Investigation of the Effect of Swelling on the Diffusion Properties of Polyethylene Glycol Hydrogel for Wound Healing Applications

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***Abstract*— The present research work aims to comprehensively analyze the effect of swelling of polyethylene glycol (PEG) hydrogel on its diffusion properties for wound healing applications. For this study, a computational model based on three fundamental theories namely, equilibrium swelling theory, rubber elasticity theory and free volume theory has been implemented to determine the diffusion parameters of PEG hydrogel having a molecular weight of 20,000 g/mol. The diffusion of two plant metabolites with inherent antimicrobial activity namely, Cinnamaldehyde and Curcumin and two synthetic antimicrobial drugs namely, Amphotericin B and Vancomycin has been simulated. The results demonstrate that the proposed theoretical framework is capable of predicting the alterations occurring in the diffusion characteristics due to the swelling of PEG hydrogel. The diffusion coefficient of the solute is found to increase with the volumetric swelling ratio (Q_v), owing to the wider mesh size of the hydrogel matrix. The diffusion time of the therapeutic compounds is observed to be in the range of 2.40 - 8.30 h.**

***Clinical Relevance*— The modelling approach employed in this study will be clinically relevant for designing hydrogel drug delivery systems capable of accelerating the treatment of the infected wounds.**

I. Introduction

Wounds are regarded as a "silent epidemic" as they impose a significant burden on the healthcare systems throughout the globe. There are numerous factors such as the size, origin and level of contamination which largely influence the properties of a wound. After the occurrence of an injury, a multitude of systems gets activated at the site to clear the foreign material as well as to restore the normal structure and functioning of the skin. Wounds are highly susceptible to the development of biofilms wherein the microbial colonies are encased in a polysaccharide matrix and remain protected from the external threats such as the antibodies and antimicrobial therapies. The biofilms are known to greatly contribute to the chronicity of wounds due to the production of the destructive enzymes and toxins [1].

The indications of an infected wound are erythema, purulent drainage, tenderness, warmth and induration. Hence, early intervention and multifactorial treatment approach are necessary to efficiently eradicate the biofilms without causing any inconvenience to the patients. In the recent years, hydrogels have emerged as versatile platforms and displayed an exceptional potential in the treatment of the hard-to-heal wounds [2]. The insoluble hydrophilic groups in the hydrogels demonstrate a remarkable capacity to swell which is caused by the repulsion of the like charges.

The swellability depends on the balance between the forces that hinder the deformation of the crosslinked network and the osmosis phenomenon that leads to the absorption of the solvent [3]. Depending on the type of polymer, number of crosslinks and presence of ionic species, the swelling behaviour can be greatly modified. The swelling ratio quantifies the mass or volume gained by the hydrogels which aids in the determination of the architecture and associated properties of the matrix. In addition to serving as an effective barrier against the microorganisms, the hydrogels are capable of maintaining a high level of moisture in the wound bed and deliver the therapeutic agents with a precise temporal and spatial control. They can be designed to swell based on the changes in the wound conditions which enables them to absorb the exudates.

Designing hydrogels for controlled drug delivery applications is a challenging task which requires comprehensive knowledge of the structure-function relationships. The equilibrium swelling theory, rubber elasticity theory and free volume theory are the three fundamental theories which have been utilized to determine the structure of the swollen network, mechanical properties and diffusion characteristics respectively. According to the equilibrium swelling theory, the opposing forces in the hydrogel become balanced once the equilibrium swollen state is attained. As the hydrogels resemble the natural rubbers, their elastic behaviour can be exemplified by the classical concepts of rubber elasticity. The free volume theory assumes that the solute molecules are diffused only through the internal space available within the hydrogel matrix. The free volume-based model with mechanical relaxation has been predominantly employed to explore the phenomenon of solute diffusion in the swollen polymeric networks.

A comprehensive assessment of the effect of swelling on the diffusion properties of the hydrogels is limited in the literature hitherto. In this research work, a mathematical modelling framework based on three major theories namely equilibrium swelling theory, rubber elasticity theory and free volume theory has been utilized to record the structural and functional changes in the hydrogels due to swelling. PEG 20000 hydrogel has been considered as the matrix for the diffusion of the natural and synthetic antimicrobial agents as it is being commonly used for wound healing applications.

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II. MATERIALS AND METHODS

The equilibrium swelling theory facilitates the analysis of the structure of hydrogels which do not possess any ionic species. The molecular weight between two adjacent crosslinks ($\bar{M}_c$) can be determined using the following equation [4]:

$$\frac{1}{\bar{M}_{\mathrm{c}}} = \frac{2}{\bar{M}_{\mathrm{n}}} - \frac{(\bar{v}/V_1)\left[\ln\left(1 - v_{2,\mathrm{s}}\right) + v_{2,\mathrm{s}} + \chi_1 v_{2,\mathrm{s}}^2\right]}{v_{2,\mathrm{s}}^{1/3} - \frac{v_{2,\mathrm{s}}}{2}} \quad (1)$$

Here, $\bar{M}_n$ is the average molecular weight of the monomers, $\bar{v}$ is the specific volume of the polymer, V_1 is the molar volume of water, $\nu_{2,s}$ is the polymer volume fraction in the equilibrium swollen state and χ_1 is the polymer-solvent interaction parameter. $\nu_{2,s}$ can be expressed as the reciprocal of the volumetric swelling ratio of the hydrogel.

$$v_{2,s} = \frac{1}{Q_v} \quad (2)$$

Rubber elasticity refers to the capacity of the polymeric substances consisting of long molecular chains to sustain large deformations and completely recover upon the removal of the applied stresses. The rubber elasticity theory establishes a relationship between the network structure and elastic properties of the hydrogel as below [5]:

$$G = \frac{\rho RT}{\bar{M}_c}\left(1 - \frac{2\bar{M}_{\mathrm{c}}}{\bar{M}_n}\right)\left(\frac{v_{2,\mathrm{s}}}{v_{2,\mathrm{r}}}\right)^{1/3} \quad (3)$$

wherein G is the shear modulus of the hydrogel, ρ is the density of the polymer, R is the universal gas constant, T is the absolute temperature and $\nu_{2,r}$ is the polymer volume fraction in the relaxed state (after the crosslinking process, but before swelling).

In the case of isotropic materials, the relationship between the elastic constants is given as follows [6]:

$$E = 2G(1 + v) \quad (4)$$

Here, E is the Young's modulus and ν is the Poisson's ratio. In the equilibrium swollen state, the mechanical behaviour of the hydrogels is similar to that of the rubber-like materials due to which the Poisson's ratio is 0.5 [7].

Based on the free volume theory, it is assumed that an encapsulated solute molecule will diffuse through the crosslinked network only if its hydrodynamic radius (r_s) is smaller than the mesh size (ξ). The following equation is employed to compute the diffusivity (D) of the compound within the swollen hydrogel [8]:

$$\frac{D}{D_{\mathrm{o}}} = \left(1 - \frac{r_{\mathrm{s}}}{\xi}\right)\exp\left(-Y\left(\frac{v_{2,s}}{1 - v_{2,s}}\right)\right) \quad (5)$$

Here, D_0 denotes the diffusivity of the solute in water which can be calculated using the Stokes-Einstein equation. Y refers to the scale factor and is defined as the ratio of the critical volume that is required for the solute diffusion and the available free volume per molecule in the aqueous solution. It is usually approximated as 1 for correlation purposes [9].

The cumulative drug release fraction from the cylindrical hydrogel film of thickness L can be estimated from the below equation [10]:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2}\exp\left(\frac{-D(2n+1)^2\pi^2 t}{L^2}\right) \quad (6)$$

The diffusion period of the compounds is considered as the time at which the value of the cumulative drug release fraction equals unity.

Hagel et al. (2013) observed a significant variation in the volumetric swelling ratio of PEG 20000 hydrogel which depends on the polymer concentration. They had synthesized PEG hydrogels with three different concentrations of the precursor molecules namely, 10, 20 and 30% (v/v) which resulted in varied swelling behavior. The corresponding Q_v values were measured as 32.67 ± 0.73, 19.06 ± 0.41 and 13.20 ± 0.33 [11].

In this study, an attempt has been made to characterize the variation in the diffusion parameters of the PEG 20000 hydrogel due to swelling. The hydrogel is assumed to be present in its equilibrium swollen state. Two plant metabolites with intrinsic antimicrobial activity namely, Cinnamaldehyde (132.16 g/mol) and Curcumin (368.38 g/mol) and two synthetic antimicrobial drugs namely, Amphotericin B (924.08 g/mol) and Vancomycin (1449.2 g/mol) have been considered as the diffusants. There are negligible intermolecular forces of attraction between the uniformly distributed chemical species and polymeric chains. The fundamental mechanism governing the dynamic transport of the solute molecules through the crosslinked network of the hydrogel is diffusion. The complete theoretical framework has been implemented in MATLAB R2021b.

III. RESULTS AND DISCUSSION

The effect of the volumetric swelling ratio on the structural parameters of the PEG hydrogel has been presented in Fig. 1. The polymer volume fraction describes the quantity of fluid imbibed into the hydrogel based on the volume. It correlates to the probability of a diffusant to interact with the crosslinked network as it moves through the matrix. As the hydrogel swells, $\nu_{2,s}$ decreases owing to the increased penetration of the solvent molecules into the network structure. When the volumetric swelling ratio is increased from 5 to 10, $\nu_{2,s}$ steeply decreases from 0.2 to 0.1. It further reduces to 0.03, in response to the increment of Q_v to 35.

The molecular weight between crosslinks is noted to monotonically increase with the volumetric swelling ratio. The degree of variation of $\bar{M}_c$ is higher at lower values of Q_v. An enhancement in the $\bar{M}_c$ value increases the distance between the adjacent crosslinks which results in the formation of a hydrogel with a wider mesh size. ξ has been observed to linearly increase with the volumetric swelling ratio of the PEG 20000 hydrogel. As Q_v increases from 5 to 35, the value of ξ ranges from 41.81 Å to 203.25 Å. The expansion of the polymeric network will facilitate the diffusion of large-sized solute molecules without any hindrance.

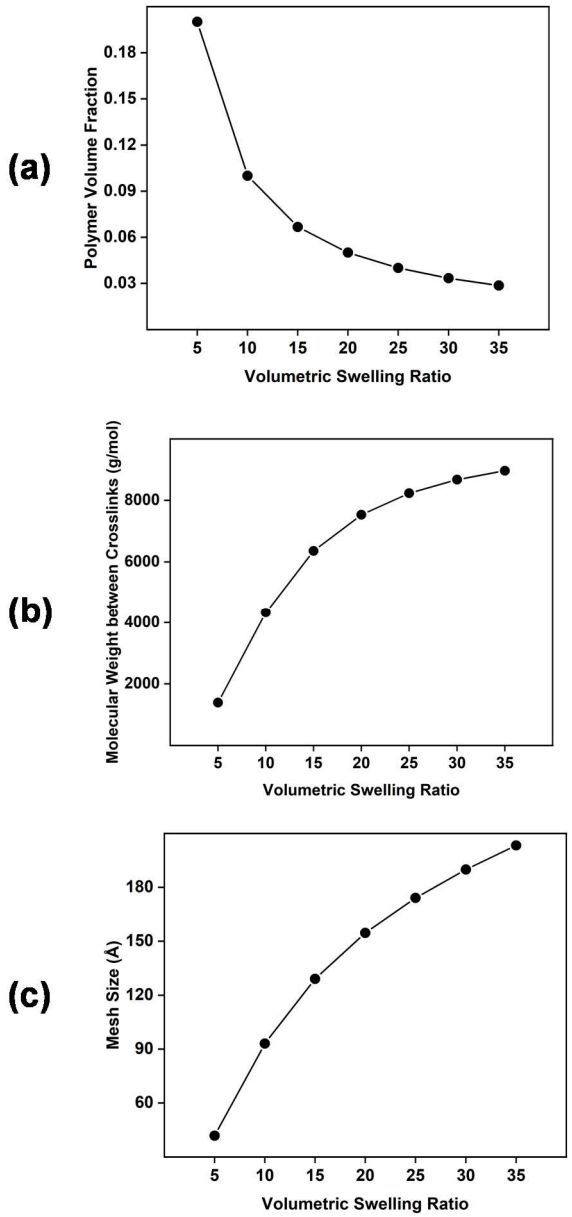

Figure 1. Variation of (a) Polymer Volume Fraction; (b) Molecular Weight between Crosslinks; (c) Mesh Size with the Volumetric Swelling Ratio of PEG Hydrogel

The degree of crosslinking plays an important role in determining the integrity, swellability and diffusion capability of the hydrogel network structure. The relationship between the mechanical properties and volumetric swelling ratio has been illustrated in Fig. 2. Higher the crosslinking density, lower is the flexibility of a hydrogel to swell. At lower Q_v values, fewer free spaces are available in the polymeric network for the absorbed solvent. Therefore, the crosslinking density decreases with an increase in the volumetric swelling ratio of the hydrogel.

The swollen hydrogels are found to be softer owing to lower crosslinking densities. The elastic behaviour of the hydrogels is usually characterized by the shear modulus which is proportional to the density of the network chains. Hence, the shear modulus and thereby the elastic modulus of the PEG hydrogel decrease due to the swelling phenomenon. The elastic modulus is found to be 3 times greater than the shear modulus of the PEG hydrogel at different Q_v values. E is observed to reduce from 3.65 MPa to 0.30 MPa, when the Q_v value increases from 5 to 35.

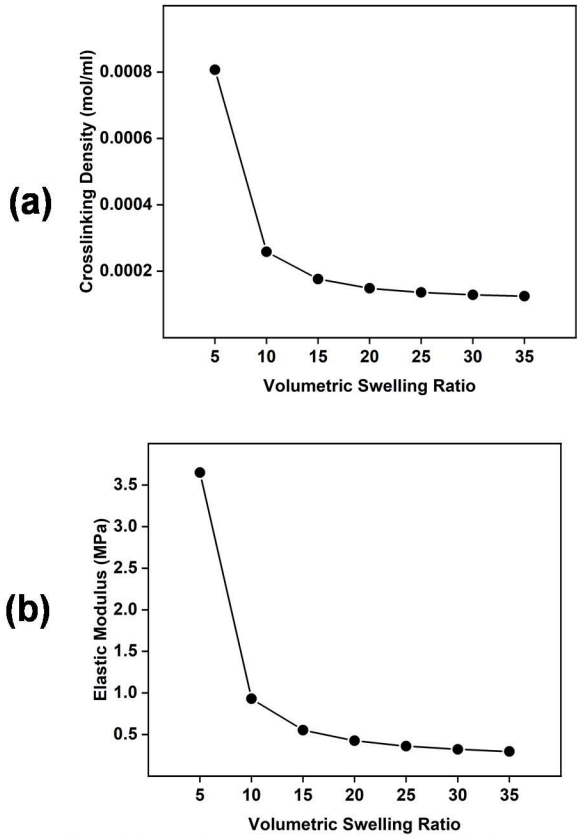

Figure 2. Effect of the Swelling Phenomenon on (a) Crosslinking Density; (b) Elastic Modulus

Fig. 3 depicts the variation in the kinetics associated with the diffusion of the antimicrobial agents with the volumetric swelling ratio of PEG 20000 hydrogel. The swelling ratio of the hydrogels is governed by the rate of water uptake into the matrix. Although there are several vital parameters influencing the release process, the solute size to mesh size determines the drug-specific diffusion characteristics in the hydrogel matrix. As the mesh size widens during swelling, the solute molecules encapsulated within the crosslinked network of the hydrogel can diffuse out at a faster rate. The diffusion coefficient of Cinnamaldehyde is greater than that of the other compounds as it possesses the smallest hydrodynamic radius. The D value increases from 4.96×10^{-6} cm^2/s to 6.79×10^{-6} cm^2/s, in response to the variation of the volumetric swelling ratio from 5 to 35.

The diffusivity ratios of the antimicrobial agents are also observed to increase with the Q_v of the PEG hydrogel. Vancomycin exhibits the least diffusivity ratio as a result of its larger molecular weight. As the diffusion coefficient increases with the volumetric swelling ratio, there is a reduction in the total duration required for the complete diffusion of the therapeutic formulations from PEG 20000 hydrogel. The diffusion time decreases from 3.3 h to 2.4 h for Cinnamaldehyde, 4.8 h to 3.4 h for Curcumin, 6.9 h to 4.6 h for Amphotericin B and 8.3 h to 5.3 h for Vancomycin.

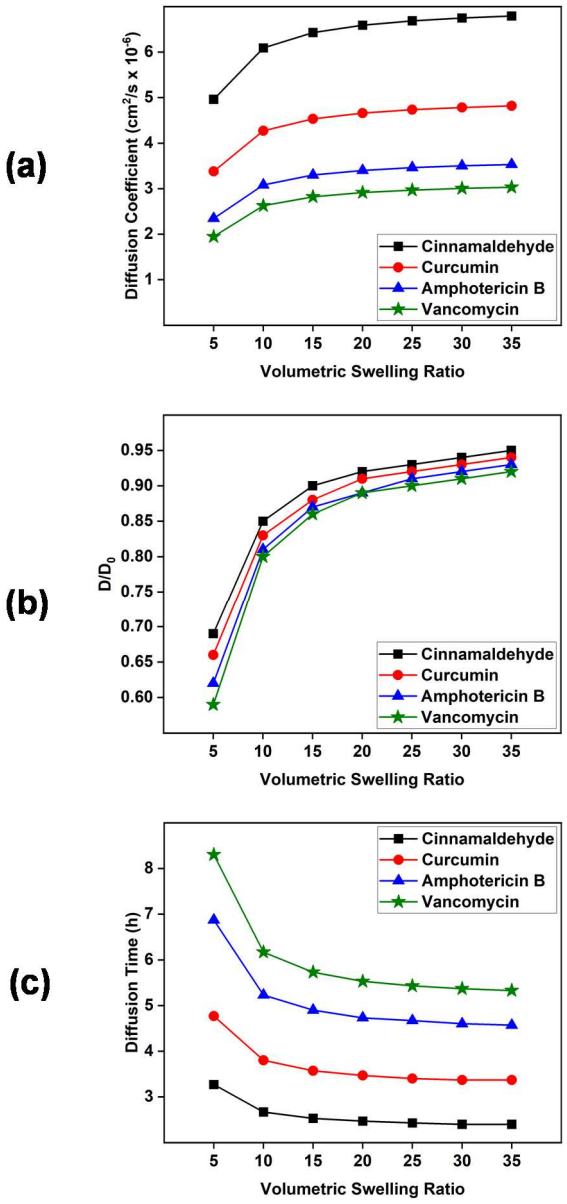

Figure 3. Effect of Increment of Q_v of PEG Hydrogel on (a) Diffusion Coefficient; (b) Diffusivity Ratio; (c) Diffusion Time

IV. Conclusion

Formation of a biofilm on the wound substantially increases the complexity of the wound care practices. Development of novel treatment strategies is urgently needed to effectively disrupt the biofilms without being toxic to the wound tissues. Hydrogels are preferred for wound healing applications due to their excellent biocompatibility, similarity of their structure to the extracellular matrix and versatility. As they are capable of imbibing and retaining large quantities of solvents in the swollen state, the hydrogels can absorb the fluids from a heavily exuding wound as well as donate the excess water molecules to the dry and devitalized tissues to promote the autolytic debridement. Hydrogels are also promising drug carriers as they offer the flexibility to tune their physicochemical properties in order to maximize the therapeutic outcomes.

This study attempts to establish a mathematical model based on the equilibrium swelling theory, rubber elasticity theory and free volume theory to systematically investigate the effect of swelling on the diffusion properties of PEG hydrogel. The diffusion of two natural and two synthetic wound antimicrobials through the PEG 20000 hydrogel matrix has been simulated. As Q_v increases, the polymer volume fraction decreases while the molecular weight between crosslinks and mesh size are found to increase. The swelling phenomenon is observed to make the hydrogel more flexible which is evident from the reduction of the crosslinking density and elastic modulus. As there is more space in the crosslinked structure, the encapsulated solute molecules diffuse out of the matrix at a faster rate.

The current theoretical framework is able to predict the changes occurring in the molecular structure and properties of the hydrogels in response to swelling. It appears that the present work will be helpful for designing hydrogel drug delivery systems to stimulate the tissue regeneration in different types of wounds. The validation of the computational model with the real-time experimental outcomes will be carried out in the future studies.

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