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Modelling of Coupled Diffusion-Deformation for Swelling-Assisted Drug Delivery Mechanism in Hydroxypropyl Methylcellulose-Controlled Release Tablet

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Predicting drug delivery mechanism from swelling device has gained significant importance due to the massive global health burden to obtain the safe and effective delivery of therapeutics at the target site of action. Hydroxypropyl methylcellulose is a promising material for controlled drug delivery due to its ability to swell and release entrapped medicines in response to physiological stimuli. In the present work, finite element method (FEM) has been employed in conjunction with hygroscopic swelling material model to thoroughly understand and investigate the complex mechanisms that govern the hydroxypropyl methylcellulose-controlled release (HPMC-CR) tablet. The computational method via FEM provides numerical solutions for mathematical modelling of complex physical phenomena that evolves during swelling-assisted drug delivery from HPMC-CR tablet. This paper addresses the mathematical formulation of coupled diffusion-deformation to simulate the swelling mechanisms of HPMC-CR tablet. The modelling of water diffusion in stressed tablet matrix is derived from Fick's second law and coupled with solid mechanics model. COMSOL Multiphysics® software is utilized to solve the initial-boundary value problems for evaluating water concentration, and displacement of HPMC-CR tablet. The implementation of a deformable mesh to model the change in diffusion length due to swelling is the novelty of this work. The effect of water concentration on swelling properties of HPMC-CR tablet is investigated via three tablet structure designs: (1) non-swellable single-layer, (2) swellable single-layer and (3) swellable three-layer tablets. The simulation results obtained from the numerical model are comparable to the experimental data where R^2 = 0.979. This study finds that the rate of water diffusion significantly decreases as the HPMC-CR tablets swell. Tablet expansion causes a reduction in water diffusivity. The results obtained demonstrate that computational predictive model can effectively envisage the drug delivery mechanism in preclinical phases, which can decrease drug failure rates, reduce the time and cost of development, thus giving patients more effective and secure therapeutic options.

1. Introduction

Nowadays, cellulose and its derivatives are the most widely used in the pharmaceutical field for control release applications such as drug delivery matrix due to their semi-crystalline structure and biochemical properties (Seddiqi et al., 2021). Cellulose-based carriers for controlled drug-delivery systems usually take the cross-linked polymer such as hydroxypropyl methylcellulose (HPMC) that is able to form hydrogels, in which both diffusion and large deformation play an important role in controlling drug release from the systems (Ramli et al., 2022). HPMC is known as nonionic cellulose ether which suitable for both highly water-soluble drugs and formulations of high significant drug concentrations. As soon as HPMC comes into contact with water, it rapidly hydrates and expands, which lowers the glass transition temperature (from 84 °C to roughly 37 °C) and creates a rubbery gel layer. It is possible to anticipate the impact of formulation, including tablet composition, initial size, and shape, on the rate of drug release using a comprehensive mathematical model that includes all major variables impacting release kinetics. In other words, the necessary formulation can theoretically be predicted to obtain a

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desired drug release profile using a thorough mathematical model (Saeidipour et al., 2017). Investigating the material properties and behaviours is significantly important to obtain the desired material design for specific application (Shamjuddin et al., 2021). Therefore, this paper emphasizes the fundamental aspects in swelling behaviours of hydroxypropyl methylcellulose-controlled release (HPMC-CR) tablet for drug delivery application. HPMC is suitable for controlled drug-delivery systems because of high swelling degree with large liquid capacity (Ciolacu et al., 2020) and biocompatible to encapsulate water-soluble compounds and possible to sustain and release the active ingredients locally. The high swellability of HPMC has a significant effect on the kinetics of drug release, especially for drugs that are highly water soluble (Rehman et al., 2022).

Hygroscopic swelling occurs when a dry HPMC-CR tablet enters a humid environment and absorbs water molecules (Fregolente et al., 2018). When the water concentration exceeds a critical value, the polymeric chains unfold and enlarge. The dissolved drug molecules in the swollen region can diffuse toward the outer medium at the desired diffusion rate. The swollen region of the matrix expands as the diffusion of water progresses through the matrix, thus generating the localised stress that leads to the weakening of the matrix structure (Zhang et al., 2019). Modelling the swelling problem involves a concurrent diffusion of the water molecules through the cellulose and large deformation of the polymeric network (Setapa et al., 2020). Understanding the hygro-mechanical behaviours of cellulose is crucial for optimum material design to encounter the targeted controlled release application. In response to an external stimulus such as a variation in relative humidity or temperature, eigenstrains were developed in crystalline polymeric chains despite the absence of externally applied forces due to the associated geometrical constraints (Katedeshmukh et al., 2021). Hygro-eigenstrains occur due to moisture-induced swelling or shrinkage. Significant research was carried out into the mechanical properties of HPMC drug carrier matrix; however, the hygric (swelling or shrinkage) behaviour of cellulose-based matrix has not been studied to the same extent (Layek and Mandal, 2020).

Accordingly, the current work focuses on developing coupled diffusion-deformation model to visualize the swelling behaviours of HPMC-CR. The validity of the numerical model was assessed in order to determine how accurately it reflected the real process. The transient model was coupled with solid mechanics material model to quantify the diffusion-induced stress within the tablet. The hygroscopic swelling material model was adopted to predict the tablet volume expansion due to water absorption. The initial-boundary problems for three tablet structure designs were investigated using finite element software, COMSOL Multiphysics®. For the water diffusion and deformation phenomena, the modules employed were Transport of Diluted Species and Solid Mechanics, respectively. The understanding of hygro-mechanical behaviours in cellulose-based hydrogel matrix is discussed by considering the coupling effect on the distribution of water concentration. This study makes a novel numerical modelling contribution to the understanding of the swelling behaviour of HPMC-CR tablets and offers a predictive tool for the development of biomedical materials in the context of a drug release matrix.

2. Methodology

2.1 Physical model description

The work of numerical simulation is the main novelty of this paper. It is important to validate that the numerical model is constructed correctly. The experimental data of Bettini el al. (2001) was used as validation to make sure the numerical model accurately captured the behaviour of the actual process. The numerical model was built based on the experimental work of Bettini et al. (2001) which the HPMC-CR tablet was locked between two transparent Plexiglas® discs for allowing water uptake and drug release at lateral side only. The physical restrictions at the top and bottom of tablet permitted both water and drug molecules moved only in radial direction thus, the tablet was deformed accordingly at the similar direction. An axisymmetric cylindrical tablet was created with an initial thickness, Z_0 of 3.3 mm and an initial radius, R_0 3.5 mm. The axisymmetric model can be extended to three-dimensional (3D) problems, especially in the view of 3D swelling phenomenon.

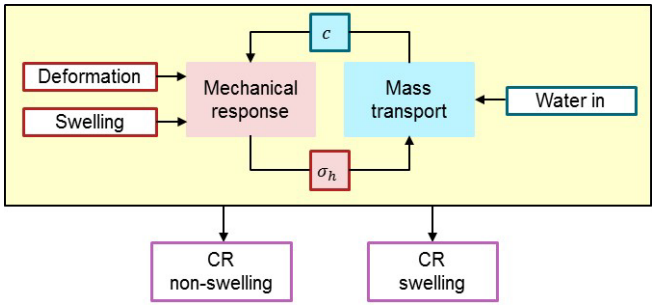

Figure 1: Framework model for coupled diffusion-deformation in swelling mechanisms of HPMC-CR tablet.

2.2 Mathematical model

The framework model of diffusion-deformation in swelling of cellulose-based hydrogel matrix is presented in Figure 1. Based on Fick's second law, the transient model used to represent the water diffusion inside the tablet is Eq(1):

$$\frac{\partial c_w}{\partial t} = \nabla\left(D_{0,w}\nabla c_w\right) \tag{1}$$

where c_w is water concentration (mol/m^3), $D_{0,w}$ is water diffusion coefficient (m^2/s), and t is time (s). For analysis, dimensionless parameters of time and water concentration were used, $\tau = D_{0,w}t/{R_0}^2$ and $\tilde{c}_w = c_w/c_{w,eq}$. $c_{w,eq}$ is the water concentration at the aqueous environment. In this study, the diffusion was assumed in one-dimensional (1D) restriction and $D_{0,w}$ is not temperature dependent and isotropic.

To quantify the diffusion-induced stress within the tablet during water absorption, a solid mechanics model was developed and coupled with the transient model. The deformation gradient was obtained by Eq(2).

$$F = I + \nabla u \tag{2}$$

where u is the displacement vector and I is the identity matrix. Water insertion leads to tablet volume expansion while the volume change depends on water concentration gradient (Δc_w) in Eq(3):

$$\frac{V}{V_0} = \det\left(F_c\right) = 1 + \Omega\Delta c_w \tag{3}$$

where V, V_0, and F_c are the current volume, initial volume, and water concentration induced deformation, respectively. The general definition of Ω is the partial molar volume change of host material after accommodating 1 mol of a guest atom. A relationship between the hygroscopic swelling strain coefficient (β_h) and the water content gradient (Δc_w) can be utilized to illustrate how the tablet swelled after absorbing water and created the hygroscopic strain in Eq(4):

$$\varepsilon_{hs} = \beta_h M_m \Delta c_w = \beta_h M_m (c_w - c_w^*) \tag{4}$$

where M_m is molar mass of water, and c_w^* is the strain-free reference water concentration (mol/m^3). Figure 2(a) displays the initial and boundary conditions for the governing equations (Eq(1)-(4)). The displacements of the tablet's left side (symmetry plane), top, and bottom were all fixed to zero, while the right side was free to deform. The initial and boundary conditions for mass transfer are: (a) the initial water concentration in the tablet was uniform and known (Eq(5)); (b) no mass flow in the symmetry region, top, and bottom of tablet (Eq(6)); (c) on the exposed tablet surface, the convective boundary condition was known (Eq(7)).

$$c_w = c_{w,0} \quad \text{for } t = 0 \tag{5}$$

$$\frac{\partial c_w}{\partial t} = 0 \quad \text{for x} = 0, \text{y} = 0, \text{and y} = Z_t \tag{6}$$

$$\frac{\partial c_w}{\partial t} = D_{0,w}\left(c_{w,eq} - c_w\right) \quad \text{for x} = R_t, \text{and } t > 0 \tag{7}$$

where $c_{w,0}$ and $c_{w,eq}$ are the initial water concentration (mol/m^3), and the equilibrium water concentration of the tablet (mol/m^3), respectively. Table 1 lists the initial conditions with the input parameters used to simulate the swelling process. R_t and Z_t radius (m) and thickness (m) of tablet at current time, respectively.

Table 1: Initial conditions and input parameters used in the simulation

Parameter	Value	Unit	Source
Water diffusion coefficient in HPMC, $D_{0,w}$	1.2 X 10^{-10}	m^2/s	Ramli N.A. et al. (2022)
Molar mass of water, M_m	0.018	kg/mol	Ramli N.A. et al. (2022)
Partial molar volume change of HPMC, Ω	1.8 X 10^{-5}	m^3/mol	Ramli N.A. et al. (2022)
Hygroscopic swelling strain coefficient of HPMC, β_h	2 X 10^{-4}	m^3/kg	This study
Strain-free reference water concentration, c_w^*	0.259	mol/m^3	Bettini et al. (2001)
Equilibrium water concentration of the tablet, $c_{w,eq}$	5.100	mol/m^3	Bettini et al. (2001)
initial water concentration, $c_{w,0}$	0	mol/m^3	This study
Initial radius of tablet, R_0	3.5 X 10^{-3}	m	This study
Initial thickness of tablet, Z_0	3.3 X 10^{-3}	m	This study

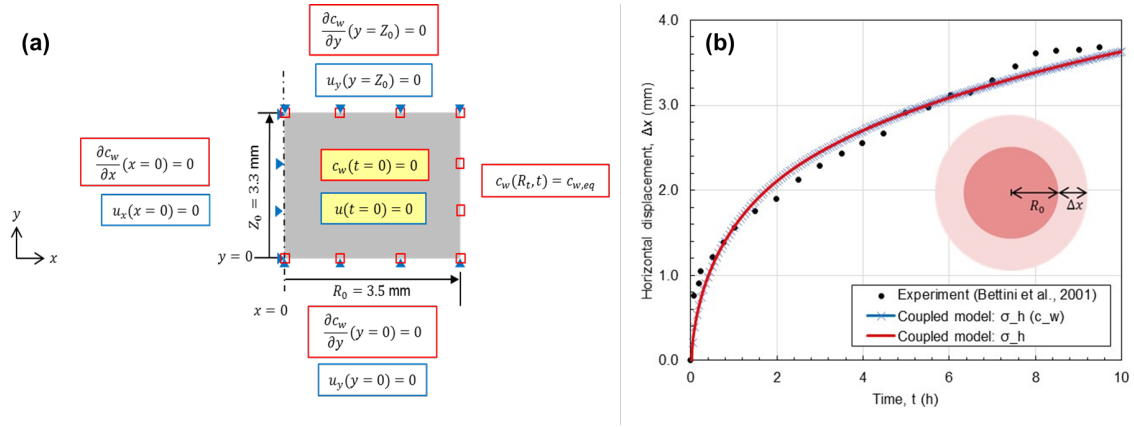

Figure 2: (a) Geometrical representation of the single layer HPMC-CR tablet with the initial and boundary conditions. (b) Horizontal displacement as a function of time. In the inset, a schematic illustration of the tablet expansion shown with initial radius, R_0 of 3.5 mm.

2.3 Numerical simulation

The essential formulation of coupled diffusion-deformation model was solved numerically via FEM using COMSOL Multiphysics® software. The numerical simulation was conducted to visualize the swelling behaviours of HPMC-CR tablet, which is crucial in developing the ideal system for a simplified model. Momentum and mass balances, together with mechanical response that governed the swelling performances of HPMC-CR tablet were integrated in a single numerical model. To illustrate the application of the current model, three examples of HPMC-CR tablet were simulated: 1) non-swellable single-layer tablet, 2) swellable single-layer tablet and 3) swellable three-layer tablet. Figure 2(a) shows a geometrical representation of the single layer HPMC-CR tablet with an indication of initial and boundary conditions. For modelling purpose, the active core of the three-layer tablet was studied as per the illustration of a single-layer tablet in Figure 2(a). Fixed constraints were applied at the top and bottom boundaries of the domain because the barrier layers are shaped using a non-swellable material. Therefore, the circular bases of the tablet core were mechanically restricted in terms of swelling. Deformable mesh was utilized to accommodate the change in diffusion length due to swelling.

3. Results and discussion

3.1 Model validation

The significant effect of water uptake on the mechanical behaviours of HPMC-CR tablet was studied by solving the governing equations in Eq(1)-(5). The simulation results obtained from the numerical model were compared with the experimental data of Bettini et al. (2001) for model validation. The horizontal displacement rate of both simulation and experimental data is presented in Figure 2(b) with the great agreement. The numerical model's fit is comparable to the behaviour of the real process, as shown by the fitted model's R^2 = 0.979 value. As a result, it gives the model builder a great confidence to predict the real-world event using FEM simulation results. The simulation results of displacement obtained using Eq(1) and Eq(3) present no significant difference due to the small contribution of hydrostatic stress in chemo-mechanical potential thus, the stress effect is negligible seen.

3.2 Evolution of water concentration

The normalized water concentration profiles along the diffusion length at specified times during the diffusion process are shown in Figure 3(a) for the three application examples. In general, the curves are initially concave, gradually become straight when steady state is eventually reached (not shown). The distribution of water concentration along the diffusion length gradually increases with diffusion time. Based on the comparison of three application examples in Figure 3(b), the results show that hygroscopic swelling decreases the diffusion rate of water as time progresses. The expansion of the matrix causes the diffusivity of water to be reduced. The initial acceleration of water concentration is higher due to the larger gradient of the chemo-mechanical potential along the diffusion length. This condition drives water molecules enter the tablet via diffusion until an equilibrium state is achieved.

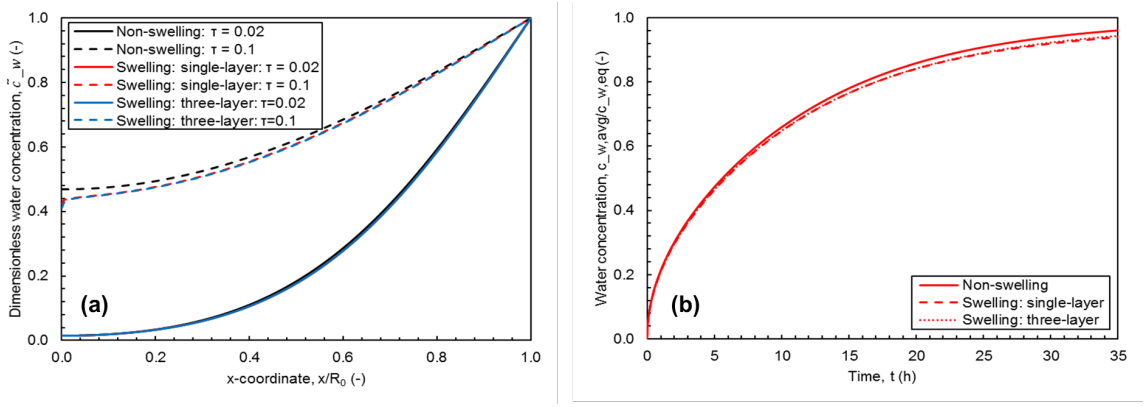

Figure 3: Evolution of water concentration versus (a) diffusion length and (b) time during diffusion-deformation process for (1) non-swellable single-layer, (2) swellable single-layer and (3) swellable three-layer tablets.

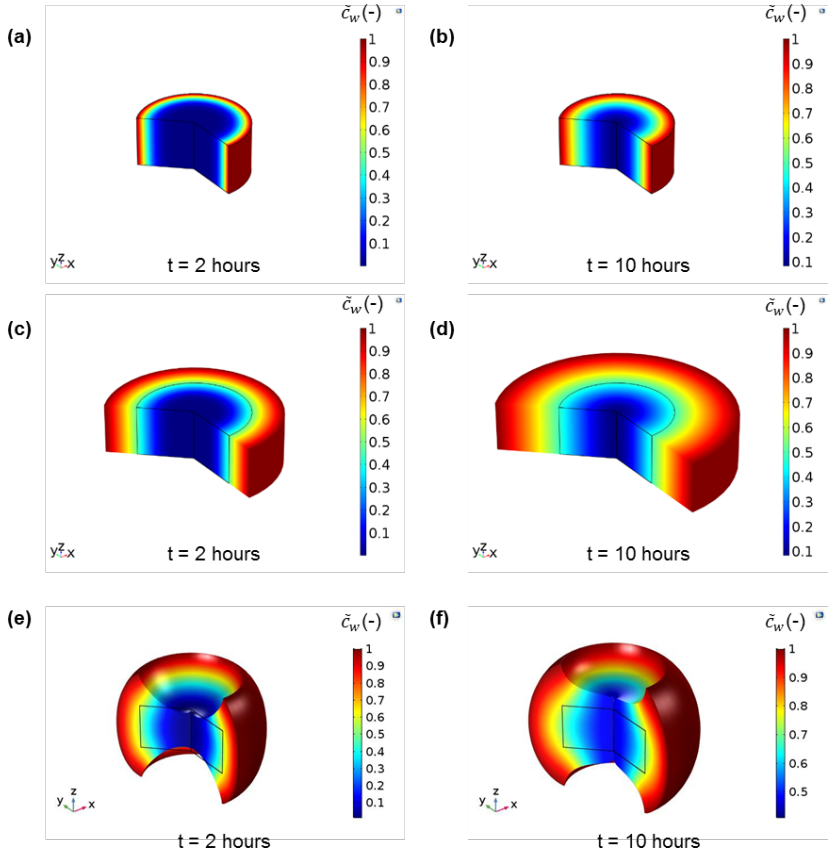

Figure 4: Contour plots of dimensionless water concentration at t = 2 h and 10 h for (a-b) non-swellable single-layer, (c-d) swellable single-layer, and (e-f) swellable three-layer tablets

Contour plots of normalized water concentration at *t* = 2 h and 10 h are shown in Figure 4 for (a-b) non-swellable single-layer, (c-d) swellable single-layer and (e-f) swellable three-layer tablets. The simulated results in Figure 4(c-d) are similar to the findings of Bettini et al. (2001). The non-swollen region (blue-coloured) shows that the water concentration inside the tablet has not yet reached the swelling threshold. In addition, the mobility of the macromolecules in the non-swollen region is very low, leading to a low diffusion rate of water (in the order of 10^{-16} m^2/s at 37 ºC). Subsequently, the development of a swollen region (red-coloured) in the swellable tablet shows that the chains initially gain rotational freedom and begin to occupy more space, causing the polymer swelling.

The diffused water molecules fill the voids between the chains and diffuses into the denser regions of the polymer, leading to additional chains being forced apart.

4. Conclusions

The novel coupled diffusion-deformation model is simulated numerically via FEM to visualize the hygroscopic swelling behaviours of single-layered and three-layered HPMC-CR tablets. As the HPMC-CR tablets swell, the rate of water diffusion considerably reduces. Water diffusivity decreases as a result of tablet expansion. The FEM numerical results are comparable to the experimental data. The proposed model provides the understanding of swelling behaviours of HPMC-CR tablet to make the technological advancement of drug delivery. In future, the model can be incorporated with drug component and used to design more complex structures for targeted applications.

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