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Mathematical Modeling of the Extractables Release from Multi-Layered Plastic Films Used in Drug Product Containers

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ABSTRACT: The release of extractables from multi-layered plastic films such as those used in containers for liquid drug products has been investigated. Targeted extractables were chosen from the film's extractable profile, as elucidated by a controlled extraction study. The total available pool of targeted extractables was ascertained via exhaustive sequential extraction of the film and the film layer responsible for the target extractables was established. This information, along with the film's structure, was used to produce a mathematical migration model for each of these targets. The film was fashioned into pouches, filled with a simulating solvent and the release of the targeted extractables to the pouches' contents was measured. The measured and modeled concentrations were found to be very similar, establishing the model's ability to effectively mimic the experimental system. This result suggests that mathematical modeling, which is widely used in the food industry to assess the safety of food packaging, may be applicable to packaged pharmaceutical products. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 41223.

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INTRODUCTION

Plastic containers (including bags, vials, bottles, syringes, etc.) are used to package pharmaceutical drug products. It is common for bags specifically to be constructed from multi-layered polymeric films, where the film's construction (number of layers, thickness of layers) and the choice of the plastics used in the layers is dictated by functional performance requirements for the bag and cost and quality considerations.

A potential concern with respect to the use of these plastic packaging systems is the interactions that could occur between the packaged drug product and its packaging. Important interactions include leaching, which is the release of packaging system entities into the packaged drug product, and binding, which is the adsorption or absorption of drug product components by the packaging. The concern associated with leachables released by the packaging is that the leachables could affect key quality attributes of the packaged drug product, including its safety, efficacy, and overall quality.

Generally speaking, there are five factors that contribute to the accumulation of packaging leachables in packaged drug products:

1. The total amount of the leachables available in the plastic packaging (the total available pool),
2. The leachables' solubility in the plastic and product phases,
3. The equilibrium partitioning of the leachables between the plastic and product phases,
4. The rate of the leachables' migration through the plastic, and
5. The leachables' stability in either the plastic or the product phases.

Items 2 and 3 are particularly relevant when the circumstances of the packaged drug product are such that the product and polymer phases establish equilibrium and the levels of leachables in the packaged drug product are thermodynamically constrained. Items 4 and 5 are particularly relevant when the circumstances of the packaged drug product are such that equilibrium is not achieved and where the levels of leachables in the packaged drug product are kinetically constrained via migration and diffusion.

In the food industry, numerous scientific investigations have established that diffusion of substances through food-contact (packaging) materials, and the migration of those substances from the packaging and into the packaged food, are well-defined and mathematically describable procceses.[1,2] Thus, mass transfer from a plastic material into food stimulants is predictable and obeys Fick's laws of diffusion,[2] as was verified and validated by the European project SMT-CT98-75133.[3] Consequently, the sixth Amendment of the European Economic Commission's Plastics

Directive 90/128/EEC introduced migration modeling as an alternate tool for conformity and quality assurance testing.[4,5] Ultimately, the use of mathematical models to simulate and predict the migration of packaging components into packaged products was adopted by the food industry[6–10] and the use of mathematical migration models to establish the compatibility of food and its packaging is well-accepted and commonly used by the global regulatory community.[11–13]

Mathematical modeling of leachables migration is not widely accepted as a suitable means of establishing the suitability for use of packaging used in the pharmaceutical industry. Although the utility of mathematical models have been demonstrated in some studies,[14–18] it is the case that far fewer pharmaceutical applications have been published versus the fairly extensive literature addressing food packaging.

This manuscript documents the series of experiments that must be performed to produce the data required to use mathematical modeling in pharmaceutical applications including:

1. Identification of targeted compounds.
2. Establishing the source of the targeted compounds in the test system.
3. Establishing the total pool of targeted compounds in their source material.

Additional information relevant to the model, including migration path lengths (film thickness), diffusion coefficients and solubility parameters for the target compounds are required inputs into the model, some of which are obtained via algorithms in the modeling software and some of which are provided by the user. Furthermore, the migration of the targeted compounds was experimentally investigated and the experimental data was compared to the model forecasts. In general, the agreement between measured and forecasted accumulation levels was sufficiently good that it can be concluded that mathematical modeling could be an appropriate means of assessing the potential quality impact of packaging-related leachables. While modeling might not necessarily replace more well-accepted approaches for establishing the magnitude of interactions, such as performing a leachables migrations study, such models may facilitate the design, the execution and the interpretation of extractables and/or leachables studies.

EXPERIMENTAL

Test Article

The test article was either a multi-layered plastic film or pouches fashioned from the film. The film consisted of four primary layers of plastic materials of known thickness and included outer polyethylene (PE) layers surrounding inner layers of nylon and polyvinylidene chloride (PVDC) materials. Intermediate adhesive tie layers were used to bond the layers. More specifically, the structure of the film was as follows: outer most layer (which becomes the outer surface of a pouch fashioned from the film) = linear low density polyethylene (≈60 μm), adhesive tie layer, polyvinylidene chloride (≈20 μm), adhesive tie layer, Nylon 6 (≈15 μm), adhesive tie layer, inner most layer (which becomes the solution contact layer of a pouch fashioned from the film) = linear low density polyethylene (≈60 μm). Pouches with a nominal volume of approximately 50 mL were manually fashioned by heat sealing the ends of portions of the film together.

Extractables Profile

The extractables profile of the test film was established by extracting portions of the film with various solvents, including low and high pH aqueous solutions and alcohol/water mixtures, at elevated temperatures (55°C or higher) for various lengths of time (1 day or longer). As the intent of the extractables profiling was to establish targets for the migration study, the extraction conditions were chosen for this purpose and not for alternate purposes, such as establishing the material's full and quantitative profile or simulating a packaged drug product's leachables profile.

The resultant extracts were screened for organic extracted substances by testing the extracts via a suite of chromatographic methods appropriate for this purpose.

Total Available Pool

The total available pool of the target extractables was established via a process of sequential extraction. Specifically, approximately 65 g of the film, cut into small pieces, was contacted with 500 mL of a 40/60 (v/v) mixture of ethanol/water in a glass bottle. Replicate test units were incubated at 70°C for 72 h, after which they were removed from the heat source and cooled to ambient temperature. The extracting solution was decanted into a secondary glass storage vessel to await analysis. The plastic pieces contained in the original glass bottle were contacted with a fresh charge of the ethanol/water extracting solvent and incubated at 70°C for another 72 h. This temperature and duration of incubation was established to be sufficient to drive the extraction to equilibrium. As was the case with the first extraction, after the extraction duration was reached the extraction units were removed from the heat source, cooled to ambient temperature and the extracting solvent was decanted off and collected for analysis. This sequential extraction process was repeated two additional times, resulting in the generation of four sequential extracts for each test unit.

Each of the sequential extracts was tested for their levels of the target extractables by appropriate chromatographic methods developed for this purpose.

Migration Study

This study was designed to address the relatively short term packaging of a sterile fill, lipophilic drug product into a bag fashioned from the polymeric test film. Thus the extraction solvent used as a 40/60 (v/v) mixture of ethanol/water, as the use of such mixtures to simulate lipophilic drug products is well-documented.[19–22] The test film was fashioned into pouches with a capacity of approximately 50 mL. Multiple individual pouches were filled with 50 mL of the extraction solvent (contacted film surface area was 4 cm^2/mL) and then stored at 60°C for 10, 24, or 48 h, consistent with the short-term application being addressed. The filling of the pouches and the initiation of their storage was staggered so that all bags reached their intended storage duration at the same time. After reaching their intended

Table I. Partition and Diffusion Coefficients Used in the Mathematical Model

		Diffusion coefficient[b] (cm^2/s)			
Compound	Log $P_{o/w}$[a]	PE layer	PVDF layer	Nylon layer	Adhesive layer
CE228 (I)	1.2	7.4×10^{-9}	3.8×10^{-9}	8.7×10^{-14}	3.3×10^{-13}
CE270	2.5	4.6×10^{-9}	2.4×10^{-9}	5.4×10^{-14}	2.1×10^{-13}
CE504	4.2	5.1×10^{-10}	2.6×10^{-10}	5.9×10^{-15}	2.3×10^{-14}
Caprolactam	−0.1	3.5×10^{-8}	1.8×10^{-8}	4.0×10^{-13}	1.5×10^{-12}
Caprolactam dimer	−0.1	4.9×10^{-10}	2.6×10^{-10}	1.1×10^{-14}	3.9×10^{-14}

[a] Input into the migration model software by the user, obtained via ACD software (Ref. [24]).
[b] Calculated by the migration modeling software using the "interpolation by T_g" approach.

storage duration, the pouches were removed from the heat source, equilibrated to ambient temperature and emptied. The collected fill solutions were analyzed for their levels of the target extractables by appropriate chromatographic methods developed for this purpose.

Mathematical Modeling

To this end, commercially available migration modeling software (AKTS AG SML Version 5, Ref. [23]), was used to generate quantitative migration profiles for the targeted extractables. In general the calculation process involves the use of numerical algorithms to solve the partial differential diffusion equation that represents Fick's second law of diffusion. The computer-generated migration profiles were based on a film structure that assigned an appropriate thickness to the individual layers and distributed the total pool of the target extractables to their source layers. Partition and diffusion coefficients for the target extractables are necessary input parameters for the model; the diffusion coefficients were estimated by the migration modeling software using the empirical "interpolation by T_g (glass transition temperature)" approach (see Table I for the values used for these coefficients). Such an approach is based on establishing a relationship between the diffusion coefficient and (1) the glass transition temperature of the polymer, (2) the molecular weight of the migrant, and (3) the temperature of the experiment. The polymer/solvent partition coefficient was estimated from the extractable's octanol/water partition coefficient ($P_{o/w}$). The extractables' $P_{o/w}$ values were manually input into the modeling software by the user and were calculated using the Advanced Chemistry Development (ACD/Labs) Software V11.02,[24] which utilizes a fragment-based algorithm based on the principle of isolating carbons and is supported by log P contributions that have been compiled for atoms, structural fragments, and intramolecular interactions derived from over 12,000 experimental log P values.

Analytical Methods

The profiling extracts of the film were screened for organic extractables using a combination of headspace gas chromatography with flame ionization and mass spectrometric detection (HS-GC/FID/MS) for volatile compounds, direct injection GC/FID/MS for semi-volatile extractables and direct injection liquid chromatography with ultraviolet and mass spectrometric detection (LC/UV/MS) for non-volatile extractables. Extracts were prepared for GC/FID/MS analysis by solvent switching (with methylene chloride) and evaporative concentration. Headspace and LC analyses were performed directly on the extracts.

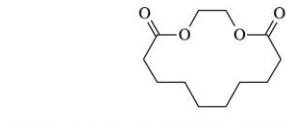
Extractables revealed by the screening methodologies were tentatively identified based on their mass spectral and elution properties. Extractables chosen as targets were more confidently identified by analysis of, and comparison to, reference standards. Approximate concentrations of the extractables in the extracts were determined using internal standards.

Target extractables were quantified in the sequential extracts and pouch fill solutions via a direct injection liquid chromatographic method with mass spectral detection (LC/MS). The reversed phase separation was accomplished with an 100 cm by 4.6 mm column with a C8 stationary phase (5 μm particle size) and a binary mobile phase gradient formed using 40/60 methanol/water (0.1% formic acid) and acetonitrile (flow rate = 0.7 mL/min, column temperature = 30°C). The individual target analytes were measured using single ion monitoring at a mass/charge ratio specific for that target (positive ion mode, $M+1$ ion for all analytes). The individual target analytes were quantified using calibration curves that were generated with standards prepared from reference standards for each targeted analyte.

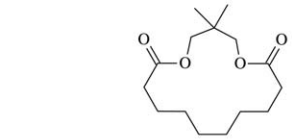
RESULTS AND DISCUSSION

Extractables Profile and Target Extractables

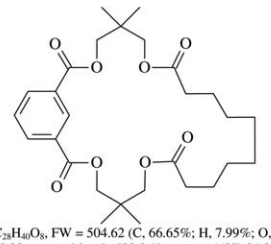
The extractables profile of the film could easily be understood in the content of its composition. Hindered phenolic antioxidants and their associated oxidative degradation products[25] were attributable to the films polyethylene layers, as were commonly encountered fatty acids such as palmitic and stearic acid. Another important class of extractables was derived from the film's adhesive, a polyester-urethane formulation. The predominant organic extractables associated with the adhesive are a class of compounds that have internally been labeled as cyclic esters. It is hypothesized that the cyclic esters are formed during the first step of the manufacture of the polyester prepolymer, that being the formation of the linear polyester. Depolymerization of the linear polyester via ester exchange could result in cyclic ester formation. Cyclic esters that were identified in this study are generally based on sebacic and isophthalic acids. In addition to the cyclic esters themselves, hydrolysis products of the low



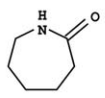
CE228(I): $C_{12}H_{20}O_4$; FW = 228.28; C = 63.14%, H = 8.83%, O = 28.03%
1,4-dioxacyclo-tetradecane-5,14-dione [CAS RN 5578-82-5]
Sebacic acid + Ethylene glycol



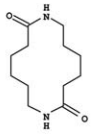
CE270: $C_{15}H_{26}O_4$, FW = 270.35 (C, 66.64%; H, 9.69%; O, 23.66%)
3,3-dimethyl-1,5-dioxacyclopentadecane-6,15-dione [CAS RN 94113-50-5]
Sebacic acid + Neopentyl glycol



CE504: $C_{28}H_{40}O_8$, FW = 504.62 (C, 66.65%; H, 7.99%; O, 25.36%)
5,5,20,20-tetramethyl, 3,7,18,22-tetraoxabicyclo-[22.3.1]octacosa-1(27),24,26,-triene-2,8,17,23-tetraone
[no CAS RN]
Isophthalic acid + 2 Neopentyl glycols + Sebacic acid



Hexahydro-2H-azepin-2-one (ε-Caprolactam); CAS RN 105-60-2, $C_6H_{11}NO$, formula weight = 113.16



1,8-Diazacyclotetradecane-2,9-dione (ε-Caprolactam cyclic dimer); CAS RN 56403-09-9, $C_{12}H_{22}N_2O_2$, formula weight = 226.32

Figure 1. Chemical Information for the Targeted Extractables.

molecular weight, sebacic acid-based cyclic esters were present in the aqueous extracts. The association of cyclic esters with polyurethane adhesives has been previously reported.[14,26]

Caprolactam and its associated cyclic and linear oligomers were clearly associated with the film's nylon layer, which is a caprolactam-based polymer. The correlation of caprolactam and its associated linear and cyclic oligomers with nylon materials has been previously reported.[27–30]

Targeted extractables were chosen from the film's entire extractables profile based on two criteria, analytical expediency and the location of the extractable's source material within the film structure. Considering analytical expediency, the major considerations were sensitivity and simplicity of the required analytical method and the availability of reference standards. Specifically, a single analytical method was desired for all the targets and it was furthermore desired that the method would require minimal sample preparation. This was achieved for the identified targets via the adoption of a direct injection, gradient LC/UV/MS method. The issue of reference standards was addressed by the in-house generation of reference standards, either produced by synthesis or generated by isolation (preparative chromatographic isolation of the compounds from a highly concentrated material extract).

Considering the aspect of the extractable's source in the film, the ultimate objective of this study, which was the generation of mathematical migration models, placed certain constraints on the choice of targets. Foremost among these was the constraint that the targets be uniquely linked to a single source layer in the film. While the mathematical model is capable of dealing with multiple sources of leachables, the experimental portion of this study was not designed to capture the multiple source circumstance. Thus the antioxidants, their degradation products and the fatty acids were not targeted as they were associated with multiple source layers. Furthermore, for the sake of analytical expediency, the targets chosen were entities that were present in the film at relatively higher levels. Lastly, targets from the inner layers of the film were given higher priority as it was expected that such targets would have more interesting migration profiles.

Considering these factors, a set of cyclic esters, derived from the adhesive, and caprolactam and its cyclic dimer, originating in the film's nylon layer, were targeted. Chemical information for these targeted extractables is contained in Figure [1(a, b)]. The three cyclic esters were chosen from the larger group of all cyclic ester extractables based on their relative amount in the film and the fact that the three esters choosen span a range of molecular weights.

Total Available Pool

As noted previously, the total pools of the targets in the film were established by sequential extraction of the film. The results of the sequential extraction are shown in Table II. For the lower molecular weight, more highly soluble targets (CE 228, CE270, caprolactam), the amount of the extractable measured in the last (fourth) extract is approximately 10% of the amount extracted in the first extraction step, meeting a commonly applied definition of an exhaustive extraction.[31] For these targets, the total listed in Table II are an accurate reflection of the targets total pool in the film. For the less soluble targets, CE504 and the caprolactam dimer, the criteria for an exhaustive extraction was not met and the total listed in Table II underestimate the total pools for these targets somewhat. However, given the trends observed in their extraction profiles (see Figure 2), one can infer that the levels of these extractables in a fifth extract would have reached the 10% threshold, signaling the completion of the extraction process. Thus, the total pools measured for these targets are significantly complete that they can be used for the purpose of mathematical modeling.

Migration Study and Mathematical Modeling

Migration profiles based on both the experimental data and the results from the mathematical models are shown in Figure 3. In general, the agreement between model and experimental is quite good for all the target extractables. The effectiveness of the

Table II. Total Available Pools of the Target Extractables

Extraction step	Amount extracted (μg/g)				
	CE228 (I)	CE270	CE504	Caprolactam	Caprolactam dimer
1	36.8	38.9	67.5	6.22	13.0
2	7.35	14.2	34.2	0.96	6.99
3	1.72	5.85	24.6	0.47	4.80
4	0.44	2.32	19.7	0.35	3.47
Total pool	46.3	61.3	146	7.99	28.3

model's ability to mimic the experimental migration behavior of the five targeted extractables is reflected in the regression line formed when comparing the measured versus model behavior (Figure 4). The high correlation coefficient, the near unit slope and the near zero intercept all suggest a strong agreement between the experimental and model data. Additionally, the profiles are consistent with the expected behavior of this system with the following caveats. First, because the source layers of the target extractables are not the solution contact layer, one expects that there could be a slight lag in the migration profile, reflecting that period of time during which the extractables migrate through the film. However, the shortest extraction time used experimentally (10 h) was beyond the lag time and thus this phenomenon is not captured in this study. At the other extreme, at long extraction time, one expects the migration models to achieve an asymptotic level, consistent with the attainment of thermodynamic equilibrium. Although the migration models illustrated this trend when the models were produced with sufficiently long extraction durations, the longest extraction time used experimentally (48 h) was generally prior to the equilibration point and thus this phenomenon is not fully captured in this study. Nevertheless, all the migration profiles exhibit a clear approach to the asymptotic equilibrium level.

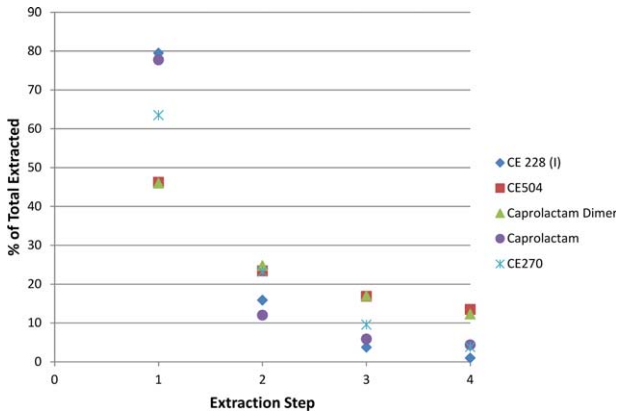


Figure 2. Sequential Extraction Profiles for the Target Extractables. The amount of CE228 (I), CE270 and caprolactam extracted in the 4th extraction is approximately 10% or less of the amount extracted in the first step, meeting the criterion for a complete extraction. Thus the measured total amount extracted for these targets accurately reflects their total pool. For the more lipophilic targets, CE504 and caprolactam dimer, the sequential extraction was not complete and the totals for these targets underestimate their total pools somewhat. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

SUMMARY AND CONCLUSIONS

A series of controlled extractions studies were performed to produce the information necessary to investigate the ability of mathematical models to mimic experimental extractables migration profiles. The first controlled extraction study was performed for the purpose of identifying target extractables, which was accomplished by establishing the test film's semi-quantitative extractables profile. Consistent with its purpose, this controlled extraction study used multiple extractions solvents, somewhat aggressive extractions conditions and screening types of analytical methods. Target extractables were chosen from the larger population of the extractables profiles based on set criteria.

The second controlled extraction study was a sequential extraction study to establish the total pool of the target extractables in the test film. Consistent with this purpose, the study used multiple steps and somewhat aggressive extraction conditions. Through the use of four sequential extraction steps, this controlled extraction study was able to produce complete pool estimates for most of the extractables and very close approximations of the total pool for the more lipophilic targets. Use of a stronger extraction solvent could have resulted in complete extraction of even these lipophilic extractables. It is unlikely that a higher extraction time or longer extraction duration would have produced a more complete extraction as the nature of the extraction profiles suggests that equilibrium was achieved in each sequential extraction step. For example, examination of Figure 3(A) suggests that equilibrium is achieved after 120 h at a temperature of 60°C. The individual extraction steps used to generate the total pool were performed at 70°C for 72 h, which is comparable to the longer exposure at the lower temperature.

The final controlled extraction study was a migration study whose purpose was to establish the time dependence of extractables levels in fill solutions stored in pouches fashioned from the film. To a certain extent, this controlled extraction was a simulation study in which the extraction solvent was chosen to represent a certain type of drug product and the extraction conditions were chosen to accelerate a certain type of product

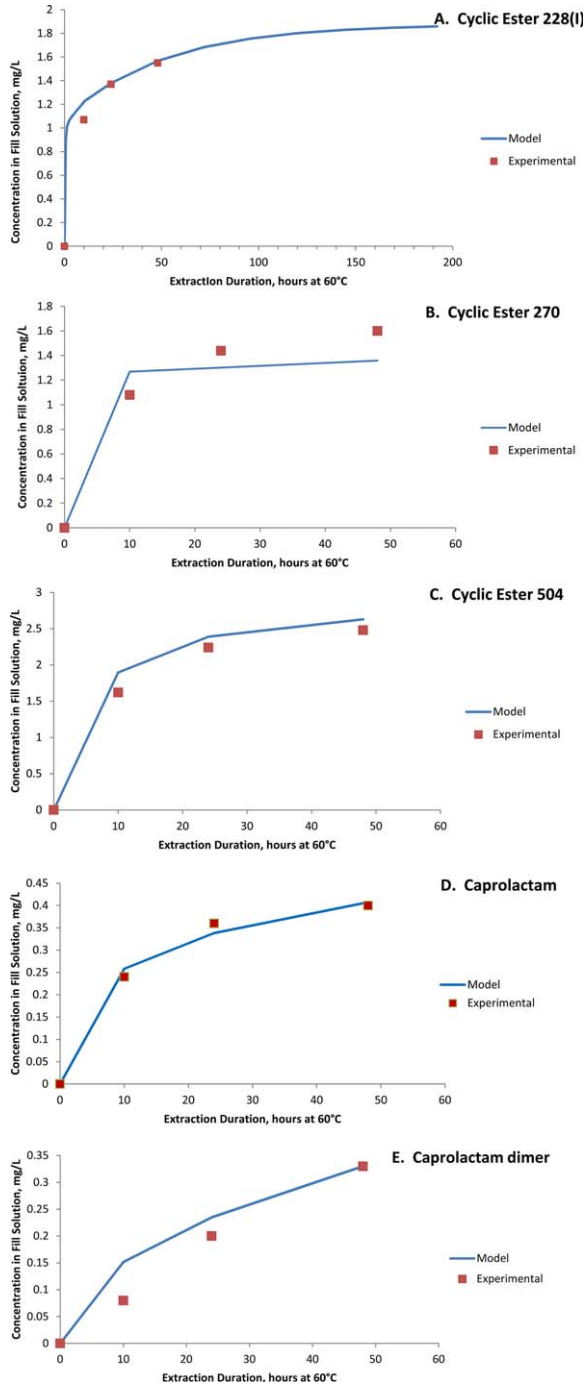


Figure 3. Migration Profiles for Target Extractables. The migration profile for CE228 (I) illustrates the model results extrapolated through equilibration, as illustrated by the approach to an asymptotic concentration. The plot for CE228 (I) thus illustrates the forecasted attainment of equilibrium, which occurs at a duration longer than that used in this study. For the other analytes, the plots include only the time duration of the actual migration study. In all cases, the mathematical model effectively mimics the experimental behavior of the target extractables. Although the models appropriately predict the attainment of an asymptotic level in the longer stages of the migration profiles, the experimental test points were such that this phenomenon was not experimentally encountered. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

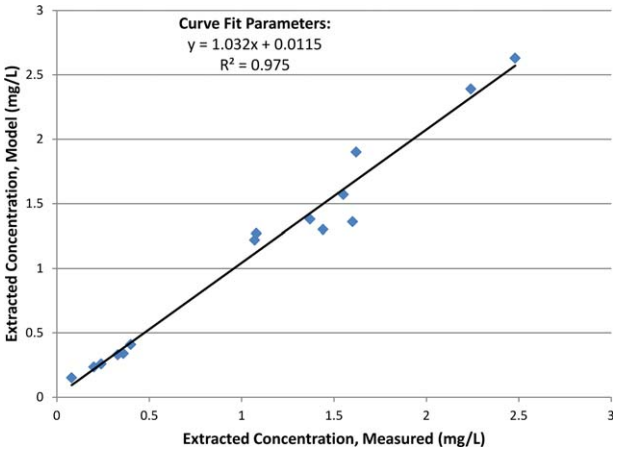


Figure 4. Comparison of the Actual versus Model Extracted Concentrations for all the Target Extractables at all Four Time Points. The effectiveness of the model's ability to mimic the experimental migration behavior of the five targeted extractables is reflected in the regression line formed when comparing the measured versus model behavior. The high correlation coefficient, the near unit slope and the near zero intercept all suggest a strong agreement between the experimental and model data. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

storage/use situation. This experiment produced migration profiles that could be mathematically modeled. Such models were generated and in general effectively mirrored the experimental behavior.

The success of this modeling exercise suggests that mathematical modeling can have a role in the effective development, registration and qualification of safe and effective packaging systems and packaged drug products. The important activity that remains to be addressed is establishing what that proper role is. While it is beyond the scope of this manuscript to establish this role, certain observations are appropriate. First and foremost is the observation that mathematical modeling may not be a replacement or substitute for well-designed and well-executed experiment-based assessments. While mathematical modeling can be used to forecast an outcome, such a forecasted outcome could suffer from the potential issues and limitations associated with forecasts, including the quality and availability of the required inputs. Thus, at the current time it is not appropriate to propose modeling as a substitute or replacement for extractables or leachables migration studies. Nevertheless, mathematical modeling could have an important place in the design, optimization, justification, and interpretation of experimental migration studies. For example, mathematical modeling may be useful in terms of establishing and justifying extraction conditions in controlled extraction studies and establishing the duration of and test intervals for a leachables migration study. Mathematical modeling may serve the purpose of setting performance expectations for analytical methods used in the experimental studies; for example, the required sensitivity and linear dynamic range. These possibilities are value added from the perspective that the effectiveness and efficiency of experimental studies can be optimized if the probable outcome of the study

can be envisioned. Furthermore, mathematical modeling can be used to evaluate and verify the results of experimental studies.

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