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Ability of chromatographic mass balance to predict solute diffusivity in drug delivery systems

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Abstract

The ability to predict the drug diffusion coefficient within hydrogel-based drug delivery devices has a pivotal role in the design of these materials. In the last years, many mathematical models have been developed, but they often rely on fitted parameters with a consequent limitation in terms of prediction. Indeed, they are mainly centered on the pure Fickian diffusion together with degradation and swelling contributions. However, especially with a drug concentration typical of pharmacological treatments, several other mechanisms such as drug–polymer and drug–drug interactions cannot be neglected. In this work, we checked the ability of a simple mathematical model to estimate diffusion coefficients of drugs loaded within hydrogel considered as a chromatographic stationary phase. Mathematical modeling satisfactorily matched with different sets of literature data proving that our assumptions are able to describe the key phenomena governing the device's behavior.

KEYWORDS

adsorption/liquid, chromatography, diffusion (in polymers), drug release, mathematical modeling

1 | INTRODUCTION

It is worldwide known that the possibility to control and sustain the release of drugs in the target tissue has represented a promising strategy for almost 50 years now.[1-3] Briefly, following this strategy it is possible to avoid risks due to overdosing, together with the inefficacy of underdosing, in order to maintain drug levels within a therapeutic range with a consequent lower amount of drug needed.[4-6] In addition, the smart possibility to control the release of molecules through a device reduces the risks linked to surgery or multiple treatments.[7-9] Taking advantage of this technology, many products have been developed and are already on the market or used in clinical trials.[2,10] Among such products, hydrogels hold great promises for many biomedical applications. Moreover, significant progress has been made in designing, synthesizing, and using these materials in different districts and diseases.[11-15] Thanks to their high flexibility and biocompatibility, they represent an ideal hydrophilic three-dimensional network capable of carrying drugs, nanoparticles and cells.[16-18] Hence, to improve the delivery performance of hydrogels, a deep understanding of the solute diffusion in gel matrices is pivotal.[19,20] An examination of the state of the art provides both experimental studies and phenomenological theories related to the diffusion mechanism of molecules from hydrophilic macromolecular 3D networks.[21-23] These theoretical descriptions can be divided into three main categories: (a) free-volume-based theories, where a solute diffusion in pure liquids was extended to polymeric systems; (b) hydrodynamic theories, that assumes the enhancement of frictional drag on the solute by slowing down the fluid flow in the proximity of polymeric chains; and (c) obstruction theories, where polymer chains are described as an almost impenetrable network that increases the effective path length of diffusive transport.[24-26] Unfortunately these three theories are not able to cover all the possibilities, mainly due to the fact that they consider only the role of pure-Fickian diffusion within the 3D polymeric network.[21,23]

In the last years, many research groups have started to consider also other mechanisms just as important to predict mass diffusivities within hydrogels.[26,27]

Hadjiev and coworkers considered the ability of the obstruction-scaling model to provide reasonable estimates of solute diffusion coefficients within hydrogels, as well as the assumption that a hydrogel can be represented as an entangled polymer solution of an equivalent concentration.[26] Liu and coworkers considered the importance of drug–polymer interactions described with local equilibrium and Henry's law.[27] Kotsmar et al. quantified the mesh size and determined how gel matrices interact with solutes.[28] Rossi and coworkers considered the parallelism between hydrogels for drug delivery and chromatography. For the first time they modeled the release of small steric hindrance drugs starting from chromatographic mass balance.[29,30] The main difference, between these two disciplines that seem to be too far each other, resides in the fact that in drug delivery it is possible to neglect convection (assumption of hydrogels with small porosity and without forced flow conditions) and consider only diffusion in term of mass transport.[31,32] Points in common are several and schematized in Figure 1. Indeed, in both systems hydrogel matrices can work as a stationary phase. They can be loaded with solute molecules diffused within the matrix interacting and adsorbing it (solute–polymer interaction) and interacting between them (solute–solute interactions). Accordingly, the aim of this study is to develop a mathematical model to predict drug diffusivity though hydrogels: such model should be simple with respect to numerical solution (thus avoiding computational expensive simulations, as it occurs with FEM); at the same time, though, it should be able to take into account all fundamental phenomena that influence the final behavior.

Several systems from literature were analyzed to prove model reliability and hypothesis coherence by comparing simulation results with experimental data.[27,28,33-35] This represents the validation with literature data of the joint between chromatography and drug delivery that could pave the way for a better design of these medical devices.

2 | MODEL DEVELOPMENT

This work presents a model for the prediction of solute diffusivity in the case of: (a) hydrogels with nanopores (convection neglectable); (b) low steric hindrance hydrophilic drugs typical of corticosteroids and anti-inflammatory drugs; (c) characteristic time of release mechanism shorter than the swelling and degradation of the polymeric network. Therefore, being the drug hydrodynamic radius smaller than the mean mesh size, drug molecules are not physically entrapped and so the motion should be driven only by the Fickian diffusion. The key role of adsorption (drug–polymer interactions) and drug aggregation (drug–drug interactions) proposed in previous work is here validated with literature data. In Figure 2, the two cases of drugs with no-tendency to aggregate (*nonaggregative drugs*) or to form dimers or trimers (*aggregative drugs*) are schematized.

2.1 | Mathematical model for nonaggregative drugs

In Figure 2, the solid lines represent the hydrogel matrix, the black circles represent the drug molecules adsorbed onto the network backbone, and the red circles represent drug molecules free to move within the network. As mentioned in the introduction, to estimate

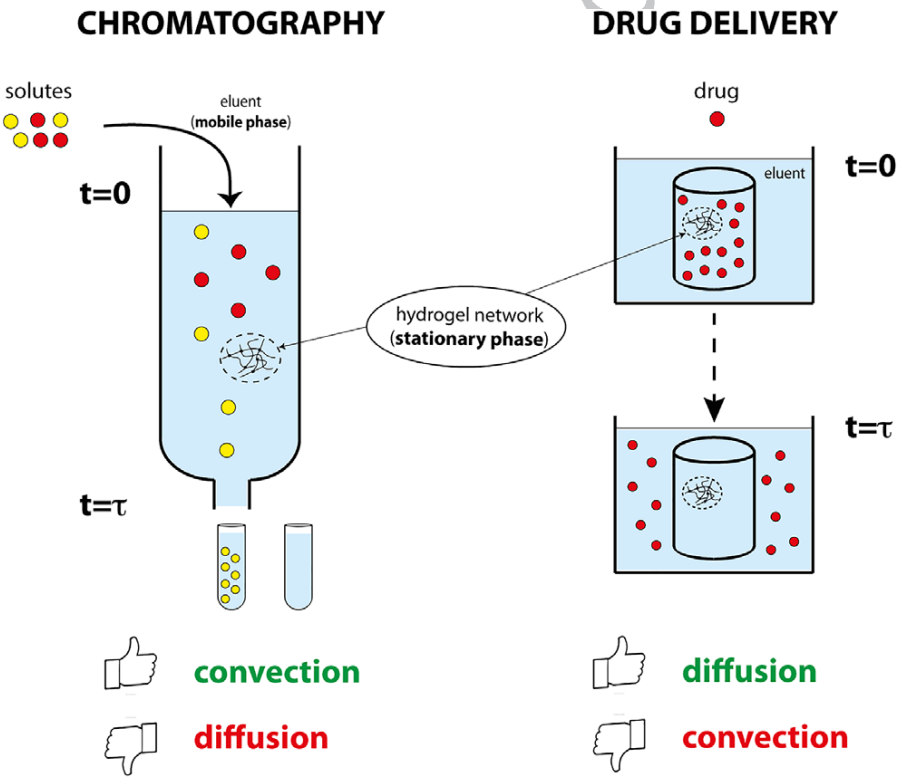

FIGURE 1 Schematic comparison between chromatography and drug delivery: stationary phase (hydrogels) and mobile phase (eluent) [Color figure can be viewed at wileyonlinelibrary.com]

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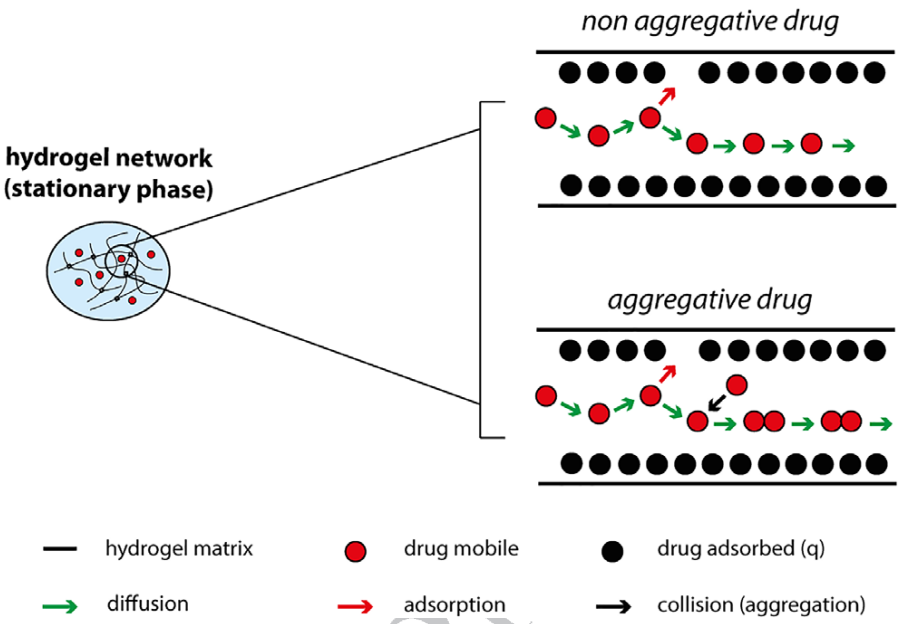

FIGURE 2 Pictorial representation of partitioning models in the case of drugs that can create oligomers (aggregative drug) or cannot (nonaggregative drug) [Color figure can be viewed at wileyonlinelibrary.com]

diffusivity this study started from the mass balance commonly used in chromatography:

$$\varepsilon \cdot D_{water} \cdot \frac{\partial^2 C_G}{\partial x^2} - u \cdot \frac{\partial C_G}{\partial x} = \varepsilon \cdot \frac{\partial C_G}{\partial t} + (1-\varepsilon) \cdot \frac{\partial q}{\partial t} \quad (1)$$

where ε is the gel porosity, C_G is the drug concentration within the hydrogel, q is the drug adsorbed and u is the superficial velocity of chromatographic columns, D_{water} is the diffusivity of the specie in water environment. Generally, in chromatography the first term that takes into account the diffusion mechanism is neglected. Here, its contribution is considered, while the second one is not considered because, as mentioned, there is no presence of pressure that induces a flow rate typical of analytes.

Following mathematics published by our group[30,36] we can obtain gel diffusivity (D_{gel}) as:

$$D_{gel} = \frac{\varepsilon \cdot D_{water}}{\left(\varepsilon + (1-\varepsilon) \cdot \frac{q^{\infty} \cdot K}{\Delta^2}\right)} \quad (2)$$

where D_{gel} is the diffusivity of the specie in gel environment and $\Delta = 1 + K \cdot C_G$.

So the diffusivity of drug molecules in gel environment depends on:

1. motion in release environment (D_{water});
2. hydrogel structural property (ε);
3. affinity between drug molecules and polymeric network (K);
4. saturation of hydrogel adsorbing sites ($q\infty$)
5. drug concentration (contained in Δ).

To understand the last contribution, that is counterintuitive, we should imagine that drug molecules are firstly interacting and adsorbed in the pores (red arrows in Figure 2) present within the gel until saturation of these adsorbing sites. Then, increasing drug concentration, no more adsorbing sites are available and transport occur by mass diffusion (green arrows in Figure 2) driven by concentration gradient present between the inner part of the hydrogel and the release environment.

2.2 | Mathematical model for aggregative drugs

In previous works we hypothesized that the ability of drug molecules to aggregate in dimers and trimers influences their behavior in term of drug delivery from hydrogel and it is different respect to what is happening in aqueous solutions.[37] Schematization present in Figure 2 represents the main phenomena: respect to the previous case (nonaggregative drug) the main difference is that here also the role of aggregation should be taken into account. In particular hydrogel network sequestrate drug monomers (adsorbing into the pores) that are not still available for aggregation. Consequently, in gel matrices dimers and trimers concentrations are minor than in water.

The drug total concentration is equal to:

$$C_{tot} = C_M + 2C_D + \frac{1-\varepsilon}{\varepsilon} \frac{q^{\infty} \cdot K \cdot C_M}{1 + K \cdot C_M} \quad (3)$$

where C_M is monomer concentration, C_D is dimer concentration and C_{tot} the total drug present, D_M is monomer diffusivity, D_D is dimer diffusivity.

Consequently, Equation (2) can be rewritten as:

$$D_{gel} = \frac{\varepsilon}{\left(\varepsilon + (1-\varepsilon) \cdot \frac{q^{\infty} \cdot K}{\Delta^2}\right)} \cdot \left(\frac{C_M}{C_{tot}} \cdot D_M + \frac{C_D}{C_{tot}} \cdot D_D\right) \quad (4)$$

Here the diffusivity of drug molecules in gel environment depends on points 1–5 described above and also on the tendency of drug molecules have to aggregate (black arrows in Figure 2) or not.

3 | RESULTS AND DISCUSSION

The wide spectrum of published experimental data addressed in this study is the following:

- 2-Hydroxyethyl methacrylate/methacrylic acid (HEMA/MAA) copolymer hydrogels with varying HEMA:MAA ratios (100:0, 99:1, 70:30, and 0:100) loaded with theophylline, acetazolamide, sodium fluorescein and riboflavin[27] (fig. 3).
- Poly-hydroxyethyl methacrylate/poly-vinylpyrrolidone hydrogel (98:2), HEMA/PVP loaded with chlorhexidine, levofloxacin and diclofenac[35] (fig. 4).
- 3-Tris(trimethylsilyloxy)silylpropyl-2-methylprop-2-enoate/N-vinylpyrrolidone/2-hydroxyethyl methacrylate (40:40:20), TRIS/NVP/HEMA loaded with chlorhexidine, levofloxacin and diclofenac[35] (fig. 5).
- Polymer 47K (Protein Polymer Technologies, San Diego, CA): a silk–elastin like protein-based (SELP) block copolymer with an amino acid sequence motifs loaded with theophylline and vitamin B12[33] (figs. 6 and 7).

In the first case examined,[27] the authors investigated the molecular diffusion coefficients of four prototypical drugs in soft-contact lens material hydrogels of varying copolymer composition and aqueous pH using two-photon fluorescence confocal microscopy and UV/Vis-absorption spectrophotometry. The four molecules (drugs and drug mimetics) tested were: riboflavin, sodium fluorescein, acetazolamide, and theophylline. The hydrogels studied by Liu and coworkers were based on copolymers of HEMA and MAA. To study the contribution of the extent of the solute adsorption, the hydrogel copolymer composition was varied in HEMA:MAA weight ratios of 100:0, 99:1, 90:10, 70:30, and 0:100. Here, the authors considered the key role of adsorption, described by Langmuir isotherm and aggregation. Indeed, at the concentration studied, all four drugs tend to form dimers.[38-41]

The mathematical model applied and described in the previous section considers the following hypotheses: (a) drug molecules adsorbed onto the three-dimensional hydrogel network in the monomeric state. The adsorption step indeed reduces the contribution of any drug-aggregation phenomenon. As a consequence, at a low drug concentration, the most important phenomenon is adsorption within hydrogel pores, which reduces the amount of drug available for the formation of dimers; (b) as the amount of the drug is increased, the adsorption sites are then saturated and the drug can diffuse quicker, as in water; the diffusion is driven only by the concentration gradient. The rationale for this is based on the observation that the ratio between the mean gel-network mesh size and the mean drug hydrodynamic radius is extremely low-diffusant. Molecules are mobile inside the entangled hydrogel network, and thus, diffuse with a high free motion. Therefore, the adsorption mechanism is expected to play a dominant role at a low drug concentration, whereas its role is negligible for a higher drug concentration. Equation (4) was therefore used

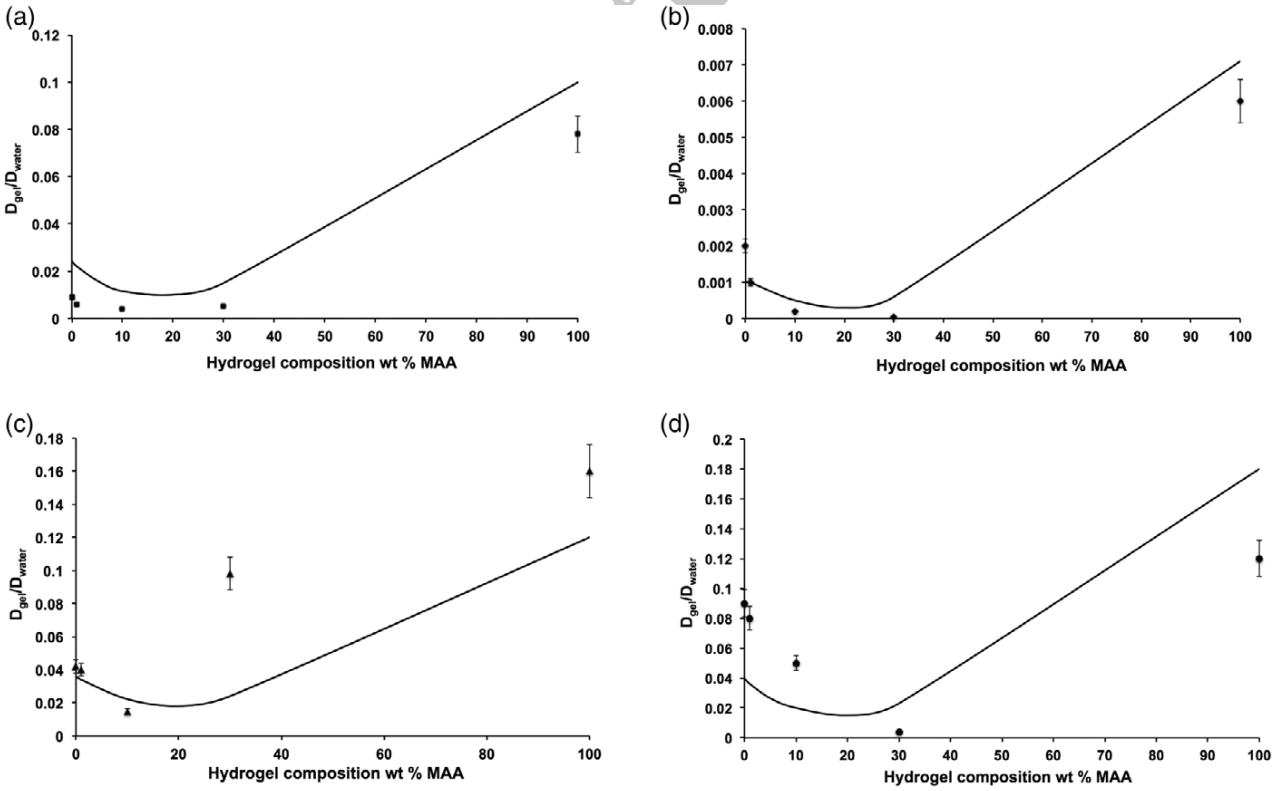

FIGURE 3 Comparison between the mathematical model (line) and the experimental results (dots) on drugs diffusivity from HEMA/MAA hydrogels: (a) riboflavin, (b) sodium fluorescein, (c) acetazolamide, and (d) theophylline. Experimental data obtained from Reference 27

to model the ratio between drug diffusivity in gel and drug diffusivity in water (D_{gel}/D_{water}) depending on the composition of the hydrogels (percentage of MAA). The comparison between the model trend and the experimental values obtained is visible in Figure 3. D_{gel}/D_{water} ratio initially declines with addition of MAA (0–10%), then after a further addition of MAA (10–100%) D_{gel}/D_{water} rises for all solutes. Despite similar solute sizes, relative diffusion coefficients vary by orders of magnitude in HEMA-containing hydrogels of identical water content. This observation is again ascribed to reduced diffusion rates arising from specific interactions with HEMA-copolymer chains. Here, however, relative diffusion coefficients also vary by orders of magnitude in 100% MAA hydrogels, suggesting solute-specific interactions with electrically neutral MAA-copolymer strands described by different adsorption mechanisms. A greater reduction of D_{gel}/D_{water} is expected to be exhibited by solutes of stronger specific interactions with MAA-copolymer. The model well matches quantitatively the observed experimental trends (Figure 3).

Pimenta and coworkers[35] measured the equilibrium partitioning and the diffusion coefficients of several ophthalmic drugs, namely, chlorhexidine, levofloxacin, and diclofenac in two contact lens materials: a pHEMA based hydrogel (HEMA/PVP) and a silicone based hydrogel (TRIS/NVP/HEMA). The diffusion coefficients were experimentally determined from the drug release profiles, from samples loaded in sink conditions, and as expected depend on their hydrodynamic radius. Here, the authors considered the key role of drug–polymer interaction (adsorption, by Langmuir isotherm) and drug–drug interactions (aggregation). Indeed, at the concentration studied, all three drugs tend to form dimers.[42-44]

Therefore, we used Equation (4) to model the ratio between drug diffusivity in gel and drug diffusivity in water (D_{gel}/D_{water}). The comparison between the model trend and the experimental values obtained is visible in Figure 4. As expected, D_{gel}/D_{water} ratio increases exponentially with the water fraction. Moreover, it is visibly clear that the model adequately reproduces the experimental trend and thus provides a good description of the synergic effects of both drug–polymer and drug–drug interactions.

Dinerman and coworkers[33] studied the role of the molecular size and volume fraction on drug diffusivity through silk-based hydrogels. They highlighted that the Fickian diffusion represented the main phenomenon that took place in the two-hydrogel families they studied (silk–elastin like protein polymer hydrogel 1.1 and silk–elastin like protein polymer hydrogel 3.2 and 4.2).

Here, the authors added the influence of drug–polymer interactions since no information was found on dimer formation. The results of the model (line) obtained with Equation (2) compared with the experimental results (points) and good matches between them are visible in Figure 5.

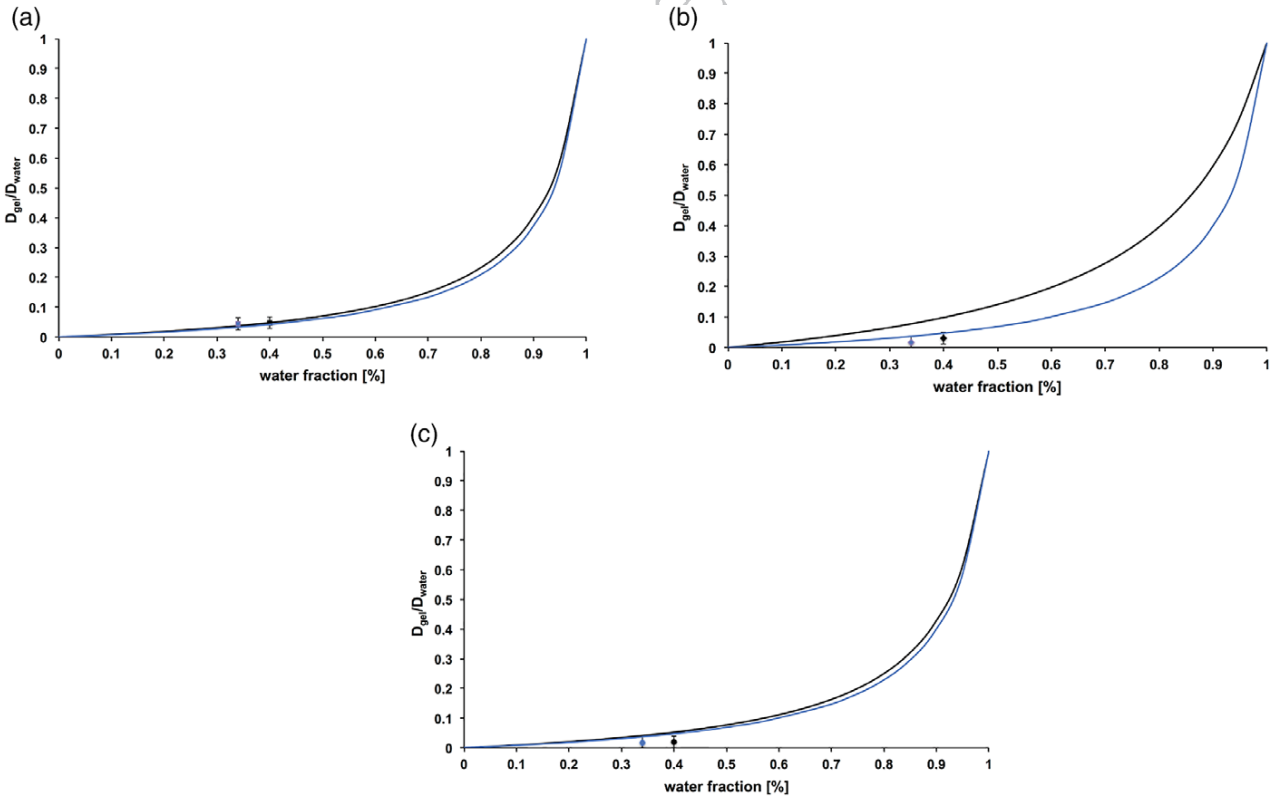

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FIGURE 4 Comparison between the mathematical model (line) and the experimental results (dots) on drugs diffusivity from HEMA/PVP hydrogels (black) and TRIS/NVP/HEMA hydrogels (blue): (a) chlorhexidine, (b) levofloxacin, and (c) diclofenac. Experimental data obtained from Reference 35 [Color figure can be viewed at wileyonlinelibrary.com]

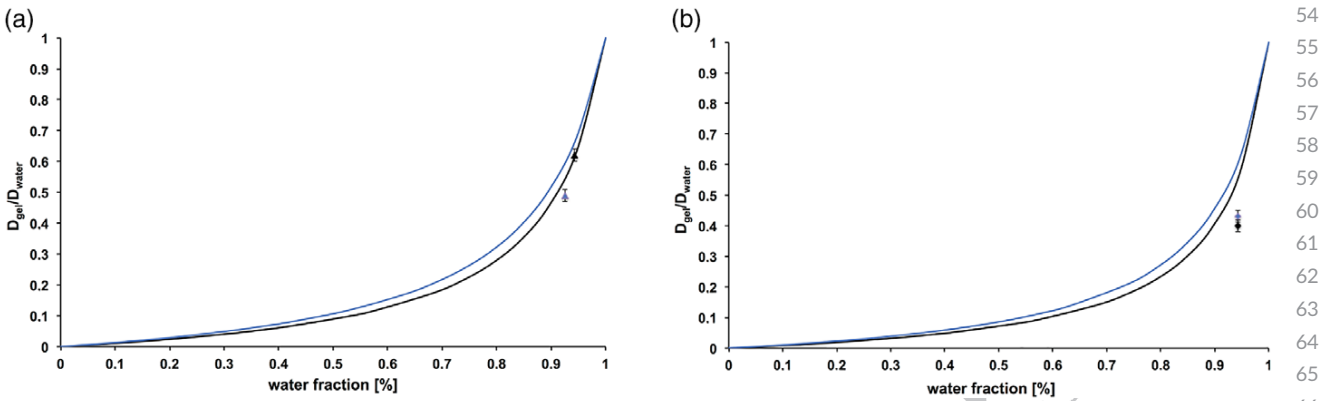

FIGURE 5 Comparison between the mathematical model (line) and the experimental results (dots) on drugs diffusivity from silk–elastin like protein polymer hydrogel 1.1 (black) and hydrogel 3.2 (blue): (a) theophylline and (b) vitamin B12. Experimental data obtained from Reference 33 [Color figure can be viewed at wileyonlinelibrary.com]

4 | CONCLUSIONS

To assess the predictive capability and model reliability of a previously derived mathematical model, and thus the validity of the needed hypothesis to formulate the equations starting from a chromatographic mass balance, this approach was validated against various and diverse sets of experimental data taken from literature. In particular, two mechanisms are very important and should be taken into account: the interaction between the mobile and the stationary phase (drug–polymer interactions) and between molecules of the mobile phase (drug–drug interactions). In all the cases examined, the simulation results exhibited a satisfactory quantitative match with the experimental data: this confirms the consistency of the hypothesis and the reliability of the chosen approach. A better match would be possible if adsorption parameters calculated experimentally could be used. These findings suggest that the model is capable of providing reasonable a priori predictions of the diffusion coefficient of a solute within hydrogel-based systems. Moreover, thanks to its simplicity and to the very low system requirements and CPU time—particularly with regard to FEM simulations—the authors' model allows to obtain immediate views of the system's behavior.

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NOTATION

C_G	drug concentration in gel, mg/mL
C_M	monomer concentration, mg/mL
C_D	dimer concentration, mg/mL
D_{gel}	drug diffusivity in hydrogel, m^2/s
D_M	monomer diffusivity in water, m^2/s
D_D	dimer diffusivity in water, m^2/s
D_{water}	drug diffusivity in water, m^2/s
K	Langmuir isotherm parameter
q	adsorbed concentration, mg/cm^3
q^∞	maximum adsorbed concentration, mg/cm^3

GREEK LETTERS

ε	porosity

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