Microneedle Innovation for Peptide Delivery via the Buccal Route

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Background: Therapeutic peptides hold great promise due to their high target specificity and low side-effect profiles. However, their poor stability in the gastrointestinal tract and limited epithelial permeability typically necessitate parenteral delivery, affecting patient compliance. Buccal route offers a non-invasive alternative, enabling direct absorption into systemic circulation while avoiding food interactions and first-pass metabolism. This study presents dissolvable microneedles (MN) as novel platform for buccal peptide delivery.

Methods: Dissolvable microneedles (MNs) were fabricated in a three-step process. A 7×7 array of cone-shaped MNs (1 mm height, 0.33 mm base radius, 3:1 aspect ratio) was 3D printed using a Phrozen Sonic Mini 8K DLP printer. This master structure was used to create negative PDMS molds. Viscous polymer solutions—with or without octreotide (OCT) as a model peptide—were cast into these molds using polyvinyl pyrrolidone (PVP), poly(methyl vinyl ether-co-maleic acid) (PMVE), or hyaluronic acid (HA). A drug-free backing layer was applied using the same polymers. MNs were analyzed via scanning electron microscopy (SEM) for morphology and structure. Ex-vivo studies on porcine buccal tissue assessed degradation and penetration, with Cryosectioning and H&E staining confirming tissue depth. Peptide stability was evaluated one week post-fabrication using ultra-high-performance liquid chromatography (uHPLC) and LC-MS. OCT content was quantified via reverse-phase uHPLC with a C-18 column and UV detection, while LC-MS identified characteristic OCT peaks using an Agilent QTOF system and FA/ACN solvent gradients.

Results: Dissolvable microneedles (MNs) were successfully fabricated using PDMS molds cast with polymer solutions (PVP, PMVE, or HA) containing sulforhodamine B for visualization. Polymer concentrations ranged from 30–50% w/w, with octreotide (OCT) loaded at 1–5% relative to polymer content. Following 48 hours of ambient drying, sharp MNs approximately 1 mm in height were formed. Upon application to porcine buccal tissue, MNs effectively penetrated the buccal epithelium, as confirmed by histological imaging. All MNs dissolved within 3 minutes, with dissolution time dependent on polymer type. The hydrophilic nature of buccal mucosa facilitated rapid MN breakdown and peptide release. Peptide stability was assessed post-fabrication using uHPLC and LC-MS. OCT integrity was preserved in PMVE and HA MNs, with over 95% recovery, while PVP-based MNs showed reduced recovery (~80%), suggesting possible peptide-polymer interactions. LC-MS confirmed consistent m/z values (1019.44 for z=1) across samples, indicating no structural degradation of OCT after MN incorporation.

Conclusions: In conclusion, dissolvable polymeric microneedles (MNs) were successfully fabricated by casting viscous polymer solutions, yielding structures with favorable mechanical and dissolution properties. These MNs effectively penetrated porcine buccal epithelium under gentle pressure and dissolved within three minutes, enabling rapid peptide release. Importantly, octreotide (OCT) retained its structural integrity during the fabrication process, indicating suitability for buccal delivery. These findings support the potential of MN-based systems for non-invasive peptide administration via the buccal route. Ongoing ex-vivo flux studies will further assess peptide bioavailability, advancing the development of a patient-friendly, effective alternative to injectable peptide therapies.