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Understanding temperatures and pressures during short radiochemical reactions

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HIGHLIGHTS

- In all radiosynthesizers, reported reaction conditions differ from actual temperature profile.
- This system-dependent difference can lead to discrepancies among different synthesizers.
- Using an example vial-based system (ELIXYS), this fundamental discrepancy is illustrated.
- Ramp times for heating/cooling, and calibration of setpoint versus actual, were determined.
- These data could facilitate translation of protocols between ELIXYS and other systems.

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ABSTRACT

Automated radiosynthesizers are critical for the reliable, routine production of PET tracers. To perform reactions in these systems, the temperature of the reactor heater is controlled, and the liquid temperature within the reaction vessel is presumed to closely follow. In reality, the liquid temperature can lag by several minutes and generally does not reach the heater temperature. Furthermore, because different synthesizers have different heating mechanisms and geometries, discrepancies are certain to exist between the actual temperatures experienced by the reaction mixture on different synthesizers. For dissimilar reactors, this can necessitate re-optimization of conditions when adapting a synthesis from one system to another, especially for the short-duration reactions common in radiochemistry. Herein, we study the relationship between the temperatures of the reactor heater and reaction liquid for various solvents using the ELIXYS radiosynthesizer as a representative example of a vial-based system. Our aims are to quantitatively illustrate this discrepancy to the community and provide data necessary to enable efficient translation of protocols between other radiosynthesizers and the ELIXYS.

1. Background

The preparation of positron emission tomography (PET) tracers has evolved over the years to include increasing automation (Alexoff, 2003; Keng et al., 2012; Krasikova, 2007). For automation to be successful, however, thorough characterization of the reagent delivery, reaction, solution transfer, and other mechanisms of the radiosynthesizer needs to be performed and understood (Sachinidis et al., 2010). Only then is one able to specify appropriate parameters for the automated radiosynthesis protocol such that the system consistently and efficiently produces the desired product from a given input of reagents.

An especially critical parameter in determining the reaction rates and yields of both the desired product and the formation of side-products is the reaction temperature. Consistent with normal practice in the field of organic synthesis, radiochemists typically report the temperature of the reactor heater (e.g., metal block, oil bath, etc.) along with the time during which the reaction vessel (e.g., glass vial) is heated at the given temperature. Though it would be desirable to directly monitor and control the temperature of the vessel contents, the combination of a harsh chemical environment, high pressure, and a small reaction vessel makes it very challenging to accurately and routinely monitor the liquid temperature. (Though IR sensors can be placed outside the reaction vessel, circumventing many of these issues, the readout may not be accurate, representing a mixture

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of the temperature of the reaction vessel contents and the temperature of the glass vessel itself.) Thus, in automated radiosynthesizers, there is a system-specific discrepancy between the monitored reactor heater temperature and the actual liquid temperature that should be considered when developing synthesis protocols. The actual liquid temperature is furthermore related to the vapor pressure that is developed when performing sealed reactions; it is critical to understand this relationship, especially when developing protocols involving reactions under superheated conditions (i.e., above the solvent's normal boiling point), so that pressure limitations of the synthesizer are not exceeded.

During relatively lengthy reaction times (e.g., >15–30 min for milliliter-scale volumes), the temperature of the reaction vessel contents is likely to equilibrate, reaching a stable value for much of the reaction time. However, as the reaction time decreases, this equilibrium may not be established, or may only be established for a relatively small fraction of the total heating time, with the rest of the time occurring during temperature ramping (i.e., heating up or cooling down). This problem is further intensified at higher reaction temperatures, which increase the equilibrium temperature and the required liquid heating time.

Performing reactions primarily during a temperature ramping phase can make it difficult to reproduce reaction conditions precisely, particularly when trying to adapt reaction conditions from one type of radiosynthesizer to another. Engineering design differences between synthesizers can significantly impact the time it takes the liquid temperature to ramp up toward the reactor heater setpoint, the liquid temperature reached at equilibrium, and the time it takes the liquid to cool back down to a certain temperature. Differences in the heating mechanism (e.g., immersion in an oil bath, resistively or thermoelectrically heating a metal “jacket” around the vessel, inductive heating, or applying microwaves) have a major impact on these parameters. Even among different synthesizers based on jacket heating (i.e., the most common approach), there can be significant differences. For example, the heating rate depends on the power output of the heater, the thermal mass of the heater and associated systems, the thickness and thermal conductivity of the reaction vessel, the effectiveness of the thermal interface between the heater and the vessel, etc. The equilibrium temperature depends on the power output of the heater and the degree of thermal insulation of the reaction vessel from the rest of the environment. The cooling time depends on the heat removal capacity of the cooling system (e.g., exposure to ambient air, exposure to forced air, or recirculating liquid coolant) as well as the same geometric and mechanical factors that affect heating rate.

With all of these potential variations, it follows that to achieve the same liquid temperature profile for a reaction on different synthesizers, it may be necessary to use different reactor heater setpoints, reaction durations, and cooling times. This could be responsible in part for the significant variation that is sometimes seen in reported protocol parameters (especially for short-duration or high-temperature heating steps) for producing the same tracer on different systems. As an example, Table 1 illustrates the conditions used for the 3-step radiosynthesis (i.e., [^{18}F]fluorination, deprotection, and *N*-hydroxysuccinimide (NHS) ester formation) of *N*-succinimidyl-4-[^{18}F]fluorobenzoate ([^{18}F]SFB), a commonly used prosthetic group for radiolabeling peptides and proteins with [^{18}F]fluoride, across different platforms. Though the reagent types and amounts vary slightly, the fundamental chemistry is the same for each reaction step, yet there is large variation in parameters among these publications. Inconsistency among radiosynthesizers, coupled with a lack of data or understanding of the reactor heating characteristics, could explain, in part, the difficulty and high cost of adopting new tracers at production facilities, which in turn creates a bottleneck in the investigation and validation of novel PET tracers. This is a particularly pressing issue in the radiopharmaceutical field and must be overcome to accelerate the expansion of PET and diversification of available tracers.

To increase awareness in the community, we illustrate the above heating-related issues (i.e., discrepancy between actual and measured temperatures, temperature ramping time, and vapor pressure limitations) via an extensive characterization of the relationship between the temperatures of the reactor heater (T_{heater}) and liquid within the vessel (T_{liquid}) for a representative vial-based radiosynthesizer (ELIXYS, Sofie Biosciences). This system was chosen for its ability to be readily modified to enable simultaneous monitoring of both temperatures, while also supporting a particularly wide range

Table 1
Reaction parameters for various [^{18}F]SFB synthesis protocols from the literature. Radiochemical yields (RCY) and reaction times reported as mean ± standard deviation for the 3-step protection of [^{18}F]SFB.

[^{18}F]fluorination	Deprotection	NHS ester formation	Decay-corrected RCY, synthesis time	Synthesizer	Reference
MeCN 90 °C 10 min	MeCN/H_2O 100 °C 5 min	MeCN 90 °C 2 min	34–39% 68 min	GE TRACERlab Fx_{FDG} (modified)	Mäding et al. (2005)
DMSO 115 °C 15 min	H_2O 115 °C 9 min	MeCN 115 °C 5 min	46 ± 5% ($n=4$) 78 min	Siemens CPCU (modified)	Marik and Sutcliffe (2007)
MeCN 90 °C 10 min	MeCN 120 °C 3 min	MeCN 90 °C 5 min	44 ± 5% ($n=10$) 60 min	Manual apparatus	Tang et al. (2008)
MeCN 90 °C 10 min	MeCN 120 °C 1 min	MeCN 90 °C 5 min	43–60%[a] 85 min	GE TRACERlab $FX_{F\text{-}N}$ (modified)	Tang et al. (2010)
DMSO 110 °C 15 min	MeCN 110 °C 10 min	MeCN 110 °C 5 min	69 ± 8% ($n=6$) 78 min	Sofie Biosciences ELIXYS	Lazari et al. (2014)

[a] Decay-corrected RCY calculated from reported not-decay-corrected RCY and overall synthesis time.