An Investigation Release and Rheological Properties of Miconazole Nitrate from Emulgel
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Abstract
In this study miconazole nitrate was formulated as topically applied emulgel; different formulas were prepared using sodium carboxymethylcellulose (SCMC) and carboxypolymethylene (carbomer 941) as gelling agents. The influence of type of gelling agent and concentration of both oil phase and emulsifying agent on drug release was studied and compared with commercially available miconazole nitrate cream (Mecozalen®). The results of in vitro release showed that SCMC emulgel bases gave better release than carbomer 941 bases and the release of drug increase from both bases as a function of increasing the concentration of emulsiyfying agent. The oil phase had retardation effect when its concentration increased. The formula which showed the highest drug release was chosen to evaluate its rheology and its stability. The rheological behavior of selected formula showed share-thinning flow indicating structural break down of intermolecular interaction between polymeric chains. Moreover, the expiration date of the selected emulgel was found to be 1.7 year as well as their physical properties like, color, pH and consistency remains constant along storage time.

Keywords: emulgel, carbomer, miconazole nitrate, carboxymethyl cellulose.

Introduction
Dermal drug delivery offer many important advantages to overcome many problems associated with drug (1). Moreover this type of drug delivery is easy, painless and simple to terminate therapy if any adverse or undesired effects occur(2, 3) . Skin delivery is an effective for targeting therapy for topical dermatological disorder as in antifungal agents (4). Emulsification as a physical process is widely used in pharmaceutical and cosmetic products for external use, since they are spread easily over affected area, Mean while, the viscosity, appearance and degree of greasiness can be controlled by the formulator (5). Currently the great attention is devoted to the gels especially hydrogels formulation since they have an attractive appearance and develop pleasant cool feeling. They are easy to apply and remove (6) and generally provide faster drug release compared with ointment and cream (2). Emulgel is emulsions either of oil-in-water or water-in-oil type, which are gelled by mixing with gelling agent. They have the advantages of both emulsions and gels. They have been recently used as vehicle to deliver various drugs to the skin (7, 8) . The validity of miconazole nitrate in treatment of fungal infections is well known. Miconazole nitrate is used topically in management of fungal infections. Clinical studies have shown that miconazole nitrate is effective for topically treatment of dermatophytes, superficial mycoses, cutaneous candidiasis and mixed infections when applied twice daily (9). The objective of this study is to formulate emulgel containing miconazole nitrate using two type of gelling agent, beside to that, determine the in vitro release of the drug from these bases, and investigation the influence of emulsiyfying agent, oil phase concentration on drug release, along with evaluation the rheological behavior of the prepared formulas.

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Materials and methods

Materials

Miconazole nitrate powder kindly supplied by AL - Safa factory, Carboxypolymethylene (carbomer 941) from (Goodrich, USA), Sodium carboxymethylcellulose (SCMC) from (BDH chemicals Ltd, Poole, England), Sodium hydroxide (Fluka AG, Puriss.p.a, Switzerland), Tween 20, Propylene glycol, Span 20 from (Merk-schuncherdt, Germany), Liquid paraffin (Riedel-De Haen AG Seelze, Hannover), Citric acid, Methylparaben, Propylparaben from (Samara Drug Industries), All other reagents were of analytical grade.

Equipment

Sartorius balance (Werke-GMBH, type 2842, Germany), Electrical mixer (Janke and Kunkel, RF16), Water bath (Memmert, Germany), pH-meter (Hanna Instruments pH 211 Microprocessor, Italy), USP dissolution apparatus, Type II (Copley Scientific TLD, England), rotational viscometer (Fungilab, Spain), Spectrometer (Specord 40, Analytikjena, Germany), HPLC (Waters, USA).

Methods

Preparation of Carbomer and SCMC Gel

Fifty grams of the carbomer gel was prepared by dispersing one gram of carbomer powder in 50 ml purified water with aid of moderate speed stirrer (50 rpm), and then the pH was adjusted to 6-6.5 using 0.5N of sodium hydroxide. While fifty grams of SCMC gel was prepared by dispersing 2.5 grams of SCMC powder in 50 ml of heated purified water, and the dispersion was cooled to room temperature and left overnight.

Preparation of emulsion

The general method was employed according to Ansel H.C. et al (5) for preparation of an emulsion was as follows: The oil phase was prepared by dissolving 1.66 g of Span 20 in liquid paraffin while the aqueous phase was prepared by dissolving 0.34 g of Tween 20 in purified water. Two grams of miconazole nitrate was dissolved in 2.5 g of ethanol, while 0.15 g of methylparaben and 0.05 g of propylparaben 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 500 rpm until cooled to room temperature.

Formulation of miconazole nitrate emulgel

Eight formulas of miconazole nitrate were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until get homogenous emulgel as shown in table 1.

<table>
<thead>
<tr>
<th>F</th>
<th>Miconazole nitrate</th>
<th>Carbomer 941</th>
<th>SCMC</th>
<th>Liquid paraffin</th>
<th>Span 20</th>
<th>Tween 20</th>
<th>Propylene glycol</th>
<th>water</th>
<th>observation</th>
<th>pH</th>
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<tr>
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<td>2</td>
<td>1</td>
<td>5</td>
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<td>0.34</td>
<td>5</td>
<td>100</td>
<td>white viscous cream</td>
<td>6.5</td>
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</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2.5</td>
<td>5</td>
<td>1.66</td>
<td>0.34</td>
<td>5</td>
<td>100</td>
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<td>6.2</td>
<td></td>
</tr>
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<td>3</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3.32</td>
<td>0.68</td>
<td>5</td>
<td>100</td>
<td>white viscous cream</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2.5</td>
<td>5</td>
<td>3.32</td>
<td>0.68</td>
<td>5</td>
<td>100</td>
<td>white softy cream</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>7.5</td>
<td>1.66</td>
<td>0.34</td>
<td>5</td>
<td>100</td>
<td>white viscous cream</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2.5</td>
<td>7.5</td>
<td>1.66</td>
<td>0.34</td>
<td>5</td>
<td>100</td>
<td>white softy cream</td>
<td>6.1</td>
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</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1</td>
<td>7.5</td>
<td>3.32</td>
<td>0.68</td>
<td>5</td>
<td>100</td>
<td>white viscous cream</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
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<td>2.5</td>
<td>7.5</td>
<td>3.32</td>
<td>0.68</td>
<td>5</td>
<td>100</td>
<td>white softy cream</td>
<td>6.2</td>
<td></td>
</tr>
</tbody>
</table>

Evaluation of miconazole nitrate emulgel

drug released

Glassy beaker with 2.5 cm in diameter was filled with 3 g of each formula and Mecolzencream. The mouth of beaker was covered with a filter paper which was kept in place with rubber band and was inverted and immersed to about 0.5 cm of surface of citrate buffer pH 5.5 in a jar of 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 0.45µm millipore filter paper and replaced with an equal volume of fresh buffer. The samples were then analyzed spectrophotometrically at λ max 272 nm.

Rheological studies

Rheograms were obtained at 37°C using rotational viscometer. The prepared formulas were sheared with spindle R7 over the range of speed setting from 1 to 10 rpm with 30 seconds between each 2 successive speeds, and then in a descending order.
**Physical properties**

The physical properties (color, odor, pH and appearance) of the selected formula (F4) was observed over the period of (4) months storage at (35°C) and at refrigerator temperature (4°C). The drug content was calculated using HPLC method (12) to predicate the expiration date. The pH of emulgel was also measured by shaking up of one gram of emulgel with 100 ml of water.

**Result and Discussion**

**Formulation of miconazole nitrate emulgel**

One of the most challenges that appear in the formulation of drug as a topical preparation is the choice of the type of base used, so the choice of appropriate base type and concentration play an important role in the topical preparation design. The present study revealed that different formulas were succeeded in incorporation of miconazole nitrate 2% w/w in different bases as shown in table1. It was seen that using of carbomer 941 1% w/w as vehicle base for (formulas 1, 3, 5 and 7) gave white viscous cream compared with white soft cream resulted when sodium carboxymethylcellulose (SCMC) used as vehicle base for (formulas 2, 4, 6 and 8). This effect may be attributed to the higher hygroscopicity of SCMC compared with carbomer (13). Meanwhile incorporation of emulsifying agent and liquid paraffin in different concentration for both types of formulas made of carbomer 941 and SCMC gave marked effect on the consistency of the resulted base as a viscous or softy cream emulgel (14), the later effect is well revealed when the viscosities of all formulas were determined as shown in table 2.

**Table 2: Viscosities (in poises) of Miconazole Nitrate Emulgel At Low and High Rates of Shear.**

<table>
<thead>
<tr>
<th>Formulas</th>
<th>η max *</th>
<th>η min **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula 1</td>
<td>752.5</td>
<td>6306.46</td>
</tr>
<tr>
<td>Formula 2</td>
<td>251.25</td>
<td>877.28</td>
</tr>
<tr>
<td>Formula 3</td>
<td>873.67</td>
<td>8305.02</td>
</tr>
<tr>
<td>Formula 4</td>
<td>494.63</td>
<td>2585</td>
</tr>
<tr>
<td>Formula 5</td>
<td>986.32</td>
<td>6589.57</td>
</tr>
<tr>
<td>Formula 6</td>
<td>615.9</td>
<td>3301.18</td>
</tr>
<tr>
<td>Formula 7</td>
<td>517</td>
<td>3367.65</td>
</tr>
<tr>
<td>Formula 8</td>
<td>410.39</td>
<td>2460.08</td>
</tr>
</tbody>
</table>

* Viscosity at high rate of shear (10 rpm).
** Viscosity at low rate of shear (1 rpm).

It was seen that both Span 20 and Tween20 increase the viscosity of formulas 1, 3 and 5 in which carbomer 941 used as abase, moreover the same effect was resulted in formulas 2, 4 and 6 when SCMC used as a base. This effect is a consistent with the results obtained by Wan L. et.al and Ban N.B. et.al (14, 15). On the other hand, increasing liquid paraffin content from 5 to 7.5 % w/w for formulas (5, 7) and formulas (6,8) at which carbomer 941 and SCMC were used as a vehicle base, respectively, revealed a reduction in the viscosities at both low and high rate of shear, this result may be attributed to the ability of liquid paraffin to contribute in a formation of emulsion with water (15), 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 (16).

**Drug released**

**Effect of gel base type**

Figure -1- illustrates the effect of gelling agent type on release of miconazole nitrate from formulas 1 and 2, it was seen that two folds higher percent release of miconazole nitrate after 3 hours of release from emulgel when 2.5%w/w SCMC used as a base in stead of 1% w/w carbomer. This result may be attributed to physical structure of the polymer network and shape of three dimension structure of the polymer, since the entrapment of miconazole nitrate within these structural network revealed high capability of 1% w/w carbomer941 compared with 2.5% w/w SCMC. The same results were obtained when fluconazole was incorporated as a topical lipogel formulation using different type of Cutina as gelling agent. They found that the kind of gelling agent have marked effect on release and flow properties of fluconazole (17).in addition, the result may be also due to higher viscosity of the carbomer emulgel compared with SCMC as shown in table -2-.

![Figure 1: The effect of gel base type on the release profile of miconazole nitrate 2 % w/w at pH 5.5 and 37 °C](image-url)
**Effect of emulsifying agent concentration**

The effect of addition of Span 20 and Tween 20 as an emulsifying agent to produce emulgel structure is illustrate in figure -2-. It was seen that increasing the concentration of emulsifying agent from 2% w/w to 4% w/w using carbomer 941(formula 1,3) and SCMC (formula 2,4) as a gel base led to significant (P<0.05) increase in the amount of miconazole nitrate released in dissolution medium. This increasing was found to be 39% and 37.5% for both SCMC and carbomer 941, respectively, compared with 27.5% and 15.8%. 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 \(^{(18)}\), 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 miconazole nitrate 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 \(^{(19)}\).

**Effect of oil phase concentration**

In an attempt to investigate the effect of oil phase concentration, when liquid paraffin was increased from 5% w/w to 7.5% w/w in formulas 5 and 6 showed significant (P<0.05) decrease in the amount of miconazole nitrate released from these bases, as shown in figure 3. This result may be explain according to the concept of escaping tendency of drugs \(^{(20)}\), 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\(^{(21)}\), the same effect was obtained by El-Bary who proved that the increase liquid paraffin led to retardation of chloramphenicol release from its emulgel formulation \(^{(21)}\). On other hand, increase the emulsifying concentration with 7.5% w/w liquid paraffin as in formulas 7 and 8 showed significant (P<0.05) increase in release of miconazole nitrate as shown in figure 4. The treatment of obtained data with Higuchi principle revealed that best fit mechanism of miconazole nitrate 2% w/w release from emulgel with linear relationship when the amount of drug released plotted with square root of time\(^{(22)}\) as shown in figure 5. The later result of formula 4 was found to be pharmaceutically bioequivalent with the reference one Mecozalen cream \(^{(6)}\) as shown in table 3.

![Figure 2](image1.png)
**Figure 2**: The effect of emulsifying agents concentration on release of miconazole nitrate 2% w/w at pH 5.5 and 37 °C.

![Figure 3](image2.png)
**Figure 3**: The effect of paraffin concentration on the release of miconazole nitrate 2% w/w from carbomer 941 emulgel at pH 5.5 and 37 °C.

![Figure 4](image3.png)
**Figure 4**: The effect of paraffin concentration on the release of miconazole nitrate 2% w/w from SCMC emulgel at pH 5.5 and 37 °C.

![Figure 5](image4.png)
**Figure 5**: The effect of emulsifying agent concentration on release of miconazole nitrate 2% w/w from emulgel.
Table 3: The rate release constant (K) of miconazole nitrate from different emulgel bases.

<table>
<thead>
<tr>
<th>Formulas</th>
<th>K (mg. min⁻²/ ml⁻¹)</th>
<th>Correlation coefficient (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula 1</td>
<td>0.0018</td>
<td>0.986</td>
</tr>
<tr>
<td>Formula 2</td>
<td>0.0031</td>
<td>0.993</td>
</tr>
<tr>
<td>Formula 3</td>
<td>0.004</td>
<td>0.986</td>
</tr>
<tr>
<td>Formula 4</td>
<td>0.0038</td>
<td>0.992</td>
</tr>
<tr>
<td>Formula 5</td>
<td>0.0012</td>
<td>0.998</td>
</tr>
<tr>
<td>Formula 6</td>
<td>0.0015</td>
<td>0.999</td>
</tr>
<tr>
<td>Formula 7</td>
<td>0.0014</td>
<td>0.998</td>
</tr>
<tr>
<td>Formula 8</td>
<td>0.0022</td>
<td>0.992</td>
</tr>
<tr>
<td>Mecozalen™ cream</td>
<td>0.0019</td>
<td>0.988</td>
</tr>
</tbody>
</table>

Rheological properties of prepared gel

In gel systems, consistency depends on the ratio of solid fraction, which produces structure, to liquid fraction. The difference in the kind of the gelling agents result changes in structure consistency (25). The selected emulgel formula F4 demonstrates pseudoplastic flow with thixotropy (figures 6). The profiles showed that as share stress is increased, the normally arranged molecules align their long axes in direction of flow orientation reduce the internal resistance of material and hence decrease viscosity (24). The presence of hysteresis loop indicated breakdown in structure occurred.

Figure 6: Rheogram of formula 4 at 37°C (SCMC gel base).

Physical properties

Stability of prepared emulgel (effect of storage time)

The selected miconazole nitrate emulgel, formula 4 was white creamy with homogenous appearance, no change in color and odor after 4 months of storage at refrigerator at 4°C and at 35°C. Figure 7 show the degradation curve of miconazole nitrate of formula 4, from which the degradation rate constants was calculated from the slopes of straight lines. They was found to be 1.73 x 10⁻⁴ and 1.64 x 10⁻⁴ (day⁻¹) after storage for 4 months at 4°C and 7 months at 35°C, respectively. Arrhenius plot was constructed as shown in figure 8 and rate constant at 25°C was obtained. The expiration date of formula 4 was found 1.7 years; with estimated pH value about 5.9.

Figure 7: Degradation rate constant of formula 4 of miconazole nitrate 2% w/w at 35°C and 4°C.

Figure 8: Arrhenius plot for expiration date estimation of miconazole nitrate Emulgel (formula 4).

Conclusion

Miconazole nitrate can be formulated as emulgel with good release and consistency. Emulsifying agent has pronounced effect on drug release from emulgel followed by the oil phase concentration and finally the type of gelling agent. The SCMC 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. The incorporation of gelling agent gives emulgel a proper consistency and exhibit shear-thinning behavior with thixotropy.
References:
10. Salmo H.M., Investigation the effect of different concentrations of carbomer and co-solvent propylene glycol on the releasing process of tinidazole from vaginal aqueous gel, Al-mustansyria journal of pharmaceutical sciences (2006), 3 (1), 75-85.