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Improvement of Digital twin for transdermal fentanyl delivery based on anomalous diffusion

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Fentanyl is potent synthetic opioid that effectively alleviate the pain in cancer patients with chronic acute pain, but the standard clinical determination of initial dose is obsolete. Appropriate dosage for each patient is crutial for minimization of under- or overdosing, and prevention of known adverse effects. Transdermal delivery fentanyl patches are used to enable slow release of the drug and increase the quality of life of frail patients compared to other delivery pathways, but the central problem to optimal therapy is immense inter individual variability of patient's physiological features.
A better understanding and description of the complexities of transport processes through the human skin provides the basis for the individual prescription of appropriate dosage. It is shown that transdermal administration of fentanyl should be mathematically described as mass transport through highly inhomogeneous structure (human skin) to accurately estimate uptake and accumulated fluxs important in minimal effective dosage determination. To predict and control the amount of metabolized drug, for each individual patient is therefore the utmost challenge for fentanyl-based pain management. Molecular diffusion through a composite multilayer system is a central process in transdermal drug delivery. This system consists of a polymer vehicle with a drug and skin of complex structure in which drug molecules are absorbed and enter into blood circulation through the capillary network. The classical Fickean approach treats this process as a pure diffusion neglecting fractal or more generaly highly heterogeneous structure of skin barrier. A possible way of overcoming this kind of simplification in modeling transdermal transport is the inclusion of anomalous diffusion effectts. We managed to test the mathematical method to derive the cumulative amount of drug absorbed, by use of fractional model. Utilizing the fractional model we developed a method to solve an inverse problem with an aim of estimation of model parameters and connection with individual patient's features. This result serve as basis for modelling of personalized digital twin (DT) for transdermal fentanyl therapy. The whole methodology described here is applied on experimental results and we demonstrated a good agreement of the theoretical model with measurements, where values of physiological features are within expected range. The model points out the role of the diffusion coefficients and fluxes delayed time of both, vehicle and skin, in control of the complex transfer mechanism and the drug kinetics across the two layers that once implemented, could increase predictive power of DT.

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Acknowledgements: This research has been financially supported by the OPO Foundation, Margit Weisheit and Parrotia Foundation to Empa Swiss Federal Laboratories for Materials Science and Technology (MC) at St. Gallen (Project Digital human avatars help customize transdermal pain therapy in real time) 2022/2023. SG was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia, (contract 451-03-47/2023-01/200017).