Printing of cutaneous patches loaded with propranolol for the treatment of infantile hemangiomas

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Topical propranolol (PR) has been used in clinics for treating cutaneous infantile hemangiomas, but frequent applications of semi-solid preparations are required to maintain therapeutic PR concentrations in the skin layers over time. The design of cutaneous patches is attractive to simplify the regimen and to maximize the residence of the dosage form at the absorption site. Indeed, cutaneous patches are designed to provide a prolonged drug delivery through the skin to achieve a local effect. Usually, they are drug-in-adhesive systems, in which the drug is dispersed and/or dissolved in a pressure-sensitive adhesive (PSA) matrix. This manufacturing approach requires expansive equipment that is not easily adaptable to the preparation of small or personalized batches.
This work aims to study the preparation of cutaneous PR patches by hot-melt ram extrusion printing, a novel technique suitable for the personalization of such dosage forms [1]. This technology allows defining easily both the patch geometry and the dose according to the patient's need avoiding any manipulation (i.e., the dosage form cutting). To prepare patches, three simple technological operations were required: i) mixing of a poly-ammonium methacrylate polymer (EuRL) with a suitable amount of plasticizer (i.e., acetyl triethyl citrate, ATEC); triacetin or tributyl citrate, TBC), and the drug (propranolol base, PR-B or hydrochloride, PR-Cl); ii) the melting in the ram extruder, and iii) the printing on the backing layer foil. The printed patches were characterized in terms of adhesive properties (i.e., tack, shear adhesion, and 180°-peel adhesion), other than drug content, in vitro drug release, and skin permeation.
The final thickness of the patches (50±10 μm), and the drug contents were uniform, exception made for the TRI-based formulations which were too-fluid to allow a reproducible deposition of the adhesive matrix on the backing layer. On the contrary, all ATEC and TBC formulations exhibited suitable adhesive properties. The tack of placebo ATEC-based patches resulted significantly higher than those obtained from TBC ones ($p < 0.01$), whereas shear adhesion resulted in a comparable pattern. The drug did not significantly affect the adhesive properties of the patches plasticized with TBC and ATEC. The in vitro release results demonstrated that PR was rapidly released from all formulations, suggesting that the thermodynamic activity of the drug at the cutaneous patch/stratum corneum interface should be guaranteed during the application on the skin. The flux (J) values, calculated from the in vitro skin permeation experiments, followed the rank order: ATEC/Pr-Cl < TBC/Pr-Cl < TBC/Pr-B, < ATEC/Pr-B ($p < 0.001$; one-way ANOVA). The PR retained amounts were similar for almost all tested formulations ($Q_{ret} \approx 14$ μg/cm^2). The overall results suggested that patches made of EuRL and TBC and containing 1% PR-Cl were the most promising formulation for ensuring the PR retention on the human epidermis ($Q_{ret}/J = 1.32$) and, therefore, it can be selected when a superficial infantile hemangioma had to be treated. Conversely, patches made of EuRL and ATEC and containing 1% PR-B ($Q_{ret}/J = 0.09$) in the case of deep infantile hemangiomas.

Literature:
[1] U.M. Musazzi, M.A. Ortenzi, C.G.M. Gennari, A. Casiraghi, P. Minghetti, F. Cilurzo, *International Journal of Pharmaceutics* **2020**, 586, 119607.