ORIGINAL ARTICLE

FORMULATION AND EVALUATION OF *IN VITRO* RELEASE KINETICS OF $NA_3CADTPA$ DECORPORATION AGENT EMBEDDED IN MICROEMULSION-BASED GEL FORMULATION FOR TOPICAL DELIVERY

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Abstract

The purpose of this study was to evaluate the *in vitro* release kinetics of $Na_3CaDTPA$, a well-known and widely-used decorporation agent, from a topical microemulsion-gel formulation in comparison with a conventional gel. For the preparation of hydrogels, Carbopol 934 polymer was used. Release studies were conducted using both hydrophobic (polycarbonate) and hydrophilic (mixed cellulose esters) membranes. The release kinetics were evaluated using Franz diffusion cells. The receptor compartment was filled with phosphate buffer pH 7.4 and magnetically stirred at 600 rpm during the experiments. The temperature of the entire setup was maintained at 32 ± 0.5°C. The microemulsion-gel showed a higher diffusion coefficient and a smaller lag time compared to the conventional gel. The release profiles were evaluated using different kinetic models: zero-order, first-order, Higuchi and Korsmeyer-Peppas. Mathematical modelling of the drug release data suggested a quasi-Fickian diffusion mechanism for both conventional and microemulsion-based hydrogels.

Rezumat

Scopul acestei lucrări a fost acela de a evalua cinetica de cedare *in vitro* a $Na_3CaDTPA$, un agent decorporator bine-cunoscut şi larg utilizat, dintr-o formulare topică de tip microemulsie-gel comparativ cu un gel convenţional. Hidrogelurile au fost preparate folosind polimerul Carbopol 934. Studiile de cedare au fost conduse utilizând atât membrană hidrofobă (policarbonat), cât şi hidrofilă (amestec de esteri celulozici). Cinetica de cedare a fost evaluată folosind celule de difuzie Franz. Compartimentul receptor a fost reprezentat de tampon fosfat pH = 7,4, agitat continuu în timpul experimentelor la 600 rpm. Temperatura de lucru a fost menţinută constantă la 32 ± 0,5°C. Cedarea din microemulsia-gel a prezentat un coeficient de difuziune şi un timp de latenţă mai mici comparativ cu gelul convenţional. Profilele de cedare au fost evaluate utilizând ecuaţii matematice corespunzătoare următoarelor modele cinetice: ordin 0, ordin 1, Higuchi şi Korsmeyer-Peppas. Modelarea matematică a datelor de cedare a sugerat un mecanism de difuziune cvasi-Fickian atât pentru gelul convențional, cât și pentru cel sub formă de microemulsie.

Keywords: microemulsion-gel, release kinetics, decorporation agents

Introduction

Although rarely occuring, radiological events have the potential of generating catastrophes, especially in the context of a terrorist attack [37, 38]. The majority of chelation agents used as radionuclides decorporators are only available as intravenous formulations and efficient on a limited range of radioactive elements. The pentetic acid (diethylene-triaminepentaacetic acid, DTPA) is one of the most efficient and widely used decorporation agents. Its trisodium Ca and Zn salts are the only FDA (Food and Drug Administration) - approved treatments for contamination with isotopes of the transuranic elements Am, Pu and Cm [5]. However, both $Na_3ZnDTPA$ and $Na_3CaDTPA$ have a poor bioavailability after oral or topical administration [41], which makes useless the non-parenteral administration of DTPA salts in the absence of a modern drug delivery vehicle [22, 23], that would be both patient compliant and easy to administrate in case of radiological events affecting a large number of people [28, 36, 40].

Microemulsions are clear, isotropic and thermodynamically stable mixtures of oil, water and amphiphilic compounds (surfactants and co-surfactants) [8]. For the past 20 years, micro-

emulsions have been widely studied as drug delivery vehicles because of their unique pharmaceutical advantages over other nano-structured-based drug carriers, such as long-term stability, ease of formation, very small droplet size, optical isotropy, high solubilisation capacity and protection of drug molecules against chemical agents or enzymes [4, 34]. These carriers are currently studied as alternative drug formulations for oral, parenteral, topical, transdermal, intranasal and ocular administration routes [9, 19, 20, 35].

Compared to conventional vehicles for topical administration (emulsions, solutions etc.), microemulsions have shown increased transdermal absorption of both hydrophilic and lipophilic drugs, through several proposed mechanisms [15]: a)increased thermodynamic activity towards the skin as a result of the high solubilizing capacity of the formulation; b)alteration of the integrity of *stratum corneum*, depending on the composition of the microemulsion; c)increased mobility for the active substance molecules within the vehicle.

The present study aims to compare the release kinetics of $Na_3CaDTPA$ decorporation agent from a proposed microemulsion-based gel *versus* a conventional gel, using appropriate *in vitro* permeability studies. The ingredients used for the preparation of microemulsion were selected based on their pharmaceutical acceptance in topical formulations. Thus, isopropyl myristate (IPM) is a long chain triglyceride, widely used as oil phase in creams and topical microemulsions. It is considered to be the most biocompatible oil used for the formulation of pharmaceutically accepted preparations, including microemulsions [12, 24]. Besides that, its permeation enhancing properties were also reported [14]. In a previous study, IPM-based quaternary system was found to generate a higher area of microemulsion existence, requiring a smaller concentration of amphiphiles (Tween 80 and 1-octanol) for microemulsion formation when compared to arachis and canola vegetable oils [6]. Tween 80 is a non-ionic tensioactive, with a hydrophilic-lipophilic balance (HLB) value of 15. It is also a widely used excipient in the pharmaceutical field, with a well-known safety profile [26]. 1-octanol is a long-chain, non-toxic alcohol, with permeation enhancing properties, also studied in various microemulsion formulations [29, 32].

Materials and Methods

Materials

$Na_3CaDTPA$ was kindly gifted by Fluka Chemika. Isopropyl myristate (IPM) was purchased from Titolchimica. Tween 80 was kindly gifted by Actavis. 1-octanol was purchased from Merck-Schuchardt. Carbopol 934 was purchased from Loba Chemie Laboratory Chemicals Ltd. All used chemicals were of analytical reagent grade and no further purification was conducted. Distilled water was used throughout the experiments.

Methods

Construction of binary phase diagram

The classical representation of a binary phase diagram for a system composed of water, oil and amphiphilic molecules (known as "Kahlweit-fish diagram") consists of a temperature *versus* concentration of surfactant or temperature *versus* water:oil ratio, at constant pressure [18]. However, from a pharmaceutical microemulsion formulation perspective, this type of representation is not always relevant, as the temperature is usually one of the constants. In the present paper, a modified version of Kahlweit phase diagram was constructed at room temperature (25 ± 3°C) and constant water-oil ratio of 1:1 (w/w), by varying the surfactant:co-surfactant ratio instead of the temperature.

The aqueous component of the system was represented by a $Na_3CaDTPA$ solution with a concentration of 2%. Three weight ratios (3:1, 1:1, and 1:3) between surfactant (Tween 80) and co-surfactant (1-octanol) were considered for the construction of the phase diagram. The percentage of the surfactant-co-surfactant mixture in the system was also varied, starting from 80% until a minimum concentration at which the microemulsion formation still occurs, using a 5% decremental step. The samples were prepared by admixing accurately weighed amounts of oil, surfactant, co-surfactant, and $Na_3CaDTPA$ aqueous solution.

The samples were vigorously stirred for homogenization, sonicated for approximately 15 minutes to remove air bubbles and let to settle for 24 h before further analysis. The obtained systems were inspected for transparency and homogeneity by visual observation against strong light and they were classified as either microemulsions, multiphase systems/liquid crystals or gel-like systems based on their visual appearance and their microscopic appearance under cross-polarized light, using a Motic B1 optical microscope with a polarized light module [10]. Only the samples that presented an optically clear, low-viscosity, non-birefringent single phase were classified as Winsor IV type microemulsions. No attempt was made to distinguish between oil-in-water, water-in-oil or bi-continuous type microemulsions. From the obtained systems, an optimal formulation was selected to be used for the preparation of the corresponding micro-emulsion-gel, based on the minimal surfactant concentration necessary for microemulsion formation.

Preparation of conventional and microemulsion gels

To the selected microemulsion (containing 2% $Na_3CaDTPA$), Carbopol 934 was slowly added in a 5% (w/w) concentration and the mixture was

stirred. After being kept at 2-8°C for 2 hours, the sample was neutralized with triethanolamine to a pH = 6.5. A clear microemulsion-based hydrogel was obtained. Similar, a conventional hydrogel containing 5% (w/w) $Na_3CaDTPA$ solution was prepared, at the same Carbopol 934 concentration and neutralization pH. Both gel formulations were maintained in a fridge prior to their *in vitro* testing. For the preparation of gels, a rather high concentration of Carbopol 934 was used, leading to pharmaceutical formulations with adhesive properties, which might assure: 1) sustained release for the active substance and 2) protection of the wounded aria, both being desired properties of the vehicle considering its clinical use.

In vitro diffusion studies

The release profiles of $Na_3CaDTPA$ from the obtained gels were assessed using both hydrophobic (polycarbonate, code number K04CP02500/1215614, manufactured by GE Water&Process Technologies®) and hydrophilic (mixed cellulose esters, code number TR-200240, manufactured by Teknokroma®) membranes, with a diameter of 25 mm and a pore size of 0.40 μm and 0.45 μm, respectively. The release kinetics were evaluated using a Hanson Microette system, composed of six Franz diffusion cells, each with a nominal volume of 12 mL (approximately 10 mL available volume) and an effective diffusion area of 1.767 cm^2. The membranes were soaked in receptor solution (degassed phosphate buffer pH 7.4) for at least 30 minutes before conducting the experiments. The donor compartment held an accurately weighed amount of probe (conventional gel or microemulsion-gel). Each gel was applied using a metal spatula, without using intense shear forces. The receptor compartment was filled with phosphate buffer pH 7.4 and stirred magnetically at 600 rpm during the experiments. The temperature of the entire setup was maintained at 32 ± 0.5°C [39].

Samples (consisting of 0.5 mL) were withdrawn from the receptor compartment at predetermined time intervals (30, 60, 90, 120, 180, 240, 300, and 360 minutes) and the same volume of fresh, preheated and degassed receptor medium was immediately replaced, using a Hamilton syringe at 1 mL/min rate. The concentration of $Na_3CaDTPA$ in the receptor phase was analysed spectrophotometrically. The cumulative amounts of the decorporation agent that permeated through the membranes per unit surface area (μg/cm^2) were plotted as function of time.

$Na_3CaDTPA$ assay

The quantitative determination of $Na_3CaDTPA$ was performed using an UV spectrophotometric method at λ = 258 nm, using a Perking Elmer Lambda 40 spectrophotometer. For this purpose, 0.5 mL withdrawn sample was mixed with 0.5 mL $FeCl_3$ solution 0.1 M in hydrochloric acid and 4 mL of phosphate buffer pH = 5.4 [33]. The obtained solutions were stirred for at least 1 minute and the corresponding absorbances were recorded.

Mathematical modelling of $Na_3CaDTPA$ release kinetics

The release profiles were evaluated by fitting the experimental data to equations describing different kinetic orders. Linear regression analyses were made for zero-order ($M_t/M_0 = K_0 \times t$), first order ($\ln(M_0 - M_t) = K_1 \times t$), Higuchi ($M_t/M_0 = K_H \times t^{1/2}$) and Korsmeyer-Peppas ($M_t/M_0 = K_{KP} \times t^n$) models, where K is the kinetic constant and M_t/M_0 is the fraction of $Na_3CaDTPA$ released at time t. The zero-order model characterizes a drug delivery system that does not disaggregate, the active substance being released slowly, independent of the initial drug concentration. In contrast, the first-order model best describes a release process that is directly proportional to the drug concentration embedded in the vehicle. Assuming a homogeneously dispersed drug in a planar matrix and under perfect sink conditions, Higuchi's mathematical model suggests a pure diffusion release mechanism of the active substance from a vehicle, with no occurring erosion or swelling of the matrix. The Korsmeyer-Peppas model can be used as a decision parameter between the Higuchi and zero order models [21]. The release mechanism is a function of the diffusion exponent n. For a thin film geometry delivery system: n = 0.5 suggests a Fickian diffusion; 0.5 < n < 1.0 supports an anomalous non-Fickian transport (both diffusional and relaxational transport); for n = 1.0, the release mechanism is represented by a case-II, relaxational transport, time-independent, zero-order model [31].

Model selection criteria

Usually, the accepted order of kinetics is the one that yields a linear function with the adjusted coefficient of determination closest to 1:

$$R^2_{adjusted} = 1 - (n-1) \times (1-R^2)/(n-p),$$

where n is the number of dissolution data point and p is the number of parameters used by the model [7]. Another method for comparing the appropriateness of different release models is the Akaike Information Criterion (AIC) [2, 25]:

$$AIC = N \ln(WSS) + 2p \quad (1)$$

$$WSS = \sum_{i=1}^{N} w_i \left(y_i^{obs} - y_i^{pre}\right)^2 \quad (2)$$

in which, *WSS* is the weighed sum of squared deviations, *N* is the number of data points, *p* is the model parameters number, w_i is the weighing factor for the i^{th} data point (which is usually equal to 1 for fitting), y^{obs} and y^{pre} are the observed and the predicted amount of drug released *versus* time. The mathematical model with the smallest AIC value is the one that fits best the data.

Statistical analysis

The values were expressed as mean ± SD. The differences in the results of *in vitro* release studies were evaluated using the univariate ANOVA test. The DDSolver software was used for the analysis of data. The plots were constructed using Microsoft Office Excel 2013.

Results and Discussion

Microemulsion formulation

In this study, microemulsions with a water:oil ratio of 1:1 were prepared in order to achieve the maximum solubilisation of both hydrophilic and lipophilic phases, at the lowest concentration of amphiphiles, that would, theoretically, ensure a superior synergic skin-permeation effect for the formulation [13].

Although formulated using a non-ionic tensioactive, the salinity may also affect the type and stability of these systems [6, 18]. Due to the influence that the active substance might have upon phase equilibrium, for the construction of the phase diagram, $Na_3CaDTPA$ was added to each sample in a concentration equal to the one used in the drug release studies. The results are represented in Figure 1, where δ is the co-surfactant fraction in the surfactant:co-surfactant mixture and α is the amphiphilic mixture fraction in the system.

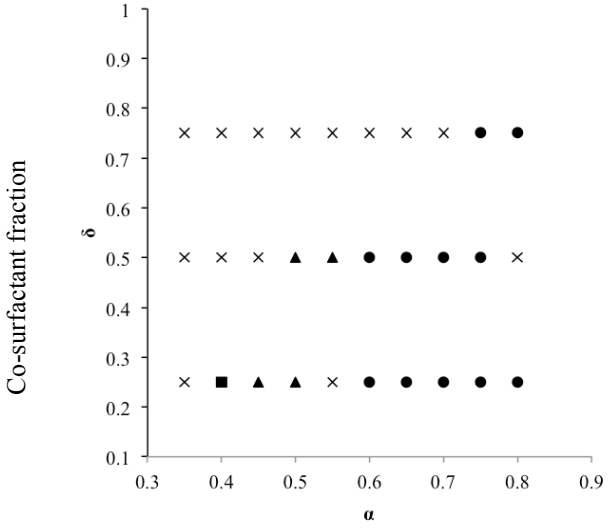

Figure 1.

Binary phase diagram corresponding to a water-IPM ratio of 1:1 (● - microemulsion, ▲- gel-like, ■ – transparent gel, × – multiphase/opalescent systems)

The apparent viscosity of the system increases with the increase of water content (lower values for α) and also with the increase of Tween 80 fraction in the amphiphilic mixture (decrease of δ). For δ = 0.25 or 0.50 and α < 0.55, gel-like systems are obtained. Based on the minimal α value necessary for microemulsion formation and the lowest apparent viscosity of the samples, an optimal formulation was proposed (Table I).

Table I

Composition of microemulsion sample further used for the microemulsion-gel preparation (δ = 0.47)

Ingredients	Fraction
Water	20.2%
Isopropyl myristate	20.2%
Tween 80	30.6%
1-octanol	27%
$Na_3CaDTPA$	2%

In vitro diffusion studies

In Figure 2 there are presented the release profiles of $Na_3CaDTPA$ from the investigated gels. The results for each tested formulation were corrected in respect to the dilution factor and to the individual volume of each diffusion cell. The release data represented the cumulated amount of diffused $Na_3CaDTPA$ through the membranes. If the release study concerned in fact the "available for release" fraction, a very long time interval would have been required for this to be appropriately evaluated. The concentration in diffused decorporation agent was obtained from the previously prepared calibration curves (regression curve for $Na_3CaDTPA$ assay is $y = 1.1075x - 0.0015$, $R^2 > 0.99$). The results are expressed as mean ± SD and are summarized in Table II (N = 3 - 6). The diffusion parameters are given in Table III.

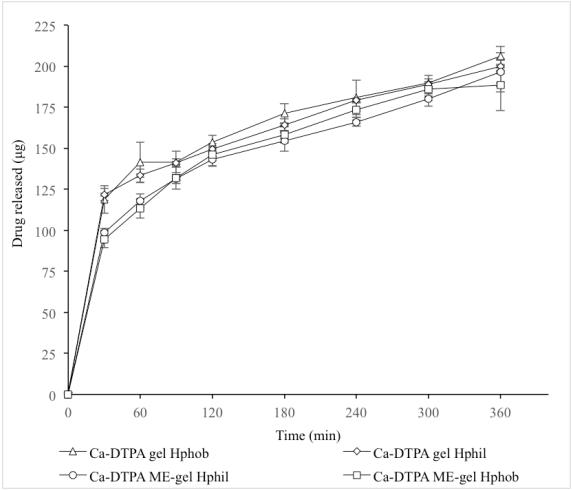

Figure 2.

Ca-DTPA release profiles from conventional gel and microemulsion-gel formulations through hydrophilic (Hphil) and hydrophobic (Hphob) membranes

The univariate ANOVA analysis suggests no significant difference (p-value > 0.05) between the $Na_3CaDTPA$ release profiles from conventional gel through hydrophilic *versus* hydrophobic membranes.

With the exception of 240 min and 300 min time points (p-value = 0.0057 and 0.0345, respectively), the same can be stated for the microemulsion-gel formulation. However, there is a significant difference at several time points of the diffusion curves through the same membrane type, corresponding to the two hydrogels. The amount of drug that permeated after 6 hours showed no significant differences between the two formulations, regardless of the membrane used (p-value > 0.05).

Table II

Drug release data from investigated gel formulations

Time (min)	Permeated amount (μg/cm^2) of drug (mean ± SD)					
	Hydrophilic membrane			Hydrophobic membrane		
	Gel	ME-Gel	p-value	Gel	ME-Gel	p-value
30	68.91 ± 2.07	55.86 ± 1.40	< 0.0001	67.15 ± 4.74	53.50 ± 2.86	0.0009
60	75.47 ± 2.31	66.75 ± 2.36	0.0012	79.99 ± 6.95	64.16 ± 3.36	0.0020
90	79.83 ± 1.54	74.32 ± 1.57	0.0016	80.14 ± 3.69	74.61 ± 3.85	0.0794
120	84.48 ± 1.11	81.10 ± 2.41	0.0584	86.89 ± 2.45	82.64 ± 3.80	0.1269
180	92.85 ± 2.16	87.49 ± 3.63	0.0536	96.89 ± 3.38	89.65 ± 3.04	0.0140
240	101.41 ± 0.63	93.97 ± 1.45	0.0001	102.42 ± 5.88	98.11 ± 2.51	0.1515
300	106.83 ± 3.17	101.86 ± 2.44	0.0337	107.35 ± 1.55	105.31 ± 2.46	0.2383
360	113.18 ± 2.01	111.15 ± 6.83	0.6397	116.61 ± 3.34	106.75 ± 8.96	0.1159

ME-Gel = microemulsion-gel

Table III

Release data parameters

Formulation	Membrane type	Diffusion coefficient (μg/cm^2/min$^{1/2}$)	Lag time (min$^{1/2}$)	Amoung of drug that permeated after 6h (μg)
Gel	Hydrophilic	3.32	-14.77	199.99 ± 3.6
	Hydrophobic	3.44	-14.03	206.05 ± 5.9
ME-Gel	Hydrophilic	3.85	-9.31	196.40 ± 12.1
	Hydrophobic	4.03	-8.17	188.62 ± 15.8

Despite having a significantly smaller concentration gradient throughout the release study (initial 2% $Na_3CaDTPA$ in microemulsion-gel *versus* 5% in conventional gel), when comparing the diffusion coefficients for conventional gel and microemulsion-based gel, higher values were observed for the later, independent of the membrane type.

As suggested by the negative lag-time values, regardless of nature of the membrane, the active substance had an initial "burst release", more than 50% of the total amount of the released drug being diffused in the first 30 minutes. This is probably due to the delayed formation of the gel barrier and thus immediate release of the drug found at the surface. Also, the values for the lag-time parameter, suggest a more rapid achievement of the steady state diffusion of $Na_3CaDTPA$ from microemulsion-gel than conventional gel. These findings are probably due to the internal structure of the microemulsion that enables the formation of continuous aqueous channels through which the active substance is directly transported to the membrane. The calculated kinetic constants have low values, corresponding to low release rates, disregarding the membrane type. This is probably the result of the high viscosity of the formulations and/or internal reorganization of gel structure that diminishes the available diffusion area and lengthens the diffusion path for the active substance [1, 27].

Model selection

The selection of an adequate model for fitting drug release data is important for determining the release characteristics using model-dependent approaches. When evaluating models with different parameters, because R^2 increases with the number of included parameters, the adjusted coefficient of determination should be used. Taking into account the initial "burst release", the mathematical equations must be adjusted accordingly. Table IV synthesizes the calculated values for the coefficient of determination corresponding to each mathematical model. As shown, the formulations didn't follow a zero-order or a first-order kinetics. The release profiles could be best explained by Higuchi and Korsmeyer-Peppas models, as the plots showed high linearity. Figure 3 and Figure 4 are the graphical representations of Higuchi and Korsmeyer-Peppas models.

Table IV

Model selection results for investigated gels

Model	Parameter	Formulation			
		Gel		ME-Gel	
		Hydrophilic membrane	Hydrophobic membrane	Hydrophilic membrane	Hydrophobic membrane
Zero-order $Q = Q_0 + K_0 \cdot t$	$R^2_{adjusted}$	0.9874	0.9593	0.9576	0.9069
	K_0	0.1325	0.1365	0.1519	0.1563
	Q_0	67.5207	68.6385	57.8599	57.3849
	AIC	27.5146	37.5554	39.6065	46.7244
First-order $\ln Q = \ln Q_0 + K_1 \cdot t$	$R^2_{adjusted}$	0.9669	0.9227	0.9043	0.8415
	K_1	0.15 x 10^{-2}	0.15 x 10^{-2}	0.18 x 10^{-2}	0.19 x 10^{-2}
	Q_0	69.2691	70.2809	59.9134	58.9742
	AIC	36.7540	41.4586	44.1738	50.8987
Higuchi $Q = Q_0 + K_H \cdot t^{1/2}$	$R^2_{adjusted}$	**0.9955**	**0.9827**	**0.9900**	0.9765
	K_H	3.3179	3.4420	3.8455	4.0253
	Q_0	49.3657	49.6438	36.5358	34.5965
	AIC	19.34	30.70	28.04	35.71
Korsmeyer-Peppas $Q = Q_0 + K_{KP} \cdot t^n$	$R^2_{adjusted}$	0.9751	0.9727	0.9887	**0.9798**
	K_{KP}	14.2367	14.2359	9.5047	8.4276
	n	0.2983	0.3061	0.3746	0.4021
	Q_0	27.5627	26.8613	22.3427	21.4020
	AIC	33.48	34.9171	29.5444	35.0459

Q is the amount of drug released at time t; Q_0 is the initial "burst release" amount of drug; K_0, K_1, K_H, K_{KP} are, respectively, the zero-order, first-order, Higuchi's and Korsmeyer-Peppas kinetic constants and n is the Korsmeyer-Peppas exponent

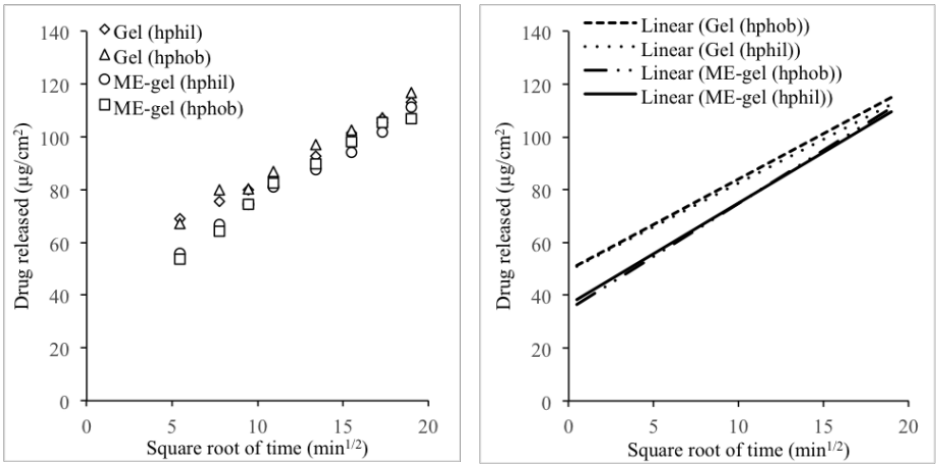

Figure 3.

Higuchi model: mean individual profiles (left) and regression lines (right)

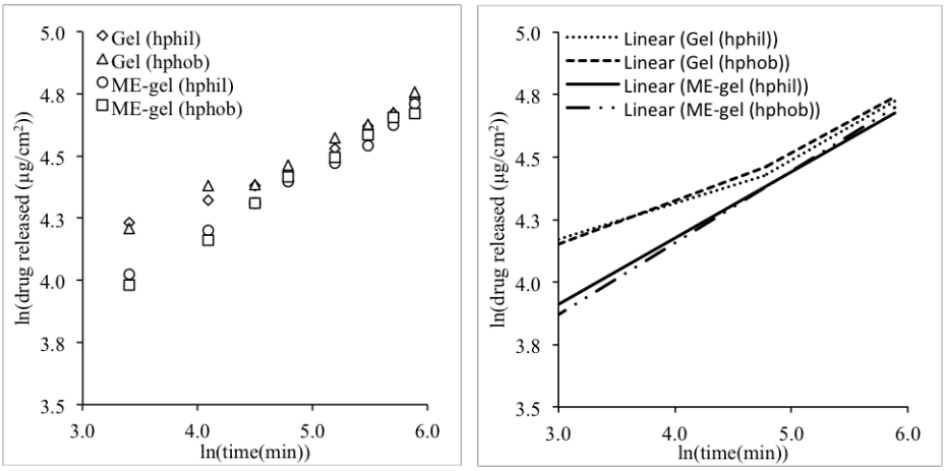

Figure 4.

Korsmeyer-Peppas: mean individual profiles (left) and regression lines (right)

Considering a formulation-independent and membrane type-independent release of the active substance, a regression line through all data points for the Higuchi model yields a coefficient of determination R^2 = 0.9365. In case of Korsmeyer-Peppas model, R^2 has a value of 0.9162 (Figure 5). The high R^2 values suggest that the release curves are somewhat parallel, but also that the Korsmeyer-Peppas model is more discriminant for curve comparisons than the Higuchi model.

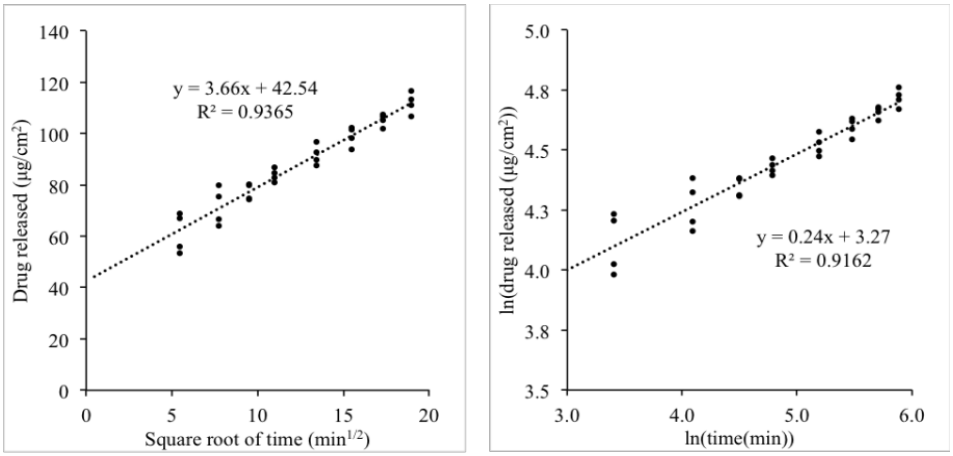

Figure 5.
Higuchi (left) and Korsmeyer-Peppas (right) models applied to all data points

As observed in Figure 4 (right), the release profiles for gel formulation can be divided into two sections, corresponding to 30-120 minutes and 120-360 minutes time ranges, respectively. Both regression lines are characterized by higher R^2 values than initial ($R^2 > 0.98$), suggesting a better fitting of the experimental data, with the exception of the regression line for the first time section in case of release study through hydrophobic membrane, for which R^2 is 0.92 (Table V). This might be the consequence of the high standard deviation obtained calculated for the 60 minutes time point.

Table V

Regression lines equations, R^2 and AIC values for the Korsmeyer-Peppas model applied to conventional gel formulation

Membrane type	Time interval (min)	Regression equation	R^2	AIC
Hydrophilic	30-120	y = 0.14x + 3.74	0.9931	11.39
	120-360	y = 0.26x + 3.15	0.9972	
Hydrophobic	30-120	y = 0.17x + 3.63	0.9254	32.12
	120-360	y = 0.25x + 3.25	0.9831	

Based on these findings, the Korsmeyer-Peppas graphical representation suggests a two-step release mechanism of the active substances embedded in conventional gel formulation, consisting of two phenomena: 1) polymer relaxation (matrix swelling) and 2) diffusion. This process can be described simply by adding the diffusion controlled and relaxation controlled drug delivery:

$$M_t / M_\infty = k_1 t + k_2 \sqrt{t}$$

Entering of dissolution medium in the polymeric matrix promotes complex processes that modify the continuously diffusion, leading to a non-Fickian release behaviour [16, 17]. Thus, for the first step, the release kinetics of $Na_3CaDTPA$ from conventional gel is controlled by the swelling process, leading to an inferior overall diffusion coefficient compared to microemulsion-gel formulation. For the second section of drug release (120-360 minutes), both conventional gel and microemulsion-gel present a similar release mechanism. For the microemulsion-gel formulation, this two-step process hasn't been observed, the drug being released in a controlled manner throughout the study.

In all cases, the values for the release exponent (n) were inferior to 0.5, being beyond the limits of Korsmeyer-Peppas "power law" model. Based on these findings, a quasi-Fickian diffusion mechanism of the drug can be considered for both conventional and microemulsion-based hydrogels. This mechanism indicates that $Na_3CaDTPA$ is partially diffusing through a swollen matrix and water filled pores in the hydrogels [3, 11, 30].

The AIC values calculated for Higuchi and Korsmeyer-Peppas mathematical models suggest no significant differences between the two models, with the exception of the release of $Na_3CaDTPA$ from conventional gel through a hydrophilic

membrane, for which the Korsmeyer-Peppas model is more suitable (Tables IV and V). Based on these results, it can only be concluded that Korsmeyer-Peppas is the more performant model for analysis of this particular data, but none of the models has statistical relevance.

Conclusions

In this study, a $Na_3CaDTPA$ containing microemulsion-based hydrogel was formulated and a comparison between the release profiles of the active substance from conventional gel and microemulsion-gel formulations through hydrophilic and hydrophobic membranes was performed. Despite having a lower concentration gradient, the microemulsion-gel showed higher diffusion coefficients and smaller lag times compared to conventional gel. No statistical significant differences were found between the amounts of drug released after 6 h from the two formulations, regardless of the membrane used. Mathematical modelling of the drug release data suggests a quasi-Fickian diffusion mechanism for both conventional and microemulsion-based hydrogels.

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