Developing a Safe and Effective Compounding Method for Hyperpolarized [1-^{13}C] Pyruvate to be Used in the Clinical Evaluation of MR Molecular Imaging in Cancer Patients

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INTRODUCTION

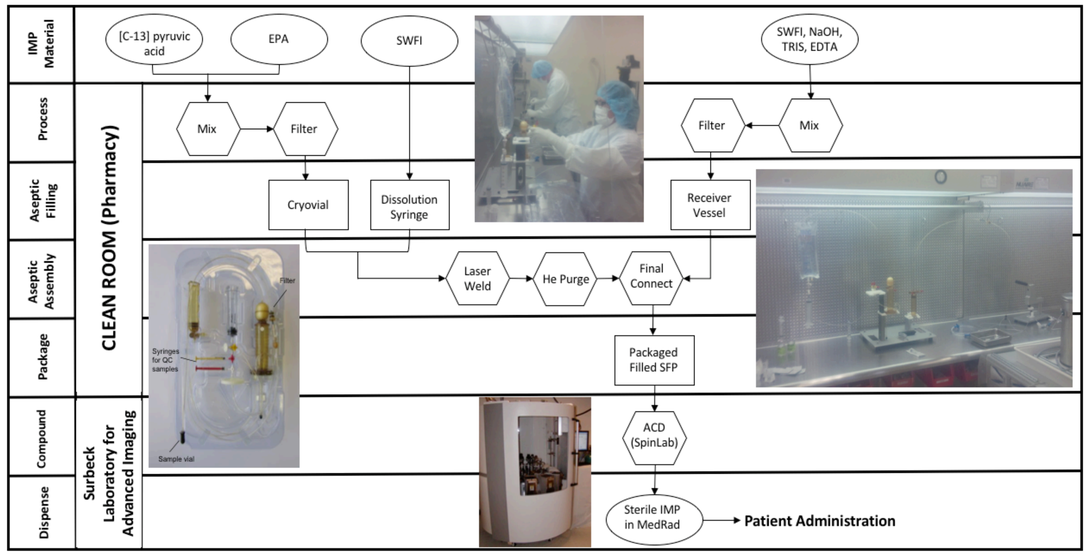
Previously reported techniques for the preparation of hyperpolarized [1-^{13}C] pyruvate used in preclinical studies are not suitable for human administration in the clinical arena. [1,2] The aim of this project is to generate a validated compounding method and appropriate process controls for the synthesis of hyperpolarized [1-^{13}C] pyruvate that withstands regulatory scrutiny and ensures the creation of a procedure that can be utilized by other institutions wishing to conduct similar clinical trials.

METHODS

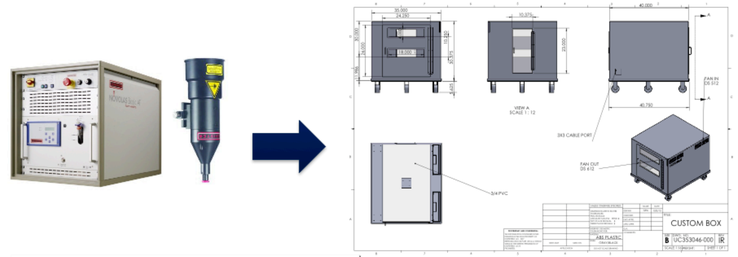
The generation of hyperpolarized [1-^{13}C] pyruvate is accomplished by the use of an automated compounding device (ACD). In order for the device to produce a sterile solution acceptable for human administration, strict preparation of the active pharmaceutical ingredient (API) ([1-^{13}C] pyruvic acid) and its excipients (paramagnetic agent, buffer, and diluent) must take place. The API and its excipients are charged into a custom sterile fluid path (SFP)- which functions as the drug container and container closure system that is processed by the ACD. The exact quantities of the API and excipients were determined by conducting a series of polarizations—each iteration varying a specific ingredient. Once optimized, the appropriate amounts of the API and excipients are then procured, sterilized by double filtration, and aseptically infused into the empty SFP within a clean room suite. The filled SFP is then purged with sterile helium gas and finally sealed via a radial laser weld. Introduction and placement of the welder into a clean room environment required the construction of a custom container to protect the clean room and the SFP from particulates emitted by the welder. Qualification and optimization of the laser weld (seal width, laser power, weld time, etc) was accomplished by series of test welds followed by a custom burst test, which examines the strength of the weld. Integrity testing of the sealed SFP was conducted by a pressure test whereby sterile helium is instilled into the SFP at a pressure of 40 psi for a total of 2 minutes.

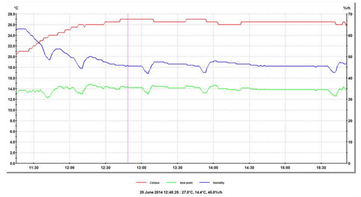
COMPOUNDING QUALIFICATION DATA

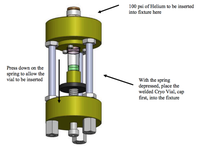
		DOSE #1	DOSE #2	DOSE #3	DOSE #4	DOSE #5	DOSE #6	DOSE #7	DOSE #8	DOSE #9	DOSE #10
		Channel #1	Channel #1	Channel #1	Channel #1	Channel #1	Channel #2	Channel #2	Channel #2	Channel #2	Channel #2
TEST	**SPECIFICATION**										
^{13}C Nuclear Polarization	NLT 15%	19.1	22.5	21.2	16.4	17.2	18.3	16.8	16.8	16.3	16.7
Pyruvate Concentration	220-280 mM	267	269	270	261	267	259	254	248	270	262
Residual Radical	NMT 3.0 μM	1.2	1.9	1.4	1.7	1.2	1.2	1.3	1.0	1.2	1.1
pH	6.7-8.0	7.6	7.5	7.6	7.6	7.5	7.7	7.8	7.9	7.6	7.7
Temperature	25.0 – 37.0°C	33.2	34.1	34.4	33.6	33.9	33.5	34.9	32.4	33.0	31.6
Volume	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL	> 38 mL



LASER QUALIFICATION & IMPLEMENTATION







RESULTS

Validation of the compounding procedure and its responsible personnel was first conducted by a series of media fills. Elution of the growth media from the SFP and subsequent testing resulted in no bacteria or fungal growth. During process qualification of the ACD, ten consecutive samples demonstrated production of a hyperpolarized drug solution that met all specifications established by a previously approved IND application from the FDA. The ten samples were then tested for sterility and endotoxins and yielded passing results.

CONCLUSION

Here we report a new compounding procedure that results in a pharmaceutically elegant, sterile hyperpolarized [1-^{13}C] pyruvate solution that is suitable for injection into humans. Moreover, this proposed method could also be extended to other molecular probes that reach investigational status in the clinic.

REFERENCES

[1] Golman K, et al. PNAS 2003; 100.
[2] Kurhanewicz J, et al. Neoplasia 2011; 13.