Development of a Smart System for the Design of Drug Encapsulated Hydrogel Dressings for Wound Healing Applications

Shib Sundar Banerjee, Pooja Vardhini Natesan, *Graduate Student Member, IEEE,* and Ramakrishnan Swaminathan, *Member, IEEE*

***Abstract*— The present research work attempts to develop a smart system for efficiently designing the drug encapsulated hydrogel dressings for wound healing applications. For this purpose, Deep Neural Network (DNN) based regression model has been implemented using Free Volume Theory (FVT) based predictions to determine the diffusion properties of PEG 20k hydrogel. The diffusion of small-molecule therapeutic compounds is modeled using this framework. The results demonstrate that the proposed theoretical framework is capable of predicting the optimized configuration of the hydrogel patch for a desired diffusion time. The prediction accuracy is high with R^2 greater than 0.9 for the considered drugs.**

***Clinical Relevance*— The modelling approach employed in this study will be clinically relevant for smart designing of hydrogel-based drug delivery systems.**

I. Introduction

Wound healing is a dynamic process which aids in restoring the barrier function of the skin. The interruption of this process results in chronic wounds that are considered as a major medical burden throughout the globe [1]. Hydrogel based wound care products are being increasingly utilized as an effective replacement for the traditional dressing materials. The encapsulated therapeutic formulations are released in a sustained manner. The structural properties of the matrix can be modulated to facilitate the controlled delivery of bioactive compounds of varying sizes.

Estimation of drug diffusivity from drug release experiments is extremely time-consuming. There is a renewed interest in the field of computational simulations which have been shown to accurately predict the diffusion characteristics of the drugs through hydrogel matrices. The integration of smart systems in the commercial production process helps manufacturers to optimize the configuration of hydrogel wound dressings as per the clinicians' specifications. Recent studies have used artificial neural network based framework for modelling and predicting the drug permeation of topical patches [2]. The diffusion of the chemical species through the crosslinked hydrogel matrix has been commonly modelled using the free volume theory (FVT) [3]. In this study, FVT based model has been employed to estimate the diffusion properties of the hydrogel patch. The synthetic data is provided as the input for the Deep Neural Network (DNN) model and the optimal thickness of the hydrogel patch is predicted.

II. Materials and Methods

A. Diffusion kinetics using FVT

In the present research work, PEG 20k hydrogel is considered to serve as the matrix for the diffusion of therapeutic compounds having molecular weights in a wide range of 0.1-1.2 kDa. The cylindrical hydrogel patch is assumed to be present in its equilibrium swollen state and the drug is homogeneously dispersed throughout the matrix.

FVT is utilized to compute the diffusivity (D) of the compound having hydrodynamic radius of r_s within the swollen hydrogel having mesh size of ξ as [4]:

$$\frac{D}{D_o} = \left(1 - \frac{r_s}{\xi}\right) \exp\left(-Y\left(\frac{v_{2,s}}{1 - v_{2,s}}\right)\right) \quad (1)$$

Here, D_0 denotes the diffusivity of the solute in water as per Stokes-Einstein equation. Y refers to the scale factor and it is usually approximated as 1 for correlation purposes [5].

The cumulative drug release fraction from the cylindrical hydrogel film of thickness L can be estimated as [6]:

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

The time taken for attaining 80% cumulative diffusion, $T_{80\%}$ is estimated using the above expression.

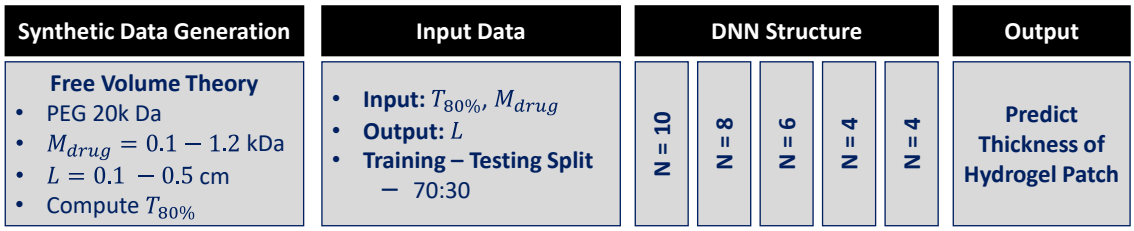

Figure 1. Process flow for proposed framework

All the authors are with the Non-Invasive Imaging and Diagnostics Laboratory, Department of Applied Mechanics and Biomedical Engineering, Indian Institute of Technology Madras, Chennai 600036, India (corresponding author e-mail: banerjeeshib2@gmail.com).

B. *DNN-based regression model*

A supervised learning scheme using DNN having five hidden layers has been implemented in this study. The network structure is adopted from Zhang et al. with the activation functions as ReLU for all the hidden layers [7]. The physics-driven model is utilized to compute $T_{80\%}$ values for the given range of molecular weights M_{drug} of the solute (0.1 to 1.2 kDa, n = 23) and hydrogel patch thickness (0.1 to 0.5 cm, n = 41). A total number of 943 input conditions have been simulated for synthetic data generation and training of the network. A split of 70%-30% is adopted to obtain the training and testing data. The prediction accuracy is calculated using the parameters, namely Mean Absolute Error (MAE) and Mean Absolute Percentage Error ($MAPE$) as the loss functions. The respective mathematical function is as follows:

$$MAE = \frac{1}{N}\sum_{i=1}^{N}|y_i - \hat{y}_i| \tag{3}$$

$$MAPE = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{y_i - \hat{y}_i}{y_i}\right| \tag{4}$$

where y_i and $\hat{y}_i$ are the actual and predicted values for the i'th input, $i = 1,2,\cdots,N$. The R-squared values are obtained to assess the prediction capability of the model. The gradient descent algorithm is adopted to minimize loss and error back propagation algorithm is also implemented. The pipeline of the proposed methodology is illustrated in Fig. 1.

III. RESULTS AND DISCUSSION

The implemented DNN has been utilized to predict the target thickness of the hydrogel patch for a given set of M_{drug} and $T_{80\%}$. The loss in progressing epochs for both training and testing data is depicted in Fig. 2 (a). The model is observed to converge quickly indicating a fast learning rate. The predicted values against the actual data are plotted in Fig. 2 (b). High prediction accuracy is noted as the R^2 is found to be 0.99 for both the training and testing data. Also, the respective *MAE* and *MAPE* values are reported in Table 1.

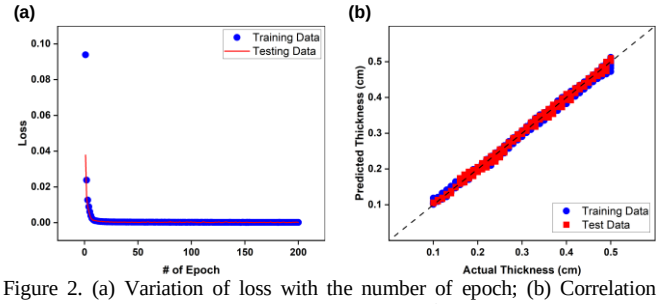

Figure 2. (a) Variation of loss with the number of epoch; (b) Correlation between predicted thickness and actual thickness of the hydrogel patch

Table 1. *MAE* and *MAPE* values

Metric	Training Data	Testing Data
MAE	0.0047	0.0050
MAPE	0.0175	0.0185

IV. CONCLUSION

In this study, a neural network based regression model has been developed to predict the optimal thickness of the hydrogel patch for a given drug and a desired diffusion time. For this purpose, a regression DNN has been implemented and validated against the synthetic data for the small molecule range (0.1-1.2 kDa) and the hydrogel patch consisting of PEG 20k. The results show that the present pipeline can be effectively utilized for the prediction of the optimal thickness of the hydrogel patch for a target diffusion time. The prediction accuracy is high with the R^2 value greater than 0.90. The current theoretical framework is able to predict the optimized geometrical configuration of the hydrogel wound dressings. It seems that the present approach can be utilized to design a smart fabrication system for tuning the structural features of the hydrogel patch depending upon the clinical requirements.

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REFERENCES

[1] X. Deng, M. Gould, and M. A. Ali, "A review of current advancements for wound healing: Biomaterial applications and medical devices," *J. Biomed. Mater. Res. Part B: App. Biomater.*, vol. 110, no. 11, pp. 2542-2573, 2022.

[2] S. Lefnaoui, S. Rebouh, M. Bouhedda, and M. M. Yahoum, "Artificial neural network for modeling formulation and drug permeation of topical patches containing diclofenac sodium," *Drug Del. Trans. Res.*, vol. 10, no. 1, pp. 168-184, 2020.

[3] K. O'Donnell, A. Boyd, and B. J. Meenan, "Controlling fluid diffusion and release through mixed-molecular-weight poly(ethylene) glycol diacrylate (PEGDA) hydrogels," *Mater*., vol. 12, no. 3381, pp. 1-14, 2019.

[4] P. V. Natesan, S. S. Banerjee, A. Arunachalakasi, and R. Swaminathan, "Analysis of diffusion of plant metabolites from polyethylene glycol hydrogels using free volume theory," *Proc. Inst. Mech. Eng. Part H: J. Eng. Med.*, no. 9544119231162772, pp. 1-10, 2023.

[5] L. M. Weber, C. G. Lopez, and K. S. Anseth, "Effects of PEG hydrogel crosslinking density on protein diffusion and encapsulated islet survival and function," *J. Biomed. Mater. Res. Part A*, vol. 90A, no. 3, pp. 720-729, 2008.

[6] C. C. Lin, and A. T. Metters, "Hydrogels in controlled release formulations: Network design and mathematical modeling," *Adv. Drug Del. Rev.*, vol. 58, no. 12-13, pp. 1379-1408, 2006.

[7] X. C. Zhang, J. G. Gong, and F. Z. Xuan, "A physics-informed neural network for creep-fatigue life prediction of components at elevated temperatures," *Eng. Frac. Mech.*, vol. 258, no. 108130, pp. 1-13, 2021.