Thermoplastic Polyurethanes (TPU) in Drug Delivery Applications

Lubrizol LifeSciences' thermoplastic polyurethanes (TPUs) are well recognized as a safe, reliable, and effective option for many drug delivery systems. Below is a partial list of reference papers, reviews and posters that support this by discussing TPU's usage and benefits in pharmaceutical applications, including combination products and oral solid dosage forms.

Drug Delivery – General

Permeability and diffusion of pharmaceuticals through thermoplastic polyurethanes (2015)

Su J , Sung S, Kulkarni P , Draganoiu E , Kiser P.F. Annual Meeting of the American Association of Pharmaceutical Sciences.

Diffusion and permeability were evaluated for a range of hydrophobic and hydrophilic drugs in three Pathway™ thermoplastic polyurethanes (TPUs). A general trend was observed: for any given drug, permeability was always highest through one of the TPUs and lower with the other two.

Polyurethane-based drug delivery systems (2013)

Cherng JY, Hou TY, Shih MF, Talsma H, Hennink WE. International journal of pharmaceutics. 450(1-2):145-62.

The synthesis and characterization of polyurethanes for biomedical and pharmaceutical applications was reviewed, as well as polymer properties in vitro and in vivo. Particular emphasis was placed on the use of polyurethanes for controlled drug release and targeted delivery of biotherapeutics.

Polyurethanes for controlled drug delivery (2016)

Basu A, Farah S, Kunduru RK, Doppalapudi S, Khan W, Domb A. Advances in Polyurethane Biomaterials. 217-246.

The chemistry and synthesis of polyurethanes was reviewed, particularly in the context of fine-tuning mechanical properties and biocompatibility. One section is dedicated to thermoplastic polyurethane (TPU) polymers and its broad capabilities within the life sciences.

Preparation and characterization of naproxen-loaded electrospun thermoplastic polyurethane nanofibers as a drug delivery system (2016)

Akduman C, Özgüney I, Kumbasar EPA. Materials science & engineering. C, Materials for biological applications. 64:383-390.

Naproxen-loaded (10-20%) thermoplastic polyurethane (TPU) nanofiber mats were produced via electrospinning for drug delivery applications. Release kinetics were evaluated and it was observed that a higher drug load resulted in faster initial release rates.

The production of solid dosage forms from non-degradable polymers (2016)

Major I, Fuenmayor E, McConville C. Current pharmaceutical design. 22(19):2738-60.

Three non-biodegradable polymers for solid dosage forms were reviewed, including thermoplastic polyurethane (TPU). A variety of possible TPU drug delivery applications were discussed along with processing methods, chemical make-up, and mechanisms of controlled drug release.

Sustained release drug delivery applications of polyurethanes (2018)

Lowinger MB, Barrett SE, Zhang F, Williams RO 3rd. Pharmaceutics. 10(2).

Polyurethanes for controlled drug delivery applications were reviewed. Numerous material properties were considered for their effect on drug delivery, including hydrophobicity, pore formation, release rates, drug diffusivity, and, specific to thermoplastic polyurethane (TPU), soft to hard segment ratio.

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Vaginal Rings

A 90-day tenofovir reservoir intravaginal ring for mucosal HIV prophylaxis (2012)

Johnson TJ, Clark MR, Albright TH, Nebeker JS, Tuitupou AL, Clark JT, Fabian J, McCabe RT, Chandra N, Doncel GF, Friend DR, Kiser PF. Antimicrobial agents and chemotherapy. 56(12):6272-83.

A novel, reservoir-type intravaginal ring (IVR) was designed for controlled, sustained drug release. Thermoplastic polyurethane (TPU) tubing was filled with a paste containing tenofovir (TFV) and evaluated for safety and pharmacokinetics. In vivo sheep studies successfully demonstrated that the IVR provided elevated TFV vaginal concentrations for 90 days compared to the 1% TFV gel control. No negative toxicological findings were found, although slight to moderate increases in inflammatory infiltrates in the vaginal epithelia were observed for some animals.

A hot-melt extruded intravaginal ring for the sustained delivery of the antiretroviral microbicide UC781 (2012)

Clark MR, Johnson TJ, McCabe RT, Clark JT, Tuitupou A, Elgendy H, Friend DR, Kiser PF. Journal of pharmaceutical sciences. 101(2):576-87.

A thermoplastic polyurethane (TPU) intravaginal ring (IVR) was prepared for the sustained delivery of UC781. A matrix rod of UC781 and TPU were hot-melt extruded and subsequently demonstrated load-dependent, diffusion-limited kinetics. In vitro data showed good cell viability, tissue integrity, and barrier function of EpiVaginal tissue. Controlled drug release kinetics from the IVR were achieved both in vivo and in vitro.

A phase 1 randomized placebo-controlled safety and pharmacokinetic trial of a tenofovir disoproxil fumarate vaginal ring (2016)

Keller MJ, Mesquita PM, Marzinke MA, Teller R, Espinoza L, Atrio JM, Lo Y, Frank B, Srinivasan S, Fredricks DN, Rabe L, Anderson PL, Hendrix CW, Kiser PF, Herold BC. AIDS. 13;30(5):743-51.

A Tenofovir disoproxil fumarate (TDF)-eluting intravaginal ring was developed from thermoplastic polyurethane (TPU) and assessed for safety and pharmacokinetics in a human clinical trial. Drug concentration in cervicovaginal fluid was evaluated over a 14-day span. The results indicated that these antiviral-loaded TPU rings were safe, efficacious in continual drug delivery, and showed significant promise for HIV prevention.

An Intravaginal Ring for the Simultaneous Delivery of an HIV-1 Maturation Inhibitor and Reverse-Transcriptase Inhibitor for Prophylaxis of HIV Transmission (2015)

Ugaonkar SR, Clark JT, English LB, Johnson TJ, Buckheit KW, Bahde RJ, Appella DH, Buckheit RW Jr, Kiser PF. J Pharm Sci. 104(10):3426-39.

Hydrophobic thermoplastic polyurethane (TPU) intravaginal rings (IVRs) were investigated to deliver an antiretroviral in combination with an HIV reverse transcriptase inhibitor. The drug-loaded matrix IVRs showed no drug degradation when subjected to accelerated stability conditions. Toxicological evaluations of the IVRs indicated no evidence of formulation toxicity and in vitro assays demonstrated efficacious drug release.

Antiretroviral eluting intravaginal rings to prevent the sexual transmission of HIV (2012)

Johnson T.J. The University of Utah, Department of Bioengineering.

Several matrix and reservoir-type polyurethane intravaginal rings (IVRs) were developed for the delivery of antiretrovirals. A multi-segmented IVR design was found to be effective in delivering dapivirine and tenofivir (TFV) in vitro at acceptable concentrations. A reservoir-type IVR was found to have zero-order release of TFV in vitro for 90 days. Toxicological evaluations to determine safety, efficacy, and biocompatibility gave positive results.

Controlling the hydration rate of a hydrophilic matrix in the core of an intravaginal ring determines antiretroviral release (2016)

Teller RS, Malaspina DC, Rastogi R, Clark JT, Szleifer I, Kiser PF. Journal of controlled release: official journal of the Controlled Release Society. 224:176-183.

A Tecoflex™ thermoplastic polyurethane (TPU) intravaginal ring (IVR) was designed to expand the class of drugs that can be administered vaginally, as often this route of administration is limited to drugs with low molecular weights. A matrix-style IVR was loaded with drug pellets inside its hollow core and investigated for controlled drug release. Controlled release rates of multiple antiretrovirals were successfully achieved by altering the orifice design, drug loading, and mass of pellets loaded in the devices.

Development and Pharmacokinetics of a 90-Day Intravaginal Ring for the Sustained Co-Delivery of the Microbicide Tenofovir and Contraceptive Levonorgestrel (2013)

Clark M.R, Clark J.T, Shelke N.B, Doncel G.F. Annual Meeting of the American Association of Pharmaceutical Sciences.

Segmented polyurethane intravaginal rings (IVRs) were formulated via hot melt extrusion and investigated for the simultaneous release of Tenofovir (TFV) and Levonorgestrel (LNG). A relatively hydrophobic polyurethane was used to form the segment containing LNG and a hydrophilic polyurethane was used to form the segment containing TFV. In vitro release testing was conducted along with in vivo pharmacokinetic studies, both of which yielded positive results.

Development of polyether urethane intravaginal rings for the sustained delivery of hydroxychloroquine (2014)

Chen Y, Traore YL, Li A, Fowke KR, Ho EA. Drug design, development and therapy. 8:1801-15.

Tecophilic thermoplastic polyurethane (TPU) intravaginal rings (IVRs) were investigated for delivery of hydroxychloroquine (HCQ). Matrix and reservoir-type IVRs were fabricated via hot melt injection molding and evaluated for drug release kinetics, stability, and biocompatibility with positive results.

Engineering a segmented dual-reservoir polyurethane intravaginal ring for simultaneous prevention of HIV transmission and unwanted pregnancy (2014)

Clark JT, Clark MR, Shelke NB, Johnson TJ, Smith EM, Andreasen AK, Nebeker JS, Fabian J, Friend DR, Kiser PF. PloS one. 9(3):e88509.

Dual-reservoir intravaginal rings were designed to deliver tenofovir and levonorgestrel. Some sections of the ring were manufactured with thermoplastic polyurethane via coaxial extrusion. Sustained, dose dependent drug release from the ring was achieved in vitro and in vivo for up to 90 days.

Impact of Hydroxychloroquine-Loaded Polyurethane Intravaginal Rings on Lactobacilli (2015)

Traore YL, Chen Y, Bernier AM, Ho EA. Antimicrobial agents and chemotherapy. 59(12):7680-6.

Hydrophilic thermoplastic polyurethane (TPU) intravaginal rings were fabricated using hot-melt injection molding and loaded with hydroxychloroquine (HCQ). The effect on vaginal epithelial cells and microflora was evaluated. The rings successfully released HCQ continuously for a 24-day span and were found to have no adverse effects on vaginal health or lactobacilli when compared to control.

Segmented polyurethane intravaginal rings for the sustained combined delivery of antiretroviral agents dapivirine and tenofovir (2010)

Johnson TJ, Gupta KM, Fabian J, Albright TH, Kiser PF. European journal of pharmaceutical sciences: official journal of the European Federation for Pharmaceutical Sciences. 39(4):203-12.

Dual segment polyurethane intravaginal rings (IVRs) were fabricated via hot melt extrusion and solvent casting for the sustained release of antiretroviral agents. This was achieved in vitro for the release of tenofovir over a 30-day period, while dapivirine exhibited linear release over the time period. Accelerated stability studies yielded positive results.

Tenofovir disoproxil fumarate intravaginal ring protects high-dose depot medroxyprogesterone acetate-treated macaques from multiple SHIV exposures (2015)

Smith JM, Srinivasan P, Teller RS, Lo Y, Dinh CT, Kiser PF, Herold BC. Journal of acquired immune deficiency syndromes. 68(1):1-5.

Hydrophilic thermoplastic polyurethane (TPU) intravaginal rings were loaded with tenofovir disoproxil fumarate (TDF) and clinically tested in monkeys in combination with a medroxyprogesterone acetate depot. The monkeys were virally challenged weekly for twelve weeks and the TPU intravaginal rings were found to provide significantly improved protection when compared to placebo.

Thermoplastic polyurethane-based intravaginal rings for prophylaxis and treatment of (recurrent) bacterial vaginosis (2017)

Verstraete G, Vandenbussche L, Kasmi S, Nuhn L, Brouckaert D, Van Renterghem J, Grymonpré W, Vanhoorne V, Coenye T, De Geest BG, De Beer T, Remon JP, Vervaet C. International journal of pharmaceutics. 529(1-2):218-226.

Thermoplastic polyurethane (TPU) intravaginal rings were processed via hot melt extrusion/injection molding in combination with lactic acid or metronidazole. These rings were evaluated for sustained drug release, homogeneous drug distribution within the polymer matrix, irritation potential, biofilm formation, and mechanical properties. Positive results were achieved in many cases, with hydrophobic TPUs found to be suitable for continual release of lactic acid and hydrophilic TPU rings determined to be well suited for metronidazol elution.

Implants

Development of a Subcutaneous Implant using Polyurethane as a Semi-Permeable Membrane for the Controlled Release of Risperidone (2012)

Schwarz A, Thoroughman S, Winstead D. Annual Meeting of the Controlled Release Society.

A non-biodegradable subcutaneous implant that utilizes select thermoplastic polyurethane semipermeable membranes was successfully developed. Controlled pseudo-zero order release of risperidone was achieved in both in vitro and in vivo models.

DUROS technology delivers peptides and proteins at consistent rate continuously for 3 to 12 months (2008)

Rohloff CM, Alessi TR, Yang B, Dahms J, Carr JP, Lautenbach SD. Journal of diabetes science and technology. 2(3):461-7.

The effectiveness of DUROS subcutaneous implants for continuous drug delivery was evaluated. DUROS technology utilizes a semipermeable membrane at one end of the device, which aids in the controlled release of drug from a reservoir. Sustained drug release was achieved in in vitro studies and stability of the product was observed for up to three years.

To read about possible thermoplastic polyurethane (TPU) usage in the osmotic membranes of these types of devices, see patent #US7682356B2.

In vivo modulation of foreign body response on polyurethane by surface entrapment technique (2010)

Khandwekar A.P, Patil D.P, Hardikar A.A, Shouche Y.S, Doble M. J Biomed Mater Res 95A: 413–423.

Tecoflex™ polyurethane was surface-modified with an entrapment technique and evaluated for an inflammatory response when implanted in vivo. Implants surfaced modified with the surfactant Tween80® exhibited a significantly reduced inflammatory response in the body compared to non-surface-treated implants.

Polyurethane as a Semi-Permeable Membrane for Controlled Release (2012)

Schwarz A, Thoroughman S, Winstead D, Decker S, Varughese J. Controlled Release Society Annual Meeting.

Several aliphatic thermoplastic polyurethanes were examined for their ability to control the rate of release (elution rate) of oxybutynin hydrochloride, USP, from subcutaneous implants with good results.

Oral Solid Dosage Forms

3D printing of high drug loaded dosage forms using thermoplastic polyurethanes (2018)

Verstraete G, Samaro A, Grymonpré W, Vanhoorne V, Van Snick B, Boone MN, Hellemans T, Van Hoorebeke L, Remon JP, Vervaet C. International journal of pharmaceutics. 536(1):318-325.

High loads (>30%) of model drugs were pre-processed in combination with thermoplastic polyurethane (TPU) via hot melt extrusion and then 3D printed into tablets. Sustained release potential and impact of printing were investigated in vitro. It was found that the TPU could be loaded with up to 60% drug concentration without experiencing severe negative effects. In-vitro release kinetics were found to be primarily affected by matrix composition and tablet in-fill degree.

A comparative study between melt granulation/compression and hot melt extrusion/injection molding for the manufacturing of oral sustained release thermoplastic polyurethane matrices (2016)

Verstraete G, Mertens P, Grymonpré W, Van Bockstal PJ, De Beer T, Boone MN, Van Hoorebeke L, Remon JP, Vervaet C. International journal of pharmaceutics. 513(1-2):602-611.

Several manufacturing methods were examined for producing thermoplastic polyurethane (TPU)-based oral solid dosage forms for sustained release of metformin hydrochloride. The processing methods evaluated included hot melt extrusion (HME), twin screw melt granulation/compression (TSMG), and injection molding (IM). HME/IM-produced tablets were drug loaded up to 70% and achieved sustained release over a 24-hour period. The TSMG-produced tablets could only be drug loaded between 85 and 90% and subsequently achieved a much quicker drug release in a 6-hour period.

Evaluation of an aliphatic polyurethane as a microsphere matrix for sustained theophylline delivery (1995)

Subhaga CS, Ravi KG, Sunny MC, Jayakrishnan A. Journal of microencapsulation. 12(6):617-25.

Tecoflex™ thermoplastic polyurethane (TPU) microspheres were prepared using a solvent evaporation technique and evaluated for the controlled release of theophylline. The TPU microspheres displayed close to zero-order drug release in simulated intestinal fluid

Hydrophilic thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding (2016)

Verstraete G, Van Renterghem J, Van Bockstal PJ, Kasmi S, De Geest BG, De Beer T, Remon JP, Vervaet C. International journal of pharmaceutics. 506(1-2):214-21.

Tecophilic™ thermoplastic polyurethane (TPU) matrices for high drug-loaded (up to 70%) oral dosage forms were formulated via hot melt extrusion/injection molding. It was observed that the TPU matrices allowed for sustained drug release kinetics without using release modifiers

The production of hot melt extruded high drug load formulations with polyurethanes and dicarboxylic acids (2014)

Bruyn SD. Ghent University, Department of Pharmaceuticals.

The capabilities of thermoplastic polyurethane (TPU) as a matrix excipient for high drug-loaded, controlled release formulations produced via hot melt extrusion and injection molding were examined. Two Tecoflex polyurethanes were tested with dyphylline. One was found to hold up to 65 WT% drug and the other up 75 WT% drug. As a second part of the study, release modifiers were investigated for their effects on release characteristics of the TPU with many showing positive results.

Thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding (2015)

Claeys B, Vervaeck A, Hillewaere XK, Possemiers S, Hansen L, De Beer T, Remon JP, Vervaet C. European journal of pharmaceutics and biopharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V. 90:44-52.

Thermoplastic polyurethanes (TPUs) were evaluated as matrix excipients for the production of oral solid dosage forms via hot melt extrusion (HME) in combination with injection molding (IM). TPU tablets were drug loaded up to 65% and achieved sustained release of Metoprolol tartrate over a 24 hour period. The TPUs were also found to not harm the human GI ecosystem when administered orally.

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