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Supplementary Materials for

3D printing of a wearable personalized oral delivery device: A first-in-human study

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The PDF file includes:

- fig. S1. Selection of active compound and polymer blends for HME.
- fig. S2. Optimization of PVA_S/PLA_S ratio for CBS-loaded filaments.
- fig. S3. Thermal properties of CBS-loaded and VA-loaded filaments.
- fig. S4. Characterizations of polymer mixtures containing CBS or VA.
- fig. S5. Surface and cross-section of unloaded filaments.
- fig. S6. Optimization of temperature for 3D printing.
- fig. S7. Evaluation of the VA concentration and the weight of the mouthguards.
- fig. S8. Release profiles of the personalized mouthguards in vitro.
- table S1. Physicochemical properties of CBS and VA.
- table S2. Feed compositions for the prepared blend filaments and the CBS loading efficiencies for the corresponding filaments.
- table S3. Solubility parameter calculations of individual components of the filaments based on the Hoftyzer and Van Krevelen method and the Hoy method.
- table S4. Mechanical properties of pure PLA_S filaments, pure PVA_S filaments, and the CBS-loaded blend filaments.
- table S5. Mechanical properties of pure PLA_{PG}, PVA_{PG} filaments, and the VA-loaded blend filaments.
- table S6. Optimization of the filament temperature and composition for the VA-free region in the mouthguard.
- table S7. AUC of VA concentrations in saliva after each cycle of wearing of the three different mouthguards.
- Methods
- References (*49*, *50*)

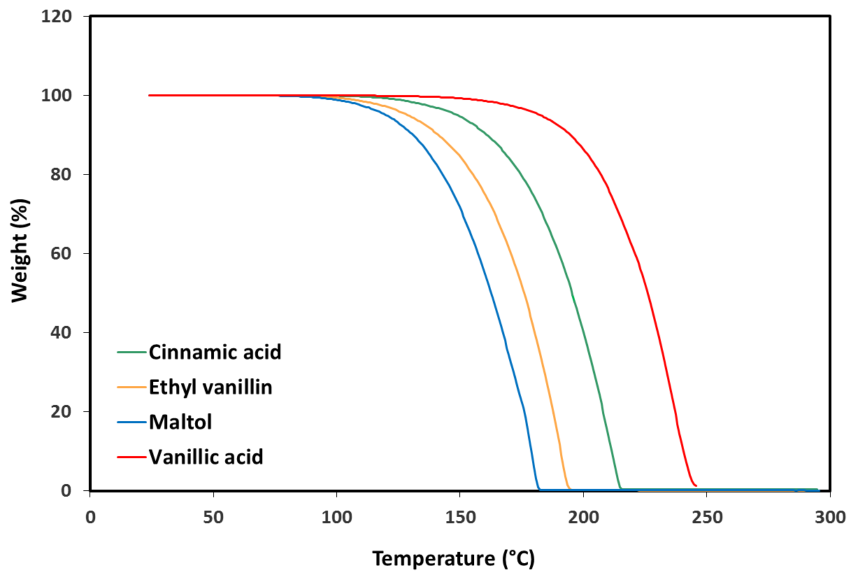
Other Supplementary Material for this manuscript includes the following:

(available at advances.sciencemag.org/cgi/content/full/4/5/eaat2544/DC1)

- movie S1 (.mp4 format). Movie summarizing the different steps involved in the preparation of the 3D-printed compound-eluting mouthguards.

Supplementary Materials

A



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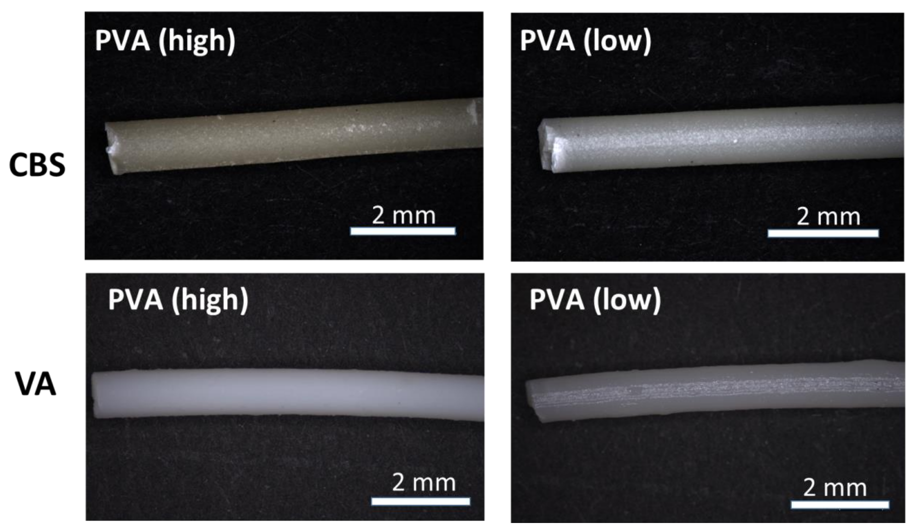
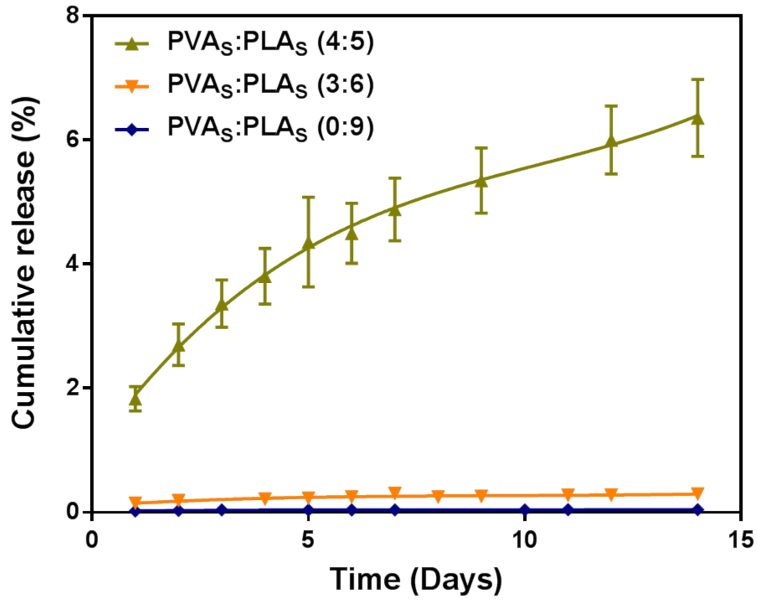


fig. S1. Selection of active compound and polymer blends for HME. (**A**) Thermal stability of vanillic acid (VA) as the flavor compound. TGA thermograms of the food-grade flavor compounds cinnamic acid, ethyl vanillin, maltol and VA. VA was selected as the flavor substitute owing to its high thermal stability, making it suitable for the HME and FDM printing processes. (**B**) **Physical appearance of filaments produced by HME**. Electron microscopy images of PVA (high) and PVA (low) filaments loaded with either CBS (top) or VA (bottom) and produced by HME. Scale bar = 2 mm.



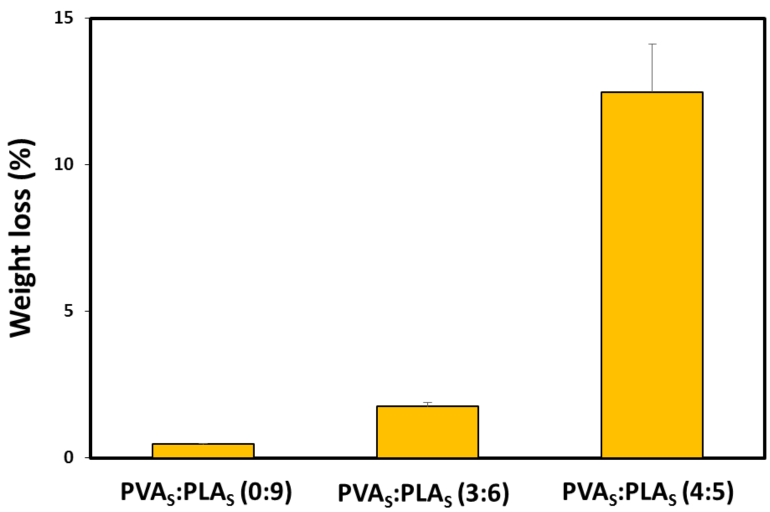


fig. S2. Optimization of PVA$_S$/PLA$_S$ ratio for CBS-loaded filaments. (**A**) Cumulative release of CBS-loaded filaments with a PVA$_S$:PLA$_S$ feed weight ratio equal to or lower than (4:5, w/w). (**B**) Weight loss of the CBS-loaded filaments with a PVA$_S$:PLA$_S$ feed weight ratio lower than (4:5, w/w) after the *in vitro* dissolution study. Data shown are the means ± s.d.; n = 3.

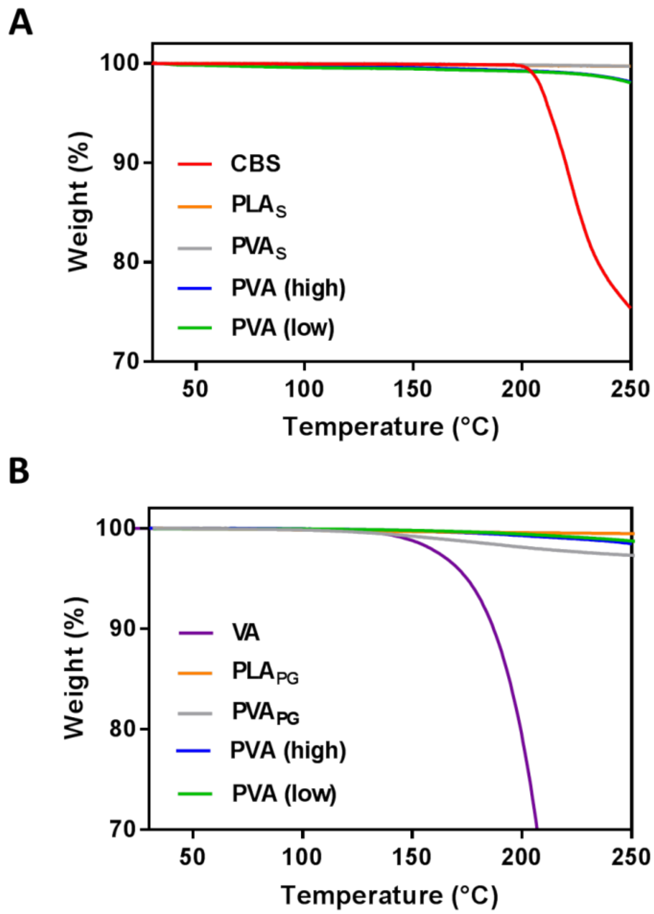


fig. S3. Thermal properties of CBS-loaded and VA-loaded filaments. TGA thermograms of (**A**) pure PLA_S, PVA_S and CBS-loaded filaments and (**B**) PLA_{PG}, PVA_{PG} and VA-loaded filaments.

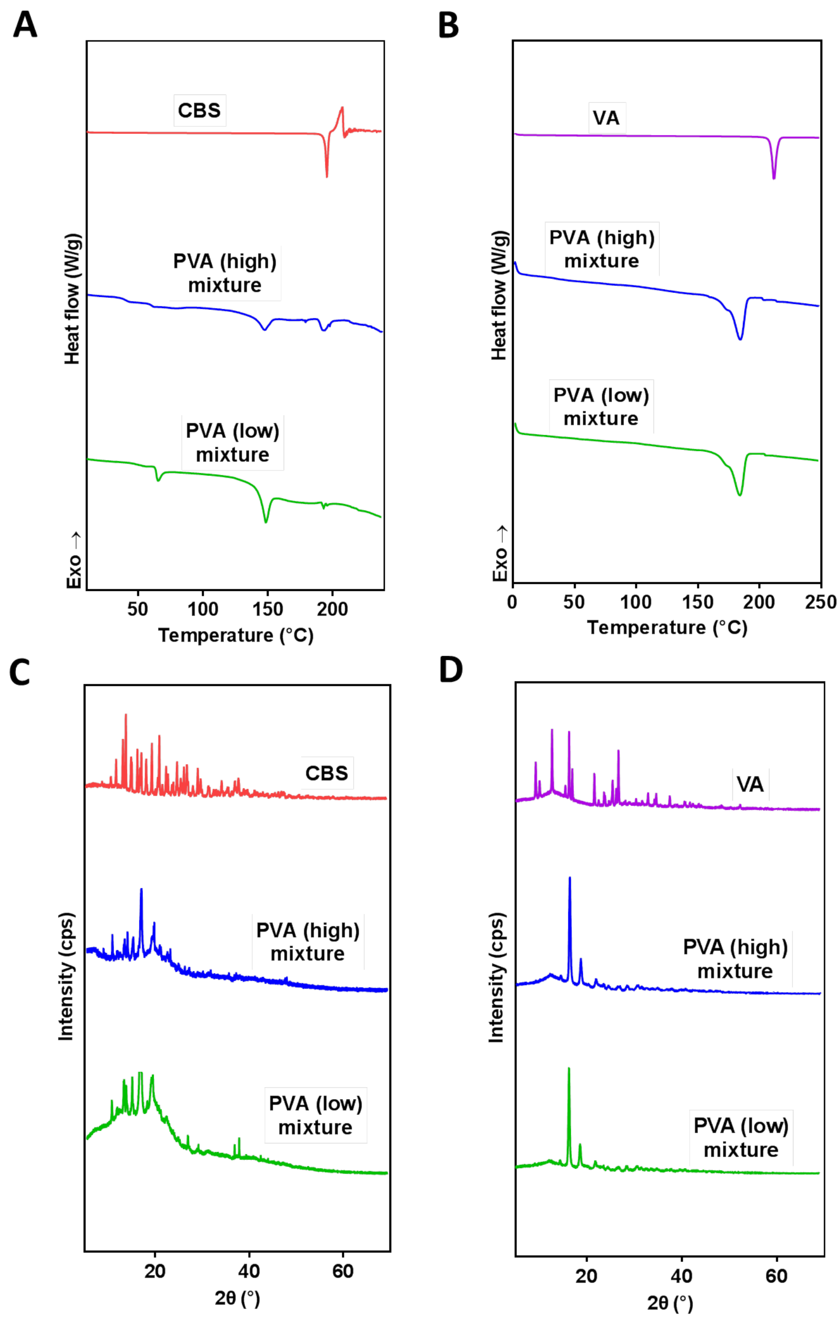


fig. S4. Characterizations of polymer mixtures containing CBS or VA. DSC thermograms of (**A**) CBS and powder mixtures of the components making up the PVA (high) and PVA (low) CBS-loaded filaments, and (**B**) VA and powder mixtures of the components making up the PVA (high) and PVA (low) VA-loaded filaments before HME. XRPD diffractograms of (**C**) CBS and powder mixtures of the components making up the PVA (high) and PVA (low) CBS-loaded filaments, and (**D**) VA and powder mixtures of the components making up the PVA (high) and PVA (low) VA-loaded filaments before HME.

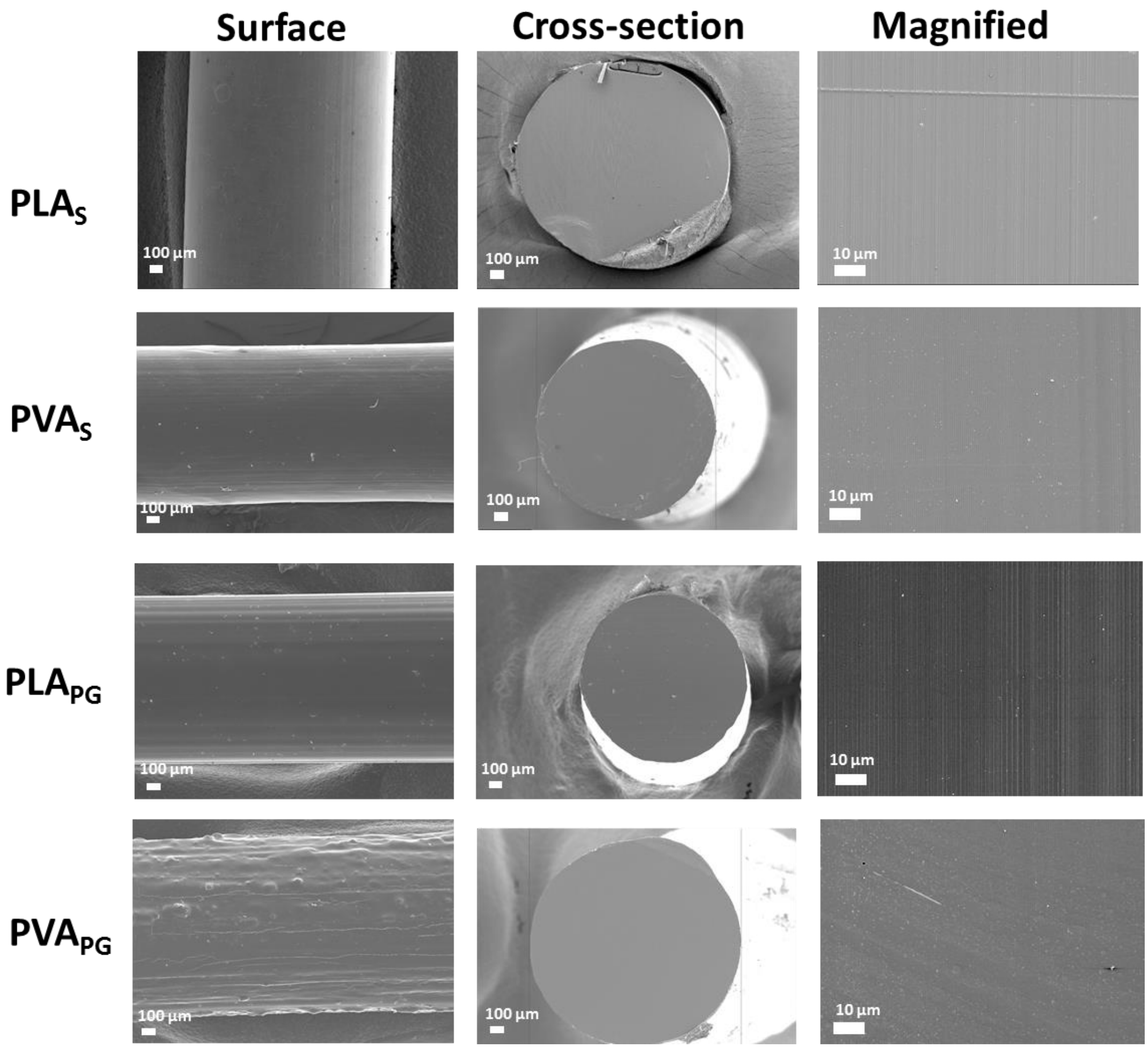


fig. S5. Surface and cross-section of unloaded filaments. SEM images – surface, cross-section and a magnified view of the cross-section – of unloaded PLA_S, PVA_S, PLA_{PG} and PVA_{PG} filaments. Scale bar = 100 µm for the surface and cross-sections. Scale bar = 10 µm for the magnified views of the cross-sections.

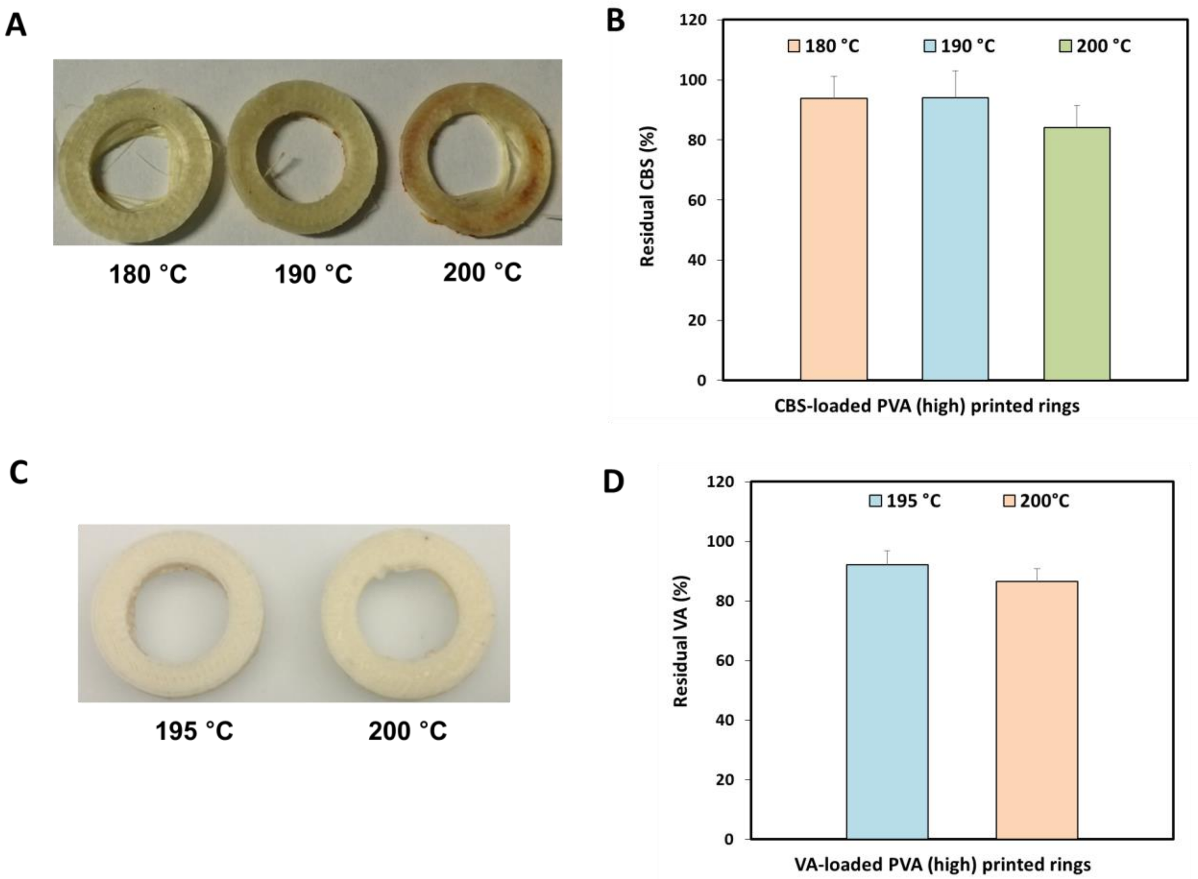


fig. S6. Optimization of temperature for 3D printing. (**A**) 3D printing of a test object using CBS-loaded PVA (high) filaments at different temperatures. (**B**) Amount of residual CBS in the prototypes following 3D printing. (**C**) 3D printing of a test object using VA-loaded PVA (high) filaments at different temperatures. (**D**) Amount of residual VA in the prototypes following 3D printing. Data shown are the means ± s.d.; n = 3.

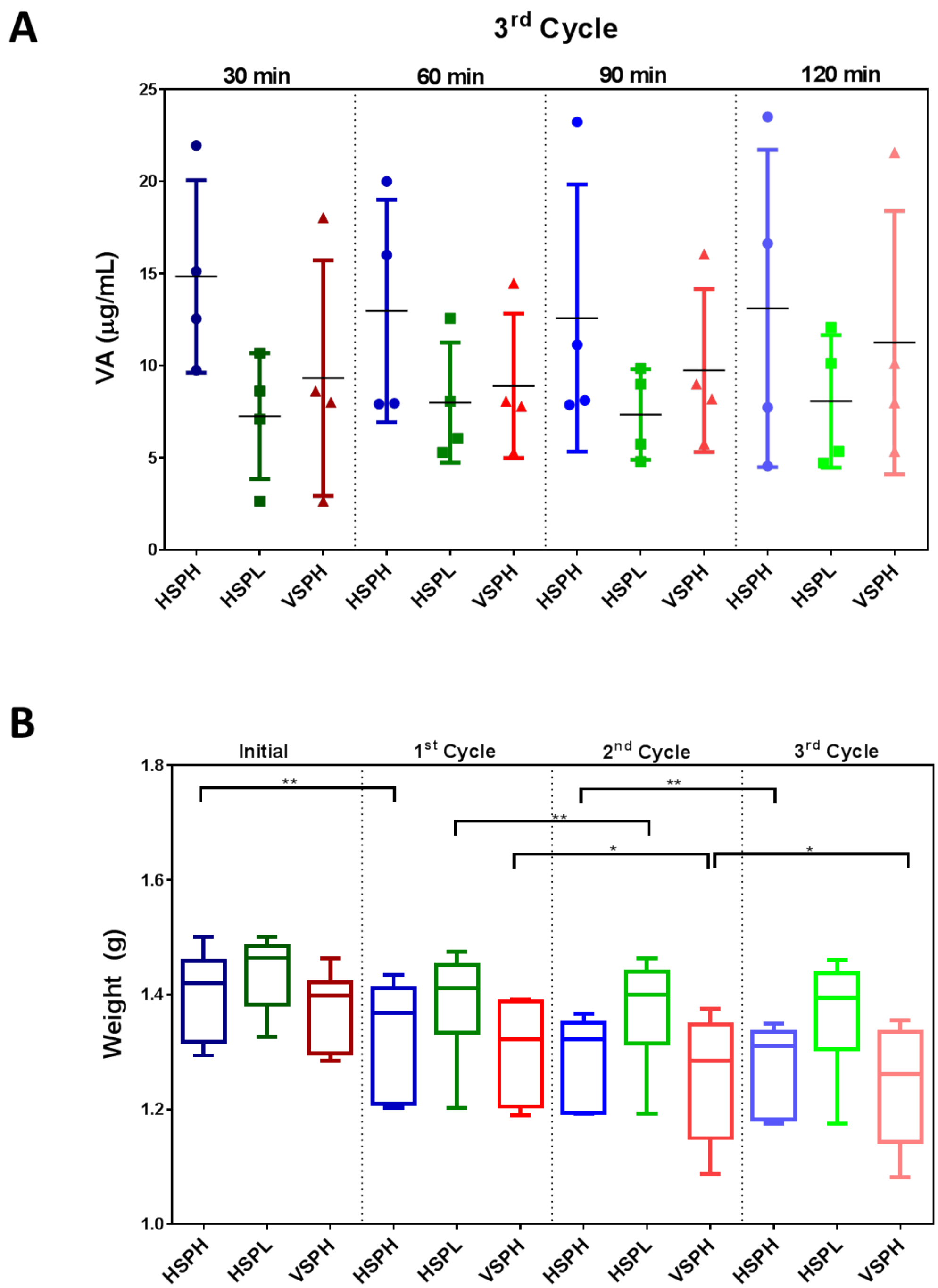


fig. S7. Evaluation of the VA concentration and the weight of the mouthguards. (**A**) Mean VA concentrations in the saliva of volunteers wearing mouthguards of the three designs during the third cycle of wearing for 2 h continuously. (**B**) Weights of the mouthguards after each cycle of wearing. * $P < 0.05$, ** $P < 0.01$

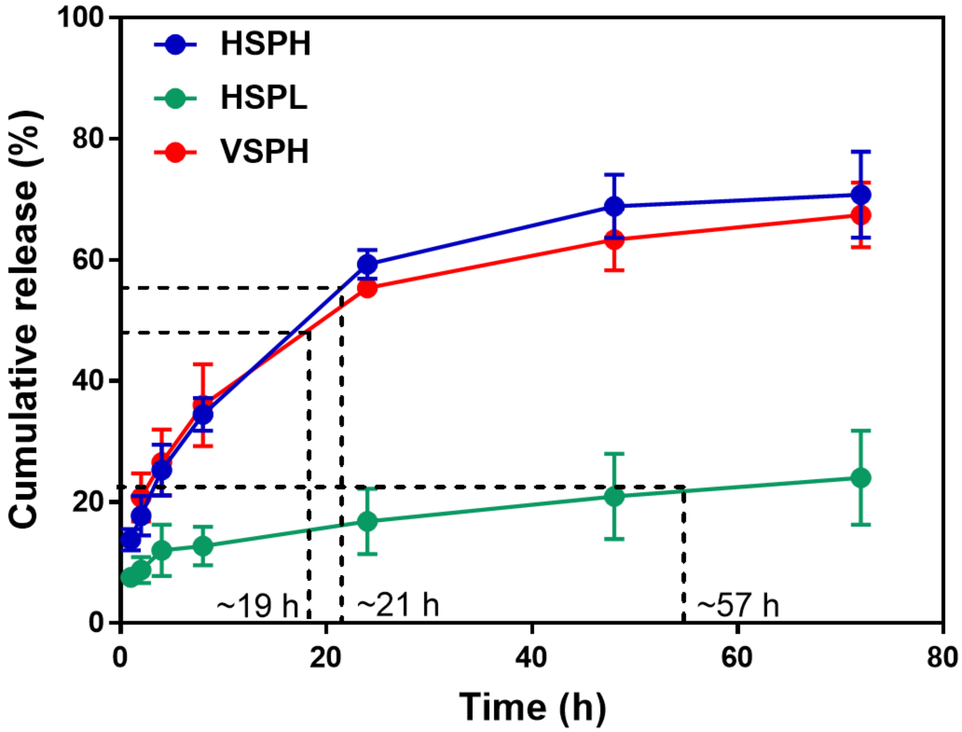


fig. S8. Release profiles of the personalized mouthguards in vitro. The time on the x-axis corresponds to the approximate length of time (extrapolated) at which VA release was reached after three 2-h cycles of wearing by the volunteers. Data shown are the means ± s.d.; n = 3.

table S1. Physicochemical properties of CBS and VA (*49*, *50*).

Property	CBS	VA
Molecular weight (g/mol)	467	168
Melting point (°C)	226	211.5
Water solubility	3.86 mg/L	1.5 g/L (14°C)
LogP	3.5	1.43

table S2. Feed compositions for the prepared blend filaments and the CBS loading efficiencies for the corresponding filaments. Data shown are the means ± s.d.; n = 3.

Filament (w/w)	Feed weight ratio PVA_S:PLA_S:CBS	Loading efficiency (%)
PVA_S:PLA_S (0:9)	0:9:1	93.9 ± 8.0
PVA_S:PLA_S (3:6)	3:6:1	71.7 ± 2.9
PVA_S:PLA_S (4:5)	4:5:1	63.5 ± 2.4
PVA_S:PLA_S (5:4)	5:4:1	64.3 ± 2.0
PVA_S:PLA_S (6:3)	6:3:1	57.6 ± 2.5

table S3. Solubility parameter calculations of individual components of the filaments based on the Hoftyzer and Van Krevelen method and the Hoy method. The difference in the solubility parameter (δ) between CBS (24.26)-PLA (22.30) and VA (28.46)-PVA (33.27) pairs is less than 5 $(MJ/m^3)^{½}$, indicating the preferential miscibility of CBS and VA in the PLA and PVA phases, respectively.

Molecule	δ $(MJ/m^3)^{½}$		
	Hoftyzer and Van Krevelen method	Hoy method	Average
CBS	24.56	23.97	24.26
VA	29.16	27.76	28.46
PLA	23.31	21.28	22.30
PVA	37.76	28.79	33.27

table S4. Mechanical properties of pure PLA_S filaments, pure PVA_S filaments, and the CBS-loaded blend filaments. Data shown are the means ± s.d.; n = 3.

Sample	Tensile strength (MPa)	Elastic modulus (GPa)	Elongation at break (%)
PLA_S	52 ± 1.4	1.79 ± 0.11	4.11 ± 0.37
PVA_S	78 ± 3.2	2.42 ± 0.07	3.55 ± 0.14
PVA (low)	47 ± 1.6	2.05 ± 0.02	2.29 ± 0.02
PVA (high)	49 ± 4.2	2.40 ± 0.24	1.91 ± 0.03

table S5. Mechanical properties of pure PLA_{PG}, PVA_{PG} filaments, and the VA-loaded blend filaments. Data shown are the means ± s.d.; n = 3.

Sample	Tensile strength (MPa)	Elastic modulus (GPa)	Elongation at break (%)
PLA_{PG}	60 ± 4.3	1.09 ± 0.59	6.90 ± 0.44
PLA_{PG}	71 ± 7.1	1.56 ± 1.70	5.11 ± 0.05
PVA (low)	41 ± 5.3	1.25 ± 0.26	3.39 ± 0.59
PVA (high)	47 ± 6.7	1.49 ± 0.53	3.38 ± 0.52

table S6. Optimization of the filament temperature and composition for the VA-free region in the mouthguard. Printing with the PLA_{PG}:PVA_{PG} (9:1 w/w) filament at 195 °C led to the best surface finish with no obvious gaps.

Composition	Printing temperature (°C)	Printed prototype (scale bar = 1 cm)
PLA_{PG}	180	
PLA_{PG}	195	
PLA_{PG}	205	
PLA_{PG}:PVA_{PG} (9:1 w/w)	195	

table S7. AUC of VA concentrations in saliva after each cycle of wearing of the three different mouthguards. Data shown are the means ± s.d.; n = 3.

Design	AUC (mg h/L)		
	1st Cycle	2nd Cycle	3rd Cycle
HSPH	116 ± 19.6	63 ± 8.8	24 ± 4.4
HSPL	42 ± 11.5	20 ± 4.2	16 ± 2.8
VSPH	106 ± 19.1	41 ± 7.6	17 ± 3.6

Methods

Gel permeation chromatography (GPC) measurements

The molecular weights and polydispersity indices of the polymers PLA, PVA and PVA (PG) were measured using a Viscotek GPC system. The instrument was conditioned in DMF at a column temperature of 45 °C and flow rate of 0.5 mL/min. Two ViscoGEL columns (GMH_{HR}-M, poly(styrene-co-divinylbenzene)) were used in series to improve separation. The results were analyzed by refractive index measurements by comparing the obtained values to poly(methyl methacrylate) standards.