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Formulation and Evaluation of Orphenadrine Citrate as a Model Drug for Topical Hydrogel

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Abstract Orphenadrine Citrate is a muscle relaxant, act as an anti- cholinergic drug and used in the treatment of Parkinson's disease. The objective of this study was to design a topical hydrogel formulation using Orphenadrine Citrate as a model drug. The topical administration is an alternative route that can minimize the side effects and may improve patient drug delivery. Different formulas were prepared using different gelling agents with different concentrations, CMC (1, 2 and 3% w/w), Xanthan gum (0.5, 1 and 1.5% w/w) and HPMC K40 (2, 2.5 and 3% w/w). The prepared formulas were evaluated for physical appearance, pH, Spreadability, drug content, viscosity besides to in- vitro drug release. All the formulas prepared had acceptable hydrogel texture, increased viscosity as the gelling agent concentration increased, while spreadability decreased; in addition the pH hydrogel surface of the formulas showed within acceptable pH of skin. On the other hand, among the polymer hydrogel used, it was found that xanthan gum gave (98.3%) Orphenadrine citrate release within 90 minutes while other polymers CMC and HPMC K40 gel was 70% and 62.6% drug release respectively within 90 minutes. Finally, F6 was the optimum formula due to its acceptable hydrogel surface pH (6.7), good spreadability (4.4 cm2) and 98.3% Orphenadrine citrate release from the hydrogel.

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Keywords: *Orphenadrine citrate, Hydrogel, Carboxy methyl cellulose, Xanthan gum , Hydroxy propyl methyl cellulose K40.*

1. INTRODUCTION

Orphenadrine citrate (ORC) is anti- cholinergic and anti-muscarinic act as skeletal muscle relaxant and used in mild symptom of Parkinson's disease. chemical structure of ORC. It's had many adverse effects due to its anti- cholinergic action like palpitation, dry mouth, urinary retention and blurred vision[(1)].

Structure of ORC was showed in a Figure (1), it has melting point 134- 138 °C, pka 8.4 with log p 3.8 (Octanol/Water). its solubility in water was 1 in 70, slightly soluble in ethanol and practically in- soluble in chloroform and ether [(2)].

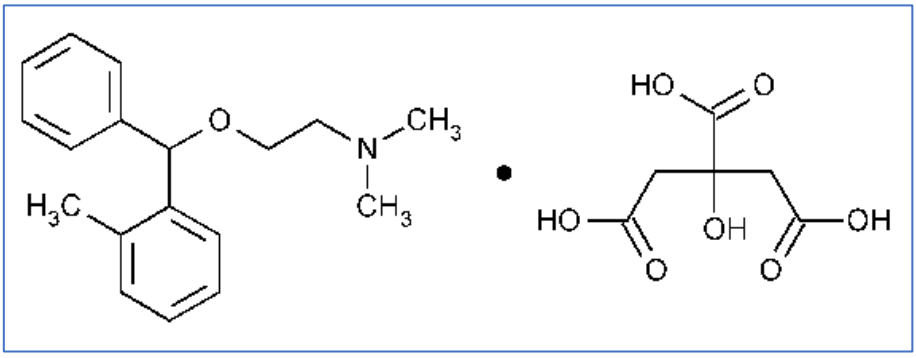

Figure (1): *Structure of orphenadrine citrate [(2)]*

Local rout of administer used the skin or mucous membrane for local effect. Skin rout can be acting as dermal or transdermal action to avoid many problems like first pass effect or decreased side effect of the drug, Examples cream, ointment and gel [(3)].

Hydrogel is a gel consist of aqueous dispersion medium that's gelled with hydrophilic polymers formed a three-dimensional network, which have ability to absorbed a large quantity of water [(4)].

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So, the main objective in this study is to formulated ORC as a model for topically hydrogel to decreased its adverse effect and to achieve patient compliance by using this easy rout of administered dosage form by using different gelling agents like Hydroxy Methyl Cellulose K40 (HPMC K40), Carboxy Methyl Cellulose (CMC) and Xanthan gum with different concentrations and select the optimum formula based on the results of the physical parameters of the *in- virto* evaluations testes.

2. MATERIAL

Orphenadrine citrate (Aleppo, Syria), Carboxy methyl cellulose (BDH. Ltd England), Hydroxy Methyl Cellulose K40 (AWIA, Erbil, Iraq) and Xanthan gum (Himedia Lab. Pvt. Ltd. India).

3. METHOD

Different formulas were prepared (Table- 1) using different types of polymers with different concentrations. A specific weight of polymer was dispersed in a phosphate buffer (7.4) solution at 60 ºC with constant starring (1000 rpm) by using magnetic starrier (Vision, Korea) for one hr. then left unstirred (24 hr.) for complete swelling as well as equilibrium [5].

ORC (0.5 % w/w) was dissolved in DW (5% w/w) by using hot plate magnetic stirrer (500 rpm/ 50 ºC, Vision, Korea) for 30 min. added it gradually to the previously prepared hydrogel at 1000 rpm for one hr., then complete weight to 100 gm by using phosphate buffer to adjusted the final pH (7.4) with continues stirring 300 rpm for 30 min., finally sonication by sonicator (Coply, UK) until a clear transparent hydrogel free from air bubbles obtained. Packed a prepared ORC hydrogel in wide mouth container with tight stoppered covered with aluminum foil in a cool place [6]

Table (1): *The composition of different formula of ORC. hydrogel (w\w)*

Formula Code	ORC (gm)	D W. (ml)	CMC (gm)	Xanthan Gum (gm)	HPMC K40 (gm)	Buffered pH up to (gm)
F1	0.5	5	1	-	-	100
F2	0.5	5	2	-	-	100
F3	0.5	5	3	-	-	100
F4	0.5	5	-	0.5	-	100
F5	0.5	5	-	1	-	100
F6	0.5	5	-	1.5	-	100
F7	0.5	5	-	-	2	100
F8	0.5	5	-	-	2.5	100
F9	0.5	5	-	-	3	100

Evaluation of the drug

Determination of ORC λ max

The stock solution (1mg/ ml) of ORC in the phosphate buffer (pH 7.4) was prepared and suitably diluted (300 µg/ml) then scanned by UV- spectrophotometer to determine the λ max of the drug.

Estimation of calibration curve of ORC

For estimation of calibration curve, Papered a serial dilution at different concentrations (50, 100, 150, 200, 250, 300 µg/ml) from stock solution of ORC at concentration (1mg/ ml).

Characterization of the preparations

Physical appearance of hydrogel formulations

All hydrogel formulation were visually inspected for clarity, color, homogeneity and presence of particles or air bubbles [7].

Spreadability test

Take 0.5 gm of each formula and pressed between two glass slide (divided into square of 5 mm), then put a weight of 20 gm over the slide and left about 5 min. until no more spreading was expected, then measured the diameter of the circles of ORC hydrogel spread by cm^2 and these results were obtained was triplicate [7].

pH determination

the pH values of the hydrogel were determined by using digital pH meter (Hanna, Italy), and the results were obtained was triplicate [8].

Drug content determination

Seven gm of ORC hydrogel (equivalent to 35 mg of ORC) added to 100 ml of phosphate buffer (pH 7.4) and stirrer (500 rpm) for 2 hr. then filtering by filter membrane syringe (450 micron), then detected the drug concentration by using UV-spectroscopy at 265 nm [9].

Viscosity

The viscosity of the prepared formulas was determined by using digitals viscometer (NDJ- 5S Germany) with spindle (No. 4) and the maximum- minimum share rate was 60- 6 rpm respectively, and this test results was a triplicate [10].

In- vitro dissolution teste

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In- vitro dissolution test for ORC hydrogel measured by using a paddle type of USP- dissolution apparatus type II, 7 gm (equivalent to 35 mg of ORC) of hydrogel was placed on the glass watch which immersed in the dissolution jar which contained 500 ml of phosphate buffered solution (pH 7.4), 32 ^{o}C at 50 rpm; withdrawing the sample (5 ml) at time interval (15, 30, 45, 60, 75, 90, 105, 120, 135, 150 ,165 and 180 min.) and replaced with equal volume from fresh phosphate buffer solution, then the absorbance of each sample was detected after filtrate (filter membrane syringe) by using UV- spectroscopy at 265 nm [11, 12].

4. RESULTS

Characterization of ORC

Determination of ORC λ max

The λ max of ORC in the phosphate buffer pH 7.4 was 265 nm (Figure- 2) as reported by the reference [13].

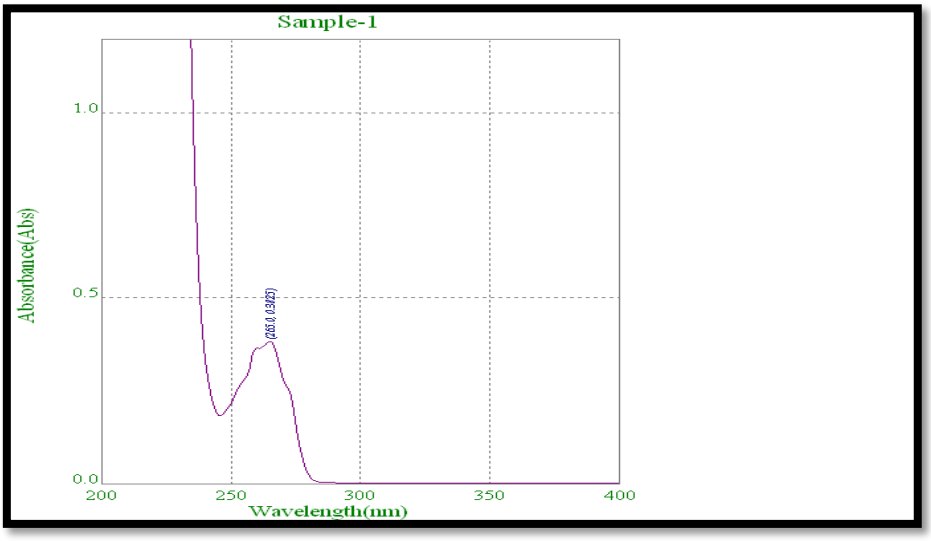

Figure (2): *The λ max of ORC. in the phosphate buffer pH 7.4*

Calibration curve of ORC

The calibration of ORC. In the phosphate buffer was showed below in the Figure (3).

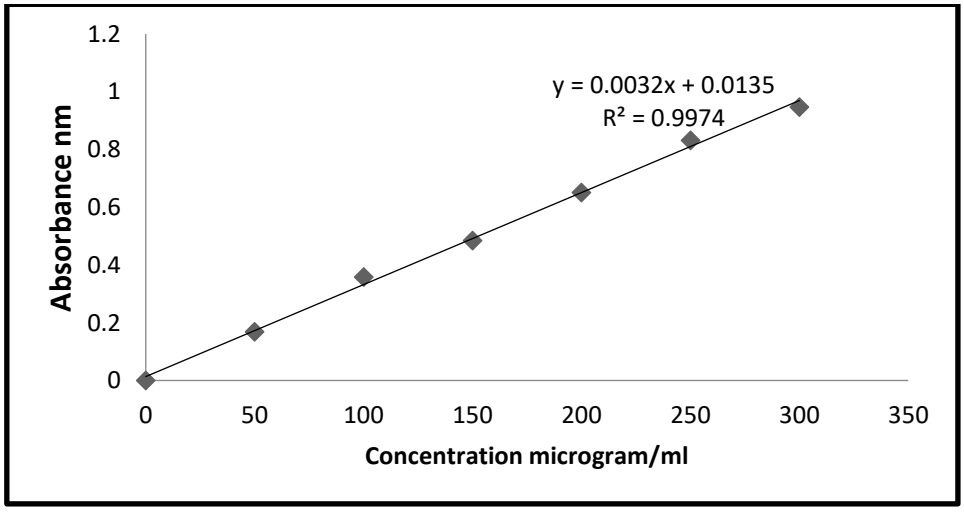

Figure (3): *The calibration curve of ORC in phosphate buffer pH 7.4*

Characterization of the preparations

Physical appearance of ORC- hydrogel formulations

All formulas were homogenous, no phase separation, transparent to white color as shown in the Table (2).

Spreadability test

the results ranged between 3.5-7.25 cm^2, as shown in the Table (2).

pH determination

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All formulas are within acceptable pH rang of skin (7.4); the pH values of all formulas are shown in the Table (2); ranged from 6.7 to 7.1, pH is important to provide patient compliance, and all the formulas in this study was not cause irritation to the skin.

Drug content

The drug content of hydrogel formulas was listed in the Table (2); ranged from 94.4 to 99.2 % and all is within the limit of the official Bp (100± 5%), and the drug content showed the drug was uniformly distributed in the hydrogel.

Table (2): *The results of physical appearance, spreadability test and surface pH and drug content for prepared formulas*

Formula Code	Physical Appearance	Spreadability test cm^2 ±SD (n=3)	pH ±SD (n=3)	%Drug content. ±SD (n=3)
F1	Transparent to white	7.25 ± 1	7 ± 0.1	96.2± 1
F2	Transparent to white	5.5 ± 0.3	6.9 ± 0.1	94.4± 0.7
F3	Transparent to white	3.5 ±0.4	6.9 ± 0.3	93.1± 0.9
F4	White	7 ± 0.9	6.9 ± 0.2	99.2± 1.1
F5	White	5 ± 0.6	6.8 ± 0.3	97.1± 1.2
F6	White	4.4 ± 0.5	6.7 ± 0.1	98.8± 0.8
F7	Transparent	7 ± 0.3	7.1 ±0.1	97± 1.3
F8	Transparent	5.5 ± 0.1	7.1 ± 0.2	96.5± 1.1
F9	Transparent	5 ± 0.2	6.9 ± 0.1	95.3± 1.2

Viscosity

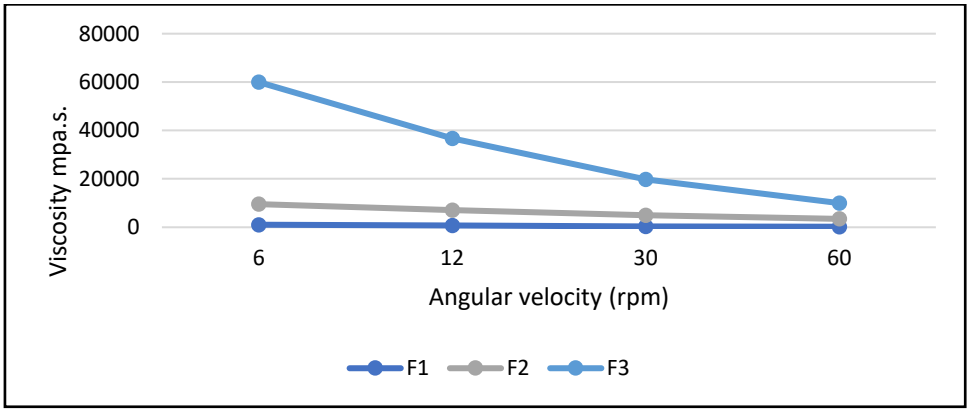
To study the effect of the concentration of polymers (CMC, Xanthan and HPMC K40) on the viscosity of all formulas were showed in the Figure (4- a, b and c) respectively.

***In-vitro* dissolution test**

The release of ORC from formulas F1, F2 and F3 which contain CMC polymer was illustrate in Figure (5-a), the drug released ranged from 65% to 70% through 100 min.

And the release of ORC from formulas F4, F5 and F6 which contain Xanthan gum polymer was illustrate in Figure (5-b), the drug released ranged from 65% to 100 % through 100 min.

While the release of ORC from formulas F7, F8 and F9 which contain HPMC K40 polymer was illustrate in Figure (5-c), the drug released ranged from 57% to 65 % through 100 min.



(a)

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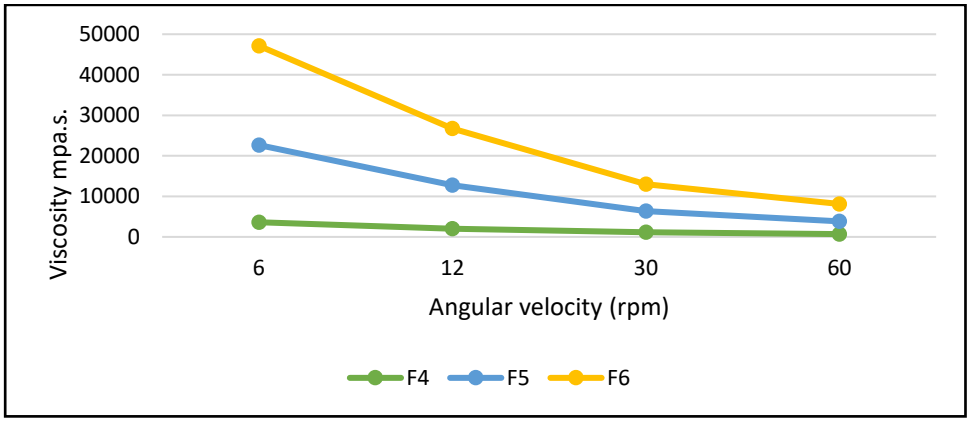
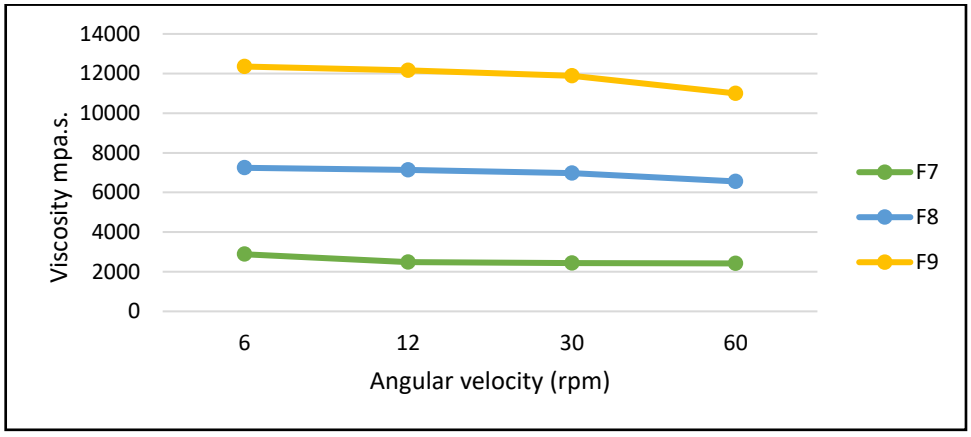
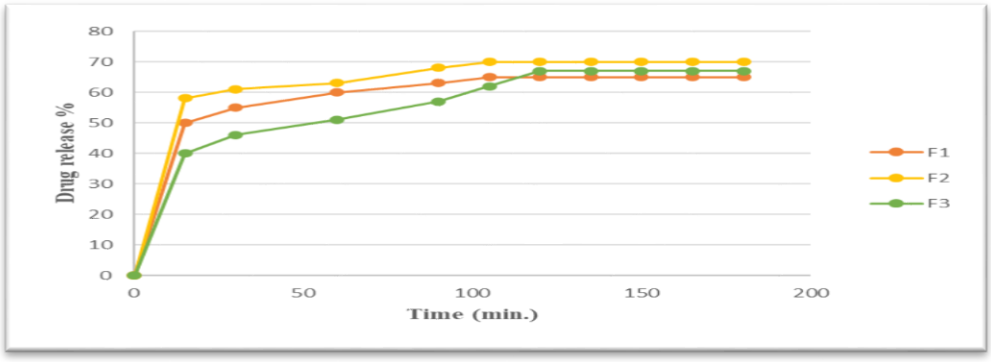


(b)

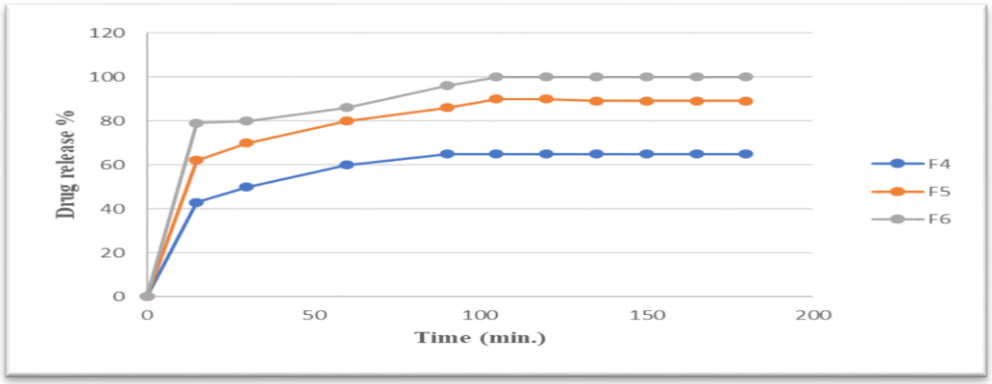


(c)

Figure (4): *a- The effect of CMC concentration on rate of shear (F1, F2 and F3), b- The effect of Xanthan Gum concentration on the rate of shear (F4, F5 and F6), C- The effect of HPMC K40 concentration on the rate of shear (F7, F8 and F9)*



(a)



(b)

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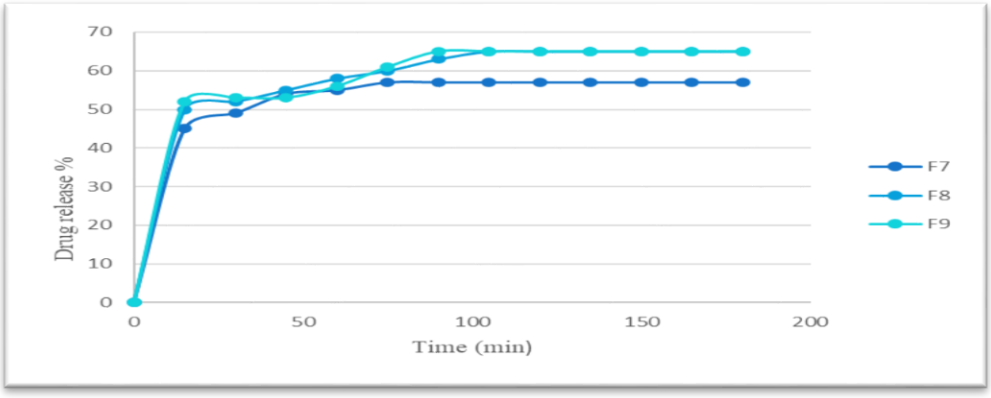

(c)

Figure (5): *The effect of concentration of polymers on ORC released in Phosphate buffer pH 7.4 at 32 °C at 50 rpm. a- CMC formulas (F1, F2 and F3), b- Xanthan gum formulas (F4, F5 and F6), C- HPMC K40 formulas (F7, F8 and F9)*

5. DISCUSSION

Spreadability test

The spreadability is important to get a correct dosage form so, the hydrogel must be spread easily when applicated on the skin. So, in this study, studies two factors effect on the spreadibility of ORC- hydrogel:

Effect of polymer concentration

As the result shown in the Table (2), the Spreadability decreased with increased the polymer concentration, that's due to increase the viscosity of hydrogel with increased polymer concentration [7, 14].

Effect of polymers type

As the result shown in the Table (2) in this study, it was found that changing in the type of polymers was showed not observed effect in the spreadability.

Viscosity

All formulas were showed increased in the viscosity as the concentration of the polymer's concentration increased regardless of the type of polymers, this increased in the viscosity due to increase in the chain interaction within the polymer.

In the CMC and Xanthan gum hydrogel showed that; the viscosity was decreased with increased of shear stress as shown in the Figure (3- a and b) and that's mean; the hydrogel exhibited Non- Newtonian pseudo plastic behavior – shear thickening, as shear stress is increased, the normally molecules disarranged of the gelling material and that's lead to align their long axes in the direction of flow, and that's orientation will reduce the internal resistance of the material and that's will decreased the viscosity [15,16].

While in the HPMC K40 hydrogel showed no observed decrease in the viscosity with increased in the share stress as showed in Figure (3- c), and that's may be that's force not enough to change in the viscosity with this no. of spinodal and this rang using of stress of instrument [15].

In- vitro dissolution test

In the general, the drug released from the hydrogel depends on the diffusion of water molecules into the polymer network that's expand the polymer and that's depending on the type, concentration, molecular weight and functional group of the polymers used [17].

The drug released from the CMC hydrogel (Figure 4- a) was 65, 70 and 67.8 % for F1, F2 and F3 respectively through 100 min. and that's showed non- significant ($p > 0.05$) variable in the drug released from the hydrogel with increased CMC concentration, and these results obtained may be due to hydrophilicity of the CMC, that permit to dissolution medium to penetrate into the hydrogel and this led to release of drug [18, 26].

ORC released from Xanthan gum hydrogel formulas was a significant ($p < 0.05$) increased with increased of polymer concentration (Figure 4- b) for F4, F5 and F6; which obtained 65, 90, and 100% ORC released respectively at 100 min. and that's may be due to more dissolution medium permeation as Xanthan gum concentration increased (high ability to uptake of medium) which in turn increased more drug by diffusion [16, 27].

While the released of ORC from F7, F8 and F9 (Figure- 4c) which contain HPMC K40 was showed non- significant ($p > 0.05$) change in the drug released with increased polymer concentrations and that's may be depends on the type of polymers, its grade and it's the concentration [19, 20,21].

Finally, Xanthan gum gave a higher of ORC released % than CMC and HPMC K 40 hydrogel because it is a polysaccharide with a very high of M.wt which (1- 2 * 10^6 Dalton) > CMC (250,000 Dalton) > HPMC K40 (55,000- 93,000 Dalton), and that's mean when increased in the M.wt of polymers, increased in the no. of hydrophilic functional group, that's increased in water uptake and that's lead to more expansion of the hydrogel network and finally diffuse the drug [22, 23, 24, 25].

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So, the optimum formula in this study, is F6 (Xanthan gum 1.5% w/w; Figure -5) due to its acceptable physical characteristic, Spreadability (4.4 cm^2), pH (6.7), drug content (98.8%), good viscosity and a higher percent of drug released (100%) at the first 100 min.

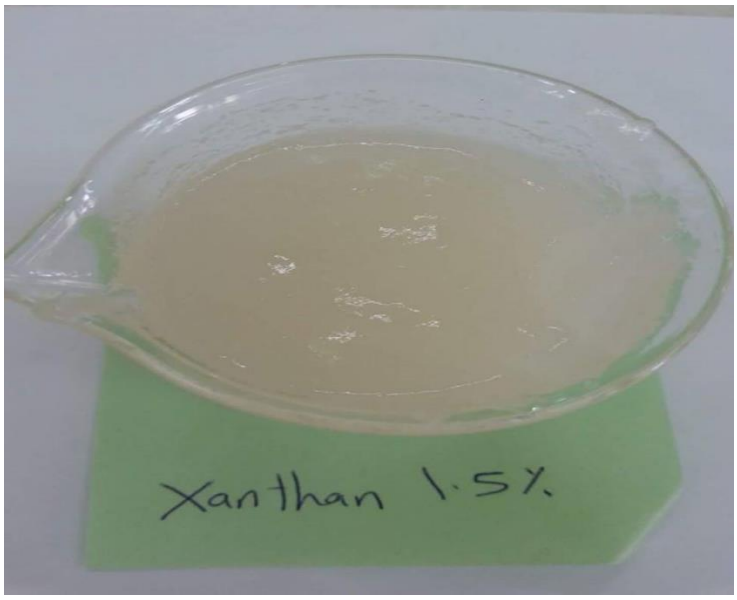

Figure (5): *The optimum formula F6*

6. CONCLUSION

In this study can concluded, all types of polymers with different concentration successful to prepare a hydrogel as a topical dosage form, but the optimum formula was F5 which contain 1:3 ratio drug: xanthan gum was successful in all *in- vitro* characterization when compared with other formulas at this study.

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