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Kinetics Modelling of Vitamin B12 Release in an Agar/κ-Carrageenan Hydrogel Blend

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Abstract. A phycocolloidal hydrogel patch is studied as a potential material for the transdermal delivery device for vitamin B12. The vitamin release kinetics from an agar/κ-carrageenan hydrogel blend as a function of mass ratio and vitamin loading. Concentration measurements were done using a colorimetric method, and the experimental data were fitted into the Korsmeyer-Peppas model, Peppas-Sahlin model, and Berens-Hopfenberg model. From the curve fitting, parameters such as first-order polymer relaxation constant and diffusivity constant were obtained. The results showed that for the Korsmeyer-Peppas model and the Peppas-Sahlin model, the release mechanism followed Fickian diffusion predominantly. On the other hand, the Berens-Hopfenberg model fit shows that the release mechanism predominantly follows non-Fickian diffusion and may need to be modified.

Introduction

Recently, there have been a growing interest in the use of hydrogels as a carrier medium for the topical application of vitamins, such as the study on the gel-to-epidermal permeation of Vitamin C (ascorbic acid), which is a naturally occurring, powerful antioxidant with numerous benefits to the skin [1]. While there have been many studies on alginate hydrogels being used for drug delivery, most of them deal with oral administration or injection. On the other hand, there have been several reports on alginate hydrogels used as wound dressing; alginate, a naturally is extensively used because of its nontoxicity, excellent water absorption capacity, hemostatic property, and non-immunogenicity [2]; however, most are primarily focused on the use of therapeutic agents that promote wound healing such as Ag nanoparticles and iodine. Thus, there is still a need to further study the sorption and drug release properties of phycocolloids to determine their potential for topical application of vitamins.

Several models have been established on the kinetics of drug release from polymeric systems, such as the Korsmeyer-Peppas, Berens-Hopfenberg, and Higuchi models [2]. However, there is limited research specifically on the release of vitamin B12 from a phycocolloidal hydrogel blend for transdermal delivery applications: for instance, Jin, et al. studied the diffusion mechanism of vitamin B12 in polyacrylic acid and copolymers of acrylic acid and N-vinyl pyrrolidinone hydrogels [3] using Peppas models but only focused on performing permeation tests. On the other hand, there have been studies such as those conducted by Rossi, et al. on agar-carbomer hydrogel blends for the diffusivity and release of ethosuximide [4] and by Li, et al. on the gelling behavior and drug release performance of agar/κ-carrageenan mixed hydrogels [5] that did not include mathematical modelling of drug release kinetics. Because drug diffusivity is significantly affected by drug-polymer interaction and by polymer network structure, it is necessary to establish sorption kinetic parameters inherent to every specific polymer system for the purpose of drug delivery material design. Establishing a mathematical model to correlate the release of vitamins to hydrogel blend formulation parameters such as mixing ratio and loading allows for optimization and improved product performance.

This study focuses on the mathematical modelling of the vitamin B12 diffusivity and release using Fickian and first-order polymer relaxation parameters for a hydrogel blend of agar and κ-carrageenan. The modelling fit aims to establish the material behavior of the agar/κ-carrageenan as well as its potential as a topical drug delivery device for vitamin B12.

Experimental

Hydrogel Blend Preparation. Mixtures of agar/κ-carrageenan powder (25:75, 50:50, 75:25, 100:0) were dissolved in distilled water at 25°C to a set biopolymer concentration of 1%, while the vitamin B12 powder was stirred into the solution at different concentrations (1×, 1.5×, 2× 1000 mcg). The polymer solutions were then poured into molds and allowed to set at room temperature for 12-18 hours. Finally, the set vitamin-loaded hydrogel samples were then placed in a drying oven at 50°C.

Drug Release Measurement. Concentration of released vitamin were measured using simple colorimetry setup. A dried vitamin-loaded hydrogel was cut into a circular shape of 23 mm diameter and placed on top of a 5-mL beaker filled to the brim with 8.61 mL of disodium phosphate-citric acid buffer (pH 7.4). The concentration of the vitamin B12 solution was determined from calibration lines generated from measuring the absorbance of the beaker solution with the released vitamin B12 against that of a blank solution.

Mathematical Modelling. Vitamin release kinetics modelling was done by fitting the experimental data on concentration C_t and equilibrium concentration C_∞ to the Korsmeyer-Peppas (Eq. 1), Peppas-Sahlin (Eq. 2), and Berens-Hopfenberg (Eq. 3) models. The Generalized Reduced Gradient (GRG) and the least-squares algorithm were employed to calculate the model parameters. Data fitting calculations and plotting were done using MS Excel® and Visual Basic Analysis.

$$\frac{C_t}{C_\infty} = K \cdot t^n \tag{1}$$

$$\frac{C_t}{C_\infty} = k_1 t^m + k_2 t^{2m} \tag{2}$$

$$\frac{C_t}{C_\infty} = x \cdot \left[1 - \frac{8}{\pi^2} \sum_{n=0}^{\infty} \frac{1}{(2n+1)^2} e^{-\frac{D}{L^2}(2n+1)^2 \pi^2 t} \right] + (1-x)\left(1 - e^{-k_R t}\right) \tag{3}$$

Results and Discussion

Korsmeyer-Peppas. As shown in Table 1, the values for the model parameters generated by the Korsmeyer-Peppas model at n^{th} order, specifically at 1× loading, it is observed that the n values ranged from 0.48 to 0.58 among different mass ratios. Thus, it can be assumed that the drug release mechanism as defined by this model equation approximately follows Fickian diffusion (n = 0.5). The vitamin release data fitted into the Korsmeyer-Peppas model with n = 0.5 are observed to give values for parameter K as listed in Table 2 for varying loading and mass ratios. Based on the observed R^2 values, it is concluded that the Fickian diffusion assumption is valid for the 1× loading, with the diffusion coefficient ranging from 0.265 to 0.290 across all variations. It is also observed that as vitamin loading is increased, the Fickian model fit becomes less accurate, which implies a decrease in drug mobility at higher concentration.

Table 1. Best fit parameters of release data from the Korsmeyer-Peppas model at different agar fractions and 1× vitamin loading.

	agar fraction			
	0.25	0.50	0.75	1.0
n	0.541	0.499	0.580	0.479
R^2	0.991	0.992	0.993	0.995

Fig. 1 shows the correlation between the predicted versus actual C_t/C_∞ values were generated to validate the Korsmeyer-Peppas model at n^{th} order. To summarize, the model best fitted release data at 1× loading, as it is evident that the R^2 value increases as agar fraction is increased.

Table 2. Best fit parameters of release data modelled on the Korsmeyer-Peppas model at $n = 0.5$.

	1× loading		1.5× loading		2× loading	
agar fraction	*K*	R^2	*K*	R^2	*K*	R^2
0.25	0.271	0.990	0.290	0.988	0.288	0.983
0.50	0.277	0.992	0.287	0.983	0.282	0.977
0.75	0.277	0.991	0.290	0.985	0.265	0.986
1.00	0.295	0.994	0.269	0.985	0.271	0.977

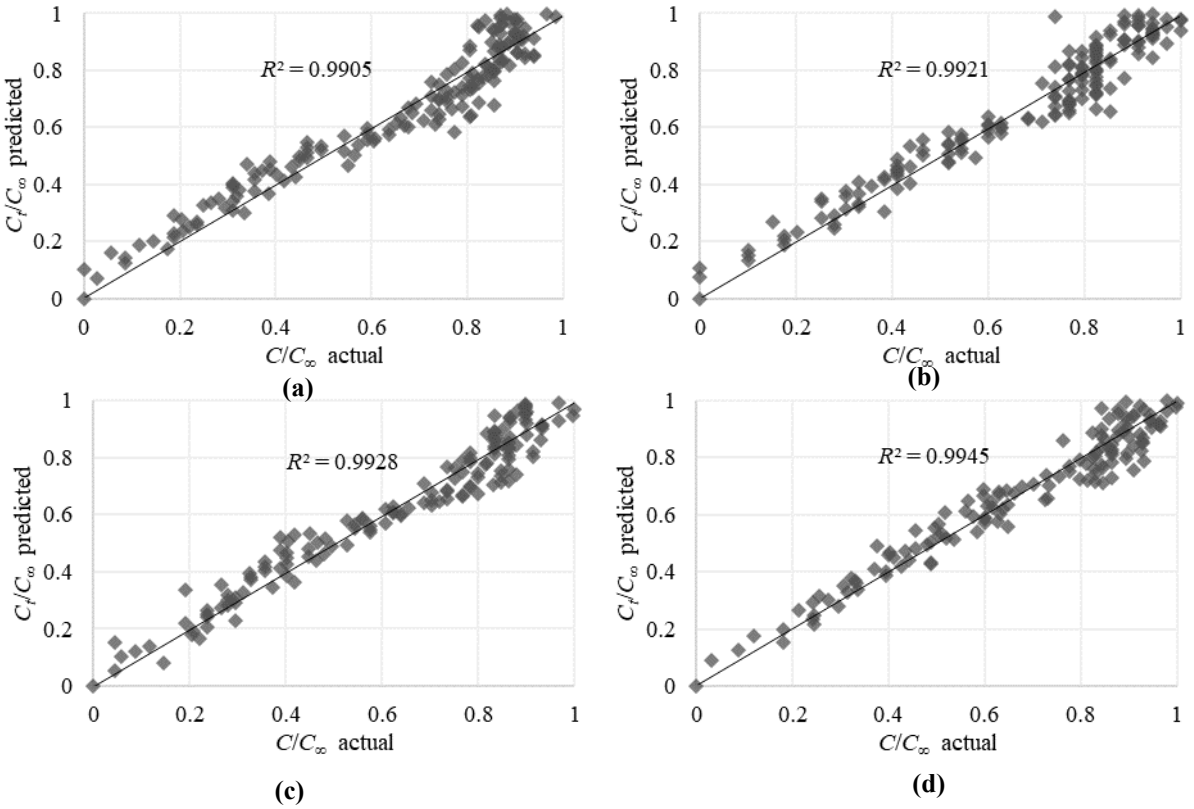

Figure 1. Predicted versus actual C_t/C_∞ values using Korsmeyer-Peppas model for (a) 0.25, (b) 0.50, (c) 0.75, and (d) 1.0 agar fractions at 1× loading.

Peppas-Sahlin. Table 3 shows the vitamin release data fit using the Peppas-Sahlin model to approximate the contribution of the Fickian and non-Fickian diffusion behavior in the release of vitamin B12 from the agar/carrageenan hydrogel. Following the study of Mircioiu, et al. [6], since the hydrogel is a thin film with a twice diameter-to-thickness ($2D/L$) ratio of 105, a value of 0.5 for m of may be assumed, which implies that diffusion mechanism follows Fickian behavior (k_1) while any non-Fickian deviations shall be attributed to hydrogel relaxation (k_2).

The obtained data show that k_1 is greater than k_2, implying that Fickian diffusion is the dominant release mechanism. These findings for the Peppas-Sahlin model parameters are somewhat consistent with the analysis of the release kinetics using the Korsmeyer-Peppas model, but with non-Fickian behavior now being accounted for by the model equation.

Table 3. Best fit parameters of release data modeled on the Peppas-Sahlin model at m = 0.5.

	1× Loading			1.5× Loading			2× Loading		
agar fraction	k_1	k_2	R^2	k_1	k_2	R^2	k_1	k_2	R^2
0.25	0.258	0.005	0.991	0.289	0	0.988	0.248	0.014	0.984
0.50	0.290	0.063	0.992	0.229	0.020	0.983	0.184	0.034	0.982
0.75	0.230	0.016	0.992	0.277	0.005	0.985	0.193	0.025	0.989
1.00	0.319	-0.008	0.995	0.222	0.016	0.987	0.142	0.045	0.977

One theory suggests that Fickian behavior is explained by the unbound water molecules present in micro and macrovoids of the rubbery agar/carrageenan hydrogel blend that are highly mobile and can easily penetrate the rubbery network [7, 8]. The unbound water serves as transport carrier for vitamin B12, which does not have ionizable groups and, therefore, has weak interactions with water and the 3D hydrogel matrix [9]. In effect, the mass transfer becomes primarily a concentration-driven mechanism but with the assistance of stress relaxation (which affects the size of pores and voids).

Fig. 2 shows the correlation between the predicted versus actual C_t/C_∞ values were generated to validate the Peppas-Sahlin model at m = 0.5. Based on the data plots, it can be concluded that the experimentally observed vitamin release behavior is in good agreement with the predictions made by the Peppas-Shalin model.

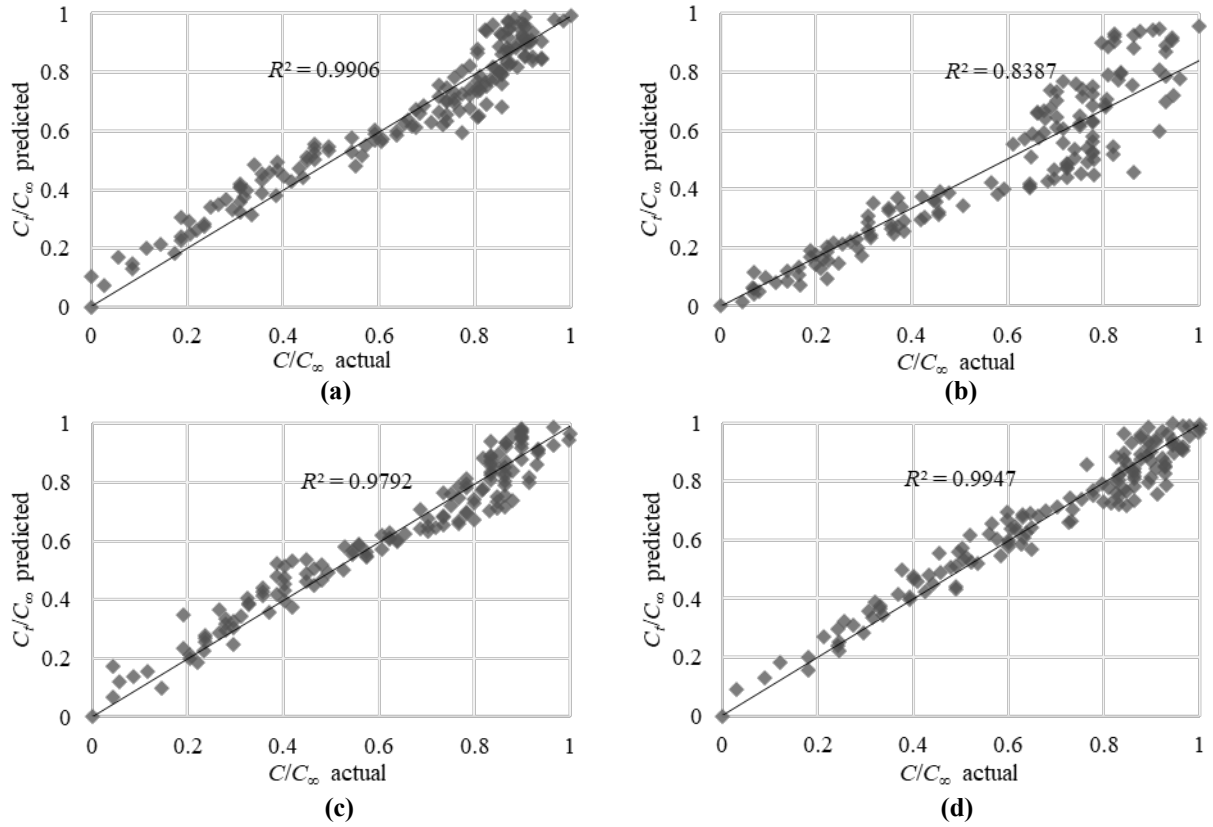

Figure 2. Predicted versus actual C_t/C_∞ values using Peppas-Sahlin model for (a) 0.25, (b) 0.50, (c) 0.75, and (d) 1.0 agar fractions at 1× loading.

Berens-Hopfenberg. Using the 13-hour vitamin B12 release data, parameters for the diffusivity constant per square thickness (D/L^2), fraction attributed to Fickian diffusion (x), and first-order relaxation constant (k_R) were determined. Tables 4-6 summarizes the obtained parameters, while Fig. 3 shows the best-fit plots for 1× loading. Since every hydrogel sample is approximated as a thin film/disk, the Berens-Hopfenberg model has been modified to fit the geometry.

Table 4. Best fit parameters of release data using the Berens-Hopfenberg model at 1× loading.

agar fraction	D/L^2	x (E10)	k_R (E03)	R^2
0.25	0.1247	1.83	3.3	0.995
0.50	0.0007	3.9E8	3.4	0.994
0.75	0.0595	18.1	3.4	0.993
1.00	0.0197	5.8E8	3.9	0.995

Table 5. Best fit parameters of release data using the Berens-Hopfenberg model at 1.5× loading.

agar fraction	D/L^2	x (E10)	k_R (E03)	R^2
0.25	0.0000	3.83	0.0039	0.989
0.50	0.0015	0.0	0.2215	0.990
0.75	0.0595	1.2E8	0.0038	0.987
1.00	0.0197	0	0.0032	0.991

Table 6. Best fit parameters of release data using the Berens-Hopfenberg model at 2× loading.

agar fraction	D/L^2	x (E-10)	k_R (E-03)	R^2
0.25	0.1247	0.0	3.7	0.987
0.50	0.0197	0.0	3.4	0.981
0.75	0.0595	8.6E7	3.0	0.989
1.00	0.0197	0.0	3.1	0.977

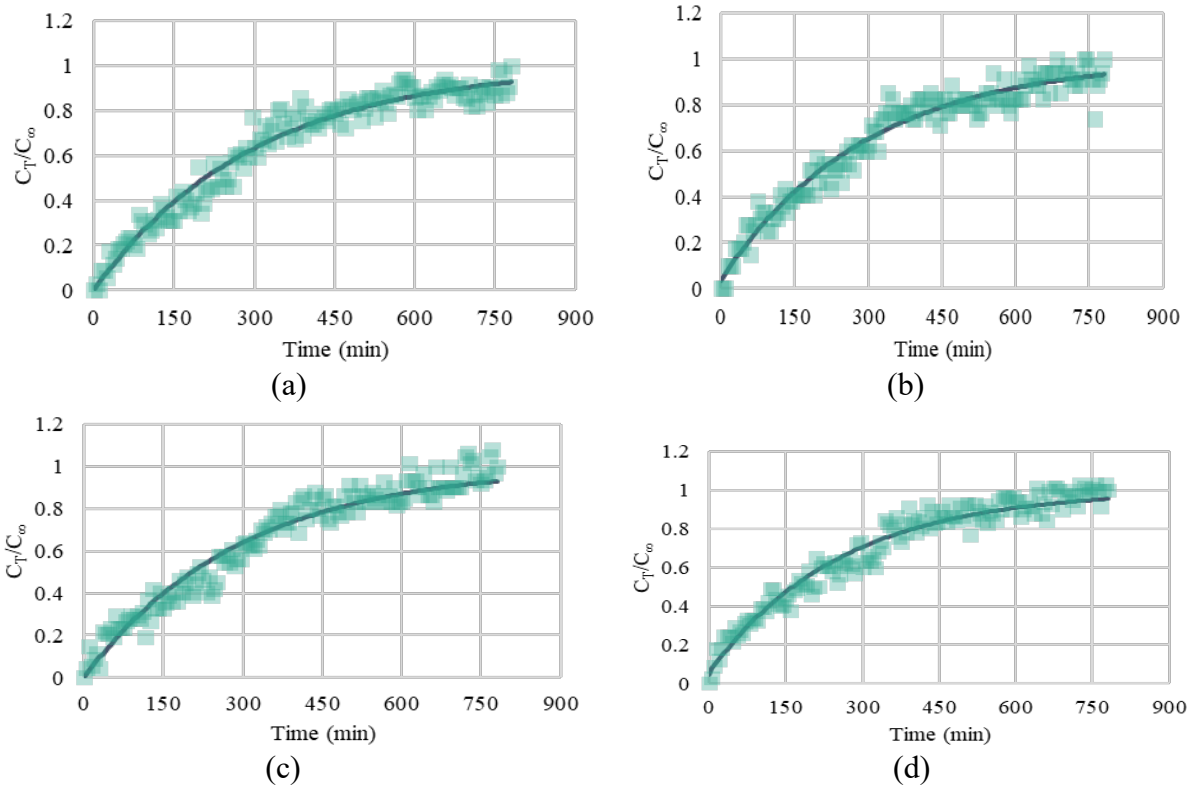

Fig. 3. C_t/C_∞ vs. time plots for Berens-Hopfenberg model at (a) 0.25,(b) 0.50, (c) 0.75, and (d) 1.0 agar fractions at 1x loading.

No discernible trend can be observed from the obtained for the parameters using the experimental data at different loading coefficients and agar mass fractions; however, one observable trend is the

relatively low values for the Fickian fraction for all loading coefficients and agar mass fractions. This modelling result from Berens-Hopfenberg curve fitting is somehow not in agreement with the those obtained from the Korsmeyer-Peppas and Peppas-Sahlin model predictions (since a low x value indicates that non-Fickian diffusion is the dominant mechanism for the vitamin B12 release). One possible reason for this deviation may be attributed to the derivation of the Berens-Hopfenberg model equation: unlike the Korsmeyer-Peppas and the Peppas-Sahlin equations, the Berens-Hopfenberg equation is based on the weighted sum of Fick's second law of diffusion and the first-order polymer relaxation model. Both differential equations are solved using boundary conditions for of an inward (i.e., absorptive) solute transport, where polymer chain disentanglement occurs with the influx of water into the hydrogel; thus, despite the observed high R^2 values (as shown in Fig. 3), the model used in this study may possibly not accurately describe the irreversible stress relaxation that is occurring with the outward transport and release of vitamin B12 from the hydrogel blend.

Summary

Vitamin B12 release for agar/κ-carrageenan hydrogel blend may be mathematically modeled using the Korsmeyer-Peppas and Peppas-Sahlin, while the Berens-Hopfenberg model may need to be further modified in order to accurately describe the physical system. Assuming stationary boundaries, the parameters for diffusivity and first-order polymer relaxation constant were determined. For the Korsmeyer-Peppas model, since the values for n are mostly greater than 0.5, the diffusion mechanism is described by anomalous non-Fickian diffusion, which involves both diffusion and relaxation. The Peppas-Sahlin model was used to approximate the individual contributions of these two types of diffusion. Curve fitting of the experimental data consistently suggests that Fickian diffusion is dominant. Modelling the release data onto the Berens-Hopfenberg equation resulted to contradictions with the findings of the two other models since the equation was designed to describe inward diffusion and not release; thus, revision and further validation are strongly recommended.

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