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Release Kinetics of Tocopherol and Quercetin from Binary Antioxidant Controlled-Release Packaging Films

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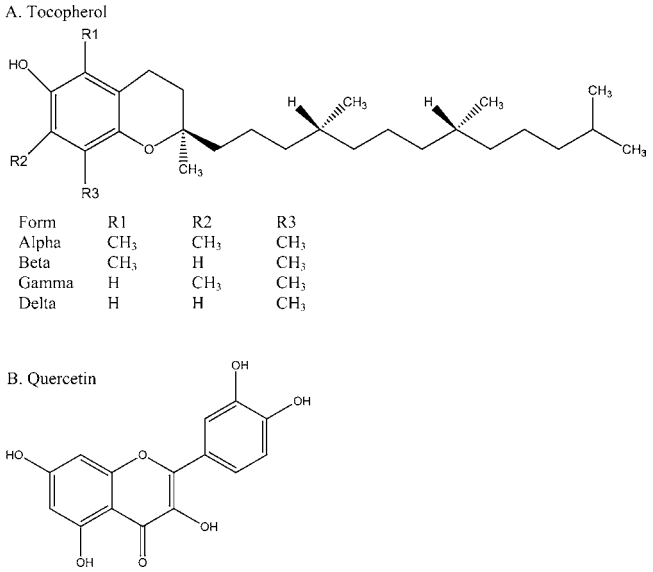
ABSTRACT: This paper investigated the feasibility of manipulating packaging polymers with various degrees of hydrophobicity to release two antioxidants, tocopherol and quercetin, at rates suitable for long-term inhibition of lipid oxidation in food. For example, one antioxidant can be released at a fast rate to provide short-term/intermediate protection, whereas the other antioxidant can be released at a slower rate to provide intermediate/long-term protection of lipid oxidation. Controlled-release packaging films containing tocopherol and quercetin were produced using ethylene vinyl alcohol (EVOH), ethylene vinyl acetate (EVA), low-density polyethylene (LDPE), and polypropylene (PP) polymers; the release of these antioxidants to 95% ethanol (a fatty food simulant) was measured using UV−vis spectrophotometry, and Fickian diffusion models with appropriate initial and boundary conditions were used to fit the data. For films containing only quercetin, the results show that the release of quercetin was much faster but lasted for a much shorter time for hydrophilic polymers (EVOH and EVA) than for hydrophobic polymers (LDPE and PP). For binary antioxidant films containing tocopherol and quercetin, the results show that tocopherol released more rapidly but for a shorter period of time than quercetin in LDPE and EVOH films, and the difference is more pronounced for LDPE films than EVOH films. The results also show the presence of tocopherol can accelerate the release of quercetin. Although none of the films produced is acceptable for long-term lipid oxidation inhibition, the study provides encouraging results suggesting that acceptable films may be produced in the future using polymer blend films.

KEYWORDS: *tocopherol, quercetin, controlled-release packaging, release kinetics*

INTRODUCTION

Controlled-release packaging (CRP) is an innovative active packaging technology by which active compounds such as antioxidants and antimicrobials are released from the package, in a slow but controlled manner, to enhance the quality and microbial safety for a wide range of foods.[1,2] Research has shown that antioxidant CRP can be more effective in inhibiting lipid oxidation than the method of adding antioxidant directly into the food formulation,[3,4] partly because the antioxidant is protected by the package from loss due to degradation and partly because the effective antioxidant concentration is maintained for a longer period of time.[4] Similar benefits have also been observed from research studies on antimicrobial CRP.[5,6] To aid the design of CRP, a new term called target release rate was developed recently by our research group to match the release kinetics of active compounds with the reaction kinetics in foods.[2,3]

To further develop the CRP technology, our research group has recently been studying the feasibility of using packaging polymers with various degrees of hydrophobicity to incorporate multiple antioxidants to produce CRP films for long-term lipid oxidation inhibition in food. Initially we studied a binary antioxidant CRP system (which consisted of both tocopherol and quercetin in a packaging polymer film) with the anticipation that these two antioxidants would release at different rates due to their different chemical structures (Figure 1); we hoped to observe complementary release rates whereby one antioxidant would release at an appropriate fast rate to



Form	R1	R2	R3
Alpha	CH_3	CH_3	CH_3
Beta	CH_3	H	CH_3
Gamma	H	CH_3	CH_3
Delta	H	H	CH_3

Figure 1. Chemical structures of tocopherol and quercetin.

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provide short-term/intermediate inhibition and the other antioxidant would release at an appropriate slow rate to provide intermediate/long-term inhibition. Tocopherol and quercetin were chosen because they are natural antioxidants, their effectiveness as antioxidants in CRP films has been demonstrated in both simulated and real food systems,[4,7−12] and their synergistic antioxidant effect due to regeneration of oxidized tocopherol by quercetin has been observed.[13]

This paper reports a part of our study that examined to what extent the release of tocopherol and quercetin could be affected by the hydrophobicity of packaging polymers. The results can help determine whether judicious selections of these polymers can produce desirable release behavior of these antioxidants. EVOH, EVA, LDPE, and PP polymers were used because they are common packaging polymers with different degrees of hydrophobicity and their applications as CRP films have been demonstrated.[4,12,14] Although the release of tocopherol from packaging films has been studied quite extensively,[4,7−11] information about the release of quercetin is still limited. Quercetin has been shown to release from hydrophilic EVOH polymer[12] but not from hydrophobic LLDPE polymer.[15] This work is the first to report the release of tocopherol and quercetin from binary antioxidant CRP systems.

MATERIALS AND METHODS

Materials. HPLC grade 95% ethanol was purchased from Fisher Scientific (Pittsburgh, PA, USA). Tocopherol extracted from soybean consisting of 10% α-, 5% β-, 65% γ-, and 20% δ-homologues was donated by Cargill (Minneapolis, MN, USA). Quercetin with 95% purity (unknown source of extraction) was purchased from Altaquimica (Barcelona, Spain). All packaging polymer resins were provided by Berry Plastics (Chippewa Falls, WI, USA). Hydrophobic polymers were LDPE (ExxonMobil LDPE LGA 105) and PP (Total PPH 3571); hydrophilic polymers were EVA (Escorene Ultra UL EVA 7760) and EVOH (Soarnol DC3203F).

Production of CRP Films. CRP films were produced using a cast film extrusion line at Berry Plastics. Hydrophilic polymers (EVA and EVOH), hydrophobic polymers (LDPE and PP), and a blend of hydrophilic and hydrophobic polymers (50% EVA/50% LDPE) were used to produce packaging films containing quercetin at 3000 ppm (3.0×10^{-3} g quercetin/g film). For binary antioxidant films, 1500 ppm tocopherol and 1500 ppm quercetin were added to EVOH and LDPE polymers. During processing, quercetin deposits were observed on the chill roll of the extruder, resulting in some loss of quercetin. To reduce the loss, two skin layers (15% of film thickness each) with no antioxidant were designed in the film structure. The loss of antioxidants during handling and processing was negligible based on our previous experience in this film production method,[4] and thus the total amount of antioxidants retained in the film was assumed to be the initial amount added.

Study To Quantify Release Kinetics of Tocopherol and Quercetin. A total immersion method was used to study the release of the antioxidants. Approximately 1.0 g of film samples was cut into small pieces (around 3 × 3 cm) and immersed into 40 mL lipid simulant (95% ethanol) in a 125 mL flask. The flask was rotary shaken at 100 rpm under 30 °C in an environmental chamber (Lab-line Instruments Inc., Melrose Park, IL, USA). One milliliter of sample solution was periodically sampled for quantification. The concentrations of antioxidants released into the solution were quantified using a UV−visible spectrophotometer (UV-1700 spectrophotometer, Shimadzu Co., Kyoto, Japan) at 295 nm for tocopherol and at 392 nm for quercetin on the basis of standard curves made from known concentrations (0−100 μg/mL). Because quercetin also has absorbance at 295 nm, the absorbance measured at 295 nm was from both tocopherol and quercetin. To obtain the true concentration of tocopherol, a standard curve was also prepared for quercetin at 295 nm. The calculation involved the following steps: (a) calculated concentration of quercetin by the absorbance measured at 392 nm, (b) calculated absorbance of quercetin at 295 nm based on quercetin concentration obtained from previous step, (c) subtracted absorbance value of quercetin at 295 nm from absorbance value obtained from measurement at 295 nm, and (d) calculated concentration of tocopherol. To eliminate the influence of other polymer additives, release studies were also conducted on control films (pure EVOH, EVA, EVA/LDPE, LDPE, and PP films with no antioxidant) in 95% ethanol, and no significant absorbance was observed at 392 and 295 nm.

Parameter Estimation for Release Kinetics of Tocopherol and Quercetin. Diffusivity and partition coefficient were estimated on the basis of experimental results from the release study. Because of the multilayer structure, there are two stages of release: diffusion of antioxidants within a film (from core layer to skin layers) during storage and release of antioxidants from package to food simulant during experiment. There are three possible scenarios of antioxidant distribution at the end of the first stage:[16] (a) antioxidants present only in the core layer, which occurs immediately after production; (b) antioxidants start to diffuse from the core layer to the skin layer, but equilibrium at the package/food interface is not reached and there exists a concentration gradient between the core and the skins; (c) diffusion reaches equilibrium, and there is a homogeneous distribution of antioxidants throughout all three layers. A numerical method developed by Tosa and Mercia[17] was used to test which was the true case in this study. Diffusivity values from the literature were used for an approximate estimation.[4,12]

Results showed that uniform distribution of both antioxidants in the films was reached after 100 h of storage. Because release studies were conducted far beyond this point, the assumption was made that antioxidants were uniformly distributed throughout all three layers.

Estimation of Partition Coefficients. The partition coefficient (K_P) was calculated as

$$K_P = \frac{C_{F,\infty}}{C_{P,\infty}} \tag{1}$$

where $C_{F,\infty}$ and $C_{P,\infty}$ are the concentrations of antioxidant in the food and in the package at equilibrium, respectively.

Estimation of Diffusivities. Diffusivities were estimated using two Fickian diffusion models (eqs 2 and 3) appropriate for the initial and boundary conditions of this study.[18] When release of antioxidant reached equilibrium, the following equation was used:

$$\frac{M_t}{M_{F,\infty}} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\left[\frac{-D(2n+1)^2\pi^2 t}{L_P{}^2}\right] \tag{2}$$

M_t is the mass of the migrant in the food at a particular time t (s), $M_{F,\infty}$ is the mass of migrant in the food at equilibrium, L_P (m) is film thickness, D (m^2/s) is the diffusivity of migrant in the film, and t (s) is time. The assumptions for this equation are that release is controlled by Fickian diffusion, antioxidants in film are homogeneously distributed initially, the initial concentration of antioxidants in food simulant is zero, no concentration gradient of antioxidants exists in food simulant due to constant agitation, partition coefficient and diffusivity are constant at a given temperature, interactions between food simulant and film are absent or negligible, and no degradation of antioxidant occurs.

When release was slow and equilibrium was not reached at the end of the experiment, the following equation was used:

$$\frac{M_t}{M_P} = \frac{4}{L_P}\left(\frac{Dt}{\pi}\right)^{0.5} \tag{3}$$

M_P is the initial loading of antioxidants in the package. This equation is valid for the initial release period when M_t/M_P is <0.6.

To estimate D in eq 2, version 7.8 (R2009a) Matlab software was used. For eq 3, D was estimated from the slope of the plot of M_t/M_P versus $t^{0.5}$. Overall film thickness was measured by a micrometer (DigiTrix II, Fowler NSK, Japan) and is shown in Table 1.

Table 1. Film Thickness

film	thickness ($\times 10^{-4}$ m)
EVOH/quercetin and tocopherol	1.30 ± 0.04
EVOH/quercetin	1.20 ± 0.05
LDPE/quercetin and tocopherol	1.70 ± 0.03
LDPE/quercetin	1.71 ± 0.03
EVA/quercetin	1.41 ± 0.02
EVA and LDPE/quercetin	1.21 ± 0.02
PP/quercetin	1.42 ± 0.04

RESULTS AND DISCUSSION

The first subsection below pertains to the release of quercetin from films containing only quercetin. The second and third subsections pertain to the release of tocopherol and quercetin from binary antioxidant films containing tocopherol and quercetin.

Effect of Polymer Hydrophobicity on Release of Quercetin. Figure 2 shows that the release of quercetin was greatly influenced by polymer hydrophobicity. The initial rate of release was much faster, the amount of release was much larger, and the time to reach equilibrium was much shorter for hydrophilic polymers (EVOH and EVA) than hydrophobic polymer (LDPE). The results from PP film are not shown because no release of quercetin was detected. The results are consistent with the observations reported in the literature.[12,15]

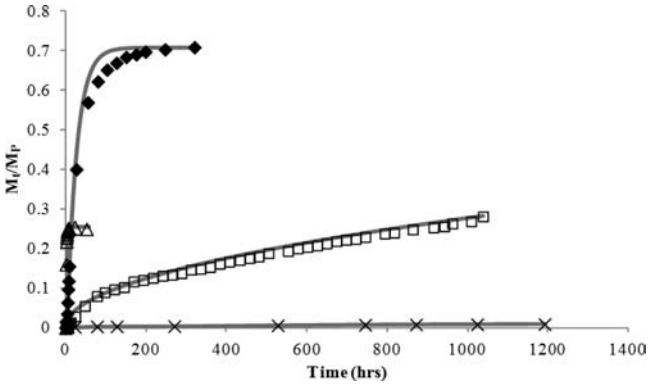

Figure 2. Release profiles of quercetin from packaging polymer films with different degrees of hydrophobicity: (◆) EVOH; (△) EVA; (□) EVA/LDPE; (×) LDPE. Lines are predictions from eqs 2 and3.

The effect of polymer hydrophobicity on quercetin release may be explained from the intermolecular force perspective. Quercetin has both hydrophilic (OH groups) and hydrophobic (ring structure) components. For a hydrophobic polymer, quercetin is not miscible in the polymer because its OH groups are exposed outside, and quercetin molecules also tend to cluster together, resulting in lower mobility. This observation has also been reported:[15] during extrusion of LLDPE with quercetin, small crystals of quercetin were formed and no release of quercetin was detected. For a hydrophilic polymer, the OH groups make quercetin more miscible in the polymer, and the hydrophobic ring prevents quercetin molecules from binding to the polymer, both allowing quercetin to move more freely.

The models (eqs 2 and 3) fit the data quite well, indicating that the release was controlled by diffusion of quercetin in the polymer films and that the model assumptions stated earlier were applicable (e.g., interactions such as binding of quercetin to polymer chain or swelling of polymer did not exist or were negligible). As shown in Table 2, hydrophilic polymers (EVOH and EVA) have diffusivities several orders of magnitude and partition coefficients many times higher than those of hydrophobic polymers (LDPE). The results obtained from EVOH in this study are comparable to literature data.[12]

Table 2. Estimated Diffusivities and Partition Coefficients for CRP Films Containing Quercetin

polymer	concn (ppm)	diffusivity (m^2/s)	partition coefficient (C_f/C_p)
EVA	3000	1.33×10^{-12} [a]	0.010
EVOH	3000	1.77×10^{-14} [a]	0.023
LDPE	3000	1.15×10^{-19} [b]	~0.001
PP[c]	3000		
EVA/LDPE (50%/50%)	3000	7.13×10^{-17} [b]	

[a]Estimated from eq 2. [b]Estimated from eq 3. [c]No detectable release of quercetin from PP film.

To provide long-term inhibition of lipid oxidation, an antioxidant such as quercetin should be released at an appropriate rate for a sufficiently long period of time. It is also desirable to release a large portion of the antioxidant originally loaded into the film; otherwise, much of the antioxidant would be wasted. As shown in Figure 2, the release of quercetin from EVOH and EVA may be too fast and too short, and the release from LDPE may be too slow and too little. However, a more promising release behavior was obtained using a polymer blend film consisting of both hydrophilic and hydrophobic polymers (50% EVA/50% LDPE). As shown in the figure, this polymer blend film had a moderate rate of release that was maintained for a long period of time. Its diffusivity was estimated as 7.13×10^{-17} m^2/s, but its partition coefficient is not included in Table 2 because equilibrium was not reached at the end of the experiment. The polymer blending ratio has been reported to significantly affect the release of tocopherol from LDPE/PP blend films.[4]

Release of Tocopherol and Quercetin from Binary Antioxidant CRP Films. Figure 3 shows that tocopherol (first and second curves) released more quickly but for a shorter period of time than quercetin (third and fourth curves) in LDPE and EVOH films. The difference is more pronounced for LDPE film (first and fourth curves) than for EVOH films

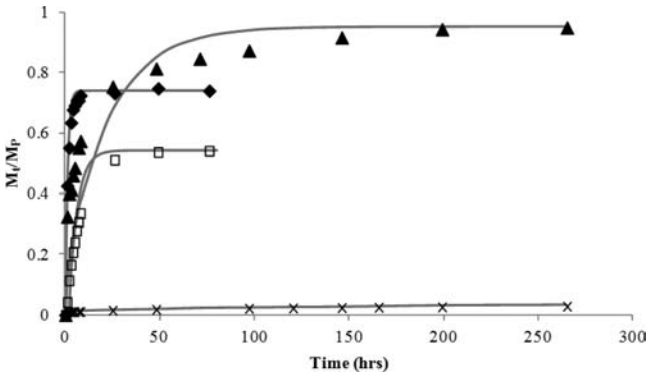

Figure 3. Release profiles of tocopherol and quercetin from binary antioxidant CRP films: (◆) tocopherol release from EVOH film; (□) quercetin release from EVOH film; (▲) tocopherol release from LDPE film; (×) quercetin release from LDPE film.

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Table 3. Estimated Diffusivities and Partition Coefficients for Binary Antioxidant CRP Films Containing Tocopherol (T) and Quercetin (Q)

	concentration (ppm)		diffusivity (m^2/s)		partition coefficient (C_F/C_P)	
polymer	Q	T	Q	T	Q	T
EVOH	1500	1500	6.33×10^{-14} [a]	1.75×10^{-13} [a]	0.024	0.059
LDPE	1500	1500	2.50×10^{-18} [b]	3.30×10^{-14} [a]	~0.001	0.723

[a]Estimated from eq 2. [b]Estimated from eq 3.

Table 4. Diffusivity of Tocopherol from the Literature

film	diffusivity of tocopherol (m^2/s)	temperature (°C)	ref
EVA bound paperboard	2.91×10^{-11}	10	10
	2.92×10^{-11} (release with nisin)		
100% LDPE/0% PP	4.6×10^{-14}	40	4
75% LDPE/25% PP	8.92×10^{-15}		
50% LDPE/50% PP	1.95×10^{-15}		
25% LDPE/75% PP	1.07×10^{-15}		
0% LDPE/100% PP	6.58×10^{-16}		
LDPE (tocopherol 20 mg/g)	1.4×10^{-11}	5	7
LDPE (tocopherol 40 mg/g)	1.3×10^{-11}		
LDPE (tocopherol 20 mg/g)	7.1×10^{-11}	20	
LDPE (tocopherol 40 mg/g)	9.6×10^{-11}		
LDPE (tocopherol 20 mg/g)	3.03×10^{-10}	30	
LDPE (tocopherol 40 mg/g)	5.11×10^{-10}		
HDPE + TiO_2/EVOH/LDPE	2.34×10^{-11}	20	8
	3.06×10^{-11}	30	
	3.14×10^{-11}	40	
LDPE	2.64×10^{-11}	7	9
LDPE (tocopherol was absorbed on adsorbent, Syloblock)	1.65×10^{-11}		
LDPE (tocopherol was absorbed on adsorbent, SBA-15)	1.66×10^{-11}		
EVA	4.23×10^{-11}		
PLA	3.16×10^{-11}	23	11
	5.29×10^{-11}	33	
	3.8×10^{-10}	43	
LDPE	1.53×10^{-11} (without encapsulation)	7	20
	1.68×10^{-12} (without encapsulation)		

(second and third curves). The difference in release behavior between these two antioxidants may be explained partly by their molecular shapes: tocopherol has a long alkyl chain, which facilitates its movement in the hydrophobic LDPE polymer, and quercetin is bulkier, which hinders its movement in the polymer matrix.

The models (eqs 2 and 3) also fit the data of the binary antioxidant CRP films quite well, and the estimated diffusivities and partition coefficients are shown in Table 3. Literature diffusivities are also summarized in Table 4; the data from this work are within the literature values, and the table also shows that a wide range of diffusivities of tocopherol spanning a few orders of magnitude may be obtained using different polymers.

It may be inferred from Figure 3 that the release of tocopherol and quercetin from neither EVOH nor LDPE is acceptable for long-term lipid oxidation inhibition. For EVOH, tocopherol and quercetin are released too quickly and stop too soon. For LDPE, tocopherol is released quite rapdily and stops quite soon, and quercetin is released too slowly. Nevertheless, it may be possible to produce a polymer blend film with more desirable releases of tocopherol and quercetin. As an example, Figure 4 shows the release of a hypothetical blend film in which the fast release of tocopherol (simulated using eq 2) provides short-term protection, followed by the sustained slow release of quercetin (simulated using eq 3) to provide intermediate/long-term protection. In this simulation, quercetin diffusivity is 7×10^{-17} m^2/s (close to the value of EVA/LDPE in Table 2), tocopherol diffusivity is 8×10^{-14} m^2/s (within the range of experimental values), film thickness is 1×10^{-4} m, quercetin concentration is 2100 ppm, and tocopherol concentration is 900 ppm. Further experiments are needed to confirm the feasibility of producing this and other possible binary antioxidant CRP films.

Effect of Tocopherol on Release of Quercetin. It is interesting to note that the release of quercetin was accelerated by the presence of tocopherol. From Table 2, quercetin diffusivities in the absence of tocopherol are 1.77×10^{-14} and 1.15×10^{-19} m^2/s in EVOH and LDPE, respectively. From

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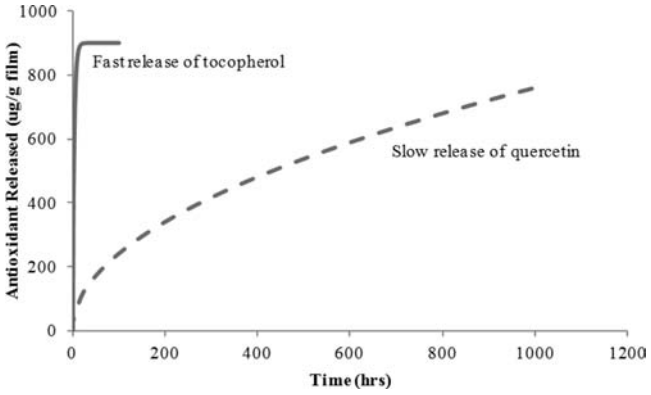

Figure 4. Simulated profiles of release of tocopherol (solid line) and quercetin (dashed line) from a binary film with blend of hydrophilic and hydrophobic polymer matrix.

Table 3, quercetin diffusivities in the presence of tocopherol are 6.33×10^{-14} and 2.50×10^{-18} m^2/s in EVOH and LDPE, respectively. Hence, adding tocopherol increased quercetin diffusivities more than 3 and 20 times in EVOH and LDPE, respectively.

A possible explanation of this observation is that tocopherol acts as a plasticizer in the polymers.[19] It has been reported that increasing tocopherol concentrations increased tocopherol diffusivities in LDPE at 20 and 30 °C due to the plasticizing effect.[7] Because quercetin is slow to release from hydrophobic polymers, the addition of tocopherol or other plasticizers may help to overcome this limitation.

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Notes

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ABBREVIATIONS USED

CRP, controlled-release packaging; EVA, ethylene vinyl acetate; EVOH, ethylene vinyl alcohol; LLDPE, linear low -density polyethylene; LDPE, low-density polyethylene; PP, polypropylene.

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