Improvement of solubility and transdermal flux of Etodolac by Microemulsion system

Laith Zainee[1], Ahmed Najim Abood[2], Muder Al Hayder[3]

1Department of pharmaceutics-Faculty of Pharmacy-University of Kufa, 2 Department of pharmaceutics-Collage of Pharmacy-University of Basrah, 3 Faculity of pharmacy/Jabir Bin Hayyan Medical University.

Keyword: Microemulsion, Etodolac, , Solubilization, In vitro-release/permeation.

Abstract

Etodolac is a member of the group of non-steroidal anti-inflammatory drugs (NSAIDs) with analgesic and anti-arthritic properties. Etodolac possess a physicochemical properties that make it a suitable candidate for transdermal drug delivery, since using the transdermal route increases patient compliance, avoids first-pass metabolism, and maintains the plasma drug level for a longer period of time. Microemulsion is a drug delivery systems capable of solubilizing poorly water soluble drugs as well as their enhancement of topical and systemic availability. The aim of the conducted study was to develop an effective percutaneous delivery system for etodolac since it characterized by low water solubility and undergoing hepatic catabolism in the way of improve drug dissolution and its bioavailability. Etodolac microemulsion formulas were prepared using phase-titration method by plotting of pseudo ternary diagram using 30% anise oil as internal phase, 30% emulsifiers (tween20/ethanol) (5:1 /1:1 /1:0) and 40% weight ratio of distilled water as the outer phase. The blanks and etodolac-microemulsions formulations were evaluated. The obtained characterization results for the prepared microemulsion formulas were; a globules size range (7.92 to19.9 nm.), PDI values in the mid-range poly-dispersity (0.117 - 0.28), FTIR studies indicates absence of any type of chemical reaction between the active drug and the excipients and the estimated viscosity values for etodolac microemulsion formulas and their blanks were inversely related with the amount of co-surfactant in the S.mix.. Finally it was concluded that the prepared microemulsion formulas of etodolac succeeded to improve solubility of the drug and protecting the drug against enzymatic degradation and oxidation, also its membrane permeability was enhanced too.

تحسين ذوبانية والتدفق عبر الجلد للعقا ايتودولاك بواسطة استخدام نظام المستحلب المايكروي

ليث زيني[1], احمد نجم عبود[2], مظر آل حيد [3]

1 فرع الصيدلانيات-كلية الصيدلة-جامعة الكوفة, 2 فرع الصيدلانيات-كلية الصيدلة-جامعة البصرة, 3 كلية الصيدلة / جامعة جا ر ن حيا الطبية.

كلمات مفتاحيه : مستحلب دقيق, الايتودولاك, الاذابه, النفاذيه/الاطلاق المختبري

الايتودولاك هو عضو في مجموعة العقاقير المضادة للالتها ات غير الستيرويدية (NSAIDs) مع خصائص مسكنة ومضادة لالتهاب المفاصل. يمتلك اللايتودولاك خوا فيزيائية وكيميائية تجعله مرشحًا منا ًا للتوصيل عبر الجلد ، حيث إ تخدام طريق الجلد يزيد من التزام المريض, يتجنب التمثيل الغذائي الأول، ويحافظ على مستوى الدواء في البلازما لفترة أطول من الزمن. المستحلب الدقيق هو عبارة عن نظام لتوصيل الأدوية قادرة

على تذوب الأدوية ذات الذ ا السيئ الماء الإ افة إلى تعزيز توفرها المو عي والنظامي. ك الهدف من الدرا ة التي أجريت هو تطوير نظام توصيل فعال للايتودولاك عن طريق الجلد ك العلاج يتميز انخفاض الذ انيه المائية ويخضع لعملية هدم الكبد اتجاه تحسين حل الدواء وتوافره البيولوجي. تم تحضير صيغ المستحلبات الصغيرة للايتودولاك وا طة طريقة معايرة الطور عن طريق ر م مخطط ثلاثي الزائف ا تخدام 30٪ من زيت اليانسو كطور داخلي ، 30٪ مستحلبات (5: 1/1: 1/1: 0) (tween20 / ethanol) ونسب 40٪ نسب الوز من الماء المقطر كطور خارجي. المستحلبات الصغيرة الفارغة ومستحلبات الصغيرة لل الايتودولاك خضعت للتقييم. كانت نتائج التمييز التي تم الحصول عليها من الصيغ المستحضر المايكروي :نطاق حجم الكريات (من 7.92 إلى 19.9), قيم مؤشر التشتت المتعدد(PDI) في البعد متو طة المدى (0.117 -0.28) للتشتت المتعدد, درا ات FTIR تشير إلى غياب أي نوع من التفاعل الكيميائي ين الدواء الفعال والسواغات وقيم اللزوجة المقدرة لصيغ المستحلبات الصغرى للايتودولاك و المستحلبات الصغيرة الفارغة الخاصة ها كانت ذات صلة عكسية كمية الفاعل السطح المشارك في S.mix. واخيراً فقد تم الانتهاء ا صيغ المستحلب الدقيق للايتودولاك المحضرة نجحت في تحسين ذ انية الدواء طريقة تغليفه وا طة مذيبات مختلفة و حماية الدواء من الأكسدة والتحطم الانزيمي كما وتم تعزيز النفاذية الغشائية ايضاً.

Introduction

Etodolac is a selective cox-2 enzyme inhibitor. It belongs to the non-steroidal anti-inflammatory agents (NSAID) which possess anti-inflammatory, analgesic, and anti-pyretic activities. It is used mainly to relief rheumatoid arthritis and osteoarthritis.
It has a molecular formula of (C17H21NO3) with a molecular weight of 287.35g/mol.[1]. Etodolac classified as class-II according to the Biopharmaceutical classification system (BCS)[2], so that characterized by slight aqueous solubility and rapid permeation rate. It is insoluble in water and of good solubility in organic solvents like methanol, ethanol, dimethylsulfoxide [2]. Etodolac present as a white crystalline powder that melt near 154°C[3] with a partition coefficient of (n-octanol: water) 11.4 at pH 7.4 (highly lipophilic) and a single ionizable group of pKa= 4.65[2] as shown in the figure(1). The elimination half-life of Etodolac is 7.4 hours[4]. Etodolac has extensive liver metabolism[5].

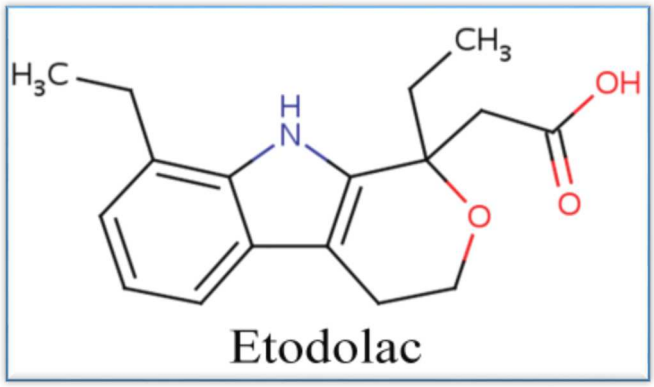

Figure (1): Chemical structure of Etodolac [6].

Microemulsion system described as transparent, monophasic, optically isotropic and thermodynamically stable colloidal dispersion system, consist of two immiscible liquids, such as oil and water with the aid of amphiphilic molecules and co-solvent, their droplet size between (5-200 nm.)[6]. Microemulsion system is easily and spontaneously formulated, since its (interfacial tension) or kinetic energy that is retarding system formation have been overcome[7]. This system possess high solubilizing capacity, protection of the active drug against oxidation, enzymatic hydrolysis and it is considered as thermodynamically stable system that do not show

phase separation or altering in the droplets size over time[8]. Microemulsion system divided into 3 types; oil-in-water (O/W), water in oil (W/O) and bi-continuous type system. Microemulsion system is a highly dynamic system that undergoes spontaneous fluctuations continuously[9]. Percolation phenomenon characteristics microemulsion system that a phase inversion from (W/O) to (O/W) may occur when its aqueous content increased which can easily detected by estimation of electrical conductivity of its outer surface[7].

Microemulsion system composed mainly from: (oil phase, water phase, surfactant and/or co-surfactant) that the colloidal droplets are despised in a continuous medium which are tied together by the use of surfactant and/or co-solvent[9]. Percutaneous flux for medication is easily and more convenient by the patients, avoiding GIT deteriorations of drugs, reducing drug dosing and frequencies of administration, and maintaining a potential control of the drug release[10].

Materials and methods

Materials

Table (1): The materials used in this study and their suppliers.

No.	The materials	The Suppliers
1.	Etodolac	Shenzhen lodi chemical co., Ltd. China
2.	Anise oil	Bar-sur-loupgrasse(A.M) France
3.	Ethanol	Grin land chemical co. UK
4.	Tween 20	Hi media Lab. Pvt. Ltd. India
5.	Methanol	GCC. analytical reagent. UK
6.	Monobasic Sodium Phosphate	Hi media Lab. Pvt. Ltd. India
7.	Dibasic Sodium Phosphate	Hi media Lab. Pvt. Ltd. India
8.	Oleic acid	Lobal. Chemical Lab. Ltd. India
9.	Olive oil	Bar-sur-loupgrasse France
10.	Propanol	Solvchem UK
11.	Iso-propanol	Solvchem UK
12.	PEG-400	Hi media Lab. Pvt. Ltd. India
13.	Tween 80	Grin land chemical co. UK
14.	Span 20	Fluka AG, Chemische Fabrik, CH-Buchs SG

The instruments

Table (2): The instruments used in the study and their manufacturers.

No.	The instruments	The manufacturers
1.	Differential scanning calorimetry (DSC)	DSC-60. Shimadzu , Japan
2.	Fourier transform infrared spectroscopy (FTIR)	IRPrestige-21, Shimadzu , Japan
3.	UV-Spectrophotometer	Sco tech, spuv-26, Germany
4.	Electronic balance	Denver Instrument, Germany
5.	Water bath shaker	Memmert, W. Germany
6.	Sonicator	Copley Scientific 2200E, U.K.
7.	pH-meter	Hanna Instrument, Italy
10.	Centrifuge universal 320 R	Hettich. Germany
14.	ABT-9000 Nano Laser particle Size analyzer	Angstrom Advanced Inc. USA
15.	Conductivity meter	Hanna Instrument, Italy
16.	Hot plate stirrer CB 162	Stuart .UK.

Methods

Pre-formulation studies

Determination of melting point

The exact melting point of etodolac powder and its crystallization status can be estimated using Differential Scanning Calorimetry (DSC) technique which detects thermo-tropic property of the sample that are given in mJ/second.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR technique have been used for the estimation of the vibration frequency of the functional group of the etodolac sample by the use of a detector cell with scanning between (4000 and 400cm^{-1}).

Determination of solubility

According to the method described by Higuchi & Connors 1965, saturated solutions of etodolac powder in different media (D.W., methanol, ethanol, propanol, iso-propanol, PEG 400, phosphate buffer pH 7.4, anise oil, oleic acid, tween 20 and tween 80) were achieved using an excess of drug powder that was added to (10ml) of each medium and put in a water bath shaker for 48 h. at 37^{o}C. Each withdrawn solution was filtered

(45µm.) and diluted. Finally, it was spectrophotometrically measured at the detected λmax. While for the estimation of solubility of etodolac in anise oil, oleic acid, tween 20 and tween 80. The same described above steps were made and the solutions of the drug in these media were properly diluted by the respective organic solvents and etodolac amounts were spectrophotometrically evaluated at the detected λmax. in each organic solvent.

Phase Diagram Construction and Microemulsion System Formulation

A drop-wise method with water by the use of pseudo-ternary diagrams was followed; in which five pseudo-ternary diagrams were developed of certain oil and S.mix (5:1, 1:1, 1:5, 1:0 and 0:1) weight ratios for each one. Nine homogenous and transparent mixtures of anise oil with (Tween 20: ethanol) at ratios of (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) were formed by gentle shaking. At the end, each mixture was titrated with water and visually inspected for optical clarity, homogeneity and fluidity.

Preparation of microemulsions and Incorporation of drug powder

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The second part of this study involve the detection of the required amount of different types of S.mix. to produce microemulsion when increase amount of oil, for the both; the blank (of similar constituents) and loaded microemulsion formulas.

Thermodynamic stability assessment for screening of Etodolac microemulsion formulas

The centrifugation test

This test was done by centrifugation of each sample for (30min.) at (5000 rpm).

Heating-cooling test

For each temperature, the tested samples were kept not less than 48 h. This test involves subjecting of the tested samples to six cycles of incubation at (40 and 45^{o}C).

Freeze–thaw cycle test

In a triplicate way, the samples have been kept for 48 h. at (-20^{o}C), then at room temperature for other 48 h.

Characterization of the selected microemulsion formulas

The selected microemulsion formulas that pass the thermodynamic assessment were exposed to numerous evaluation tests:

pH determination

The pH-digital meter was used to measure pH value of the blank and loaded microemulsions in triplicate at room temperature.

Electrical Conductivity

This test was carried out using conductivity meter, to estimate the type of continuous phase of the prepared microemulsion formulas (blank and loaded). It was performed in triplicate

The Globule size determination test

The light scattering technique was applied at 25ºC by the ABT-9000 Nano laser particle size analyzer to measure the droplet size ranges of the prepared microemulsions formulas (blank and loaded).

The poly dispersity index assay

This test was applied for detection of the uniform distribution of the droplets within the dispersion, the lower values estimate a higher uniformity of globules size.

FTIR study

FTIR spectra were taken for row etodolac powder, blank microemulsions, loaded microemulsions to exclude presence of any chemical interactions.

In vitro permeation /release studies

These studies were achieved by the use of Franz diffusion cells with synthetic dialysis membrane between the donor and receptor compartments at 37± 0.5ºC. Phosphate buffer pH 7.4 was used as receptor fluid in volume of (100 ml) with stirring. 2 mL-sample was with drown up to (24 h.) from the receptor fluid and replaced with the same volume of phosphate buffer. Samples were collected and analyzed using UV-spectrophotometer.

Statistical studies

The data analysis of the experiments was expressed as the mean of the triplicate samples ± standard deviation (STDEVA).

Results and Discussion

Pre-formulation studies (etodolac powder assay)

Determination of Melting Point

The estimated melting point of etodolac powder was a sharp endothermic peak at 154.6ºC, which is in agreement with the references [3], that indicated the purity of drug powder.

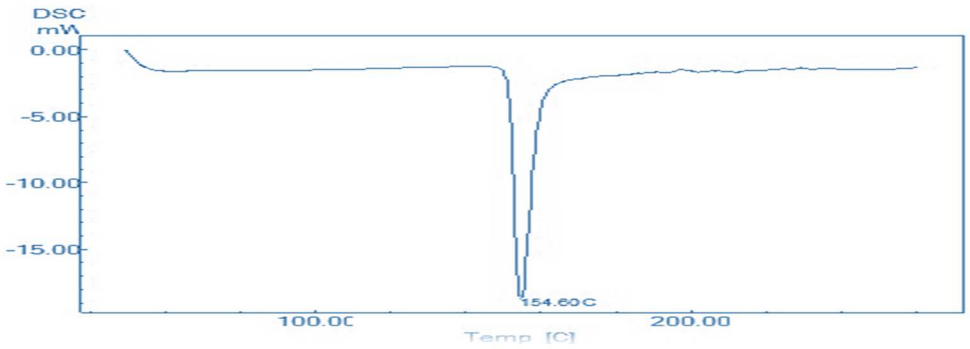

Figure (1): DSC thermogram analysis of Etodolac powder

Fourier Transform Infrared (FTIR) Spectroscopy

The chemical nature of raw material of etodolac was characterized by similar vibration frequencies of the functional groups that detected by Dipak D. et al 2017[5]. Powder etodolac were identified by the weak peak (N-H stretching vibration) of secondary amine was around (3340cm^{-1}), aromatic C-H stretching vibration was near (3000cm), carbonyl C = O stretching vibra^{-1}tion was around(1739cm^{-1}), aliphatic C-H asymmetrical and symmetrical stretching vibrations were around (2972 and 2931cm^{-1}) respectively, the O-H bending was(1411cm^{-1}), C-O stretching was (1033cm^{-1}) and the C-O stretching band appear at(1262cm^{-1}).

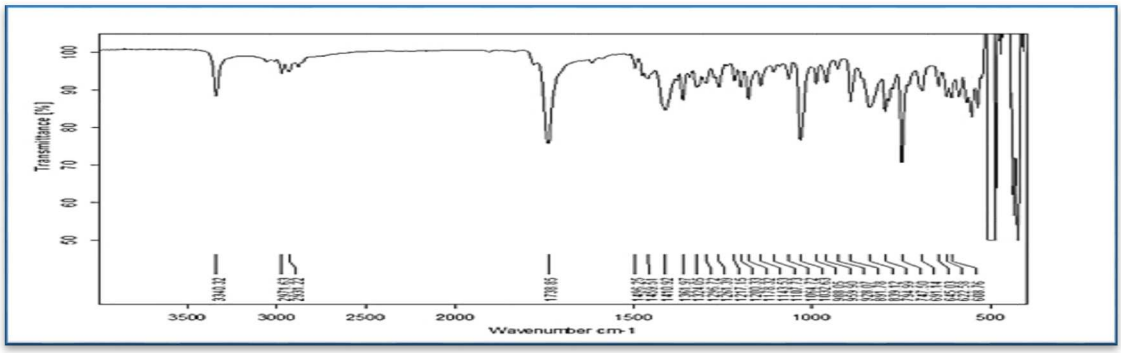

Figure (2): FTIR – spectra of Etodolac

Determination of solubility of Etodolac

Anise oil was selected(as the oil phase) because it records higher solubility value among the other oils that have been screened since only the dissolved amount of the drug will be able to cross the skin, tween 20 provides larger microemulsion areas compared to tween 80 (on the base of the HLB-values) so that tween 20 was selected as surfactant to form stable system[12]. Ethanol was selected as a co-solvent because of its short carbon chain length that required to maintain flexibility of the curvatures of the interfacial film, higher solubilizing value than other co-solvents, more safety, and it is less viscous than PEG 400[13]. Table (3) shows solubility values of etodolac in different media

Table (3): Saturated solubility of etodolac in different media

No.	Media type	Solubility (mg/ml)
1.	Water	0.0393125 ± 0.021
2.	Anise oil	5.743 ± 0.065
3.	Oleic acid	0.06 ± 0.033
4.	Tween 20	0.166 ± 0.041
5.	Tween 80	0.183 ± 0.055
6.	PEG-400	1.942 ± 0.029
7.	Methanol	27 ± 0.053
8.	Ethanol	25.3 ± 0.051
9.	Propanol	14.646 ± 0.081
10.	Iso-propanol	11.709 ± 0.046
11.	Phosphate buffer pH 7.4	0.48 ± 0.087

Phase Diagram Construction and Microemulsion System Formulation

Only the translucent, clear, single phase of low viscosity mixtures represents microemulsion boundary regions in the pseudo-ternary diagrams. As shown in Figure (3) various weight ratios of (tween 20: ethanol) were displayed in the ternary plots.

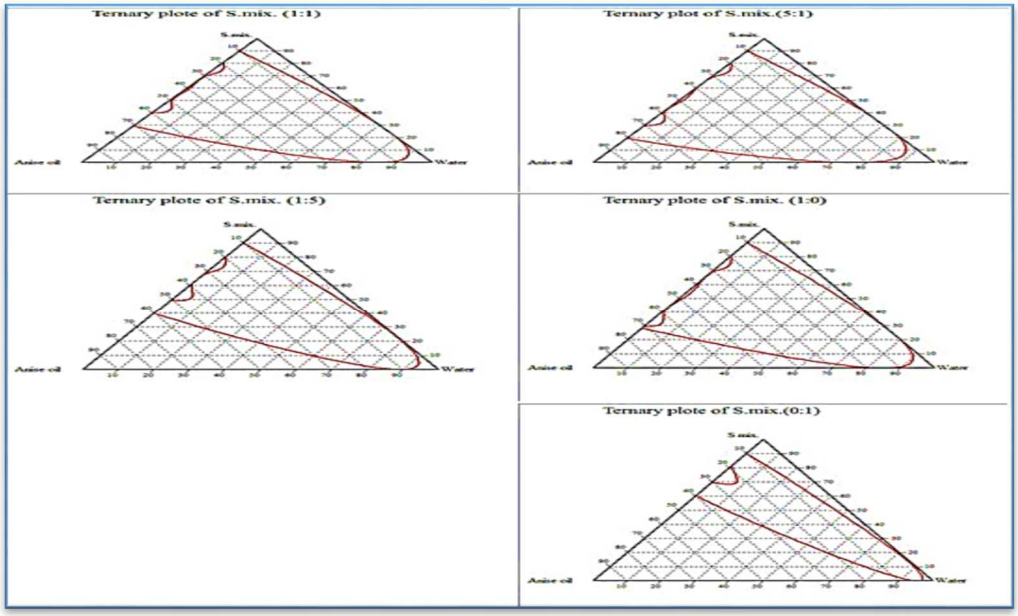

Figure (3): Phase diagrams of (Oil-S.mix-H2O system) at different (tween 20: ethanol) ratios of (1:0, 1:1, 1:5, 5:1and 0:1)

It was observed that when the amount of (tween 20) increased, the microemulsion area increased, ethanol able to produce the smallest microemulsion area when used alone and the biggest isotropic area was achieved when tween 20 was five parts greater than Ethanol. . Therefore, eighteen sample within the ternary-triangle of the S.mix.(1-5) and (0-1) were discarded and neglected because they produce the smallest area of microemulsions, the recorded observations meet with that described by Lianli Li et al 2002[14].

Preparation of Etodoalc microemulsions

Regarding phase diagram, only twenty seven blank formulas were succeed to construct microemultion system. These formulas were loaded by etodolac powder (400mg) firstly then subjected to the study of the amount required to produce successful etodolac microemulsion by changing the amount of oil within the system. The results of this study were illustrated in table (4) as below.

From table (3-2), it was obvious that the amount of tween 20 in different S. mix. types was the determinant factor to produce microemulsion and this was corresponding to concentration of surfactant monomers required to reach CMC to produce a stable system of microemulsion[15]. The selection of the each formula was made on the bases of the concentration of oil required to solubilize the drug and the corresponding of different types of S.mix (20% and 30%w/w) were enough to emulsify the oil phase with water.

Table (4): The results of Incorporation of Etdolac powder within the blank microemulsion formulas

Formula code	Result	Formula code	Result
F1	**-ve**	F24	**+ve**
F2	**-ve**	F26	**+ve**
F4	**-ve**	F27	**+ve**
F6	**+ve**	F29	**+ve**
F7	**-ve**	F31	**-ve**
F9	**+ve**	F32	**-ve**
F11	**+ve**	F34	**-ve**
F12	**+ve**	F36	**+ve**
F14	**+ve**	F37	**-ve**
F16	**-ve**	F39	**+ve**
F17	**-ve**	F41	**+ve**
F19	**-ve**	F42	**+ve**
F21	**+ve**	F44	**+ve**
F22	**-ve**		

Fifteen isotropic and low viscous microemulsion system were successfully prepared (signed by **+ve** symbols) and providing single-phase.

Thermodynamic stability assessment for Screening of Etodolac micro emulsion formulations

These series of study were conducted to evaluate the physical stabilities of etodolac loaded micro emulsions and their blanks. These stress studies demonstrated that temperature have a drastic effects on the physical stabilities of the microemulsion formulas. This may because of dehydration of surfactants ethylene oxide chains upon increase the temperature and then induction of bending instabilities at the interface of the microemulsion which was contribute as separation of dispersions or aggregation of the colloidal droplets resulted from the un-equilibrium state in the Gibbs free energy of the colloidal dispersions[16]. Therefor only three formulas (F41, F42 and F44) with their blanks passes these tests.

Characterization of the selected Etodolac microemulsions

pH determination test

the measured pH values for the microemulsion formulas and their blanks were near the physiological skin-pH (4 to 7)[17] shown in the Table(5). It was observed that the acidic nature of the drug affected the resulted values(similar to the results obtained by E. Monteagudo et al 2012)[18].

Table (5): pH values of Etodolac microemulsion formulas and their blanks.

Formula code	pH (Blank)	pH (Loaded)
F41	5.6 ± 0.06	5.05 ± 0.08
F42	5.55 ± 0.03	5 ± 0.02
F44	5.57 ± 0.07	5.1 ± 0.05

Electrical Conductivity

The obtained data for the blank formulas and for etodolac microemulsions seen in Table (6) provide information that the continuous phase was water ((o/w) type) and that the drug loading proses not induce phase inversion of microemulsions[9].

Table (5):Conductivity values of Etodolac microemulsions formulas and their blanks

Formula code	Conductivity in µS/cm (Blank)	Conductivity in µS/cm (Loaded)
F41	50 ± 1.02	45 ± 2.03
F42	35 ± 1.12	40 ± 1.25
F44	66 ± 0.7	50 ± 0.32

The Globule size determination

The readings were predominantly in the nano-level of (5-20 nm) for both the blank and loaded formulas, as shown in Table (6). Etodolac microemulsions were with slight enlargements in the mean size of the globule, that the lipophilic nature of the etodolac directed the drug towered the oil core of the microemulsion. Such observations were also detected by E.Monteagudo et al 2012[18].

Table (6):Values of globule size range (in nanometer) for Etodolac microemulsion formulas and their corresponding blanks

Formula Code	Blank microemulsion	Etodolac microemulsion
F41	5 - 5.61	15.8 - 19.9
F42	9.97 - 11.1	12.5 - 17.7
F44	5 - 7.06	7.92 - 9.97

The polydispersity index assay (PDI)

Generally, PDI - values less than 0.3 indicates monodisperse pharmaceutical nanoparticles [19]. As seen in Table (7), we conclude the presence of mid-range polydispersity quality of etodolac microemulsion formulas, While, blank formulas were of mono-disperse quality. The PDI-value of empty and loaded miceroemulsions were decreased as the tween20 concentration increased. This data were also detected by Hélder D. et al 2015[20].

Table (7): poly-dispersity index (PDI) values of Etodolac microemulsion formulas and their corresponding blank formulas.

Formula Code	PDI (blank)	PDI (loaded)
F41	0.011 ± 0.02	0.186 ± 2.01
F42	0.05 ± 1.01	0.28 ± 1.3
F44	0.007 ± 1.03	0.117 ± 1.04

FTIR study

As shown in the Figure 2 (etodolacs` spectra) and the FTIR-spectra of the final microemulsion formulas(F41, F42 and F44), there was no disappearance of existing peaks nor appearance of new once related to the etodolac's peaks

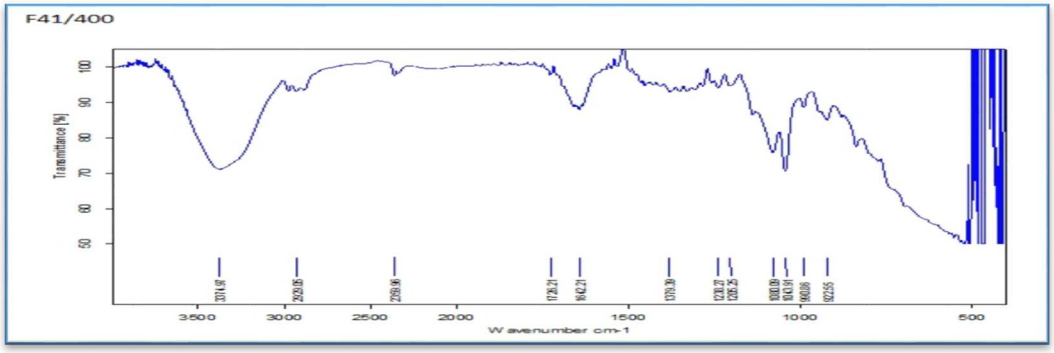

Figure (4): FTIR- spectra of loaded microemulsion F41

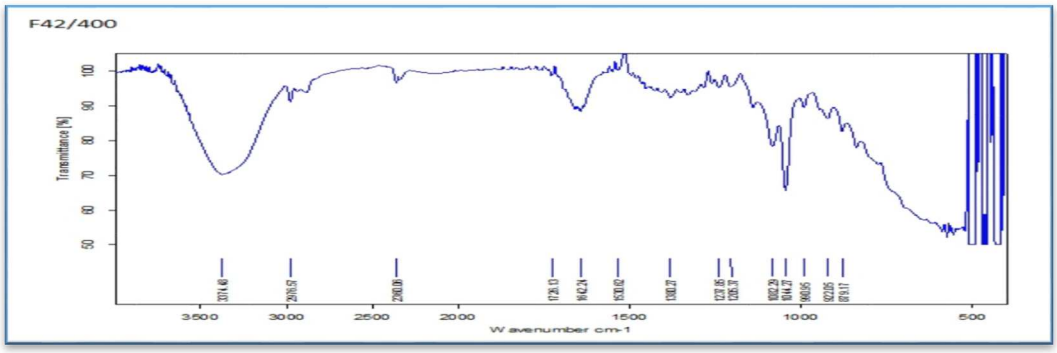

Figure (5): FTIR-spectra of loaded microemulsion F42

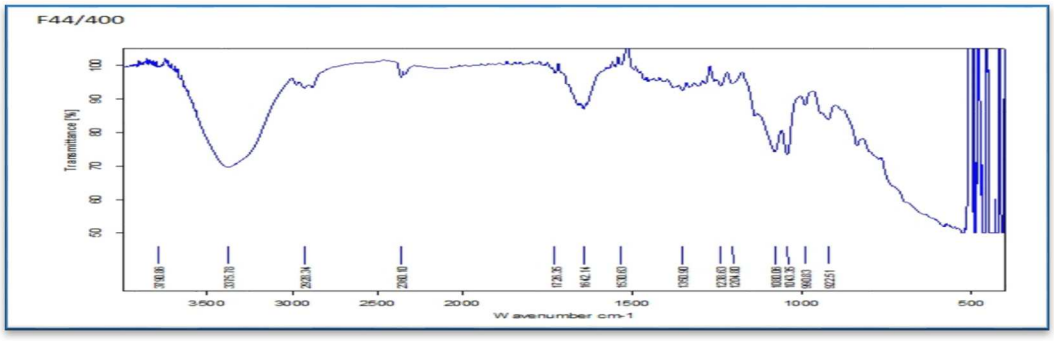

Figure (6): FTIR-spectra of loaded microemulsion F44

The N-H vibration frequency of etodolac at (3340 cm^{-1}) was overlapped with the broad band of the hydrogenated (-OH) that appears at (3374, 3374 and 3375 cm^{-1}) in the formulas (F41, F42 and F44), The characteristic carbonyl was appear at the (1726cm^{-1}) with slight shifting by the effect of intermolecular hydrogen bond formation in relation to the surrounding environments, the appearance of the C-H stretching of the -CH3 in their ranges within the formulations and the remaining of both the O-H alcohol bending

and C-O Stretching vibrations in their specialized sites at the range of (1450-1300cm^{-1}) and (1300-1000 cm^{-1}) respectively. All the above evidences confirm the absence of any chemical reactions. These observations were agreed with that reported by Kirolos R. et al 2018[21].

In vitro permeation /release studies

The obtained results of these study were carried out in triplicate for the prepared etodolac microemulsion (F41, F42 and F44), and explained in Figure (7).
Many observations have been recorded; retardation of etodolac dissolution noticed when tween 20 concentration was (30%) in F44 and the release process was reduced, but the release of etodolac from the system was increased when the co-solvent (ethanol) ratio was increased. Other observation was that the microemulsion system maintaining a prolonged etodolac release through its ability to retain the lipophilic drug within its internal oil phase of the system. We can see that etodolac as microemulsion was of faster release when compared with etodolac emulsion dosage form, this may be due to the difference in the solubilization abilities between two systems and another factor may be contributed which was the reduction of particle size of etodolac when prepared as microemulsion because it increases the surface area of particle toward improvements of the dissolution rate and fluidity. These results were also reported by Mona G. et al 2017 [22].

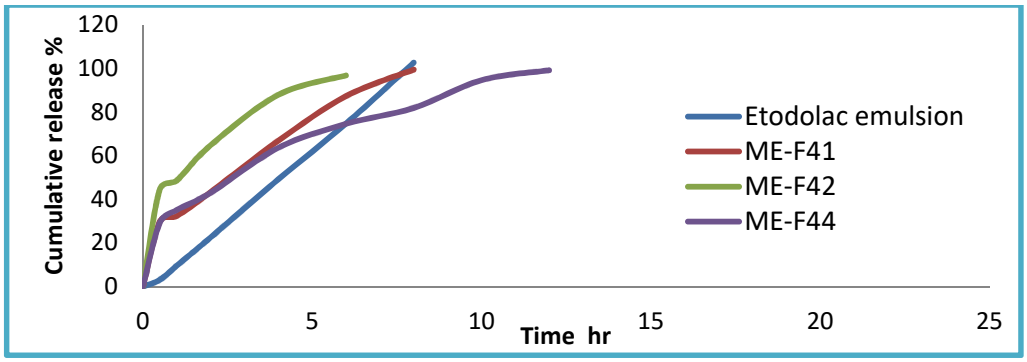

Figure (7): Comparison of the release profiles of the prepared etodolac emulsion and microemulsion formulas.

Conclusions

1. Microemulsion system successfully increases the solubility of etodolac (poorly water soluble drug).
2. Isotropic, stable and low-viscous o/w microemulsion system was constructed using (tween20 and ethanol) / anise oil / water within the ratio of (30:30:40).
3. Etodolac loading possess was achieved successfully and all the formulated etodolac-micro emulsion has a particle size occur within the Nano-level.
4. There was no etodolac-excipient chemical interaction in the preparation of etodolac microemulsion.
5. The temperature have a drastic effect on the physical stability of etodolac-microemulsion formulations.
6. The increase in the amount of tween20 increases the viscosity of micro emulsion, while the amount of ethanol has inverse effect by their ability to increase wettability and fluidity.

7. Etodolac microemulsions potentially maintains faster permeation (rapid onset of action) and F44 was of longer release time than others.

References

1. Atty Deepthi, Venugopal K., Sadak Vali S., Sunitha. R Suresh Kannan V and Sivakameswari S.2016. DESIGN AND EVALUATION OF MUCOADHESIVE SUSTAINED RELEASE TABLETS OF ETODOLAC BY USING NATURAL POLYMERS. World Journal of Pharmaceutical Research, 5(2): 433-465.
2. Rohini Pilli, M.V. Nagabhushanam and SDVS Kiran Kadali. 2014. ETODOLAC DISSOLUTION IMPROVEMENT BY PREPARATION OF SOLID DISPERSIONS WITH CYCLODEXTRIN COMPLEX'S. International Journal of Pharmaceutical Sciences and Research, 5(11): 4774-4791.
3. Shaikh Amir A.,Chaudhari Praveen D. and Lavte Pravind K. 2017. CENTRAL COMPOSITE DESIGN FOR ENHANCEMENT OF ETODOLAC SOLUBILITY VIA INCLUSION COMPLEXATION WITH PVP K-30 AND HYDROXYPROPYL β –CYCLODEXTRIN. EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH, 4(2): 657-663.
4. Ginette Jacob, Marianne Messina, Jacqueline Kennedy, Carol Epstein, Marie Sanda and John Mullane. 1986. Minimum Effective Dose of Etodolac for the Treatment of Rheumatoid Arthritis. Journal of clinical pharmacology,26(1):195-202.
5. Dipak D. Gadade, Sanjay S. Pekamwar, Swaroop R. LahotI, Santosh D. PatnI and Mahesh C. Sarode. 2017. Cocrystallization of Etodolac: Prediction of Cocrystallization, Synthesis,Solid State Characterization and In Vitro Drug Release. Marmara Pharmaceutical Journal, 21(1):78-88.
6. Rahul Rama Hegde, Anurag Verma and Amitava Ghosh, 2013. Microemulsion: New Insights into the Ocular Drug Delivery. Hindawi Publishing Corporation ISRN Pharmaceutics 826798:1-11.
7. Luciana B. Lopes. 2014. Overcoming the Cutaneous Barrier with Micro emulsions. journal of Pharmaceutics,6(1): 52-77.
8. S. Madhav and D. Gupta. 2011. A REVIEW ON MICROEMULSION BASED SYSTEM. International journal of pharmaceutical science and research, 2(8):1888-1899.
9. Christofori M. R. R. Nastiti, Thellie Ponto, Eman Abd, Jeffrey E. Grice, Heather A. E. Benson and Michael S. Roberts. 2017. Topical Nano and Microemulsions for Skin Delivery. journal of pharmaceutics,9 (37):2-25.
10. Bhumika M. Chhatrani and Dr. Dhiren P. Shah.2017. A Review on Micro Emulsion Based Gel: A Novel Approach for Enhancing Topical Delivery of Hydrophobic Drug .International journal of pharmacy and pharmaceuticalreserch,8 (4):.21-29.
11. Fathy I. Abd-Allah, Hamdy M. Dawaba and Ahmed M. S. Ahmed. 2010. Development of a microemulsion-based formulation to improve the availability of poorly water-soluble drug. Journal of Drug Discoveries & Therapeutics. 4(4):257-266.

12. Idrees MA., Rahman NU., Ahmad S., Ali MY. and Ahmad I, 2011. Enhance transdermal delivery of flurbiprofen via microemulsions: Effects of different types of surfactants and cosurfactants. DARU Journal of Pharmaceutical Sciences,19(6)P433-439.

13. HAYDER KADHIM DRAIS and AHMED ABBAS HUSSEIN. 2015. FORMULATION AND CHARACTERIZATION OF CARVEDILOL NANOEMULSION ORAL LIQUID DOSAGE FORM. International Journal of Pharmacy and Pharmaceutical Sciences,7(12):216-209

14. Lianli Li , Indranil Nandi, and Kwon H. Kim. 2002. Development of an ethyl laurate-based micro emulsion for rapid-onset intranasal delivery of diazepam. International Journal of Pharmaceutics, 237:77–85.

15. T G Mason, J N Wilking, K Meleson, C B Chang and S M Graves. 2006. Nanoemulsions: formation, structure, and physical properties. JOURNAL OF PHYSICS: CONDENSED MATTER 18 (41):635-666.

16. Bruce A. Kerwin.2008. Polysorbates 20 and 80 Used in the Formulation of Protein Biotherapeutics: Structure and Degradation Pathways. JOURNAL OF PHARMACEUTICAL SCIENCES, 97(8): 2924- 2935.

17. Jayashri Gajananarao Mahore, Suvarna Dinkarrao Suryawanshi, Satish Vasudeo Shirolkar and Sanjeevani Shekhar Deshkar.2017. Enhancement of Percutaneous Delivery of Dapsone by Microemulsion Gel. Journal of Young Pharmacists,9(4) 507-512.

18. E. Monteagudo, Y. G´andola, L. Gonz´alez, C. Bregni, and A.M. Carlucci. 2012. Development, Characterization, and In Vitro Evaluation of Tamoxifen Micro emulsions. Journal of Drug Delivery,1(1):1-11.

19. R.K. Thapa, R. Baskaran, T. Madheswaran, J.Y. Rhyu, J.O. Kim, C.S. Yong and B.K. Yoo. 2013. Effect of saturated fatty acid on tacrolimus-loaded liquid crystalline anaoparticales. Journal of drug del. sci. tech., 23 (2):137-141.

20. Hélder D. Silva, Miguel A. Cerqueira and António A. Vicente. 2015. Influence of surfactant and processing conditions in the stability of oil-in-water nano emulsions. Journal of Food Engineering ,167:98–89 .

21. Kirolos R. Georgy , Ragwa M. Farid , Randa Latif and Ehab R. Bendas. 2018. A new design for a chronological release profile of etodolac from coated bilayer tablets: In-vitro and in-vivo assessment. Journal of Advanced Research,1(1): 1-11.

22. Mona G. Arafa and Bassam M. Ayoub. 2017. DOE Optimization of Nano-based Carrier of Pregabalin as Hydrogel: New Therapeutic & Chemometric Approaches for Controlled Drug Delivery Systems, www.nature.com/scientificreports.