

Preparation and Evaluation of Emulgel as Topical Drug Delivery for Nimesulide by Using Conventional Emulsion

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Abstract:

Topical drug administration is a mean by which various types of dosage forms such as ointments, creams, gels and emulgels are applied at a specific site of the body such as skin, ophthalmic, vagina and various parts of gastrointestinal tract to

give either local or systemic effect. Nimesulide is non-steroidal anti-inflammatory drug (NSAID) which has good anti-inflammatory, analgesic and antipyretic activity.

In this study, eight formulations of nimesulide emulgel containing conventional emulsion were prepared to investigate the effects of different variables on the physical appearance, pH, spreadability, viscosity and in vitro drug release. These variables are the type of oil phase of the emulsion (olive and coconut oil), type and concentration of emulsifying agent (span 80 and tween 80), type of gelling agent (carbopol934 and HPMCK15M), preservative and penetration enhancer.

The results revealed that (F4) which consist of 2.5% HPMCK15M, 4% (combination of span80 and tween80), 8% coconut oil and 1% nimesulide was an optimum formulation, since it shows maximum drug release after 7 hrs in addition to excellent physical appearance.

Key words: Emulgel, nimesulide, carbopol934, HPMCK15M.

المستحلب باستخدام للنيمسولاييد موضعي كناقل دواء المستخدم المستحلب للجل والتقييم التحضير التقليدي

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الخلاصة:

الاستخدام الموضعي للدواء يعني تطبيق انواع مختلفة من الاشكال الدوائية مثل المراهم، الكريمات، الجل، و الايمولجل على اماكن محددة من الجسم مثل الجلد، العين، المهبل، واجزاء مختلفة من الجهاز الهضمي لاعطاء التأثير العلاجي الموضعي او الجهازى. نيمسولاييد يعتبر من مضادات الالتهاب الالاستيرويدية وتتميز بمفعوله الجيد كمضاد للالتهابات وكمسكن وخافض للحرارة.

في هذه الدراسة تم اعداد ثمانية صيغ من ايمولجل للنيمسولاييد الحاوية على المستحلب التقليدي للتحقيق من تأثير المتغيرات المختلفة على المظهر الخارجى، درجة الحامضية، معامل الانتشار، اللزوجة، معدل تحرير الدواء. هذه المتغيرات شملت نوع الطور الزيتي من المستحلب (زيت الزيتون وزيت جوز الهند)، نوع وتركيز مواد الاستحلاب المستخدمة (سبان 80 و توين 80) (نوع ماده البوليمر) (كارببول 934 و هايديروكسي بروبيل ميثيل سيليلوز) ونوع المواد حافظة ومحسنة للنفاذية.

وقد كشفت النتائج عن ان (ف) التي تتكون من ٢,٥% هايدروكسي بروبييل ميثيل سيليلوز, ٤% مزيج من سبان ٨٠ وتوين ٨٠, (٨% زيت جوز الهند و ١% نيمسولايد كانت افضل صيغة لانها بينت الحد الأقصى لتحرر الدواء بعد مضي ٧ ساعات, بالإضافة إلى خصائص فيزيائية ممتازة .
الكلمات المفتاحية: ايمولجل, نيمسولايد, كاربوبول ٩٣٤, هايدروكسي بروبيل ميثيل سيليلوز.

Introduction

Skin is one of the most easily reachable organs on human body for topical administration of various types of drug product. The majority of conventional topical preparations are applied to the skin mainly for local effect, where systemic effects can be achieved through new technology and inclusion penetration enhancer in the preparations [1].

Topical drug delivery systems are localized system used to treat the local infection or diseases. Topical drug delivery systems are designed to deliver drug molecule through rectal, vaginal, ophthalmic and skin. It is including a large varieties of pharmaceutical dosage forms like powder, plasters poultices, lotion, solution, suspension, emulsion and semisolid (cream, gel, ointment and paste) [2]. Major group of semisolids is transparent gel. Regardless of many advantages of gels, a major restriction is their failure to carry hydrophobic drugs. To surmount this limitation a new dosage form approach was developed based on the use of emulsion with gel, as a result of that hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels [3].

The name emulgel is suggested from emulsion which is gelled by mixing it with gelling agent like HPMC, carbomer. When emulsion and gel are combined together in the formulation, they form a type of dosage form which is named emulgel or gellified emulsion. In fact, the presence of a gelling agent in water phase of emulsion allows the formulation of stable emulgel by decrease interfacial tension between the two immiscible phases and increase the viscosity of aqueous phase and it converts emulsion into emulgel.

Emulgel is the most preferred topical delivery system for hydrophobic drugs and

it provides stability and better bioavailability for this type of drugs [4]. Nimesulide (NIM) is N-(4-Nitro-2-phenoxy- phenyl) methane sulfonamide belong to non-steroidal anti-inflammatory drug (NSAID) that is weakly acidic differs from other (NSAIDs) that contain benzothiazine and thiazole moiety in their chemical structure while nimesulide contain a sulfonanilide moiety as the acidic group. Nimesulide is class-II drug, according to biopharmaceutical classification (BCS) with low solubility and high permeability character [5] and it is used in the long-term therapy of rheumatoid arthritis, in alleviating pain and inflammation. Short half-life of drug (3-4 hrs) necessitates multiple daily dosing for maintaining therapeutic effect throughout the day. The oral use of nimesulide shows a number of side effects like gastrointestinal disturbances, epigastric pain, nausea, heartburn, vomiting and diarrhea. Topical application of the drug could reduce these side effects and shows potential advantage for delivering the drug to the site of action [6].

The aim of this study to prepare a sustained release topical emulgel containing nimsulide and investigation the influence of type of gelling agent, emulsifying agent and the type of oil phase on in vitro release of drug and evaluate the rheological behavior of the prepared formulations. The study of Janki Patel., et al. for formulation and evaluation of diacerein emulgel for psoriatic arthritis show diacerein is poorly water-soluble drug (BCS Class II) an appropriate candidate to be incorporated in oil-in-water emulgel and it evaluates the influence concentration of emulsifying agents, gelling agent and oil phase on physical appearance, rheological behavior and in vitro drug release [7].

Materials and methods

Materials:

Nimesulide powder was purchased from Hong kong Goukang Bio-technology co., limited, olive oil was obtained from Solvochem, (UK), coconut oil was obtained from Thomas Beaker, (India), tween 80 and span 80 was purchased from Merck, (Germany), HPMCK15M was supplied from HIMEDIA, (India), sodium acetate tri hydrate provided from Xilong chemical industry incorporated co.,Ltd. China, methyl paraben and propyl paraben was provided from Interchimiques SA, (France), tri ethanol amine was gained from Hopkins and Williams Ltd (England), acetic acid Scharlab , spain and propylene glycol supplied from Avonchem, (UK).

Methods:

Preparation of emulgel

1. The gel base was prepared by dispersing HPMCK15M powder in heated distilled water with continuous stirring and the dispersion was cooled to room temperature then left for one day. While Carbopol934 was prepared by dispersed in distilled

water with vigorous stirring, afterward the pH was adjusted to (6 - 6.5) by adding drops of tri ethanol amine (TEA) and was left for one day to confirm hydration of the gel^[8].

2. The aqueous phase of emulsion was prepared by dissolving the required quantity of tween80 in purified water, Methyl paraben and propyl paraben were mixed with propylene glycol as preservative and mixed with previously prepared tween 80 solutions, whereas the oil phase was prepared by dissolving desired quantity of span 80 in the oil phase. One gram of NIM was added and mixed with oil phase until completely dissolved. The aqueous and oil phases were heated at range 70°C to 80°C then the oil phase was added to aqueous phase with constant stirring then the emulsion was left to cool down at room temperature^[9].

3. The emulsion and gelling agent were mixed together at (1:1) weight ratio with continuous stirring to form smooth homogenous emulgel formulation^[10]. Table (1) shows the main composition of each formulation.

Table (1): The main composition of emulgel formulations %(w/w)

Formula NO.	Nimesulide	HPMCK15M	Carbopol934	Olive oil	Coconut oil	Span 80	Tween 80	Propylene glycol	Methyl paraben	Propyl paraben	Oleic acid	Purified water up to mL
F1	1	2.5		8		0.5	1.5	5	0.03	0.01	1	100
F2	1	2.5		8		1	3	5	0.03	0.01	1	100
F3	1	2.5			8	0.5	1.5	5	0.03	0.01	1	100
F4	1	2.5			8	1	3	5	0.03	0.01	1	100
F5	1		0.5	8		0.5	1.5	5	0.03	0.01	1	100
F6	1		0.5	8		1	3	5	0.03	0.01	1	100
F7	1		0.5		8	0.5	1.5	5	0.03	0.01	1	100
F8	1		0.5		8	1	3	5	0.03	0.01	1	100

Characterization and evaluation of nimesulide emulgel formulations

Physical appearance

The prepared emulgel formulations were examined by naked eyes for their color, homogeneity, consistency and phase separation^[11].

pH Determination

The pH of all emulgel formulations was determined by digital pH meter (manufacture by Oahu's Corporation. (USA)). One gram of emulgel was dissolved in 100 mL of acetate buffer prepared with 2.5% tween80 and it was placed aside for two hours. The pH measurement was done in triplicate and average value was reported^[12].

Spreadability studies

A sample of (1gram) from each emulgel formulations was put between two glass slides then (0.5 gm) weight was applied on and left for about (five minutes) or when no further spreading was predictable. The diameter of spread circle was marked and measured in centimeter then compared with the original circle diameter (diameter of the spread circle that was measured before the application of 0.5 gm weight^[13].

Viscosity measurements

The Viscosity of all prepared emulgel formulations was measured using Brookfield Viscometer (Brookfield LV, spindle no. S-64) by filling the glass container with emulgel sample and then put it in a beaker (fill with water) which positioned on heat source to maintain the temperature at 37 °C. Then the spindle was allowed to rotate at different speeds (5, 10, 20, 30, 50, 60 and 100 rpm) and the viscosity of the formulation was measured after 30 seconds between two successful measurements. All measurements were made in triplicate^[14].

Drug content determination

One gram of emulgel sample was dispersed in 100 mL of prepared acetate buffer with (2.5%) tween 80 then the

mixture was sonicated for 2hrs. The obtained sample was filtrated by using 0.45µm Millipore filter, then diluted and analyzed at the determined λ_{\max} against acetate buffer (blank sample)^[15].

In Vitro release test of nimesulide emulgel

The in vitro release of NIM from emulgel formulations was done by rotating paddle dissolution apparatus-type II. One gram of the prepared formulation that comprise (10 mg NIM) were putted in a small beaker of 2.5 cm in diameter then the opening of the beaker was covered by 0.45µm Millipore filter which was fixed with rubber band, then inverted and immersed in the dissolution jar that previously occupied with (500 mL) of freshly prepared acetate buffer (pH 5.5) with (2.5%) tween 80 at 32±0.5°C with stirring rate 50 rpm. Samples of 5 mL were withdrawn after (30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420 min) and filtered through 0.45µm Millipore filter and replaced with an equal volume of fresh buffer then analyzed spectrophotometrically λ_{\max} at of the drug^[2].

Effects of variables on the emulgel preparation

Effect of type of the oil used

The effect of the oil type (olive oil, coconut oil) used in preparation of emulgel was investigated in formulations (F1 and F3) respectively. In each formulation, the amount of surfactant and the type of gelling agent (HPMCK15M) were kept constant.

Effect of the type of gelling agents with each of the utilized oil

The effect of gelling agent type (Carbopol934 and HPMCK15M) was examined in the formulations F5 and F1 respectively. Type of oil (olive oil) and amount of surfactant (2%) were kept constant in these formulations. Whereas, formulations F8 and F4 were prepared to examine the effect of gelling agent with

fixed type of oil (coconut oil) and fixed amount of surfactant (4%).

Effect of the total amount of surfactant

Formulations F7 and F8 were prepared to study the effect of total concentration of surfactant (span80 and tween80) on the preparation of the emulgel using 2% and 4% respectively.

Statistical analysis

The results of all experiments are taken as a mean sample \pm of standard deviation and they were analyzed according to one-way ANOVA at which significant results equal to ($p < 0.05$) and non-significant results equal to ($p > 0.05$)

Result and Discussion

Characterization of nimesulide emulgel formulation

Physical appearance

Coconut oil was used as oil phase in the emulgel formulations and gave white creamy appearance with good consistency to the product, while when olive oil was used as oil phase in emulgel formulations the product showed light yellow appearance with smooth and homogenous consistency. Carbopol934 based emulgel formulations were thick in their

consistency than other formulations. On the other hand, HPMCK15M based formulations were soft and have light consistency this could be related to physicochemical properties of the gelling agent used.

pH Determination

The pH values of all prepared emulgel formulations were ranged from 5.94 to 6.55 which matched the requirements of topical preparations for skin, thus avoid skin irritation. However, emulgel in which carbopol 934 was used as gelling agent, the pH values were between (3.5-4.3) and was adjusted by using TEA in order to achieve the required pH that match that of the skin. The difference in pH values of emulgel formulations was related to the chemical structure of the polymer since the pH value of carbopol934 is related to acidic groups (COOH) in chemical structure. Upon ionization of carboxylate groups with the TEA the desired pH value was reached [16]. While, the pH of the formulations containing HPMCK15M were similar to the pH ranges of polymer solutions. The pH values of emulgel formulations are shown in Figure (1) and Table (2).

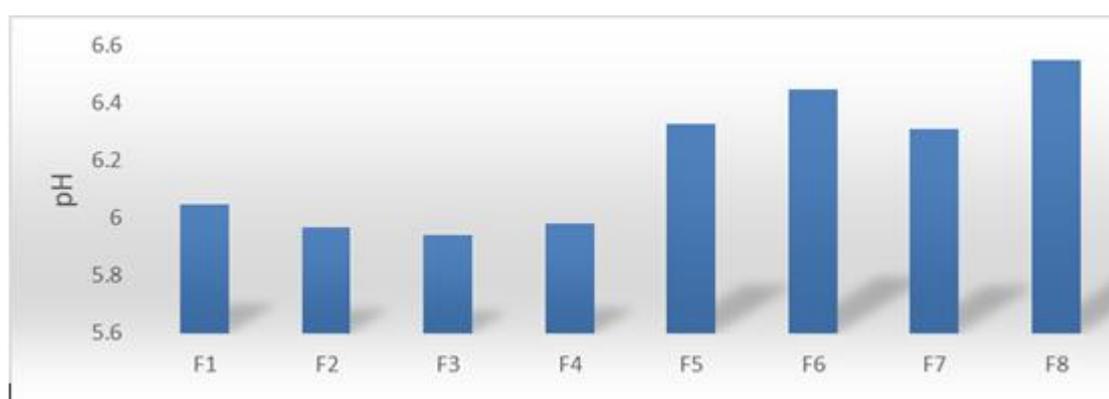


Figure (1): The pH values of the prepared emulgel formulations (F1-F8) (Values are means \pm SD) (n=3)

Spreadability

Spreadability of emulgel formulations was affected by the type of gelling agent and the type of oil used in emulgel preparation.

As a general view, the spreadability of HPMCK15M based emulgel formulations (F1-F4) which have higher spreadability than other formulations containing

carbopol934 (F5-F8) as shown in Figure (2) and Table (2), this is due to the lower viscosity of emulgel formulations obtained

using HPMCK15M which can be easily spread with modest application of shear.

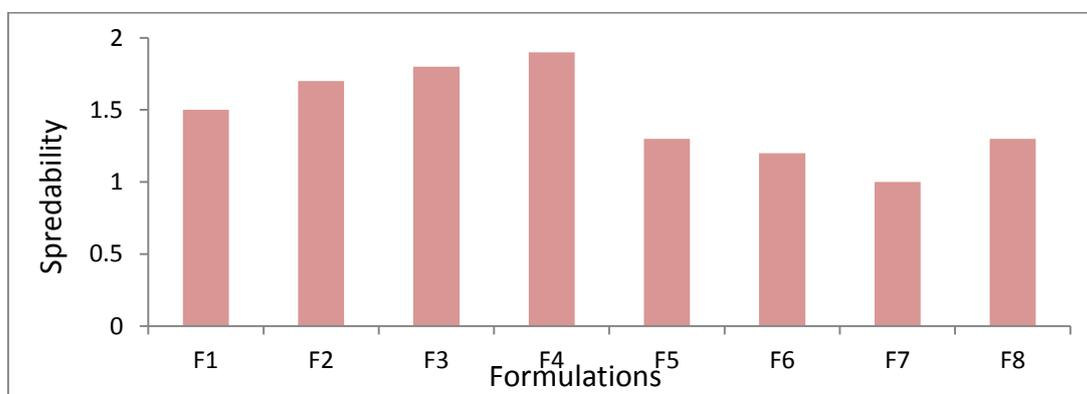


Figure (2): Spreadability values of the prepared emulgel formulations (Values are means ±SD) (n=3)

Table (2): Physical properties of emulgel formulation (Values are means ±SD) (n=3)

	Polymer	Oil	Surfactant	pH	Spreading (cm)
F1	HPMC K15M	Olive oil 8%	S.80, T.80 2%	6.05 ± 0.02	1.5 ± 0.2
F2		Olive oil 8%	S.80, T.80 4%	5.97 ± 0.01	1.7 ± 0.62
F3		Coconut oil 8%	S.80, T.80 2%	5.94 ± 0.01	1.8 ± 0.05
F4		Coconut oil 8%	S.80, T.80 4%	5.98 ± 0.01	1.9 ± 0.25
F5	Carbopol 934	Olive oil 8%	S.80, T.80 2%	6.33 ± 0.02	1.3 ± 0.4
F6		Olive oil 8%	S.80, T.80 4%	6.45 ± 0.02	1.2 ± 0.7
F7		Coconut oil 8%	S.80, T.80 2%	6.31 ± 0.02	1 ± 0.4
F8		Coconut oil 8%	S.80, T.80 4%	6.55 ± 0.05	1.3 ± 0.61

Viscosity study

The type of oil was expected to have an impact on the viscosity of emulsion. It was found that olive oil formulations have higher viscosity than coconut oil formulations as shown in Figure (3). This is because oil with long chain of fatty acid has higher viscosity than those of short chain. Olive oil consists of long chain of fatty acid (C16-C18), whereas coconut oil consists of short chain of fatty acid^[17]. To

explore this effect of the oil, two formulations F1 and F3 were used for comparison; in both formulations the amount of surfactant and type of gelling agent (HPMCK15M) were kept constant. F1 which contained olive oil showed higher viscosity than F3 which contained coconut oil.

About the effect of gelling agent on the viscosity, all formulations of carbopol934

(F5-F8) have higher viscosity than other formulations as shown in Figure (3), because Carbopol934 is a high molecular weight cross linked polymers of acrylic acid which when neutralized with the TEA has the ability to absorb and retain water, resulting in a viscous gel. Hydroxypropyl

methylcellulose-based formulations (F1-F4) have lower viscosity than carbopol934 based emulgel formulations (F5-F8), due to the higher hygroscopicity of cellulose derivatives as compared to carbopol934 [18].

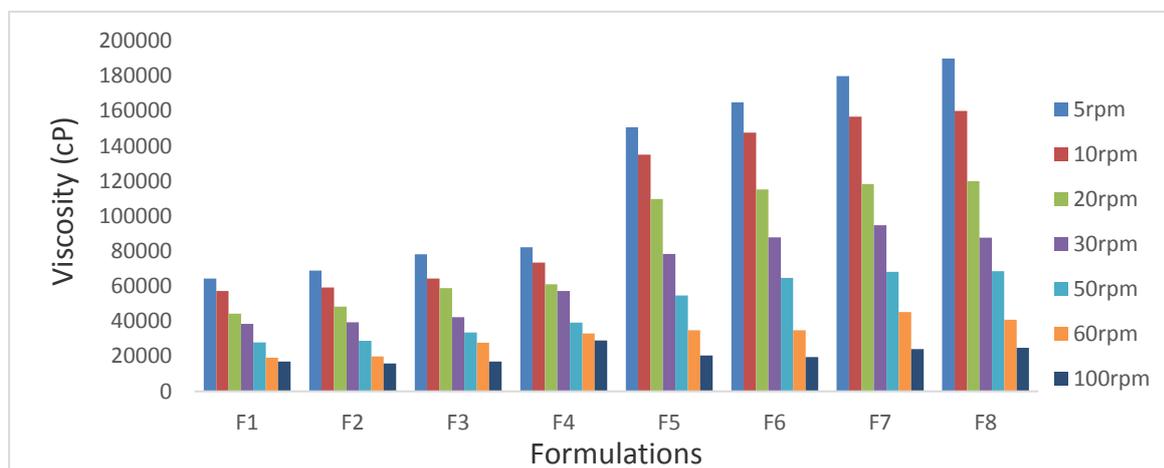


Figure (3): Effect the type of oil and gelling agent on the viscosity of the prepared emulgel formulations at different speed rate. (Values are means ±SD) (n=3)

Emulgel drug content

The content of NIM in the emulgel formulations were determined using ultraviolet (UV) spectrophotometer. NIM content in the emulgel formulations was

ranged between (85-92%) this percentage agreed with the acceptable range according to the USP (85-115%) [19], as shown in Figure (4).

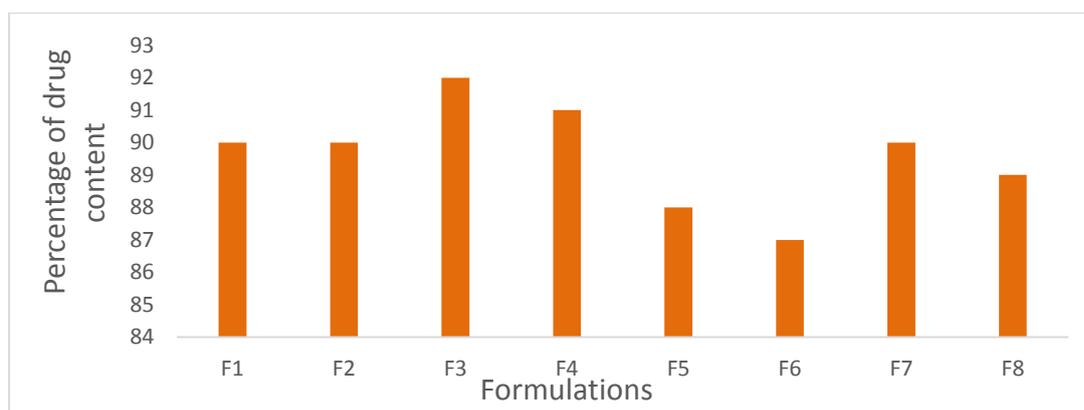


Figure (4): Percentage of NIM content in different emulgel formulations (Values are means ±SD) (n=3)

In vitro dissolution test of NIM emulgel Effect of the type of oil

Effect of the oil type on the release of NIM is shown in Figure (5). It was observed that using of coconut oil as oil phase (F3) caused a significant increase ($p < 0.05$) in

the release of NIM from the formulation after 7hrs when was compared with (F1) in which olive oil had been used, The reason behind these results could be related to the short chain of fatty acid that form the backbone of coconut oil compared to the long

chain of fatty acid in the olive oil resulting less viscous oil and faster release from

formulation containing coconut oil as oil phase^[17].

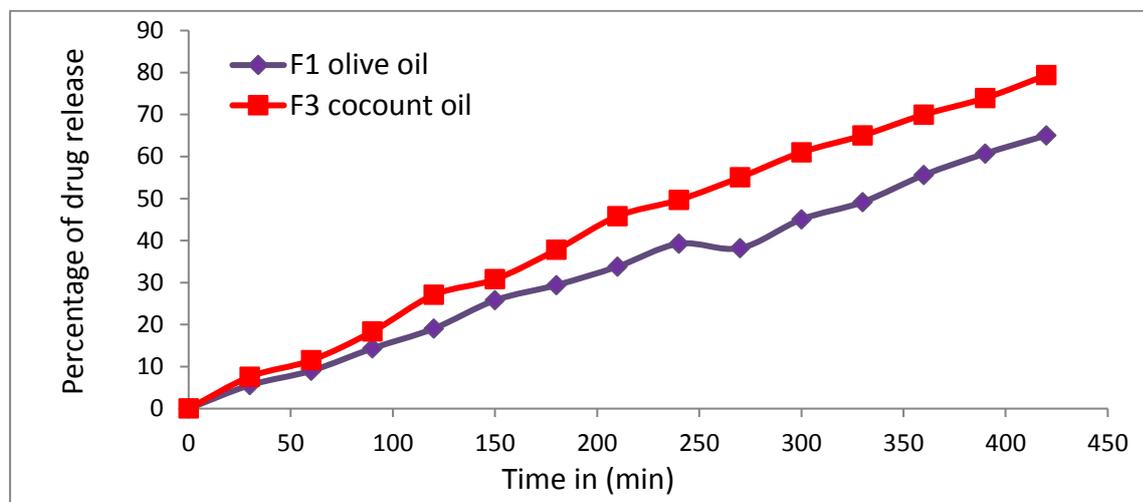


Figure (5): Effect of type of oil on the release profile of NIM in acetate buffer solution (pH 5.5) prepared with (2.5%) tween 80 at 32°C (Values are Means ±SD) (n=3)

Effect of the type of gelling agent

The effect of the gelling agents on the release of NIM was shown in the Figures (6 and 7). It was observed that there was a significant increase ($p < 0.05$) in the amount of NIM released after 7 hrs. from F4 as compared with F8. The order of the release in the coconut oil formulations was F4 ($78.16 \pm 0.1\%$) > F8 ($52.4 \pm 0.5\%$) and was also observed that there was a significant increase ($p < 0.05$) in the amount of NIM released after 7 hrs. from

F1 as compared with F5 in olive oil formulations. The order of release was F1 ($65.1 \pm 0.15\%$) > F5 ($46.6 \pm 0.6\%$). These observations may be due to the lower viscosity HPMCK15M based formulation. The viscosity of carbopol934 based formulations was higher than other formulations of emulgel due to the three-dimensional structure and cross-linking effects of the polymers^[20], thus retarding the release of the drug.

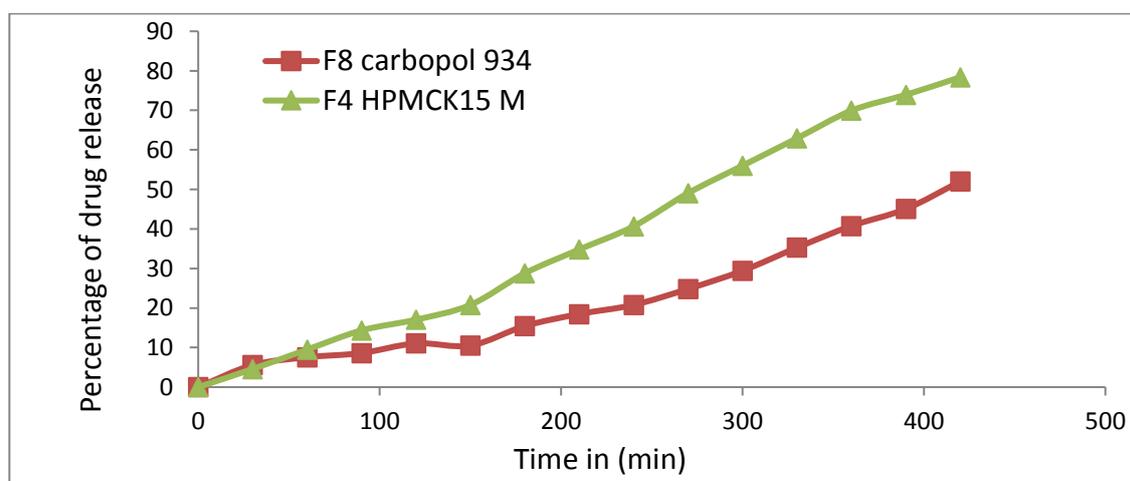


Figure (6): Effect of type of gelling agents on the release profile of NIM for coconut oil-based formulations in acetate buffer solution (pH 5.5) prepared with (2.5%) tween 80 at 32°C (Values are Means ±SD) (n=3)

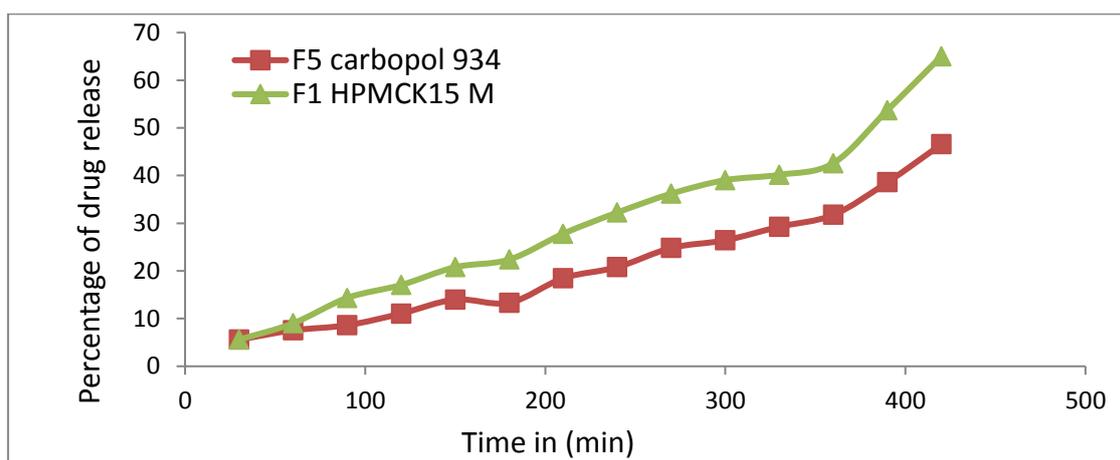


Figure (7): Effect of type of gelling agents on the release profile of NIM for olive oil-based formulations in acetate buffer solution (pH 5.5) prepared with (2.5%) tween 80 at 32°C (Values are Means \pm SD) (n=3)

Effect of total amount of surfactant

The effect of increasing the concentration of surfactants (span 80 and tween 80) from 2% in F7 to 4% in F8 was found no significant increase ($p > 0.05$) in the amount of NIM released after 7 hrs as shown in Figure (8). The release of NIM was increased from ($45.71 \pm 0.2\%$) using F7 to ($50.25 \pm 0.4\%$) using F8 after 7 hrs.

This effect may be referred to the ability of these emulsifying agents to lowering the interfacial tension between oil and aqueous layer in the dispersion medium indicating an increasing the hydrophilicity of emulgel which in turn increase penetration of dissolution medium into the emulgel structure and consequently increasing the amount of NIM released^[21].

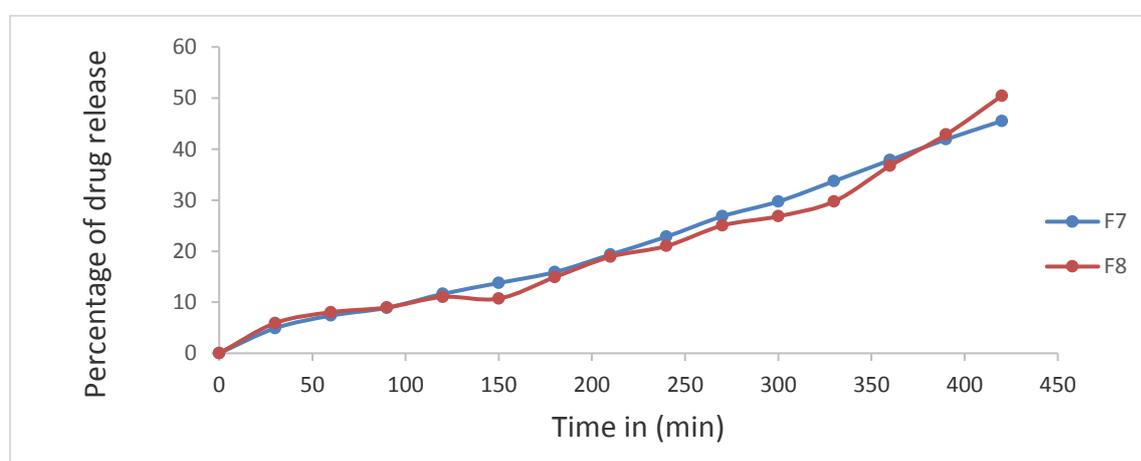


Figure (8): Effect of total amount of surfactants (span 80 and tween 80) on the release profile of NIM for coconut oil-based formulations in acetate buffer solution (pH 5.5) prepared with (2.5%) tween 80 at 32°C (Values are Means \pm SD) (n=3)

Conclusions

Emulgel containing conventional emulsion could be prepared for hydrophobic drug (Nimesulide) using emulsion consists of either coconut oil or olive oil as oil phase with (Span 80) and (Tween 80) as

emulsifying agents in presence of gelling agents like HPMCK15M and Carbopol 934. Varying the type and amount of oil, surfactant and gelling agent could efficiently affect on the physical properties

and *in vitro* release profile of the drug from emulgel formulations. The emulgel formulation (F4), containing coconut oil as an oil phase, (Span80 and Tween80) as an emulsifying agent and HPMCK15M as a gelling agent was the optimum formulation due to its excellent consistency, homogeneity, and spreading properties in addition to highest percent drug release during 7hrs dissolution test.

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