Almac Voice

Radiochemical stability of carbon-14 compounds

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Exploring the factors affecting the radiochemical stability of carbon-14 compounds and techniques for assessing and enhancing their stability.

Introduction

Carbon-14 [^{14}C] is a radioactive isotope of carbon, naturally occurring in trace amounts in the Earth's atmosphere. Its conversion to nitrogen-14 through beta decay forms the basis of radiocarbon dating, a powerful technique for determining the age of various materials. Carbon-14 is one of the key isotopes used to radiolabel drug substances for clinical trials. Here at Almac, we have a dedicated team of highly skilled chemists and analysts performing synthesis, purification, and analysis of [^{14}C] radiolabelled Active Pharmaceutical Ingredients (API) and intermediates in our state-of-the-art GMP isotope chemistry laboratories.

One key aspect to consider when designing the synthesis of, or handling [^{14}C]-radiolabelled compounds, is the radiochemical stability of both intermediates and final compounds. This article explores the factors affecting the radiochemical stability of carbon-14 compounds and discusses techniques for assessing and enhancing their stability.

Factors affecting radiochemical stability

- Chemical structure: the radiochemical stability of a [^{14}C]- compound is significantly impacted by its chemical structure; the position of the carbon-14 atom and the functional groups in the molecule are both important. For instance, compounds containing carbon-14 in a primary, secondary, or tertiary position will have different stability profiles.
- Environmental factors / storage conditions: external factors such as temperature, pH, and exposure to light, air (oxygen) or other chemicals can influence the radiochemical stability of carbon-14 compounds. In general, radiochemical stability decreases with increasing temperature, due to the increased probability of chemical reactions, radical formation, and bond dissociation. For solutions the pH can impact the stability of [^{14}C]- compounds due to hydrolysis reactions that may occur at extreme pH values.
- Presence of radicals: the presence of free radicals can cause degradation of carbon-14 compounds. These highly reactive species can initiate chain reactions, leading to the breakdown of [^{14}C]-compounds and a decrease in radiochemical stability.
- Concentration: the concentration of the [^{14}C]-compound in a solution or solid state can impact its radiochemical stability. Higher concentrations can lead to increased intermolecular interactions, potentially causing degradation or precipitation of the compound. High specific activity solids (50-60 mCi/mmol) will generally have a lower stability than diluted, low specific activity solids (<20 mCi/mmol).
- Radiation effects: [^{14}C]-compounds undergo radioactive decay, generating beta particles in the process. These beta particles can cause radiolysis, a process where the energy from the emitted particles induces the formation of free radicals, which can then react with the [^{14}C] compound or other molecules in the system, leading to a decrease in radiochemical stability.

Techniques to enhance radiochemical stability

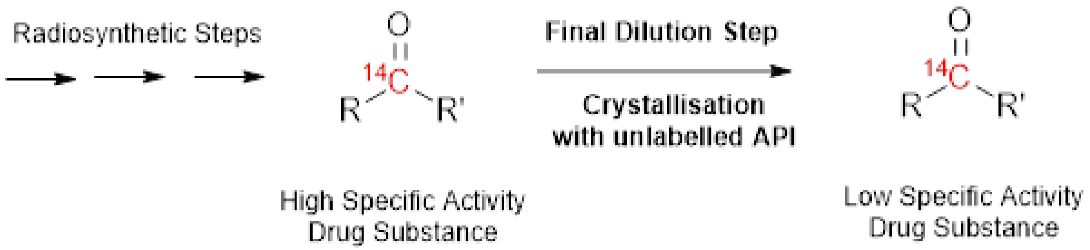
- Compound selection and synthesis: choosing the appropriate [^{14}C]-labelled compound for a specific application is crucial. Selecting a compound with inherently higher radiochemical stability and optimising the synthesis of the [^{14}C]-API can help minimise the formation of impurities or unwanted side products, which could otherwise compromise radiochemical stability.
- Purification: thorough purification of carbon-14 intermediates and final products can help remove impurities and contaminants that may negatively impact radiochemical stability. Techniques such as column chromatography, semi-preparative

HPLC, recrystallisation, and distillation can be employed to achieve high levels of purity. These techniques are performed regularly here within the isotope chemistry team at Almac, and can be performed at the intermediate or final stages of both non-GMP and GMP syntheses using GMP-validated equipment.

- Storage conditions: the correct storage conditions are essential for maintaining the radiochemical stability of carbon-14 compounds. Factors such as temperature, humidity, and light exposure should be carefully controlled to minimize degradations. Storage in inert atmospheres, such as nitrogen or argon, can also help prevent oxidation and other reactions that could reduce radiochemical stability. Within Almac Sciences' isotope laboratories, there are various storage conditions, to fit the needs of our customers including GMP validated 2-8°C, -20°C and -80°C fridges and freezers, and stability chambers for long-term storage. Our UK, European, and US state-of-the-art, walk-in stability chambers provide 300m^3 of ICH-compliant, climatic storage facilities to satisfy all requirements.

- Antioxidants and radical scavengers: the addition of antioxidants or radical scavengers to the [^{14}C]-compound can help reduce the formation of free radicals and protect the compound from degradation. These substances can either prevent the formation of radicals or mop them up before they can react and damage the [^{14}C]-molecule. Examples of such additives include ascorbic acid, butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA).
- Encapsulation and protective coatings: encapsulating carbon-14 compounds, or using protective coatings, can help shield them from environmental factors that could negatively impact radiochemical stability. Techniques such as microencapsulation, the use of polymeric coatings, or embedding the compound in a solid matrix can provide a barrier against external factors, including temperature, moisture, and light.

- Stabilising agents: the use of stabilising agents can help enhance the radiochemical stability of carbon-14 compounds by reducing the likelihood of unwanted side reactions. These agents can be chelating agents, buffers, or other substances that help maintain the compound's stability under the desired conditions.
- Solvent selection: for solutions, the choice of solvent can have a significant impact on the stability of radiolabelled compounds. Selecting a solvent with low reactivity, low susceptibility to radiolysis, and suitable solubility properties for the compound can help maintain its stability during storage and use. An example of a poor choice of solvent for pyridine-based compounds is dichloromethane (DCM), as it can react with the molecule to form methylenebispyridinium dichloride compounds[1], a reaction which may be enhanced by the presence of free radicals within the radiochemical solution.
- Isotopic dilution: dilution of [^{14}C] drug substances with high purity, unlabelled API (i.e., carbon-12) will increase the overall stability of the compound by reducing the concentration of ^{14}C, thereby reducing the potential for radiolytic degradation. Isotopic dilutions can be performed at the end of a synthetic route in conjunction with a recrystallisation and are routinely carried out at Almac to manufacture high quality APIs with good radiochemical stability.
- Minimising Handling of [^{14}C]-Compounds: reducing the amount of time that carbon-14 compounds are handled and reducing the number of manipulations to the molecule can help improve radiochemical stability e.g., reducing the number of synthetic steps, introducing the [^{14}C] label at the latest possible stage in the radiosynthesis, and avoiding complicated work-up procedures.
- Monitoring and quality control: regular monitoring of the radiochemical stability of carbon-14 compounds is essential to ensure their continued efficacy in clinical studies. Analytical techniques such as high-performance liquid chromatography (HPLC), gas chromatography (GC), and mass spectrometry (MS) can be used to assess the purity and integrity of the compound over time. It is critical for patient safety to understand how a drug product will modify over time and guidance is required on the storage and disposal of the product. Within Almac, our dedicated, expert radio-analytical team provide an all-inclusive stability service, which encompasses protocol design, analytical method transfer, study management, sample analysis, QA approved reporting, transport simulation and in-use stability programmes.



Conclusion

By employing these techniques, we can enhance the radiochemical stability of carbon-14 intermediates and APIs, and by monitoring both radiochemical and chemical purity over time we give our customers the crucial data on drug stability required for their clinical studies.

[1]Rudine AB, Walter MG, Wamser CC. Reaction of dichloromethane with pyridine derivatives under ambient conditions. J Org Chem. 2010 Jun 18;75(12):4292-5. doi: 10.1021/jo100276m. PMID: 20469919.

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