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RESEARCH PAPER

Evaluation of Mathematical Models Describing Drug Release from Estradiol Transdermal Systems

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ABSTRACT

The in vitro release profiles of 13 patches of estradiol (from five marketed products) were determined by the paddle-over-disk method. The transdermal systems were membrane-controlled type or matrix diffusion-controlled type. The estradiol content of test aliquots of the dissolution medium was determined by HPLC. To analyze the release mechanism, several release models were tested such as zero order, first order, Higuchi, Weibull, Korsmeyer–Peppas, and Makoid–Banakar. The release profiles showed that the drug was released at a constant rate for three patches. The drug-release rate from the other 10 patches was not constant, and diminished with the square-root of time (Higuchi model).

Key Words: Estradiol; Transdermal systems; Drug release; Kinetic models.

INTRODUCTION

In the last two decades, transdermal therapeutic systems (TTS) have been introduced for providing controlled drug-delivery via skin into the systemic circulation. The first transdermal patch was scopolamine and reached the market in 1981.[1] Other transdermal therapeutic systems have been approved for drugs such as nitroglycerin, testosterone, clonidine, nicotine, fentanyl, estradiol, and norethisterone (the last one in combination with estradiol). Estradiol is the most potent naturally occurring estrogen in mammals. Estradiol transdermal systems provides systemic estrogen replacement therapy. The aim of this work was to evaluate the in vitro release profile of some estradiol transdermal therapeutic systems (patches) commercially available (13 in total). The applicability and reliability of some mathematical kinetic models to describe the drug release from these systems was also evaluated. The transdermal systems (Table 1) were matrix diffusion-controlled type, STT 1 (37.5, 50, 75), STT 3 (25, 50, 100), STT 4

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Table 1. Transdermal delivery systems evaluated.

	TTS product name	Estradiol content (mg)	Manufacturer	Surface area (cm^2)	Claimed in vivo release (μg/24 h)	Release rate ($\mu g\, h^{-1/2}$)
STT 1	Menorest® 37.5	3.29	Rhône-Poulanc Rorer	11	37.5	438
	Menorest® 50	4.33	Rhône-Poulanc Rorer	14.5	50	544
	Menorest® 75	6.57	Rhône-Poulanc Rorer	22	75	812
STT 2	Estraderm TTS® 25	2	Novartis	5	25	—
	Estraderm TTS® 50	4	Novartis	10	50	—
	Estraderm TTS® 100	8	Novartis	20	100	—
STT 3	Estraderm MX 25	0.75	Novartis	11	25	250
	Estraderm MX 50	1.5	Novartis	22	50	477
	Estraderm MX 100	3	Novartis	44	100	1048
STT 4	Dermestril® 25	2	Delta	9	25	318
	Dermestril® 50	4	Delta	18	50	613
	Dermestril® 100	8	Delta	36	100	1199
STT 5	Climara®	3.9	3M Pharmaceuticals	12.5	50	1853

(25, 50, 100), and STT 5, or membrane-controlled type, STT 2 (25, 50, 100).

The drug-release rate is now a fundamental parameter of a pharmaceutical dosage form. The quantitative analysis of the values obtained in these tests is easier when mathematical formulas are used expressing the dissolution results as a function of some of the dosage forms' characteristics. The dissolution of drugs from the pharmaceutical dosage forms has been described by kinetic models in which the dissolved amount of drug (M) is a function of the time (t), or $M = f(t)$. In order to analyze the drug-release mechanism, the following mathematical expressions were used:[2]

Zero-Order Model[3,4]:

$$M_t = M_0 + K_0 t$$

where M_t is the amount of drug released at time, t, K_0 is the apparent dissolution rate constant or zero-order release constant, and M_0 is the initial amount of the drug in the solution in result of a burst effect. In this case, the drug release runs at a constant rate.

First Order Model[5,6]:

$$\ln M_t = \ln M_0 + K_1 t$$

where K_1 is the first-order release constant. In this case, the drug released at each time is proportional to the residual drug inside the dosage form.

Higuchi Model[7–9]:

$$M_t = M_0 + K_H t^{1/2}$$

where M_t is the amount of drug released at time t and K_H is the Higuchi release rate. This is the most widely used model to describe drug release from pharmaceutical matrices.

Weibull Model[10–13]:

$$\log[-\ln(1-(M_t/M_\infty))] = \beta \times \log t - \log \alpha$$

where β is the shape parameter of the dissolution curve and α is the scale parameter that defines the time scale of the process. This last parameter can be replaced by a more informative dissolution parameter, T_d, representing the time interval necessary to release 63.2% of the drug in the pharmaceutical-dosage form.

Korsmeyer–Peppas Model[14–18]:

$$M_t/M_\infty = M_0/M_\infty + K_{KP}t^n$$

where K_{KP} is a constant incorporating structural and geometric characteristics of the drug-dosage form and n is the release exponent, indicative of the drug-release mechanism. Peppas[16] used this n-value in order to characterize different release mechanisms. When $n = 0.5$ (for a slab), the drug diffuses through and is released from the matrix with a quasi-Fickian diffusion mechanism. For $n > 0.5$, an anomalous, non-Fickian drug diffision occurs. When $n = 1.0$, a non-Fickian, Case II or zero-order release kinetics could be observed. To the determination of the exponent n, it should only be used the portion of the release curve where $M_t/M_\infty < 0.6$. To use this equation it is also necessary that release occur in a one-dimensional way and that the system width/thickness or length/thickness relation be at least 10, such as in TTS cases. This model is generally used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not well known or when more than one type of release phenomena could be involved.

Makoid–Banakar Model[19]:

$$M_t/M_\infty = K_{MB}t^n e^{(-ct)}$$

where K_{MB}, n, and c are empirical parameters (K_{MB}, n, $c > 0$) and M_t/M_∞ is the accumulated fraction of the drug in solution at time t.

The coefficient of determination, the correlation coefficient, the adjusted coefficient of determination, the sum of squares of residues, the mean square error, the Akaike Information Criterion (AIC), and the F-ratio probability are commonly used as a drug-release model selection criterion.[2] For the same number of parameters, the coefficient of determination (R^2) can be used to determine the best of the model equations. When comparing models with different numbers of parameters, as in this case, the adjusted coefficient of determination (R^2_{adjusted}) is more meaningful.

$$R^2_{\text{adjusted}} = 1 - \frac{(n-1)}{(n-p)}\left(1 - R^2\right)$$

where n is the number of dissolution data points (M/t) and p is the number of parameters in the model. Whereas the R^2 always increases, or at least stays constant, when adding new model parameters, R^2_{adjusted} can actually decrease, thus giving an indication if the new parameter really improves the model or might lead to overfitting. In other words, the "best" model would be the one with the highest adjusted coefficient of determination. In this study, both the coefficient of determination and the adjusted coefficient of determination were used as indicators of best fitting.

EXPERIMENTAL METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: estradiol (Sigma Chemical Co, St. Louis, MO), sodium lauryl sulfate (Sigma Chemical Co, St. Louis, MO). All chemicals used were analytical reagent grade. In HPLC procedure, HPLC-grade acetonitrile (Merck KGaA, Darmstadt, Germany) and double-distilled water were used.

The studied estradiol transdermal therapeutic systems (13 in total) were commercially available in Portugal (Table 1). The estradiol-release profiles of five marketed products, each with three different sizes and one with only one size, from four different companies were determined. One of the companies meanwhile replaced its original formulations (TTS), here referred as STT 2, by another totally different (MX), here referred as STT 3. While the first was a membrane-moderated TTS, the second one was a matrix TTS, of

the type of the already commercialized by other companies.

In Vitro Release Study

The estradiol release was studied using the USP 23 apparatus 5, paddle over disk, with 500 mL of dissolution medium (water + SLS 0.3%),[20] at $32 \pm 0.5^{\circ}C$, with a stirring speed of 100 rpm.

Samples (5 mL) were removed at predetermined time intervals (30 min and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hr), filtered, and assayed by HPLC. An equal volume of fresh medium was immediately added to maintain the dissolution volume. An accumulative correction factor, L, was applied to account for previously withdrawn samples. Dissolution studies were performed with six TTS.

The HPLC system consisted of a Varian model 9012 pump, a 200-μL loop, a Varian model 9050 detector, and a C18 column (Spherisorb ODS1 10U, 250×4.6 mm, Varian, Inc., Walnut Creek, CA, USA). The mobile phase consisted of acetonitrile and water (50:50) with a flow rate of 1.5 mL/min. The validation of the analytical method was made in accordance with the ICH Harmonized Tripartite Guidelines.[21,22]

RESULTS AND DISCUSSION

In the case of estradiol transdermal patches, the limiting step is the estradiol absorption through the skin, and in such case, the drug-release rate from these systems should be at least equal to the absorption rate. The drug release rate ($\mu g\,h^{-1}$) in the case of the membrane-controlled transdermal systems was 1.4, 2.4, and 10.4, respectively, for STT 2 25, STT 2 50, and STT 2 100 and the drug-release rate per surface area was around $0.35\,\mu g\,h^{-1}\,cm^{-2}$. For these systems the drug release was slow, but enough to allow the necessary amount of estradiol to be absorbed by the skin at the right rhythm. These systems seemed safer, having the additional advantage of preventing over dosage cases when the skin barrier function was diminished.

The drug-release rate ($\mu g\,h^{-1}$) in the case of the matrix transdermal systems was not constant during the release period. The drug-release rate ($\mu g\,h^{-1/2}$) for the matrix transdermal systems were obtained from Higuchi model, and can be seen in Table 1.

The drug-release rate ($\mu g\,h^{-1/2}$) for the STT 1 systems was 438, 544, and 812. Dividing these rates by the system area we find that the drug-release rate ($\mu g\,h^{-1/2}\,cm^{-2}$) was almost the same for the three different dosages, 38.1. Then the main difference between those systems was the surface area in contact with the dissolution fluid. For the other matrix systems we found the same thing and the drug-release rate per surface area ($\mu g\,h^{-1/2}\,cm^{-2}$) was, respectively, 22.7, 35.1, and 148.3 for STT 3, STT 4, and STT 5. The release rates from these matrix systems were very different from brand to brand, with the STT 5 diffusion rate (highest) 6.5 times bigger than the STT 3 diffusion rate (smallest).

The net release, i.e., the ratio between the amount released in 24 hr and the theoretical amount in TS, was high, except for STT 2, where it was inferior to 5%[23] and can be seen in Table 2. The net absorption, i.e., the ratio between the amounts absorbed after 1 day and after 4 days and the theoretical amount in TS, was extremely low for these systems (Table 2). It should be noted that in the STT 2 case, the net absorption changed from 1.25% and 5.0% (1 and 4 days) to a percentage of 3.3% and 13.3% (only because of the diminution of the estradiol amount in each STT 3), with consequent economic benefits. Remember that these systems should be replaced at the end of 4 days maximum, originating a huge waste in estradiol of more than 85%, reaching almost the 98% in same cases. For these marketed TTS formulations, the higher therapeutic safety in the STT 2 case was exchanged by an economical advantage, or at least by a lesser economical disadvantage in face of the con-

Table 2. TS net release and absorption.

		Net absorption (%)	
	Net release (%)	1 Day	4 Days
STT 1 37.5	66.3	1.14	4.56
STT 1 50	62.5	1.15	4.62
STT 1 75	61.5	1.14	4.57
STT 2 25	1.7	1.25	5.00
STT 2 50	1.5	1.25	5.00
STT 2 100	3.4	1.25	5.00
STT 3 25	96.1	3.33	13.33
STT 3 50	99.3	3.33	13.33
STT 3 100	93.1	3.33	13.33
STT 4 25	76.8	1.25	5.00
STT 4 50	74.3	1.25	5.00
STT 4 100	73.5	1.25	5.00
STT 5	98.2	0.64	2.56

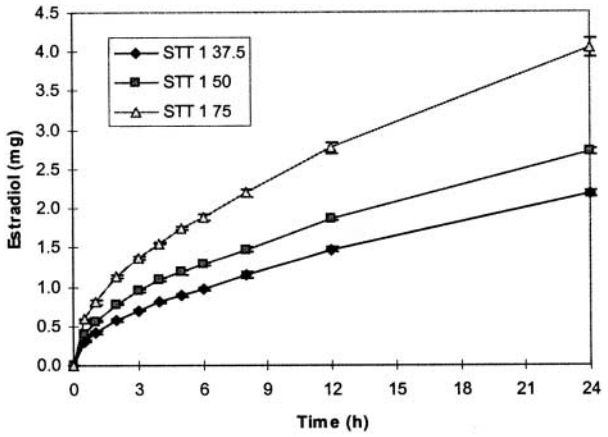

Figure 1. STT 1 release profiles.

currency, because a matrix system has a much more cheaper production than a membrane-controlled system of the previously commercialized type.

The estradiol-release profiles (μg) for the several commercial estradiol patches can be seen in Figs. 1–3, where the symbols represents the mean value and the error bars represent the standard variation. The drug release was very fast, except for the STT 2 case and especially in the STT 5 case, where the total release occurred within 8 hr. The results obtained by the several samples for each TTS were very similar as can be seen by the small error bars in the figures.

For STT 1, the mathematical expressions best describing drug release were Higuchi, Korsmeyer–Peppas, and Makoid–Banakar models, with a coefficient of determination (R^2) higher than 0.995 and an adjusted coefficient of determination (R^2_{adjusted}) higher

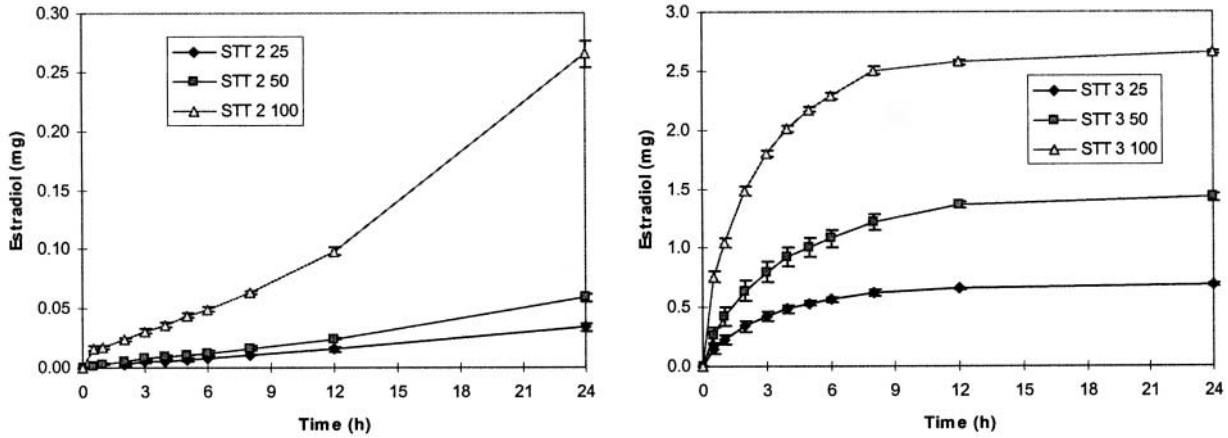

Figure 2. STT 2 and STT 3 release profiles.

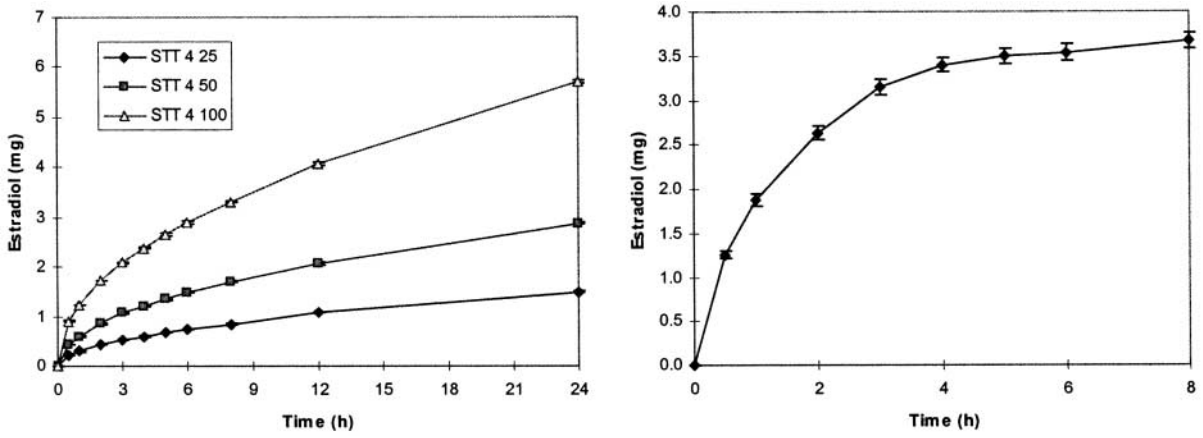

Figure 3. STT 4 and STT 5 release profiles.

Table 3. Model fitting of the estradiol release profiles.

		STT 1 37.5	STT 1 50	STT 1 75	STT 2 25	STT 2 50	STT 2 100	STT 3 25	STT 3 50	STT 3 100	STT 4 25	STT 4 50	STT 4 100	STT 5
Zero order	K_0	0.0829	0.1016	0.1525	0.0014	0.0024	0.0105	0.1154	0.2211	0.5536	0.0591	0.1131	0.2215	0.9796
	R^2	0.9300	0.9091	0.9173	**0.9979**	0.9901	0.9716	0.9396	0.9465	0.9051	0.8988	0.8849	0.8904	0.9048
	R^2_{adj}	0.9222	0.8990	0.9082	**0.9976**	0.9889	0.9685	0.9245	0.9331	0.8734	0.8876	0.8721	0.8782	0.8730
First order	K_1	0.073	0.070	0.071	0.104	0.128	0.117	0.331	0.342	0.342	0.073	0.070	0.068	0.353
	R^2	0.7764	0.7469	0.7637	0.8618	0.8155	0.9381	0.9077	0.9047	0.9490	0.7186	0.7110	0.7348	0.9191
	R^2_{adj}	0.7485	0.7153	0.7341	0.8387	0.7924	0.9304	0.8770	0.8730	0.9236	0.6834	0.6748	0.7017	0.8786
Higuchi	K_H	0.439	0.545	0.814	0.007	0.011	0.049	0.250	0.478	1.048	0.319	0.615	1.201	1.853
	R^2	**0.9950**	**0.9983**	**0.9978**	0.8706	0.8507	0.8039	**0.9960**	**0.9942**	**0.9999**	**0.9990**	**0.9995**	**0.9999**	**0.9992**
	R^2_{adj}	**0.9945**	**0.9981**	**0.9976**	0.8521	0.8341	0.8039	**0.9950**	**0.9927**	**0.9999**	**0.9989**	**0.9994**	**0.9998**	**0.9989**

Amount released expressed in mg. Best results are in bold.

Table 4. Model fitting of the estradiol release profiles.

		STT 1 37.5	STT 1 50	STT 1 75	STT 2 25	STT 2 50	STT 2 100	STT 3 25	STT 3 50	STT 3 100	STT 4 25	STT 4 50	STT 4 100	STT 5
Weibull	β	0.6046	0.5838	0.5842	1.0124	0.8639	0.7040	0.7662	0.7757	0.6509	0.6604	0.6346	0.6091	0.8093
	T_d	6.5176	6.4089	6.5123	970.6285	405.6635	66.7453	2.7505	3.9994	2.2014	6.2728	6.1334	5.8135	1.5816
	R^2	0.9809	0.9899	0.9873	**0.9901**	0.9854	0.8995	**0.9995**	**0.9996**	**0.9968**	**0.9903**	**0.9933**	0.9887	**0.9977**
	R^2_{adj}	0.9785	0.9886	0.9857	0.9884	0.9836	0.8870	**0.9994**	**0.9995**	**0.9952**	0.9891	**0.9925**	0.9873	**0.9966**
Korsmeyer–Peppas	K_{KP}	0.1079	0.1177	0.1099	0.0006	0.0003	0.0003	0.302	0.2807	0.3512	0.1522	0.1590	0.1537	0.4747
	n	0.5640	0.5199	0.5360	1.0520	1.2520	1.5150	0.567	0.5860	0.4950	0.5140	0.4900	0.4930	0.5010
	R^2	**0.9983**	**0.9987**	**0.9990**	**0.9984**	**0.9979**	**0.9988**	**0.9992**	**0.9993**	**0.9999**	**0.9992**	**0.9996**	**0.9999**	**0.9992**
	R^2_{adj}	**0.9978**	**0.9983**	**0.9987**	**0.9976**	**0.9970**	**0.9985**	**0.9987**	**0.9988**	**0.9998**	**0.9990**	**0.9995**	**0.9999**	**0.9983**
Makoid–Banakar	K_{MB}	0.1244	0.1284	0.1215	0.0008	0.0008	0.0020	0.3155	0.2912	0.3502	0.1456	0.1510	0.1544	0.5142
	n	0.4716	0.4573	0.4682	0.8530	0.6730	0.4295	0.6677	0.6776	0.4903	0.5493	0.5280	0.4921	0.6124
	c	−0.0075	−0.0055	−0.0057	−0.0135	−0.0330	−0.0584	0.0492	0.0444	−0.0029	0.0033	0.0034	0.0000	0.0714
	R^2	**0.9995**	**0.9996**	**0.9998**	**0.9999**	**0.9997**	**0.9952**	**1.0000**	**0.9999**	**0.9999**	**0.9995**	**0.9999**	**0.9999**	**0.9999**
	R^2_{adj}	**0.9994**	**0.9995**	**0.9997**	**0.9999**	**0.9996**	**0.9938**	**1.0000**	**0.9998**	**0.9999**	**0.9993**	**0.9999**	**0.9999**	**0.9999**

Amount released expressed in mg. Best results are in bold.

than 0.994 (Tables 3 and 4). The release exponent (n), obtained from the Korsmeyer–Peppas model, was approximately 0.5, confirming the results obtained with the Higuchi model showing that the estradiol-release mechanism was the drug diffusion (Fickian) through the polymeric matrix.

For STT 2, the expressions that allowed a good fitting for the drug-release values were Korsmeyer–Peppas and Makoid–Banakar models, with $R^2 > 0.995$ and $(R^2_{\text{adjusted}}) > 0.993$. For STT 2 25, the zero order model also showed good results ($R^2 > 0.997$). From the release exponent ($n \approx 1$) it can be seen that the estradiol-release mechanism, for this particular system, was Case-II transport (constant release rate). The shape parameter, β, obtained from the Weibull model, showed that the estradiol-release profile for STT 2 25 was exponential ($\beta = 1$). For STT 2 50 and STT 2 100, the estradiol-release mechanism, according to Korsmeyer–Peppas model, was super Case-II transport. The Weibull shape parameter was lower than 1. For STT 2 100, the results obtained with this model were very weak, with a low value of R^2 (lower than 0.99).

For STT 3, the mathematical expressions best describing drug release were Higuchi, Weibull, Korsmeyer–Peppas, and Makoid–Banakar models, with $R^2 > 0.994$ and $(R^2_{\text{adjusted}}) > 0.992$. The Korsmeyer– Peppas release exponent, ($n \approx 0.5$), confirmed the results obtained with Higuchi model showing that the estradiol-release mechanism was the diffusion (Fickian) of drug through the matrix.

For STT 4, the mathematical expressions that best described drug release were Higuchi, Korsmeyer–Peppas, and Makoid–Banakar models, with $R^2 > 0.999$ and $(R^2_{\text{adjusted}}) > 0.998$. The Korsmeyer–Peppas release exponent ($n \approx 0.5$), confirmed the good results obtained with Higuchi model and showed that the release mechanism was the drug diffusion (Fickian) through the polymeric matrix.

The mathematical expressions best describing estradiol release from STT 5 were Higuchi, Weibull, Korsmeyer–Peppas, and Makoid–Banakar models, with $R^2 > 0.997$ and $(R^2_{\text{adjusted}}) > 0.996$. The Korsmeyer–Peppas release exponent ($n \approx 0.5$), confirmed the good results obtained with Higuchi model showing that the release mechanism was also the drug diffusion (Fickian) through the polymeric matrix.

CONCLUSIONS

The mathematical fitting of the estradiol-release profiles with the several kinetic models studied showed that the models best describing drug release from these transdermal systems were Higuchi model (except for STT 2), Korsmeyer–Peppas, and Makoid–Banakar model, all with R^2 and (R^2_{adjusted}) higher than 0.99. The Higuchi and Korsmeyer–Peppas models, largely used, can be pointed out as simple and good kinetic models to describe the estradiol release from matrix TTS. Due to the fact that drug release in TTS cases occurs in a one-dimensional way and that the system width/thickness or length/thickness relation is by far more than 10, following the Korsmeyer–Peppas indications, this equation represents a good choice in the study of these pharmaceutical systems. The Higuchi model has the advantage, in relation to the Korsmeyer–Peppas model, of a faster and easier calculation. The Makoid–Banakar mathematical expression gave the best results of all the models tested, but it is by far the most complex model to calculate.

When the c parameter of the Makoid–Banakar model is equal to zero, this expression becomes the Korsmeyer–Peppas power law expression ($e^{-0t} = 1$). As can be seen in Table 4, the c values obtained for all the systems were very small, almost zero, and the results obtained for the parameters n and K of both expressions were very similar, with the exception of the STT 2.

Because Makoid–Banakar and Weibull are empiric models, not deducted from any kinetic fundament, they present some deficiencies such as the fact that there is not any kinetic fundament and that they can only describe, but do not adequately characterize, the drug dissolution kinetic properties. The absence of a single parameter related with the intrinsic drug dissolution rate is another disadvantage of these models.

As can be seen by the release exponent (n), and by the good results of higher than 0.994 of the coefficient of determination (R^2) in Higuchi model, the estradiol main release mechanism was Fickian diffusion. As the c parameter of the Makoid–Banakar model was almost zero, the n parameter of this expression become similar to the release exponent of the Korsmeyer–Peppas expression. In this situation the n values of the Makoid–Banakar model were also ≈ 0.5, showing that diffusion was the principal mechanism responsible for the drug release. The shape parameter β, from the Weibull model, showed that the estradiol release was parabolic with a higher initial slope, and after that, consistent with the exponential curve for all matrix systems ($\beta < 1$). The use of mathematical kinetic models permits the characterization of some dissolution parameters and the best description of drug-release process.

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