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RESEARCH ARTICLE

A new approach for the development of etodolac emulgels for rheumatic arthritis cure: *in vitro* and *in vivo* assessments

Shaaban K. Osman[a], Ahmed M. Mohammed[a], Khaled I. Saleh[a], Taher M. Yassin[b], Ahmed M. Abdelsalam[a], Adel A. Marzouk[c], Fatma Ahmed[d] and Mohamed A. Ibrahim[e]

[a]Department of Pharmaceutics and Pharmaceutical Technology, Al-Azhar University, Assiut, Egypt; [b]Department of Pharmaceutical Technology, Minofia University, Minofia, Egypt; [c]National Center for Natural Products Research, School of Pharmacy, University of Mississippi, MS, USA; [d]Department of Zoology, Sohag University, Sohag 82524, Egypt; [e]Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Objectives: Etodolac (ETD), an insoluble anti-inflammatory drug, undergoes first-pass metabolism, which limits its oral bioavailability. The current study presents the trials for improvement of drug solubility on one hand and formulation of different emulgel systems loaded with modified drug on the other hand.

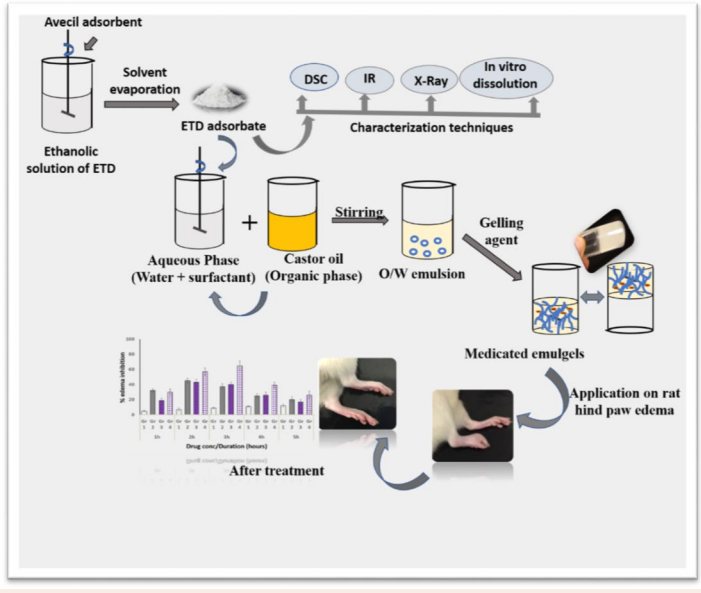
Significance: The Prolonged oral administration of ETD results in serious gastrointestinal problems. Therefore, the improvement of its solubility and modifying an alternative route of administration will increase its bioavailability and lessen its adverse effects, providing an alternative safe delivery system for inflammatory signs treatment.

Methods: The current study focused on the formulation of different emulgel systems since medicated emulgels were constructed by loading the emulgels with either pure ETD or modified ETD adsorbate (ETD/Avicel, 1:2 ratio). Finally, the *in vivo* studies were accomplished by studying the anti-inflammatory activity of ETD emulgels using albino rats.

Results: All the prepared emulgels showed acceptable physical properties since sodium alginate emulgel showed superior drug release compared with other gelling agents. The drug release profile was affected significantly by both emulsifying and gelling agents' concentration. The release kinetics data showed that the main mechanism of drug release was the Higuchi diffusion model. concerning the *in vivo* results, the extreme edema inhibition was obtained upon using emulgel formulae containing modified ETD with penetration enhancer (5% PG + 5% oleic acid). The modified emulgels did not show any sign of irritation on rats' dorsal skin.

Conclusion: The obtained results highlighted the promising application of topical ETD emulgels as an alternative anti-inflammatory drug delivery system.

GRAPHICAL ABSTRACT



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CONTACT Shaaban K. Osman shaabanosman@azhar.edu.eg, mhamoudah@ksu.edu.sa Department of Pharmaceutics and Pharmaceutical Technology, Al-Azhar University, Assiut, 71524, Egypt

Introduction

ETD is prescribed for pain and inflammation control, especially that accompanying osteoarthritis or rheumatoid arthritis [1,2]. ETD, a pyranocarboxylic acid derivative, is a nonsteroidal anti-inflammatory drug. It is a white-yellow crystalline powder with poor water solubility (less than 100 mg/L), with a half-life of 7h and a molecular weight of 287.35 g/mol [3–5]. Like any anti-inflammatory drug, the oral administration of ETD (usually with an oral dose of 300–400 mg) exhibits several side effects, including stomach irritation, which limits its applications, especially for patients who suffer from ulcers or any GIT disorders [4]. The bad solubility of ETD may be the cause of its side effects, which also limit its pharmaceutical applications. Therefore, the improvement of ETD solubility may lead to a decrease in gastric residence time following oral administration and, consequently, will reduce or avoid GIT adverse effects [3,5].

Recently, the poor solubility of drugs was overcome by several amorphization techniques, which were utilized for the drug transformation from crystalline to amorphous, including solid dispersion, nanoparticulation, co-crystalization, liposome or microemulsion formation, and amorphization [6], self-emulsifying [7], or the inclusion complexation with cyclodextrins [8,9].

Solid dispersion is an advanced technique that was reported to improve drugs' sustained release, solubility, dissolution, pharmacokinetics, pharmacological, and therapeutic efficacy [10–12]. Nanoparticulation of water-insoluble reagents follows specific and easy techniques and has been proven as an effective approach for many different biomedical applications *in vitro* as well as *in vivo* [13–16]. Co-crystalization is an emerging, environmentally friendly approach reported to enhance the solubility and bioavailability of several insoluble reagents [17–20]. Liquid formulations of nanoparticles, liposomes, microemulsions, and self-emulsifications are available by simple techniques; however, their stability is still not sufficient for wider pharmaceutical applications [6]. Also, both solid dispersion and co-crystallization methods require specialized manufacturing techniques, and the obtained products exhibit insufficient physicochemical stability.

Another amorphization technique is the adsorption of crystalline, insoluble drugs on porous carriers to change these drugs into their amorphous state. It was reported that the adsorption technique is very promising for the improvement of drug solubility and bioavailability without changing their chemical structure (sufficient physicochemical stability) [6,21,22]. Various adsorbents have been utilized as carriers for drug adsorption, such as porous calcium silicates (Florite R) [23] Avicel pH 101 [24], and (Aerosil 200) [25]. The improvement of drug solubility may be attributed to the process of surface adsorption leads to an increase in the drug surface area, porosity, and wettability [26,27]. All the above-mentioned methods help to improve the drug solubility, bioavailability, and reduce its required dose and consequently decrease its side effects.

Alternatively, it was reported that the topical administration of such drugs may overcome such oral side effects [26,28]. Especially, emulgels, constructed *via* combining an emulsion with a suitable gelling agent [29], are unique systems that have the advantages of both aqueous phase (gels) and oil phase (emulsions), making them promising and attractive for different pharmaceutical applications [30,31]. Emulgels exhibit several advantages, including acceptable release from the tubes and ease of application on the skin, high stability, and their ability to load different kinds of hydrophilic or hydrophobic drugs depending on the kind of preformulated emulgels (either o/w or w/o) [32,33].

In the current study, we are focusing on the formulation of a new and safe drug delivery system named emulgel for loading and local delivery of ETD. For the improvement of the native drug, we used our previously modified ETD/Avicel adsorbate in a comparative study with native drug-loaded systems. The modified emulgel systems were evaluated and evaluated by different analyses, including the physicochemical properties, and *in vitro* release studies. In addition, the mechanism of drug release was investigated by fitting the release profiles with different kinetic models. Finally, the *in vivo* studies were carried out in a rat model to examine the anti-inflammatory activity of the applied system on hind paw edema induced by rheumatic arthritis, which causes severe inflammatory signs in the internal organs and joints' synovial membranes [34,35].

Materials and methods

Chemicals and materials

ETD was obtained from PHARCO (Alexandria, Egypt). Carbopol 934, Sodium carboxymethyl cellulose, Hydroxypropyl methylcellulose, sodium alginate, Tween 80, ethanol, methanol, castor oil, and oleic acid were delivered from El-Nasr Chem. Co., (Cairo, Egypt). Avicel pH 101 and Carrageenan were provided by Sigma Aldrich (Frankfurt, Germany). Dialysis membranes (MWCO = 12 KDa) were obtained from Carl Roth GmbH (Karlsruhe, Germany).

Preparation of ETD adsorbate

The co-evaporation of ETD with Avicel PH 101was prepared at a (1:3) drug: carrier ratio using the solvent evaporation technique according to our previously reported procedure [23]. The obtained solid adsorbates were collected and placed for 48 h in a desiccator for complete drying. Then, the collected dried mass (ETD adsorbates) was ground in a mortar and sieved (a sieve no. 60, 250 µm), and stored in tightly closed containers until further analysis.

Characterization of ETD adsorbates

Dissolution studies

The dissolution rate of pure ETD in comparison with either ETD/Avicel 1:1 w/w adsorbate or the corresponding physical mixture was investigated using a dissolution tester from Hanson Research Corporation (Chatsworth, CA 31311, USA). All experiments were carried out in phosphate buffer pH 6.8 (500 ml) at 32 ± 1 °C with a stirring rate of 50 rpm. The dissolution studies were started by the dispersion of 20 mg ETD (pure or modified) in the dissolution medium. After a certain interval, samples (5 ml) were taken, filtered, and the drug concentration was investigated spectrophotometrically at 280 nm [23,36].

Differential scanning calorimetry (DSC)

DSC analysis was performed using a TA 50 PC system with the Shimadzu software program (Shimadzu-DSC-T50, Japan). Indium was utilized for the calibration of the DSC analyzer. The samples were scanned thermally in a range of 30 to 200 °C with a heating rate of 10 °C/min [37].

X-ray diffraction studies

This kind of analysis was utilized for determining the crystallinity of ETD (before and after modification). The measurements were accomplished using an X-ray diffractometer (Philips X-ray PW1710, USA) since the samples were irradiated by monochromatized Cu-Kα radiation with a current of 30 mA and at a voltage of 40 kV. Then, the data were collected over a 2θ (diffraction angle) range from 4° to 60° at a scanning speed of 5°/min at room temperature [6].

Preparation of ETD emulgels

The emulgels were formulated according to the previously reported method [38] with little modification. Firstly, an o/w emulsion was constructed *via* mixing of aqueous phase (half of the water amount) with oil phase (castor oil) with the aid of tween 80 (emulsifier). The second step is the addition of a gelling agent (pre-swollen in water) to obtain emulgel. Drug loading was achieved by thoroughly mixing 1% w/w of either pure or modified ETD (ETD/Avicel, 1:2 ratio) into the preformulated emulgel for 20 min using a homogenizer. Different emulgel systems were formulated by changing the type and concentration of gelling base, emulsifying agents, and oil phase, as presented in Table 1.

Table 1. Composition of different modified emulgels.

	Concentration (% w/w)					
Ingredient	F1	F2	F3	F4	F5	F6
Oil	20	20	20	20	20	20
Tween 80	2	2	2	2	2	2
Carbopol 934	2					
HPMC		2.5				
CMC-Na			5			
Na-alginate				5	7.5	10
Water	To 100					

Characterization of ETD emulgels

Visual inspection

The modified ETD emulgels were inspected visually for color, homogeneity, consistency, and smoothness.

Viscosity studies

Viscosity is the most important parameter that can affect the whole other properties of the modified emulgel systems. It can affect the consistency, spreadability, extrudability, and drug release rate. It can be affected by both the type of gelling base. Therefore, the viscosity of the constructed systems was measured by using a cone and plate ultra-viscometer with a T-D 94 spindle (Brookfield Co., USA). The viscometer/rheometer was connected to a water bath, which was adjusted to 25 °C. The spindle was allowed to rotate freely into the investigated samples at a fixed rate (50 rpm), and the viscosity value was recorded for each sample [39].

pH assessment

Due to the modified emulgel system is to be applied to the skin, it must be safe and nonirritant. Therefore, the pH value of such a topical formulation should be suitable for skin pH. Practically, the pH values were investigated *via* immersing the probe of a pH meter (Ama Co., Germany) into the gel samples, and the readings were recorded [40].

Spreadability and extrudability studies

To ensure the ability of the modified gel to be easily applied to the skin, the gel's spreadability was

investigated using the glass plate method, which was reported previously [40]. The weighed quantity of emulgel samples (1.0 g) was added to a glass plate on which a second calibrated glass plate was set. A glass plate was then covered with a 500 g mass for a minute. The following equation (Equation (1)) was used to determine the spreadability values, based on the change or increase in the average diameter of the spreading emulgels [40]:

$$\textbf{Spreadability}(\mathbf{P}) = \mathbf{r}^2\pi \quad (1)$$

Where the spreadability values (surface area occupied by the emulgel) were presented in a unit of cm^2 since (r) represents the sample radius (cm).

In vitro release studies

In vitro release of ETD (pure or modified adsorbate) from the formulated emulgels was investigated by using the diffusion Franz device. Typically, the amount of emulgel samples (1 gm), containing 10 mg ETD (pure or modified), was placed over a presoaked semi-permeable dialysis membrane (MWCO = 12,000 Da). Then, the Franz cells were suspended over the surface of the receptor release medium (200 ml phosphate buffer, pH 6.8), maintained at 32 ± 0.1 °C with a 50-rpm shaking rate [41]. After each predetermined interval, 5 ml of the receptor medium was withdrawn, filtered, and the ETD concentration was measured spectrophotometrically at λmax 280 nm [23]. Subsequently, the factors that might affect the drug release were evaluated as follows. The effect of the utilized gelling agent (Na-alginate, Na-CMC, HPMC, and Carbopol 934 in distilled water at 32 °C) was investigated at different concentrations (5, 7.5, and 10% w/v). In addition, the impact of the medium pH (5.5, 7, and 7.4) and the oil type (Castor oil, paraffin oil, and oleic acid) was evaluated. Furthermore, the effect of the Tween 80 concentration (2, 4, and 6%) as an emulsifying agent was studied. Moreover, the influence of the utilized penetration enhancers (menthol, ethanol, oleic acid, and propylene glycol) was investigated.

Release kinetic treatment

The mechanism of drug release from the modified emulgels was explored *via* constructing concentration/time plots and fitting the produced plots with different kinetic models, including Higuchi diffusion, first-order, zero-order, and Korsmeyer-Peppas. The extent of plot fitting was evaluated according to the values of R (correlation coefficient) [9,42–45]. Table 2 summarizes the equations and release rate constant units of the different kinetic models. Qt is the amount of drug at a specific time (t), and Q_0 is the initial amount of drug. In the case of Kosmeyer-Peppas, M_t/M_∞ represents the fraction of drug released at a specific time, M_∞ is the amount of drug at equilibrium, and n is the exponent that determines the release mechanism. K is the release rate constant for all models [46]. Zero-order model is applicable to different sustained and controlled release dosage forms that do not disintegrate [47]. First-order model is applicable for the release of water-soluble drugs from porous matrices [48]. Higuchi diffusion model is applied for the release of soluble and insoluble drugs from different solid and semisolid matrices [49]. Finally, the Korsmeyer-Peppas model is utilized to describe the drug release mechanism (erosion and/or dissolution) from different polymers [50,51].

Table 2. The equations and the release rate constant units of different kinetic models.

No.	Release mechanism model	Equation	K (model constant) as a function of time
(2)	Zero-order	$Q_t = Q_0 - K_0\ t$	$(M.t^{-1})$
(3)	First-order	$LogQ_t = Log\ Q_0 - K_1\ t/2.303$	(t^{-1})
(4)	Higuchi diffusion	$Q_t = K_H\ t^{0.5}$	$(g.\ t^{-0.5})$
(5)	Korsmeyer-Peppas	$Mt/M_\infty = K_k\ t^{n}$ $Log\ M_t/M_\infty = logK + n\ log\ t$	(t^{-n})
	Different sub-models depending on (n) value of the Korsmeyer equation		
(5A)	Higuchi diffusion (Fickian, case I)	$n = 0.5$	$(t^{0.5})$
(5B)	Non-Fickian (anomalous)	$0.5 < n < 1$	(t^{n-1})
(5 C)	Like zero-order	$n = 1$	Time independent
(5D)	Super case II transport (relaxation mechanism)	$n > 1$	(t^{n-1})

*Q_t is the amount of drug at a specific time (t); Q_0 is the initial amount of drug; M_t/M_∞ represents the fraction of drug released at a specific time; M_∞ is the amount of drug at equilibrium; n is the exponent that determines the release mechanism; and K is the release rate constant for all models.

In vivo studies

The *in vivo* proposal was approved by the Faculty of Pharmacy, Al-Azhar University, under the number AZ-/PH/12/C/2024, using 36 healthy male albino rats as animal models (200 ± 20 g). The rheumatic arthritis induction was accomplished by following the previously reported paw edema procedure [52]. Briefly, the rats were injected with 100 µL of carrageenan solution (1% w/v) into their right paws, while their left paws were left non-inflamed to represent the -ve controls. The diseased rats were classified into six separate groups (6 rats each). Group 1 (Gr1) represents the control

(received the unmedicated placebo gel to exclude the gel soothing effect), group 2 (Gr 2) received standard oral medication (indomethacin suspension 50 mg/kg), group 3 (Gr3) is the group that received 1% w/w pure ETD loaded emulgels, and group 4 (Gr 4) is the group of rats that received the 1% w/w modified ETD-adsorbate loaded alginate emulgel. The results are presented as the means ± SD ($n = 6$). To investigate the dose-response relationship, three different concentrations of ETD (0.5, 1% and 3% w/w) were loaded into the selected alginate emulgel system (the system that showed the highest *in vitro* release rate). Therefore, two more groups received the medicated emulgel besides the previous four groups. Group 5 (Gr 5) received emulgel loaded with 0.5% w/w ETD adsorbate, and group 6 (Gr 6) received emulgel loaded with 3% w/w ETD adsorbate. The extent of edema was investigated and measured before and after emulgel application by using a plethysmometer. The extent of edema inhibition was monitored after time intervals and presented as the percentage of edema inhibition as described by the following equation (Equation (2)) [9,52,53]:

$$\%\,\mathbf{EdemaInhibition} = \mathbf{1} - \mathbf{V_t} / \mathbf{V_0} \times \mathbf{100} \quad (2)$$

Since V_0 is the volume of edema before treatment, and Vt is the edema volume at each time interval after the treatment.

Skin irritation test

The irritation studies were performed on the dorsal skin. The amounts (2 g) of the investigated ETD-loaded emulgel systems were applied to the shaved rat skin by rubbing. Then, the skin was washed after 24 h, and the erythema/edema scores were determined according to the following ranks: Score 0, 1, 2, or 3 for no erythema, mild erythema, moderate erythema, or severe erythema [54,55].

Statistical and data analysis

The obtained results were presented as means ± standard deviation (SD). One-way analysis of variance (ANOVA) and SPSS were utilized for group comparison and data analysis. The homogeneity and significance were considered by the values of the probability (P). When the p-value is ($P < 0.05$), the effect is considered significant. The p-value is less than 0.01 for a highly significant effect. In contrast, a p-value more than 0.05 means a non-significant effect.

Results

Characterization of ETD adsorbate

The *in vitro* dissolution of ETD before and after modification was carried out, and the results are illustrated in Figure 1(A). It was detected that the dissolution rate of the drug in the form of adsorbate (composed of ETD/Avicel at a 1/1 w/w ratio) is better than the corresponding physical mixture and both are significantly ($p < 0.05$) higher than pure drug at all-time intervals. For example, the amounts of dissolved drug after 1h are 38.8%, 84.6%, and 100% for pure drug, physical mixture, and adsorbate, respectively.

Also, the DSC thermograms of pure ETD in comparison with the adsorbate and physical mixture

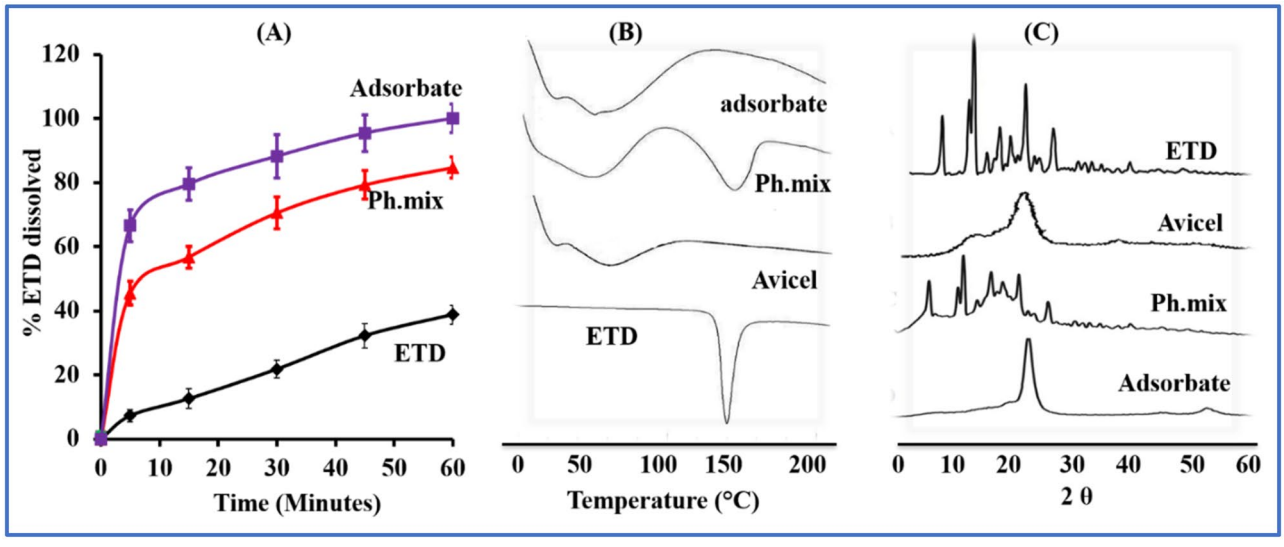

Figure 1. The *in vitro* dissolution (A), DSC thermograms (B), and X-ray diffraction (C) of pure ETD in comparison with ETD/Avicel 1:1 w/w adsorbate and the corresponding physical mixture.

were illustrated in Figure 1(B). Regarding pure ETD, a sharp endothermic peak at 152.3 °C was detected, which is due to the melting point of the drug, indicating the crystalline nature of ETD. In contrast, the thermogram of Avicel showed just a shallow broad endothermic band at 70–80 °C, corresponding to the water content. In the case of physical mixture, the same melting peak of the drug was detected at the same region with lower intensity due to the dilution effect. Interestingly, regarding the thermogram of the adsorbate, it was observed that the endothermic peak of the ETD had disappeared. This finding indicated the complete drug amorphization (transformation of the drug from a crystalline state to an amorphous one).

Regarding the morphological changes of ETD, the X-ray diffraction analysis was accomplished on ETD, Avicel, and ETD/Avicel adsorbate. The results, illustrated in Figure 1(C), showed that the X-ray pattern of pure ETD exhibited sharp, distinct peaks at diffraction 2θ angles (9.16°, 13.6°, 14.38°, 18.58°, 22.9°, and 27.28°), indicating ETD's crystalline nature. In contrast, Avicel showed no x-ray diffraction peaks, indicating that the existing Avicel an amorphous state.

Regarding the physical mixture, the characteristic peaks of ETD were detected, indicating the existence of the drug in a crystalline state even after physical mixing with the carrier. In the case of the corresponding adsorbate, it was noted that the characteristic peaks of the drug had mostly disappeared.

Table 3. Physicochemical properties, including pH, viscosity, and spreadability of different emulgel formulations.

Code	Gelling agent	pH	Viscosity (cP x10^3)	Spreadability (cm^2)
F1	Carbopol 934 (2%)	6.3 ± 0.15	185.6 ± 2.10	3.0 ± 0.15
F2	HPMC (2.5%)	7.1 ± 0.21	85.3 ± 2.08	3.8 ± 0.12
F3	Na-CMC (5%)	6.2 ± 0.10	64.5 ± 1.40	3.7 ± 0.12
F4	Na-alginate (5%)	6.8 ± 0.15	82.3 ± 2.57	3.9 ± 0.21
F5	Na-alginate (7.5%)	6.8 ± 0.10	150.9 ± 1.10	3.5 ± 0.20
F6	Na-alginate (10%)	6.5 ± 0.06	171.9 ± 1.76	3.2 ± 0.26

Preparation of ETD emulgel

Different ETD emulgels were successfully constructed and characterized for their physicochemical properties. The results showed that all constructed emulgels exhibited an acceptable color (creamy white creamy gels), consistency (smooth), homogeneity, and drug content since ETD concentration in all modified gels ranged from 96.5 to 102.5%. in addition, there is no evidence of clumping or separation between phases that have been detected for all modified systems.

Physical characteristics of ETD emulgel

pH measurements

The results revealed that the pH values of the emulgel formulations ranged from 6 to 7.2, as presented in Tables 3 and 4, indicating the suitability of all constructed emulgels for transdermal or topical applications without fear of skin irritation [45].

Spreadability measurements

Spreadability of the constructed emulgels was evaluated and listed in Tables 3 and 4. The results showed that the spreadability values of all modified systems ranged from 3 to 4.2 cm^2, which is considered an acceptable value for topical formulations [40,56].

Viscosity measurement

The viscosity of the formulated emulgels was examined to assess their rheological characteristics (Tables 3 and 4). A positive relationship was observed between the polymer (gelling base) concentration and the viscosity of the constructed emulgels.

In vitro release studies

The ETD release profiles from the investigated emulgels are illustrated in Figure 2. The obtained results revealed that the drug release rate is higher in the

Table 4. Kinetic data for etodolac release from certain emulgels.

Model		Emulgel formulae			
		Na-alginate	HPMC	Na-CMC	Carbopol 934
Zero-order	K_0 ($mg.min^{-n}$) × 10^{-2}	0.769	0.1209	0.1882	0.3670
	R^2	0.895	0.992	0.962	0.988
First-order	K_1 (min^{-n}) × 10^{-2}	0.005	0.002	0.003	0.004
	R^2	0.0930	0.974	0.985	0.974
Higuchi diffusion	K_H (min^{-n}) × 10^{-2}	5.489	2.276	3.646	6.194
	R^2	0.987	0.957	0.995	0.985
Korsmeyer-Peppas	K_k (min^{-n}) × 10^{-2}	0.5691	0.4190	0.4211	0.7636
	R^2	0.977	0.987	0.987	0.976
	N	0.5891	0.9942	0.6811	0.7056
The fitted model		Higuchi + Fickian	Zero order + non Fickian	Higuchi + Fickian	Higuchi + Fickian

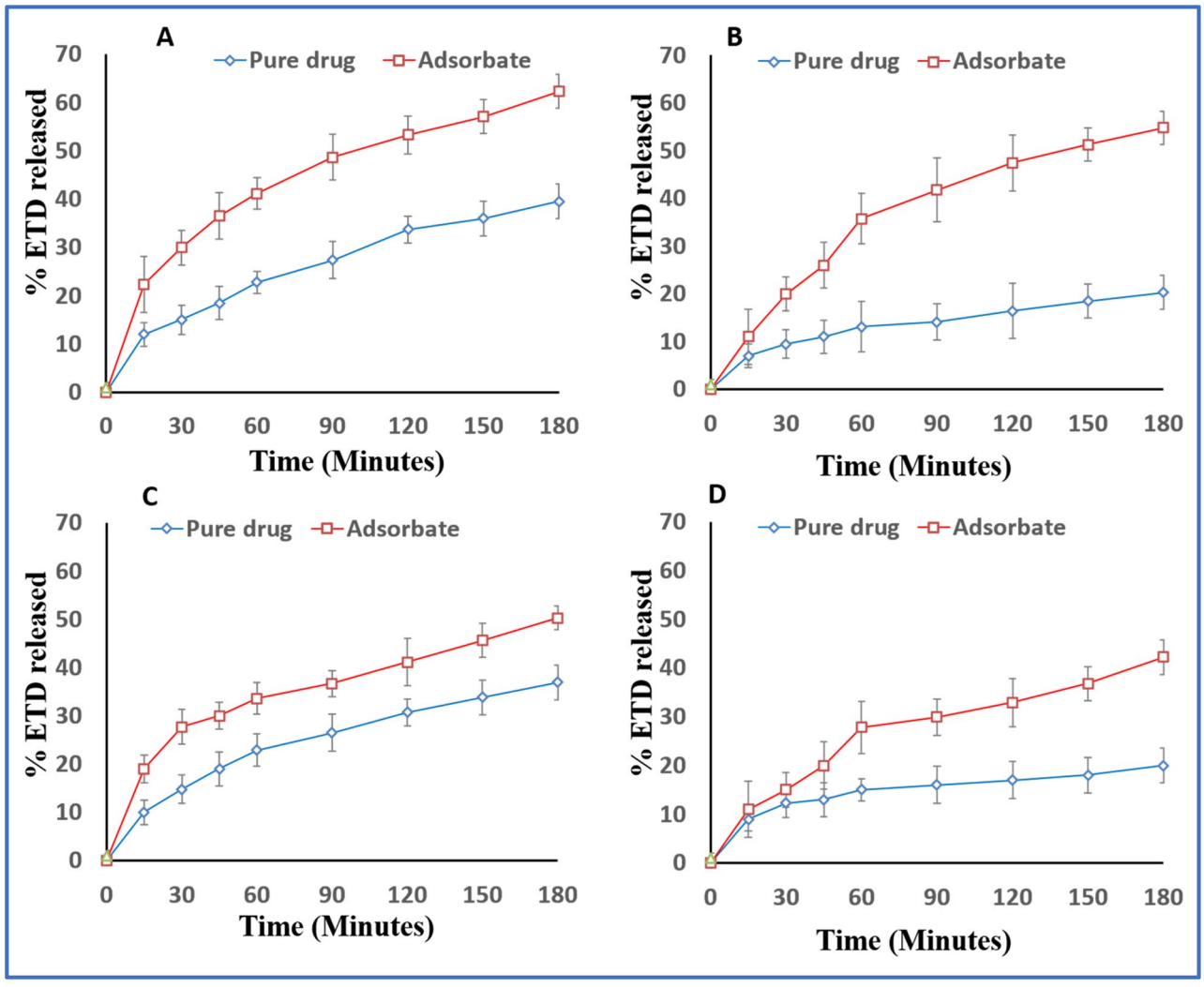

Figure 2. The percentage of the cumulative drug released (% CDR) of 1% w/w plain or modified ETD from different emulgel bases, (A) Na-alginate, (B) Na-CMC, (C) HPMC, and (D) carbopol 934 in distilled water at 34 °C.

case of modified forms than in the case of the plain drug. Also, the highest release rate was achieved by the ETD adsorbate compared to the corresponding physical mixtures. Concerning the impact of the gel base on the ETD release rate, the results revealed that the percentage of drug release was the highest from the sodium alginate emulgel base (57.3% after 3 h). The release of ETD from alternative emulgel bases followed a decreasing order as follows: Na-alginate > Na-CMC > Carbopol 940 > HPMC.

Figure 3(A) illustrates the impact of medium pH on the *in vitro* release behavior of ETD from Na-alginate emulgel. The increase in the pH value of the release medium from 5.5 to 7 was associated with an increase in the release profile. Further increase in pH value was accompanied by a slight reduction in the drug release. Also, Figure 3(B) showed the influence of polymer concentration on the release of ETD from the Na-alginate emulgel. The results exhibited an inverse relationship between the polymer concentration and the quantity of the released drug.

Regarding the effect of emulsifying agent concentration, the obtained finding indicated that the increase in emulsifying agent concentration increased the release rate of ETD from the emulgel base (Figure 4(A)). The effect of the oil utilized in emulgel construction is displayed in Figure 4(B). The results showed that the highest release was achieved in the case of oleic acid compared with both castor oil and liquid paraffin (Figure 4(B)).

Kinetics (mechanism of ETD release)

Regarding the mechanism of drug release from the modified emulgels, Table 4 displays the values of each formulation's slope (constant of release model, K), and the correlation coefficient value (R^2) for the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. As

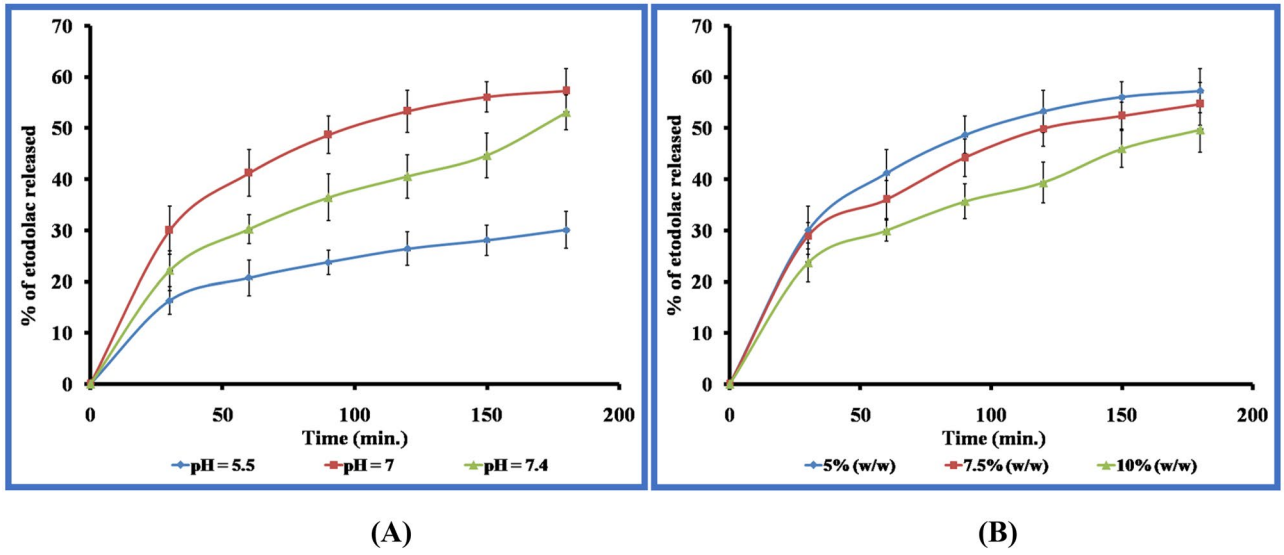

Figure 3. *In vitro* release of ETD adsorbate from sodium alginate emulgel as a function of pH (A), and polymer concentration (B). All experiments are done in distilled water at 32 °C. The results are presented as the average of three separate experiments SD.

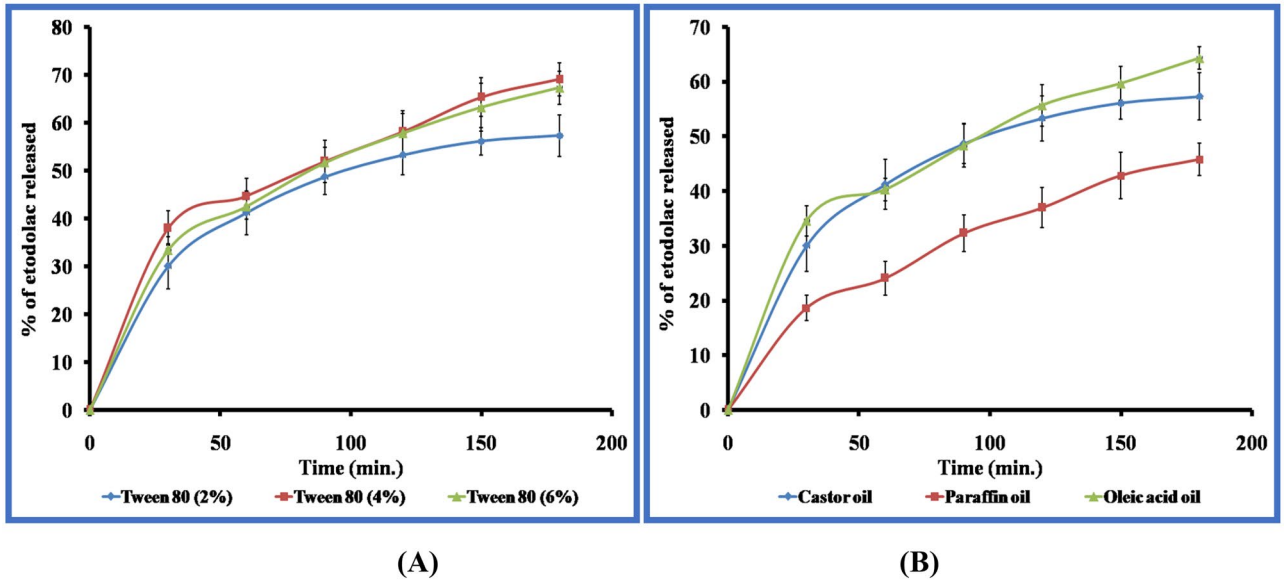

Figure 4. *In vitro* release of ETD adsorbate from sodium alginate emulgel as a function of emulsifying agent (A), and the utilized oil (B). All experiments are done in distilled water at 32 °C. The results are presented as the average of three separate experiments ± SD.

a result, it was noted that the drug's release from all emulgel systems follows the Higuchi diffusion model except for the HPMC-based emulgel, which follows the zero-order model.

In vivo studies

The *in vivo* anti-inflammatory activity of Na-alginate emulgel formula was evaluated by the paw edema method. The % inhibitions of edema thickness after application of emulgels containing 1% w/w pure ETD or ETD adsorbate (ETD/Avicel, 1:2 w/w ratio) are illustrated in Figure 5. The statistical analysis for the comparison between groups is displayed in Figure 6(A,C).

The edema swelling was significantly ($p < 0.05$) inhibited in all treated groups of rats, either treated with the modified emulgels or in the group that received standard drugs (oral indomethacin ®). The release of ETD and the extent of edema inhibition obtained from the emulgel formula containing a penetration enhancer are higher than those from other formulae (Figure 5). At the first hour post-treatment, oral indomethacin® exhibited a

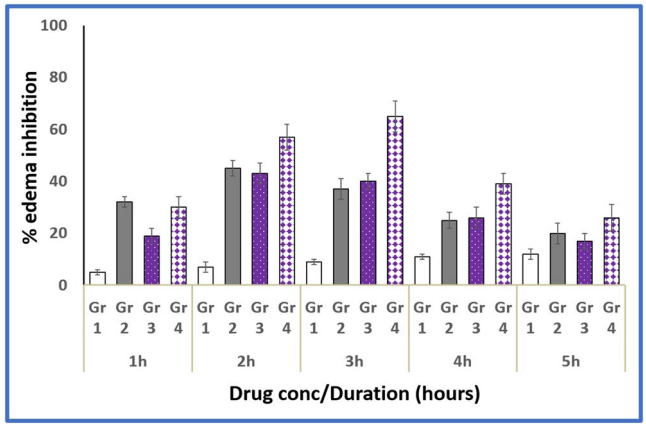

Figure 5. The percentage of carrageenan-induced edema inhibition as a function of treatment duration for different investigated groups, since the G1 control group, G2 is the group of animals that received oral standard Indomethacin suspension, G3 is the group that received pure ETD-loaded emulgels, and G4 is the group of rats that received the modified ETD-adsorbate-loaded alginate emulgel. The results are presented as the means ± SD ($n = 6$).

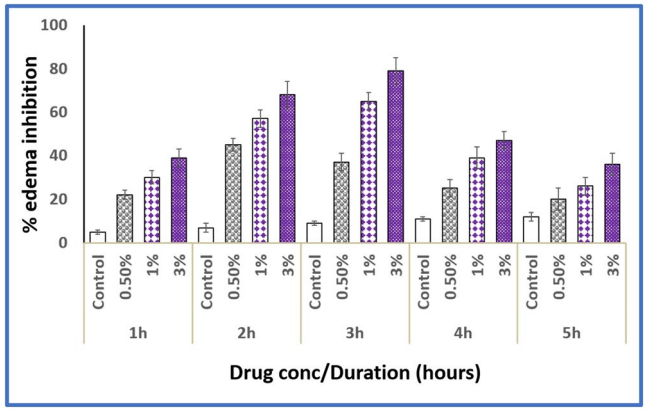

Figure 6. The effect of ETD concentration (0.5, 1%, and 3% w/w), which were loaded onto the selected emulgels, on edema inhibition of rat hind paw ($n = 6$).

higher anti-inflammatory effect than topical formulations. This is because topical vehicles exert their effect by releasing and diffusing ETD through the skin layers. Importantly, ETD emulgel still had a significant anti-inflammatory effect ($p < 0.05$) between 2 and 3 h, while the effect of oral indomethacin® started to decline after 2 h (Figure 6(A,C)).

The percentage of inhibition after 2h was 47.61, 45.6, and 58.7(%) for oral drug (G2), Na-alginate emulgel containing plain drug (G3), Na-alginate emulgel containing ETD adsorbate (G4). The inhibition percentages after 3h were 40.4, 44.3, and 63.9 (%) for G2, G3, and G4, respectively. Then the effect of all drugs decreased significantly after 5 h, as indicated by the values of edema inhibition, which showed 23, 20, and 28.4 (%) for the investigated groups, respectively. Notably, compared with the control group, the modified formula showed significant differences ($p < 0.05$) in edema inhibition even after a longer period (4 or 5 h) (Figure 5).

Dose/response studies

To determine the impact of ETD concentration on the drug activity (extent of edema inhibition), three different ETD concentrations (0.5, 1, and 3%, w/w) were incorporated into the modified Na-alginate emulgel system. The results, illustrated in Figure 7, indicated that the extent of edema inhibition was significantly ($p < 0.05$) affected by the loaded drug concentration since the highest edema inhibition was obtained in the case of emulgel loaded with 3% ETD adsorbate (Figure 6(B,D)).

Skin irritation test

The results of irritation studies revealed that there were no signs or manifestations of irritation (edema, redness, etc.) since a zero erythema/edema score was detected within the examination period (24 h). The obtained finding indicated the safety of the modified ETD emulgel system as an alternative drug delivery

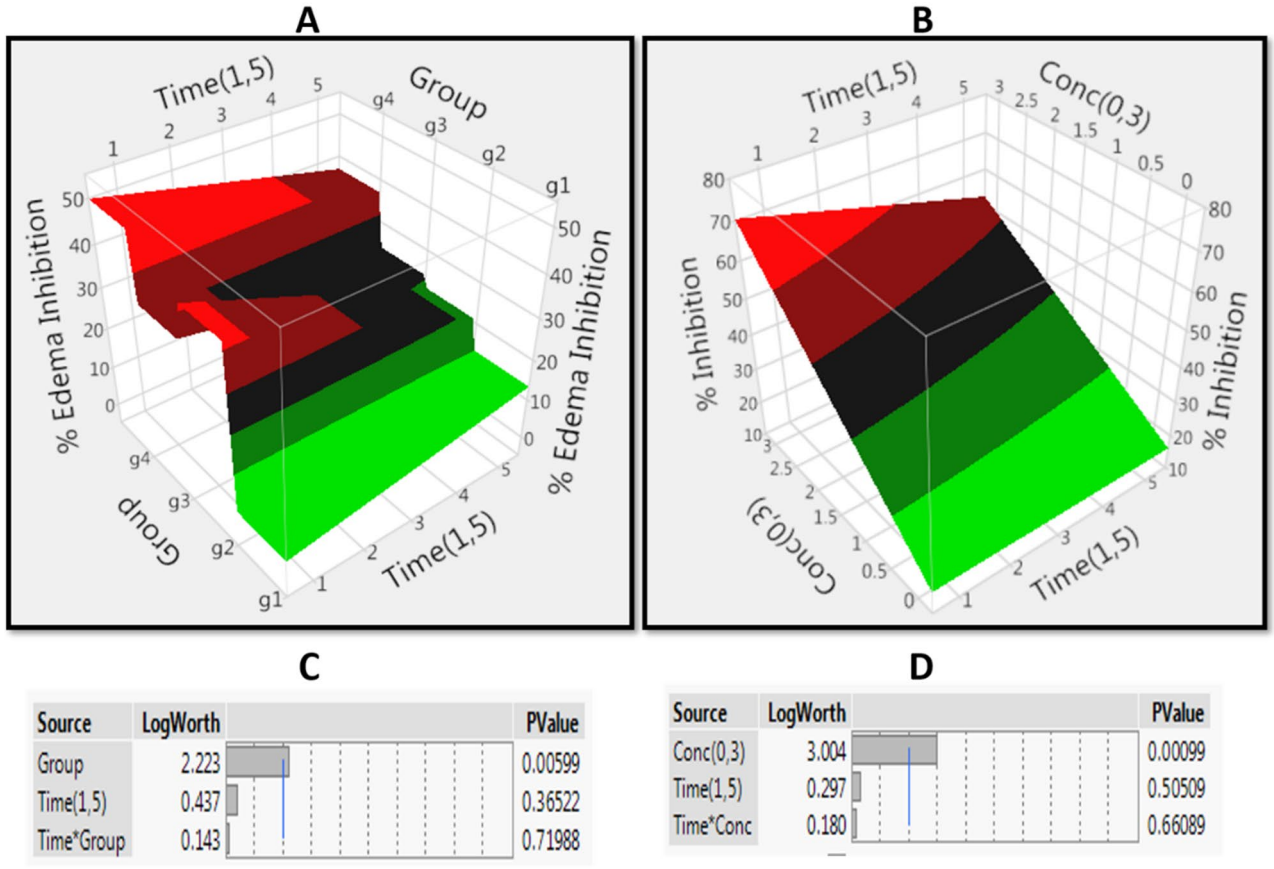

Figure 7. Statistical analysis of the obtained *in vivo* results. (A) Surface plot representing the effect of different emulgel groups on the extent of edema inhibition, (B) a surface plot that represents the effect of drug concentration on edema inhibition, (C,D) Pareto chart for the effect of different investigated groups, and drug concentration, respectively, on the extent of edema inhibition.

system for topical administration of ETD instead of the oral route.

Discussion

The poor solubility of ETD is considered the main cause for its limited application in topical delivery systems [23]. Our contribution to the current work is to enhance the solubility, dissolution rate, and bioavailability of ETD, on the one hand. Also, we attempted to mitigate or avoid the severe side effects associated with its oral administration by using an alternative topical dosage form, known as an emulgel, on the other hand. The first goal of the present study was achieved *via* drug adsorption over the surface of an inert carrier, named Avicel pH 101, in a 1:1 drug/carrier ratio, as the corresponding physical mixture was prepared for comparison, which was followed owing to its easy production and assurance of the physicochemical stability of the product.

Regarding the dissolution studies, the results showed that drug absorption was associated with a significant enhancement of drug dissolution. While only 30% of the pure drug was dissolved within 30 min, around 90% of the drug was dissolved in the drug/Avicel adsorbate during the same period (i.e. 3-fold improvement). Also, it was observed that the extent of solubility improvement in the case of the adsorbate was higher than that of the physical mixture. A similar finding was obtained by Mohamed et al. who studied the effect of the adsorption technique using porous silica on the solubility enhancement of etodolac [23].

As for the DSC analysis results, the existence of a sharp endothermic peak at 159 °C corresponding to the melting point of pure ETD indicates its crystalline nature. The obtained result correlates with other previously reported data [23,57]. In contrast, the DSC thermogram of Avicel did not show any endothermic or exothermic peak, indicating its amorphous nature, which correlates with the reported data of Ibrahim and Al-Anazi [58]. The endothermic melting peak of ETD was partially diluted and reduced in the case of a physical mixture, while in the case of ETD adsorbate, this peak disappeared completely, indicating the complete conversion of ETD from crystalline to amorphous

form. These results explain the above-mentioned results of *in vitro* release studies and correlate with the previously reported data [23,55]. In other words, this result refers to the importance of solid adsorption and indicates that the physical mixture is not enough to achieve the goal.

Consequently, the X-ray diffraction results demonstrated that the drug is a typical crystalline, as evidenced by the presence of various diffraction peaks at different 2θ angles. In contrast, Avicel showed no X-ray diffraction peaks, indicating its amorphous nature as an inert carrier. These findings align with the previously reported data of Ibrahim and Al-Anazi [58]. Regarding the ETD/Avicel physical mixture, there are several small peaks that were detected, which might be attributed to the dilution effect. In contrast, the X-ray pattern of ETD/Avicel adsorbate showed the disappearance of most characteristic peaks of ETD, indicating the conversion of ETD into its amorphous form and confirming the results of DSC analysis. This finding may be due to the transformation of ETD to an amorphous state *via* surface adsorption. The obtained results confirm those obtained by DSC analysis and explain the higher dissolution rate of ETD in the case of the adsorbate in comparison with either the pure drug or the physical mixture [55,57,59].

Furthermore, we formulated different emulgel systems that were loaded with the modified form of ETD (ETD/Avicel, 1:1 ratio) according to the previously reported procedure of Rosiak et al. [38]. We used several gelling agents for the emulgel construction, including sodium alginate, HPMC, sodium CMC, and Carbopol. The physicochemical properties (viscosity, drug content, pH, spreadability, and extrudability) of our modified emulgel systems indicated their homogeneity, smoothness, creamy white color, with no signs of phase separation. Also, the drug content in all modified systems ranged from 95 to 101%, and their viscosity is significantly affected by the kind and concentration of the utilized gelling agent. In addition, all modified systems exhibited acceptable pH and spreadability values [40,56]. Regarding the effect of adsorption on drug release from the modified emulgels, the rate is higher for the modified forms than for the plain drug. Moreover, the highest release rate was obtained by the ETD adsorbate compared to the corresponding physical mixtures. This result may be explained by the change of ETD into the amorphous state, the extreme reduction of particle size, and the rapid desorption of ETD from the surface of the adsorbate (Avicel PH-101) [23]. Earlier, Mohamed, I [60]. reported similar outcomes by examining the effects of gelling agent type, oil phase, and emulsifying agent concentrations on drug release from emulgel.

The measured pH values for all formulated emulgels existed in the range of 6 to 7.2, indicating the suitability of all constructed emulgels for transdermal or topical applications without fear of skin irritation [45]. Also, the spreadability values of all modified systems ranged from 3 to 4.2 cm^2, which is considered an acceptable value for topical formulations [23,40]. Moreover, the viscosity of the formulated emulgels was examined to assess their rheological characteristics. A positive relationship was observed between the polymer (gelling base) concentration and the viscosity of the constructed emulgels.

The *in vitro* release of all systems was studied to investigate the effect of viscosity, gelling agent, and pH. The results showed that sodium alginate exhibited the best release profile compared with other gelling agents. The observed effect may be attributed to the sodium alginate emulgel base's lower viscosity and the presence of sodium ions [23,40]. These ions interact with the drug, transforming ETD into its sodium salt form, which exhibits enhanced solubility compared to the native acidic drug [61]. Consequently, this formula (alginate emulgel) will be the subject of studying the impact of all other factors on the ETD release profile.

Effect of pH of the release medium on ETD release. The results showed that the release of the drug was retarded by the increase in pH. This result may be attributed to a higher degree of ionization of ETD at these higher pH values [61,62]. Besides, the effect of polymer concentration on the ETD release profile was studied. The release rate is retarded by the increase in gelling agent concentration. This may be due to the low viscosities resulting in more channels in which the drug can diffuse, and, consequently, increasing the release rate. The obtained findings and explanations are in accordance with several previous reports [63,64]. Also, the kind and concentration of the utilized emulsifying agent play a crucial role in the final emulgel properties since the increase in emulsifying agent concentration was accompanied by an increase in the release rate of ETD from the emulgel base. One possible explanation for this observation is that the emulgel becomes more hydrophilic when the emulsifying agent is present at the proper concentration (2% – 4%), which promotes the drug's diffusion from the emulgel to the release medium [65]. Similar outcomes and explanations were obtained and previously reported [60].

Kinetically, the drug release mechanism from different emulgels was explored. The kinetic parameters named formulation's slope (constant of release model, K), the correlation coefficient value (R^2), and n, deduced from the curve of drug release profiles, can determine

that the drug fits with which kinetic model (the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models). In the present study, it was noted that the drug's release from emulgels follows the Higuchi diffusion model in certain formulas and zero-order kinetics in others, as indicated by the highest R^2 value (which will be the nearest value to 1), upon fitting with the zero-order model in the case of HPMC emulgel, since the value of R^2 was 0.992. While the release mechanism of ETD from Na-alginate, Na-CMC, and Carbopol 940 emulgels follows the Higuchi diffusion model, the values of R^2 were 0.987, 0.995, and 985, respectively.

Also, n values determine which kind of release (Fickian or non-Fickian). As shown from the presented results in Table 4, the values of n are ($0.5 > n < 1$), which exhibit non-Fickian release controlled by a combination of diffusion and chain relaxation mechanisms [43,66].

Similar results were obtained by Karatas, who investigated the kinetic models for the release of ketolac from hydrogel and reported that the sorption of water in hydrogels exhibited non-Fickian (ranging from Fickian to Case-II) release [67].

Another study was carried out by Asghar, A. et al. [68] who investigated the release mechanism of pregabalin from Carbopol gel. The obtained results showed that the main release mechanism fitted with the Higuchi diffusion model (the drug released *via* diffusion from the swollen gel matrices) as indicated by both R and n values. Comparable behaviors have been reported in previous work in which the authors investigated the kinetics of drug release from polymeric hydrogel. The results showed that the diffusion mechanism is the dominant mechanism due to polymer swelling and limited water penetration [69,70].

Likewise, the *in vivo* studies were accomplished by following the previously reported paw edema procedure. It was noted that the edema swelling was significantly ($p < 0.05$) inhibited in all treated groups compared with the untreated group and that treated with a placebo. Also, the extent of edema inhibition in the case of the group treated with the emulgel formula that contains the modified ETD adsorbate is higher than that of other formulae. These results may be attributed to the improved drug solubility and bioavailability *via* the amorphization process, which is caused by the drug adsorption onto the surface of the utilized adsorbent (Avicel). The obtained results confirm the *in vitro* release results and agree with previously reported data [23].

Upon studying the impact of the loaded drug concentration on the edema inhibition, it was noted that the extent of edema inhibition was significantly increased by increasing drug concentration, since the formula composed of 3% ETD showed the highest edema inhibition. Similar findings were obtained and reported previously [23,71,72]. Finally, the irritation ability of the constructed emulgels was investigated to confirm the safety of their topical application. The results indicated that there were no signs of skin irritation on the rat skin. Considering the obtained results, it could be concluded that the modified emulgel system is considered a promising and safe alternative drug delivery system for topical administration of ETD instead of the oral route.

Conclusion

ETD adsorbates were prepared by the co-evaporation technique using Avicel PH 101 as an adsorbent to improve its solubility and bioavailability. Then, the modified ETD was loaded onto different emulgel formulations. All the prepared emulgels showed acceptable physical properties concerning drug content, consistency, color, homogeneity, pH values, and spreadability. From all modified emulgels, the alginate-based emulgel showed superior *in vitro* ETD release. The results also indicated that the most important factor for enhancing the drug release from the modified emulgels was the emulsifying agent concentration, followed by the type of the oil phase, and then the gelling agent concentration. According to the release kinetics data, the drug's release from emulgels occurs according to Higuchi diffusion models in some cases and zero-order kinetics in others. Finally, regarding the *in vivo* results, the maximum edema inhibition was obtained upon using emulgel formulae containing modified drug (ETD adsorbate). Importantly, it was observed that the modified medicated Na-alginate emulgel systems did not cause skin irritation since the erythema/edema score was zero, indicating the suitability of the modified system for topical delivery of ETD as an alternative anti-inflammatory drug delivery system.

Consent to publish

All authors have agreed to the publication of this manuscript.

Author contributions

CRediT: **Shaaban K. Osman**: Conceptualization, Project administration, Validation, Visualization, Writing – review & editing; **Ahmed M. Mohammed**: Data curation, Writing – review & editing; **Khaled I. Saleh**: Data curation, Supervision; **Taher M. Yassin**: Investigation, Methodology; **Ahmed M. Abdelsalam**: Data curation, Investigation, Validation; **Adel A. Marzouk**: Investigation, Validation; **Fatma Ahmed**: Software, Visualization, Writing – original draft; **Mohamed A. Ibrahim**:

Formal analysis, Project administration, Resources, Visualization, Writing – review & editing.

Disclosure statement

There is no conflict of interest with any other authors or companies that may influence the work in the current paper.

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Data availability statement

All data are contained within the current article.

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