Supplementary Information

Thermally-drawn porous sutures for controlled drug release using thermally induced phase separation

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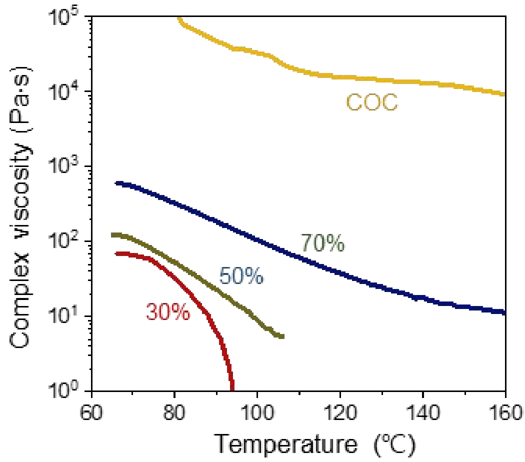

Fig. S1 Viscosity of PLGA/DBP solutions and cladding polymer (COC) according to temperature change.

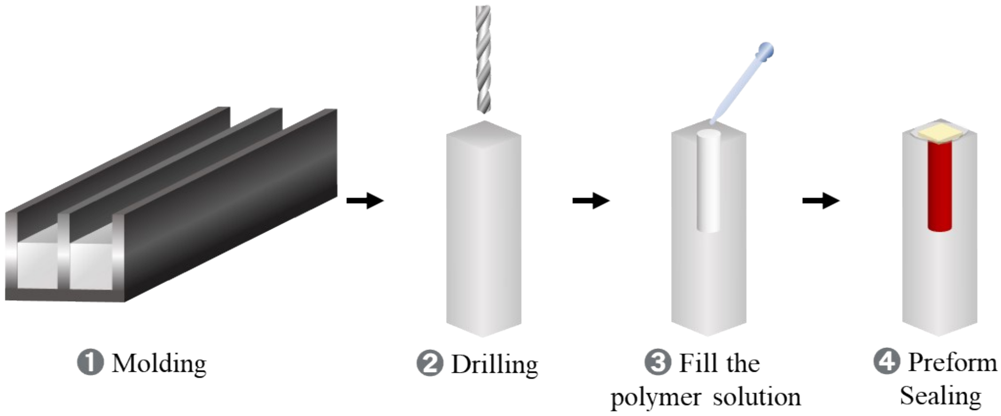

Fig. S2 Preform preparation.

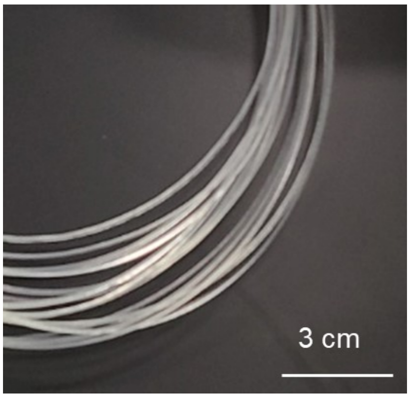

Fig. S3 Thermally drawn fibers before cladding removal.

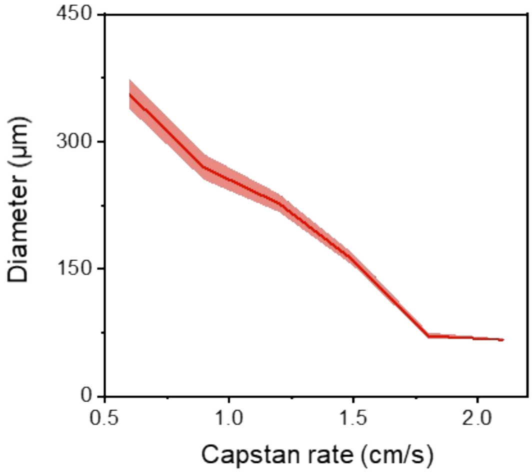

Fig. S4 Diameter of PLGA/DBP gel reservoir according to capstan speed.

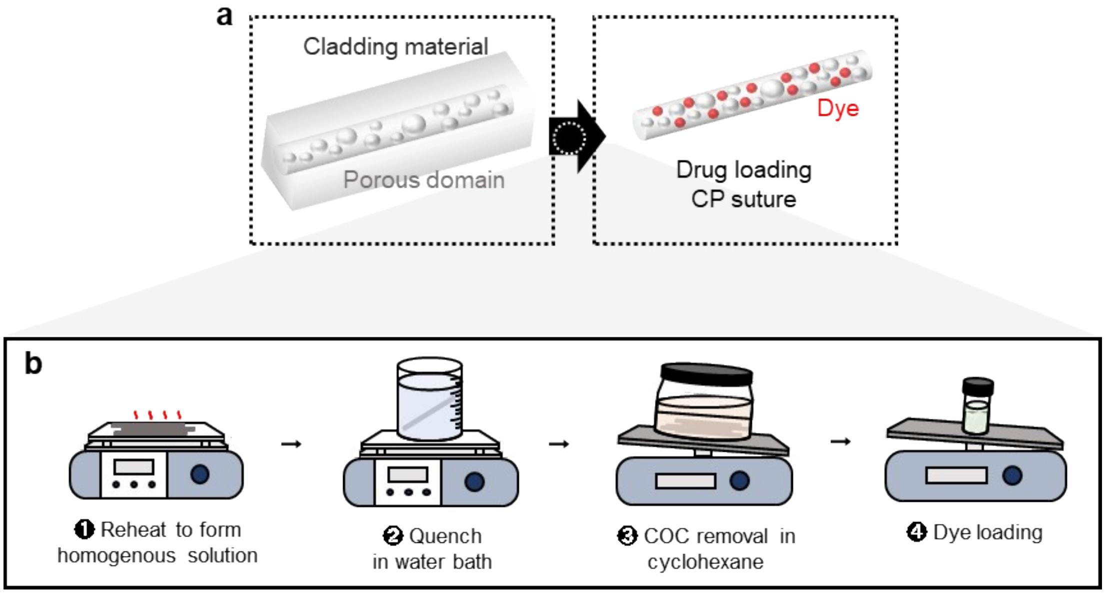

Fig. S5 Cladding removal and dye loading process.

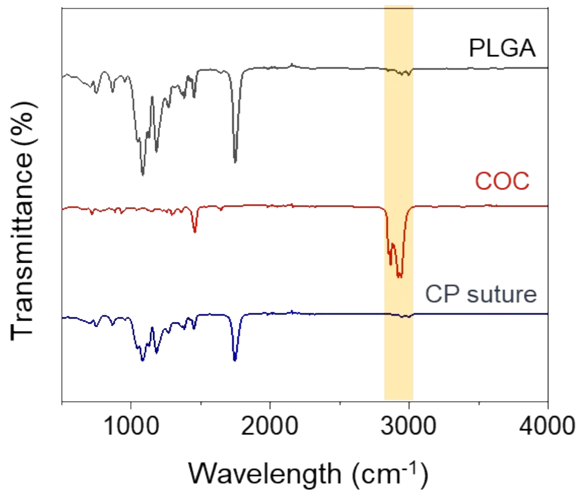

Fig. S6 FTIR spectrum of PLGA, COC, and CP suture.

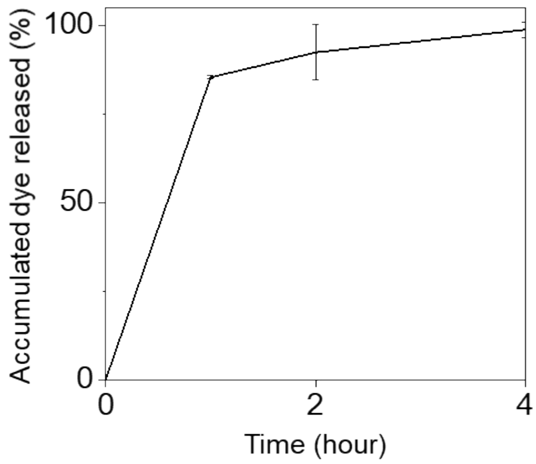

Fig. S7 Release profile of dye-loaded commercially-available braided suture.

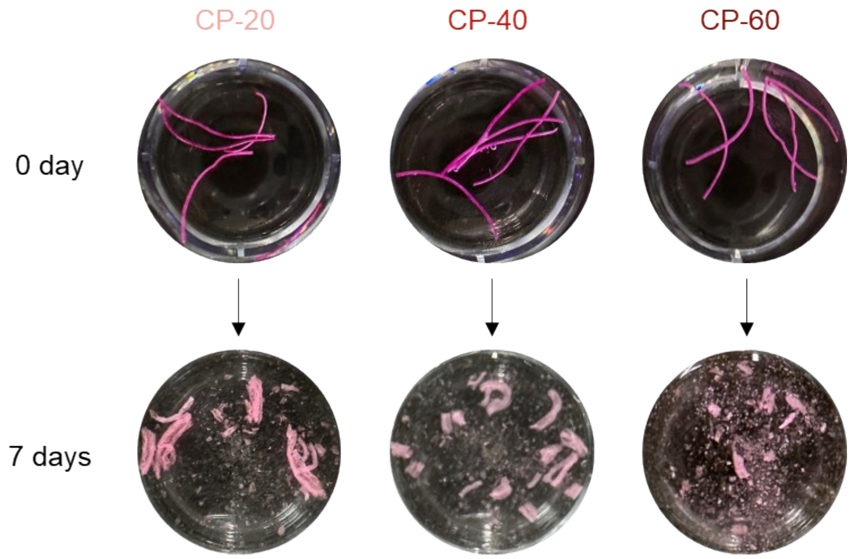

Fig. S8 Degradation test of CP sutures.

Supplementary Note S1: Polymers and solvents criteria for the TIPS-TDP

To successfully perform the TIPS-TDP, selecting an appropriate polymer and solvent is critical. Key factors in choosing a TIPS polymer include melting point (Tm), melt viscosity, crystallinity, chemical and mechanical stability, specific solubility, and molecular weight. Before initiating TIPS, the polymer should be dissolved in a non-solvent at a temperature near its Tm to form a homogeneous solution[1]. For polymers with a high Tm, identifying suitable solvents and cladding materials can be challenging. Since TIPS induces polymer crystallization through temperature reduction, the polymer's crystallinity is a critical factor. Semi-crystalline polymers such as isotactic polypropylene (iPP), polyvinylidene fluoride (PVDF), and polyethylene (PE) are typically employed as TIPS polymers. In contrast, amorphous polymers like polymethyl methacrylate (PMMA) and atactic polypropylene (aPP) undergo phase separation without crystallization, resulting in insufficient mechanical strength for use as sutures after phase separation. To be suitable as a TIPS solvent, the solvent should possess a high boiling point, low vapor pressure and low molecular weight (Mw). The boiling point of solvent should be significantly higher than the TIPS temperature to prevent solvent evaporation, which could cause preform instability or explosion of solution during TDP. Additionally, a lower Mw is preferred after phase separation to facilitate easier solvent extraction.

As mentioned in the main text, the solubility parameter of the solvent is a critical factor for the TIPS (**Supplementary Table 1**). In general, a polymer with a high Mw is considered fully dissolved when $\chi \leq 0.5$. Conversely, the polymer and solvent exist as two phases when $\chi > 0.5$. For TIPS to occur, , the solvent should be chosen such that $\chi > 0.5$ at the quenching temperature and $\chi \leq 0.5$ at the boiling point of the solvent[2, 3]. Following TDP, the quenching temperature is approximated as room temperature (RT). **Supplementary Table 1** provides a comparison of χ values for poly(lactic-co-glycolic) acid (PLGA) and solvents (more details in **Supplementary Note 1**). Dibutyl phthalate (DBP) fulfilled the required conditions, demonstrating $\chi \leq 0.5$ below its boiling point and $\chi > 0.5$ at room temperature.

Supplementary Note S2: Pore size distribution through quenching temperature

The variation in pore size with quenching temperature is attributed to the kinetic aspects of the TIPS, as explained by lumped system analysis[18]. The heat transfer by convection is equivalent to the change in the internal energy of the fiber. Assuming no temperature gradient within the fiber and the negligible thermal resistance, this relationship can be described by the following equation.

$$hA(T - T_\infty) = -\frac{d}{dt}(mC_pT)$$

where h is the heat transfer coefficient, A is the surface area, m is the mass, C_p is the specific heat of fiber. By rearranging and integrating both sides, time can be expressed as a function of temperature.

$$t = -\frac{mC_p}{hA}\ln\left(\frac{T_0 - T_\infty}{T_i - T_\infty}\right)$$

where T_i is the initial temperature of the fiber ($\sim T_{reheat}$) and T_∞ is the temperature of a quenching bath. Assuming the solution inside the cladding is fully solidified at the TIPS temperature, T_0 can be substituted for the TIPS temperature. Although factors such as the thickness of the cladding material and the heat transfer coefficient also play a role, this equation provides an indirect validation of the cooling rate's relationship to the quenching temperature.

Supplementary Note S3: Combinations and conditions satisfied the TIPS-TDP

The TIPS process should satisfy two essential conditions to be concurrently proceeded with TDP: the temperature condition and the solubility condition. First, to ensure homogeneity of the internal solution during TDP, the drawing temperature should exceed the TIPS temperature. Additionally, to prevent phase separation from recurring after quenching, the cladding should be chemically removed at a temperature below the TIPS temperature.

The second condition pertains to solubility. To avoid interactions between the cladding polymer and the TIPS solution, the cladding polymer should be insoluble in the TIPS solvent. Conversely, the cladding solvent used for cladding polymer's removal should not dissolve the suture polymer. The specific TIPS polymers, TIPS solvents, cladding polymers, and cladding solvents that satisfy all of these conditions are detailed in **Supplementary Table 3**.

Supplementary Table S1: Solubility parameter of polymers and solvents for TIPS

Polymer/Solvent	δ_d	δ_p	δ_H	*Boiling point*	χ_{RT}	$\chi_{boiling\ point}$	*TIPS possibility*	*Ref*
PLGA	17.4	8.3	9.9	-	-	-	-	[4]
DMSO	18.4	16.4	10.2	189°C	0.4996	0.3223	No	[5]
Water	15.5	16.0	42.3	100°C	3.797	3.034	No	[5]
DBP	17.8	8.6	4.1	340°C	0.9188	0.4468	Yes	[6]

Supplementary Table S2: Comparison of Methods for Fabricating Porous Polymer Structures

Method	*Pore Formation Mechanism*	*Advantages*	*Disadvantages*	*Ref*
Thermally Induced Phase Separation (TIPS)	Phase separation is induced by temperature changes; polymer solidifies from a liquid phase	Producing uniform and interconnected pore Providing good control over pore size and structure	Dependent on precise temperature control	[7-11]
Non-Solvent Induced Phase Separation (NIPS)	Phase separation occurs due to solvent exchange	Simple process Suitable for fabricating thin films and membranes	Challenging to achieve homogeneous porous structures due to uneven solvent exchange rates and gradients.	[12-14]
Salt Leaching	Dissolution of leached salt particles creates pores; heat is used for polymer curing or melting	Simple and cost-effective Creating highly porous structures	Difficult to achieve uniform pore distribution Limited interconnectivity	[15, 16]
Gas Foaming	Gas expansion under heat creates bubbles that form pores within the polymer matrix	Solvent-free process Producing pores without additional materials	Limited in controlling pore size and distribution Structural unstable	[17]

Supplementary Table S3. Material selections and manufacturing conditions for the TIPS-TDP

TIPS Polymer	*TIPS Solvent*	*Cladding polymer*	*Cladding solvent*	*TDP temp.*
PVDF	Benzophenone	COC	Cyclohexane	130°C
PCL[19]	Propylene carbonate / triethylene glycol	COC	Cyclohexane	130°C
UHMWPE	Paraffin oil	Polycarbonate	N, N-Dimethylformamide	180°C
PLGA	DBP	COC	Cyclohexane	130°C

REFERENCES

1. J. Kim, J. Jung, H. Wang, E. Drioli and Y. M. Lee, *Compr. Membr. Sci. Eng.*, 2017, **1**, 386.
2. C. P. Callaway, K. Hendrickson, N. Bond, S. M. Lee, P. Sood and S. S. Jang, *ChemPhysChem*, 2018, **19**, 1655-1664.
3. G. Ovejero, P. Perez, M. Romero, I. Guzman and E. Dı, *Eur. Polym. J.*, 2007, **43**, 1444-1449.
4. S. Schenderlein, M. Lück and B. Müller, *Int. J. Pharm.*, 2004, **286**, 19-26.
5. S. Ashtiani, M. Khoshnamvand and A. Shaliutina-Kolesova, *Int. J. Adv. Eng. Nano Technol*, 2018, **3**.
6. S. Abbott, *University of Leeds: Leeds, UK*, 2017, 109-110.
7. K. V. Pochivalov, A. V. Basko, T. N. Lebedeva, A. N. Ilyasova, M. Y. Yurov, R. Y. Golovanov, V. V. Artemov, V. V. Volkov, A. A. Ezhov and A. V. Volkov, *Mater. Today Commun.*, 2021, **28**, 102558.
8. E. Torino, R. Aruta, T. Sibillano, C. Giannini and P. A. Netti, *Sci. Rep.*, 2016, **6**, 32727.
9. R. Zeinali, L. J. Del Valle, J. Torras and J. Puiggali, *Int. J. Mol. Sci.*, 2021, **22**, 3504.
10. X. Tan and D. Rodrigue, *Polymers*, 2019, **11**, 1310.
11. A. G. Abdelaziz, H. Nageh, S. M. Abdo, M. S. Abdalla, A. A. Amer, A. Abdal-Hay and A. Barhoum, *Bioengineering*, 2023, **10**, 204.
12. J. T. Jung, J. F. Kim, H. H. Wang, E. Di Nicolo, E. Drioli and Y. M. Lee, *J. Membr. Sci.*, 2016, **514**, 250-263.
13. M. G. Kang, I. W. Kim, Y. Lee and Y.-J. Kwark, *Fibers Polym.*, 2023, **24**, 941-946.
14. Y. H. Cho, S. D. Kim, J. F. Kim, H.-g. Choi, Y. Kim, S.-E. Nam, Y.-I. Park and H. Park, *J. Membr. Sci.*, 2019, **579**, 329-341.
15. D. Shahriari, G. Loke, I. Tafel, S. Park, P. H. Chiang, Y. Fink and P. Anikeeva, *Adv. Mater.*, 2019, **31**, 1902021.
16. J. M. Lowen and J. K. Leach, *Adv. Funct. Mater.*, 2020, **30**, 1909089.
17. M. Costantini and A. Barbetta, *Funct. 3D Tissue Eng. Scaffolds*, 2018, 127-149.
18. P. Li, Y.-M. Li and J. C. Leong, *Appl. Math. Model.*, 2015, **39**, 5507-5520.
19. B. Grena, J.-B. Alayrac, E. Levy, A. M. Stolyarov, J. D. Joannopoulos and Y. Fink, *Nat. Commun.*, 2017, **8**, 364.