Radiolabeled Mass Balance Studies in Preclinical Animals

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Abstract

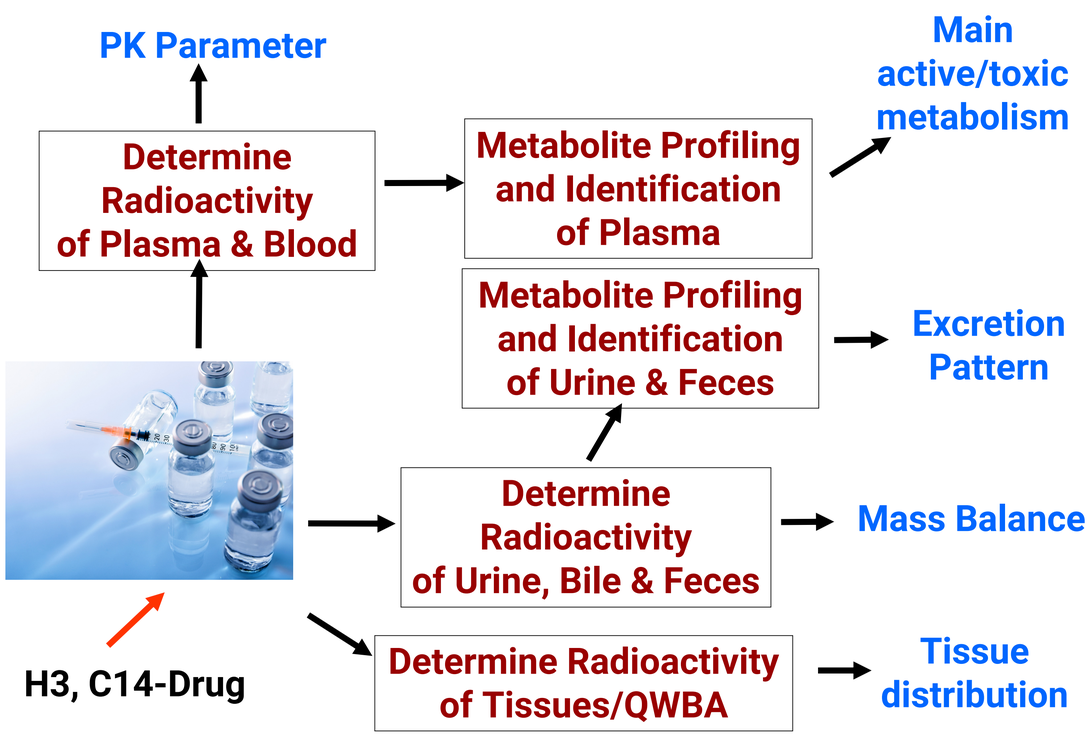
Radiolabeled absorption, distribution, metabolism, and excretion (ADME) studies in preclinical species (rodent and large animal) offer a quantitative and comprehensive overall picture of the disposition of a drug, including excretion pattern and metabolite profiles in circulation and excreta. The data gathered from the animal ADME studies are highly informative for developing a cohesive strategy of human ADME studies.

Since 2010, WuXi AppTec DMPK at Nanjing site has conducted over 400 radiolabeled preclinical ADME studies, covering a range of drugs across wide therapeutic areas. Here we summarized 133 mass balance studies from 2020 to present, to show the current practice and pharmacokinetic characters of drugs under development, including radioactive dosage, sample collection duration, sample analysis methods and total recovery data, etc.

Objective

To offer a useful reference for preclinical radiolabeled mass balance study design and data interpretation.

Experiment Capability



Instrument

Liquid Scintillation Counter

Microplate Counter

Multifunctional Laser Imager

Radio-LC System

Cryomacrotome

High Resolution MS

Results

With respect to the drug formulation, the administered radioactivity dosage used in the 133 studies ranged from 10 μCi/kg to 200 μCi/kg for rodents, and 25 μCi/kg to 100 μCi/kg for large animals, respectively. 90.23% (n = 120) of the mass balance studies were single-dose oral studies, the others were single-dose intravenous and subcutaneous. Because of practical considerations, IV was used for pulmonary candidate drugs instead of inhalation administration.

Urine, feces, bile and cage rinse/wash were collected to allow for a reliable determination of the contribution to elimination pattern. Typically, the excreta collection time from intact and BDC animals were 168 hours and 72 hours post-dose, respectively. Only 1.5% studies of intact animals were more than 168, less than 288 hours. The liquid samples were determined with LSC directly. Homogenized solid samples (feces and tissues) were pretreated with combustion or solubilization. Having compared these two methods, we recommend solubilization before radioactivity quantitation, which had a decreased sample repetition rate from 3.8% to 0.3% (Figure 1).

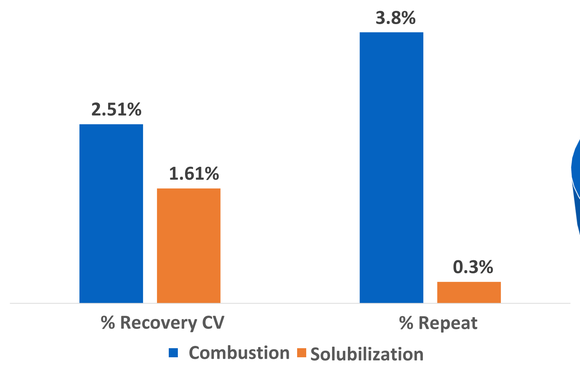


Figure 1. Comparison between combustion and solubilization pretreatment

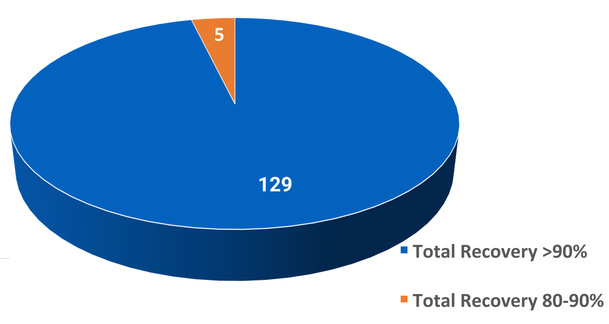


Figure 2. % Recovery of Mass balance studies

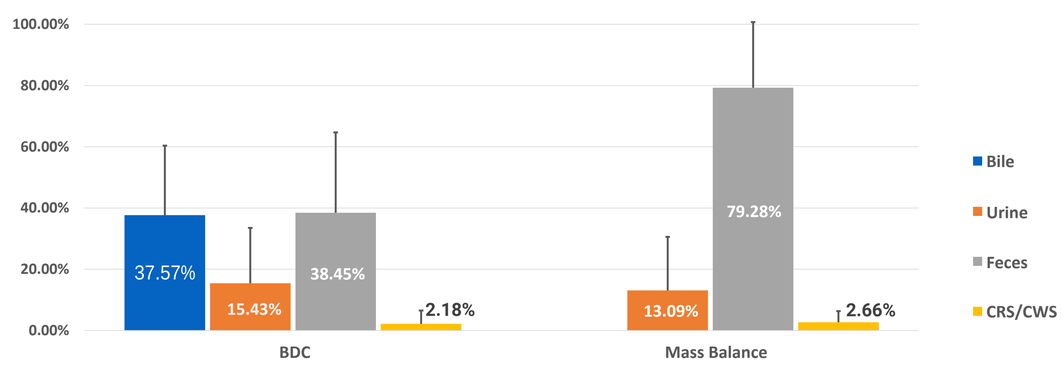


Figure 3. Distribution of various excretion pattern

The cumulative total recovery of 94.74% (n =126) mass balance studies exceeded 90% of the administrated dose (Figure 2). After carcass was detected in rodents, the percentage increased to 96.99% (n =129) studies. In our analysis, main reasons for incomplete mass balance recovery is the long half-life of the parent drug/metabolite or low dosage or unstable labeling position.

A wide range in the percentage of the ^{14}C dose excreted in urine (0.05~82.8%, average 13.09%) and in feces (3.21~98.66%, average 79.28%) was observed in intact preclinical animals, while bile (0.33~98.03%, average 38.38%), urine (0.07~60.86%, average 12.38%) and feces (0.76~98.76%, average 41.40%) in BDC animals (Figure 3). These results indicate 38.38% of administrated dose were excreted by bile into feces, and the bioavailability for current candidate drugs was almost 50.76%, based on the average oral administration data.

Conclusions

1. We have well-established platform to use radiolabeled (^{14}C or ^{3}H) compounds to conduct the radiolabeled ADME studies in mouse, rat, dog, monkey and mini-pig. In 95% of mass balance studies, the total recovery exceeded 90% of the administrated dose.
2. Compared with combustion, we recommend solubilization as the pretreatment method due to its lower repetition rate.
3. Within the studies we conducted in the past three years, a wide range in the percentage of ^{14}C excretion in urine, bile and feces was observed. Based on the average oral administration data, the bioavailability of current candidate drugs was about 50.76%.

Contact