Preparation and Evaluation of Physical and, Rheological Properties of Clotrimazole Emulgel

Yehia I. Khalil*,[1] , Abeer H. Khasraghi* and Entidhar J. Mohammed*

*Department of Pharmaceutics , College of Pharmacy , University of Baghdad , Baghdad , Iraq .

Abstract

Recently, emulgel has emerged as one of the most interesting topical preparations in the field of pharmaceutics. In this research clotrimazole was formulated as topically applied emulgel ; different formulas were prepared. The prepared emulgels were evaluated for their physical appearance , rheological behaviour , and in vitro drug release . The influence of the type of gelling agent (carbopol 934 and methyl cellulose), the concentration of both the emulsifying agent (2% and 4% w/w of mixture of span 20 and tween 20) and the oil phase (5% and 7.5% w/w of liquid paraffin) and the type of oil phase (liquid paraffin and cetyl alcohol), on the drug release from the prepared emulgels was investigated. Commercially available topical canestin® cream was used for comparison. All the prepared emulgels showed acceptable physical properties concerning colour, homogeneity, consistency, and pH value. Rheological studies revealed that all emulgels formulations exhibited a shear – thinning behaviour with thixotropy, indicating structural break down of intermolecular interaction between polymeric chains. Clotrimazole emulgels exhibited higher drug release than canestin® cream. The results of in vitro release showed that methyl cellulose – based emulgel gave better release than carbopol 934 – based one. Also 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, which has a retardation effect, and finally the type of the gelling agent. It was suggested that the clotrimazole emulgel formulation prepared with methyl cellulose, with low concentration of oil phase (5%w/w liquid paraffin) and high concentration of emulsifying agent (4%w/w), showed an optimum formula for highest drug release (74.4% after three hours), which followed higuchi diffusion model with a diffusion-controlled mechanism.

Key words: Emulgel , carbopol , methyl cellulose , clotrimazole

الخلاصة

بزغ المستحلب الجيلاتينى كأحد المستحضرات الصيدلانية المهمة ذات الاستعمال الموضعى. تضمن هذا البحث تحضير مستحلب جيلاتينى لمادة الكلوترايمازول ، حيث تم تحضير عدد من الصيغ المختلفة . كما تم تقييم هذه المستحلبات الجيلاتينية المختلفة من حيث المظهر الفيزياوى ، سلوك الانسيابية ، وتحرر الدواء خارج الجسم . كذلك تمت دراسة تأثير نوع العوامل الجيلاتينية (الكاربوبول ٩٣٤ والمثيل سيليلوز) وتركيز كل من عوامل الاستحلاب (٢٪ و ٤٪ من مزيج سبان ٢٠ و توين ٢٠) والطور الزيتى (٥٪ و٧,٥٪من البرافين السائل) إضافة إلى نوع الطور الزيتي (البرافين السائل و كحول السيتيل) على سرعة تحرر الدواء من المستحلب الجيلاتينى ومقارنتها مع المستحضر التجارى (كريم كانستين) . كافة الصيغ المحضرة للمستحلب الجيلاتينى أظهرت خصائص فيزياوية مقبولة متعلقة باللون ، التجانس ، القوام والأس الهيدروجينى . كما لوحظ ان سرعة تحرر الدواء من كافة صيغ المستحلب الجيلاتينى اكثر من المستحضر التجارى ، كذلك تم الحصول على تحرر افضل للدواء لصيغ المثيل سيليلوز مقارنة مع صيغ الكاربوبول ٩٣٤ . ايضا وجد ان تركيز عوامل الاستحلاب له تأثير ملحوظ على سرعة تحرر الدواء يتبعها تركيز الطور الزيتى ، حيث انه يعمل على اعاقة تحرر الدواء ، واخيرا نوع العامل الجيلاتينى . كذلك وجد ان نوع الطور الزيتى ايضا يؤثر على سرعة تحرر الدواء . يقترح بان الصيغة الدوائية للمستحلب الجيلاتينى المحضرة باستعمال المثيل سيليلوز مع اقل تركيز من الطور الزيتي(٥٪ من البرافين السائل) و اعلى تركيز من عوامل الاستحلاب (٤٪) هي الصيغة المختارة لإعطاء اعلى سرعة لتحرر الدواء (٧٤,٤٪بعد ثلاث ساعات) كما انها تتبع نظرية هيكوجي حيث ان سرعة انتشار الدواء هى الخطوة المحددة لتحرر الدواء.

Introduction

The array of formulations and compositions employed for topical application confounds attempts at categorization . By far majority of commercial dermatologic drug products are formulated in an emulsion (or cream) base. Topical formulations apply a wide spectrum of preparations both cosmetic and dermatological, to their healthy or diseased skin[(1)]. These formulations range in consistency nature from solid through semisolid to liquid. Drug substances are seldom administered alone, but rather as part of a formulation, in combination with one or more adjuvant agents that serve varied and specialized pharmaceutical functions. Drugs are administered topically for their action at the site of application, or for systemic effects[(2)]

[1] Corresponding author E- mail : ybmmaz@yahoo.com
Received : 22/3/ 2011
Accepted : 16/7/2011

Drug absorption through the skin is enhanced if the drug substance is in solution, with a favorable lipid/water partition coefficient, and nonelectrolyte. For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and, as such, are formulated to provide prolonged local contact, with minimal systemic drug absorption. Drugs applied to the skin for their local action include antiseptics, antifungal agents, skin emollients, and protectants[3,4]. Stratum corneum (SC) is the outermost, and least permeable, layer of the skin, it is a formidable barrier for both water transport out of the body and chemical inward permeation. In fact, the majority of drugs do not appear to penetrate the skin at a rate sufficiently high for therapeutic efficacy, and only the most potent once with appropriate physicochemical characteristics is valid candidate for transdermal delivery[5]. skin delivery is an effective for targeting therapy for topical dermatological disorder as in antifungal agents [6]. Several antifungal agents are available on the market in different topical preparations (e.g., creams, ointments, and powders for the purpose of local dermatological therapy). One of these antifungal agents is clotrimazole. Clotrimazole is 1-[(2-chlorophenyl) diphenylmethyl]-1H-imidazole. It has antifungal effect [7,8] .It inhibits growth of pathogenic dermatophytes .It shares with econazole, miconazole, first – choice status for topical treatment of tinea pedis, tinea cruris, and tinea corporis due to any of the a forementional organisms, candidiases due to candida albicans . It is effective for the topical treatment of vulvovaginal and oropharyngeal candidiasis [8-10] . For skin care, and the topical treatment of dermatological diseases, a wide choice of vehicles ranging from solid to semisolids and liquid preparations, is available to physician and patients. Within the major groups of semisolid preparations, the use of transparent emugels has expanded, both in cosmetics and pharmaceuticals. Emulgel or gellified emulsion is stable one and better vehicle for hydrophobic or water insoluble drugs [11]. It is an emulsion either of the oil in water or water in oil type, which are gelled by mixing with a gelling agent [12]. 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 [13,14] . Emulgels have a high patient acceptability since they possess the advantages of both emulsions and gels. Therefore, they have been recently used as vehicles to deliver various drugs to the skin [15-18] . Many emulgels are available such as commercial Voltaren emulgel (Novartis Pharma, Basle, Switzerland), containing diclofenac diethylamine.The aim of this study is to formulate emulgel containing clotrimazole using two types of gelling agent : carpobol 934 and methyl cellulose and study some variables that may affect the formulation such as the type of the gelling agent, concentration of the emulsifying agent ,the concentration and the type of the oil phase on the rheological properties besides to the in vitro release of the drug from the prepared emulgels and comparing all the obtained results with a commercial available formulation (canestin® cream) .

Materials , Equipments and Methods

Materials

Clotrimazole powder , methyl paraben , and propyl paraben were supplied by Samara Drug Industry . Methyl cellulose , cetyl alcohol , ptoassium dihydrogen phosphate , and span 20 from (BDH chemicals Ltd , Poole , England). Carbopol 934 from (J. T. BAKER , Indian). Tween 20 from (Merk – Schuncherdt , Germany) . Liquid paraffin from (Riedel – De Haen AG Seezle , Hannover) . Ethanol and disodium hydrogen phosphate from (Gainland chemical company , factory RO AD , Sandycroft , Deeside , Clwyd – U.K.) . Triethanol amine and propylene glycol from (Searle company Hopkin and Williams , Chadwell health Essex , England) and canestin® cream from Bayer Company. All other reagents were of analytical grade .

Equipments

Sartorius balance (Werke- GMBH , type 2842 , Germany) , electrical mixer (Janke and Kunkel , RF 16) , water bath (Memmert , Germany) , pH –meter (Henna Instruments PH 211 Microprocessor , Italy) , USP dissolution apparatus , type 11 (Copley Scientific TLD , England) , rotational viscometer (Fungilab , Spain) , spectrometer (Specord 40 , Analytikjena , Germany) .

Methods

Preparation of carbopol and methyl cellulose gel

Fifty grams of carpobol gel was prepared by dispersing one gram of carbopol powder in 49grams purified water with aid of moderate speed stirrer (50 rpm) , and then the pH was adjusted to 6 – 6.5 using triethanol amine [19]. Also fifty grams of methyl cellulose gel was prepared by dispersing 3.5 grams of methyl

cellulose powder in 46.5 grams of heated purified water (80 °C) , and the dispersion was cooled to room temperature and left overnight to ensure hydration of the gel [20,21] .

Preparation of emulsion

The general method was employed according to Ansel H.C.et al [22] for preparation of emulsion was as follows : The oil phase was prepared by dissolving certain amount of span 20 in liquid paraffin , while the aqueous phase was prepared by dissolving the required amount of tween 20 in purified water . One gram of clotrimazole powder was dissolved in 2.5 gm of ethanol , while 0.03 gm of methyl paraben and 0.01 gm of propyl paraben were dissolved in 5 gm of propylene glycol and both were mixed with aqueous phase . Both the oily and aqueous phases were separately heated to 70-80° C. Then, the oil phase was added to the aqueous phase with continuous stirring at 50 rpm until cooled to room temperature[22].

Preparation of clotrimazole emulgel

Ten formulas of clotrimazole were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until homogenous emulgel was obtained [21] **,** as Shown in table -1- .

Table 1 : Compositions of different formulas of clotrimazole emulgel (% w/w) .

F	Clotrimazoe	Carbopol 934	Methyl cellulose	Liquid Paraffin	Cetyl alcohol	Span 20	Tween 20	Propylene glycol	Ethanol	Methyl paraben	Propyl paraben	Purified water to
1	1	1		5		1.16	0.84	5	2.5	0.03	0.01	100
2	1	1		7.5		1.16	0.84	5	2.5	0.03	0.01	100
3	1	1		5		2.32	1.68	5	2.5	0.03	0.01	100
4	1	1		7.5		2.32	1.68	5	2.5	0.03	0.01	100
5	1	1			5	0.42	1.58	5	2.5	0.03	0.01	100
6	1		3.5	5		1.16	0.84	5	2.5	0.03	0.01	100
7	1		3.5	7.5		1.16	0.84	5	2.5	0.03	0.01	100
8	1		3.5	5		2.32	1.68	5	2.5	0.03	0.01	100
9	1		3.5	7.5		2.32	1.68	5	2.5	0.03	0.01	100
10	1		3.5		5	0.42	1.58	5	2.5	0.03	0.01	100

Evaluation of Clotrimazole Emulgel

Physical examination

The prepared emulgel formulations were inspected visually for their colour , homogeneity , consistency , appearance , and pH . The pH values of 1% (w/w) aqueous solutions of the prepared emulgels were measured by a pH meter [15].

Rheological study

The viscosity of the different emulgel formulations was measured and rheograms were obtained at 25°C using rotational viscometer . The prepared formulas were sheared with spindle R 7 over the range of speed setting from 2 to 10 rpm with 30 seconds between each 2 successive speeds , and then in a descending order [23] .

In vitro release studies

A glass beaker with 2.5 cm in diameter was filled with 3 gm of each formula and canestin ® cream separately . The mouth of the beaker was covered with a filter paper which was kept in place (sealed) with a rubber band and was inverted and immersed to about 0.5 cm of surface of phosphate buffer[24] (500 ml) of pH 5.5 in a jar of USP dissolution test apparatus with stirring rate of 50 rpm . The study was carried out at 37 ± 0.5 °C . Samples of 5 ml were withdrawn after (15 , 30 , 45 , 60 , 90 , 120 , and 180 minutes) through 0.45 µm Millipore filter paper and replaced with an equal volume of fresh buffer [20] . The drug content in the withdrawn samples was determined spectrophotometrically at λ_{max} 260 nm using a UV spectrophotometer [25] . The commercial product canestin ® cream was used as a reference for drug release from the base .

Data and Statistical Analysis

All data were represented as mean ± SD (n = 3) .Statistical comparisons were made using Student's t - test. The differences were considered to be statistically significant when ($p < 0.05$) .

Results and Discussion

Physical properties

It is clearly evident that, all the prepared clotrimazole emulgel formulations were white viscous creamy preparations with a smooth and homogeneous appearance. The pH values of all prepared formulations ranged from 6.4 ± 0.04 to 6.9 ± 0.04 , which lies with the normal pH range of the skin and is considered acceptable to avoid any irritation upon application to the skin [26] .

Rheological properties

Viscosities (in poise) of clotrimazole emulgel formulations at low and high rates of shear were shown in table -2- . In gel systems, consistency depends on the ratio of solid fraction, which produces structure, to liquid fraction. The difference in the type of the gelling agents result changes in structure consistency [27]. The viscosity of the emulgel formulations generally reflects its consistency [26] .Carbopol 934– based formulations (F_1 , F_2 , F_3 , F_4 , and F_5) possessed considerably higher viscosities than the methyl cellulose – based formulations (F_6 , F_7 , F_8 , F_9 , and F_{10}) , respectively . This effect may be attributed to the higher hygroscopicity of methyl cellulose compared with carbopol 934[28] .So that , the type and the concentration of the base used play an important role in the topical preparation design since it affects the viscosity of the emulgel. Meanwhile incorporation of emulsifying agent and liquid paraffin in different concentration for both types of formulas made of carbopol 934 and methyl cellulose gave marked effect on the consistency of the resulted base as a viscous or softy cream emulgel[29] .

Table 2 : Viscosities (in Poises) of clotrimazole emulgel at low and high rates of shear

Formulas	η max*	η min**
F1	470.15	1445.86
F2	364.14	1105.71
F3	619.28	2888.3
F4	587.48	2558.56
F5	1064.2	4316.11
F6	360.11	1072.65
F7	345.58	998.33
F8	385.63	1137.93
F9	367.84	1194.10
F10	401.68	1226.82

* Viscosity at high rate of shear (12 rpm)
**Viscosity at low rate of shear (2 rpm)

It was seen that increase the concentration of emulsifying agents (tween 20 and span 20) , from 2% w/w to 4% w/w , led to increase in the viscosity of carbopol 934 – based formulations (F_3 , F_4) as compared with (F_1 , F_2) , respectively , at both low and high rate of shear as shown in table -2- .The same effect was resulted in methyl cellulose – based formulations (F_8 , F_9) as compared with (F_6 , F_7) , respectively . These results are in agreement when recombinant human growth hormone [30] and miconazol [20] were formulated using these surfactants. On the other hand increasing liquid paraffin content from 5 to 7.5 % w/w for formulas (F_2 , F_4) at which carbopol was used as a vehicle base and formulas (F_7 , F_9) at which methyl cellulose was used as a vehicle base , revealed a reduction in the viscosity as compared with formulas (F_1 , F_3) and (F_6 , F_8) , respectively , at both low and high rate of share . These results may be attributed to the ability of liquid paraffin to contribute in a formulation of emulsion with water[30] , that make the utilization of span 20 and tween 20 as a surfactants is possible and then decrease the amounts of later surfactants in each previous later formula[31] .Using cetyl alcohol as oil phase instead of liquid paraffin in formulas (F_5 , F_{10}) resulted in an increase in the viscosity as compared with formulas (F_1 , F_6), respectively , so the type of the oil phase also had showed an important role in the topical preparation design. All the prepared emulgel formulations exhibited a shear thinning behaviour 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 [19]. Figures 1 and 2 show the rheograms (shear rate vs. shear stress) of (F_8) and (F_3) respectively, these formulas were chosen for this study since they gave us the highest release of clotrimazole from the emulgel. These figures show that clotrimazole emulgel formulations possessed pseudoplastic flow with thixotropic behaviour, 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 two 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[28, 32]. It is noteworthy that thixotropy is a desirable

characteristic in pharmaceutical preparations in order to deliver an initially thick product as a thinner, easily spreadable material. These findings are in agreement with chloramphenicol emulgel using carbopol 940 as the gel-forming material[15], chlorphenesin emulgel using carbopol 934 and HPMC as gelling agents[19], and miconazole nitrate emulgel using carbomer 941 and SCMC as gelling agents[20] .

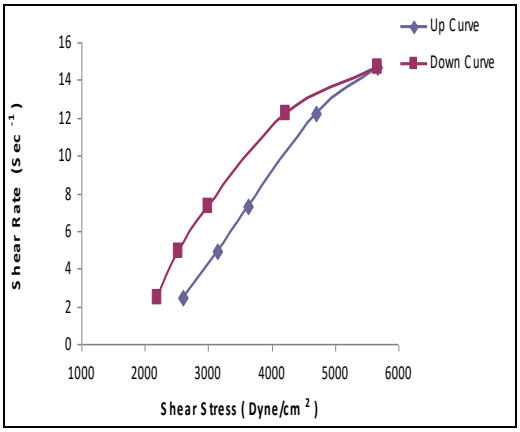

Figure 1 : Rheogram of formula (8) at 25°C (Methyl cellulose gel base) (Mean ± SD , n=3)

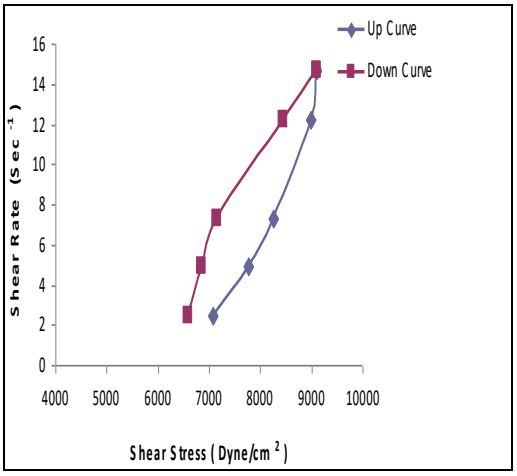

Figure 2 : Rheogram of formula (3) at 25°C (Carbopol 934 gel Base) (Mean ± SD , n=3)

Effect of Polymer Base Type

The effect of gelling agent type on the release of clotrimazole was shown in figure -3- .It was seen that a significant increase ($p<0.05$) in the amount of clotrimazole released after three hours was obtained when 3.5% w/w methyl cellulose used as a base (F_6) instead of 1% w/w carbopol 934 (F_1) . This result may be attributed to the physical structure of the polymer network and shape of three dimension structure of the polymer, since the entrapment of clotrimazole within these structural network revealed high capability of 1% w/w carbopol 934 compared with 3.5% w/w methyl cellulose . In addition, the result may be also due to higher viscosity of the carbopol emulgel compared with methyl cellulose emulgel as shown in table -2-.The same results were obtained for F_7 , F_8 , F_9 , and F_{10} as compared with F_2 , F_3 , F_4 , and F_5 , respectively .These results are in agreement with chlorophenesin[19] , miconazole nitrate[20], and itraconazole[21] emulgel where cellulosic derivative polymer – based formulas gave higher release than carbopol – based formulas . However the choice of appropriate base type and concentration play an important role in the topical preparation design.

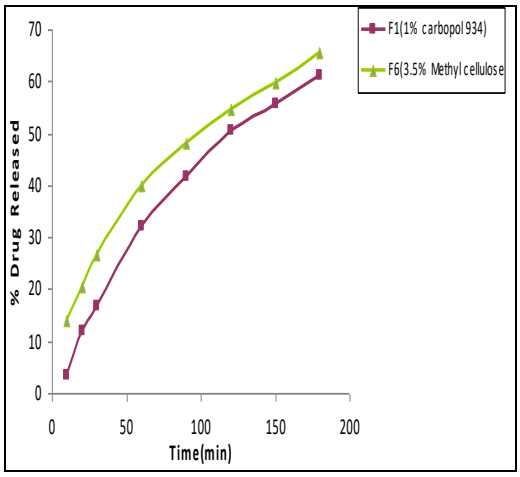

Figure 3: The effect of gel base type on the release profile of clotrimazole 1% w/w at pH 5.5 and 37 °C (Mean ± SD , n=3)

Effect of surfactant added (emulsifying agents) concentration

Tween 20 and span 20 were used as emulsifying agents to produce emulgel formulations, the effect of increasing their concentration on the release of clotrimazole was shown in figure -4- . It was seen that increasing the concentration of emulsifying agent from 2% to 4% led to significant ($p< 0.05$) increase in the amount of clotrimazole released in dissolution medium , as seen in carbopol 934 – based formulas (F_1 , F_3) and methyl cellulose –based formulas (F_6 , F_8).The clotrimazole release was increased from 55.88% (F_1) to 67. 4% (F_3) and from 63.76% (F_6) to 74.4% (F_8) after three hours. This effect may be referred to the ability of these emulsifying agents to lower the interfacial tension between oily and aqueous layer in the dispersion medium [33], indicating an increasing the hydrophilicity of emulgel which in turn increase penetration of dissolution medium into the emulgel structure

and then increasing the amount of clotrimazole released . This result was in consistent with that result obtained when increase the concentration of emulsifying agents from 1.5% to 2.5% in both carbopol and hydroxypropyl methyl cellulose emulgel base led to increase the release of chlorphenesin from topical emulgel [19].Also the results are in aggrement with miconazole nitrate emulgel , when increase the concentration of emulsifying agents from 2% to 4% in both carbomer 941 and SCMC emulgel base led to increase the release of miconazole nitrate from topical emulgel [20] .

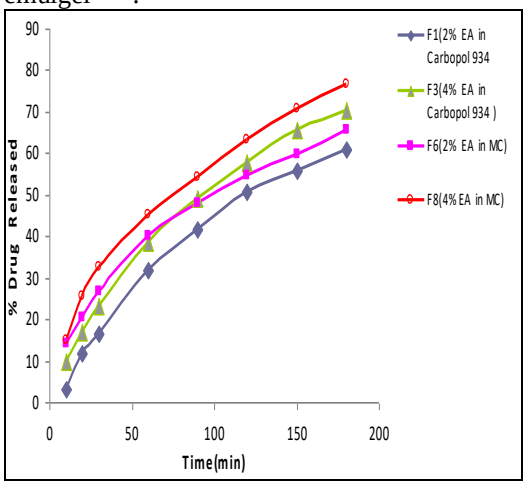

Figure 4 : The effect of emulsifying agents concentration on the release of clotrimazole 1`% w/w at pH 5.5 and 37 °C (Mean ± SD , n=3)

Effect of oil phase concentration

The effect of paraffin concentration on the release of clotrimazole from carbopol 934 emulgel and methyl cellulose emulgel was represented in figure -5- and figure -6- , respectively .Increasing the liquid paraffin concentration from 5% w/w to 7.5% w/w in carbopol 934 – based formulations (F_2 , F_4) and in methyl cellulose - based formulations (F_7 , F_9) , led to significant decrease ($p < 0.05$) in the amount of clotrimazole released from these bases as compared with formulas (F_1 , F_3) and (F_6 , F_8) , respectively. This result may be explained according to the concept of escaping tendency of drugs [34], it was supposed that increasing the thermodynamic activity which can be expressed in terms of relative solubility of drug lead to enhance the releasing of drugs from vehicle[35].The same effect was proved that the increase liquid paraffin led to retardation of miconazole nitrate release from its emulgel formulation[20].

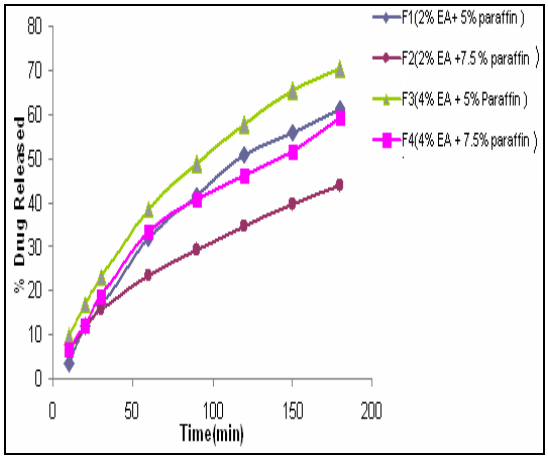

Figure 5 : The effect of paraffin concentration on the release of clotrimazole 1`% w/w from carbopol 934 emulgel at pH 5.5 and 37 °C (Mean ± SD , n=3)

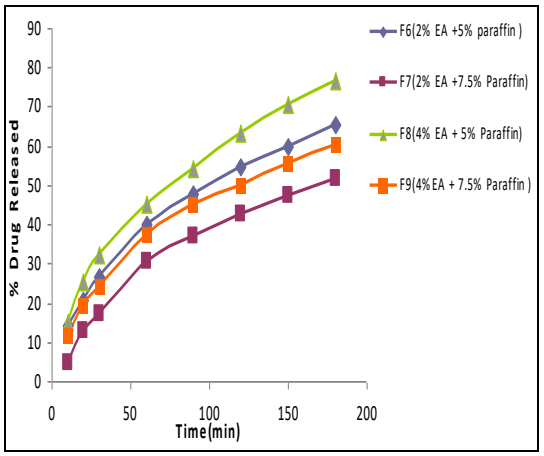

Figure 6 : The effect of paraffin concentration on the release of clotrimazole 1`% w/w from methyl cellulose emulgel at pH 5.5 and 37 °C. (Mean ± SD , n=3)

Effect of type of oil phase

The effect of type of the oil phase on the release of clotrimazole was shown in figure - 7 - .It was observed that using of cetyl alcohol as oil phase in formulas (F_5) and (F_{10}) causing a significant ($p < 0.05$) reduction in the release of clotrimazole as compared with formulas that had been used liquid paraffin (F_1 and F_6) , respectively, whether the gel base was carbopol 934 or methyl cellulose . This may be attributed to the increase in viscosity of emulgel as shown in table - 2 - .The treatment of the obtained data with Higuchi principle revealed that best fit mechanism of clotrimazole 1% w/w release from emulgel with linear relation – ship when the amount of the drug released plotted with square root of time[36] (figure -8-) , as proposed by the Higuchi's theory , indicating the diffusion controlled mechanism of drug release . 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. The rate release constant (K) of clotrimazole from different emulgel formulas was shown in table -3 - , with a correlation coefficient ranging from 0.991 to 0.999 , which means an excellent model fit . The rate release constant (K) of Formulas (F_8 and F_3) was 5.879 and 6.09 %($min^{-1/2}$) respectively, which were the highest rates as compared with that of canestin® cream which was 2.88 %($min^{-1/2}$) .

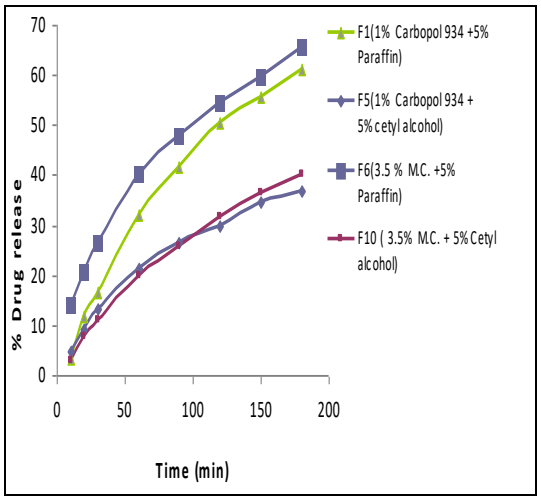

Figure 7 : The effect of oil phase on the release of clotrimazole 1`% w/w from carbopol 934 and methyl cellulose emulgel at pH 5.5 and 37 °C. (Mean ± SD , n=3)

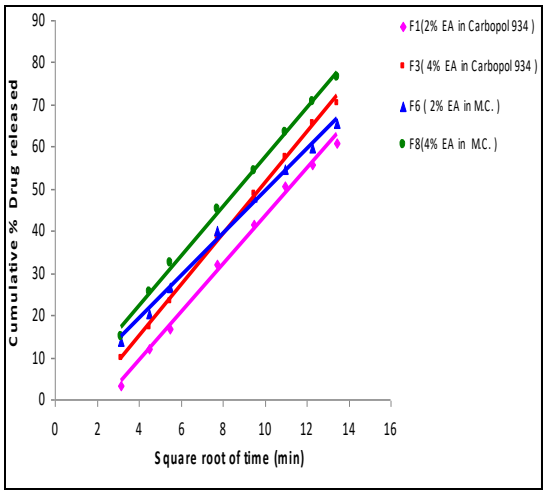

Figure 8 : The effect of emulsifying agents concentration on the release of clotrimazole 1`% w/w from emulgel (Mean ± SD , n=3)

Table 3 : The rate release constant (K) of clotrimazole from different emulgel bases

Formula	K %($min^{-1/2}$)	Correlation coefficient
F1	5.718	0.996
F2	3.575	0.999
F3	6.09	0.998
F4	5.152	0.998
F5	3.154	0.995
F6	5.04	0.996
F7	4.518	0.991
F8	5.879	0.997
F9	4.691	0.998
F10	3.576	0.998
Canestin Cream®	2.88	0.997

Conclusion

- Clotrimazole can be formulated as emulgel with a proper consistency, exhibiting shear-thinning behaviour with thixotropy , and good release which follows Higuchi diffusion model .
- The Factors which affect on the drug release from the emulgel can be arranged as follows: The emulsifying agent concentration > oil phase concentration and type > the gelling agent type .
- Methyl cellulose – based emulgel showed highest drug release when 5% w/w liquid paraffin and 4% w/w emulsifying agents were used and it is the formula of choice .

References

1. Lawrence H. Block. Medicated Topicals, Ch. 44 in Remington , The science and practice of pharmacy 21st Edition, Lippincott Williams and Wikins , A wolters Kluwer Company Philadelphia, New York, London ,copyright 2006 , p.879-883 .
2. Rashmi M. Topical gel: A review august vol. 2008; available from http:// www.pharmainfo.com.
3. Sharma S. Topical preparations are used for the localized effects at the site of their application by virtue of drug penetration into the underlying layers of skin or mucous membranes. Pharmaceutical reviews 2008; 6:1- 10.
4. Laithy HM. and El. shaboury KMF. The development of Cutina Lipogels and gel microemulsion for topical administration of fluconazole. Ame Pharm Sci. PharmSciTech. 2003; 3: 10 - 25.
5. Carmelo Puglia, Francesco Bonina, Giuseppe Trapani, Massimo Franco,

Maurizio Ricci. Intl J. Pharm. 2001; 228:79-87.

6. Salama M., Ghazy F., Bosela A., Ismail A., In vitro and clinical evaluation of chlorphensin polymeric films, Alex.J.Pharm.Sci (1997), 11 (2), 59-64.

7. British Pharmacopoeia, vol.1 , 2010 , p 552.

8. Steven P. Gelone. Anti-infectives, Ch. 90 in Remington, The science and practice of pharmacy 21st Edition, Lippincott Williams and Wikins , A wolters Kluwer Company Philadelphia, New York, London , copyright 2006, p.1670-1671.

9. The Merk Index, fourteenth edition. An encyclophedi of Chemicals, Drugs , and Biologicals. Maryadele J .O, Neil, Editor Mreck and co., INC. White house station, NJ, USA. 2006, 2417

10. Martindale, The complete Drug reference , Thirty-sixth edition. Edited by Sean C Sweetman BPharm , FRPharmS. Published by the Pharmaceutical Press 2009 P. 530.1

11. Guido S, Fred V, Martien A, Cohen S, George A. Oil droplet release from emulsion filled gels in relation to sensory perception. Food hydrocolloids 2007; 21: 977-985.

12. Hideaki T and Yuya K. Preparation of poly (N-isopropyl acryl amide) emulsion gels and their drug release behaviours. Coll. and surf. B: Bioinformatics 2008; 67:92-98.

13. Lachman L. and Lieberman Ha .The Theory and Practice of Industrial Pharmacy. Special Indian edition 2009; p.503.

14. Chojnicka A, Sala G, Cornelus G. The interaction between oil droplets and gel matrix affect the lubrication properties of sheared emulsion filled gels. Food hydrocolloids 2009; 23:1038-1046.

15. Abd El-Bary A, Shalaby S, Abd El-Aal S. Formulation and stability of chloramphenicol gel and emulgel. Bull Fac Pharm. 2001; 39:89-99.

16. Hamed M.R., Metwally S.A., El-Shafey A., Geneidi A.S, Comparative percutaneous absorption of diclofenac emulgel preparations in normal volunteers, J. Drug. Res (1994), 21(1-2), 133-141.

17. Hamza YE, Molokhia AM, Soliman II, Ahmed FH, Soliman NA. Formulation and evaluation of topical preparations containing phenol and local vesicants. Az J Pharm Sci. 2002; 29:412-432.

18. Ozguney S.I., Karasulu Y.H., Kantarci G., Transdermal delivery of diclofenac sodium through rat skin from various formulations, AAPS Pharm.Sci.Tech. (2006), 7 (4), article 88.

19. Magdy I., Mohamed, Optimization of Chlorophenesin Emulgel Formulation, The AAPS . J, 2004; 6 (3) Article 26. Lubna A.S., Hala T.S., and Yehia I.K., An Investigation Release and Rheological Properties of Miconazole Nitrate from Emulgel. Iraqi J. Pharm. Sci , vol. 18 (2) 2009: 26-31

20. Piyusha D., Ankur J., Naveen V.,Hemant K., Sanjay J., Gellified emulsion for sustain delivery of Itraconazole for topical fungal diseases. International Journal of Pharmacy and Pharmaceutical Sciences, vol. 2 , Issue 1 , 2010 .

21. Howard C. A. , Loyd V., Allen J.R. , Nicholns G.P., Lippincot Williams & Wilkins ,Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems , Eighth Edition ,Copyright (2005) , p 404-423 .

22. Masar B.M., Formulation and evaluation of meloxicam as a topical preparation, thesis, college of pharmacy, University of Baghdad, 2004.

23. British Pharmacopoeia ,vol. iv , 2008 ,Appendix I D , A 143 .

24. CLARCK'S ISOLATION AND IDENTIFICATION OF DRUGS in pharmaceuticals, body fluids, and post-mortem material. Second Edition, Senior Consulting Editor A. C. Moffat. London, the pharmaceutical press 1986, p 487

25. Malay K., Das and Abdul B.A., Formulation and Ex Vivo Evaluation of Rofecoxib Gel for Topical Application , Acta poloniae- Drug Research , vol. 63 No. 5 pp. 461-467 , 2007 .

26. Martin's Physical Pharmacy and Pharmaceutical Sciences, Fifth edition, Copyright 2006, Lippincott Williams & Wilkins, pp. 565-569 .

27. Danester Q., Evone S. G., Formulation and characterization of nystatin gel. PRHSJ. March 2008 vol. 27 No.1. p. 61-67.

28. Wan LSC, Viscosity change in salicylic acid-cetrimide system by surfactants, J.Pharm.Sci. (1973), 62 (Jan), 142-144.

29. Ban N.B., Cleland J.L., Yang J., Manning M.C., et-al, Tween protects recombinant human growth hormone against agitation-induced damage via hydrophobic interactions, J. Pharm.Sci (1998), 87 (Dec), 1554-1559.

30. Eros I., Ugri-Hunyadvari H., Investigation of the rheological characteristic of ointment gels containing

emulsifier and emulsion type ointments, Cosmetics and Toiletries (1979), 94(Oct), 67-70.

31. Klich CM. Jels and Jellies. In: Swarbrick J, Boylan JC, eds. Encyclopedia of Pharmaceutical Technology. vol. 6. New York, NY: Marcel Dekker Inc; 1992:415-439 .

32. Sheikh N., Faiyaz S., Sushma T., Javed A.,et al, Formulation development and optimization using nanoemulsion technique: a technical note, AASP Pharm.Sci.Tech. (2007), 8 (2), article 28.

33. Higuchi T., In vitro drug release from ointment and creams; dermal and transdermal absorption, Stuttgart, Germany; Wissenschaftliche Veriagsgesellschaft (1982), 90-100 .

34. Raghavan S.L., Trividic A., Davis A.F., Hadgraft J., Effect of cellulose polymer on supersaturation and in vitro membrane transport of hydrocortisone acetate, International Journal of Pharmaceutics (2000), 193, 231-237.

35. Higuchi WI., Analysis of data on the medicament release from ointment, J.Pharm.Sci. (1962), 51, 802-804.