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Radiolabeling and Pre-Clinical Evaluation of Y-90-DOTATATE - Formulated Using Y-90-Acetate from High Level Liquid Waste

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Background:

The effectiveness of Y-90-DOTATATE as a therapeutic radiopharmaceutical for Peptide Receptor Radionuclide Therapy(PRRT) in treatment of large volume neuroendocrine lesions is well established. The high energy of β- particle emission(Emax: 2.28MeV) is suitable for treatment of neuroendocrine lesion with diameter of 5cm and more. The challenges involved in the formulation of this radiopharmaceuticals is the purity of the radiochemical(Y-90-Chloride/Y-90-Acetate) used, which in turn necessitates the cost-effective extraction in clinical grade, from high level liquid waste(HLLW). Towards this Y-90-Acetate was sourced from HLLW based on supported liquid membrane(SLM) technology. Y-90-Acetate thus isolated complies with the regulatory requirement with respect to its use as a clinical grade API. This Y-90-Acetate were used in radiolabeling of DOTATATE and the radiopharmaceuticals was evaluated on *in-vitro* cell-binding and *in-vivo* biodistribution studies in suitable animal model. The present work documents the effort towards development of an indigenous cost-effective Y-90-based radiopharmaceutical for PRRT of neuroendocrine tumors.

Methodology:

Clinical grade Y-90-Acetate sourced from two-stage Sr-90/Y-90 generator based on SLM technology. The formulation of Y-90-DOTATATE carried out using Y-90-Acetate, 0.2N ammonium-acetate buffer(pH˜5.5) and DOTATATE. The reaction mixture was incubated at 95degC for 35minutes at pH˜4.0. On cooling, 60mg of gentisic acid/mL of saline was added. RCP assessed by TLC-SG{(0.1M sodium-citrate buffer(pH-5.0)} and HPLC using RP18 with gradient(0.1%TFA in water and acetonitrile). Gel-clot BET-assay and Sterility test were performed. *In-vitro* and serum-stability of the product on storage at -20degC was evaluated by TLC/HPLC at 24h and 48h post radiolabeling.
Pancreatic carcinoma cell-line AR42J used for in-vitro evaluation, was grown in IMDM with 10%FBS at 37degC. *In-vitro* cell-binding was performed by incubating AR42J cells in 1mL of internalization buffer containing radioligand(˜5pmol peptide) for 15, 30, 60 and 120minutes and washed with PBS. For membrane receptor binding assay, AR42J cells homogenates were incubated for above time points. Biodistribution studies carried out in AR42J cell-line xenograft tumor bearing nude mice at 6h, 24h, 48h & 72h intervals and quantified by β-spectrometer.

Results and Discussions:

Using pharmaceutical-grade Y-90, formulation of 50-55 mCi of Y-90-DOTATATE prepared. Y-90-DOTATATE was clear, pale-yellow color, pH between 5.0-5.5. RAC between 8-12 mCi/mL. RCP of Y-90-DOTATATE estimated by TLC was >98% with retention-factor 0.0-0.1. RCP derived by HPLC was >98% with retention-time of radioactive-chromatogram between 10.4-11.4minutes. EL was <6EU/mL, radiopharmaceutical was sterile. *In-vitro* and serum stability of the product indicated stability upto 48hrs upon storage at -20degC with stabilizer.
Y-90-DOTATATE showed rapid binding(30%) in AR42J cells, reaching a plateau after 15-30minutes. In biodistribution study, radioactivity in the blood and most of the organs decreased after 24h post-injection. High-uptake and long-term retention of radioactivity were found in the kidney(8.01% ID/gm) and tumor(3.17% ID/gm) which corroborates with scintigraphy studies.

Conclusion:

The Y-90 isolated from HLLW has been approved as a clinical grade radiochemical. This has been utilized in the formulation of patient doses of Y-90-DOTATATE, used in the treatment of large NET lesions. This development offers an affordable treatment option to a large number of patients.

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