) level.

Eight Clotrimazole emulgel formulations were prepared according to $2^3$ full factorial designs to optimize the formulation factors and evaluate the main effects. The independent variables were the type of gelling agent ($X_1$), liquid paraffin % ($X_2$) and emulsifying agent % ($X_3$). Two levels of gelling agent type were used carpobol and HPMC, denoted the value -1 and 1in the above design respectively.

Two levels of liquid paraffin concentration were chosen to be 5% and 7.5% denoted -1 and 1 respectively. Finally the emulsifying agent concentration were 1.5 and 2.5 % denoted -1 and 1 respectively. The eight experimental trials and the respective observed responses are given in Table 1.

**Table 1 Variablesand observed response in $2^3$factorial designfor emulgel formulations**

| Formulations | Independent variables | | | Dependent variables | |
|---|---|---|---|---|---|
| | X1 | X2 | X3 | Y1 | Y2 |
| F1 | -1 | -1 | -1 | 29.55 | 38.5 |
| F2 | 1 | -1 | -1 | 32.81 | 43.4 |
| F3 | -1 | 1 | -1 | 27.46 | 32.2 |
| F4 | 1 | 1 | -1 | 28.68 | 35.7 |
| F5 | -1 | -1 | 1 | 38.58 | 48.5 |
| F6 | 1 | -1 | 1 | 43.22 | 57.5 |
| F7 | -1 | 1 | 1 | 30.47 | 40.6 |
| F8 | 1 | 1 | 1 | 35.33 | 46.7 |

- X1= Gelling agent (-1) = Carbopol, (1)= hydroxpropylmethyl cellulose HPMC
- X2= Liquid paraffin % (-1)= 5%, (1) = 7.5%  Y1= Drug release after 3 hrs. Y2= antifungal activity
- X3= Emulsifying agent % (-1)= 1.5%, (1)= 2.5%

**Table 2 Composition and codes of Clotrimazole Emulgel formulations (%W/W)**

| | Formula's code | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Components** | **$F_1$** | **$F_2$** | **$F_3$** | **$F_4$** | **$F_5$** | **$F_6$** | **$F_7$** | **$F_8$** |
| Clotrimazole | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Carbopol 934 | 1 | - | 1 | - | 1 | - | 1 | - |
| HPMC2910* | - | 2.5 | - | 2.5 | - | 2.5 | - | 2.5 |
| Liquid paraffin | 5 | 5 | 7.5 | 7.5 | 5 | 5 | 7.5 | 7.5 |
| Tween20 | 0.6 | 0.6 | 0.6 | 0.6 | 1 | 1 | 1 | 1 |
| Span20 | 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: Hydroxypropyl methyl cellulose

**2.2.3Evaluation of Emulgel**

***2.2.3.1 Physical Appearance and pH Determination***

The prepared Clotrimazole emulgel were inspected visually for their color, homogeneity, consistency and pH.The pH values of 1% aqueous solutions of the prepared emulgelswere measured by a pH meter (Orion Research, Inc., USA) [11]. Experiments were carried out in triplicates.

#### *2.2.3.2 Drug Content Determination*

Experiments were carried out in triplicates. The drug content of Clotrimazole emulgel was measured by dissolving a known weight of the emulgel formulation in methanol. Absorbance was measured after suitable dilutionat 260 nm using UV- spectrophotometer (Shimadzu UV 1700, Japan) [12].

#### *2.2.3.3 Rheological Studies*

The viscosity of different Clotrimazole emulgel formulations was determined at 25˚C using a cone plate viscometer with spindle(52)(Brookfield model HBDV-III, USA) [13]. Experiments were carried out in triplicates.

#### **2.2.3.4** *In Vitro release Studies*

The study was carried out using the modified USP apparatus type II (Hanson SR8-plus 80, USA). Two grams of each emulgel was spread on the cellophane membrane previously soaked overnight in the dissolution medium. The loaded membrane was stretched over a glass cup of diameter 3 cm, and then the cup was immersed in 100 ml of the dissolution medium (25%v/v DMF in 0.02N HCl), the temperature was maintained at 37±0.5°C with paddle agitation speed 50 rpm. An aliquot of 5 ml was withdrawn at different intervals of time. The withdrawn samples were replaced by equal volumes of fresh release medium. The samples were assayed spectrophotometry at $\lambda_{max}$ 260nm using ultraviolet spectrophotometer. Experiments were carried out in triplicates. The effect of gelling type, the liquid paraffin concentration and emulsifying agent concentration was studied.

#### *2.2.3.5 Kinetic Analysisof the Drug Release*

Kinetic analysis was carried out by the data to determine the release model which describe the proper order of drug release as follow: Zero order (cumulative% drug release vs. time, first order (log cumulative % drug retained vs. time), and Higuchi model (cumulative % drug retained vs. square root of time) [14] [15] [16].

#### *2.2.3.6 Antifungal activity studies*

The prepared emulgel formulations were tested in a triplicate manner using agar cup method against candida albican strain. Cups of 10mm diameter were made aseptically in sabouraud dextrose agar after being inoculated with tested fungal suspension strain by spreading on the agar surface. The cups were filled with each prepared formulation by sterile syringe. The zone of inhibition of each cup was observed and the radius of the zone of inhibition was measured and compared to the control canestin ®cream [17].

#### **2.2.3.7** *Stability studies*

The prepared Clotrimazole emulgel were packed in aluminum tubes (5 grams) and subjected to stability studies at 25˚C/ 60 % relative humidity (RH) and 40˚C/ 75 % RH for a period of 3 months. Samples were withdrawn at time intervals of 15 day and evaluated for physical appearance, pH, rheological properties, drug content and drug release.

## 3.RESULTS AND DISCUSSION

### 3.1 *Physical Appearance and pH Determination*

The prepared Clotrimazole emulgel formulations were inspected visually for color, homogeneity, phase separation, consistency and pH. All formulations show white color, formulations prepared using carbopol 934 as gelling agent show glossy appearance. No phase separation was noticed, also formulations show suitable homogeneity and consistency. The pH of the emulgel formulation was in range of 5.66-6.53 which considered acceptable to avoid the risk of skin irritation upon application to skin [18] [19]. Results are shown in Table 3and Figure1.

**Table 3 Physical appearance, pH, and drug contentof Clotrimazole emulgel formulations**

| Formulations | Color | Phase Separation | Homogeneity | Consistency | pH | Drug content (mg %) |
|---|---|---|---|---|---|---|
| F1 | Shiny white | None | +++ | +++ | 6.13 | 95.55 |
| F2 | White | None | + | ++ | 6.38 | 96.34 |
| F3 | Shiny white | None | +++ | +++ | 6.33 | 98.21 |
| F4 | White | None | ++ | ++ | 6.13 | 98.09 |
| F5 | Shiny white | None | +++ | +++ | 6.53 | 96.84 |
| F6 | White | None | ++ | ++ | 6.35 | 96.39 |
| F7 | Shiny white | None | +++ | +++ | 5.66 | 97.44 |
| F8 | White | None | ++ | ++ | 6.39 | 98.45 |

Excellent +++, Good++, Satisfactory+

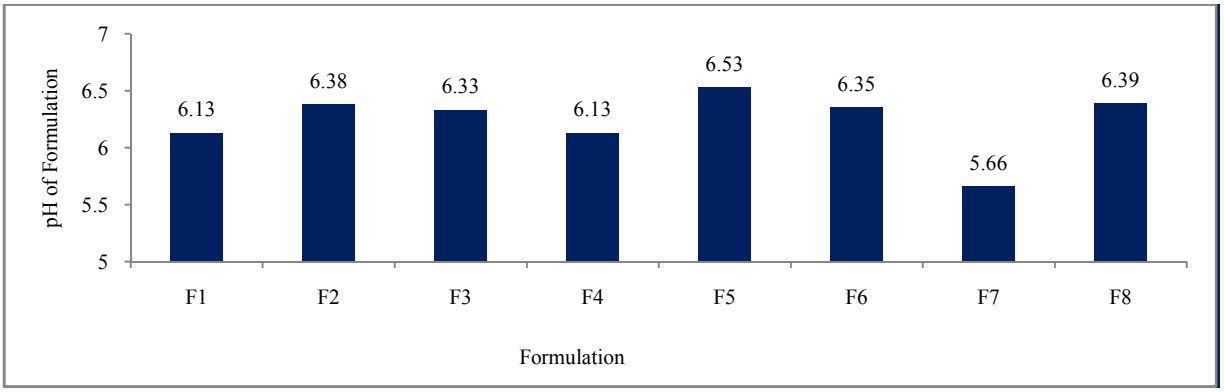



**Fig1. pH of Emulgel Formulation ($F_1$-$F_8$)**

### 3.2 Drug Content

Results of drug content are shown in Table 3 and represented in Figure 2. The drug content of different emulgel formulations was estimated and the results were in official limits with range of 95.55 to 98.45 mg%which indicate uniform distribution of the drug throughout the emulgel.

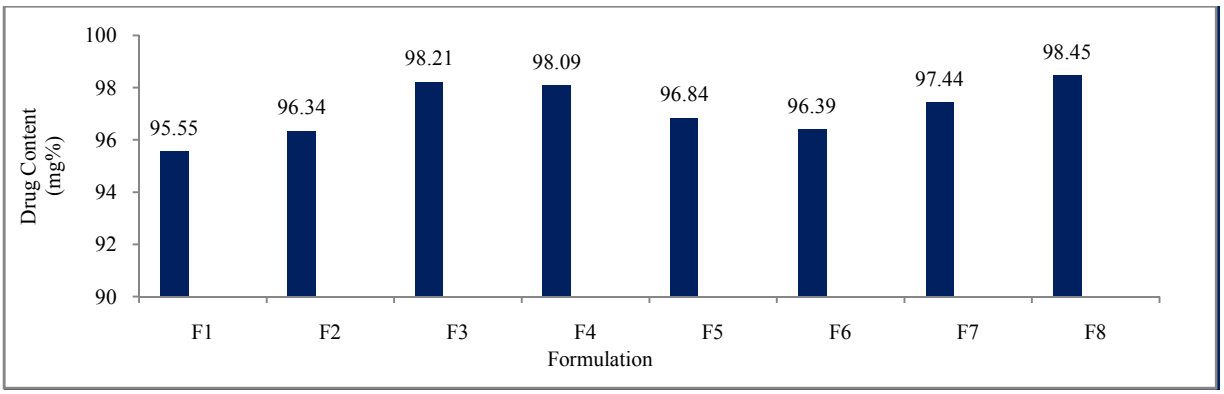



**Fig.2. Drug Content (mg %) of Emulgel Formulation (F1-F8)**

### 3.3 Rheological Studies

Viscosities of different Clotrimazole emulgel formulations at both low and high shear rates are shown in Table 4, the results showed that the emulgel formulations prepared using carbopol as gelling agent (F1, F3, F5 and F7) possessed higher viscosities than emulgel formulations prepared using HPMC 2910(F2,F4,F6 and F8). This is due to the difference in the type of gelling agent result in changing the structure consistency [20], also this effect may be due to the higher hygroscopicity of HPMC compared with

carbopol 934[21]. Figure 3, 4 and 5 show the rheograms of Clotrimazole emulgel containing carbopol, HPMC and the market product canesten ® cream. As represented in the Figures, all the prepared emulgel exhibited a shear- thinning behavior as the viscosity decreased by increasing the shear rate. The figures also show that all Clotrimazole emulgel formulations possessed thixotropic behavior, where the down curve was displaced with regard to the up curve, 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 up curve and the down curve. Thixotropy(time dependent flow needs a definite time to rebuild its original structure that breaks down during continuous shear measurements [22], the results of Clotrimazole emulgel are in agreement with Abd El- Bary et al who had prepared Chloramphenicol emulgel using Carbopol 940 as a gelling agent [23].

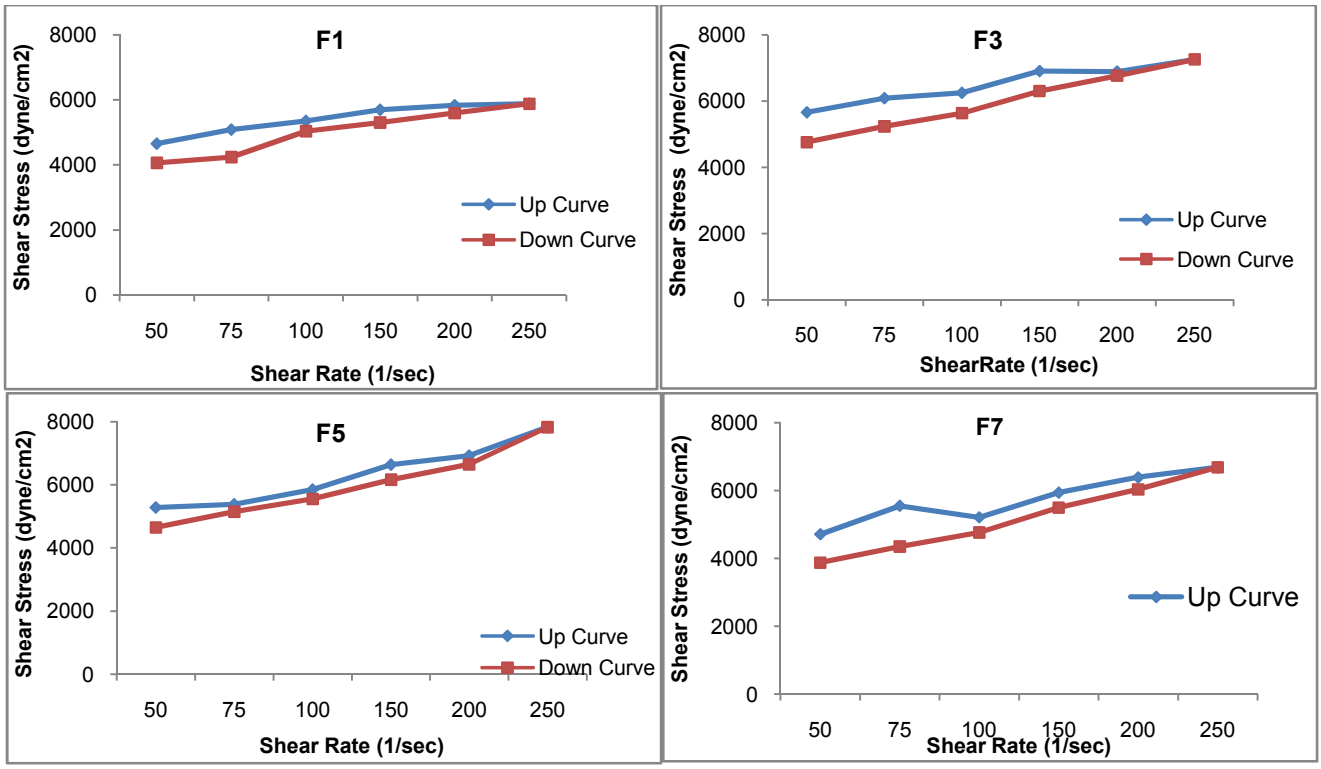



**Fig.3. Show Rheograms of Carbopol 934 Emulgel (F1, F3, F5 and F7)**

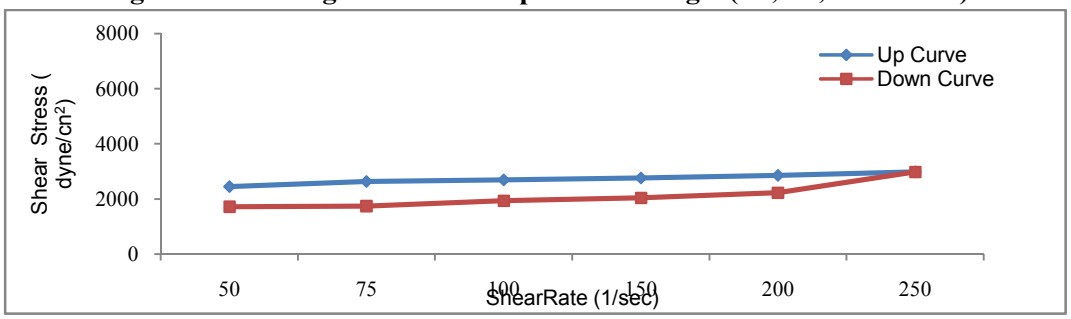



**Fig.4. Show Rheogram of the Market Product (Canesten ® Cream)**

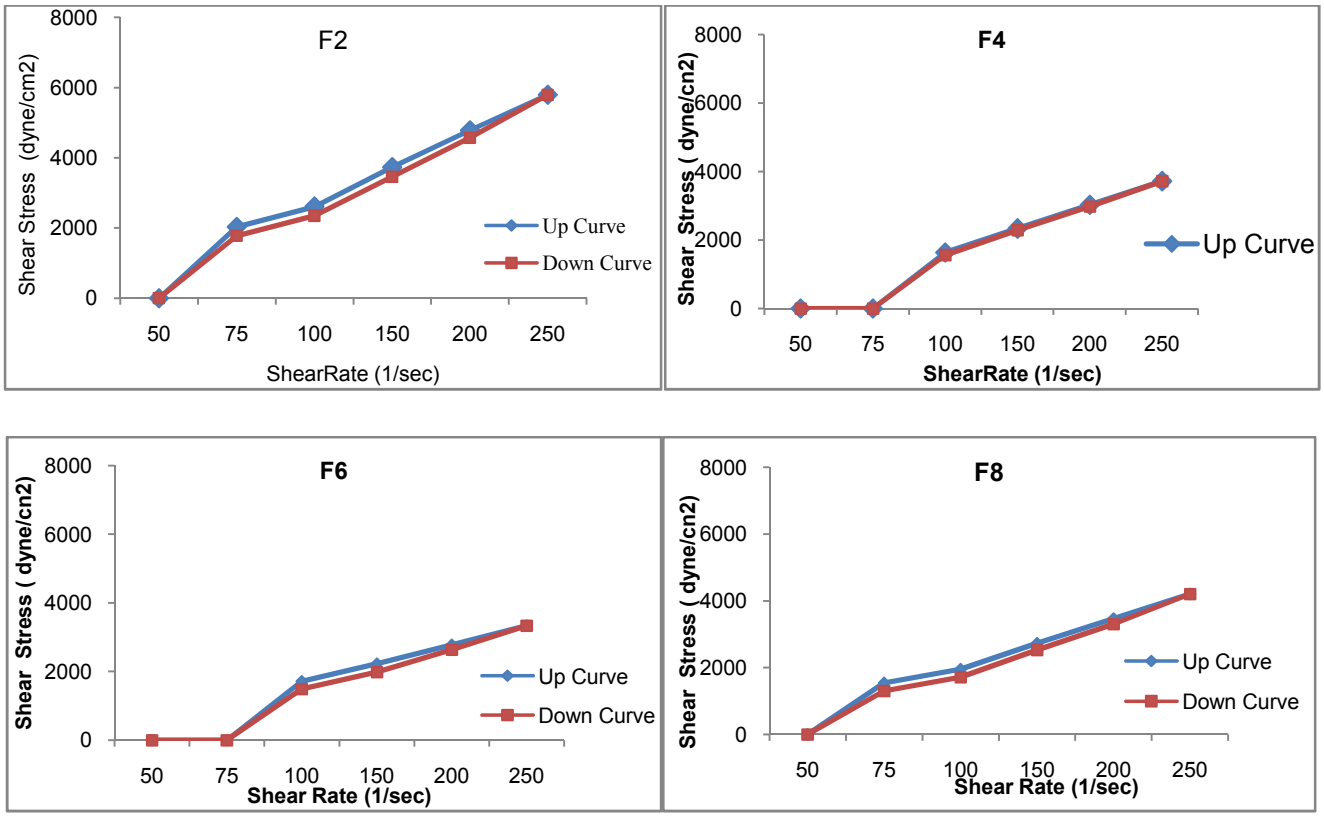



**Fig.5. Show Rheograms of HPMC 2910 Emulgel (F2, F4, F6 and F8)**

**Table4. Viscosities (cp) of Clotrimazole emulgel formulationsat low and high rateof shear**

| Formulations | ŋ min* | ŋ max± | Formulations | ŋ min* | ŋ max± |
|---|---|---|---|---|---|
| **F1** | 1926 | 180 | **F2** | 1365 | 1162 |
| **F3** | 4062 | 7255 | **F4** | 817 | 743 |
| **F5** | 3894 | 1502 | **F6** | 800 | 666 |
| **F7** | 3145 | 1321 | **F8** | 1027 | 841 |
| **Canesten** | 1152 | 606 | | | |

*Viscosity at low rate of shear

± Viscosity at high rate of shear

### 3.4.In vitro drug release

The in vitro release of Clotrimazole from different emulgel formulations and the market product at 37˚C was investigated and the results are represented in Figure 6. It was noticed that the release of emulgel formulations are higher than that of canesten cream (the market product). The release of Clotrimazole from its emulgel can be ranked in the following descending order: F6> F5> F8> F2> F7> F1> F4> F3 where the amount of drug release after 3 hours was found to be 43.22%, 38.58%, 35.33% 32.81%, 30.47%, 29.55%, 28.66% and 27.46%, respectively. While the release of Clotrimazole from the canesten cream after 3 hours was found to be 25.32%.

Formulations F6 and F5 was observed to have the highest release, this was due to the presence of liquid paraffin and emulsifying agent in low and high level, respectively. These results were due to the increase of hydrophilicity of emulgel which facilitate the penetration of the release medium into the emulgel and the diffusion of the drug fromemulgel. The results of Clotrimazole emulgel are in agreement with Abd El- Bary et al. [23], who showed that the presence of liquid paraffin led to retardation of Chloramphenicol release from its emulgel formulation.

The release of drug from formulation F5 was found to be lower than the release from F6 this may be due to the higher viscosity of Carbopol emulgel formulation as observed in Table 4. [24]. In contrary to F6 and F5formulations, F4 and F3 showed the lowest drug release this may be due to the presence of liquid paraffin and emulsifying agent in high and low level, respectively.F8 has both liquid paraffin and the emulsifying agent in their high levels and exhibited higher release than F2 formulation containing both liquid paraffin and the emulsifying agent in their low levels. The previous result indicated that the effect of emulsifying agent in high level on the drug release was more pronounced than the effect of liquid paraffin in low level on the drug release.

Although F5 has Carbopol as gelling agent, it showed higher drug release than F8 which has HPMC as a gelling agent. This result is due to that F5 has liquid paraffin in low level while F8 has liquid paraffin in high level. The same explanation was found when comparing F1 and F4 formulations. These results showed that the effect of liquid paraffin in decreasing the drug release from emulgel formulation was more than the effect of HPMC on the drug release. Thus we can arrange the studied factors according to their effect on drug release from the emulgel formulation as follows: The emulsifying agent concentration>the liquid paraffin concentration>the gelling agent type.

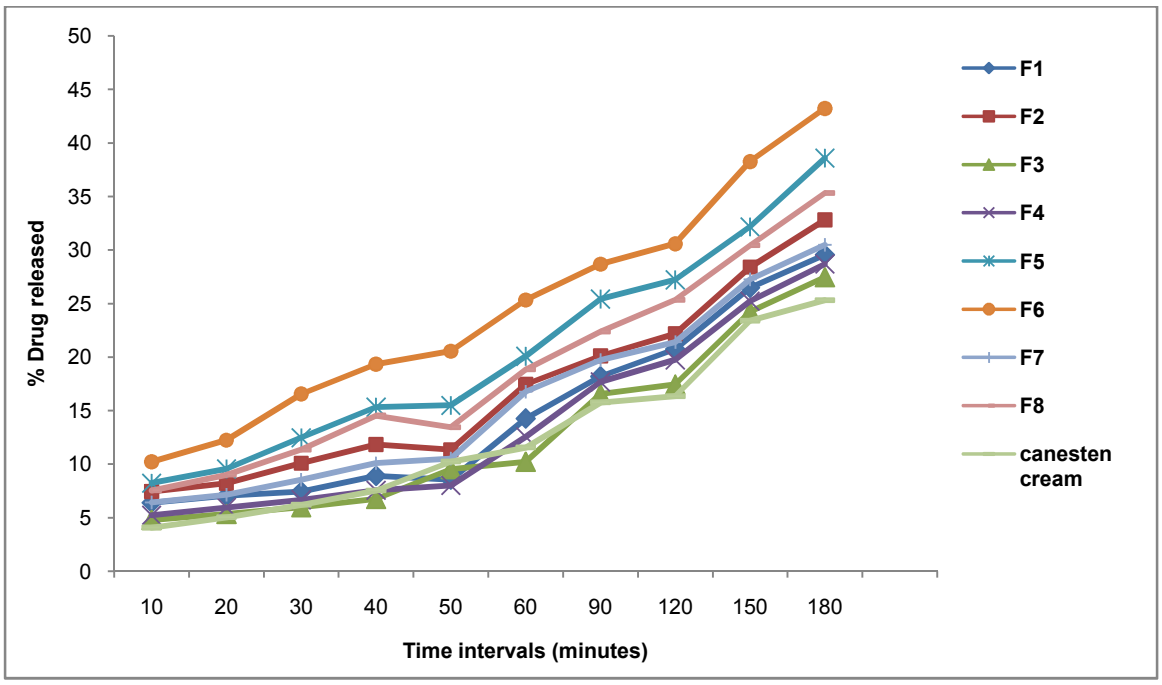



**Fig.6. Release profiles of Clotrimazole from its emulgel formulations.**

### 3.5.Kinetic Analysisof the Drug Release

Kinetic analysis was carried out by the data to determine the release model which describe the proper order of drug release as follow: Zero order (cumulative% drug release vs. time), first order (log cumulative % drug retained vs. time), and Higuchi model (cumulative % drug retained vs. square root of time) [25] [26] [27].The correlation coefficient (R2) values are tabulated in Table 5. Most of the formulation showed first order release except formulations F3 and F7 which showed zero order kinetics and diffusion model kinetic respectively.

**Table5. The kinetic study of the In vitro release data of Clotrimazole from is different emulgel formulations.**

| Formulation | Correlation Coefficient (R2 | | |
|---|---|---|---|
| | Zero Order | First Order | Diffusion |
| **F1** | 0.98881 | **0.98896** | 0.97038 |
| **F2** | 0.98940 | **0.98973** | 0.97737 |
| **F3** | **0.99213** | 0.99109 | 0.97190 |
| **F4** | 0.99125 | **0.99181** | 0.97338 |
| **F5** | 0.98619 | **0.98851** | 0.97951 |
| **F6** | 0.99050 | **0.99270** | 0.98951 |
| **F7** | 0.98458 | 0.98935 | **0.99076** |
| **F8** | 0.98613 | **0.98851** | 0.97957 |
| **Canesten cream** | 0.99144 | **0.99376** | 0.98835 |

### 3.6 Antifungal activity studies

The antifungal activity of Clotrimazole from its different emulgel formulations as well as in its market available cream form (Canesten® cream) are shown in Table 5 and Figure 7. The zone of inhibition was taken as a measure of the drug antifungal activity. The greatest activity was observed with F6 where the zone of inhibition was 57.5mm, while the lowest activity was found with F3 where the zone of inhibition was 30mm.These results were due to the increase of hydrophilicity of emulgel in F6 which facilitate the penetration of the release medium into the emulgel and the diffusion of the drug from emulgel. The results are in agreement with the results obtained from the in vitro release study which indicates good correlation between the in vitro and the antifungal activity studies.

**Table5. The inhibition zone as a criterion for Clotrimazole antifungal activity in its different emulgel formulations**

| Formulation | Inhibition Zone (mm) | Formulation | Inhibition Zone (mm) |
|---|---|---|---|
| **F1** | 38.5 | **F5** | 48.5 |
| **F2** | 43.4 | **F6** | 57.5 |
| **F3** | 32.2 | **F7** | 40.6 |
| **F4** | 35.7 | **F8** | 46.7 |
| **Canesten cream** | 28.5 | | |

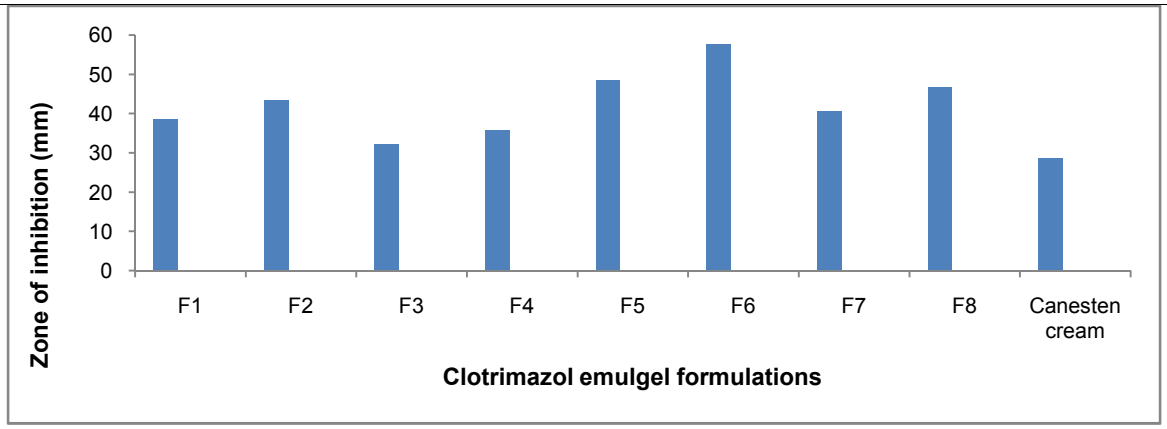



**Fig.7. Zone of inhibition of Clotrimazole emulgel formulations**

### 3.7. Stability studies

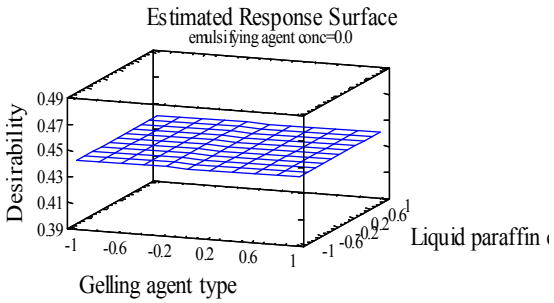
The prepared Clotrimazole emulgel formulations were found to be stable after subjected to stability studies at 25˚C/ 60 % relative humidity (RH) and 40˚C/ 75 % RH for a period of 3 months. No significant change was noticed in the parameters evaluated for physical appearance, pH, rheological properties, drug content, drug release and antifungal activity.

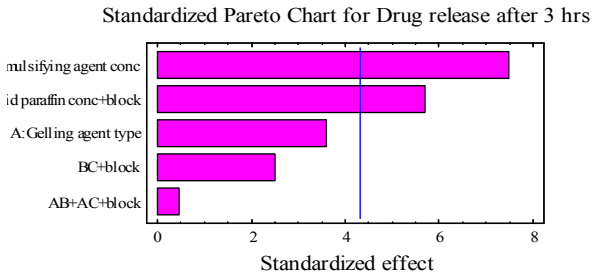
### 3.8. Multifactorial design

Eight Clotrimazole emulgel formulations were prepared according to $2^3$ full factorial designs to optimize the formulation factors and evaluate the main effects. The independent variables were the type of gelling agent ($X_1$), liquid paraffin % ($X_2$) and emulsifying agent % ($X_3$). Two levels of gelling agent type were used carpobol and HPMC, denoted the value -1 and 1in the above design respectively.

Two levels of liquid paraffin concentration were chosen to be 5% and 7.5% denoted -1 and 1 respectively. Finally the emulsifying agent concentration were 1.5 and 2.5 % denoted -1 and 1 respectively.

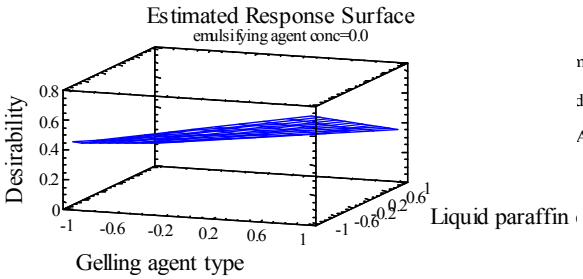
Three – dimensional (3D) plots and standard pareto chart for the drug release (Y1) and antifungal activity (Y2) were drawn using Statgraphics plus design software (version 4.1) is shown in Figure 8 and 9 respectively.

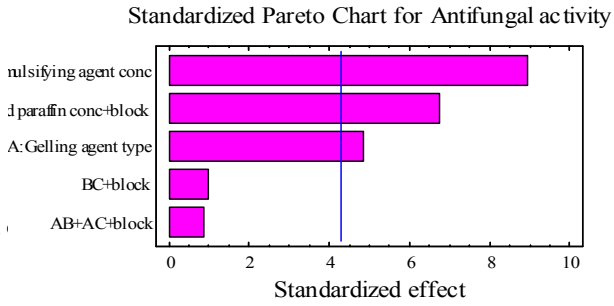



**(Fig.8.a)** **(Fig8.b)**

**Fig (8.a) Response surface plot and Fig (8.b) standard pareto chart showing the effect of X1, X2 and X3 on the drug release after 3 hrs.(Y1)**




**(Fig9.a)** **(Fig.9.b)**

**Fig (9.a) Response surface plot and Fig (9.b) standard pareto chart showing the effect of X1, X2 and X3 on the antifungal activity (Y2)**

X1= Gelling agent type,X2= Liquid paraffin %, X3= Emulsifying agent %

Regression analysis of the data was carried out in statistical analysis system (SAS) by a special cubic model. From ANOVAstudy on the data of Clotrimazole release after 3 hours (Y1) and the antifungal activity (Y2) which is shown in Table 6, the standard error was below 5%, indicating that the observed responses were very close to predicted values. The Durbin-Watson (DW) statistic tests the residual to determine if there is any significant correlation between data, since the DW value is greater than 1.4, there is probably not any serious autocorrelation in the residuals.

**Table6 Summary of results of regression analysis for responses Y1 (drug release after 3 hrs.) and Y2 (antifungal activity)**

| Response | $R^2$ | Adjusted $R^2$ | Standard error | Mean absolute error | Durbin- Watson statistic |
|---|---|---|---|---|---|
| **Drug release after 3 hrs. ($Y_1$)** | 98.18 | 93.62 | 1.37 | 0.627 | 1.7099 |
| **Antifungal activity ($Y_2$)** | 98.69 | 95.41 | 1.71 | 0.837 | 2.23 |

The promising Formulation was selected on the basis of the accepted criteria of both the drug release after 3 hrs. and the drug antifungal activity. From the obtained results, Hydroxypropyl methyl cellulose as a gelling base was used in addition to liquid paraffin in its low level (5%) and emulsifying agent in its high level (7.5%). These criteria was found in formulation F6 as the observed values were very close to the predicted ones as shown in Table 7,

**Table7 Observed and predicted values of the responses for the optimized Clotrimazole formulation (F6)**

| Response | Observed value | Predicted value | Residual |
|---|---|---|---|
| **Drug release after 3 hrs. ($Y_1$)** | 43.22 | 42.87 | 0.35 |
| **Antifungal activity ($Y_2$)** | 57.5 | 56.4 | 1.1 |

## 4. CONCLUSION

From the above results we can conclude that emulgel will be a solution for incorporating hydrophilic drugs in water soluble gel bases. Clotrimazole emulgel formulations prepared using either Carbopol 934 or HPMC 2910 showed acceptable physical properties, pH, drug content, viscosity, antifungal activity and stability. Also the study shows that the use of $2^3$factorial designs is valid in predicting the optimized formulation which found to be HPMC-based emulgel with liquid paraffin in its low level and emulsifying agent in its high level since it shows the highest drug release and antifungal activity.

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