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MATHEMATICAL MODEL CONTROLLED POTASSIUM CHLORIDE RELEASE SYSTEMS FROM CHITOSAN MICROSPHERES

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ABSTRACT

Chitosan can be prepared in the form of microspheres that serve as a depot for bioactive compounds released in a controlled way to diseased organs. In this study, a mathematical model of potassium chloride release from chitosan microspheres was developed. The model was validated using experimental data. The potassium chloride-loading percentages of 10.01%, 20.84%, and 20.57% were prepared using a cross-linking method. The potassium chloride loading was kept constant at about 20% when the potassium chloride mass in the preparation stage was above 5.024 mg/mL. Experiments and a model calculation of potassium chloride release from the microspheres with a loading of 10.01% and 20.57% were performed. In general, the model reproduces the experimental data. The experiments and the calculation show that during the same period, microspheres containing more potassium chloride release a higher percentage of potassium chloride than do microspheres containing less potassium chloride.

Keywords: Chitosan; Microspheres; Moldeling controlled drug release system; Simulation

1. INTRODUCTION

Controlled drug release systems maintain drug concentrations in the blood or in diseased tissues at desired values and therefore control drug release rates and durations. Controlled drug release systems are systems to exploit modern therapeutic concepts to improve drug effectiveness (Frenning et al., 2003). The design stage is an essential part of the realization and fabrication of controlled drug release systems, and therefore, the use of mathematical models in engineering controlled drug release systems is helpful because it can predict drug release profiles before system fabrication.

One approach for a controlled drug release system is to insert drugs into hydrophobic (e.g., wax, polyethylene, polypropylene, and ethylcellulose) or hydrophilic (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, and alginate) matrices. Matrices are three-dimensional networks containing drugs and other substances, such as solvents and excipients, required in the manufacture of controlled drug release systems.

Chitosan is a widely available polysaccharide in nature after cellulose and comes from shrimp and crab wastes, which are broadly available in Indonesia. The natural polymer is environmentally friendly and has great potential for pharmaceutical applications because of its

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biocompatibility, biodegradability, and nontoxic and mucoadhesion properties. It can be prepared in the form of microspheres serving as a depot for bioactive compounds controlling the release to diseased organs (Prabaharan, 2009). In polymer systems, such as chitosan, matrix swelling takes place. Therefore, in addition to dissolution and diffusion restrictions, the drug release kinetics are also limited by the solvent permeation process.

Many models for drug release from swelling and dissolving polymer matrices have been studied, and models of sphere or tube systems have been developed (Narasimhan & Peppas, 1997; Frenning et al., 2003; Borgquist et al., 2006; Wang et al., 2007). Most of these are empirical or semi-empirical models, but none have used a comprehensive theoretical model.

The present study was performed to understand the drug release behavior from chitosan microspheres using a theoretical model. For validating the model, we performed an experiment on controlled release from chitosan microspheres using potassium chloride as the drug and glutaraldehyde as the cross-linking agent, although its use in pharmacy is no longer recommended because it is a molecule regulator between covalent bonds and polymer chains and results in a more rigid polymer as a core material (Park et al., 1993).

2. METHODOLOGY

A solution consisting of chitosan, glutaraldehyde, and potassium chloride was prepared to produce microspheres, using the method of Dubey and Parikh (2004). Although glutaraldehyde is not recommended in pharmaceuticals, we used this substance to facilitate obtaining chitosan microspheres. Microspheres of two different potassium chloride concentrations were prepared and tested in vitro in water (pH 3) to determine the potassium chloride release profiles.
A mathematical model was developed to predict the potassium chloride release from the microspheres. We validated the model by comparing the calculated percentages of potassium chloride release to the experimental percentages.

2.1. Experiments

Two grams of powdered chitosan and 0.2512 g of potassium chloride were weighed and placed in a glass beaker. We then gradually added 100 mL of 5% acetic acid while stirring with a magnetic stirrer at a speed of 1000 rpm for 15 min. The resulting solution was added to a 100-mL volumetric flask for calibration with the 5% acetic acid and homogenized.

Microspheres were prepared using the cross-linking method with glutaraldehyde as the cross-linking agent. Paraffin oil (50 mL) was placed in a 250-mL glass beaker, and 1 mL of SPAN 80-type surfactant was added while stirring. We then added 3 mL of chitosan potassium chloride solution while stirring at 3000 rpm for 5 min. To this was added 0.25 mL of 25% glutaraldehyde solution in water. The solution was stirred at 3000 rpm for 5 min before reducing the speed to 500 rpm for 1 h. An additional 0.25 mL of 25% glutaraldehyde solution in water was added and stirred for 1 h. This was followed by another 0.25 mL of 25% glutaraldehyde solution in water and stirring for 1 h. The emulsion that formed was allowed to stand for 1 h and was then filtered with Whatman 40 filter paper, washed four times with petroleum ether, washed with distilled water, dried in open air, and stored in a desiccator at room temperature. The microsphere preparation was repeated with different masses of potassium chloride (0.5204 g and 0.7544 g).

A particle size analyzer (PSA; LS 100 Q model) was used to determine the distribution and average size of the microspheres. A scanning electron microscope (SEM) was used to determine the microsphere morphology.

A number of containers were prepared, with each container used for certain potassium chloride release duration. We placed 40 mg of microspheres into each container to which 40 mL of

swelling liquid (pH 3) was added. The containers were covered with cotton plugs and allowed to stand at ambient temperature. The filtrates in each container were stirred, filtered, and placed in 10-mL vial bottles for potassium chloride concentration tests using inductively coupled plasma (ICP).

2.2. Modeling

Once the microspheres were added to the swelling liquid, water permeated the microspheres and dissolved the potassium chloride, glutaraldehyde, and potassium chloride–glutaraldehyde complex. This led to the formation of pores that were immediately filled with water. The potassium chloride dissolved in water diffused out of the microspheres through the pores. In the model, the concentrations of glutaraldehyde and the potassium chloride–glutaraldehyde complex were assumed to be very small and so were neglected. Potassium chloride was assumed to be uniformly distributed in the microspheres.

In the solid phase of the microspheres, potassium chloride occupies a volume fraction fd. In the microspheres, the water concentration C_w at spatial positions and time represents the local porosity. If the water concentration in the solution surrounding the microspheres is known, the maximum concentration of water within the microspheres is f_dC_{w+} and the maximum density of the pores within the microspheres can be evaluated as f_dC_w (Wang et al., 2007).

As the microspheres are added to the water, water immediately permeates the microspheres with the diffusion coefficient D_w being very low. When water meets potassium chloride in the solid phase of the microspheres, potassium chloride dissolves in water and gives rise to the pores in the microspheres. The pores lead to a higher surface area for the dissolution of potassium chloride, a higher effective diffusion coefficient, and consequently faster molecular transportation of water in the microspheres. The pores increase in size with time. The diffusion coefficient is proportional to the pore density $D_w \approx \alpha C_w$ (Frenning et al., 2003), and the mass balance of water in the microspheres is as follows:

$$\frac{\partial C_w}{\partial t} = D_w(C_w)\left[\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial C_w}{\partial r}\right)+\frac{1}{r^2\sin\theta}\frac{\partial}{\partial\theta}\left(\sin\theta\frac{\partial C_w}{\partial\theta}\right)+\frac{1}{r^2\sin^2\theta}\frac{\partial^2 C_w}{\partial\phi^2}\right] \quad (1)$$

On the external surface of the microspheres where the dissolution is expected to reach its maximum limit, the boundary condition is

$$r = \mathrm{R},\ t > 0:\ C_w = f_dC_{w+} \quad (2)$$

In the center of the sphere, there is a symmetry boundary condition

$$r = 0,\ t > 0:\ \frac{\partial C_w}{\partial r} = 0 \quad (3)$$

but for the initial condition, there is no water in the microspheres

$$t = 0,\ 0 \geq r > \mathrm{R}:\ C_w = 0 \quad (4)$$

The potassium chloride concentration at every position in the solid phase $C_{d,s}$ decreases as it dissolves in water at a rate of $G_d(r, \theta, \phi, t)$ and increases due to crystallization at a rate of $H_d(r, \theta, \phi, t)$.

$$\frac{\partial C_{d,s}}{\partial r} = H_d - G_d \tag{5}$$

where

$$H_d = \gamma_d \left(C_d - C_d^{sol} \right) \tag{6}$$

and where γ_d is the potassium chloride dissolution coefficient, C_d is the potassium chloride concentration in water, and C_d^{sol} is the potassium chloride solubility in water. Equation 6 applies for $C_d > C_d^{sol}$, and

$$G_d = \gamma_{d,s} \left(C_d^{sol} - C_d \right) C_w C_{d,s} \tag{7}$$

where $\gamma_{d,s}$ is the potassium chloride crystallization coefficient. Equation 7 applies for $C_d^{sol} > C_d$.

The initial concentration of potassium chloride is specified as follows:

$$t = 0,\ 0 \geq r > \mathrm{R}:\ C_{d,s} = C_{d,s}^0 \tag{8}$$

The dissolved potassium chloride diffuses into the liquid bulk outside the microsphere. The mass balance of potassium chloride in the liquid phase is as follows:

$$\frac{\partial C_d}{\partial t} = D_d \left[\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial C_d}{\partial r} \right) + \frac{1}{r^2 \sin\theta} \frac{\partial}{\partial \theta} \left(\sin\theta \frac{\partial C_d}{\partial \theta} \right) + \frac{1}{r^2 \sin^2\theta} \frac{\partial^2 C_d}{\partial \phi^2} \right] + G_d - H_d \tag{9}$$

where D_d is the diffusion coefficient of potassium chloride dissolved in water.

The solution surrounding the microspheres has a very large volume, and potassium chloride is assumed to be completely mixed in the solution so that its concentration is negligible. The boundary condition at the external surface of the microsphere is

$$r = \mathrm{R},\ t > 0:\ C_d = 0 \tag{10}$$

In the center of the sphere, there is a symmetry boundary condition

$$r = 0,\ t > 0:\ \frac{\partial C_d}{\partial r} = 0 \tag{11}$$

For the initial condition, there is no potassium chloride in water

$$t = 0,\ 0 \geq r > \mathrm{R}:\ C_d = 0 \tag{12}$$

Validation was performed by comparing the calculated percentages of potassium chloride release with the experimental percentages. To calculate the percentages of potassium chloride release, the potassium chloride concentration profile in the solid phase at different times according to the experimental time range $C_{d,s} = f(r, \theta, \phi, t)$ is needed. From the concentration profile, the remaining mass of potassium chloride in the solid phase can be calculated. The mass

of potassium chloride released at any time $M_d(t)$ can be calculated by subtracting the remaining mass of potassium chloride from the initial mass of potassium chloride in the solid phase $M_{d,s}^0$ as shown in Equation 13.

$$M_d(t) = M_{d,s}^0 - \frac{4}{3}\pi \mathrm{MW}_d \int_0^R C_{d,s} r^3 dr \tag{13}$$

where MW_d is the molecular weight of potassium chloride.

The percentages of potassium chloride release at each time period can be calculated as follows:

$$\%\ \text{release} = \frac{M_d(t)}{M_{d,s}^0} 100\% \tag{14}$$

The model was solved by using COMSOL Multiphysics (2013). The potassium chloride diffusion coefficient in chitosan D_d was obtained from the literature (Jamnongkan & Kaewpirom, 2010). The solubility coefficient $\gamma_{d,s}$ and the proportionality constant for the water diffusion coefficient α are the setting parameters. The values of the two parameters were changed such that the calculated percentages of potassium chloride release and the experimental ones were in agreement.

3. RESULTS AND DISCUSSION

3.1. Percentages of Potassium Chloride Loading

A standard curve for potassium chloride concentration in water was prepared. The intensities of the different concentrations of potassium chloride were measured using an ICP instrument. The curve was linear, and its regression equation was I = 795CKCl + 228.3 with R2 = 0.999953.

To determine the potassium chloride loading in the microspheres, the microspheres were dissolved in 2 mL of concentrated HNO3. The solution was diluted with distilled water until reaching a volume of 25 mL. The intensity of the solution was measured using an ICP and compared against the standard curve to obtain the potassium chloride concentration. The potassium chloride mass was calculated, and the ratio of the mass of potassium chloride to the microsphere mass was the percentage of potassium chloride loading in the microspheres (Table 1).

Table 1 The percentages of potassium chloride loading in the microspheres

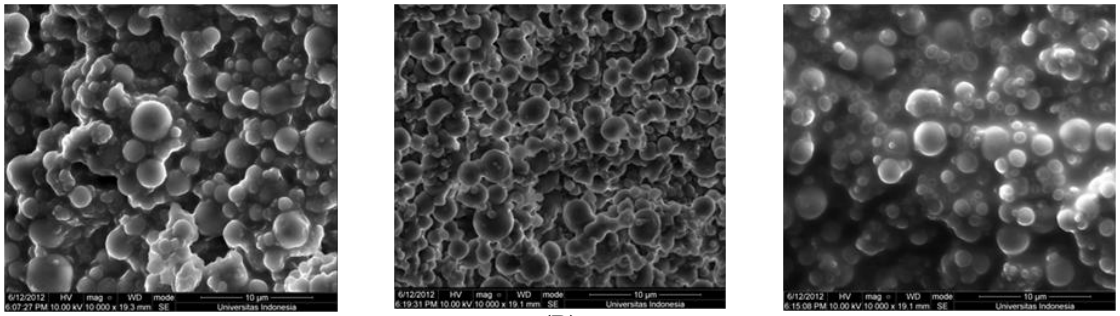
Microsphere	Potassium chloride mass at the preparation stage (g)	Potassium chloride loading (%)
A	0.2512	10.01
B	0.5204	20.84
C	0.7544	20.57

The highest potassium chloride loading was from microspheres prepared with 0.5024 g potassium chloride (B). The value is nearly equal to that of the microspheres prepared with 0.7544 g potassium chloride (C). The similar values probably result from the limitation of

potassium chloride solubility during the process of microsphere preparation, which reaches its maximum at 0.5024 grams of potassium chloride.

3.2. Average Diameter and Morphology of Microspheres

The PSA tests indicated that the average diameter of microsphere A was 0.696 μm, B was 0.626 μm, and C was 0.743 μm. Overall, the sizes of the microspheres were smaller than those obtained in the experiments by Dubey and Parikh (2004). The SEM tests showed that the micro-sized particles generated in the study were spheres (Figure 1), and although some stuck together, they remained as spheres.



(A) (B) (C)

Figure 1 Morphology of microspheres A, B, and C

3.3. Potassium Chloride Release from the Microspheres

To measure the potassium chloride concentration in water at pH 3, we produced a standard curve. The curve was a straight line with linear regression $I = 932.1C_{KCl} + 147.9$ and $R^2 = 0.99983$.

Figure 2 presents the potassium chloride release profile from the microspheres up to 10 min. It can be seen that the percentages of potassium chloride release from microspheres with a higher potassium chloride loading were greater than those with a lower potassium chloride loading. This is because the microspheres with the higher potassium chloride loading have a higher driving force. Consequently, the release rate was also higher, which occurs provided that the maximum solubility limit has not been reached. The release profiles for the microspheres with similar potassium chloride loadings (B and C) were about the same. Microsphere B and microsphere C released about 50% of the potassium chloride, while microsphere A released only 21%.

To clarify the longer release behavior, we extended the release time up to 100 min for microsphere A and microsphere C (Figure 3). We did not include microsphere B because its potassium chloride loading was the same as that of microsphere C. The curve shows that potassium chloride release from the microspheres follows Higuchi's square-root model as seen for releases of other drugs from microspheres (Dubey & Parikh, 2004; Mothilal et al., 2012). The percentage of potassium chloride releases sharply increased up to 10 min; over 10 min, the gradients of the percentage curves were lower. This phenomenon occurs because the driving force for mass transportation decreases with increasing time. At the 100th minute, microsphere A released about 42% of the potassium chloride while microsphere C released about 77%.

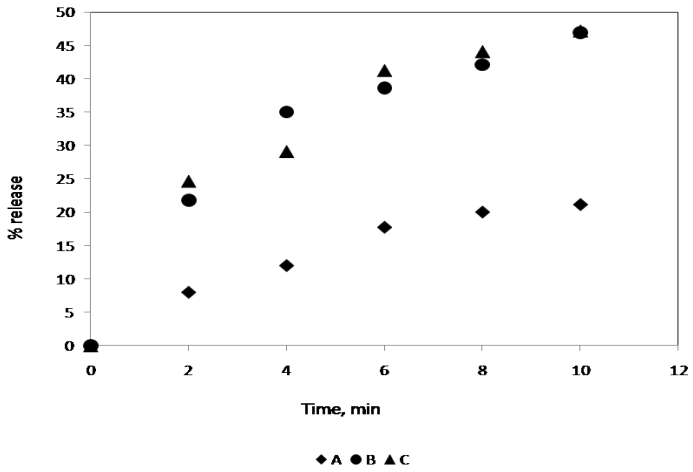


Figure 2 Potassium chloride release profiles from microspheres A, B, and C up to 10 min

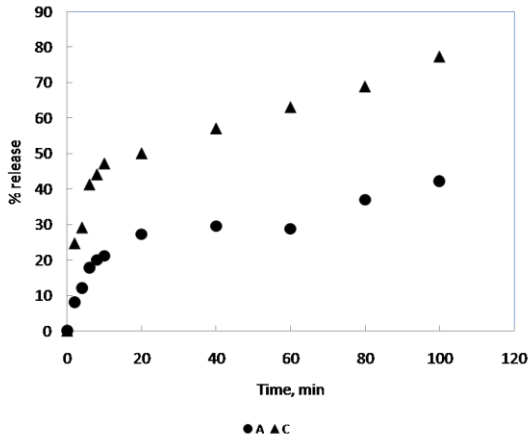


Figure 3 Potassium chloride release profiles from microspheres A, B, and C up to 100 min

3.4. Model Validation

We first validated Microsphere C possessing the same compositionwith Microsphere B. The validation process was done by changing the values of the solubility coefficient and the proportionality constant for the water diffusion coefficient α such that the calculation results were in agreementwith the experimental ones.The results of the calculations were plotted on the same graph with those of the experiments (Figure 4). In general, the model was shown toreproduce the experimental results; however, the models underpredict the experimental condition before 20 min of release. The optimum values of the solubility coefficient and the proportionality constant for the water diffusion coefficient are 3×10^{-10}cm^2·mol^{-2}·h^{-1} and 5×10^{-9}cm^5·h^{-1}·mol^{-1}, respectively.

Calculations for microsphere A were carried out use the optimum values of the solubility coefficient and the proportionality constant for the water diffusion coefficient determined in the first validation process. Figure 5 shows the comparison between the calculated and experimental percentages of the potassium chloride release for microsphere A.

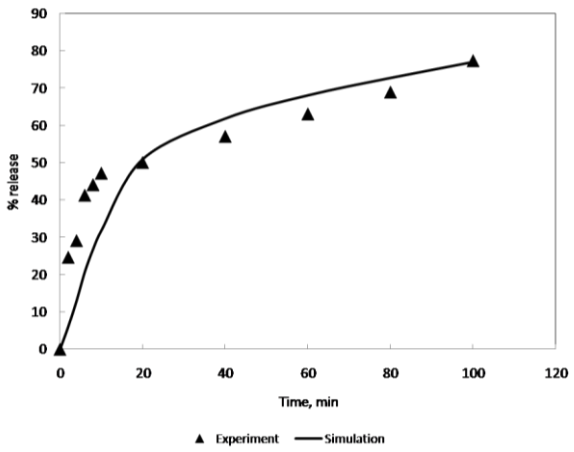


Figure 4 The percentage of potassium chloride release from microsphere C showing experimental and calculation results

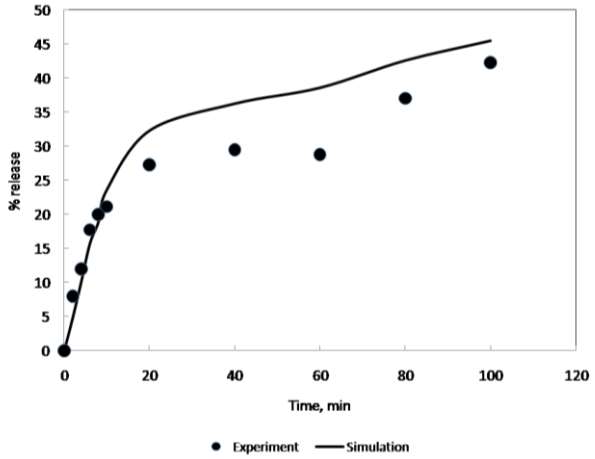


Figure 5 The percentage of potassium chloride release from microsphere A showing experimental and calculation results

It is clear from Figure 4 that within the first 10 min, the model reproduces the experimental results. After 10 min, the calculated results are greater than the experimental ones; however, the two curves have the same trend.

3.5. Profiles of Water and Potassium Chloride Concentrations

The validated models can be used to predict the behavior of water and potassium chloride in the solid or liquid phases. With the models, the influence of potassium chloride and water transportation resistance can be determined. Figure 6 shows the profiles of water concentration in microsphere C. Water permeation within the microspheres at the beginning of the process is high. This is clearly seen from the wide differences in concentration at the same position near the external surface of the microspheres (e.g., r = 0.25 μm) at 0 min and 20 min. The difference decreases from the 20 min to 30 min. Water reaches the center of the microspheres after about 20 min. The difference in water concentration at 80 min and 100 min shows that the release process is still unsteady, indicating that water continues to permeate and enlarge the pore density after 100 min.

The profiles of potassium chloride concentration in the solid and liquid phases are shown in Figures 7 and 8. The decrease in the potassium chloride concentration in the solid phase due to dissolution largely takes place in the half radial position from the external surface. When water permeates within the microsphere, it provides a solvent for dissolving potassium chloride from the solid phase. The difference in the potassium chloride concentration at 80 min and 100 min is still high, indicating that the potassium chloride dissolution process has not reached a steady state.

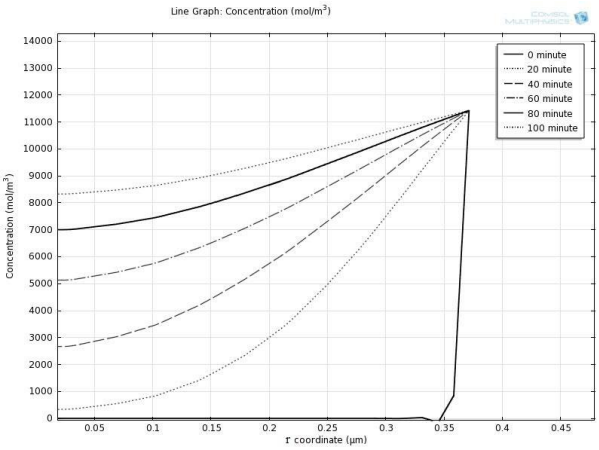


Figure 6 Water concentration profile in microsphere C

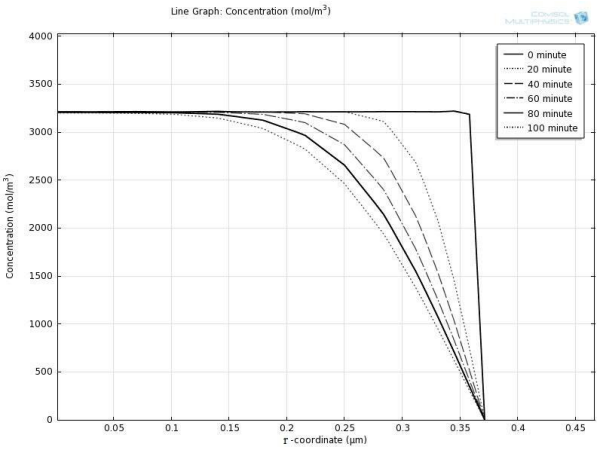


Figure 7 Solid-phase potassium chloride concentration profiles in microsphere C

Figure 8 shows that the potassium chloride dissolved at very low concentrations, with the lowest concentrations occurring at positions close to the external surface of the microspheres and the concentration increasing toward the center of the sphere. However, Figure 7 shows that the mass of dissolved potassium chloride decreased toward the center of the sphere, indicating that the pore density decreased toward the center of the sphere.

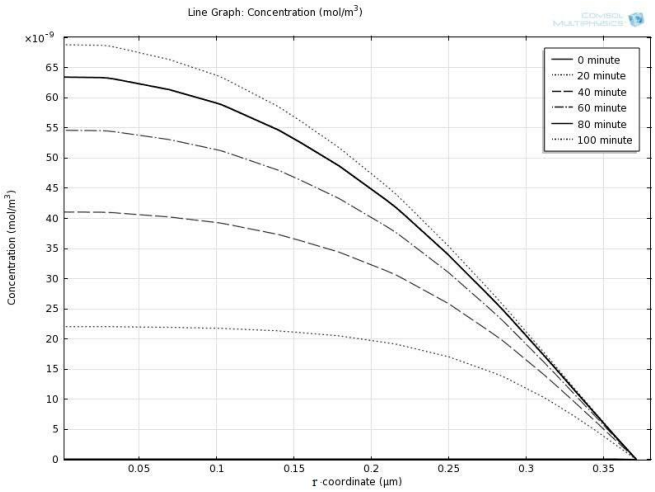


Figure 8 Liquid-phase potassium chloride concentration profile in microsphere C

4. CONCLUSION

We developed a mathematical model of a controlled drug release system from chitosan microspheres and validated the model using experimental data. The calculated percentages of potassium chloride release from the system agreed well with the experimental percentages. As shown by the experiments and the calculation, microspheres with more potassium chloride release a higher percentage of potassium chloride compared to microspheres with less potassium chloride during the same period.

5. ACKNOWLEDGEMENT

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