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Abstract

2.5D melt printing of full spectrum medicinal cannabis delivery microdepots

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When a droplet of molten polymeric excipient/API (active pharmaceutical ingredient) mixture is deposited onto a superoleophobic surface, unlike conventional 3d printing, the surface is not wetted, resulting in the rapid production of discrete spherical molten droplets, that when solidified, generate near-perfect microspheres (hence 2.5D). Microparticle-based polymeric depots are commonly applied toward the sustained release of drugs over prolonged periods, resulting in a reduction of the frequency of injecting drugs and improved pharmacokinetics. Thus, melt printing was evaluated as a solvent-free, cost-effective, and versatile technique to rapidly print microspheres of polymer melts using non-wetting surfaces using a specialized dispensing valve.

Initially polycaprolactone-based microspheres with varying amounts of ibuprofen as a model drug were produced. In vitro release studies revealed that one can control the crystal characteristics of both the excipient and the API, ensuing tunable drug-release rates. To further evaluate the clinical prospect of melt printing for API encapsulation, whole medicinal cannabis extract microspheres were prepared using anticonvulsant cannabis strand oil, mixed with polycaprolactone. The generated particle size distribution was $d_{50} = 257.80 \pm 2.49$ μm, with the encapsulation efficiencies of all the phytocannabinoids measured being more than 90%. Microdepot subcutaneous injections in mice indicated a first-order release profile, with elevated serum levels of multiple, major, and minor phytocannabinoids for over 14 days, compared to Cannabis extract injection. An empirical model for the release kinetics of the phytocannabinoids as a function of their physical traits was developed. Their long-term efficacy was evaluated via a single administration of the microdepots compared to a single administration of Cannabis extract in a mice pentylenetetrazol-induced convulsion model. One week following administration, the microspheres reduce the incidence of tonic-clonic seizures by 40%, increase the survival rate by 50%, and the latency to first tonic-clonic seizures by 170%. These results suggest that a long-term full-spectrum Cannabis delivery system from melt-printed microspheres may provide in the future a new form of Cannabis administration and treatments.

AUTHOR'S STATEMENT

Conflict of interest: Authors state no conflict of interest. Animal models: All procedures and protocols were approved by the Technion Administrative Panel of Laboratory Animal Care (#:IL_050–05–2018). Informed consent: Informed consent has been obtained from all individuals included in this study.

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