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# Application of the Refined Integral Method in the mathematical modeling of drug delivery from one-layer torus-shaped devices

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ABSTRACT

A mathematical modeling of controlled release of drug from one-layer torus-shaped devices is presented. Analytical solutions based on Refined Integral Method (RIM) are derived. The validity and utility of the model are ascertained by comparison of the simulation results with matrix-type vaginal rings experimental release data reported in the literature. For the comparisons, the pair-wise procedure is used to measure quantitatively the fit of the theoretical predictions to the experimental data. A good agreement between the model prediction and the experimental data is observed. A comparison with a previously reported model is also presented. More accurate results are achieved for small $A/C_s$ ratios.



## 1. Introduction

The vagina has been studied and described as an alternative route for drug delivery since this has some advantages over the oral and transdermal routes of administration (Alexander et al., 2004; Cicinelli, 2008; Hussain and Ahsan, 2005). Controlled release devices for vaginal administration have been explored and the most widely used actually are the intravaginal rings (Ballagh, 2001; Johansson and Sitruk-Ware, 2004; Sitruk-Ware, 2006; Yoo and Lee, 2006). These rings can have one of several configurations: reservoir, matrix, sandwich type, etc. (Burton et al., 1978; Kalkwarf et al., 1972; Malcolm et al., 2002, 2003a; Matlin et al., 1992; Woolfson et al., 1999, 2003). The release kinetic varies depending on the type of configuration. Of these, the matrix-type ring has the greatest advantages and better properties to be used in the pharmaceutical area. Basically, this type of ring is composed by a polymeric support that contains the active agents. The device can also contain other ingredients such as fillers and plasticizers. Matrix-type rings can be used for both local and systemic treatments. For example, these rings have been used for local atrophy treatments, as a method of birth control, to treat menopause-related symptoms, among others.

Clinical safety and user acceptability of vaginal rings have been tested (Dieben et al., 2002; Novak et al., 2003; Roumen, 2008; Tuppurainen et al., 2004). It seems that vaginal rings will emerge as one of the most important devices of this decade. Due to this, it is important to have a mathematical tool to adequately predict and study the release kinetics of these devices. Mathematical models allow the description, analysis and optimization of the systems. Only in some cases, the exact solution for a given system is available. On the contrary, in most cases, an approximate solution that predicts the cumulative amount of drug released should be adopted.

Several strategies have been employed to derive approximate analytical solutions. One of the most used is to consider the pseudo steady state approximation (PSSA). This approach has been used in the mathematical modeling of drug delivery from non-erodible devices with different geometries like slab, cylinder and sphere (Higuchi, 1963; Roseman and Higuchi, 1970; Zhou et al., 2005). Also, the PSSA was used in the derivation of the solution for non-erodible laminated devices and for erodible devices, having the geometric shapes mentioned above (Fischel-Ghodsian and Newton, 1993; Helbling et al., 2010b; Thombre and Himmelstein, 1984). In addition, it was successfully applied to derive an analytical solution for the case of one-layer and two-layer matrix-type torus-shape systems (Helbling et al., 2011a,b).

It is well known that the PSSA yields satisfactory results for the cases in which the initial drug loading ($A$) is much higher than its maximum solubility in the polymer ($C_s$). However when $A \to C_s$ the PSSA introduces some error in the approximation and the prediction of the model may fail (Lee, 1980). This drawback can be overcome if the Refined Integral Method (RIM) is used in the derivation of the solution. This method allows the derivation of models

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**Nomenclature**

| | |
|---|---|
| $a_{dis}$ | area of the interface of the dispersed-drug zone/depleted drug zone ($cm^2$) |
| $a_{rel}$ | release area of the device ($cm^2$) |
| $A$ | initial drug loading in the device ($mg/cm^3$) |
| $C_t$ | dissolved-drug concentration in the depletion zone ($mg/cm^3$) |
| $C_s$ | maximum drug solubility in the polymer ($mg/cm^3$) |
| $D_p$ | drug diffusion coefficient in the polymer ($cm^2/s$) |
| $k$ | integration constant |
| $m$ | cumulative amount of drug released (mg) |
| $Q$ | cumulative amount of drug released per unit area of the device ($mg/cm^2$) |
| $r$ | spatial coordinates (cm) |
| $R_e$ | distance from the rotation axis to the external surface of the torus (cm) |
| $R_g$ | distance from the rotation axis to the center of the generating circle (cm) |
| $R_0$ | radius of the generating circle (cm) |
| $S(t)$ | position of the "dissolution–diffusion moving front" (cm) |
| $t$ | time (s) |
| $V_s$ | volume of the torus ($cm^3$) |

*Greek letters*

| | |
|---|---|
| $\alpha$ | radii ratio |
| $\delta(t)$ | position of the dissolution–diffusion moving front |
| $\eta$ | $\xi/\delta$, integration variable |
| $\theta$ | dissolved-drug concentration in the depletion zone |
| $\xi$ | spatial coordinates |

that can be used on all range of values of $A/C_s > 1$. In the past, RIM has been successfully employed to obtain analytical solution for the release from non-erodible planar (Helbling et al., 2010a; Lee, 1980) cylindrical (Tan et al., 2001) and spherical (Lee, 1980) devices. Also, RIM was used in erodible planar devices (Lee, 1980).

The purpose of the present work was to derive a mathematical model to predict the release of drug from one-layer torus-shaped devices (e.g., matrix-type vaginal ring) in a wider range of $A/C_s$, including the case where $A \to C_s$. In order to achieve the aim, Refined Integral Method was applied.

## 2. Model development

The mathematical model is developed for one-layer torus-shaped devices containing solid drug particles dispersed inside (Fig. 1a and b). When the torus is placed in the release medium, the liquid takes contact with the device over its entire surface. As the liquid contacts the device, the solid drug particles dissolve in and then diffuse out of the matrix. The discrete crystals in the layer closer to the device surface are the first to elute. When this layer becomes "exhausted", the solid drugs in the next layer begin to be depleted. So, a drug depletion zone is created. The thickness of this zone increases with time and as more solid drugs elute out of the device, thus leading to the inward advancement of the interface of the dispersed-drug zone/depleted drug zone, phenomenon commonly referred to as "dissolution–diffusion moving front". The dissolved-drug concentration profile in the depleted-drug zone is schematically illustrated in Fig. 1c. Because the liquid comes in contact with the device over its entire surface at the same time, the formation of the depletion zone and therefore the inward advancement of the interface of the dispersed-drug zone/depleted drug zone takes place in all radial directions at the same time (considering a radial direction as the direction of the radius of the generating circle). Therefore, for the mathematical analysis only the half section of the area of the generating circle ($R_g < r < R_e$) is considered since in both halves the same phenomenon occurs simultaneously (Helbling et al., 2011b). The analysis can then be extrapolated to the entire device (Helbling et al., 2011b).

The parameters present in Fig. 1 are: $r$ is the dimensional spatial coordinates, $R_0$ is the radius of the generating circle, $R_g$ is the distance from the rotation axis to the center of the generating circle, $S(t)$ is the dimensional position of the "dissolution–diffusion moving fronts", $R_e$ is the distance from the rotation axis to the external surface of the matrix, $\omega$ and $\varphi$ are angles, $C_t$ is the dimensional dissolved-drug concentration in the matrix and $C_s$ is the maximum solubility of drug in the polymeric matrix.

### 2.1. General assumptions

The assumptions of the model to be mathematically formulated are the following: (i) The system is a torus-shaped single-layer device; (ii) the device is considered as an isotropic medium; (iii) the device is composed by a polymeric matrix that contain solid drug particles dispersed in its interior; (iv) the initial distribution of the drug in the polymeric matrix is homogeneous; (v) the initial drug loading in the matrix is higher than the maximum drug solubility in the polymer; (vi) for simplicity, all the drug particles have the same size and a spherical form; (vii) the polymeric matrix is inert, unswellable and non-erodible; (viii) the dissolution of the solid drug particles in the polymeric matrix occurs at a high rate and does not constitute a controlling step of the general release process; (ix) the rate controlling step of the release process is the drug diffusion across the polymeric matrix, which is described according to Fick's laws; (x) the mass transport of drug is assumed to be radial at all points; (xi) the drug diffusion coefficient in the polymeric matrix is considered constant; (xii) resistance to external mass transfer is negligible; (xiii) the volume of the release medium is considered infinite to ensure the "sink" condition; (xiv) for a given time $t$, there exist a drug depletion zone with a thickness $R_e - S(t)$; (xv) the model formulated is valid till all solid drug particles dissolve in the polymer and no discrete crystals remains in the device. This stage is achieved when the "dissolution–diffusion moving front reaches $r = R_g$; (xvi) at the initial time ($t = 0$), the elution medium has not been yet in contact with the dispersed drug and therefore there is no depletion zone. It is considered that the "dissolution–diffusion moving front" is outside of the device ($S = R_e$) at the initial time.

### 2.2. Mathematical modeling

In the following analysis, all the variables (except time) were transformed to dimensionless variables in order to generalize the analysis. Even though other authors have considered dimensionless time, the present work has excluded the dimensionless time variable since it is considered that otherwise the notion of real-scale applicability of the devices would be lost (Helbling et al., 2010b). For the transformation step to dimensionless variables, the following relationships are used:

$$\xi = \frac{R_e - r}{R_0}, \quad \delta(t) = \frac{R_e - S(t)}{R_0}, \quad \theta = \frac{(C_s - C_t)}{C_s}\frac{U(0)}{U}, \quad \alpha = \frac{R_e}{R_0} \tag{1}$$

where $\xi$ is the dimensionless spatial coordinates, $\delta(t)$ is the dimensionless position of the "dissolution–diffusion moving fronts", $\theta$ is the dimensionless dissolved-drug concentration in the matrix and $U$ is a function that allows us to simplify the governing equation for diffusion for one-layer torus-shaped devices (see Appendix). From Fig. 1, the following relationship can be expressed:

$$R_e = R_g + R_0 \tag{2}$$

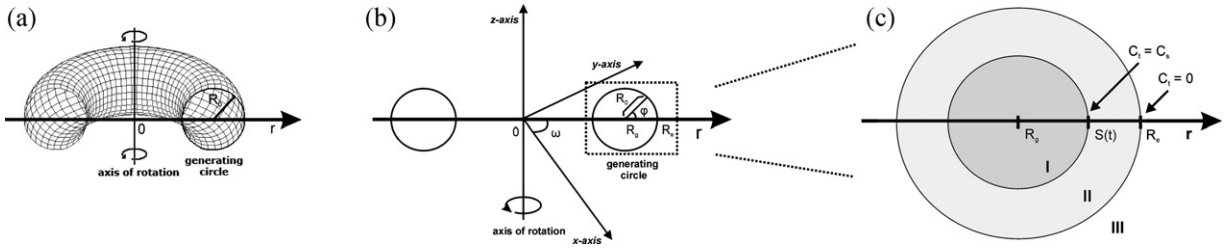


**Fig. 1.** Schematic illustration of a torus: (a) Construction of a torus. (b) Schematic representation of a torus in Cartesian coordinate system. (c) Dissolved-drug concentration profile in the drug depletion zone. I. Dispersed-drug zone; II. Dissolved-drug zone; III. Infinite release medium.

For one-layer torus-shaped device with solute diffusion being radial at all points, the governing equation for diffusion in the depletion zone formed inside the matrix is (Helbling et al., 2011b):

$$\frac{\partial C_t}{\partial t} = \frac{D_p}{r(R_g + r)} \frac{\partial}{\partial r}\left( r(R_g + r)\frac{\partial C_t}{\partial r} \right) \tag{3}$$

where $t$ is the time and $D_p$ is the drug diffusion coefficient in the polymeric matrix. Assuming equilibrium between the surface of the device and the external fluid at all $t$, the initial and boundary conditions are:

$$C_t = C_s \quad t = 0 \quad R_g \le r \le \mathrm{R_e} \tag{4}$$

$$C_t = C_s \quad t > 0 \quad R_g \le r \le S(t) \tag{5}$$

$$C_t = 0 \quad t > 0 \quad r = \mathrm{R_e} \tag{6}$$

$$D_p a_{rel} \frac{\partial C_t}{\partial r} = (A - C_s) a_{dis} \frac{\partial S}{\partial t} \quad r = S(t) \tag{7}$$

$$S = R_e \quad t = 0 \tag{8}$$

where $A$ is the initial drug loading in the device, $a_{rel}$ is the release area of the device and $a_{dis}$ is the area where the dissolution process occurs (area of the interface of the dispersed-drug zone/depleted drug zone). With reduced dimensionless variables defined in Eq. (1) and using Eqs. (A.5) and (A.6) given in the appendix, a more general set of equation is obtained:

$$\frac{\partial \theta}{\partial t} = \frac{D_p}{R_0^2} \frac{\partial^2 \theta}{\partial \xi^2} \tag{9}$$

$$\theta = 0 \quad t = 0 \quad 0 \le \xi \le 1 \tag{10}$$

$$\theta = 0 \quad t > 0 \quad \delta(t) \le \xi \le 1 \tag{11}$$

$$\theta = 1 \quad t > 0 \quad \xi = 0 \tag{12}$$

$$-\frac{\partial \theta}{\partial \xi} = \left( \frac{A}{C_s} - 1 \right) \frac{R_0^2 (3\alpha - 1 - 2\delta)}{D_p (3\alpha - 1)} \frac{\partial \delta}{\partial t} \quad \xi = \delta(t) \tag{13}$$

$$\delta = 0 \quad t = 0 \tag{14}$$

Utilizing Eqs. (9) and (11), Eq. (13) can be rewritten as:

$$-\left( \frac{\partial \theta}{\partial \xi} \right)^2 = \left( 1 - \frac{A}{C_s} \right) \frac{(3\alpha - 1 - 2\xi)}{(3\alpha - 1)} \frac{\partial^2 \theta}{\partial \xi^2} \quad \xi = \delta(t) \tag{15}$$

The approximate solution of Eq. (9) can be obtained using the Refined Integral Method (Lee, 1980; Tan et al., 2001). Integrating directly twice, combining with Eq. (13) gives:

$$\frac{\partial}{\partial t}\left[ \delta^2 \int_1^0 \int_1^2 \theta \, \partial\eta \, \partial\eta + \left( \frac{A}{C_s} - 1 \right) \frac{(3\alpha - 1 - 2\delta)\delta^2}{2(3\alpha - 1)} \right] = \frac{D_p}{R_0^2} \tag{16}$$

where $\eta$ is an integration variable defined as $\eta = \xi/\delta$. The next step is to assume a functional form which approximates the solute concentration distribution in the partially extracted region. A polynomial concentration profile satisfying the boundary condition (11), (12) and (15) has the form:

$$\theta = a_0 + a_1 \frac{\xi}{\delta} + a_2 \left( \frac{\xi}{\delta} \right)^2 \tag{17}$$

where

$$a_0 = 1 \tag{18}$$

$$a_1 = -1 - a_2 \tag{19}$$

$$a_2 = \frac{A}{C_s}\left( 1 - \frac{2\delta}{3\alpha - 1} \right) + \frac{2\delta}{3\alpha - 1} - \left[ \left( \frac{A}{C_s}\left( 1 - \frac{2\delta}{3\alpha - 1} \right) + \frac{2\delta}{3\alpha - 1} \right)^2 - 1 \right]^{1/2} \tag{20}$$

Upon substitution of Eq. (17) into Eq. (16), an implicit expression of the dimensionless position of the "dissolution–diffusion moving front" can be obtained:

$$\frac{12 D_p t}{R_0^2} = -\frac{12}{(3\alpha - 1)}\left( \frac{A}{C_s} - 1 \right)\delta^3 + \left( \frac{6A}{C_s} - 4 - a_2 \right)\delta^2 \tag{21}$$

Thus, the dimensionless position of the "dissolution–diffusion moving front" can be obtained from Eq. (21) using an adequate computational software that finds zeros of a function of one variable. The cumulative amount of solute released ($m$) in a given time is calculated from a mass balance equation (Helbling et al., 2011b):

$$m = 2\pi^2 R_g \left[ A R_0^2 - A(S - R_g)^2 - 2\int_S^{Re} C_t (r - R_g) \partial r \right] \tag{22}$$

Introducing the reduced dimensionless variables defined previously and with the use of Eq. (17), Eq. (22) results in:

$$m = V_s \left[ (A - C_s)(2\delta - \delta^2) - \frac{C_s(3\alpha - 1)(\alpha - 1)}{24\delta^2} \left[ \frac{4(a_2 - 3)\delta^3}{(\alpha - 1)} + 18(a_2 + 2)\delta^2 - 18(3\alpha - 1)a_2\delta + 9g_1 \ln\left( \frac{3\alpha - 1}{3\alpha - 1 - 2\delta} \right) \right] \right] \tag{23}$$

where

$$g_1 = 4\delta^2 - (3\alpha - 1)(2 + 2a_2)\delta + (3\alpha - 1)^2 a_2 \tag{24}$$

and $V_s$ is the volume of the torus. The cumulative amount of drug released in a given time can be calculated from Eq. (23) for the case of one-layer torus-shaped devices. This analysis is valid till all drug dispersed in the device is dissolved (this stage is achieved when $\delta = 1$).

## 3. Results and discussion

In order to use the developed model to predict the drug release profiles, it is convenient to use suitable computational programs

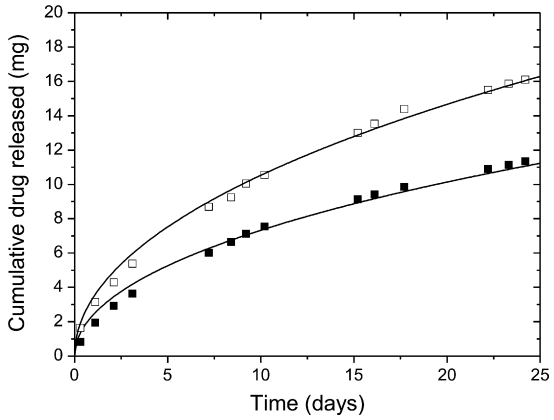


**Fig. 2.** Comparison of release profiles calculated according to Eq. (23) (—) and the experimental data reported by Jackanicz (1981) (symbols) for levonorgestrel release from a silicone vaginal ring: (■) $A/C_s = 86.47$ (□) $A/C_s = 258.56$. The parameters used are: $R_0 = 0.42$ cm; $R_e = 2.85$ cm; $a_{rel} = 40.29\ cm^2$; $V_s = 8.46\ cm^3$; $C_s = 0.016\ mg/cm^3$.

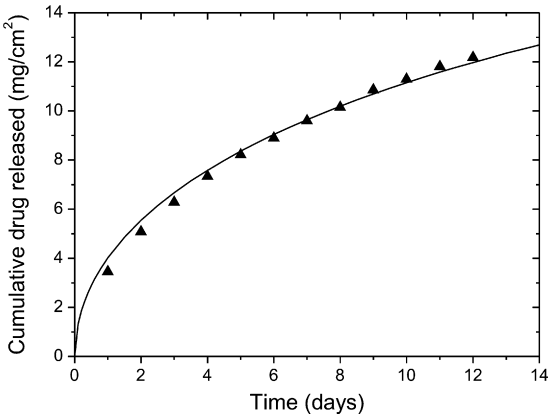


**Fig. 3.** Comparison of release profile calculated according to Eq. (23) (—) and the experimental data reported by Chien et al. (1974) (▲), for ethynodiol diacetate release from a silicone device. The parameters used are: $A/C_s = 517.13$; $R_0 = 0.30$ cm; $R_e = 3.15$ cm; $a_{rel} = 33.75\ cm^2$; $V_s = 5.06\ cm^3$; $C_s = 1.4791\ mg/cm^3$.

to simplify the calculations (for example MATLAB®, FORTRAN® or MAPLE®). These programs allow the creation of a "routine" in programming language to perform the simulations. Once the routine is created, the user only needs to load the values of the parameters that make up the model and then run the program. In the present work, all the simulations were performed in the computational software MATLAB®.

### 3.1. Model validation with experimental release profiles

In order to illustrate the validity and usefulness of the model in the analysis and prediction of controlled drug release from one-layer torus-shaped devices, several examples of vaginal rings experimental release reported in the literature are presented and compared with the theoretical results given by the developed mathematical model. To compare drug release profiles, the *difference factor* and the *similarity factor* were used (Center for Drug Evaluation and Research, 1995; Committee for Proprietary Medicinal Products, 1999; Costa and Sousa Lobo, 2001; Moore and Flanner, 1996; Pillay and Fassihi, 1998). The difference factor ($f_1$) measures the percent error between two curves over all time points while the similarity factor ($f_2$) is a logarithmic transformation of the sum-squared error of differences between both curves over all time points. In all cases shown below, the experimental data reported in the literature was selected as the reference product while the model prediction was chosen as the test product. The difference factor is zero when the test and reference profiles are identical and increase proportionally with the dissimilarity between the two profiles (Costa and Sousa Lobo, 2001; Pillay and Fassihi, 1998). The similarity factor is 100 when the test and reference profiles are identical and tends to 0 as the dissimilarity increases. In general, $f_1$ values lower than 15 (0–15) and $f_2$ values higher than 50 (50–100) show the similarity of the profiles (Costa and Sousa Lobo, 2001; Pillay and Fassihi, 1998).

Figs. 2–4 present experimental examples of controlled release of drug from one-layer torus-shaped devices. In all the examples, the initial drug loading in the device is higher than the maximum solubility of drug in the polymeric matrix. Fig. 2 shows experimental data reported by Jackanicz (1981) and the release profiles calculated according to Eq. (23) for levonorgestrel release from silicone vaginal rings. The values used for the parameters were taken from Jackanicz (1981) except for the levonorgestrel solubility in the silicone which was reported by Chien (1982). The diffusion coefficient $D_p = 3.21 \times 10^{-7}\ cm^2/s$ was obtained from the fitting.

Fig. 3 shows experimental data reported by Chien et al. (1974) and the release profile calculated according to Eq. (23) for ethynodiol diacetate release from a silicone device. To obtain the cumulative drug released in the units of $mg/cm^2$, the result of Eq. (23) was divided by $a_{rel}$. The values of the parameters employed were taken from Chien et al. (1974). The drug diffusion coefficient in the matrix was found to be $D_p = 5.51 \times 10^{-7}\ cm^2/s$ from the model adjustment and is in accordance with the value of $10^{-7}\ cm^2/s$ reported by Chien et al. (1974).

Fig. 4 presents experimental data reported by Malcolm et al. (2003b) and the release profiles calculated according to Eq. (23) for norethisterone release from silicone intravaginal rings. Again, to obtain the cumulative drug released in the units of $mg/cm^2$, the result of Eq. (23) was divided by $a_{rel}$. The values of parameters were taken from Malcolm et al. (2003b). The diffusion coefficient $D_p = 5.90 \times 10^{-7}\ cm^2/s$ was calculated from the model fitting.

The $f_1$ and $f_2$ factors calculated for the release profiles shown in Figs. 2–4 are presented in Table 1. The $A/C_s$ ratios and the values of $D_p$ obtained from the model fitting for each system are also presented. From the results it can be seen that in all cases $f_1$ are lower than 15 and $f_2$ are higher than 50. So, the two profiles under analysis can be considered similar. Then, it can be concluded that the model predicts very well the drug release data reported in the literature.

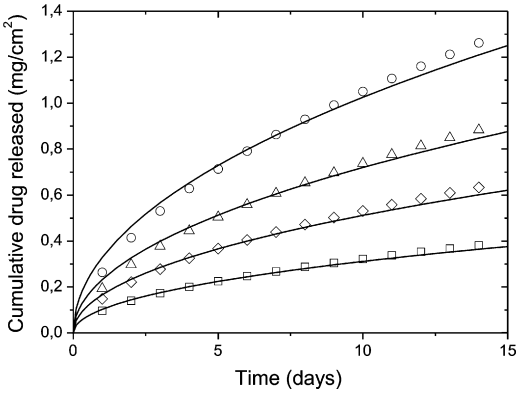


**Fig. 4.** Comparison of release profiles calculated according to Eq. (23) (—) and the experimental data reported by Malcolm et al. (2003b) (symbols) for norethisterone release from a silicone intravaginal ring: (□) $A/C_s = 475.53$ (◊) $A/C_s = 1188.80$ (△) $A/C_s = 2377.53$ (○) $A/C_s = 4755.13$. The parameters used are: $R_0 = 0.375$ cm; $R_e = 2.90$ cm; $a_{rel} = 37.40\ cm^2$; $V_s = 7.01\ cm^3$; $C_s = 0.015\ mg/cm^3$.

**Table 1**
The *difference* and *similarity* factors for experimental and theoretical drug release profiles comparison.

| Reference | $A/C_s$ | $D_p$ ($\times 10^{-7}$ cm$^2$/s) | $f_1$ | $f_2$ |
|---|---|---|---|---|
| [a] | 86.47 | 3.21 | 4.37 | 98.58 |
| [a] | 258.56 | 3.21 | 2.81 | 98.58 |
| [b] | 517.13 | 5.51 | 2.63 | 99.19 |
| [c] | 475.53 | 5.90 | 2.90 | 100.00 |
| [c] | 1188.80 | 5.90 | 3.49 | 100.00 |
| [c] | 2377.53 | 5.90 | 3.28 | 99.99 |
| [c] | 4755.13 | 5.90 | 3.53 | 99.98 |

[a] Jackanicz (1981).
[b] Chien et al. (1974).
[c] Malcolm et al. (2003b).

$D_p$ values calculated from the model fitting for each release profile and presented in Table 1 are very similar to those obtained in our previous work (Helbling et al., 2011b). This result indicates that both models behave similarly under the conditions analyzed. It is known that, regardless of the device geometry, when $A \gg C_s$ the pseudo-steady state approximation gives satisfactory results. As can be seen in Table 1, the $A/C_s$ ratio for the systems in Figs. 2–4 varies between 86.47 and 4755.13, which are large values of the ratio. Hence, the obtained results were expected since $A \gg C_s$ in all experimental situations analyzed and therefore for this condition the PSSA gives results with an accuracy similar to those obtained by the Refined Integral Method.

However when $A \to C_s$ the PSSA introduces some error and the accuracy of predictions decreases. For small $A/C_s$ ratios, the PSSA-based model reported previously (Helbling et al., 2011b) and the model presented in this work have different behaviors. In order to illustrate this, fractions of drug released at a given time predicted by both models for systems with small $A/C_s$ ratios are presented in Fig. 5a. To obtain the fraction of drug released, the result of Eq. (23) was divided by the initial amount of drug present in the device ($A \times V_s$). It can be seen that the difference between the predictions of both models is greater at low $A/C_s$ ratios and decreases with increasing the value of $A/C_s$. The simulation shown in Fig. 5a corresponds to two time points. To generalize the analysis, the complete drug release profiles predicted by both models were compared using the *difference factor* for different $A/C_s$ ratios. The prediction of the model developed in the present work was considered as the reference whereas the prediction of the PSSA-based model was chosen as the test product. The results are shown in Fig. 5b. It can be observed that as expected, for systems in where $A \gg C_s$, the drug release profiles predicted by both models are similar ($f_1 < 15$). However, when $A \to C_s$, the PSSA is less accurate and therefore the profiles are different ($f_1 > 15$). This difference between the theoretical profiles increases as the value of $A/C_s$ decreases. This behavior is reflected in an increase in the value of $f_1$. The analysis was made for three values of $D_p$ and similar conclusions can be obtained.

To complete the analysis, theoretical dimensionless releases calculated according to Eq. (23) and according to the analytical solution reported by Helbling et al. (2011b) were compared for various values of $A/C_s$. Dimensionless release was calculated for each model as follows: $Q/C_s\sqrt{D_p t}$ where $Q$ is the cumulative amount of drug released per unit area of the device (and is obtained by dividing the result of Eq. (23) by $a_{rel}$). The comparison result is presented in Table 2. The dimensionless release comparison was employed previously by others authors for geometries like slab or spheres (Lee, 1980). The "% Difference" is defined as the subtraction between the values predicted by both models, divided by the value predicted by the PSSA-based model and multiplied by hundred (Lee, 1980). From the table it can be observed that for small values of $A/C_s$, the percentage difference between the equations is high, reaching approximately 55%. This discrepancy decreases with increasing the ratio between $A$ and $C_s$. Note that for $A/C_s = 86$, which corresponds to the lowest ratio of the experimental profiles presented in Table 1, the percentage difference is 0.34. This shows that for this experimental example the PSSA gives results with accuracy similar to those obtained by the Refined Integral Method. Naturally, for the others experimental profiles discussed in Table 1, which have a ratio greater than 86, both models behave similarly. This conclusion is in total agreement with the results previously obtained.

**Table 2**
Comparison of analyses between theoretical releases of solute from torus-shape single-layer devices.

| $A/C_s$ | $Q/C_s\sqrt{D_p t}$ | | |
|---|---|---|---|
| | PSSA[a] | RIM[b] | % Difference |
| 1.1 | 2.5289 | 1.1526 | 54.42 |
| 1.2 | 2.1112 | 1.2282 | 41.82 |
| 1.3 | 1.9809 | 1.3022 | 34.26 |
| 1.4 | 1.9366 | 1.3734 | 29.08 |
| 1.5 | 1.9295 | 1.4415 | 25.29 |
| 1.8 | 1.9930 | 1.6302 | 18.20 |
| 2.0 | 2.0616 | 1.7451 | 15.35 |
| 2.5 | 2.2533 | 2.0044 | 11.05 |
| 3.0 | 2.4457 | 2.2342 | 8.65 |
| 5.0 | 3.1305 | 2.9836 | 4.69 |
| 8.0 | 3.9586 | 3.8461 | 2.84 |
| 10.0 | 4.4284 | 4.3277 | 2.27 |
| 15.0 | 5.4310 | 5.3473 | 1.54 |
| 25.0 | 7.0235 | 6.9554 | 0.97 |
| 50.0 | 9.9517 | 9.8985 | 0.53 |
| 86.0 | 13.0660 | 13.0210 | 0.34 |

[a] Helbling et al. (2011a,b).
[b] This work.

The release kinetics from torus-shaped matrices presents the typical proportionality between the cumulative amount of drug released and the square root of time characteristic of the matrix devices in which diffusion is the dominant mechanism. For this reason, several diffusion-based models have been used in the past to predict drug release from vaginal rings. Examples of these are the Higuchi equation and the Fickian diffusion model. Although the mentioned models can provide a good fit to the vaginal ring release profiles, their uses are inadequate from a conceptual point of view. Some of the assumptions made in the derivation of these equations are not fulfilled for the case of vaginal rings. For example, Higuchi's model was originally developed for a planar device where the surface parallel to the release area remains constant throughout the thickness of the device. This assumption is clearly not fulfilled for the case of a ring. For geometries different than planar geometry, the variation of the area along the thickness must be taken into account in the derivation of the analytical solution. This task was performed for cylindrical and spherical devices by others authors (Higuchi, 1963; Roseman and Higuchi, 1970; Zhou et al., 2005). For torus-shaped devices, the variation of the area was taken into account in the derivation of the analytical solution in our previously published article (Helbling et al., 2011b). A similar situation occurs with the Fickian diffusion model which was originally derived for thin films.

Unfortunately, these models are often misused and applied to controlled drug delivery systems which do not fulfill with all the assumptions made in the derivation of the models. In these cases, any conclusion should be viewed with great caution. In contrast, the model presented in this paper was developed exclusively for torus-shaped devices. Thus, the equations obtained can be properly applied because the system fulfills all the assumptions made in mathematical development.

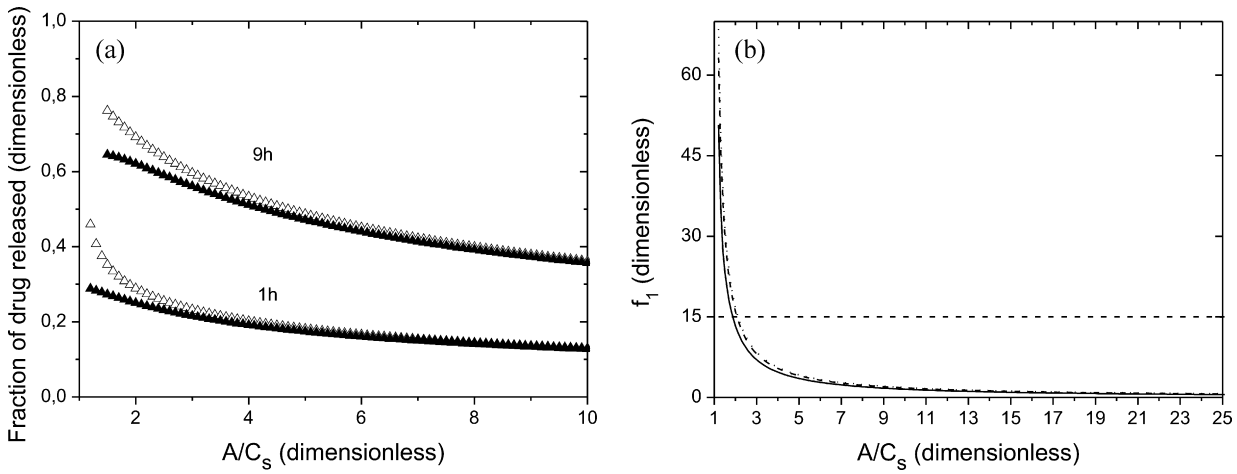


**Fig. 5.** (a) Comparison of the fraction of drug released at 1 h and 9 h calculated according to Eq. (23) (▲) and according to the model previously reported by Helbling et al. (2011a,b) (△) for different $A/C_s$ ratios. (b) Values of $f_1$ for comparison of drug release profiles predicted by Eq. (23) and the model reported by Helbling et al. (2011a,b) for different $A/C_s$ ratios: (—) $D_p = 5.51 \times 10^{-7}$ cm$^2$/s; (—) $D_p = 5.51 \times 10^{-8}$ cm$^2$/s; (···) $D_p = 5.51 \times 10^{-9}$ cm$^2$/s. The parameters used are: $R_0 = 0.30$ cm; $R_e = 3.15$ cm; $a_{rel} = 33.75$ cm$^2$; $V_s = 5.06$ cm$^3$; $C_s = 1.4791$ mg/cm$^3$.

## 4. Conclusions

Analytical solutions based on the Refined Integral Method have been successfully derived for both the position of the "dissolution–diffusion moving front" and the cumulative amount of drug released from one-layer torus-shaped devices. The validity and usefulness of the model were corroborated by comparison with several examples of matrix-type vaginal rings experimental release reported in the literature. The results given by the developed equations are consistent with the experimental data. A comparison with a previously reported model (Helbling et al., 2011b) was also presented. For systems in where $A \rightarrow C_s$ the model developed in the present work gives better results than the previously one. For large $A/C_s$ ratios both models can be employed with excellent accuracy. It should be noted however, that the developed model can be used only in matrix-type torus-shaped devices in where the initial drug loading exceeds its solubility in the polymer. In systems where all the initial amount of solute is dissolved or when the device has more than one layer, the model loses its applicability.

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## Appendix A.

For one-layer torus-shaped device with solute diffusion being radial at all points, the governing equation for diffusion is (Helbling et al., 2011b):

$$\frac{\partial C_t}{\partial t} = \frac{D_p}{r(R_g + r)} \frac{\partial}{\partial r} \left( r(R_g + r) \frac{\partial C_t}{\partial r} \right) \tag{A.1}$$

Using the dimensionless relationship defined in Eq. (1) and solving the derivative symbolically, Eq. (A.1) becomes:

$$\frac{\partial \theta}{\partial t} = \frac{D_p}{R_0^2 g_2 U} \left[ \theta \frac{\partial}{\partial \xi} \left[ g_2 \frac{\partial U}{\partial \xi} \right] + g_2 \left( \frac{\partial U}{\partial \xi} \frac{\partial \theta}{\partial \xi} + U \frac{\partial^2 \theta}{\partial \xi^2} \right) + \frac{\partial \theta}{\partial \xi} \frac{\partial}{\partial \xi} [g_2 U] \right] \tag{A.2}$$

where

$$g_2 = \xi^2 + (1 - 3\alpha)\xi + 2\alpha^2 - \alpha \tag{A.3}$$

To eliminate the terms containing $\theta$ and $\partial\theta/\partial\xi$ in Eq. (A.2), two conditions are necessary:

$$\frac{\partial}{\partial \xi} [g_2 U] = -g_2 \frac{\partial U}{\partial \xi}$$
$$\frac{\partial}{\partial \xi} \left[ g_2 \frac{\partial U}{\partial \xi} \right] = 0 \tag{A.4}$$

Developing both conditions and replacing the second condition in the first, the expression of $U$ can be found:

$$U = \frac{2\kappa}{(3\alpha - 1 - 2\xi)} \tag{A.5}$$

where $\kappa$ is a integration constant. Naturally,

$$U(0) = \frac{2\kappa}{(3\alpha - 1)} \tag{A.6}$$

Using Eq. (A.5), Eq. (A.2) becomes:

$$\frac{\partial \theta}{\partial t} = \frac{D_p}{R_0^2} \frac{\partial^2 \theta}{\partial \xi^2} \tag{A.7}$$

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