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FORMULATION AND EVALUATION OF TOPICAL ITRACONAZOLE EMULGEL

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ABSTRACT

Itraconazole is one of the important orally and topically triazole antifungal drugs which is extreme example of class II biopharmaceutical classification system and has side effects such as nausea, vomiting, hypokalemia, rash and other side effects when its taken orally. The drug was prepared as emulgel which has emerged as one of the most interesting way to deliver hydrophobic drug topically as it has dual release control system i.e., emulsion and gel. The prepared formulations were evaluated on basis of pH, spreadability, drug content, and *In vitro* release, *In vitro* antifungal activity, Skin irritation studies on rat and rheological behavior was also performed to the selected formula which gave the maximum release (95.3%) in 6 hours. The result of *In vitro* antifungal compared with marketed clotrimazole cream (1%), shows a wider zone of inhibition for the itraconazole emulgel as compared with marketed cream. While the result of irritation test showed no edema and erythema and demonstrated shear thinning thixotropic behavior. Hence it can be concluded that emulgel based system is more effective and safe system for delivery of antifungal agents.

Key Words: - Itraconazole, Emulgel, Carbopol 971P NF, Topical drug delivery.

INTRODUCTION

Topical administration of therapeutic agents offers many advantages than oral and intravenous administration (Muzib Y *et al.*, 2012). It is not only the application of drug on the skin, but it's also the localization of drug anywhere in the body through ophthalmic, rectal and vaginal topical routes. It is applied on a broad spectrum of preparations for both cosmetic and dermatological to their healthy or diseased skin (Panwar A *et al.*, 2011).

Topical drug delivery is an attention-grabbing route for local, regional and systemic treatment (Mikari B *et al.*, 2010). The topical formulations are more valuable, less noxious than the conservative dosage forms (Loveleen P *et al.*, 2013).

Emulgel, between emulsion and gel in order to win the advantages of both in favor of TDDS and to eliminate the limitation of the hydrogel in delivering hydrophobic (class II) drugs (Sai S *et al.*, 2015). Itraconazole is an effective broad-spectrum synthetic triazole antifungal drug with activity against histoplasmosis, blastomycosis and onychomycosis (Gamal M *et al.*, 2009). Itraconazole is arelatively well- permeable drug, and it has a low solubility and a low dissolution rate, which are limiting factors for its absorption rate (classII) (British Pharmacopia., 2009). The aim of this work is to formulate emulgel which is suitable to deliver itraconazole as an extreme example of lipophilic drug to get benefit from its local action of the fungal diseases

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MATERIAL AND METHOD

Materials

Itraconazole powder (Provizer pharma), Liquid paraffin (Solvochem, UK), Olive oil (Solvochem, UK),

(Span 20, Span 80, Tween 80, Tween 20) (Merck Germany), Propylene glycol (Avonchem, UK), (propyl paraben, methyl paraben) (Gain land Chemical Community UK), Chitosan (HIMEDIA, India) (Carbopol 940, Carbopol 934) (HIMEDIA, India), Carbopol 971P NF (Provizer pharma) Triethanolamine (Hopkins and Williams Ltd England), Acetic acid (Merk Germany), Sodium metabisulfite (HIMEDIA, India) .

Methods

Preparation of emulsion

The oil and aqueous phases were prepared separately as follows, the oil phase was prepared by dissolving certain amount of span in the oil while the aqueous phase was prepared by dissolving the needed quantity of tween in the purified water ,the quantity of surfactants used according to HLB theory. One gm of ITZ dissolved in the oil phase and sonicated for 30 min then triturated by mortar and pestle. The propyl paraben and methyl paraben added to propylene glycol. The last solution mixed with aqueous phase, and antioxidants added to the aqueous phase in case of natural oil then sonicated for 30 min. The oil and aqueous phases heated by hot plate magnetic stirrer to 70°C and 80°C respectively then the oil phase added to aqueous phase with continuous stirring at (50 rpm) until cooled near room temperature, left for 24 hr to ensure the steadiness of the emulsion, then mixed with gel to get the emulgel (Reiger MM. *editors.*, 1986), table (1).

CHARACTERIZATION AND EVALUATION OF ITRACONAZOLE EMULGEL FORMULAS

Physical appearance

The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation (Swapnil S *et al.*, 2014).

pH determination:

The pH of the prepared emulgel was measured using pH-meter by putting the tip of the electrode into the emulgel without dilution and after (2 min) the result was recorded, (n = 3) (Ahmad F *et al.*, 2008).

Spreadability (spreading coefficient):

A sample of (0.5 gm) of each formula was pressed between 2 slides with 500g weight and left for about (5 min) where no more spreading was expected. Diameters of spread circles were measured in cm and compared with initial circle diameter (diameter of the spread circle –initial diameter), (n = 3) (El-Houssieny B *et al.*, 2010), (Doaa A *et al.*, 2012).

Determination of ITZ content in the emulgel formulas

ITZ content in the emulgel was determined by taking 0.5gm of the prepared emulgel which is equivalent to (5 mg) of ITZ and transferred to (100 ml) volumetric flask containing absolute ethanol then sonicated and filtered through a filter (0.45 μ m, millipore), then suitably diluted and analyzed at λ max of ITZ. The content of ITZ was determined by using uv-visible spectrophotometer at λ max of ITZ (263nm) against blank (Saleem M *et al.*, 2010).

Rheological study

The viscosity of emulgel formulas was determined by using Myr Rotational (cup and bob) digital viscometer with spindle no. R7 with an optimum speeds 2, 3, 4, 5, 6, 10, 12, 20, 30 and 50 rpm at room temperature (Doaa A *et al.*, 2012).

In vitro dissolution test of ITZ emulgel

In vitro release of ITZ from emulgel formulas was performed by modified method using dissolution apparatus-II (paddle type). A weighing quantity of a emulgel (0.5) gm that contain 5mg of ITZ was uniformly spread on the cellulose nitrate filter then fixed on the mouth of inverted glass tube and fixed around the paddle of the apparatus and immersed in the dissolution jar filled with 900ml of freshly prepared dissolution media (phosphate buffer pH 5.5 with 1% Brij 35) at 32 \pm 0.5°C (Prakash B. *et al.*, 2014), (Parmpreet S, *et al.*, 2014). The surface of glass tube was about 0.5cm under the surface of the media , and rotated at speed of 100 rpm, samples of 5 ml were withdrawn at intervals of 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 minutes and were replaced with equal volume of the fresh buffer solution each time to maintain constant volume to keep the sink condition. The samples were filtered through a filter (0.45 μ m, millipore) and analyzed at λ max of ITZ using a double-beam UV-visible spectrophotometer. The drug release experiments were conducted in triplicate (n = 3) (Prakash B. *et al.*, 2014), (Parmpreet S, *et al.*, 2014).

Rheological behavior

After selection the best formula which gave the highest percentage of release, shear rate was drawn vs. shear stress to know the rheological behavior, which is very essential to know it in the topical semisolid dosage form (Parmpreet S, *et al.*, 2014).

Skin irritation study

The preparation is applied on the properly shaven skin of rat and its adverse effects like change in

color, change in skin morphology should be checked after (24 hr) (Sunny K *et al.*, 2014).

In vitro Antifungal activity:

In vitro antifungal activity of ITZ of the optimized formula was carried out using *Candida albicans* as representative fungi, adopting the cup – plate method. Marketed clotrimazole cream (OPIZOLE 1% cream) was taken as a reference standard. Clotrimazole is a well known effective antifungal drug and it is available as a topical formulation. Suspension of *Candida albicans* was inoculated in sabouraud dextrose agar medium and then decanted into the sterile petridish and allowed to solidify for 15 min. Wells were done in plate using borer and the formulations were poured into wells. These plates were incubated at 37°C for 24 hr; the inhibition zone diameter around each well was measured using a ruler, (n=5) (Chinmaya *et al.*, 2013), (Manisha K *et al.*, 2013).

RESULTS

Physical appearance

It is obviously that the liquid paraffin emulgel prepared formulas are generally white creamy but ranged from viscous to soft ones according to the constancy of the gel base. Chitosan gave formulations more viscous than that of C940 and the last more viscous than C934, C971P NF with smooth and homogenous appearance ie, no phase separation, and the same thing with olive oil formulas except the color incline to more yellowing (Yehia I. *et al.*, 2011).

pH determination

The pH of the formulas ranged from 5.5 to 6.7 and this matched with skin requirements for topical preparations to avoid skin irritation, except (F4, F12) which were formulated with chitosan. These results explained by the chemistry of the constituents of the formulas, in case of carbopol emulgel the reasonable pH caused by neutralization of the formulas by TEA (Rowe R. *editors.*, 2009), while the pH of the formulas containing chitosan is similar to the pH range of polymer solution which is acidic. The pH values of the prepared formulas using Cs, C940, C934 and C971P NF are shown in the figure (1).

Spreadability (Spreading coefficient)

The spreadability is an essential characteristic of topical formulations efficacy and ease of application because if the patient cannot spread the standard dose on the desired site, the therapeutic efficacy is limited (Joshi B. *et al.*, 2012). It is obvious from the figure (2) that the spreadability of emulgel formulas of C940 less than that of

C934 formulas and the last ones less than C971P NF formulas and this is related to the polymers nature and this is explained by a truth that the spreadability of any semisolid preparation decreased as the viscosity of the polymer increase and this include the cross linking of the structure of the polymer or the concentration of it, and as a general view on formulas, liquid paraffin formulas gave higher spreadability (Joshi B. *et al.*, 2012).

Determination of ITZ content in the emulgel formulas

The content of ITZ in the emulgel formulas were determined using ultra violet technique. The ITZ contents of the formulas are ranged between (98.5%-101.5%) (USP, 2007). The drug content of the formulations showed that the drug was evenly distributed in the emulgel. The drug contents of the formulas shown in the figure (3):

Rheological study

By measuring the viscosity at different shear rates, it was very clear that when the shear rate increased the viscosity decreased (Yehia I. *et al.*, 2011), as illustrated in figure (4).

In vitro dissolution test of ITZ emulgel

At the end of experiment each of prepared formulas gave different percentage of dissolution according to its contents of the emulgel that affects the release profile of ITZ.

Generally it can be observed from the curves of the release profiles that:

1. The oil type affects on the release profile of ITZ because it produces dissimilar curves ($f_2 < 50$) and this is obviously from the correspondable liquid paraffin and olive oil formulas. (F1, F9) were exploited to study this effect, F1 gave percentage of release higher than that of F9, shown in figure (5), this finding is due to the higher viscosity of olive oil as compared to liquid paraffin viscosity and in turn gave more retardation to the drug to be released (Naveed A. *et al.*, 2009).
2. The gelling agent type produces significant effect ($p < 0.05$) on the release profile of ITZ, this finding is clearly observed from the release profiles of (F1, F2, F3) from liquid paraffin formulas and (F9, F10, F11) from olive oil formulas, shown in figures (6, 7). This finding may be due to the cross linking density and viscosity of the polymers, C934 and C940 are considered as highly cross linked polymers (short rheology) while C971P NF is considered as lightly cross linked polymer (long rheology) (Piyusha D. *et al.*, 2010).
3. The total amount of emulsifying agents was studied in (F3, F5) from liquid paraffin formulas and in (F11, F13) from olive oil formulas, it was observed the

dissimilarity in the release profiles because (8%) of surfactants in F5 and in F13 gave higher percentage than (5%) in F3 and in F11 as shown in figures (8,9). The probable cause behind this finding is the increment in the hydrophilicity of emulgel which lead to increase in the penetration of the dissolution medium into the emulgel, in turn the dissolution and release of the drug increase (Magdy I. *et al.*, 2004).

4. Oil phase concentration was studied in (F5,F6) from liquid paraffin formulas and in (F13,F14) from olive oil formulas, this factor affected on the release profile of ITZ from those formulas and this was concluded from the dissimilarity between two curves ($f_2 < 50$), 15% from both oils gave higher release percentages than 30% of the same oils as shown in figures(10,11), the probable cause behind this finding that increasing the thermodynamic activity of the drug in term of relative solubility between the oil phase and dissolution medium lead to enhance the dissolution of the drug, there is good agreement with what had founded in miconazole nitrate release from its emulgel (Lubna A. *et al.*, 2009).
5. The effect of the type of emulsifying agents was studied in (F6,F7,F8) from liquid paraffin formulas and demonstrated that not only the amount of surfactants affects the release but also the type of surfactant affect the release significantly ($p < 0.05$) [figure(12)] this finding was probably due to two reasons, firstly the chemical structure of the oil and surfactant as span 20 has saturated lipophilic tail which attract the saturated oil (liquid paraffin) which is more efficient than span 80 so F7 (span 20 and tween 80) gave higher release than F8 (span 80 and tween 80) (Ashish G. *et al.*, 2014). And by regarding to F6 (span 20 and tween 20) in spite of exploiting span 20 but gave release percentage lower than that of F7, this may be due to the closer HLB values between (span 20 and tween 80) than in between (span 20 and tween 20) (Reiger MM. *editors.*, 1986).
6. F14 and F15 were exploited to see whether the blending of surfactants more effective or the single surfactant on the release of drug from its carrier (emulgel). F15 in which mixture of surfactants used imparted the drug in higher percentage ($f_2 < 50$) than F14 in which only single surfactants used with the same HLB value of the mixture, this result may be due to the multiple interfaces produced by mixture led to decrease in the particle size and in turn increase in the release of the drug (Reiger MM *et al.*, 1986), as shown in figure (13).
7. F15 and F16 were exploited to estimate gelling agent effect on the release profile of ITZ, the comparison

between F15 (1% C971P NF) and F16 (2% C971P NF), their release profiles demonstrated nearly similar curves ($f_2 > 50$), this finding may be due to that the increment in the concentration of lightly cross linked polymer don't result in slowing the release (Rowe R. *editors.*, 2009), [figure (14)]

After completing the experiment and studying these factors, F7 were nominated as the best formula because gave higher release (95.3%) in addition to good physical attributes.

Rheological behavior

Rheological behavior was studied for the selected formula F7 by drawing shear rates vs. shear stress as illustrated in figure (15), it is very clear the pseudoplastic thixotropic behavior which means a relatively slow recovery of consistency through shearing on standing of material ie;breakdown and alignment of the structure of polymer and require non-zero time to return to its original structure before applying the stress (Parmpreet S. *et al.*, 2014). Thixotropy presented by the hysteresis loop between the up and down curve (obtained by increasing and decreasing shear rate respectively).

Skin irritation study

The results of skin irritation test of the optimized selected emulgel formula (F7), there is no irritation signs on the rat skin like erythema, oedema and ulceration after application of the emulgel and monitoring of the irritation signs for 7 days, this results indicates that this formula is safe and suitable for the topical drug delivery (Sunny K. *et al.*, 2014).

In vitro antifungal activity

Five trials were made to analyze the the antifungal activity of the selected formula F7 in comparison with marketed clotrimazole cream (opizole cream 1%) manufactured by Oman Pharmaceutical Products Co. L.L.C. The result showed that prepared selected formula (F7) has larger zone of inhibition compared to the marketed cream, this may be due to composition and properties of the emulgel that lead to perfect drug release (Piyusha D. *et al.*, 2010), (Sunam V. *et al.*, 2014) and this is supported by some studies confirmed that the itraconazole and clotrimazole equieffective (Gare E. *et al.*, 2013), the diameter of inhibition zone is illustrated in figures (16A,B).

Table 1. Composition of itraconazole emulgel formulas (w/w)% (amounts in gram)

Formulas	Itraconazole	Liquid paraffin	Olive oil	Sod. metabisulfite	Span 20	Span 80	Tween 80	Tween 20	Propyl paraben	Methyl paraben	Propylene-glycol	C934	C940	C971pNF	Chitosan	Acetic acid ml	P.W up to
F1	1	30			3.5			1.5	0.01	0.03	5	1					100
F2	1	30			3.5			1.5	0.01	0.03	5		1				100
F3	1	30			3.5			1.5	0.01	0.03	5			1			100
F4	1	30			3.5			1.5	0.01	0.03	5				3	1	100
F5	1	30			5.6			2.4	0.01	0.03	5			1			100
F6	1	15			5.6			2.4	0.01	0.03	5			1			100
F7	1	15			4.8		3.2		0.01	0.03	5			1			100
F8	1	15				3.2	4.8		0.01	0.03	5			1			100
F9	1		30	0.1	1.65			3.35	0.01	0.03	5	1					100
F10	1		30	0.1	1.65			3.35	0.01	0.03	5		1				100
F11	1		30	0.1	1.65			3.35	0.01	0.03	5			1			100
F12	1		30	0.1	1.65			3.35	0.01	0.03	5				3	1	100
F13	1		30	0.1	2.7			5.3	0.01	0.03	5			1			100
F14	1		15	0.1	2.7			5.3	0.01	0.03	5			1			100
F15	1		15	0.1			8		0.01	0.03	5			1			100
F16	1		15	0.1			8		0.01	0.03	5			2			100

Figure 1. pH of the prepared formulas

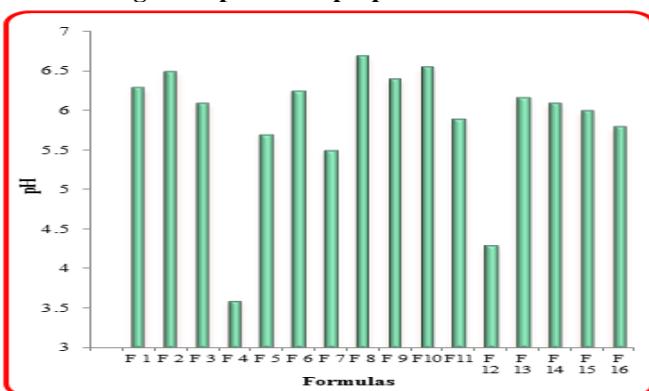


Figure 2. Spreadability of the prepared formulas

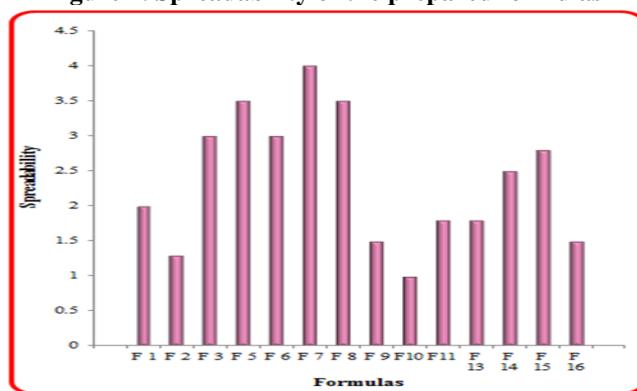


Figure 3. Drug content of the prepared formulas

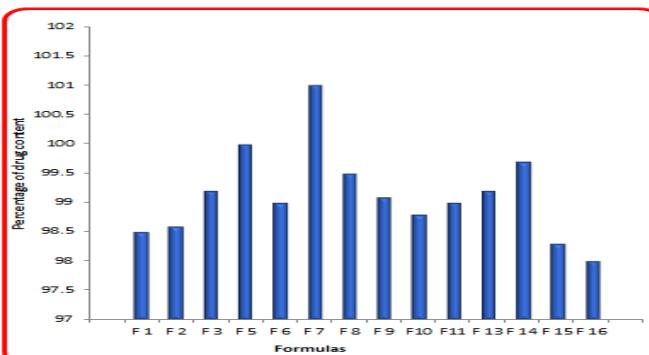


Figure 4. Viscosity of the formulas at 2, 50 rpm at room temperature

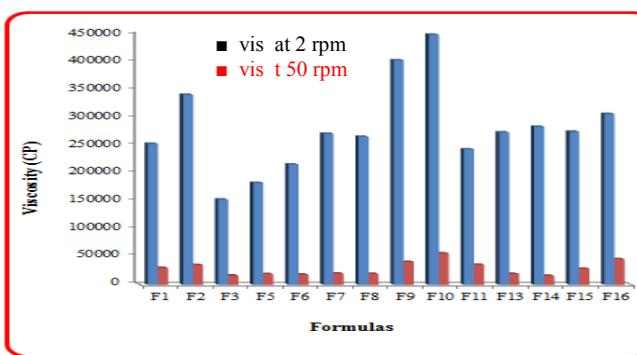


Figure 5. Effect of type of oil on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) With (1%) (w/v) Brij 35 at 32°C

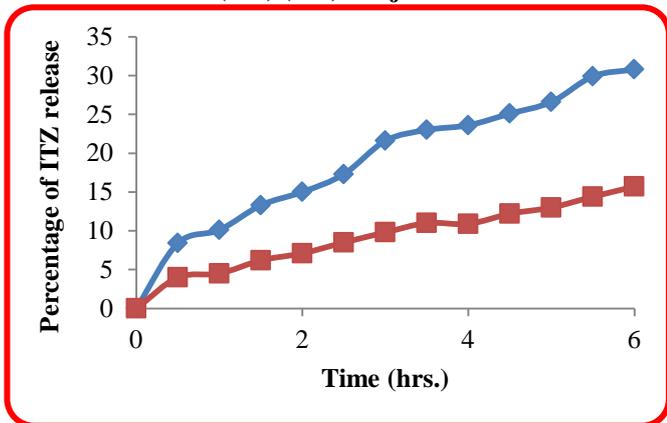


Figure 6. Effect of type of gelling agents on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

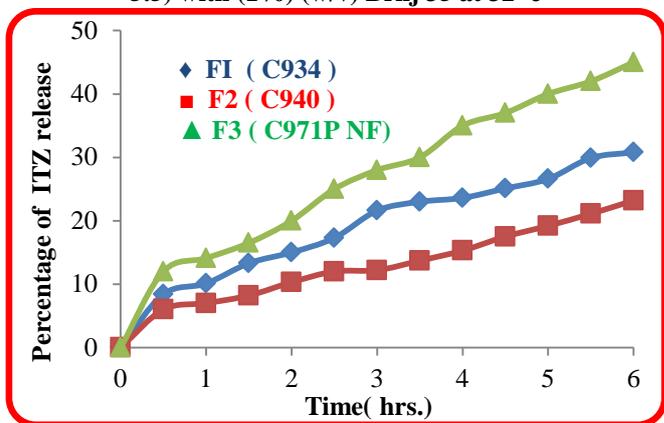


Figure 7. Effect of type of gelling agents on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

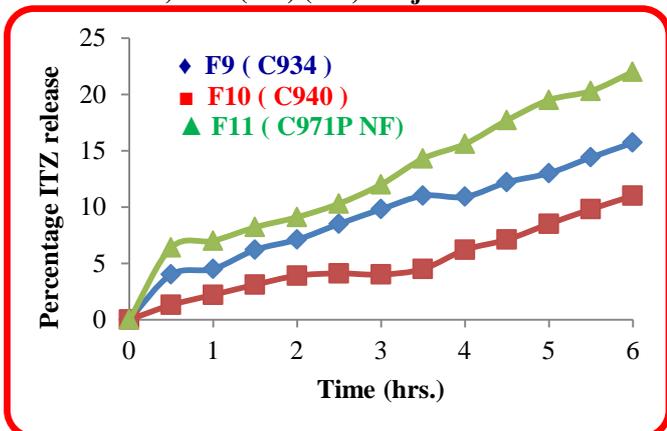


Figure 8. Effect of total amount of surfactant on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

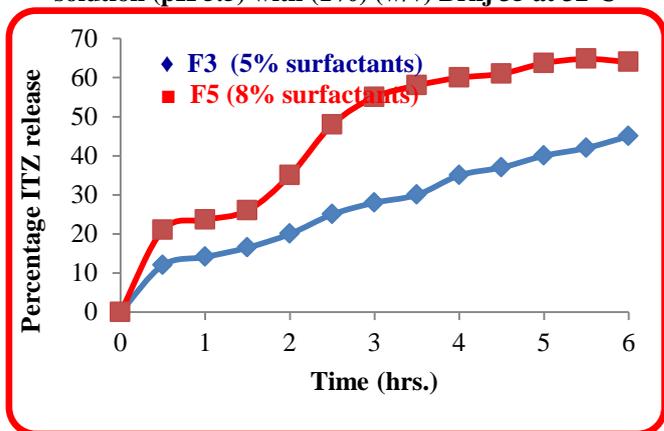


Figure 9. Effect of the total amount of surfactant on the release Profile of ITZ in the phosphate buffer solution (pH 5.5) with (1%) Brij 35 at 32°C

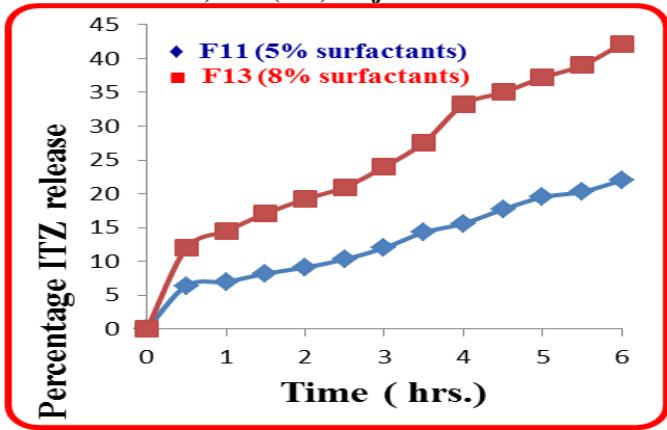


Figure 10. Effect of amount of oil on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) Brij 35 at 32°C

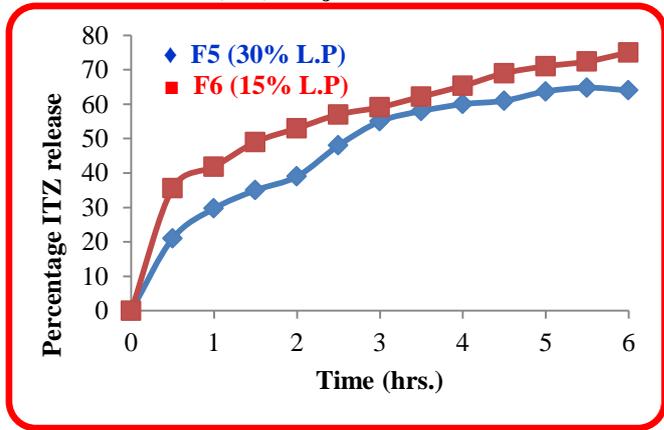


Figure 11. Effect of amount of oil on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

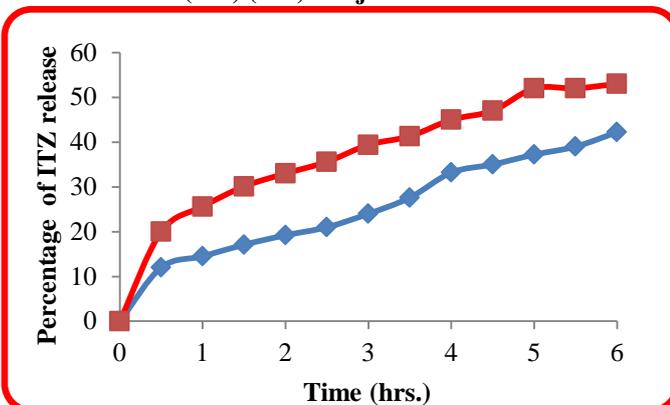


Figure 12. Effect of the type of surfactants on the release profile of Itraconazole in phosphate buffer (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

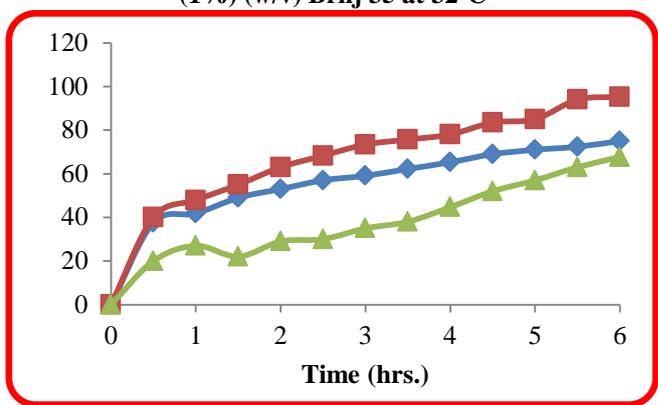


Figure 13. Effect of blending of surfactants on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

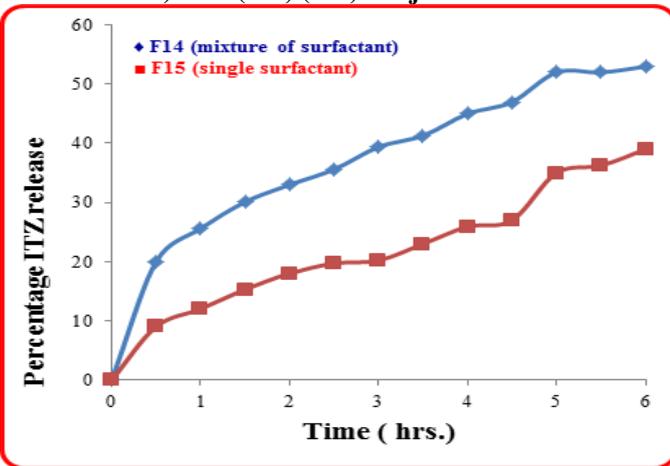


Figure 14. Effect of the amount of the polymer on the release profile of Itraconazole in phosphate buffer solution (pH 5.5) with (1%) (w/v) Brij 35 at 32°C

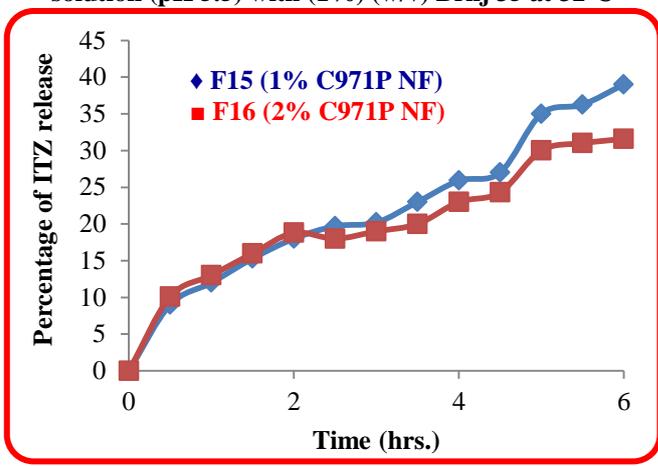


Figure 15. Thixotropic behavior of selected formula at room temperature

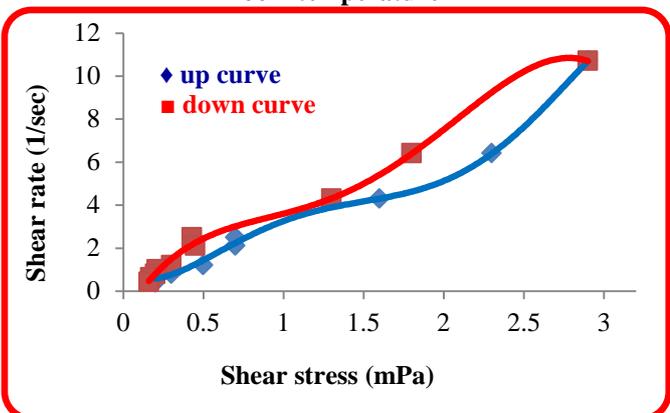
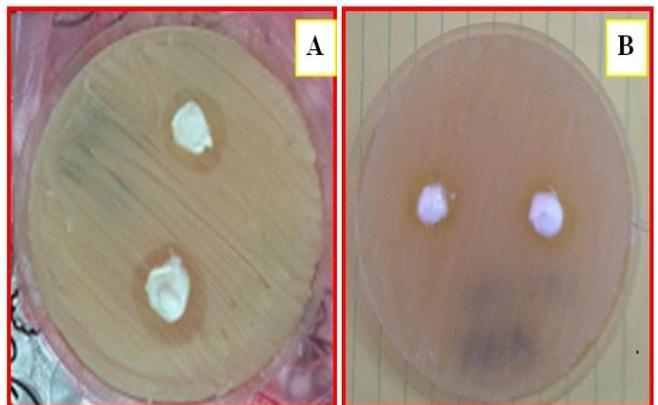


Figure 16. A) Zone of inhibition of (F7), B) Zone of inhibition of marketed OPIZOLE cream



CONCLUSION

1. ITZ can be formulated as emulgel with a proper consistency.
2. The Factors which affect on the drug release from the emulgel can be arranged as follows: The emulsifying agent type and concentration, oil phase concentration and type and the gelling agent type, while the gelling agent concentration has nonsignificant effect on the ITZ release.
3. Carbopol 971P NF- based emulgel gives highest drug release when 15% w/w liquid paraffin and 8% w/w

emulsifying agents (Span 20 and Tween 80) were used and it is the formula of choice.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

- Ahmad F, Alam M, Khan Z, et al. Development and *In vitro* evaluation of an acid buffering bioadhesive vaginal gel for mixed vaginal infections. *Acta Pharm.* 2008; 58(4): 407-19.
- Ashish G. Determination of hydrophilic-lipophilic balance value. *IJSR.* 2014; 3(4): 573-5.
- British Pharmacopoeia, 2009.
- Chinmaya K, Satyanarayana K, Naveen G. Formulation and evaluation of bifonazole organogel for the application of topical drug delivery system. *Der Pharmacia Sinica.* 2013, 4(3): 67-74.
- Doaa A, Dalia A, Sally A, et al. Formulation and evaluation of fluconazole topical gel. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2012; 5(4): 176-83.
- El-Houssieny B and Hamouda H. Formulation and evaluation of clotrimazole from pluronic F127 gels. *Drug discovery and therapeutics.* 2010; 4(1): 33-43.
- Gamal M and Abdullah H. Synergistic enhancement of itraconazole dissolution by ternary system formation with Pluronic F68 and hydroxypropylmethylcellulose. *Sci Pharm.* 2009; 77: 401-17.
- Gary E and Nancy M. Placebo-Controlled Trial of Itraconazole for Treatment of Acute Vaginal Candidiasis. *Antimicrob. Agents Chemother.* 1993; 37(1): 89-92.
- Joshi B, Singh G, Rana A and Saini S. Development and characterization of clarithromycin emulgel for topical delivery. *Int. J. Drug Dev. & Res.* 2012; 4(3): 310-23.
- Loveleen P and Tarun K. topical gel: A recent approach for novel drug delivery. *Asian Journal of Biomedical and Pharmaceutical Sciences.* 2013; 3(17): 1-5.
- Lubna A, Halah T and Yehia I. An investigation release and rheological properties of miconazole nitrate from emulgel. *Iraqi J Pharm Sci.* 2009; 18(2): 26-31.
- Magdy I, Mohamed, Optimization of Chlorophenesin Emulgel Formulation. *AAPS.J.* 2004; 6(3): 1-7.
- Manisha K, Vilasrao K, Nikhil M et al. Formulation and evaluation of topical delivery of antifungal drug bifonazole using microemulsion based gel formulations. *World Journal of Pharmacy and Pharmaceutical Sciences.* 2013; 2(6): 6405-22.
- Mikari B and Mahadik K. Formulation and evaluation of topical liposomal gel for fluconazole. *Indian J .Pharm.Sci.* 2010; 44(4): 324-5.
- Muzib Y and Kalpana K. Study on transmucosal permeation of diclofenac diethylamine microemulsion gel. *IJPBR.* 2012; 3(4): 160-5.
- Naveed A, Qazi A, Mahmood A, et al. rheological studies and characterization of different oil. *J.Chem.Soc.Pak.* 2009; 31(2): 201-6.(126)
- Panwar A, Upadhyay N, Bairagi M, et al. Emulgel: a review. *Asian Journal of Pharmacy and Life Science.* 2011; 1(3): 333-43.
- Parmpreet S, Sunny K, Rajni B and Naresh S. Development and characterization of clindamycin phosphate emulgel for topical delivery. *Int J Recent Adv Pharm Res.* 2014; 4(3): 47-62.
- Piyusha D, Ankur J, Naveen V, et al. Gellified emulsion for sustain delivery of itraconazole for topical fungal disease. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2010; 2(1): 104-12.
- Piyusha D, Ankur J, Naveen V, et al. Gellified emulsion for sustain delivery of itraconazole for topical fungal disease. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2010; 2(1): 104-12.

- Prakash B. Development of *In vitro* release test for capsaicin topical gel formulations by using franz diffusion cell. *Int J Pharm Bio Sci.* 2014; 5(1): 285-93.
- Rieger MM, Lachman L, Lieberman Ha and Kang JI. Emulsion: The theory and practice of industrial pharmacy. 3rd ed. Philadelphia, PA: Lea and Febiger; 1986: 502-33.
- Rowe R, Sheskey P, Marian E. Handbook of pharmaceutical excipients. 6th ed. London UK: Pharmaceutical press; 2009.
- Sai S, Vinay K, Sarada P, *et al.* Thermal, mechanical and electrochemical characterization of gelatin-based physical emulgels. *Int J Electrochem Sci.* 2015; 10: 1233-48.
- Saleem M and Sumanji B. Formulation and evaluation of meloxicam solid dispersion incorporated topical gels. *International Journal of Pharma and Bio- Sciences.* 2010; 1(3): 1-9.
- Sonam V, Charu S, Easwari T and Shukla V. Emulsion based gel technique: novel approach for enhancing topical drug delivery of hydrophobic drugs. *IJPRS.* 2014; 3(2): 649-60.
- Sunny K, Gurpreet S, Seema S and Gill N. Topical drug delivery system. *International Journal of Universal Pharmacy and Bio Sciences.* 2014; 3(5): 124-37.
- Swapnil S, Wankhade N and Deokar G. Microemulsion based gel system: A novel approach for topical drug delivery. *An International Journal of Advances in Pharmaceutical Sciences.* 2014; 5(1): 1776-82.
- USP30-NF25 UP. United State Pharmacopeial Convention. USA, Rockville MD Inc. 2007.
- Yehia I, Abeer H and Entidhar J. Preparation and evaluation of physical and, rheological properties of clotrimazole emulgel. *Iraqi J Pharm Sci.* 2011; 20(2): 19-27.