Development of a biodegradable subcutaneous implant for the treatment of hypothyroidism

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Background:

Hypothyroidism effects more than 1.3 million people in the UK [1]. Oral administration of levothyroxine (LEVO) is highly dependent on the co-administration of food and other drugs and good patient compliance [2]. Poor compliance has been reported. This work aimed to develop a subcutaneous implant for prolonged delivery of LEVO to treat hypothyroidism.

Implant fabrication:

Implants were produced by solvent casting mixtures (Table 1) of poly(caprolactone) (PCL) of differing molecular weight (H-PCL M_w 50,000 Da and L-PCL M_w 550 Da) and different LEVO sodium loadings (20% or 40% w/w) into silicone moulds (Fig. 1).

Table 1. *Composition of each formulation.*

Formulation	Composition
H100	H-PCL (100%)
H70L30	H-PCL (70%):L-PCL (30%)
H40L60	H-PCL(40%):L-PCL (60%)

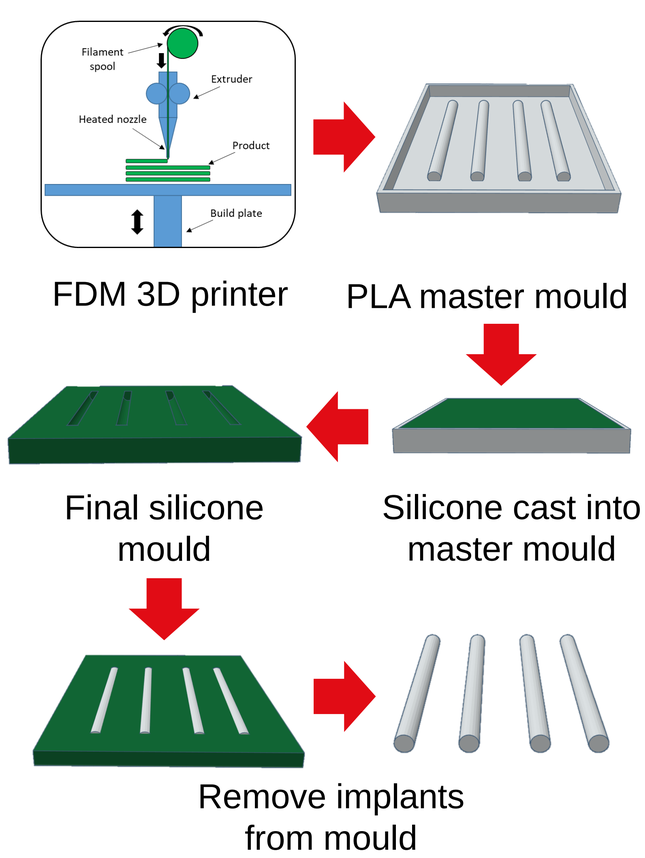

Fig. 1. *Schematic diagram of implant production.*

LEVO sodium quantification:

Quantification of LEVO sodium was achieved using RP-HPLC coupled with UV detection (Table 2).

LEVO sodium was found to be stable in 0.1% bovine serum albumin (BSA) for at least 14 days (Fig. 2).

Table 2. *LEVO sodium RP-HPLC calibration properties (means, n=9).*

Concentration range (µg/mL)	r^2	y-intercept	Slope	LoD (µg/mL)	LoQ (µg/mL)
0.012 – 25	1.0	17.94	108.18	0.03	0.09

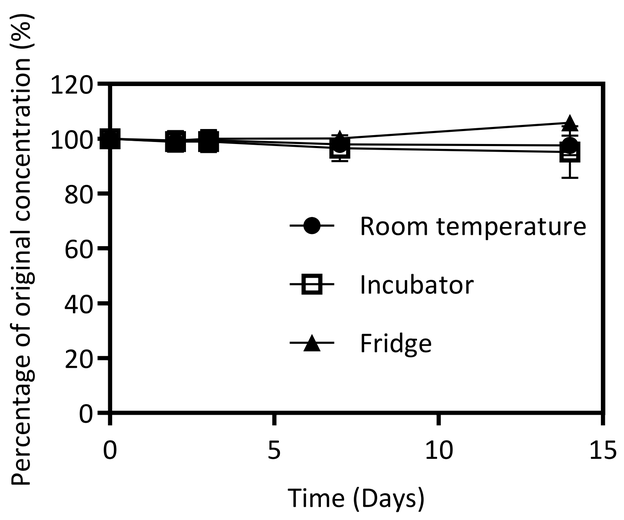

Fig. 2. *LEVO sodium stability in 0.1% BSA (means ± SD, n=3).*

Implant Characterisation:

Rod shaped implants of 2.5 x 40 mm were produced by solvent casting into silicone moulds (Fig. 3). LEVO sodium content of each implant formulation was tested (Table 3). SEM images of each of the implant formulations (Fig. 4) show the drug distribution within the implants.

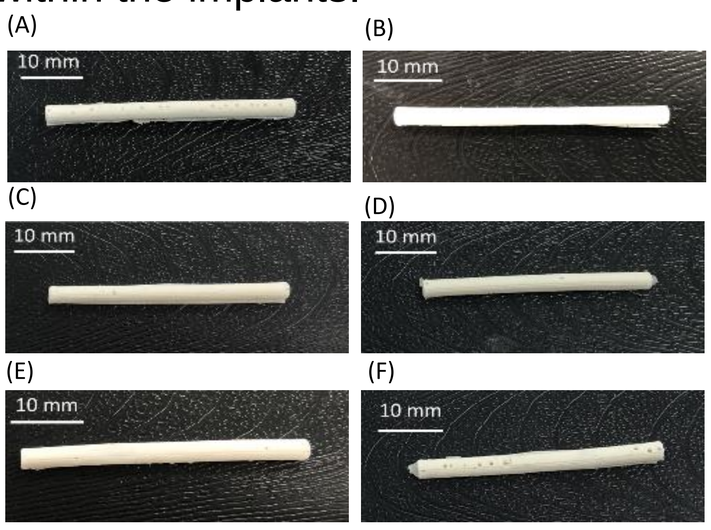

Fig. 3. *Images of formulation (A) H100 20% LEVO sodium (B) H100 40% LEVO sodium (C) H70L30 20% LEVO sodium (D) H70L30 40% LEVO sodium; (E) H40L60 20% LEVO sodium; (F) H40L60 40% LEVO sodium.*

FTIR, SEM and DSC results suggest that LEVO sodium is insoluble in the solvent used and is dispersed throughout, but not interacting with, the polymer matrix.

Table 3. *LEVO sodium drug content in each implant formulation (means ± SD, n=4)*

Formulation	Content (%)	
	20% Drug loading	40% Drug loading
H100	95.43 ± 5.80	87.69 ± 8.90
H70L30	94.78 ± 5.34	97.21 ± 2.59
H40L60	84.38 ± 2.78	97.33 ± 2.52

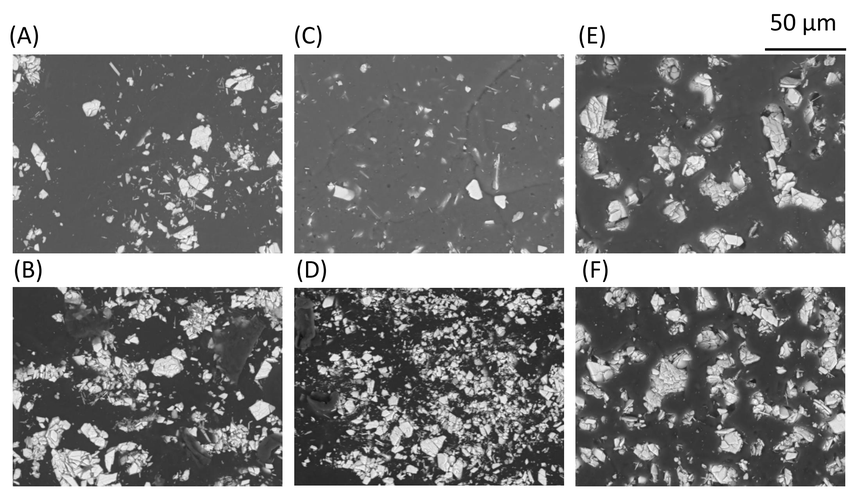

Fig. 4. *SEM images of formulation (A) H100 20% LEVO sodium (B) H100 40% LEVO sodium (C) H70L30 20% LEVO sodium (D) H70L30 40% LEVO sodium; (E) H40L60 20% LEVO sodium; (F) H40L60 40% LEVO sodium.*

In vitro release:

In vitro release studies were carried out in 0.1% BSA (with 0.05% sodium azide to prevent bacterial growth). At predetermined time points the release medium was analysed for LEVO sodium content and replaced. Cumulative release was calculated and plotted against time (Fig. 5).

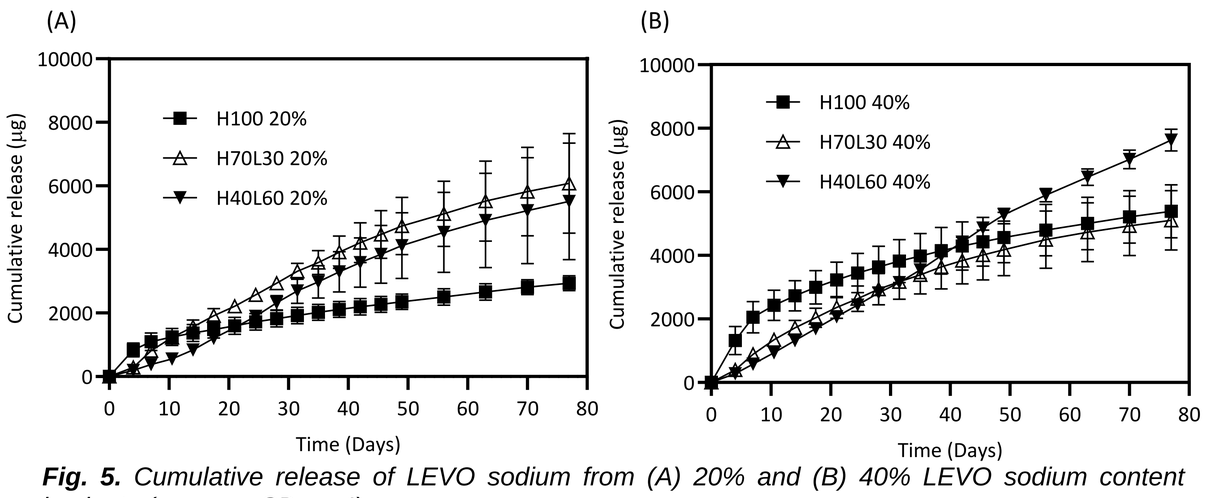

Fig. 5. *Cumulative release of LEVO sodium from (A) 20% and (B) 40% LEVO sodium content implants (means ± SD, n=4).*

Release rates ranging from 40.80 – 103.38 µg/day were achieved. These release rates are promising as the daily dose of LEVO sodium is 100 – 200 µg/day [3].

Table 4. *Daily release rate (means ± SD, n=4).*

Formulation	Daily release rate (µg/day)	
	20% LEVO sodium	40% LEVO sodium
H100	40.80 ± 1.59	82.12 ± 13.61
H70L30	88.71 ± 19.31	76.53 ± 14.72
H40L60	78.51 ± 22.72	103.38 ± 3.96

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Conclusion:

The implants produced in this work showed promising *in vitro* release rates for the delivery of LEVO sodium for the treatment of hypothyroidism. Future work will aim to optimise the implant formulation and investigate *in vivo* release rates.

References

[1] National institute for health and care excellence. (2019). Thyroid disease: assessment and management (NICE guideline (NG145)). Accessed April 8, 2020, from https://www.nice.org.uk/guidance/ng145/chapter/Context.

[2] Balla, M., Jhingan, R. M., & Rubin, D. J. (2015). Rapid Levothyroxine Absorption Testing: A Case Series of Nonadherent Patients. *International Journal of Endocrinology and Metabolism*, 13(4).

[3] Joint formulary committee. (2020). Levothyroxine sodium - BNF monograph. British National Formulary (Online). Accessed January 22, 2020, from https://bnf.nice.org.uk/drug/levothyroxine-sodium.html#indicationsAndDoses.