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Fluorescent labeled cyclodextrin derivatives as novel exogenous markers for transcutaneous measurement of renal function

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Transcutaneous GFR measurement technique provides various merits and validates against gold standard plasma/urine clearance method. In an attempt to employ and popularize the transcutaneous approach, the main challenge is to develop novel fluorescent GFR markers.
In this work, we designed, synthesized and evaluated of novel fluorescent markers for transcutaneous assessing renal function. 2-hydroxypropyl-CDs (HPCDs) have been chosen as alternatives for inulin and sinistrin. Compared to inulin and sinistrin, HPCDs are chemical structures and molecular weight well defined. Their good water solubility and no toxicity merits resulted in a FDA approval. We developed two series of fluorescent dyes labeled HPCDs as exogenous markers. One belongs to the xanthene family of dyes, the other to the cyanine family of dyes. In addition, different charged near infrared markers were designed for understanding the relationship between the charge distributions and their plasma protein binding (PPB), pharmacokinetics as well as half-life. These HPCDs based markers were prepared under three different chemical reactions such as esterification, reaction of isothiocyanates with hydroxyl, and Cu-catalyzed click chemistry reaction. All the markers can be easily synthesized and exhibit favorable fluorescence properties. No supermolecules formation or nanometer aggregates were observed.
PPB studies were carried out for all of the markers. All the candidate markers displayed very low PPB (<10%), which is lower than some of the gold standard renal markers, for example iothalamate. We demonstrated that PPB of markers is not only dependent on the hydrophilicity, but also related to their molecular charge number and distributions. In vitro experiments, the cytotoxicity was evaluated by MTT viability assay. No significant cytotoxic response was detected. They displayed a pronounced stability in plasma and resisted esterase enzymatic lysis. In preliminary transcutaneous bolus clearance measurements, xanthenes dyes labeled HPCDs, zwitterionic cyanine labeled HPβCD (ABZWCY-HPβCD and AAZWCY-HPβCD) can be excreted in the urine. No metabolites were found in urine. Those candidate markers have a great potential as exogenous fluorescent agents for real time monitoring of renal function.