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VARIABLES AFFECTING FORMULATION AND RELEASE OF NIMESULIDE FROM TOPICAL EMULGEL FORMULATIONS

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Abstract

Objective: This study involves preparation and investigating different variables affecting on properties of the nimesulide emulgels formulation and in-vitro release profile of the drug.

Methods: This study involves preparation of eight nimesulide emulgel formulations containing primary emulsion for topical application of the drug on the skin and characterized for pH, spreadability, viscosity, drug content and in vitro drug release. The optimum formulation was formulated as emulgel by using multiple emulsion.

Result: The optimum formulation (F8) that prepared with primary emulsion showed pH (5.64), spreadability (2.8cm) and percentage of drug release (98%) with good physical appearance and viscosity. While, F2′ selected as optimum formulation containing multiple emulsion with PH (5.72), Spreadability (2.5cm), and percentage of drug release (77%)

Conclusion: This work succeeded in preparing emulgel contain primary emulsion which 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 Methylcellulose and combination of HPMCK15M and Carbopol934. Varying the type and amount of oil, surfactant and gelling agent could efficiently effect on the physical properties and *in vitro* release profile of the drug from emulgel formulations. The emulgel containing multiple emulsion with different ratio of external aqueous phase to conventional emulsion showed that good physical appearance, viscosity, spredability, drug content and highest drug release was obtained with F2′ The release of drug could be suppressed using emulgel containing multiple emulsions, as the results of release study showed that this type of emulgel released 77% of the drug after 8hrs, where 98% of the drug was release from emulgel containing conventional emulsion after 7hrs.

Key words: Emulgel, nimesulide, methylcellulose**,** carbopol934, HPMCK15M.

Introduction:

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 [1]. Semisolid preparations are corresponding to the dosage forms that demonstrate properties in the middle of that of solid and liquid dosage forms and possess distinctive rheological properties such that they can be easily applied on the biological membranes and can be retained on the site of application for an extent period of time [2]. They act as delivering systems for drugs that are topically applied to the skin, nasal mucosa, vagina, buccal tissue, urethral membrane, cornea and external ear. 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]. Emulsion is one of dosage forms that are used for internal and external uses. It is biphasic, heterogeneous system consist of two immiscible liquid one of which is called dispersed phase or internal phase and another one is called continuous phase or external phase. The internal phase is divided into finely and uniformly globules dispersed throughout the external phase [4]. Depending upon the nature of the dispersed phase, emulsion is classified into two types; if the oil phase dispersed as droplets throughout the aqueous phase then the emulsion is known as oil-in-water (o/w) and if the water phase is

dispersed throughout the oil phase is termed as water-in-oil (w/o) emulsion. Multiple emulsion is one of the recent types of emulsion, it consists of the two immiscible liquid (water in oil and oil in water) in single emulsion. Multiple emulsion is more complicated in their formulation than ordinary simple emulsion and also has more retardation effect on drug release [5]. 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. Both types of emulsion (conventional and multiple emulsions) can be used in emulgel formulation as a vehicle to deliver different drugs to the skin [6]. Emulgel is the most preferred topical delivery system for hydrophobic drug. Nimesulide is a 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. It has good anti-inflammatory, analgesic and antipyretic activity [7].

Material and method

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).

Preparation of gelling agent

a. Methyl cellulose powder was dispersed in heated distilled water (80°C), and the dispersion was cooled to room temperature then left for one day to confirm hydration of the gel [8].

b. Combination of Carpobol934 and HPMCK15M gel: carpobol934 powder was dispersed in distilled water with vigorous stirring and the pH was adjusted to (6 - 6.5) by adding drops of tri ethanol amine (TEA) and was left for one day to complete hydration of the gel. HPMCK15M was prepared by dispersing in heated distilled water at 70 ^{o} C with continuous stirring and the dispersion was cooled then left for one day. Then the two gelling agents were mixed together [9].

Preparation of primary emulsion

Both continuous and dispersed phases were prepared individually; the continuous phase was prepared by dissolving the required quantity of tween80 in purified water, the amount of surfactants used according to HLB theory. Methyl paraben and propyl paraben were mixed with propylene glycol as preservative at concentrations of 0.03% w/w and 0.01% w/w respectively then mixed with previously prepared tween 80 solution. The dispersed phase was prepared by dissolving desired quantity of span80 in the oil phase. One gram of NIM was added and mixed with dispersed phase until completely dissolved. The continuous and dispersed phases were heated at range 70ºC to 80ºC then the dispersed phase was added to continuous phase with constant stirring to form homogeneous emulsion, then the emulsion was left to cool down at room temperature, the emulsion and gelling agent were mixed together at (1:1) weight ratio with continuous stirring to from smooth homogenous emulgel formulation [10]. The main compositions of emulgel formulation containing primary emulsion are shown in table (1)

Table (1): Main composition of emulgel formulation containing primary emulsion

Formula NO.	Nimesulide	HPMCK15M	Carbopol934	Methyl cellulose	Olive oil	Coconut oil	Span 80	Tween 80	Propylene glycol	Methyl paraben	Propyl paraben	Oleic acid	Purified water up 100 mL
F1	1	1.5	0.5		8		0.5	1.5	5	0.03	0.01	1	100
F2	1	1.5	0.5		8		1	3	5	0.03	0.01	1	100
F3	1	1.5	0.5			8	0.5	1.5	5	0.03	0.01	1	100
F4	1	1.5	0.5			8	1	3	5	0.03	0.01	1	100
F5	1			3.5	8		0.5	1.5	5	0.03	0.01	1	100
F6	1			3.5	8		1	3	5	0.03	0.01	1	100
F7	1			3.5		8	0.5	1.5	5	0.03	0.01	1	100
F8	1			3.5		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 100mL of acetate buffer prepared with 2.5% tween80 and placed aside for two hours before measuring its pH. 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 Kg) 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 0.5Kg 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 ^{o} 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 [14].

Drug content determination

One gram of emulgel sample was dispersed in 100 ml acetate buffer containing (2.5%) tween 80 and then the mixture was sonicated for 2hrs. The obtained sample was filtrated using 0.45 µm Millipore filter, then diluted and analyzed at the determined λ_{max} of the drug [15].

In Vitro release test of nimesulide emulgel

The in vitro release of NIM from emulgel formulations was done by USP dissolution apparatus-type II (paddle). Three grams of the prepared formulation that comprise (30 mg NIM) were putted in a small beaker of 2.5 cm in diameter then the opening of the beaker was covered by 0.45 µm 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 50rpm. 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 0.45 µm Millipore filter and replaced with an equal volume of fresh buffer then analyzed spectrophotometrically at the λ_{max} of the drug [16].

Effects of variables on the emulgel preparation containing primary emulsion

Effect of type of the oil used

The effect of the oil type (olive oil, coconut oil) used in the preparation of emulgel was investigated in formulations (F5 and F7) respectively. In each formulation, the amount of surfactant 2% and type of gelling agent used (methylcellulose) were kept constant.

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

The effect of gelling agent type (methyl cellulose and combination of carbopol934 and HPMCK15M) was examined using 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 concentration of surfactant

Formulations F7, F1 and F8, F2 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.

Selection the best emulgel formulations containing primary emulsion

Four best formulations (F2, F4, F6 and F8) were selected from sixteen emulgel formulations containing conventional emulsion according to excellent physical characterization then were examined for skin irritation, extrudability and skin permeation.

Skin irritation test

Animal model was used to examine the skin irritation test by application the selected formulation on the skin of mice after being shaved. Eight mice (35 g) were selected for this examination study and any alteration in the skin color and morphology were checked for 24hrs. The procedure was repeated after three days to ensure that there was no sensitivity to the emulgel formulations [17].

Determination of extrudability

The extrudability of the four best emulgel formulations contain conventional emulsion were determined by using modified method from reported in literature [18], in which feeding syringe with a tip of 0.5cm was filled with the formulation and measured the amount of pressure which applied on feeding syringe. Different weights were used to determine the weight required for extruding the formulation from feeding syringe, and the following equation was used to calculate the extrudability value for each formulation.

$$Extrudabilit = \frac{\text{weight applied to extrude emulgel from tube in gm.}}{\text{Area in } cm^2}$$

In vitro permeation study of emulgel formulations containing primary emulsion through skin membrane

One gram of each best NIM emulgel formulations containing 1% (w/w) nimesulide was introduced in a test tube and the skin was stretched over the mouth of the test tube and ligated with rubber band. The test tube and all the assemble was used as diffusion cell which was then inverted and immersed in the jar of the dissolution apparatus containing 500mL freshly prepared acetate buffer (pH 5.5) with (2.5%) tween 80. The system was kept at 32±0.5°C and the buffer solution was stirred at 50 rpm [19], samples of 5 ml were taken every 30 min and were substituted

with the same volume acetate buffer solution pH (5.5) with (2.5%) tween 80 and filtered through 0.45μm, Millipore filter and analyzed spectrophotometrically at λ_{max} of the drug.

Selection optimum emulgel formulation containing primary emulsion

The Selection of optimum formulation from the four best emulgel formulations containing primary emulsion was done according to the result of skin permeation.

Stability study for optimum nimesulide emulgel formulation containing primary emulsion

Effect of accelerated temperature [Determination of expiration date]

The effect of temperature on the stability of optimum selected NIM emulgel was studied. The emulgel formulations were kept in amber glass container in ovens at different temperatures of (40, 50 and 60° C), for three months. Samples were withdrawn at certain time intervals to determine the content of NIM by measuring their UV absorbance at λ_{max} of the drug [20].

Preparation emulgel using multiple emulsion (w/o/w emulsion)

Two multiple emulsion were prepared by two step emulsification process. Specific amount of purified water containing preservative was gradually added to oil phase containing lipophilic emulsifier (span 80) and one gram of NIM was added with continuous stirring to form primary emulsion (w/o). The primary emulsion was further emulsified with an external aqueous phase containing hydrophilic emulsifier (tween 80). The primary emulsion (w/o) was added slowly into continuous phase with constant stirring rate to form a stable multiple emulsion. The obtained multiple emulsions were mixed with gelling agent at (1:1) weight ratio with moderate stirring to from two smooth homogenous emulgel formulations [21]. The main compositions of the two emulgel formulations containing multiple emulsion are shown in table (2)

Table (2): Main compositions of emulgel formulation containing multiple emulsions % (w/w)

Formula NO.	Ratio of external aqueous phase to conventional emulsion	Nimesulide	Methyl cellulose	Coconut oil	Span 80	Tween 80	Propylene glycol	Methyl paraben	Propyl paraben	Oleic acid	Purified water up to 100 ml
F1′	35:15	1	3.5	8	1	3	5	0.03	0.01	1	100
F2′	30:20	1	3.5	8	1	3	5	0.03	0.01	1	100

Characterization of nimesulide emulgel formulations containing multiple emulsion

The same tests as previously described for emulgel were performed here to inspect the physical appearance, pH, spraedability, viscosity and drug content.

Optimization of nimesulide emulgel formulations containing multiple emulsion

Effect volume of internal aqueous phase on emulgel formulations

The effect of internal aqueous phase volume was investigated using two formulations (F1′ and F2′). Formulation (F2′) was prepared with higher volume of internal aqueous phase than in formulation (F1′). In each formulation the type of oil, the amount of surfactant and the type of gelling agent (methylcellulose) were kept constant.

Selection the optimum emulgel formulation containing multiple emulsion

Selection of the best formulation was done according to its excellent consistency, high spreading coefficient property, and high drug content with high percent of release profile.

Result and Discussion

Characterization of NIM emulgel containing primary and multiple emulsion

Physical Appearance

It was found that coconut oil used as oil phase in two types of emulgel formulations gave white creamy appearance with good consistency, while when olive oil was used as oil phase in

emulgel formulations containing primary emulsion showed light yellow appearance with smooth and excellent homogenous consistency. Methylcellulose based formulations were very soft and exhibited light consistency.

pH Determination

The pH values of all prepared emulgel formulations containing primary emulsion ranged from 5.64 to 6.55 and this matched with skin requirements for topical preparations, thus avoid any excepted skin irritation. The pH values of emulgel formulations contain multiple emulsions ranged from 5.72 to 5.93.

Spreadability

In general, the spreadability is an essential characteristic for topical formulations efficacy which indicates that the formulations can easily spread on the skin by small application of shear. Spreadability of emulgel formulations affected by types of gelling agent and their viscosity and could be affected by type of oil used as oil phase in emulgel preparation. Generally, the spreadability of methylcellulose based emulgel formulations containing primary emulsion displayed higher spreadability than other formulations due to the excellent homogenecity and lower viscosity of emulgel.

Spreadability of emulgel formulations containing multiple emulsions was affected by the external aqueous phase ratio [22]. When the external aqueous phase ratio was increased, emulgel viscosity decreased and spreadability of formulations increased. For this reason, F1′ has higher spreadability than F2′. The physical properties of the two types of emulgel formulations are shown in Tables (3 and 4).

Table (3): Physical properties of emulgel formulations contain primary emulsion

Formulation no.	Polymer	Oil	Surfactant	pH	Spreading (cm)
F1	**Carbopol934 and HPMC K15M**	Olive oil 8%	S.80, T.80 2%	6.13 ± 0.05	1.9 ± 0.1
F2		Olive oil 8%	S.80, T.80 4%	6.27 ± 0.05	2.2 ± 0.1
F3		Coconut oil 8%	S.80, T.80 2%	6.37 ± 0.04	2.1 ± 0.1
F4		Coconut oil 8%	S.80, T.80 4%	6.23 ± 0.04	2.06 ± 0.11
F5	**Methylcellulose**	Olive oil 8%	S.80, T.80 2%	5.76 ± 0.01	2.5 ± 0.51
F6		Olive oil 8%	S.80, T.80 4%	5.75 ± 0.01	2.6 ± 0.11
F7		Coconut oil 8%	S.80, T.80 2%	5.77 ± 0.01	2.6 ± 0.42
F8		Coconut oil 8%	S.80, T.80 4%	5.64 ± 0.01	2.8 ± 0.044

Table (4): Physical properties of emulgel formulations contain multiple emulsion

Formulation	Polymer	Oil	Surfactant	pH	Spreading(cm)
F1′	**methylcellulose**	Coconut oil 8%	S.80, T.80 4%	5.93±0.2	2.7±0.4
F2′		Coconut oil 8%	S.80, T.80 4%	5.72±0.1	2.5±0.2

Viscosity study

The viscosity study was performed to assess the effect of the type of the oil, gelling agent and emulsifying agent on the physical properties of the final emulgel products and their viscosity.

The viscosity of oil affects the viscosity of emulsion which is the chief part of the emulgel formulation; it was found that olive oil formulations have higher viscosity than coconut oil formulations because the olive oil consists of long chain of fatty acid usually long carbon atom chain of (C16-C18) while the coconut oil consists of short chain of fatty acid, hence the oil has greater chain length has greater viscosity [23].

About the gelling agent effect on the viscosity, generally formulations containing combinations

of gelling agents (carbopol934 and HPMC K15M) (F1-F4) had higher viscosity than other formulations because Carbopol934 is high molecular weight cross linked polymer of acrylic acid, which when ionized with the base have the ability to absorb and retain water, resulting in a viscous gel. While methylcellulose-based formulations (F5-F8) had lower viscosity due to the higher hygroscopicity of cellulose derivatives [24]. Regarding the effect of emulsifying agent on the viscosity; generally increasing the amount of emulsifying agent caused in increasing the viscosity of the emulsion which in turn increased the viscosity of the emulgel. On the other hand, the ratio of external aqueous phase in multiple emulsions showed a great influence on the viscosity of the emulgel formulations. When the external aqueous phase ratio was increased, a decrease in the viscosity of both emulsion and emulgel was observed. For this reason, F2′ has higher viscosity than F1′ [25]. Figures (1and 2) showing the viscosity of two types of emulgel formulations.

Emulgel drug content

The content of NIM in the emulgel formulations were determined using UV spectrophotometer. NIM content of the two types of emulgel formulations containing primary and multiple emulsion was ranged between (87%-98%) and (94%-96%) respectively. The percentages of NIM content of two types of emulgel formulations are shown in Figures (3 and 4).

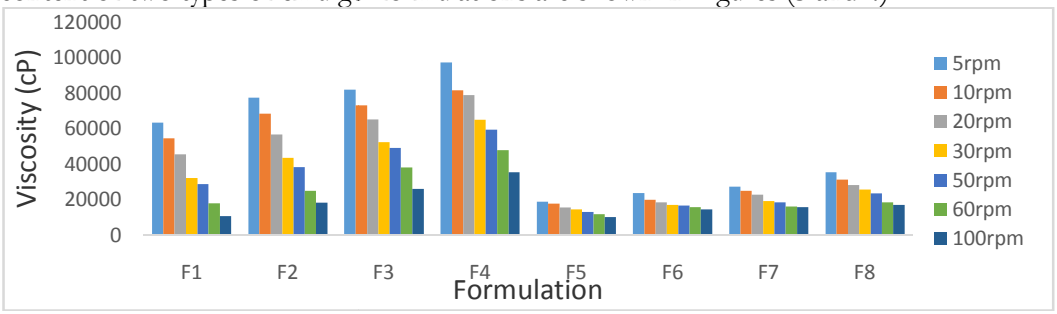


Figure (1): The Viscosity of emulgel prepared formulation containing primary emulsion at different speed rate

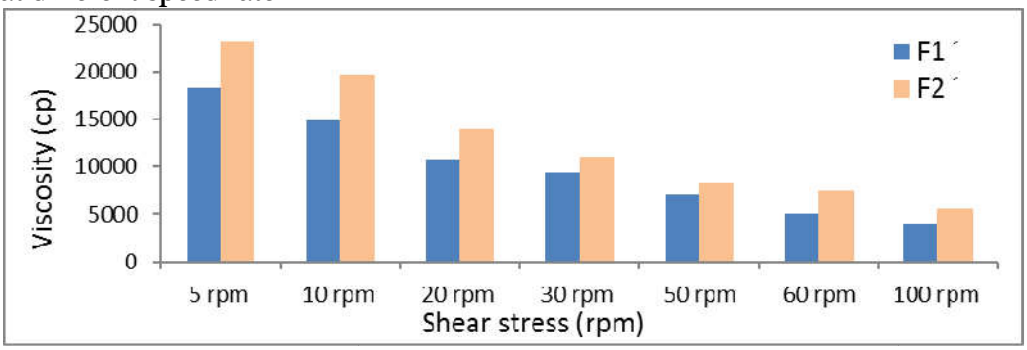


Figure (2): The Viscosity of emulgel prepared formulation containing multiple emulsion at different speed rate

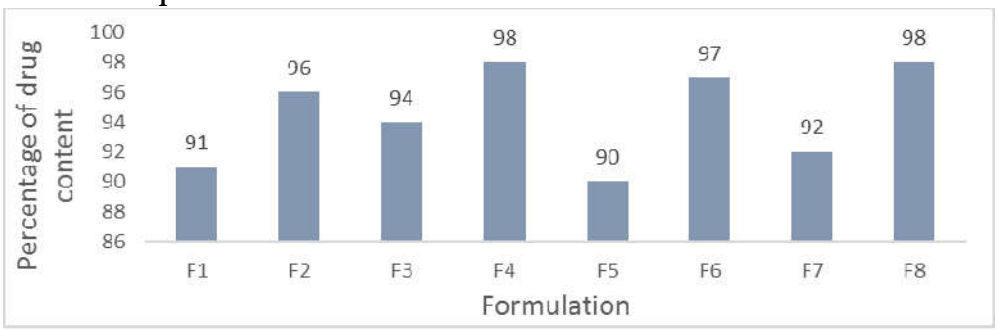


Figure (3): Percentage of NIM content in different emulgel formulations contain primary emulsion

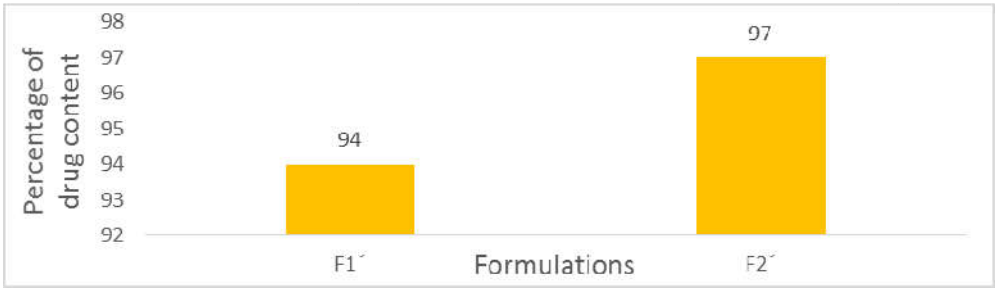


Figure (4): Percentage of NIM content in different emulgel formulations contain multiple emulsions

In vitro dissolution test of NIM emulgel containing primary emulsion

Effect of the type of oil

Figure (5) shows a significant increase in the release of NIM after 7hrs from F7 in which coconut oil was used in preparing the oil phase of the emulsion when compared to F5 in which olive oil was used in preparing oil phase. In both formulations the gel base was methyl cellulose and the percentage of surfactants was 2%. The reason behind these results could be related to the short chain of fatty acid that form the back bone of coconut oil compared to the long chain of fatty acid in the olive oil resulting in less viscous oil and faster drug release from formulation containing coconut oil as oil phase [23].

Effect of the type of gelling agent with each type of oil

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 F8 as compared with F4. The order of the release in the coconut oil formulations was F8 (98.3 ± 0.3%) > F4 (94.4.1 ± 0.2%). It was observed that there was a significant increase ($p < 0.05$) in the amount of NIM released after 7hrs from F5 as compared with F1 in olive oil formulations. The order of release was F5 (95.5 ± 0.34%) > F1 (91.5 ± 0.4%). These observations may be due to the lower viscosity of methylcellulose-based formulations as compared with combination of gelling agents (carbopol934 and HPMCK15M) based formulations due to the three-dimensional structure of carbopol934 and cross-linking effects of the polymers, thus retarding the release of NIM [26].

Effect of total amount of surfactant

The effect of increasing the concentration of surfactants (span 80 and tween 80) from 2% in (F7 and F3) to 4% in (F8 and F4) was found to cause significant increase ($p < 0.05$) in the amount of NIM released after 7 hrs. as shown in Figures (8 and 9). The release of NIM was increased from (88.71 ± 0.2%) using (F7) to (98.25 ± 0.4%) using (F8) and from (87.4% ± 0.15%) using (F3) to (94.5% ± 0.4%) using (F4) after 7hrs. This effect may be referred to the ability of these emulsifying agents to lower the interfacial tension between oily and aqueous layers in the dispersion medium indicating increasing the hydrophilicity of emulgel which in turn increased penetration of dissolution medium into the emulgel and increasing the amount of NIM released [27].

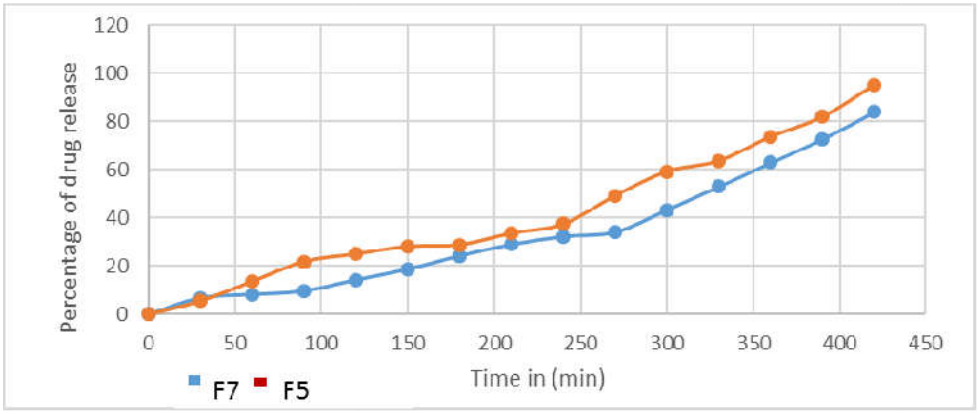


Figure (5): Effect type of oil on the release profile of NIM

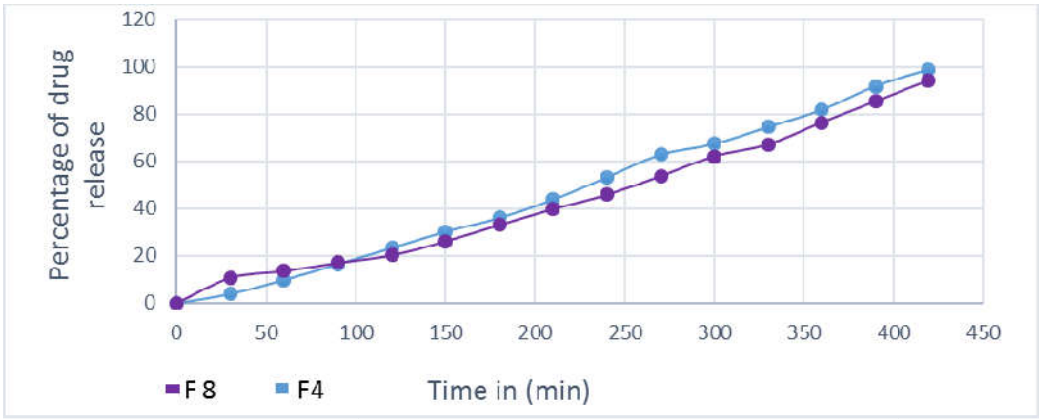


Figure (6): Effect of type of gelling agents on the release profile of NIM for coconut oil-based formulations

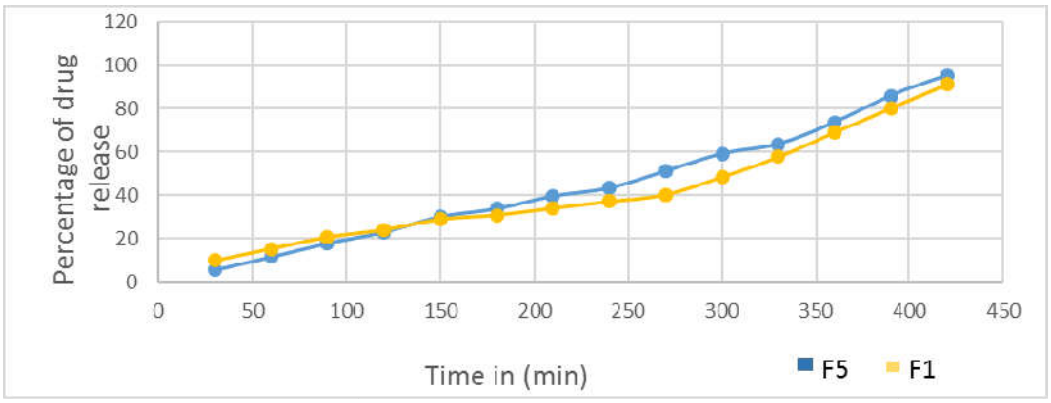


Figure (7): Effect of type of gelling agents on the release profile of NIM for olive oil-based formulations

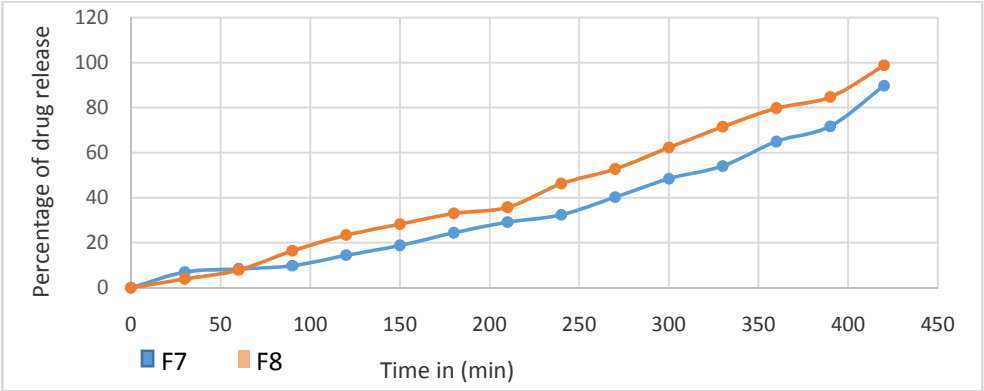


Figure (8): Effect of total amount of surfactants (span 80 and tween 80) on the release profile of NIM for coconut oil-based formulations

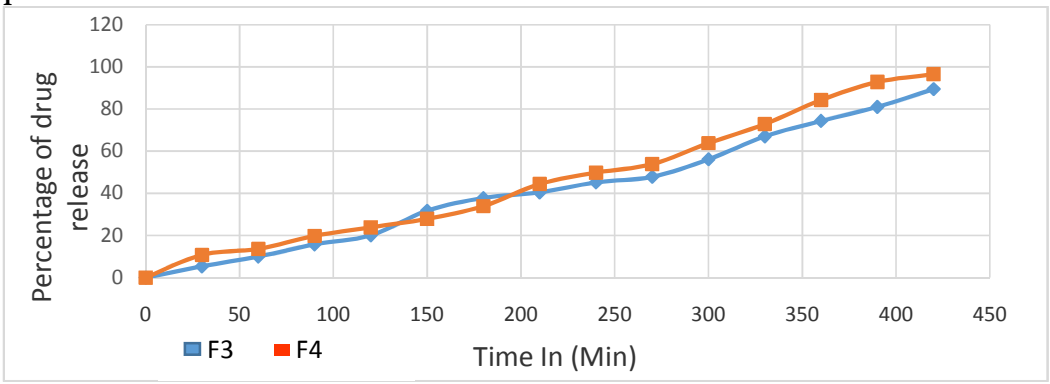


Figure (9): Effect of total amount of surfactants (span80 and tween80) on the release profile of NIM for coconut oil-based formulations

Selection the best emulgel formulations containing primary emulsion

Four best formulation (F2, F4, F6 and F8) were selected from eight emulgel formulations containing primary emulsion according to their excellent consistency, high spreading coefficient property and high drug content with high percent of drug release within 420 min of dissolution test in (pH 5.5) acetate buffer.

Skin irritation study

The results of skin irritation test of the emulgel Formulations contain primary emulsion are as follows: there is no irritation signs on the rat skin like erythema, edema and ulceration after application of the formulations and monitoring of the irritation signs for 24hrs. In addition, there is no irritation sign after repeated formulations application after one weak, which means that formulations have no irritation capability and did not cause any sensitivity reactions**.**

Determination of extrudability

The extrudability test shows the extent to which emulgel formulations is extruded out from the syringe. The extrudability depends on the viscosity and consistency of any formulation. The less viscous formulation, the more extent to which the formulation is extruded out. F6 and F8 showed good extrudability than formulations [28] (F2 and F4).

In vitro permeation of the best emulgel formulations containing primary emulsion through skin membrane

The percentage of drug release from emulgel formulation and permeation through the skin could be affected by the major constituents of emulgel formulations such as oil phase, surfactant and gelling agent. The use of coconut oil and olive oil as oil phase in emulgel preparation could enhance the permeation of the drug through the skin by alteration in the lipid layer of stratum corneum [29]. On the other hand, the nonionic surfactants are classified as one of the compounds that have been tested for their enhancer action it was reported to enhance drug permeability.

Regarding to the gelling agents used carbopol934 is a high molecular weight polymer which is known to form a dispersion of swollen gel particles in solvent with an expanded configuration of polymer molecules in network structure that hinders the diffusion of drug between gel-skin interface thus reduce drug permeation. While, HPMCK15M is hydrophilic in nature that increase penetration of solvent inside the emulgel resulting in enhance drug permeation [30]. For this reason, a combination of these two types of gelling agent affected on skin permeation of F2 and F4 as shown in Figure (10). Methylcellulose as gelling agent used in F6 and F8 showed good skin permeation, this effect could be related to low molecular weight of the gelling agent and it is viscosity. F8 was selected as the best formulation since it showed 86% of drug permeation through the skin during 7hrs. In addition to the pH value of this formula (i.e.,5.64) with no irritation issue from the use of this formulation. Furthermore, (F8) has an acceptable physical property, homogeneity, consistency, drug content and viscosity.

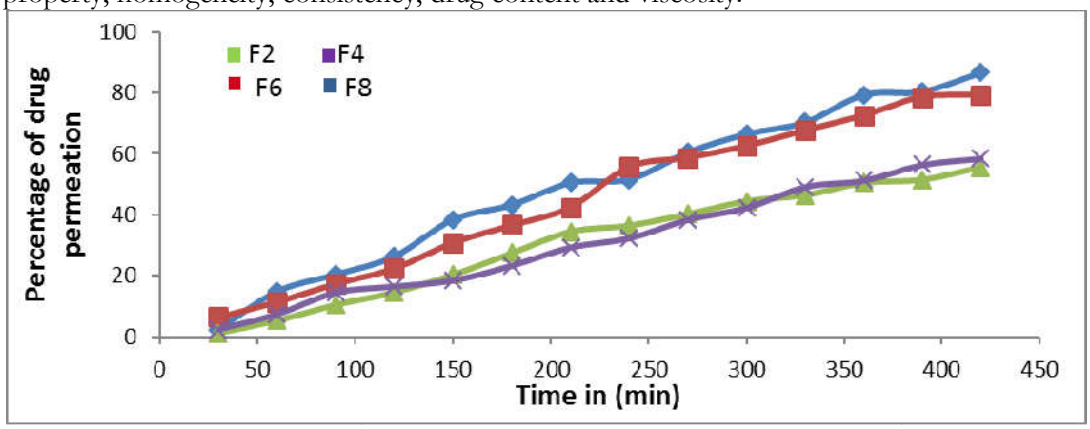


Figure (10): Percentage of drug permeate through the skin

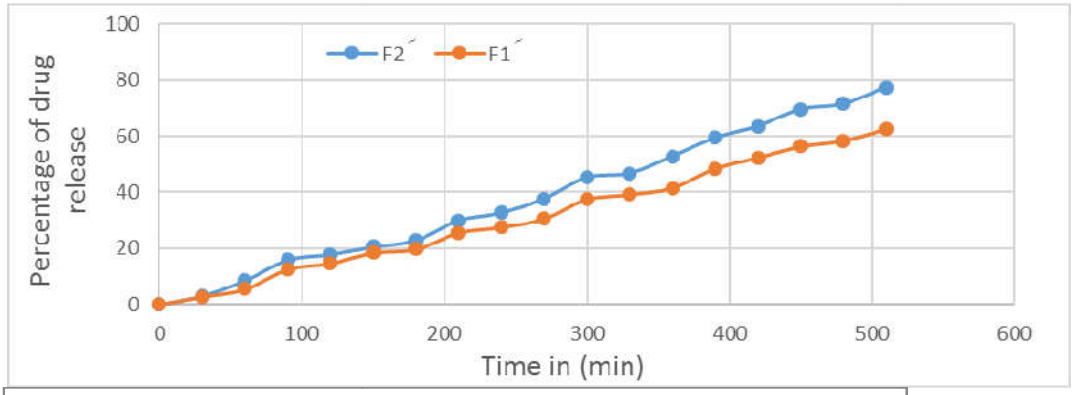
Stability study of optimum emulgel formulation (F8)

The stability of NIM selected emulgel formulation (F8) was studied at three different temperatures 40°C, 50°C and 60°C for three months. Samples of the emulgel formulation were taken at two weeks interval and were studied for NIM content. The self-life was 2.6 years.

Optimization of nimesulide emulgel formulations containing multiple emulsion

Effect of internal aqueous phase volume on emulgel formulations

Effect of internal aqueous phase volume on in vitro drug release profile is shown in Figure (11). It was observed that increase in volume of internal aqueous phase in (F2′) caused a significant increase ($p < 0.05$) in the release of NIM from the formulation after 8hrs (77.33% ± 0.2) compared with the release from F1′ (62.44% ± 0.4). It was suggested that enhancement of in the release from F 2′ may be the result of the oil phase layer thinning effect. Since, the thickness of the layer is inversely proportion to the internal phase volume and this enhance the diffusion of drug from the oil phase [31]. Formulation F2′ was considered as an optimum formulation since it possesses favorable properties than F1′ such as good viscosity, spreadability, drug content and amount of drug release (77% after 8hrs).



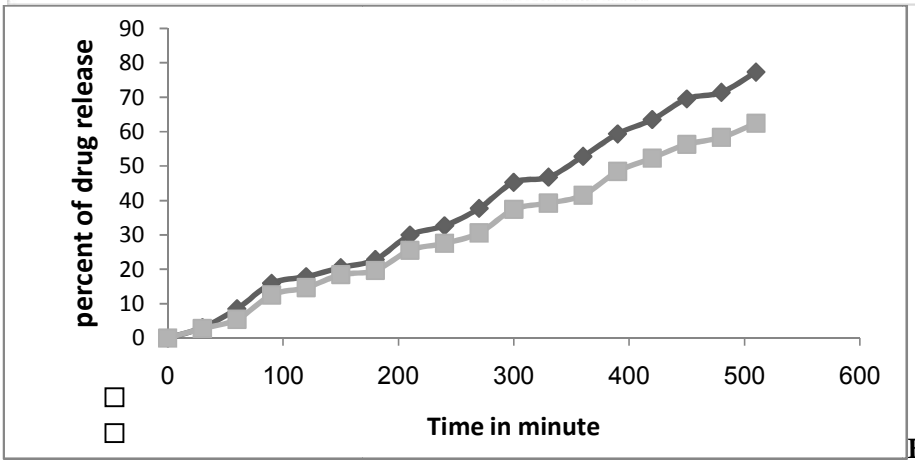


Figure (11): Effect volume of internal aqueous phase on the release profile NIM

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