Clinical formulation development for poorly soluble ^{14}C labelled molecules

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INTRODUCTION

Clinical studies involving the administration of ^{14}C radiolabelled drug substances provide critical information during development. The main application is the regulatory ADME study to assess the mass balance, routes and rates of elimination, and to provide plasma, urine and faecal samples for metabolite profiling and structural identification. These data ensure there is coverage for human metabolites in toxicological or reproductive studies, and also identifies any potential DDI risks. ^{14}C radiolabelled drug substances are also dosed in intravenous (IV) microtracer studies (IVMT), where an oral therapeutic dose of a reference formulation is concomitantly administered with a microdose IV infusion containing microtracer amounts of ^{14}C (Figure 1). This allows measurement of both IV and oral kinetics to generate absolute bioavailability without the need of a conventional IV formulation or an IV toxicity safety package, or local tolerability studies as long as pharmacopoeial excipients are used.

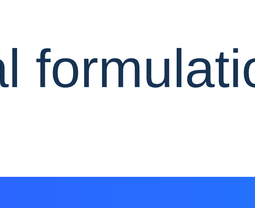

Figure 1: IV and oral plasma concentration profiles

Clinical protocols can also involve both IVMT and ADME components which allows a range of additional endpoints to be determined from an integrated two period study (Table 1 and Figure 2). By completing a comprehensive analysis of samples and enhancing the data analysis, significant additional information on drug performance and disposition can be generated, which creates a platform for understanding how drug performance can be enhanced by improvements in formulation.

Table 1: Integrated ^{14}C Human ADME Study Designs

	Data typically required for NDA submission	Data beneficial in drug formulation/ development	ADME	^{14}C IVMT/ ADME
Mass balance –therapeutic dose	Y	Y	✓	✓
Therapeutic dose routes/rates of elimination	Y	Y	✓	✓
Met profiling	Y	Y	✓	✓
Met ID	Y	Y	✓	✓
Absolute bioavailability	(Y)	Y	X	✓
IV PK and clearance	N	Y	X	✓
Mass balance –IV dose	N	Y	X	✓
Fraction surviving gut metabolism	N	Y	X	✓
Fraction absorbed	N	Y	X	✓
IV routes/rates of elimination	N	Y	X	✓

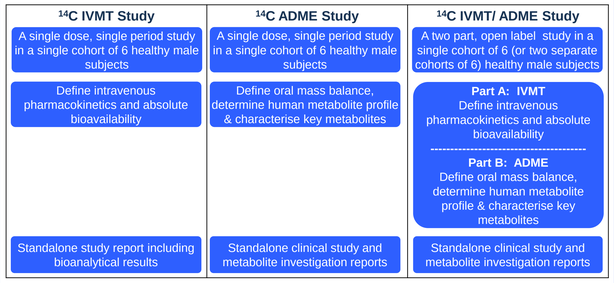

Figure 2: ^{14}C clinical study design

^{14}C drug products do not need to be identical to formulations used in clinical development, but do need to ensure adequate, representative systemic exposure. For DCS I highly soluble ^{14}C APIs, simple formulations and manufacturing processes (solutions (IVMT and ADME) and drug in capsule (ADME)) are sufficient to ensure this objective is met. Development of formulations for DCS II poorly soluble ^{14}C APIs can be challenging as conventional strategies are not suitable to overcome poor solubility and achieve the desired bioavailability.

For IVMT studies as the dose to be administered is very low (typically 100µg in a 5mL infusion), the poor solubility can be circumvented using conventional solubilisation techniques such as pH modification, co-solvents and surfactants, additionally complexation may be applied.

For ADME studies the dose may be 1000-fold higher. For clinical and commercial formulation development, a range of enabling technologies are available for DCS II APIs to overcome poor solubility; strategies can be used to increase dissolution rate (DCS IIa) or increase apparent solubility (IIb). Dissolution rates can be improved by particle size reduction (micronisation or nanoparticles). Improvement of apparent solubility can be facilitated using lipidic systems, cyclodextrin complexes, solubilised systems with surfactants and amorphous formulations (spray drying, melt extrusion etc). However, implementing these strategies for ^{14}C APIs can be problematic, therefore, alternative approaches need to be considered.

METHODS

A review was conducted of alternative strategies to achieve 'enabled' formulations for DCS Class II ^{14}C APIs at Quotient, for both IVMT and ADME applications (Figure 3).

Quotient's approach for IVMT formulations is to formulate a concentrated stock containing functional excipients, dilute with saline/water for injection to give the bulk solution, which is then sterilised via aseptic double filtration. For poorly soluble APIs most of the formulations used have included co-solvents, cyclodextrins and surfactants, the latter to prevent adhesion to fluid transfer tubing and IV lines.

Additional formulation considerations are minimisation of solvents due to potential incompatibilities with filters and lines and minimisation of surfactants as high levels can result in adverse events (not acceptable for healthy volunteer studies).

For ADME studies drug product manufacturing processes and equipment selection are critical due to the risk of cross-contamination from the long half-life of ^{14}C radioactivity (5,730 years [1]). Standard enabling techniques using complex equipment i.e. spray drying, hot melt extrusion and jet milling are not suitable for poorly soluble ^{14}C APIs.

For DCS IIa APIs, particle size reduction techniques have been implemented mainly via wet milling processes, including a pestle and mortar for small scale suspensions. If radio-dilution is required, in-situ controlled co-precipitation of labelled and unlabelled drug substance from an alcohol solution into a suspending vehicle was used to achieve micro-suspensions. In this case the same particle size distribution can be achieved for both labelled and unlabelled drug substance.

For DCS IIb APIs, excipient selection is focused on those that can provide sufficient drug solubilisation but don't pose potential interference in the MS/MS analysis of drugs and their metabolites, such as with PEGs and PEGylated surfactants. PEG free co-solvent solutions and Type I lipid formulations are the first choice. If a surfactant is required phospholipid or its preformulated vehicle (Phosal) can be used.

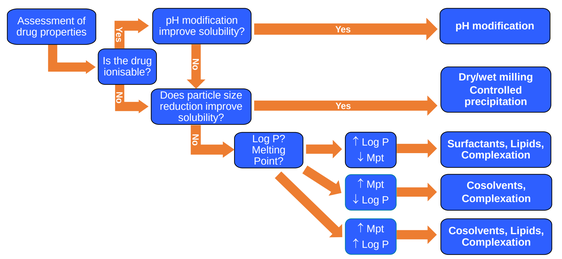

Figure 3: IVMT and ADME formulation strategies for poorly soluble APIs

RESULTS AND DISCUSSION

A review has been performed for recent ^{14}C studies performed at Quotient involving administration of 75 bespoke ^{14}C formulations and two case studies are described to illustrate approaches that have been used.

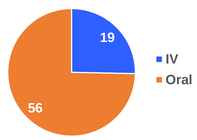

Figure 4: Route of delivery for ^{14}C formulations at Quotient

Case Study 1: Drug X (DCS IIb) was dosed in an integrated IVMT/ADME study. The IV formulation was prepared using a cyclodextrin solution added to a ethanolic solution of drug which enabled solubilisation. Identification of the optimum level of ethanol and optimum concentration of cyclodextrin was key. The sequence of addition and mixing also impacted the solubilisation of the drug substance. By optimizing the concentration of solubilising agents and using simple processing techniques successful solubilisation of a poorly soluble API was achieved resulting in a successful ^{14}C IV formulation. For the much higher dose oral formulation achieving an amorphous system was not possible due to potential cross-contamination risks for multi-use equipment and GMP facilities. Improvement of the apparent solubility was facilitated using a Type I lipid, with careful consideration of excipients negating the potential for metabolite interference. A Caprylic acid formulation was selected and dosed in the clinical study.

Case Study 2: Drug Y (DCS IIa) was dosed in an ADME study, where a particle size reduction approach was implemented. For ^{14}C ideally a single pharmaceutical form of the API (at the correct specific activity) should be used, not a physical mixture of unlabelled and labelled API, to ensure identical in vivo performance (dissolution, solubility, absorption, PK). For Drug Y ^{14}C API was not provided from the radiochemistry provider at the correct specific activity and thus an in situ radio-dilution was required. To ensure equivalent exposure from labelled and unlabelled API a co-precipitation approach was used to provide the same particle size distribution of both moieties. The approach used to formulate the oral suspension involved dissolving both labelled and unlabelled Drug Y in an ethanol stock solution, this was added with stirring to a suspending vehicle containing both a polymer (Kollidon 30) and a wetting agent (sodium lauryl sulphate) in a controlled manner to produce a radio-labelled micro-suspension with a particle size below 25µm. Using this technique the same particle size was achieved for both the labelled and unlabelled API.

CONCLUSION

ADME formulation development for poorly soluble ^{14}C radiolabelled APIs is especially challenging given the need to use simple processing methodologies and excipients which do not interfere with metabolite analysis. Quotient Sciences has developed alternate strategies to enable successful formulation which are suitable to achieve the important study objectives.

REFERENCES

[1] H. Godwin, (1962). "Half-life of radiocarbon". Nature. 195 (4845): 984

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