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Slow-DEET-Release Mosquito-Repellent System Based on Poly(butylene succinate)

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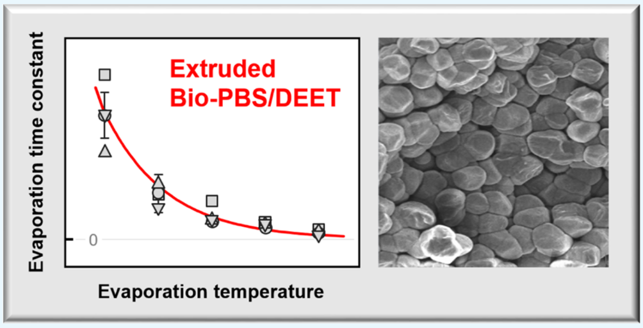
ABSTRACT: Bio-sourced and biodegradable poly(butylene succinate) (PBS) strands containing up to 40 m% mosquito-repellent *N*,*N*-diethyl-3-methylbenzamide (DEET) were obtained by extrusion, for an initial evaluation of the DEET evaporation characteristics and the possible application of such strands as biodegradable slow-release repellent-delivery devices. For DEET concentrations up to 20 m%, DEET is entrapped in the semicrystalline spherulitic superstructure of PBS. In contrast, at higher DEET concentrations, the liquid repellent, at least partially, is not fully incorporated in the PBS spherulites rather than segregates to form an own macrophase. Quantification of the release of DEET to the environment by thermogravimetric analysis at different temperatures between 60 and 100 °C allowed estimation of the evaporation rate at lower service temperatures, suggesting an extremely low release rate with a time constant of the order of magnitude of 1−2 years at 25 °C, independent of the initial concentration.



■ INTRODUCTION

Malaria is a deadly tropical disease caused by parasites transmitted by mosquitoes, most commonly in Africa. Malaria cases and the mortality rate in Africa account for 94% of the world incident number according to the World Health Organization (WHO) statistics in 2019.[1] Although many successful prevention ways are available,[2−4] malaria continues to be a severe problem for many countries. The fact that current prevention methods are not sufficient also shows up in the number of reported cases. In 2015, in risk-zones, 9 cases per 1000 population were reported, while this number increased to 10.4 in 2019,[1] documenting that further urgent research is needed to fight malaria and to decrease the number of incidents.

Common prevention strategies for indoor protection are the use of long-lasting insecticidal bednets and indoor residual spraying.[5−9] However, efficient prevention methods for outdoor cases are also required because a significant amount of mosquito bites occur outdoors, on the feet and ankles.[10−12] As such, several studies, described below, reflect a serious effort toward developing routes against outdoor mosquito bites.

A specific approach to protect against outdoor mosquito bites is the development of drug-delivery devices, which release mosquito repellents.[13,14] While commercial solutions are available, to be effective over short time periods,[15,16] long-lasting protection devices are hardly present. A possible route is the generation of a polymer scaffold hosting a sufficient amount of repellent in its open pores, being effective by evaporation over a long time.[17,18] The formation of microporous polymeric scaffolds typically is achieved by thermally induced phase separation (TIPS) on cooling solutions, either by crystallization-caused solid−liquid (S−L) phase separation or by liquid−liquid (L−L) phase separation, followed by polymer crystallization.[19−23]

Several polymer/repellent systems have been explored, including low-density polyethylene (LLDPE)/citronellal,[24] poly(L-lactic acid) (PLLA)/*N*,*N*-diethyl-3-methylbenzamide (DEET),[25−28] or PLLA/ethyl butylacetylaminopropionate (IR3535),[29] with all of these studies focusing on repellent-rich mixtures and on gaining fundamental information about systems thermodynamics.

In the first view, high-repellent-content preparations may be considered efficient regarding repellency; however, the high liquid content typically leads to gel-like structures, which cannot be used stand-alone. For this reason, also polymer-rich

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Table 1. Sample Compositions and Extrusion Parameters

						melt temperature				
PBS/DEET ratio [m%]	screw speed [1/min]	main feeder [1/min]	volumetric pump [mL/min]	engine load [%]	die pressure [bar]	die [°C]	zone 2 [°C]	zone 4 [°C]	zone 6 [°C]	zone 8 [°C]
100/0	215			91	21	124	119	126	131	131
90/10	200	37.0	16	84	15	123	120	126	128	128
80/20	200	16.5	16	49	5	121	120	125	127	127
70/30	200	9.6	16	36	2	122	124	125	127	128
60/40	200	6.2	16	28	1	121	121	125	126	127
50/50[a]	200	4.2	16							

[a] No stable process was achieved; therefore, no values were taken.

combinations were considered, to be processed by electrospinning,[30−32] fiber-spinning,[33,34] or melt extrusion.[35,36] Regarding the latter, LLDPE or poly(ethylene-*co*-vinyl acetate) (EVA) strands containing DEET or Icaridin as a mosquito repellent were prepared by twin-screw extrusion.[35]

The extruded strands showed a distinct skin-core structure, with the liquid repellents entrapped in the porous polymer matrix after spinodal decomposition of the initially homogeneous mixture. Although the strands contained only 30 m% repellent, foot-in-cage tests revealed protection against mosquito bites after aging up to 12 weeks at 50 °C,[35] illustrating the potential in disrupting outdoor malaria transmission where vectors preferably bite humans on ankles or feet when seating or standing.[11]

Despite the very promising results, both LLDPE and EVA are petroleum-based polymers and, in addition, not biodegradable. For these reasons, targeting the development of a more environmentally friendly system, bio-sourced and fast degrading poly(butylene succinate) (PBS) is considered a promising alternative as a polymeric repellent carrier. PBS crystallizes at a relatively (compared to PLLA) high rate with a maximum crystal fraction between 35 and 45%. PBS found many applications in the fields of packaging, mulching films, or implants and also serves as a base material for the generation of scaffolds for bone-tissue engineering.[37−42] Recently, TIPS-based PBS scaffold formation was successfully proven for DEET-rich mixtures;[43] however, with the above-mentioned shortcoming to not be applicable as is, due to lack of mechanical performance. In detail, it was shown that PBS dissolves above the PBS melting temperature in DEET, being a stringent precondition for TIPS. By variation of the polymer content and the crystallization temperature, the density of crystal nuclei and therefore the size and degree of intermeshing of spherulites are tunable, and with that the intra- and interspherulitic pore size.

In an extension of the initial study, focus of the present work is the investigation of the possibility of obtaining extruded PBS-rich strands containing DEET at an amount to be efficient to repel mosquitos, that is, around 20−40 m%. Accordingly, PBS strands containing up to 40 m% DEET were prepared using a co-rotating intermeshing twin-screw extruder, with TIPS enforced by quenching the molten strand into cold water. As one of the main results, besides data about the structure and the PBS crystallization behavior, the DEET release characteristics were quantified by the estimation of concentration-dependent time constants at an elevated temperature, allowing prediction of the evaporation kinetics at ambient temperature.

■ EXPERIMENTAL SECTION

Materials and Preparation. An extrusion-grade PBS homopolymer (BioPBS FZ91PM from PTT MCC Biochem Co., Ltd. (Thailand)) with a mass-average molar mass and polydispersity of 123 kg/mol and 4.4, respectively, was used.[44,45] DEET (purity 97%) was purchased from Sigma-Aldrich (Product number D100951)[46] and used without any further purification.

PBS compounds with varying contents of DEET were prepared in a co-rotating intermeshing twin-screw extruder LTE20−44/00 from Labtech Engineering Co., Ltd., Samutprakarn (Thailand), with a screw diameter of 20 mm and an L/D ratio of 44. A special screw design with a low number of shear- and kneading elements was used for processing. PBS as a hydrophilic material was dried for 4 h at 60 °C in a dry-air drier prior processing. The throughput of the PBS was varying, depending on the required repellent concentration in the compound (see Table 1). The dry PBS was fed via the main hopper, and the screw speed for the preparation of the compounds was set at 200 1/min except for the neat reference PBS samples where 215 1/min were used. The temperature profile of the extruder was set from the feeding zone (zone 1) to the die (zone 11) as follows: 120, 120, 125, 125, 130, 130, 130, 130, 130, 130, and 130 °C. The liquid repellent was added via a volumetric pump, eco-PEN600 (preeflow) from ViscoTECPumpen- u. Dosiertechnik GmbH, Töging am Inn, Germany, at zone 6. The melt was extruded through a dual strand die with a diameter of 3 mm, before being cooled in a water bath at 15 °C, and subsequently pelletized. Note that thermal degradation of DEET under the extrusion conditions is excluded, based on dedicated DEET-stability experiments described elsewhere.[36]

Instrumentation. *Thermogravimetric Analysis (TGA).* TGA was employed to measure the actual content of DEET after extrusion and to analyze the DEET evaporation kinetics. A TGA 2 system (Mettler Toledo, Greifensee, Switzerland), calibrated by the instrument provider, was used. Samples with a mass of around 3 mg were prepared by cutting sections with a thickness of about 500 μm across the whole strand, that is, perpendicular to the extrusion direction, and placed into 70 μL alumina pans. Nitrogen gas at a flow rate of 50 mL/min was used to purge the sample environment. In nonisothermal DEET evaporation experiments, a heating rate of 5 K/min was employed, while isothermal experiments were performed at temperatures between 70 and 100 °C for 24 h. To gain knowledge about slow DEET release at a lower temperature, release-time constants obtained at temperatures between 70 and 100 °C were extrapolated to 25 °C, using a fit function.

Differential Scanning Calorimetry (DSC). DSC was employed for analysis of the crystallinity of the strands. We employed a calibrated heat-flux type DSC 1 from Mettler Toledo (Greifensee, Switzerland) connected to a Huber intracooler TC 100 (Offenburg, Germany). Nitrogen gas with a flow rate of 60 mL/min was used as a purge gas. Samples with a mass between 5 and 10 mg, prepared from the strands as described for TGA measurements, were placed into Mettler Toledo 40 μL aluminum pans and heated to 150 °C at 20 K/min.

Polarized-Light Optical Microscopy (POM). POM served for analysis of the spherulitic superstructure of the extruded strands and for the possible identification of phase separation of PBS and DEET. We used a DMRX microscope (Leica, Wetzlar, Germany) in transmission mode, with samples located between crossed polarizers. For the preparation of sections with a thickness of about 10 μm, a rotary microtome CUT 5062 (Slee, Mainz, Germany) equipped with a tungsten carbide knife was used. In addition, samples were heated using a hotstage THMS 600 (Linkam, Tadworth, UK), for confirmation that the initial micrometer-scale structure of the strands is preserved on heating to 100 °C, being the maximum evaporation temperature in TGA.

Scanning Electron Microscopy (SEM). A Tescan Vega 3 SBU SEM (Dortmund, Germany) was used and operated in high-vacuum mode, with an acceleration voltage of 10 kV. Extruded, nonpelletized strands with a length of 15 cm were placed in liquid nitrogen and kept there for 15 min. The cooled samples were then cryo-fractured to obtain rather flat faces of the cross section before placing pieces of appropriate length onto the SEM sample holder stage.

■ RESULTS AND DISCUSSION

DEET Concentration. The effective amount of DEET in the extruded PBS/DEET strands was measured using TGA to explore possible evaporation of DEET during the initial melt-mixing/extrusion process. Figure 1 shows the normalized mass loss of neat PBS and DEET (black curves) and of PBS samples containing DEET (colored curves) as a function of temperature during heating at 5 K/min. The evaporation of DEET at the given experimental conditions begins at about 120 °C and is completed slightly above 200 °C. This behavior is expected and in agreement with independent studies.[47−49] Degradation of PBS, in contrast, occurs at a much higher temperature between, roughly, 300 and 400 °C, as also reported in the literature.[50−52] The rather large difference of the temperature ranges of evaporation/degradation of DEET and PBS allows to estimate the effective DEET content in the various extruded PBS/DEET strands, by analysis of the in-between plateau value of the observed two-step mass loss. The legend in Figure 1 provides information about the expected/target DEET content (right column; see also the anticipated mixture compositions in Table 1) and measured DEET content (left column). Considering minor errors in the determination of the effective DEET content in the mixtures due to the interplay of kinetics of evaporation and the heating rate, causing, e.g., a non-constant plateau in the 90/10 PBS/DEET sample, the observed data suggest that the target and achieved DEET concentration in the extruded strands are very similar. Obviously, there did not occur distinct evaporation of the liquid DEET during the melt-mixing process at the chosen extrusion parameters.

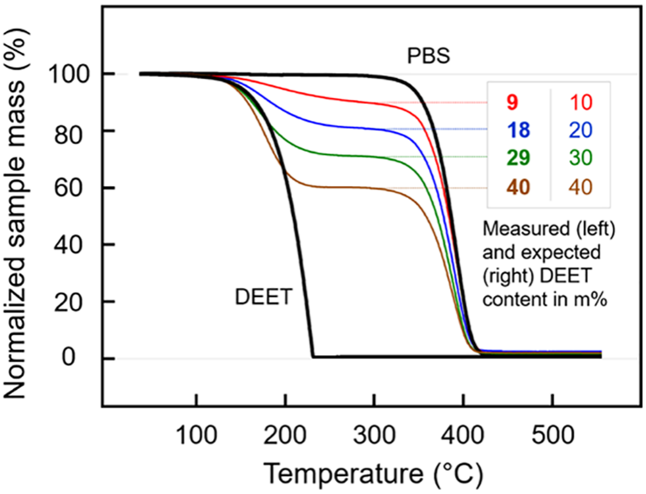

Figure 1. TGA heating scans, normalized mass as a function of temperature, of neat DEET and extruded strands of neat PBS and PBS/DEET mixtures containing different amounts of DEET. The measured and expected DEET contents in the various mixtures are provided with the left and right columns of the legend, respectively. Measurements were performed in a nitrogen atmosphere, using a heating rate of 5 K/min and a sample with a mass of around 3 mg. Measurements were performed after storing the strands at room temperature for about 12 weeks after extrusion.

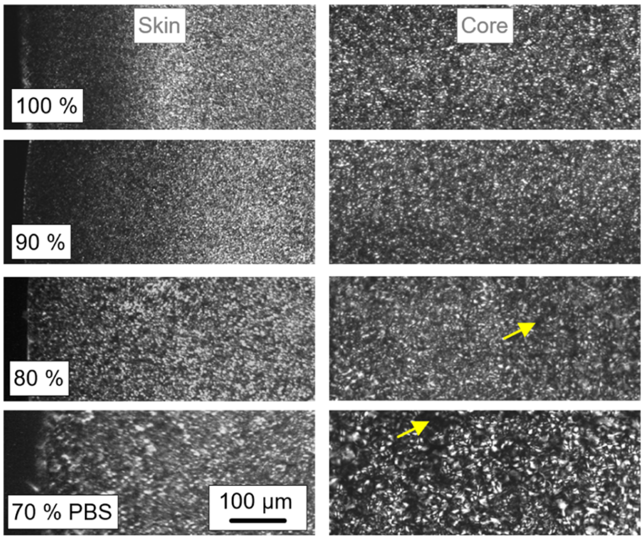

Figure 2. Micrometer-scale morphology of extruded strands of neat PBS (top) and of PBS/DEET mixtures containing up to 40 m% DEET (bottom), observed by POM. Images of the left and right columns were obtained on thin sections taken perpendicular to the extrusion direction at the skin and the core of the strands with a diameter of 3 mm, respectively.

POM and SEM Structure. Figure 2 shows the micrometer-scale morphology of extruded strands of neat PBS (top) and of PBS/DEET mixtures containing up to 30 m% DEET (bottom), observed by POM, with the images of the left and right columns obtained on thin sections taken perpendicular to the extrusion direction at the skin and the core of the strands with a diameter of 3 mm, respectively. All micrographs indicate with the white spots that crystallization of PBS occurred, with the fine-grainy structure caused by the rather high supercooling of the melt when extruding into cold water. High melt-supercooling yields a high number of crystal nuclei and, consequently, large spherulites cannot grow.[53−55] At a low DEET concentration of 10 m% (second-row images), the liquid DEET component cannot be identified, which either may be caused by its dissolution in PBS or, if separated from PBS, by the smallness of particles. In contrast, at higher DEET contents of 20 and 30 m% DEET, black areas in the POM images indicate phase separation (see also yellow arrows). Although the differences may be considered marginal, a comparison of images taken at the skin and the core of the thin sections suggests a slightly finer morphology in skin-near regions, which, again, likely is caused by faster cooling of the latter, and crystallization of PBS at a lower temperature. In the context of using such strands for repellent release, such skin-core morphology may affect the release rate as proposed in the literature.[17,35]

Figure 3 shows SEM micrographs of cryo-fractured cross-sectional surfaces of extruded strands of neat PBS (top) and of PBS/DEET mixtures, with the PBS content provided in the images of the left column. Images in the left and right columns provide an overview of the cross section and details of the structure of the core at a higher magnification, respectively. Regarding neat PBS (upper row images), the obtained rather smooth and flat surface indicates brittle fracture. Furthermore, the cross-sectional overview image on the left reveals a skin-core morphology, which is also detected for PBS/DEET mixtures; at higher DEET concentrations, however, it fades and in the case of the sample containing 40 m% DEET (bottom left image), structure differences across the cross section cannot be seen anymore.

Inspection of the fractured surfaces of various PBS/DEET mixtures at higher magnification suggests less brittle deformation behavior with increasing DEET content up to 20 m%, as the surface becomes more structured. However, if the DEET content exceeds 20 m%, then distinct particle-like heterogeneities with a size of around 10 μm, well-separated from each other, are detected. At a DEET content of 40 m%, even larger holes in between particle-rich domains can be seen. The latter observation is in agreement with the corresponding POM image of Figure 2. Regarding the particle-like structures, we assume that these are PBS spherulites, being surrounded by liquid DEET (before SEM sample preparation that involved the evaporation of the repellent) expelled during their growth. It appears that extruded strands can accommodate up to 40 m% DEET; however, disconnected spherulites and large heterogeneities may be disadvantageous regarding the mechanical performance and limit a possible stand-alone application.

DSC Crystallinity. Crystallization of PBS during cooling the extruded strands into cold water, and/or afterward, has been confirmed above with the POM images, and is further quantified regarding the achieved crystal fraction by DSC. Melting peaks were evaluated regarding the enthalpy of melting, which is plotted, after normalization by the actual PBS content, as a function of the composition of the various samples. The experimental data reveal an enthalpy of melting of neat PBS of slightly higher than 60 J/g, which corresponds to a crystal fraction of close to 1/3 when using 200 J/g as a bulk enthalpy of melting.[56,57] Adding DEET, however, yields slightly higher values, that is, crystallization in the presence of a solvent is enhanced, confirming earlier performed crystallization research of solvent-rich compositions of the same system.[43] Whether the minor increase of the crystallinity with increasing DEET content has a measurable effect on DEET evaporation is evaluated as shown in Figure 4.

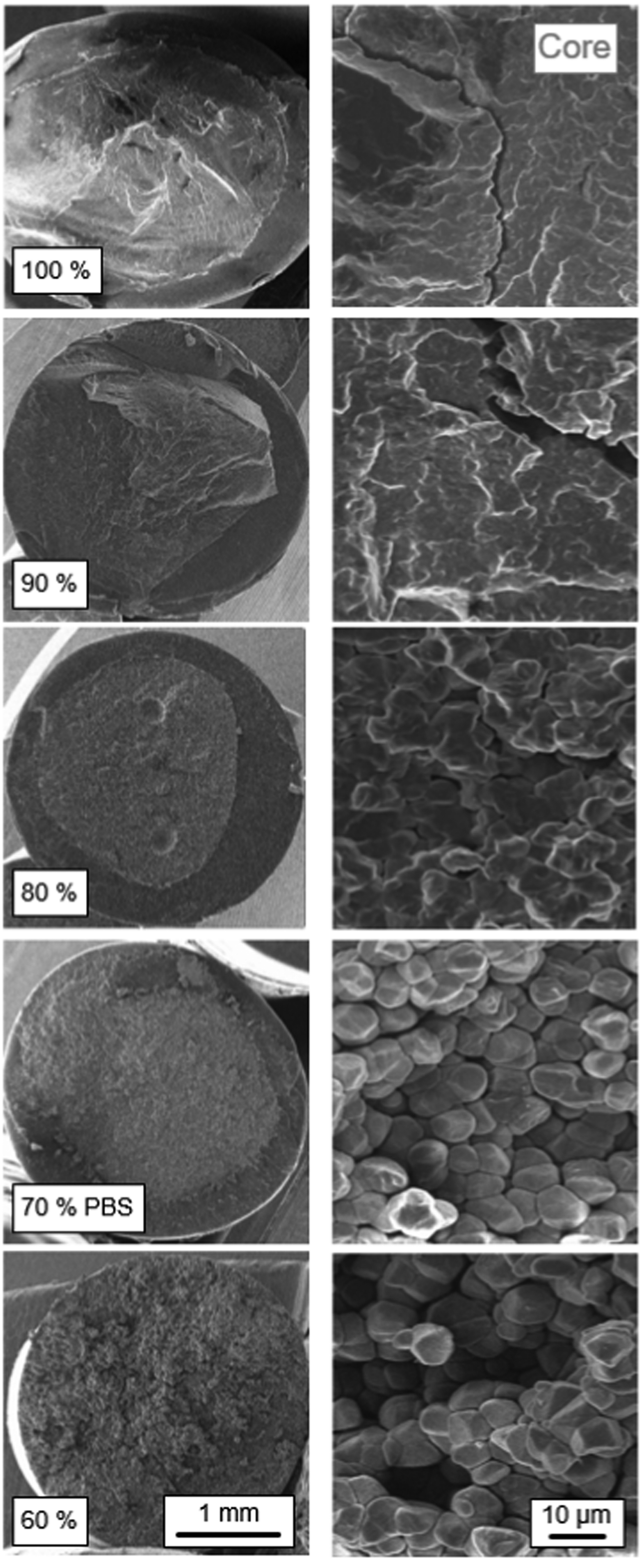

Figure 3. Morphology of extruded strands of neat PBS (top) and of PBS/DEET mixtures containing up to 30 m% DEET (bottom), observed by SEM. Images on the left and right columns provide an overview of the strand-cross-section and details of the structure of the core, respectively.

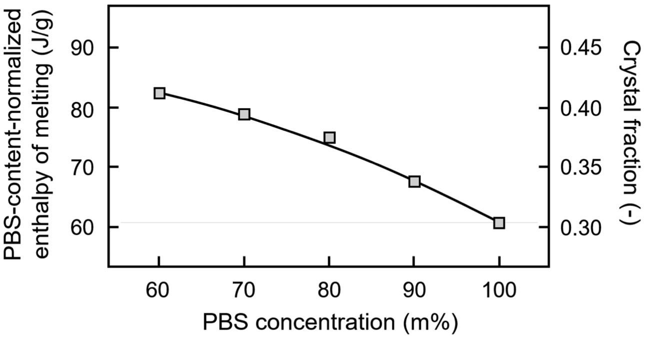

Figure 4. PBS-content-normalized enthalpy of melting as a function of the PBS-concentration.

Repellent Release from Extruded Strands. The retention of the repellent in the polymer matrix and its slow release to the environment determines the efficiency regarding repelling mosquitoes. Figure 1 shows that the repellent release at ambient temperature (around 21 °C) is negligible since storing the extruded strands for several weeks did not cause a measurable change of the initial DEET concentration. To obtain quantitative information about the repellent release rate, the extruded PBS/DEET strands were heated to a predefined temperature between 60 and 100 °C, and then the release was monitored under isothermal conditions by the mass loss. Figure 5 shows with the top, center, and bottom plots the percentage sample mass, normalized to the initial value (around 3 mg), as a function of the annealing/evaporation time, recorded for 24 h, for samples initially containing 10, 20, and 30 m% DEET, respectively; note that data are also available for samples containing 40 m% DEET. Differently colored curves denote different evaporation temperatures, as indicated in the legend. Note again that, besides identical measurement conditions, care was taken regarding assuring similar sampling, sample mass, and sample placement in the alumina pan, as all of these factors may affect the evaporation rate. In all cases, a nonlinear decrease of the sample mass with time is observed. If the evaporation temperature is 100 °C, then evaporation even can complete within the experiment time of 24 h, as indicated by reaching a plateau at the expected percentage polymer masses of 90, 80, and 70 m% (from top to bottom). At temperatures lower than 100 °C, evaporation cannot complete within 24 h.

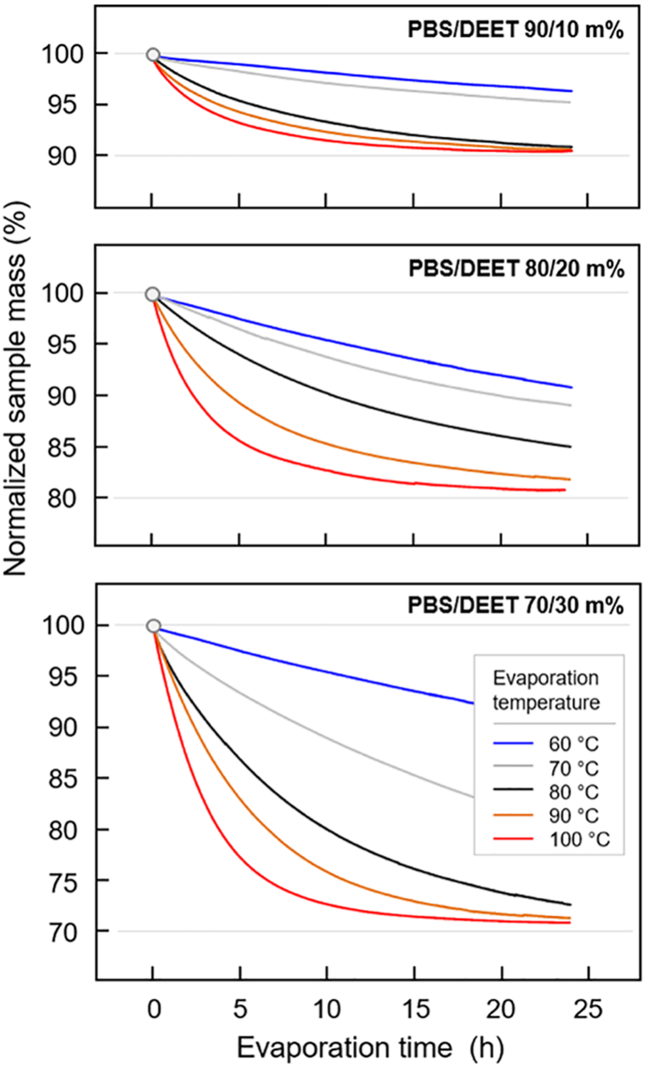

Figure 5. Percentage sample mass, normalized to the initial value of around 3 mg, as a function of the annealing/evaporation time, recorded for 24 h. The top, center, and bottom plots were obtained on samples initially containing 10, 20, and 30 m% DEET, respectively, and the differently colored curves denote different evaporation temperatures, as indicated in the legend.

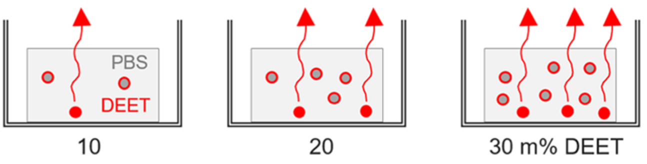

Figure 6. Schematic of DEET evaporation/diffusion in PBS samples containing different amounts of DEET (red circles), emphasizing a different total flux at a predefined time and similar kinetics/diffusion-time of particles at a similar location.

A further, striking observation is the apparent independence of the evaporation time, at a given temperature, on the initial concentration. For example, annealing at 70 °C does not allow completion of the evaporation process, and regardless of the initial DEET content, only about 50 m% of the repellent evaporates within 24 h. This finding supports the notion that the time dependence of the evaporation process of DEET mainly is controlled by the diffusion path length in the polymer while the total flux at a given time is governed by the concentration. For illustration, Figure 6 provides sketches for a qualitative interpretation of the experimental data of Figure 5, emphasizing that evaporation/diffusion of DEET molecules, located at a specific position in the samples, see, e.g., red-filled points, requires similar time in all samples regardless of the initial total concentration. Surprisingly, both the change of the crystallinity of the polymeric matrix (see Figure 4) and possible, though not proven, twofold distribution of the repellent in intra- and interspherulitic spaces of samples containing 30 m% repellent, or more, seem not affecting the evaporation characteristics. Note furthermore that heating the extruded strands to the evaporation temperature does not cause a change of the morphology, that is, global melting always occurred at temperatures above 100 °C.

For quantification of the evaporation of DEET in TGA experiments, the experimental data were fitted using an exponential decay function, assuming that the release of DEET follows a first-order process according to eq 1

$$m(t) = m_{\mathrm{DEET}}\, \mathrm{e}^{-t/\tau} + m_{\mathrm{PBS}} \tag{1}$$

In eq 1, $m(t)$, m_{DEET}, and m_{PBS} represent the time-dependent total mass of the sample, the initial mass of DEET, and the (constant) mass of PBS, respectively. Furthermore, t is the evaporation time and τ is a time constant describing the rate of evaporation. The latter provides information about the time needed to decrease the DEET concentration by a factor of 1/e, that is, by 36.7%.

Figure 7 shows time constants of DEET evaporation of samples initially containing between 10 and 40 m% DEET as a function of the evaporation temperature. As expected, τ values decrease with increasing temperature, approaching values close to zero if the temperature increases to above 100 °C. On the opposite, the time constant exponentially increases on lowering the evaporation temperature to quickly reach a value of several days when annealing the samples at 60 °C. The data of Figure 7 furthermore reveal that there is no systematic trend regarding an effect of the initial DEET concentration. At best, we recognize that the reproducibility of the experiment seems to decrease when lowering the evaporation temperature. The independence of the evaporation-time constant on the initial DEET concentration suggests using all data of Figure 7 for obtaining a single function describing the temperature dependence of the evaporation kinetics. The curve shown is an exponential fit according to eq 2

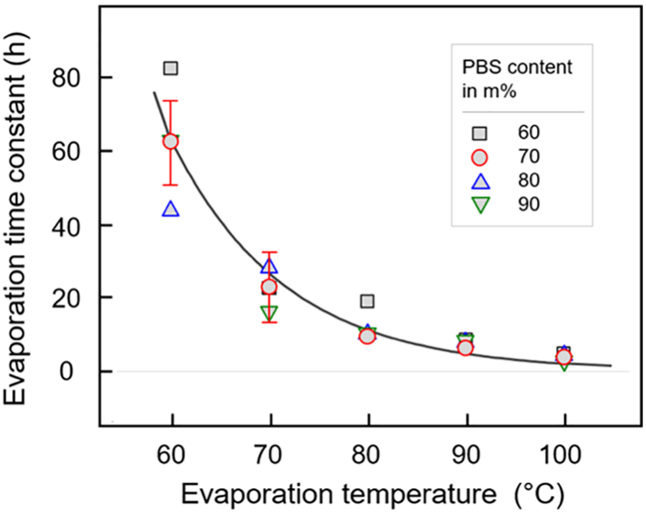

Figure 7. Time constant of DEET evaporation from PBS extrudates of different initial DEET contents as a function of the TGA-evaporation temperature.

$$\tau(T) = B\mathrm{e}^{-T/T_{\mathrm{char}}} \tag{2}$$

where $\tau(T)$ is the temperature-dependent evaporation-time constant (see eq 1), B is a constant, and T_{char} is a characteristic temperature. The advantage of eq 2 is the possibility to calculate the evaporation-time constant for any temperature of interest. As such, the data of Figure 7 predict an evaporation-time constant of around 545 days at 25 °C. In other words, at 25 °C, around 37% [≈1/e × 100%] of the initial DEET concentration evaporates within around 1.5 years.

■ CONCLUSIONS

PBS and DEET, as potential system components for developing slow-release mosquito repellent devices, were successfully melt-compounded by twin-screw extrusion. Extruded strands contained up to 40 m% DEET, which is entrapped in intra- and interspherulitic spaces of partially crystallized PBS. Evaporation of DEET, as evaluated by TGA, shows an exponential time dependence, slowing down with time. The evaporation rate increases with temperature, to be completed within a few hours at temperatures around 100 °C, or higher. Evaporation-time constants were determined for temperatures between 60 and 100 °C, being independent of the initial DEET content, and pointing to similar diffusion pathways in the various samples. Minor differences of the polymer crystallinity and of possible segregation of DEET in interspherulitic spaces at high loading levels seem not affecting the evaporation kinetics. The evaporation experiments performed between 60 and 100 °C allow estimation of the release rate at ambient temperature and prediction of a corresponding time constant of around 1.5 years, at the given conditions realized by TGA. The long evaporation time classifies the combination of PBS and DEET as a slow-release system, regardless of the not-yet-known efficacy regarding repellence properties.

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Notes

The authors declare no competing financial interest.

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