A fully automated synthesis for the preparation of ^{64,67}Cu-SARTATE using the iPHASE Multisyn Radiosynthesiser

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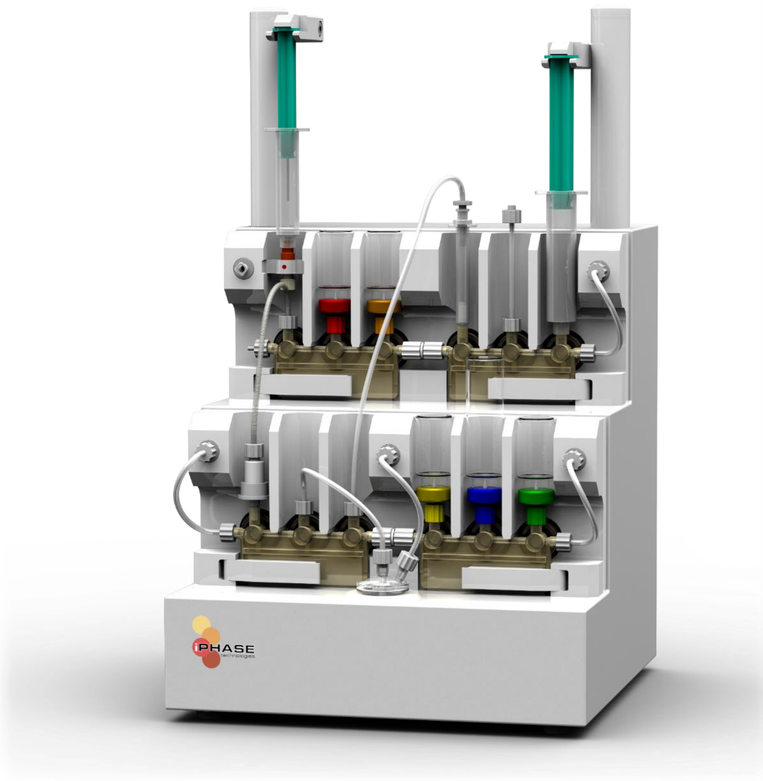


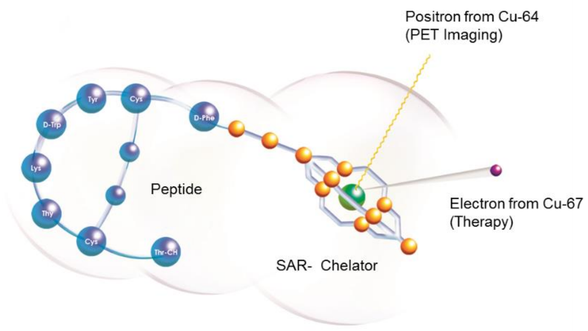
INTRODUCTION

SARTATE is a proprietary molecule being developed by Clarity Pharmaceuticals Pty Ltd, which has been developed for the paired PET/CT imaging and radiotherapy of somatostatin receptor 2-expressing cancers, utilising the complementary radioisotopes copper-64 and copper-67.

Previously, ^{64}Cu-SARTATE ([^{64}Cu]-Cu-[MeCoSar0,Tyr3]-Octreotate)had been prepared for use in humans by utilising a manual synthesis method.

The MultiSyn (iPHASE technologies, Melbourne) is a compact and GMP-compliant radiosynthesis module, which utilises kit-based technology for radiolabelling molecules with a variety of isotopes for PET imaging and radiotherapy – including ^{68}Ga, ^{64,67}Cu, ^{177}Lu, ^{18}F, ^{124}I, ^{89}Zr, ^{90}Y.

In this study, the automated manufacture of ^{64}Cu-SARTATE and ^{67}Cu-SARTATE on the MultiSyn was implemented and evaluated.



EXPERIMENTAL

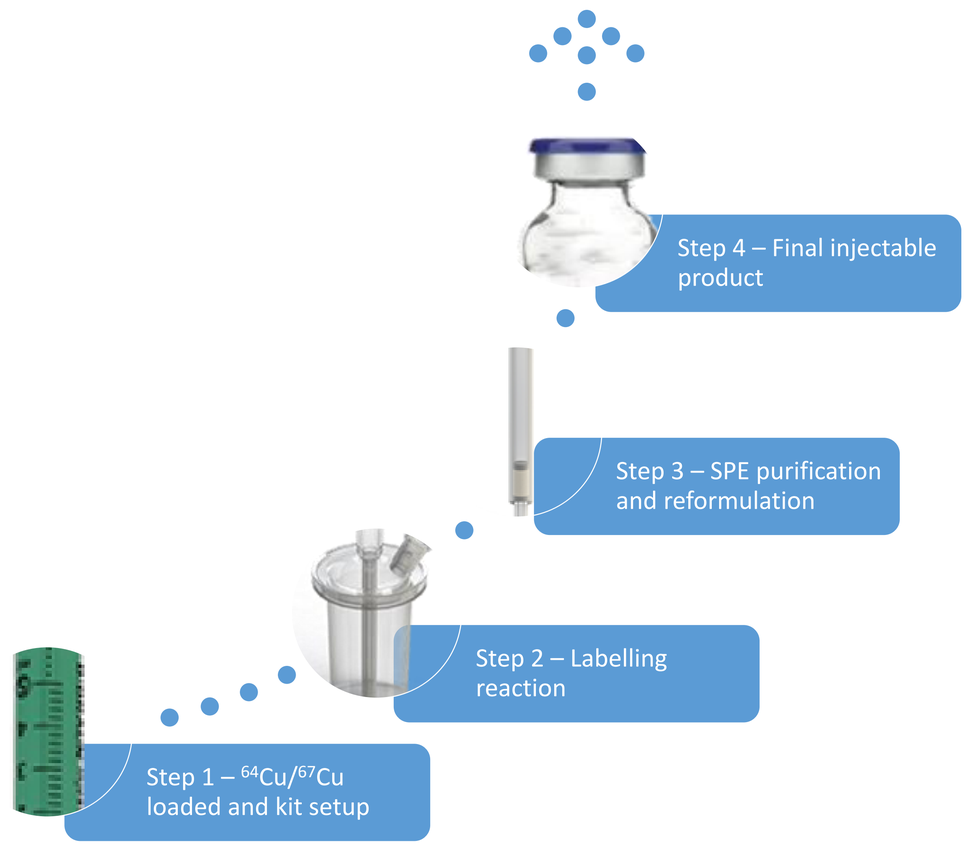
Experiments were undertaken to adapt the established manual ^{64}Cu-SARTATE synthesis method to the MultiSyn, looking to optimise the radiolabelling conditions with varying reaction temperatures and times. Further experiments were then performed using ^{67}Cu to produce the companion therapy radiopharmaceutical.

Step 1: During setup, the commercially-available disposable kit is loaded onto the MultiSyn, including the commercially-available reagents (ethanol, saline and water) and SPE cartridge. The ^{64}Cu or ^{67}Cu solution (0.05 - 0.1M HCl) is loaded in a syringe onto the kit and the lyophilised SARTATE peptide is dissolved in buffer (5mL) before being manually loaded into the reactor vial. The SPE cartridge is automatically conditioned during setup phase with ethanol, followed by water.

Step 2: The ^{64}Cu or ^{67}Cu solution is automatically dispensed into the reactor containing the peptide, and reacted under one of the following conditions:
a) Room temperature for 30mins
b) 95°C for 10mins.

Step 3: The reaction mixture is passed through a Phenomenex Strata-X SPE cartridge and washed with saline. The radiolabelled peptide is eluted with 0.5-1mL ethanol and reformulated in saline.

Step 4: The final product is passed through a sterile filter into a sterile product vial.



RESULTS AND DISCUSSION

A total of 5 productions of ^{64}Cu-SARTATE have been performed – 3 reactions were completed at room temperature for 30mins, and 2 reactions were completed at 95°C for 10mins. The chelator attached to the octreotate molecule, MeCOSAR, is highly specific for copper, and has fast reaction kinetics – which means that heating is not required for complete radiolabelling. Performing the reaction at room temperature was therefore preferred. There was no significant benefit to radiolabelling yield from heating the reaction – nor was there any noticeable change to the quality of the product.

The average radiolabelling yield is 74±8% at room temperature, which is a commercially viable yield, and comparable to that achieved through manual synthesis of ^{64}Cu-SARTATE. This yield has been achieved from a starting activity of copper-64 of up to 500MBq. Small amounts of activity are lost to all parts of the kit that come into contact with the radioactive product – in general, less than 5% of the starting copper-64 activity remains as free $^{64}Cu^{2+}$, which is passed through to waste.

A total of 4 productions of ^{67}Cu-SARTATE have been performed – all reactions have been completed at room temperature for 30mins. After optimising the amount of starting peptide, the average yield of product at room temperature is 74±6%. Copper-67 is a therapy isotope and is used at higher activities – up to 1.5GBq has been used for labelling successfully. The amount of unchelated $^{67}Cu^{2+}$ is again less than 5% of the starting activity.

	^{64}Cu-SARTATE	^{67}Cu-SARTATE
Total number of trials	5	4
ROOM TEMP, 30 MIN		
Number of trials	3	4
Average yield (%, non d.c.)	74±8%	74±6%
Total synthesis time	45min	45min
95°C, 10 MIN		
Number of trials	2	0
Average yield (%, non d.c.)	71	N/A
Total synthesis time	26min	N/A

CONCLUSION

Results show that a consistent, efficient and reliable automated method for the manufacture of ^{64}Cu-SARTATE and ^{67}Cu-SARTATE using the MultiSyn radiosynthesiser has been developed, which results in a high yield of product suitable for use in clinical trials, that can be compliant to GMP requirements.

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