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Conservative Exposure Predictions for Rapid Risk Assessment of Phase-Separated Additives in Medical Device Polymers

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Abstract—A novel approach for rapid risk assessment of targeted leachables in medical device polymers is proposed and validated. Risk evaluation involves understanding the potential of these additives to migrate out of the polymer, and comparing their exposure to a toxicological threshold value. In this study, we propose that a simple diffusive transport model can be used to provide conservative exposure estimates for phase separated color additives in device polymers. This model has been illustrated using a representative phthalocyanine color additive (manganese phthalocyanine, MnPC) and polymer (PEBAX 2533) system. Sorption experiments of MnPC into PEBAX were conducted in order to experimentally determine the diffusion coefficient, $D = (1.6 \pm 0.5) \times 10^{-11}$ cm^2/s, and matrix solubility limit, $C_s = 0.089$ wt.%, and model predicted exposure values were validated by extraction experiments. Exposure values for the color additive were compared to a toxicological threshold for a sample risk assessment. Results from this study indicate that a diffusion model-based approach to predict exposure has considerable potential for use as a rapid, screening-level tool to assess the risk of color additives and other small molecule additives in medical device polymers.

Keywords—Medical device, Risk assessment, Diffusion, PEBAX, Color additive.

INTRODUCTION

The biocompatibility of a medical device is an important performance criterion to assess if the device materials, or additives and impurities contained within, elicit adverse patient reactions that outweigh device benefits. Evaluation of biocompatibility based on the ISO 10993 standards often involves an analysis of the extractables/leachables from the device, and their comparison to a toxicological threshold for risk assessment.[22] However, evaluation of this risk using traditional extraction/chemical characterization and/or animal testing can be expensive and time-consuming. Developing and documenting alternative approaches for evaluating potential exposure to these additives over time may accelerate the evaluation of medical device biocompatibility. In this manuscript, such an approach is proposed for phase separated additives that exist as agglomerates dispersed in medical device polymers, such as many color additives.

Color additives receive special regulatory supervision in the United States as mandated by Title 21 of the Code of Federal Regulations (C.F.R.) Parts 70–82.[32] They are used in a wide range of medical devices for various purposes including labeling, coding for instructions, market appeal and advertising graphics.[32] An important class of color additives that have widespread use in various device applications are metal phthalocyanines, primarily due to their high chemical and thermal stability,[37] and their excellent fastness in plastics.[12] They are macrocyclic compounds that consist of an internal ring structure made up of 4 isoindole units, and a central complexed metal ion.[12] These pigments possess high molecular weights and low-solubility in various solvents.[17] Figure 1 shows the structures and molecular weights of three commonly used metal phthalocyanine color additives in polymeric medical devices—manganese phthalocyanine (MnPC,

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pale green colored), phthalocyanine blue (PC—blue, bright blue colored) and phthalocyanine green (PC—green, bright green colored).

Patient exposure to these color additives will depend largely on diffusion of the additive within the polymer matrix, which depends on several factors including temperature, additive size and shape, compatibility and solubility of the additive in the polymer, interactions that may occur between the polymer and external phase (solvent), *etc*. If the amount of additive released over time can be predicted using an appropriate diffusion based model, a risk assessment can be readily conducted by comparing the exposure estimate to acceptable threshold levels based on available toxicity data.[7] Exposure modeling approaches have been widely applied in the areas of food packaging[5,14] and environmental exposure,[36] where databases of material properties have been developed and used to provide informed diffusion-based exposure estimates. For example, the widely used Piringer model,[2] as well as other models that over-estimate the diffusion coefficient[20,25] have been successfully applied in regulatory compliance testing of food contact materials to provide "worst-case" leaching estimates. Although material considerations used in food packaging and polymeric medical devices are often very similar, data and application of such models for medical device relevant systems are limited. The goal of this work is to develop and expand such data, and thus provide guidance on application of simplified diffusion models to predict leaching of additives for rapid risk assessment of medical devices.

This exposure modeling approach has been recently illustrated for smaller color additive molecules (anthraquinone dyes) with relatively high solubility in solvents and polymer matrices.[8] In this study, we apply a similar approach to evaluate the migration of device additives that are typically used at concentrations above their matrix saturation limits such as pigments and fillers, which results in phase-separation, with color additive agglomerates dispersed within the polymer matrix.[3] While there is a rich history of modeling transport in multi-phase systems,[13] including methods proposed to estimate transport parameters,[15,23,27] we propose that the classical Higuchi equation can be employed as a conservative (i.e., worst-case) model for patient exposure to these additives.[21] The potential benefits of the Higuchi equation include more clinically relevant estimates of patient exposure to poorly soluble polymer additives, without significant added complexity.[28,34] In fact, as we will illustrate, the two transport parameters in the Higuchi equation can both be obtained from the same equilibrium sorption experiments.

The proposed exposure model approach is illustrated here using phthalocyanine color additives in medical devices that are intended to come into contact with biological fluids. The transport parameters (diffusion coefficient and matrix solubility limit) of a representative system consisting of a phthalocyanine color additive (MnPC) in PEBAX (poly(ether-block-amide) were experimentally determined using equilibrium sorption experiments. These transport parameters were validated with extraction/leaching studies from a PEBAX matrix into a sample solvent that mimics physiological conditions. Model predicted exposure values for MnPC were compared to a provisional tolerable exposure (pTE) value for MnPC to demonstrate a sample risk assessment.

MATERIALS AND METHODS

Transport Equations Governing Diffusion and Leaching

The goal of this work was to develop a conservative, yet clinically relevant model to estimate exposure of a color additive that is present as phase-separated agglomerates within the polymer. Previously, we showed that for color additives below the saturation limit of the polymer, assuming simple Fickian diffusion of the additive within the polymer matrix resulted in reasonable, conservative estimates of leaching.[8] How-

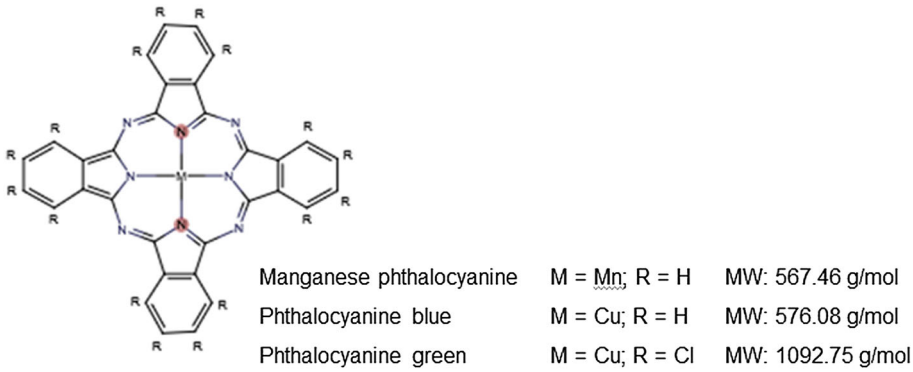

FIGURE 1. Chemical structure and molecular weights of phthalocyanine color additives.

ever, for poorly soluble additives that phase separate within the polymer matrix at concentrations typically used in medical device applications, this approach can severely overestimate the leaching rate, because the sparse matrix solubility limit of the additive is not considered in the model. Therefore, we propose that for phase-separated systems, the Higuchi equation can provide more clinically relevant exposure estimates.

The Higuchi equation requires the following assumptions,[34] (1) the initial additive concentration (C_i) $\gg$ matrix solubility limit (C_s), defined as the saturation limit of the additive in the polymer, or concentration at which the activity in the polymer is one, (2) the additive particles are much smaller than the component thickness, (3) the additive is homogeneously distributed, (4) the dissolution of the additive particles is rapid compared to the diffusion coefficient of the additive, D, in the matrix, (5) D is constant and independent of time, t, and position, x, within the component, (6) edge effects are negligible, (7) the polymer does not swell or degrade, and (8) perfect sink boundary conditions exist at the interface between the polymer component and release media. Under these assumptions, the classical Higuchi equation yields the mass released per unit area, M_t:

$$M_t = \sqrt{2DC_sC_it}. \tag{1}$$

We note that the above equation is valid for "short times," or when the total mass released is less than about 60% of the initial mass.

Leaching predicted by the Higuchi model was compared with our previous efforts for systems in which the color additive is present in concentrations far below saturation under similar assumptions,[8]

$$M_t = 2C_i\sqrt{Dt/\pi}. \tag{2}$$

Comparison of Eqs. (1) and (2), reveals the extent to which leaching may be overestimated if the previous model (Eq. (2)) is applied to phase separated systems under the specified assumptions. While both imply $M_t \propto \sqrt{(Dt)}$, the ratio of the right-hand sides of Eqs. (1) and (2) ($\sqrt{(C_s)}/\sqrt{(2C_i/\pi)}$) demonstrates that the prefactor of the Higuchi equation will be significantly less ($C_s \ll C_i$) than the previous model. While Eq. (2) does have the benefit of requiring only a single material parameter to be specified (D), this simple analysis suggests the extent that Eq. (2) will overestimate additive leaching can be substantial. Further, Eq. (1) requires only a single additional parameter to be determined, C_s, which can be established using the same sorption experiments used to measure D.

To establish the model transport parameters, we conducted sorption experiments for MnPC using neat PEBAX samples. Saturated solutions of MnPC were prepared by adding an excess of MnPC into PBS buffer solutions containing 20 wt.% Pluronic F87 at 55 °C for 24 h. Solutions were then cooled to 4 °C for >4 h followed by equilibrating at 37 °C for 24 h. Sorption experiments were carried out with neat PEBAX 2533 films (0.07 mm thick) and PEBAX 4033 tubing (0.127 mm thick). Samples were immersed in saturated MnPC solution for various times. The solution was incubated at 37 °C and stirred at 130 RPM to ensure adequate mixing. Polymer samples were withdrawn at various times, rinsed with distilled water and analyzed for MnPC concentration using ICP-MS. Matrix saturation of MnPC in PEBAX (C_s) was determined when equilibrium was achieved.

The uptake of MnPC into the polymer sample was analyzed in terms of C_i, the average concentration of MnPC within the sample at time t. In the analysis, we assume the neat polymer samples could be approximated as having planar geometry with thickness $2l$, contained no color additive at the beginning of the experiment, and were at all times in equilibrium with the saturated solution at the interfaces ($C(\pm l, t) = C_s$). Under these assumptions, the exact solution to Fick's second law of diffusion yields,[10]

$$C_t = 2C_s\left(\frac{Dt}{l^2}\right)^{1/2}\left[\pi^{-1/2} + 2\sum_{n=1}^{\infty}(-1)^n \mathrm{ierfc}\frac{nl}{\sqrt{Dt}}\right]. \tag{3a}$$

At short times when $C_t/C_s < 0.6$, the summation in Eq. (3a) is not significant, and the solution can be reduced to,[10]

$$C_t = \frac{2C_s}{l}\sqrt{\frac{Dt}{\pi}}. \tag{3b}$$

D was calculated from a linear regression of experimental C_t/C_s values to ($t_{0.5}\ l^{-1}$) from Eq. (3b). The uncertainty in D was calculated based on the 95% confidence limits obtained by regression.

MATERIALS

Poly(ether-block-amide) copolymers were chosen here as a model polymer system because they are a useful set of thermoplastic elastomers with good permeation, elasticity and toughness,[1] and are used widely in medical devices such as catheters and tubing.[24] PEBAX 2533 pellets (Arkema) with a composition of 80 wt.% poly(tetramethylene) oxide (PTMO) and 20 wt.% Nylon 12 were obtained from Fisher Scientific. This grade of PEBAX has a hardness of 25 (Shore D). Extruded medical grade catheter tubing (127 μm wall thickness) prepared from PEBAX 4033 pellets (40D hardness) were purchased from Apollo Medical

Extrusion Technologies (Sandy, UT). Manganese phthalocyanine (MnPC, CAS# 14325-24-7) was purchased as a pure dye powder (≤100%) from Sigma Aldrich. Phthalocyanine Blue (PC-blue, CAS# 147-14-8, 95% purity) was obtained from Acros Organics. Phthalocyanine Green (PC-green, CAS# 1328-53-6, ≥90% purity) was purchased from TCI America. Pluronic F87 non-ionic detergent was obtained from BASF.

Extruded Polymer Sample Preparation

Extruded PEBAX 2533 films were prepared using a DSM Xplore twin screw micro-compounder using the method described by Chandrasekar *et al.* (2017) with slight modifications. For colored PEBAX samples, the color additive mass was carefully weighed out based on the desired concentration in the final polymer sample and sprinkled over the neat PEBAX resin prior to addition to the feed hopper. After mixing for 12–15 min, the screw speed control was set to force control mode with a force setting of 400 N, and a maximum speed setting of 120 RPM. The polymer melt was cooled using an air-knife set to a flow rate of 35 L/min.

Aggregate Size Characterization

The macroscopic morphology of extruded PEBAX 2533 samples containing PC-green was evaluated by reflection-mode optical microscopy at 100× magnification (Hirox, Tokyo, Japan). The nano- and submicron-scale morphology of cryogenically ultramicrotomed sections of polymer samples were characterized by transmission electron microscopy (TEM). For cryogenic sectioning, the PEBAX film was first cut into a triangle shape (4 mm × 4 mm × 4 mm) and then placed into an ultramicrotome chuck. The sample was cooled to −140 °C for 30 min in the cryochamber of the ultramicrotome (Leica EM UC7) and pre-trimmed vertically by a diamond knife to obtain a flat block surface. The sample was then cut into ultrathin slices (80 nm). Sections were collected directly from the diamond knife surface using a loop with a saturated sucrose droplet and then deposited on a copper TEM grid (200 mesh, Ted Pella, Inc.). TEM imaging was performed on a Jeol JEM1400 TEM (Jeol USA), with an operating voltage of 80 kV.

Color Additive Quantification

The concentration of metal phthalocyanine color additives was determined using a Thermo X-Series II quadrupole inductively coupled plasma mass spectrometer (ICP-MS). Small sections (approximately 2–4 mg) were excised from the center of polymer samples containing metal phthalocyanine color additives. Samples were first digested with concentrated sulfuric acid (1 mL/mg polymer) for 24 h at room temperature, followed by dilution in 2% nitric acid solutions to suitable concentrations of color additive (between 0 and 100 ppb) before analysis.

The ICP-MS instrument was tuned with 1 ppb Tune A solution (Thermo Fisher) prior to analysis to meet the required performance standards. NIST standard solutions for copper (for PC-blue and PC-green) and manganese (for MnPC) were used as calibration standards. Standard solutions were run from 0 to 100 ng/mL concentration range in order to develop a calibration curve for each run. A 50 ng/mL internal standard solution (VHG, contains Bi, Ga, In, Sc, Tb, and Y) was introduced along with the respective samples through a T-connector to correct for signal drift and matrix effects. The concentration of metal ions detected were correlated back to color additive concentrations, and reported in units of mass of color additive per mass of polymer sample.

Model Validation

Leaching experiments were conducted from extruded PEBAX samples containing various phthalocyanine color additives into an extraction solvent that mimics physiological conditions to validate the diffusion model. The extraction solvent consisted of PBS buffer containing 20 wt.% Pluronic F87 maintained at 37 °C. Pluronic is a nonionic surfactant that was added to help disperse the phthalocyanine color additive in solution.[35] The extraction media was frequently replenished with fresh solvent to mimic a "perfect sink" environment in which the color additive concentration in the surrounding bulk fluid can be considered negligible. Samples were removed at various times, rinsed with distilled water, and the amount of color additive remaining in the polymer sample was determined using ICP-MS.

RESULTS

Sample Morphology

A representative reflection-mode optical micrograph of extruded PEBAX 2533 samples containing dilute concentrations of PC-green ($C_i = 0.11$ wt.%) is shown in Fig. 2a. The color additive is present in solution within the polymer (signified by the uniform green colored background), as well as phase-separated aggregates (signified by the presence of green colored occlusions against the background). A rapid qualitative analysis indicates that the color additive aggre-

gates are significantly smaller than 70 μm (scale bar in Fig. 2a), which is equivalent to the average thickness of our extruded polymer films. The nano-scale structure of the PEBAX/PC-green sample was evaluated by TEM of cryogenically ultramicrotomed thin sections, and a representative micrograph is shown in Fig. 2b. The darker regions represent the electron-dense color aggregates, with diameters ranging roughly from 50 to 350 nm. Since PC-green has similar polarity and chemical structure compared to the other phthalocyanines under study here, we anticipate a similar morphology to be present for samples made with the other phthalocyanines (PC-blue and MnPC) using our micro-compounding process. Hence the diffusion model assumption that requires the size of the additive to be smaller than the device dimensions is considered valid, and the model can be employed here to describe phthalocyanine color additive transport.

Determination of Transport Coefficients

The matrix solubility limit of MnPC in PEBAX 2533 (C_s) was determined experimentally by soaking neat PEBAX 2533 extruded samples into saturated solutions of MnPC for various times. Polymer samples were removed at various times and photographs of representative samples are shown in Fig. 3a. There is gradual uptake of the color additive into the polymer over time until saturation is reached. PEBAX 2533 samples equilibrated at the end of 20 weeks of soaking, and subsequent soaking periods did not increase the concentration of MnPC within the polymer (Fig. 3a). C_s was determined to be 0.089 wt.% at 37 °C. The matrix solubility limit of additives is an important parameter when considering the physical state (molecular vs. particulate) and migration potential of the additive from the polymer matrix. For example, quinizarin blue (an anthraquinone dye with molecular weight 329.35 g/mol) has a solubility of 0.3 wt.% in PEBAX 2533, which is significantly higher than that of MnPC. Phthalocyanine color additives with higher molecular weights (such as PC-blue and PC-green) are expected to possess even lower C_s values.[17]

The diffusion coefficient (D) of MnPC in PEBAX was obtained through sorption experiments of device-representative PEBAX 4033 tubing in saturated MnPC solutions at 37 °C. This grade of PEBAX has a composition of approximately 27.1 wt.% Nylon 12 and 70.4 wt.% PTMO,[33] and a hardness of 40 (Shore D). These samples are more rigid than extruded PEBAX 2533 films and do not stack or fold in solution, which can compromise accurate estimations of additive uptake kinetics. Color additive concentration in samples was analyzed as before using ICP-MS, and the concentration of MnPC over reduced time normalized to thickness of the samples ($t_{0.5}/l$) is shown in Fig. 3b. As evident from the figure, the uptake of MnPC within polymer samples is consistent with Fickian diffusion kinetics, and the diffusion coefficient was calculated by regression of the early portion of the sorption curve ($M_t/M_\infty < 0.6$) to Eq. (3b) to obtain $D = (1.3 \pm 0.1) \times 10^{-11}$ cm^2/s.

Diffusion of small molecules such as CO_2 and N_2 have been shown to be significantly affected by the fraction of crystalline impermeable regions within the PEBAX block copolymer. In order to verify the experimentally determined D of MnPC from device-representative PEBAX 4033 samples for our softer PEBAX grade, leaching experiments were conducted with extruded PEBAX 2533 films containing 2 wt.% MnPC into PBS buffer containing 20 wt.% Pluronic F87 at 37 °C. The amount of MnPC leached from the films over time is shown in Fig. 4. It is clear from $C_i > C_s$ that our polymer samples contain phase-separated color additives. The experimentally determined leaching data were found to be suitably described by the Higuchi model (Eq. (1)), and an effective diffusion coefficient was calculated from the regression to obtain $D_e = (1.6 \pm 0.5) \times 10^{-11}$ cm^2/s. This value is very close to D obtained from sorption experiments into

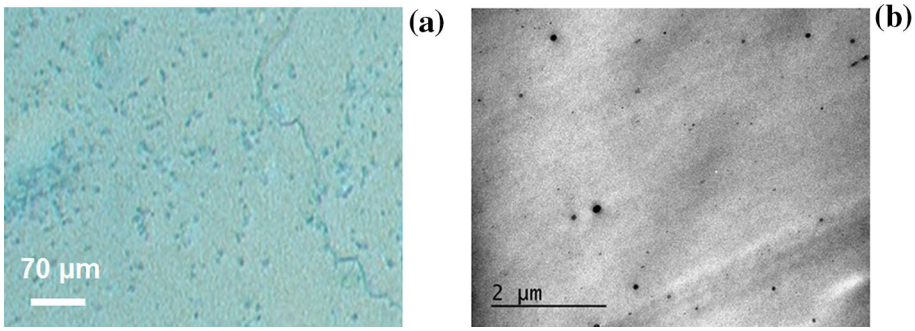

FIGURE 2. Representative micrographs of extruded PEBAX 2533 films containing PC-green (C_i = 0.11 wt.%) using (a) reflection-mode optical microscopy (100× magnification) and (b) transmission electron microscopy (TEM) of cryogenically ultramicrotomed sections.

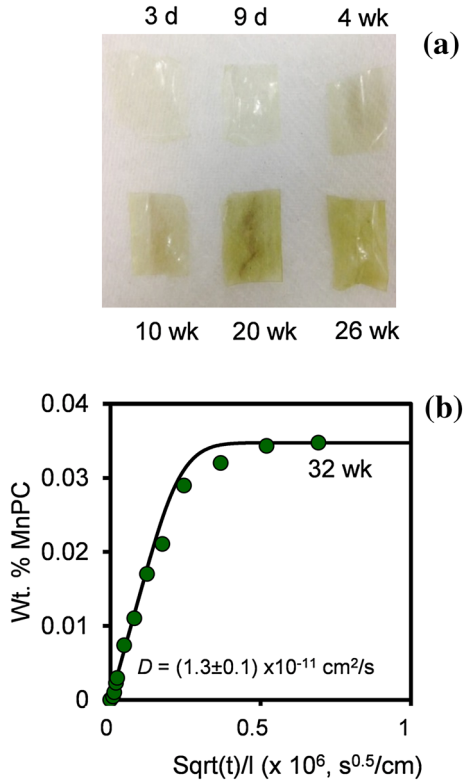

FIGURE 3. Transport coefficients of MnPC in PEBAX samples was determined by sorption experiments. (a) Representative photographs of PEBAX 2533 samples in saturated MnPC solution at various times to determine matrix solubility (C_s), and (b) measured MnPC concentration in device representative PEBAX 4033 samples soaked for various times in saturated MnPC solution at 37 °C (data points), and diffusion coefficient (D) estimated by fitting to Eq. (3) (line).

PEBAX 4033 samples, indicating that the difference in the fractions of Nylon 12 and PTMO between these two grades of PEBAX do not seem to have an effect on diffusion of MnPC, and similar other large molecular weight molecules (≥567 g/mol).

Our transport coefficients for MnPC correspond to values obtained for similar molecular weight diffusants in low-density polyethylene at 25 °C,[31] which is also a semi-crystalline polymer. In several cases, we note that obtaining accurate transport coefficients experimentally at physiological temperatures can be challenging. In the absence of experimentally available transport coefficients, computational methods such as molecular dynamics (MD) simulations can be employed to predict D of additives within polymer matrices.[16]

Model Validation

Transport coefficients obtained *via* sorption experiments were validated by comparing model predicted values to leaching data from extruded PEBAX 2533 samples containing 0.29 wt.% MnPC. We used an

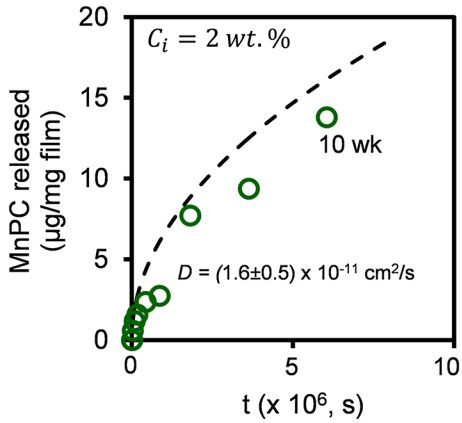

FIGURE 4. Leaching kinetics of MnPC from PEBAX 2533 films containing C_i = 2 wt.% MnPC into PBS buffer at 37 °C and estimation of diffusion coefficient from Eq. (3).

extraction media consisting of frequently replenished solutions of PBS buffer containing 20 wt.% Pluronic F87 at 37 °C as before. The amount of MnPC leached from the films increases monotonically with time as shown in Fig. 5. The data are compared to model predictions from both the Fick model (Eq. (3a) when $C_t/C_s \geq 0.6$ and Eq. (3b) when $C_t/C_s < 0.6$) and Higuchi model (Eq. (1) when $C_t/C_s < 0.6$, with average film surface area, $A = 7.05\ cm^2$), using the experimentally determined transport coefficients (D and C_s). Leaching kinetics were found to be over-predicted by the Fickian diffusion model particularly at higher leaching times ($t > 1$ day). Since C_i (0.29 wt.%) is significantly greater than C_s (0.089 wt.%) which indicates the presence of phase separated additive within the polymer, the data were compared to Higuchi model predictions using the D for MnPC obtained from Fig. 4. This is a less conservative model which in general, will result in lower exposure predictions than Eq. (3) because it accounts for the reduction in D caused by limited solubility. Leaching kinetics were found to be better described by the Higuchi model particularly at short times upto 10 days ($t < 24$ h is shown in the "1 day" data inset in Fig. 5).

In order to evaluate whether our exposure model can reliably predict leaching of metal phthalocyanines, leaching experiments were conducted with extruded PEBAX 2533 samples containing various initial MnPC concentrations. Extractions were carried out at 37 °C for 3 days into PBS buffer containing 20 wt.% Pluronic F87. As is evident from Fig. 6, as the color additive concentration in the polymer sample increased, the amount of MnPC leached also increased. The extraction data were compared to the Fickian transport model as well as the Higuchi model using the experimentally determined transport coefficients for MnPC in PEBAX. Higuchi model predictions were very close

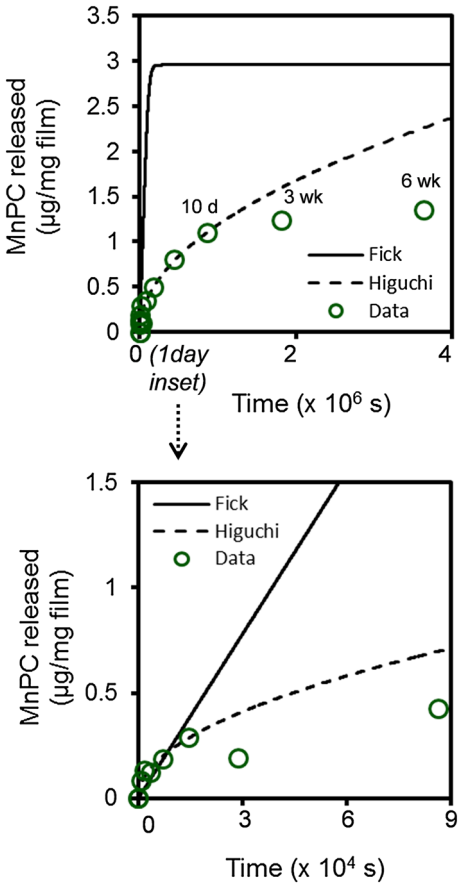

FIGURE 5. Experimental leaching kinetics of MnPC from PEBAX 2533 films with C_i = 0.29 wt.% MnPC into PBS buffer at 37 °C, compared to Fick and Higuchi models.

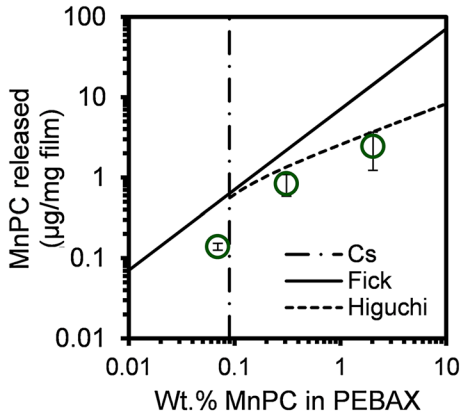

FIGURE 6. Comparison between experimentally obtained and model predicted leaching of MnPC from PEBAX 2533 films containing different MnPC loading concentrations extracted into PBS buffer at 37 °C for 3 days. Error bars represent the standard deviation between triplicate measurements.

to experimentally determined leaching data, particularly at higher C_i (self-evidently since D_e was fit for C_i = 2 wt.%). Model predictions at lower C_i values (when $C_i \leq C_s$) represent conditions that are inconsistent with model assumptions and cannot be estimated from this model. However, the Fickian model was shown to over-predict leaching of MnPC from PEBAX samples over the range of C_i tested, by as high as a half order of magnitude (Fig. 6). Based on the comfortably conservative nature of the Higuchi model in predicting leaching of MnPC from systems in which $C_i > C_s$, we propose using Higuchi in our exposure estimates for subsequent risk assessments. However in cases where the color additive concentration within the polymer is very low ($C_i \leq C_s$), the Fickian diffusion model can be used as the conservative exposure model.

Leaching of small molecules from polymer materials is not only dependent on the additive size, but also on the type of solvent used for extraction.[9] By definition, an additive must be soluble in the extraction solvent for leaching to occur; furthermore strong solvent-polymer interactions cause swelling that accelerates leaching. Extraction conditions specified by ISO 10993-12 recommend varying the solvent polarity when carrying out extraction experiments. Extruded PEBAX 2533 films compounded with different phthalocyanine additives (MnPC, PC-blue and PC-green) were extracted using polar (PBS buffer), non-polar (toluene), and mid-polar (ethanol) solvents. Extractions were carried out at 37 °C for 3 days as before, and the average amounts extracted are shown in Fig. 7. The data are compared to Higuchi model predictions represented by the dashed line (Fig. 7). The solubility of PC-blue and PC-green in PBS, ethanol and toluene has been shown to be several orders of magnitude below the corresponding solubility of MnPC in those solvents.[17] Consequently, extremely low amounts of PC-blue and PC-green were leached compared to MnPC. Therefore, it would be a valid approach to use transport coefficients determined for MnPC (i.e., a surrogate) for predicting worst-case leaching of other phthalocyanine color additives that have larger molecular weights and lower solubility characteristics for risk assessment purposes.

We observe from Fig. 7 that the highest amount of MnPC leaching was observed in toluene followed by ethanol and PBS. The effects of these solvents on swelling of the PEBAX matrix was determined by measuring the weight of PEBAX 2533 samples before and after immersion into the solvent held at 37 °C for 24 h, and are shown in Table 1. The degree of swelling in PEBAX can be correlated to the MnPC extraction amounts, with solvents having high degrees of swelling showing greater leaching of MnPC (such as toluene and ethanol) compared to solvents having lower degrees of swelling (such as PBS). In fact, the amount of MnPC leached into toluene at the end of 3 days extraction exceeded the model predicted value by 4.9 times. The degree of interaction between a polymer

and solvent can be expected to depend on the mutual solubility of the polymer matrix and solvent. Hildebrand solubility parameters can be used to evaluate the affinity between two materials, and is defined as the square root of cohesive energy per molar volume.[6] This parameter can be calculated by group contribution methods,[29] and affinity of various solvents to PEBAX can be quantified from the absolute value of the difference between their respective Hildebrand solubility parameters, $|\delta_{solvent} - \delta_{PEBAX}|$. The smaller this value is, the greater the affinity between the solvent and matrix, resulting in matrix swelling and leaching of additives. The solubility parameter for PEBAX 2533 (δ_{PEBAX}) is 19.51 $MPa^{1/2}$,[26] and values for the solvents tested are listed in Table 1.[4,11] It is evident from the absolute difference values that solvent interaction with the matrix supports the leaching data (Fig. 7). This approach in using solvent solubility parameters can be useful for evaluating solvent choice when conducting extraction experiments. It is important to note that since our exposure model is confined to systems that do not swell or degrade, applications for evaluating leaching from solvent systems that have high affinity with the polymer matrix is limited.

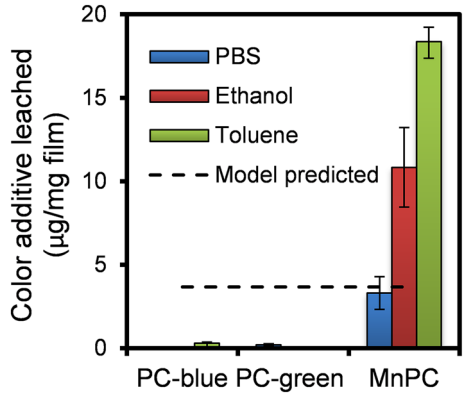

FIGURE 7. Leaching of metal phthalocyanine color additives from PEBAX 2533 films (C_i = 2 wt.%) at 37 °C for 3 days using various solvents.

DISCUSSION

In this manuscript, we propose a conservative exposure model for metal phthalocyanine color additives in polymer devices using Higuchi transport kinetics. This model was validated to provide moderately conservative exposure estimates for risk assessments. Transport coefficients determined for MnPC can be applied to predict exposure of other larger and less soluble metal phthalocyanine additives as illustrated here for PC-blue and PC-green. In evaluating device biocompatibility, application of model-predicted exposure values can prove more valuable than the case where exposure is estimated by assuming instantaneous release of the full additive mass into the external environment. The exposure values can then be compared to a provisional tolerable exposure (pTE) threshold value for the color additive for a rapid screening-level risk assessment.

A pTE value for MnPC was derived to be 9.31 mg/person/day (please see Supporting Information). While the exposure model can be solved numerically for any complex device geometry, a sample exposure-based risk assessment is illustrated in Fig. 8a for a PEBAX 2533 catheter tube of thickness $\Delta r (\Delta r = r_o - r_i)$, containing MnPC. Model predicted leaching of MnPC at the end of 1 day from the sample device containing various initial color additive loadings is shown in Fig. 8b, based on the Higuchi model for a thin film geometry (assuming Δr is small relative to r_i such that $(\Delta r / r_i \ll 1)$). Diffusion model predicted values are compared to the simple "total release approach" which assumes instantaneous release of all color additive from the device. As evident from Fig. 8b, our exposure model predictions are significantly lower by as much as two orders of magnitude when comparing to total release, providing greater clinical relevance for exposure compared to considering total additive release.

We can calculate a margin of safety (MOS) for the device as the ratio of the threshold value (pTE) for the color additive to its worst-case daily exposure. In general, it is accepted that if the MOS values should exceed 1, the toxicological risks associated with the daily exposure for the color additive can be considered

TABLE 1. Swelling of PEBAX 2533 samples in various solvents at 37 °C.

Solvent	Degree of swelling[a] (%)	Hildebrand solubility parameter, $\delta_{solvent}$ ($MPa^{1/2}$)[4,11]	$\lvert\delta_{solvent} - \delta_{PEBAX}\rvert$($MPa^{1/2}$)
Ethanol	54.7 ± 5.1	26.2	6.69
Toluene	85.3 ± 8.3	18.3	1.21
PBS	2.1 ± 0.4	48.0	28.49

[a]Average ± standard deviation from three measurements.

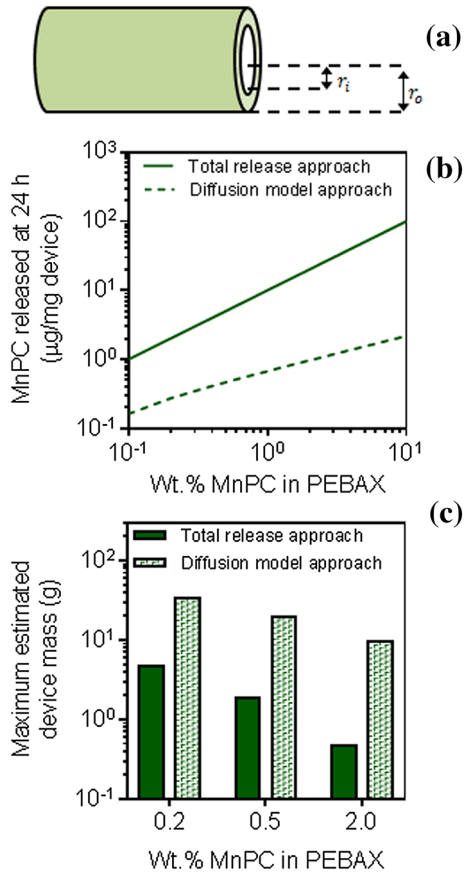

FIGURE 8. (a) Schematic representation of catheter tube composed of PEBAX 2533 containing MnPC (wall thickness, $\Delta r = r_o - r_i$), (b) comparison between total release approach and diffusion model approach for predicting leaching of MnPC from the catheter with different color additive loading concentrations, and (c) estimated maximum device mass calculated when MOS = 1, using the total release approach and diffusion model approach.

acceptable provided that the method to derive the pTE is appropriate.[38] This parameter can be useful to provide an estimate of the maximum device mass that will not exceed the threshold value. The estimated device mass calculated using both the "total release" and "exposure model" approach when the MOS equals 1 (pTE = exposure) is shown in Fig. 8c. It is clear that as the initial additive loading in the device increases, the maximum estimated device mass decreases. The exposure model approach provides an enhancement in device mass by at least about an order of magnitude compared to the total release approach, when the MOS approaches one. This indicates that a larger device mass can be screened for toxicological concerns before requirements for expensive and time-consuming extraction testing outlined by ISO 10993 may be needed to mitigate risk. For example, for a catheter tube containing 2 wt.% MnPC, about 20.7 times longer tubing would still be considered safe when using the diffusion model approach compared to the total release approach (calculated assuming device density 1 g/cm^3, $r_o = 0.4$ cm, $r_i = 0.3$ cm). This example demonstrates the benefit of using the exposure model as a screening-level risk assessment tool when evaluating medical devices containing phthalocyanine color additives. In conjunction with risk assessment-based device mass estimates, CFR listings for color additives used in medical devices indicate that only the minimum amount of color additive required to impart functionality be used.

The proposed approach assumes sink conditions ($C = 0$) at the material/environment interface, which is the worst-case for leaching and ensures that the model will not underestimate the amount of additive released in any implant application. Typically, device systems containing color additives such as catheters and other tubing, can be placed such that one side is in contact with a lumen where fluid flow will result in a scenario where perfect sink conditions will be more or less realized. On the abluminal side of these devices, release may be slowed if the migration of the additive away from the device interface is limited by diffusion. Again, this would result in the model overestimating release rate, which is ideal from the standpoint of estimating exposure within a risk assessment context. While data on color additive diffusion in tissues are not widely available in the literature, there have been extensive studies on the diffusion of drugs, which are comparable in molecular size, in biological tissues. These studies reveal diffusion coefficients in the range of ~ (1×10^{-10}–1×10^{-5}) cm^2/s,[18,19,39] which implies that diffusion of these specific color additives will be at least an order of magnitude (and likely much more) faster in the peri-implant tissue relative to the polymer matrix. This suggests that, in the majority of cases, sink conditions at the material/environment interface are appropriate.

While we demonstrate the benefit of the diffusion model approach as a risk assessment tool using extruded polymer samples compounded with pure pigments, commercial medical device materials may contain various other additives such as dispersing agents, wetting agents, extenders, stabilizers, *etc.*[30] These additives may potentially affect diffusion of the color additive by changing material properties such as glass transition temperature. Processing history is another parameter that can affect polymer morphology. One way to account for these unknown effects in our model predictions might be accomplished by incorporating appropriate safety factors to ensure that color additive leaching from medical device polymers is not under-predicted.

The approach demonstrated here with color additives can easily be extended to other small molecules

that can be released from devices including antimicrobials, drugs and other polymer additives such as antioxidants, plasticizers, ultraviolet light absorbers, antimicrobial agents, *etc*. that can migrate out of the polymer device over time. The transport coefficients (D and C_s) determined here for manganese phthalocyanine may be extended to conservatively predict leaching of larger phthalocyanine color additives, as well as other structurally similar additives with similar or larger molecular weights. Developing a database of material properties for a wide range of additives used in medical device polymers is critical to enable informed diffusion-based exposure estimates. Using the predictive exposure model in conjunction with toxicological threshold values for the additive of concern can be a viable risk assessment tool that can be used to screen device materials for potential risks to patients.

CONCLUSIONS

We describe a conservative diffusion-model approach to predict leaching of phase separated additives from polymer devices. This approach was validated using a model color additive (manganese phthalocyanine) and polymer matrix (PEBAX 2533). The use of the Higuchi diffusion model was found to provide conservative leaching predictions for the dispersion system, and can be used for obtaining worst-case exposure estimates. Model predicted exposure values can then be compared to acceptable toxicological threshold values for the additive for a screening-level risk assessment. This approach can be applied to various other additives with limited matrix solubilities in medical device polymers.

ELECTRONIC SUPPLEMENTARY MATERIAL

The online version of this article (doi: 10.1007/s10439-017-1931-4) contains supplementary material, which is available to authorized users.

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