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Permeability and Diffusion of Pharmaceuticals through Thermoplastic Polyurethanes

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ABSTRACT

Thermoplastic polyurethanes (TPU) have been in use for a variety of drug delivery systems, including osmotic pumps, implants, and intravaginal rings, for controlled release of a broad range of drug substances including clonidine, dapivirine, dolutegravir, elvitegravir, IQP-0528, tenofovir, naltrexone, and dexamethasone. Selection of the appropriate polymer and dimensions to achieve a target controlled release rates of these drugs in TPU devices remains poorly understood. The objective of this study was to measure the diffusion, permeability, and partition of a range of hydrophobic and hydrophilic model drugs through three PathwayTM TPU designed for drug delivery systems. The parameters were used to generate a predictive model for diffusion-controlled steady-state release from cylindrical reservoir device.

The study design included hydrophobic and hydrophilic drugs (tenofovir, bupivacaine, risperidone, IQP-0528, levonogestrel, and ibuprofen) and three Pathway™ TPUs: PY-PT60D, PY-PT87AE, and PY-PT95AE60. The three TPUs varied in the hydrophobicity of the soft segment and the amount of physical crosslinks between chains imparted by the hard segment content in the polymer. Permeability and diffusion coefficient of the model drugs through polymer films in phosphate buffer was measured using side by side diffusion cells. Partitioning of drug into each polymer film was also measured.

Drug concentration over time in the acceptor compartment followed the expected membrane permeability curve, with characteristic linear steady state regime (Figure 2). Permeability coefficients were calculated through using the equation $Kp = Q/AtC_1$, where Q is the total mass transported over time t through a membrane of area A given donor concentration C_1. Similarly, diffusion coefficients were calculated using the lag-time approach: $D=l^2/6L$, where L is the time-axis intercept, and l is membrane thickness. For Pathway PY-PT60D, drug concentration for IQP-0528, Ibuprofen, and Levonorgestrel remained below our lower limit of quantitation even after 100 hours; diffusion and permeability could not be quantified and were noted as 'low'.

We observed a general trend: for any given drug, permeability was highest through the PY-PT95AE60, with less permeability through the PY-PT87AE, and the least permeability through the PY-PT60D. Interestingly, this trend was valid for both hydrophilic and hydrophobic drugs. Higher diffusion through PY-PT95AE60 is correlated with increased free volume available for diffusion due to polymer swelling (145% of the initial mass). Drug permeability through PathwayTM PY-PT95AE60 film was influenced by drug solubility, with the more hydrophobic drugs (levonogestrel, IQP-0528) permeating slower compared to the hydrophilic drugs (tenofovir, bupivacaine, risperidone, ibuprofen). In the case of PY-PT87AE and PY-PT60D, despite having similar swelling (~101% of initial mass), the permeability was lower for PY-PT60D due to the higher crystallinity of the polymer. For Pathway PY-PT60D, drug concentration in the receptor compartment for IQP-0528, ibuprofen, and levonorgestrel remained below quantification limit even after 100 hours.

Diffusion, permeability, and partition of hydrophobic and hydrophilic model drugs through films of Pathway TPUs films was governed by polymer hydrophobicity and crystallinity and drug properties. A predictive tool to be used for the design of controlled release systems was created based on diffusion-controlled steady-state drug release.

PURPOSE

- Many drugs have been formulated in polyurethanes for controlled release, including clonidine, dapivirine, dolutegravir, elvitegravir, IQP-0528, tenofovir, tenofovir alafenamide fumarate (TAF), and tenofovir disoproxil fumarate (TDF).
- Polyurethanes are useful for controlled drug delivery, selection of the appropriate polymer and dimensions to achieve a desired target controlled release rates of these drugs in polymer devices remains poorly understood. As a result, design of polyurethane controlled release devices requires a great deal of trial and error.
- These studies explore mechanisms and rates of diffusion of a range of hydrophobic and –philic drugs through polyurethane films.

METHODS

- Pathway™ PY-PT60DE, PY-PT87AE, and PY-PT95AE60 were extruded into films of 150 um thickness using a single screw extruder through a film die.
- Polymer film swelling was measured after 96 hours.
- Solutions of tenofovir, IQP-0528, levonorgestrel, bupivicaine, ibuprofen, and risperidone were placed in the acceptor compartment of Permegear side by side diffusion cells and donor concentrations measured over a period of 72 - 120 hours using an Agilent 1200 series HPLC attached to a DAD. Temperature of the diffusion cell was maintained at 37°C throughout the experiment.
- Drug permeability and diffusion coefficient was measured through these membranes (Table 2). Diffusion coefficient was calculated both by using lag time and a curve-fitting method which took partitioning into account.
- Partitioning of drug from solution into the film was measured. Films of known mass were incubated in drug solution for one week at 37°C. Mass of drug in the films was measured using an Agilent 1200 series HPLC attached to a DAD.

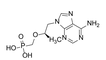
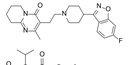
Drug Name	Chemical Structure	Predicted LogP	Molecular Weight (g/mol)	Solubility in PBS with 2% Solutol (mg/mL)
Tenofovir		-1.51	287.21	2.6
Levonorgestrel		3.25	312.45	0.03
Bupivicaine		3.31	288.43	3.9
Risperidone		3.27	410.48	0.3
IQP-0528		4.1	340.42	0.01
Ibuprofen		3.5	206.29	1.2

Table 1. Pharmaceutically relevant drugs with a range of hydrophobicities were selected for this study. LogP was predicted using ALOGPS 2.1.

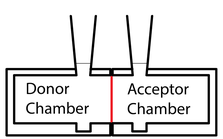


Figure 1. Side by side diffusion cell. The donor chamber is filled with concentrated drug solution, while the acceptor chamber is filled with buffer. A water jacket maintains the system at 37°C. Both chambers are constantly stirred to minimized boundary affects.

RESULTS

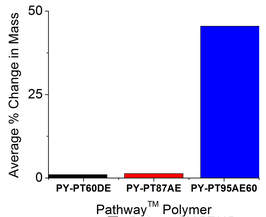


Table 2. Swelling of Pathway™ PY-PT60DE, PY-PT87AE, and PY-PT95AE60 after being hydrated for 96 hours. PY-PT95AE60 swelled considerably more (45.51%) than either PY-PT-60DE or PY-PT87AE (1.07% and 1.31%, respectively).

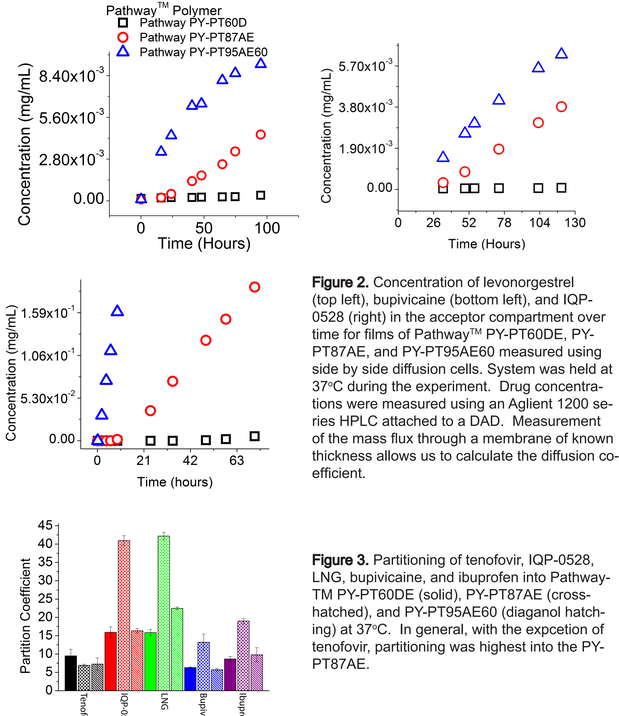


Figure 2. Concentration of levonorgestrel (top left), bupivicaine (bottom left), and IQP-0528 (right) in the acceptor compartment over time for films of Pathway™ PY-PT60DE, PY-PT87AE, and PY-PT95AE60 measured using side by side diffusion cells. System was held at 37°C during the experiment. Drug concentrations were measured using an Aglient 1200 series HPLC attached to a DAD. Measurement of the mass flux through a membrane of known thickness allows us to calculate the diffusion coefficient.

Figure 3. Partitioning of tenofovir, IQP-0528, LNG, bupivicaine, and ibuprofen into Pathway-TM PY-PT60DE (solid), PY-PT87AE (cross-hatched), and PY-PT95AE60 (diaganol hatching) at 37°C. In general, with the expcetion of tenofovir, partitioning was highest into the PY-PT87AE.

Drug	Polymer	Permeability (cm/s)	Diffusion Coefficient (lag time) (cm^2/s)	Diffusion Coefficient (partition) (cm^2/s)
Tenofovir	PY-PT60DE	1.17×10^{-6}	Less than 4.7×10^{-8}	1.11×10^{-10}
	PY-PT87AE	2.20×10^{-7}	Less than 5.4×10^{-8}	1.60×10^{-11}
	PY-PT95AE60	1.1×10^{-4}	1×10^{-7}	3.98×10^{-9}
IQP-0528	PY-PT60DE	LOW	LOW	9.72×10^{-12}
	PY-PT87AE	1.16×10^{-6}	3.47×10^{-10}	4.60×10^{-10}
	PY-PT95AE60	2.23×10^{-6}	5.71×10^{-9}	1.84×10^{-9}
Levonorgestrel	PY-PT60DE	LOW	LOW	9.08×10^{-11}
	PY-PT87AE	1.63×10^{-6}	5.53×10^{-10}	8.42×10^{-10}
	PY-PT95AE60	3.96×10^{-6}	Less than 5.8×10^{-8}	3.14×10^{-9}
Bupivicaine	PY-PT60DE	5.82×10^{-6}	1.82×10^{-10}	1.72×10^{-10}
	PY-PT87AE	9.31×10^{-5}	1.07×10^{-9}	1.30×10^{-9}
	PY-PT95AE60	8.19×10^{-4}	1.19×10^{-7}	2.06×10^{-8}
Ibuprofen	PY-PT60DE	LOW	LOW	LOW
	PY-PT87AE	3.63×10^{-7}	3.49×10^{-9}	$8.42x10^{-10}$
	PY-PT95AE60	2.24×10^{-6}	3.28×10^{-8}	$3.92x10^{-8}$
Risperidone	PY-PT60DE	LOW	LOW	
	PY-PT87AE	8.31×10^{-7}	2.8×10^{-8}	
	PY-PT95AE60	1.19×10^{-5}	4.9×10^{-7}	

Table 3. Permeability and diffusion coefficients of drug through polymer films at 37°C. Diffusion coefficients are calculated through lag time and partition methods. If lag time was not evident, upper bound is given based on lag time of less than 10 minutes.

CONCLUSIONS

- For all drugs, regardless of differences in solubility, permeability was highest through the HP 100A-60, then the PY-PT87AE, with the least permeability through PY-PT60D.
- Higher diffusion through the Tecophilic HP100A-60 polymers can be attributed to the increased swelling, in accordance with free volume models for diffusion.
- Similar swelling in the PY-PT60D and PY-PT87AE (1.31% vs. 1.07%), but diffusion through the Pathway PY-PT60D was generally lower for all drugs studied. This is likely due to the increased crystallinity in the Pathway PY-PT60D. This leads to increased diffusional path-length due to increased tortuousity.
- The influence of solute-solvent interaction on transport through the films will require further investigation; differences in diffusion coefficient in similar systems does not appear to be explainable solely through size differences.
- One possible explanation for this difference in diffusion coefficients is solute-polymer interaction, though other factors, including solute-solvent interactions and shape factors could also explain some of this discrepancy. Isolation of these mechanisms will require further work and careful selection of the systems of study.

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FURTHER INFORMATION

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