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ScienceDirect
International Journal of Pharmaceutics 323 (2006) 64–71
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Modeling film-coat non-uniformity in polymer coated pellets: A stochastic approach

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Received 29 December 2005; received in revised form 27 March 2006; accepted 24 May 2006
Available online 6 June 2006

Abstract

The objective of the present study is to include coating thickness non-uniformity in the development of a drug release model using coated ion-exchange pellets through the use of stochastic approaches. Drug release from ion-exchange resins was described using a Nernst–Plank model. Complexes of a model drug (dextromethorphan) and Dowex® 50WX4-200 were prepared using a modified batch method and coated with Kollicoat® SR 30D polymer. The deterministic model, validated using experimental drug release profiles for different coating thicknesses at 0%, 10%, 15%, 20% (w/w), was in agreement with the experimental data with a maximum root mean square error (RMSE) of 2.4%. An arbitrary Lagrangian–Eulerian approach was pursued to develop models of spherical pellets with non-uniform coating thicknesses. The Monte Carlo method was used to simulate the effect of the level of coating deformity on the cumulative drug release profile. Considering the co-existence of equal percentages of deformed and undeformed pellets in a batch, the cumulative release profile can vary by approximately ±6% as a result of coating non-uniformity. The release profile obtained for a model of an arbitrary pellet with an actual non-uniform coating profile was in good agreement with the average release profile for the models of the theoretical randomly deformed pellets. The developed mathematical model is a useful tool to evaluate and predict release profiles of polymer coated ion-exchange resin complexes.

Keywords: Mathematical modeling; Numerical methods; Ion-exchange; Coated pellets; Coating non-uniformity; Sustained release

1. Introduction

Often modification to the release properties (kinetics) of pharmaceutical products is required to achieve a desirable rate of drug delivery. Several methods such as encapsulation, coating, emulsion, and liposome are used to control drug release. Among these, coating is the most popular and widely available. The essential components of a coated pharmaceutical product are the core, which contains the active agent and excipients, and the coating, often a polymeric material. The drug is initially loaded in the core matrix or encased and then one or more layers of the coating material are applied.

The primary mechanism controlling drug release from polymer coated controlled delivery systems is diffusion of the dissolved drug from the core through the polymeric coating. The intrinsic and extrinsic factors influencing the *in vitro* performance of a coated controlled delivery include (i) the loading distribution and properties of the active component, (ii) the device geometry and thickness of coating and (iii) the inherent variabilities in the thickness of coating and the biological (gastrointestinal tract (GIT)) environment.

Various theoretical models have been developed to predict the drug release from coated controlled release products (Borgquist et al., 2002; Farrell and Sirkar, 1999, 2001; Frenning et al., 2003; Koizumi et al., 2001; Lee and Liao, 1995; Liao and Lee, 1997; Sirotti et al., 2002). Rhodes and Porter (1998) argue that these models are often insufficient to predict the *in vivo* dissolution and release rates reliably and precisely. The inadequacy of these models, we believe, can largely be attributed to the exclusion of inherent variability related to the coating quality (thickness uniformity, pores, etc.) and the biological environment in the development of the models. The quality of the coating is highly dependent upon the type of process and the parameters used

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doi:10.1016/j.ijpharm.2006.05.064

during the coating process. For example, a fluidized bed coating has many parameters such as fluid flow, spray flow and temperature which affect the quality of the coating. Variability in the biological environment (pH, transit time, etc.) of the GIT is dependent upon the physiological and pathological condition of the subject. To date few studies have attempted to include coating related non-uniformities in their mathematical model analyses (Chen and Lee, 2001, 2002; Dincer and Ozdurmus, 1977; Liao and Lee, 1997) and to our knowledge there exists only one work (Haddish et al., 2005) that addresses biological variability with respect to modeling of controlled delivery of coated pharmaceutical products. Dincer and Ozdurmus (1977) have reported that the disintegration time varied from 6 to 28 min for polymeric coatings in simulated intestinal fluid as a result of non-uniformity in the coating thickness. Similar observations were reported by Haddish et al. (2005) for commercially available polymer coated colon targeted drug delivery systems resulting in 30–100% drug release at the target site. Chen and Lee (2001) reported that the region of the coating with the smallest thickness in a given pellet was the driving factor influencing drug release regardless of the average thickness. These studies imply that non-uniformity in the coating thickness plays an important role in the accurate prediction of *in vivo* drug release and should be included when developing theoretical models.

The objective of the present study is to develop a drug release model of coated ion-exchange pellets that incorporates non-uniformity in the coating thickness using stochastic approaches. The advantage of the present approach over prior methods such as perturbation analysis (Chen and Lee, 2001) is the relatively large degree of deformation that can be imposed on the coating and the randomness of the deformations capturing the stochasticity of the non-uniformity. This implies that the same methodology allows the random generation of different sizes of pellets from a given distribution to study the effect of size distribution on the prediction of the release profile. However, relatively long computational time is required with the present method. Such models can be used to investigate the effect of the coating non-uniformity and provide a better prediction of *in vivo* release rates.

2. Materials and methods

2.1. Experimental work

Dextromethorphan (DM)–Dowex® 50WX4-200 (polystyrene sulfonate, H^+ form, content of divinylbenzene 4%) complex was used as a drug–resin system and coated with Kollicoat® SR 30D (27% polyvinyl acetate (PVA), 2.5% polyvinylpyrrolidone (povidone), and 0.3% sodium lauryl sulfate) polymer.

2.1.1. Preparation of DM-loaded resin complex

The DM-loaded Dowex® 50WX4-200 complex was prepared by a modified batch process. The purified resin particles were dispersed in a 1.9% (w/v) drug solution with magnetic stirring at room temperature for 3 h. After decanting the clear supernatant carefully, the same volume of fresh drug solution was added and stirred again for 5 h at room temperature. The complex was separated from the supernatant by vacuum filtration, washed with deionized water to remove any uncomplexed drugs and then dried in the oven. The drug content of the resin complex was examined.

2.1.2. Preparation of polymer coated resin complexes

The DM-loaded resin complex was coated with Kollicoat SR® 30D in a fluidized-bed coater, MFL-01 (Vector Corporation, Marion, IA) to obtain a predetermined weight gain. Bottom spray coating method (Wurster process) was applied for this process. The dried resin complex (40 g) was mixed with micronized talc (0.8 g) to improve the initial flowability before the coating process. The coating solution was diluted to 10.0% (w/w) solid content. In order to enhance the film formation and the flexibility of the films, plasticizer (triethyl citrate) was added.

2.1.3. Determination of diffusion coefficients through the polymer film

Kollicoat® SR 30D polymer films were prepared by casting aqueous polymer dispersions on a Teflon surface. The films were dried in an oven for 24 h at 60 °C, and then stored for 1 h at room temperature and 75% relative humidity. Film thickness was determined using a manual micrometer (Mitutoyo Corp., Kawasaki, Japan) with an accuracy of ±1 μm at a minimum of seven random positions on the films. The cast films were then placed between the two side-by-side diffusion cell (PermeGear Inc., Bethlehem, PA) chambers for permeation studies of DM. One compartment of the cell was filled with 3.0 ml of DM-saturated solution with excess drug particles and the other compartment was filled with 3.0 ml of 0.1N HCl, respectively, maintained at 37 °C throughout the experiments. An equal volume of fresh buffer was immediately added to the side where sample was taken. DM concentrations were quantified by HPLC analysis and corrected for dilution by sampling. Effect of compound withdrawal was taken into account when calculating accumulated amount of drug permeated. The effective diffusion coefficients were then calculated from Fick's law (Datta, 2002).

2.1.4. Drug release test

The drug release study for the uncoated and coated resin complex particles was conducted according to USP 27 apparatus two guidelines (paddle method) (Vankel® VK 7000, Vankel, Edison, NJ) with 900 ml dissolution medium maintained at 37 ± 0.5 °C and mixed at 100 rpm. The dissolution media used in this study were 0.1N HCl (pH 1.1–1.2). Samples were withdrawn at predetermined time intervals and analyzed for drug content using an HPLC system (Agilent 1100 Series with diode array wavelength detector, Agilent Technologies, Waldbronn, Germany) at a wavelength of 280 nm.

2.1.5. Scanning electron microscopy (SEM)

Dried samples were attached to specimen stubs using double-sided copper tape and sputter coated with gold–palladium in the presence of argon gas using a Hummer I sputter coater (Anatech Ltd., Denver, NC). The samples were imaged with a JEOL JSM-840 scanning electron microscope (JEOL USA Inc., Peabody,

MA) using 5 kV accelerating voltage, 26–28 mm working distance, and probe current of 3×10^{-11} A.

2.1.6. Confocal laser scanning microscopy (CLSM) and image processing

The internal structure of the coated resin particles was also imaged using an MRC-1024 laser scanning confocal imaging system (Bio-Rad) equipped with a krypton/argon laser and a Nikon Diaphot 300 inverted microscope. All confocal fluorescence pictures were taken with a 20× objective. A nile red, a lipophilic fluorescence dye, was added to the coating solution to visualize the coating film and the core appeared blue due to the self-fluorescence of the DM. Red and blue fluorescence images and transmission images were obtained from separate channels. The confocal images were further processed to obtain a geometric model of the pellets using Matlab (MathWorks Inc.) image processing tool. First the confocal images were converted to tagged image file format (TIFF) using the Confocal Assistant™ V4.02 software (free software). A 2D isolevel data was then created from the TIFF image and a contour plot with distinctions of coating and core of the pellet was generated. Finally a FEMLAB (Cosmol AB) geometry object was created which was used as a geometric model of the pellet.

2.2. Mathematical modeling

The ion-exchange reaction in the resinate matrix (DM-Dowex® 50WX4-200) can be represented by Eq. (1):

$$\text{Resin}^{-}\text{Drug}^{+} + \text{I}^{+} \rightarrow \text{Resin}^{-}\text{I}^{+} + \text{Drug}^{+} \quad (1)$$

where I^{+} represent the counterions in the gastrointestinal tract diffusing into the resinate matrix.

The processes involved during the release phase are: (i) diffusion of the counterion through the boundary layer, coating, and resin complex, (ii) ion-exchange (chemical reaction, usually very fast) and (iii) diffusion of freed drug through the core and/or coating. Since the drug release kinetics of the delivery system is directly correlated with the functionality of individual pellets, it is a common practice to consider a single pellet for the mathematical treatment. The mathematical model was formulated based upon the following assumptions: (i) The effects of convection and pressure gradients can be ignored. (ii) The pellets were considered spherical in shape, based on the SEM and CLSM images shown in Fig. 1a and b. (iii) The boundary layer on the surface of the coating was ignored due to the existence of vigorous mixing and a perfect sink condition (drug molecules reaching the surface are removed from the surrounding of the pellet) with equilibrium counterion concentration on the surface was considered. (iv) Even though the resin matrix is swellable, due to the presence of the non-swellable coating, the swelling of the matrix is constrained, thus minimal. As a result, a constant pellet volume was considered. This assumption was confirmed in our previous work (Jeong et al., 2006). (v) The diffusion coefficients of the drug and the counter ion in the resin complex and the coating were considered constant as a result of the foregoing constant volume assumption. (vi) Pellets were considered homogeneous and isotropic resulting in a symmetry assumption. Thus a 2D model of a single pellet was considered.

Given these assumptions the processes can generally be described by the reaction-transport equation.

$$\frac{\partial c_i}{\partial t} = \nabla J_i + \text{Rx} \quad (2)$$

where c is the concentration of the diffusing species in the pellet and the subscript i denotes the species ($i = 1$ for the counterion and $i = 2$ for the drug) t the time, J_i the net flux, and Rx is the reaction source term. The most important feature that distinguishes ion-exchange from isotopic exchange is the electric coupling of the ionic fluxes. The resulting flux of the species can be described by the Nernst–Plank equation (Helfferich, 1962):

$$J_i = (J_i)_{\text{diff}} + (J_i)_{\text{el}} = -D_i \left(\nabla c_i + z_i c_i \frac{F}{RT} \nabla \vartheta \right) \quad (3)$$

where D is the diffusion coefficient, z the valence, F the Faraday constant, R the gas constant, T the absolute temperature and ϑ is the electric potential. The subscript i represents the diffusing species.

Assuming that there are no co-ions present, the restrictions of electro-neutrality ($\sum z_i c_i = \text{const.}$) and absence of electric current $\sum z_i J_i = 0$ apply. Applying these constraints on Eq. (3)

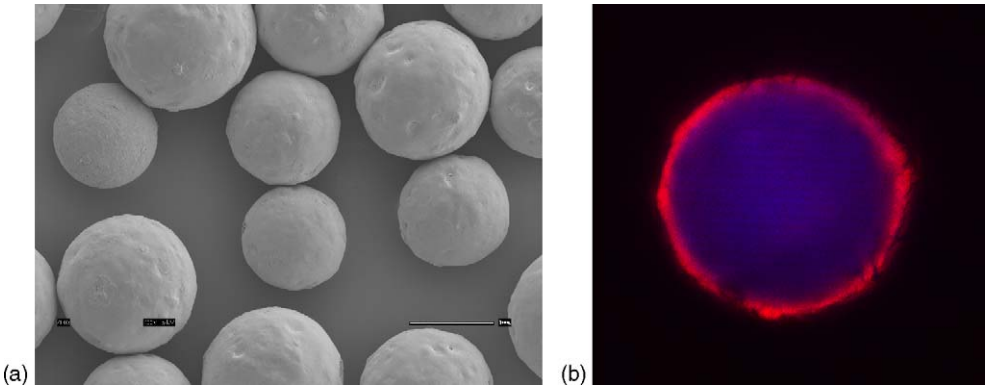

Fig. 1. (a) SEM image of the pellets and (b) confocal image of a particle (for the 20% coating). In the confocal images the red color is the coating and the blue core is the matrix.

yields:

$$J_i = D_{\mathrm{DI}} \nabla c_i \tag{4}$$

$$D_{\mathrm{DI}} = \frac{\left(\prod D_i\right)\left(\sum z_i c_i\right)}{\sum z_i^2 D_i c_i} = \frac{\sum z_i c_i}{\sum z_i^2 \frac{c_i}{D_i}} \tag{5}$$

The reaction source term Rx can be described as:

$$\mathrm{Rx} = k \prod_n c_i \tag{6}$$

where the subscript n represents the reactant species, in this case, the counterion and the drug–resin complex, and k the reaction rate constant. The physical interpretation of the reaction constant has little in common with the rate constants in the actual chemical reaction; rather it is a partition coefficient describing how the ions are partitioned between the phases. Moreover, the reaction term is constrained by the availability of the resin–drug complex and once depleted the term disappears. Thus for fast reactions such as the ion-exchange, the reaction term can be ignored. Note that these equations only apply to the core matrix. For the coating, only Fickian diffusion occurs and the reaction source term does not apply.

Since the core matrix is not hydrated, it was assumed that initially there was no free drug and no counterions in the pellet. At the boundary (outer coating), the counterion concentration was considered as the equilibrium concentration and a perfect sink condition for the drug. These considerations result in the following initial and boundary conditions for the diffusing species:

$$c_i(t = 0 \forall r) = 0 \tag{7}$$

$$c_1(t > 0, r = R) = c_{1,\mathrm{eq}} \tag{8}$$

$$c_2(t > 0, r = R) = 0 \tag{9}$$

The amount of released drug was calculated according to:

$$W = \int_{\mathrm{d}s} J \cdot n \, \mathrm{d}s \tag{10}$$

where W is the average release rate and n is the normal vector at the boundary. The amount of released drug M_t is then given by:

$$M_t = \int_{\mathrm{d}t} W(t) \, \mathrm{d}t \tag{11}$$

The fractional drug release M can then be calculated from:

$$M = \frac{M_t}{M_\infty} \tag{12}$$

where M_∞ is the amount of release after a long time.

2.3. Coating non-uniformity

During the coating process, often using a fluidized bed method, there are several factors that result in the non-uniformity of the coating: (i) Particles stick together and create dents on the coating. (ii) Stresses which develop during the coating process and gravitational forces can result in a thinner coating along the front in the traveling direction and a thicker coating on the opposite side. (iii) If higher rates of evaporation of the solvent are experienced along one side due to the direction of air flow, the reduction in temperature can cause surface tension gradients leading to the surface deflection know as the Marangoni instability. To include the deformation caused by the foregoing effects in the model, the ideal perfect sphere pellet was randomly deformed. First, the surface of the pellet was divided into segments and each segment was deformed using a deformation factor sampled randomly from a normal distribution. The deformation factor for a given segment can result in bulging or denting the segment depending on its value. Normally, the bulges in the coating tend to be smaller than the dents; therefore, a filter was applied to the deformation factor sampling which limited the size of the bulging. However, the average coating thickness was kept constant in each of the cases. The deformation of each segment was applied to the model using the arbitrary Lagrangian–Eulerian (ALE) approach (Donea et al., 2004). The sampled deformation factors were used as mesh velocities to move the segment to generate the resulting dents or bulges in the coating profile. After defining the initial domain $\Omega(x_j)$ and the deformed domain $\hat{\Omega}(\hat{x}_j)$, Eq. (2) (after substitution of Eq. (4)) can be rewritten using the weak formulation in the deformed coordinate system as:

$$\int_{\hat{\Omega}} c_i^t \frac{\partial c_i}{\partial t} \mathrm{d}\hat{\Omega} = \int_{\hat{\Omega}} \left\{ -D_{i,k} \sum_j c_{i,\hat{x}_j}^t c_{i,\hat{x}_j} + c_i^t \, \mathrm{R}_i \right\} \mathrm{d}\hat{\Omega} + \int_{\partial\hat{\Omega}} D_i c_i^t \nabla c_i \cdot n \, \mathrm{d}\hat{s} \tag{13}$$

where c^t is the test function, n unit normal vector and c_i,x_j, the spatial derivatives of the concentration of the species. To account for the deformation, the movement of the mesh (moving domain) was described by the Poisson equation expressed in the weak form in the moving domain as:

$$\int_{\hat{\Omega}} u_{\hat{x}_j}^t . u_{\hat{x}_j} \, \mathrm{d}\hat{\Omega} = 0 \tag{14}$$

where $u = \partial \hat{x}_j / \partial t$ is the prescribed deformation obtained from the randomly sampled deformation factor $u = \varepsilon(\delta)$, with initial condition given by:

$$\hat{x}_j(t = 0) = x_j \tag{15}$$

where ε is the deformation factor of the coating polymer sampled from a distribution δ. It should be noted that the deformation only applies to the coating and not the core matrix.

The mapping between the original fixed domain and the deforming domain can be derived using the chain rule, which results in the Jacobian, $\Im$:

$$\Im = \frac{\mathrm{d}\hat{x}_j}{\mathrm{d}x_j} \tag{17}$$

The mapping of the variables between the two domains can be expressed as:

$$c_{i,x_j} = \Im^{-1} c_{i,\hat{x}_j} \qquad c_{i,x_j}^t = \Im^{-1} c_{i,\hat{x}_j}^t \qquad u_{x_j} = \Im^{-1} u_{\hat{x}_j}$$

$$u_{i,x_j}^t = \Im^{-1} u_{i,\hat{x}_j}^{\mathrm{t}} \quad \text{and } \mathrm{d}\hat{\Omega} = \det(\Im) \, \mathrm{d}\Omega, \tag{18}$$

where $\det(\Im)$ is the determinant of the Jacobian.

Model parameters used in the simulation were determined experimentally and obtained from literature (Hering and Bliss, 1963) and manufacturer manual. Eq. (2) is non-linear and hence a finite element formulation (Zienkiewicz and Taylor, 1994) was used to numerically solve the model equations (2)–(11). In this method, the domain under consideration is discretized into a finite number of elements and the unknown concentrations in the elements are approximated by second order polynomials (basis functions). The Galerkin weighted residual method is then applied resulting in a set of first order differential equations that are solved numerically using the implicit Euler method. Depending on the difference between diffusion coefficients of the counterion and the drug in the core matrix, some linearization techniques can be applied to Eq. (5) to avoid problems with solution convergence. A Monte Carlo (Fishman, 1996) simulation was then employed by considering the deformation factor to be a random parameter. The algorithm for the simulation was:

(i) Random generation of the deformation factors from a normal distribution.
(ii) Generation of the non-uniform pellet coating using Eqs. (14)–(17) and subsequently,
(iii) Solving the model Eqs. (13) and (18) in the deformed (non-uniformly coated pellet) domain using the ALE-FEM approach.
(iv) This process was repeated n times for each deformation level and statistical characteristics (average and standard deviation) were calculated.

FEMLAB 3.1 software (Cosmol AB) utilizing the MATLAB 7.0.1 kernel (MathWorks Inc.) was used to solve these equations. The model was run on a Pentium IV 3.06 GHz with 2 GB RAM dual processor PC.

3. Results and discussion

3.1. Model validation

The deterministic model was validated using experimental drug release profiles from uncoated and coated pellets at different coating levels (0%, 10%, 15%, and 20% (w/w)).

In Fig. 2, the comparison between the simulated and experimental drug release profiles is presented. The model has captured the release dynamics of the coated pellets well, as can be visually confirmed by the fit between model predictions and experimental results. To compare the observed fit quantitatively, root mean square error (RMSE) values were calculated for each case. The calculated RMSE ranges from 1.24% to 2.44% deviation. The maximum deviation was observed for the 20% coated pellets. Due to the presence of a thicker coating, one expects an initial lag period which the model has predicted. However, the experimental results show what appears to be an initial burst phenomenon. This could be due to the existence of a fraction of uncoated surface or unwashed drug particles on the surface of the coating. The SEM (Fig. 1a) and confocal (Fig. 1b) images show that presence of dents on the surface of the coated pellets caused by the sticking of two particles during coating. Defects and holes in the coating were also observed in the confocal images. Thus, coating non-uniformity and variation in particle size have played a role on the observed discrepancy. In the case of uncoated pellets, since the resin is swellable (approximately 195% when initially dry), it is expected that the swollen resin can provide more space for the drug molecules to diffuse in and/or intercalate between the function groups. However the degree of swelling of the drug loaded resinate complex measured (in the buffer solution of 0.1N HCl) after equilibration was only 16% increase in volume. When translated into radius increase this amounts to 5% increase. Hence, this minimal swelling does not seem to affect the release profile. For the coated pellets, as the coating was

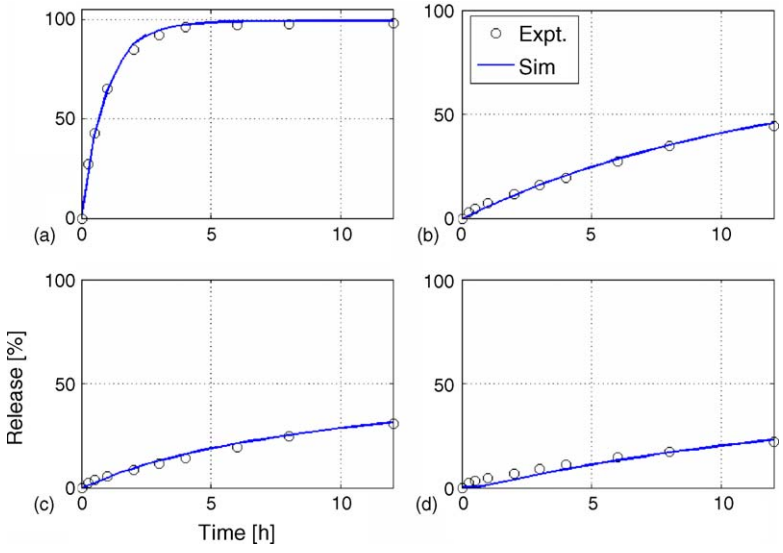

Fig. 2. Simulated (solid lines) and experimental (circles) profiles for: (a) no coating, (b) 10% (w/w) coating, (c) 15% (w/w) coating, and (d) 20% (w/w) coating.

exposed to the aqueous environment, the plasticizer material of the coating was leached resulting in the increased diffusion coefficient for the coating. A similar observation with the same type of coating was also reported by Shao et al. (2002). Sensitivity of the model prediction to 30% (obtained from experiment) variation of the coating diffusion coefficient showed a maximum error of 3% in drug release prediction at 30% release level. This error is comparable to the upper bound of the calculated RMSE values between experiment and model prediction.

3.2. Coating variability

Using the outlined methodology, varying degrees of coating deformation were simulated. For this study, the 20% (w/w) coating was considered and three levels of deformity, classified as slightly deformed, moderately deformed and highly deformed, were generated. Fig. 3 shows some of the randomly generated, deformed coating pellets from the three levels of deformity. The level of deformity is related to the coating thickness in the dented regions. Thus for the highly deformed level the dent extended to the core matrix (the coating thickness can be 0 μm for a given dent). For the moderately and slightly deformed levels the minimum coating thickness was set approximately to one-half and three-fourths of the original thickness, respectively. It should be noted that in the case of maximum deformation, a critical coating thickness is required in order for mathematical solution to converge. As a result, a very thin coating (0.05%) was considered as a cut-off thickness representing no thickness. It can be observed from Fig. 3a–c that larger deformations are imposed as compared to Fig. 3d–f or g–i. Monte Carlo runs were performed for each deformation level (20 runs) simulating their release profiles. It is worthwhile to note that the non-uniformity obtained by using this method is different from the actual non-uniformity as observed in Fig. 1a and b in that due to the symmetry assumption such deformation produces grooves as opposed to dents.

Fig. 4 shows the release profiles of the three deformation levels and the undeformed pellets with their confidence intervals. Average cumulative drug releases of approximately 39 ± 9, 34 ± 3, 31 ± 2.5 and 22% (mean ± S.D.) were attained for the highly deformed, moderately deformed, slightly deformed and undeformed pellets, respectively, after 12 h. Comparing the three deformity levels and the undeformed geometries after 12 h, the cumulative drug release varied by as much as 15% between the highly deformed and undeformed levels. It can be observed here that despite the constant average thickness of the coating, a higher average release amount was obtained from the highly deformed level and decreased with less coating deformity. This agrees with the finding by Chen and Lee (2001) that regardless

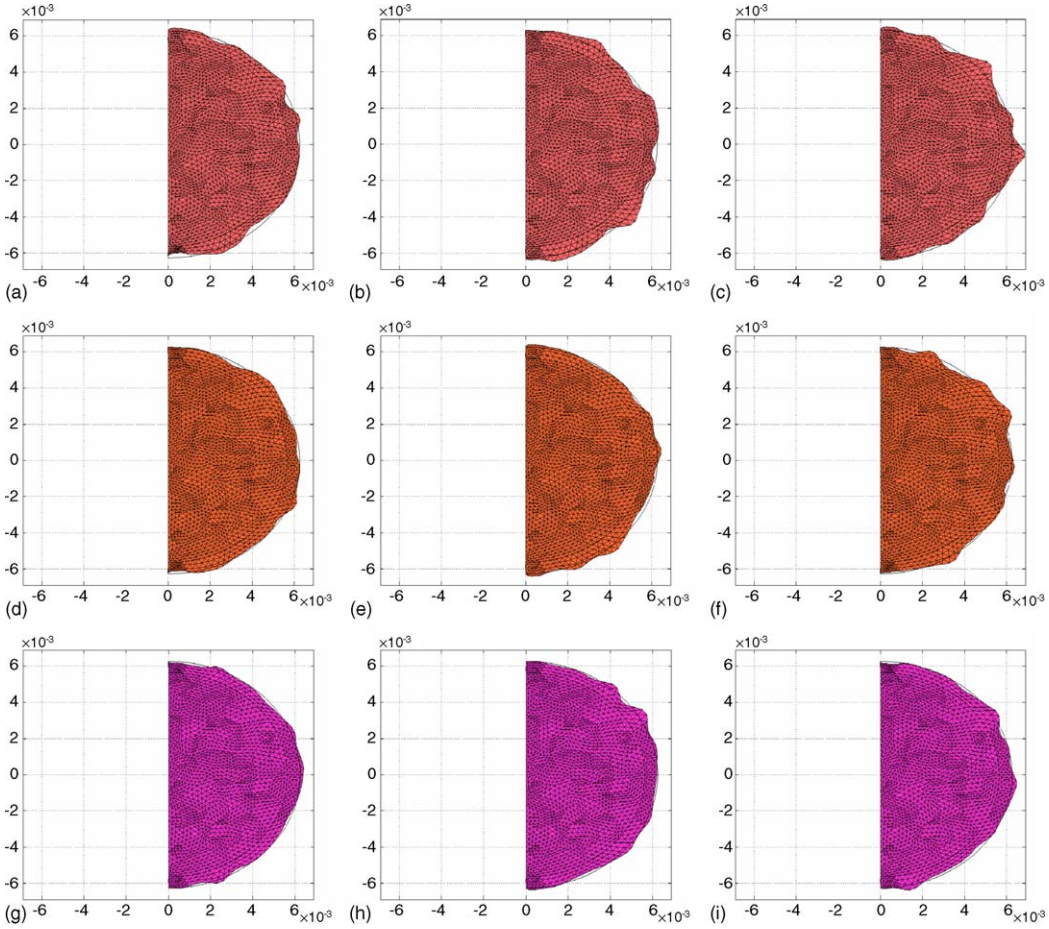

Fig. 3. Randomly generated coated pellets with non-uniform coating from: (a)–(c) maximum deformation, (d)–(f) moderately deformation and (a)–(c) slightly deformation levels.

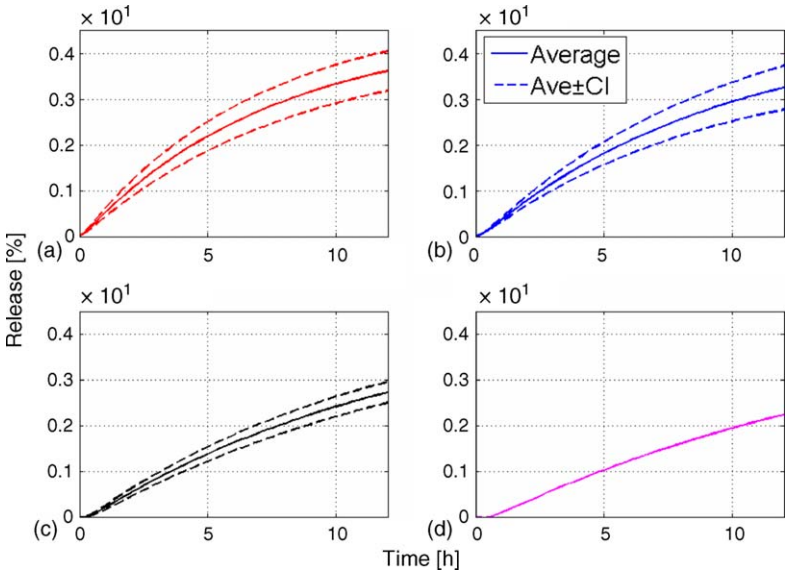

Fig. 4. Release profiles of the three levels of deformation and the un-deformed pellets: (a) highly deformed, (b) moderately deformed, (c) slightly deformed and (d) undeformed.

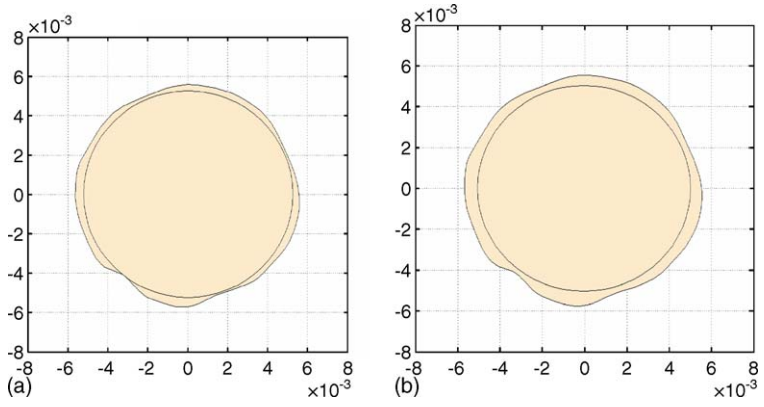

Fig. 5. Real geometrical models obtained from the confocal images of an arbitrary pellet. The fuzzy inner boundary between the coating and matrix was approximated by fitting circles in the obtained contours resulting in: (a) thinner coating and (b) thicker coating.

of the average thickness the smallest coating thickness in the pellet governs the release. For the purpose of comparison, confocal images of an arbitrary particle were taken and processed using the Matlab image processing tool to create a model with an actual non-uniform coating profile. This geometrical model was the used to simulate the drug release profile and compared to the profiles from the simulated (deformed) particles. Due to the difficulty to accurately identify the boundary between the core and the coating, two circles were fitted following the fuzzy contours (from image processing), resulting in thinner and thicker coatings as shown in Fig. 5a and b, respectively. The size of the arbitrary pellet was smaller than the average size; however, during the simulation, for the purpose of comparison, the cumulative release was calculated using the respective amount of release after a long time, M_∞. Moreover, it should be noted that the present minimal 2D image analysis, the 3D features of the pellets were nor captured and thus the obtained geometric model serves only for approximate comparison purposes.

Fig. 6 shows the release profiles for the average of the three deformity levels and the undeformed geometry with the con-

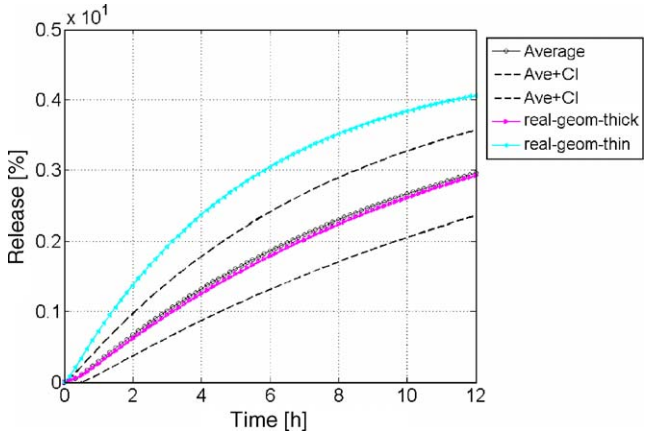

Fig. 6. Comparison between the release profiles of the average of the three theoretically considered deformed and undeformed levels, and the real geometries obtained from the confocal image.

fidence intervals and the actual coating profile obtained from the confocal image. The average release profile was obtained assuming that a batch of pellets contained an equal number of deformed and undeformed pellets. An average cumulative release of 30% ± 6% release at the end of the 12 h is expected. The predicted release with the thicker coating was within the calculated average cumulative release. However the prediction from the actual non-uniform coating profile with the thinner coating was outside of this range showing that the thicker approximation was the better representative of the boundary between the coating and the core.

Normally, when developing deterministic models, after the initial estimation of the model parameters, especially the diffusion coefficients, "tuning" of the model is performed to obtain a best fit scenario. As a result, pseudo-parameter values are generated for the given experimental data set. When the model is used for a different set of data, it must be "re-tuned" making the mathematical model inadequate for *in vivo* predictions. The deterministic model developed in this study assumed that all of the pellets were spherical. The model might not perform as well in representing another snap shot of reality represented by another set of data which might show up to 6% discrepancy with the experimental data according to the present analysis. Hence, in the development of models for polymer coated drug delivery systems non-uniformity in the coating of the pellets under consideration should be assessed and incorporated into the model if flexible models that reliably predict *in vivo* conditions are to be developed. It should be noted here that the extent of modification to the release profile as a result of the deformation depends upon the ratio between the diffusivities of the drug in the core matrix and the coating film (in the present case it is 0.2). As this ratio increases, modification to the release profile decreases. Hence, for higher diffusivity ratios the significance of considering deformity might be minimal and thus can be ignored.

4. Conclusions

A mathematical model of the drug release from coated ion-exchange pellets was developed and validated using different coating levels (0%, 10%, 15%, 20%, w/w) with good agreement. The coating non-uniformity was incorporated into the model using an ALE approach to impose deformities in the coating surface. A Monte Carlo method was employed to assess the effects of coating non-uniformity on the cumulative drug release by considering different deformity levels. It was shown that cumulative drug release varied by approximately 6% as a result of coating non-uniformity. The cumulative drug release for the model of an arbitrary pellet with the actual non-uniform coating profile obtained from confocal images was found to be comparable to the predicted average release profile. The verified model developed for this study can be used to examine the effects of changes to design parameters such as resin type, coating type and thickness, and particle size on the drug release profiles of coated pellets (not only ion-exchange but also any matrix or reservoir type) for sustained and targeted release of drugs. It can also be used further to examine the effects of coating non-uniformity in order to establish acceptable minimum coating thicknesses for a given coating process. Moreover, using the approach, the effect of the particle size distribution on the drug release can be studied. In the future, the variability related to the particle size (distribution) and the dissolution environment (biological variability) will be incorporated to obtain clinically relevant predictions.

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