PHARMACOKINETICS AND PHARMACODYNAMICS OF GLUCAGON-LOADED PLGA NANOSPHERES FOR INHALATION THERAPY

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**[Purpose]** Dry powder inhaler (DPI) of glucagon is believed to be a promising new dosage form, and the present study aimed to develop a novel glucagon-loaded PLGA nanospheres for improved pharmacokinetics and pharmacodynamics.

**[Methods]** Glucagon-loaded PLGA nanospheres were prepared by emulsion solvent diffusion method, and the DPI form was prepared with a jet mill. The physicochemical properties were characterized by dynamic light scattering, electron microscopy, dissolution test, laser diffraction, and cascade impactor. Aggregation of glucagon in PLGA nanospheres was evaluated by cytotoxicity test, spectroscopic analysis, and β-sheet-specific dye. Pharmacokinetic profiles and hyperglycemic activities of new glucagon DPI were also characterized after the pulmonary administration in rats.

**[Results and Discussion]** Although preparation of PLGA nanospheres using glucagon solution at concentrations over 10 mg/mL led to significant formation of cytotoxic glucagon aggregates, glucagon solution at less than 5 mg/mL did not cause structural changes. The drug release behavior of nanospheres showed a biphasic pattern with an initial burst and slow diffusion. Laser diffraction and cascade impactor analyses of the newly developed glucagon-DPI suggested high dispersion and deposition in the respiratory organs with an emitted dose and fine particle fraction of 98.9 and 20.5%, respectively. After the intratracheal administration of new DPI form (200 μg-glucagon/kg) in rats, glucagon was released in a sustained manner, leading to sustained hyperglycemic effects, compared with normal glucagon powder.

**[Conclusions]** These data would suggest a therapeutic benefit of the new inhalable glucagon-loaded PLGA nanospheres as an alternative to the injection form of glucagon currently used.

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COMBINED USE OF PHOTOBIOCHEMICAL AND CASSETTE DOSING PHARMACOKINETIC DATA FOR PREDICTING PHOTOTOXIC POTENTIAL OF PHARMACEUTICAL CHEMICALS

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**[Purpose]** A main purpose of the present study was to develop a new reliable and high-throughput screening strategy to predict phototoxic risk of pharmaceutical chemicals in the early stage of drug discovery.

**[Methods]** Photochemical properties of 6 fluoroquinolones (FQs) were evaluated by UV spectral and reactive oxygen species (ROS) assays, and phototoxic potentials of FQs were also assessed using 3T3 neutral red uptake phototoxicity test (3T3 NRU PT) and intercalator-based photogenotoxicity (IBP) assay. Cassette dosing pharmacokinetics on FQs was conducted with aim of calculating pharmacokinetic parameters and potential dermal distribution.

**[Results and Discussion]** All the FQs exhibited strong UVA/B absorption, and exposure of the FQs to the simulated sunlight led to ROS generation. These physicochemical data suggested the potent photosensitivity of the FQs, which might be a key trigger for phototoxic reactions. The photoinrritant and photogenotoxic risks of the FQs were also elucidated on the basis of the results from the 3T3 NRU PT and the IBP assay. The cassette dosing pharmacokinetic studies on FQs were conducted with focus on potential dermal distribution to estimate in vivo phototoxic risks of FQs tested. These present data were combined, and in vivo phototoxic risks of the FQs would be predicted.

**[Conclusions]** A combined use of in vitro photobiochemical and cassette dosing pharmacokinetic data will be useful for predicting in vivo phototoxic potentials of drug candidates with high productivity and reliability.