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A Review on Microdosing: Reduction in Cost & Time



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ABSTRACT

Now a days as research methods and technology involved in Phase 0 trials become more Sophisticated. Microdosing is an early drug development process where exploratory pharmacokinetic data are acquired in humans using inherently safe sub-pharmacologic doses of drug. Microdosing may not help only in patients but also in the pharma industry with earlier availability of new test drugs, reduced drawbacks of compounds at later stages and reduce the cost of drug development. It is new kit urgently needed to improve predictability and efficiency of drug. Microdose studies are importance in clinical drug development because they have the potential to decrease time and costs. Thus Microdosing is a new viable concept in the 'toolbox' of the drug development activity.



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INTRODUCTION

Microdose involves a study to obtain the pharmacokinetic data of drug candidate at early stage of development. Thus Microdosing methodology is a new viable 'tool' in the drug development. In microdosing, extremely low, nonpharmacologically active doses of a drug are used to give the agent's pharmacokinetic profile in humans.^[1] In microdosing uses of 'less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance to a maximum dose of <100 micrograms (European Medicines Agency paper).' In addition to this, the US FDA suggests a maximum microdose of <30 nanomoles for protein products.^[2,3]

Human drug development is a dynamic process that keeps pace with the recent advances within the pharmaceutical analytical labs, combined with a precise understanding of the integrated pharmacokinetic pharmacodynamic pharmacogenomic drug profile. New drugs are a great need for many clinical conditions but, unfortunately, development costs are rising and the number of drugs receiving marketing approval has fallen.

The dose administered is in picograms to femtograms, it may not cause any adverse events also, but may produce useful pharmacokinetic information and help in further development of the compound.^[4]

ADVANTAGES OF MICRODOSING:

1. Microdosing requires minute quantities of the drug for safety testing. A microdose is so small for human subjects, it is not intended to produce any pharmacologic action; hence less risk of adverse effects.
2. It required a smaller toxicology package. As per the regulatory requirement, animal studies, at least in one species, are required to produce microdose in humans, but at a much-reduced level, fewer animal studies are required before Phase I clinical trials.
3. To explore clinical characteristics of a candidate agent with very less number of patients in a short duration of time.^[5]
4. The cost of conducting a microdose study is less, as compared to a full Phase I study.^[6]
5. Micro dosing useful in the discovery of endogenous biomarkers, which is helpful in quantitative evaluation of the *in vivo* effects of drugs.

6. Beneficial in oncology by reducing the number of subjects exposed to toxic effect of chemotherapeutic agent.^[7]

LIMITATIONS OF MICRODOSING:

1. The main drawback is regarding the predictive accuracy of microdosing. We still do not have sufficient studies to clearly exemplify whether the body’s reaction to a particular compound is similar, when used as microdose and in its pharmacological dose; otherwise, it could lead to false negatives (compound being rejected) or false positives (compound acceptable based on microdose data but rejected subsequently when used in pharmacological doses).^[8]
2. It have limited solubility at higher doses, it may be difficult to predict the absorption characteristics at the microdose levels.^[9]
3. It requires AMS (accelerator mass spectrometry) and PET (positron emission tomography) are applied to analyze the concentration of the drugs in low picogram to femtogram range.^[10,11]
4. Microdosing studies have very small database.^[12]

COMPARISON OF MICRODOSING STRATEGY VS CONVENTIONAL STUDIES

Features	Microdosing strategy	Conventional approach
Time from preclinical to first in man studies	6-8 months	12-18 months
Cost of early phase of drug development	US\$ 0.3 -.0.5 million	US\$ 1.5-5.0 million
Amount of drug required	<100 micrograms	About 100 grams
Special requirements	C14 labeled compound if using AMS None required	None required
Regulatory requirements	Very few and limited	Established firmly

ROLE OF FDA IN PHASE 0 TRIALS:

FDA said that a phase 0 is take place very early in phase I, and involves limited human exposure receiving only sub-therapeutic dose and this means the patients (study subjects enrolled) produce a pharmacologic response than the toxic effect, and the risk occurred is less than conventional

phase I trials. The administration of drug is continued if there is evidence of clinical benefit and thus phase 0 trials lack even therapeutic intent (Marchetti and Schellens, 2007).

ANALYTICAL METHODS WITH MICRODOSING:

A microdose technique applicable to four to six healthy male subjects (although female subjects have been used)^[13] followed by the collection of plasma and sometimes biopsy samples for prolonged time. The samples are analysed as parent drug or metabolites to ascertain the pharmacokinetic profile. The low doses administered so used highly sensitive analytical techniques in order to measure the plasma drug concentrations over sufficient time. A human microdose studies reported in the literature have been conducted using ¹⁴C-labelled drug and analysis performed by using the ultrasensitive isotope-ratio technique of AMS although studies have also been performed using non-labeled drug and sensitive LC-MS.^[14,15] The sensitivity of LC-MS assay is highly compound dependent and the sensitivity of an AMS assay depends upon the specific radioactivity of the analyte and is independent of structure and matrix effects.

Care should be taken when comparing the sensitivity of an LC-MS assay developed over long periods of time when a microdose study is performed. Drugs dosed at 100 µg therefore with expected volumes of distribution greater than 300 L or orally administered drugs with limited bioavailability may, therefore, require assays with greater than 10 pg/mL sensitivity.^[16]

In AMS analytical method the drug has to be isotopically labeled with ¹⁴C. The microdose study is performed at a relatively early stage of drug development. Study ¹⁴C-drug synthesis is necessary for the microdose. The administration of various mixtures of compounds as a microdose cassette has the main advantage that several candidate drugs can be tested in a single dosing. This approach has been investigated using LC-MS and LC and AMS. Resolution of compounds for AMS analysis depends upon the chromatographic separation.

Technique	Requirements	Characteristics
Accelerator Mass Spectrometry (AMS)	Radioactive Isotopes with a long half-life such as ^{14}C	<ol style="list-style-type: none"> 1. Highly sensitivity. 2. Capable of constructive analysis of metabolite of the compound.
Liquid Chromatography – Mass Spectrometer.	No labeling required.	<ol style="list-style-type: none"> 1. For profile prediction of properties of the compound. 2. Suitable for cassette dose test
Positron Emission Tomography(PET)	Position emitting nuclide with a short half life such as $^{11}\text{C}, ^{13}\text{N}, ^{18}\text{F}$	<ol style="list-style-type: none"> 1. Capacity to measure distribution and concentration of the compound in the body. 2. Required large facilities and equipment.

CONCLUSION

Microdosing is a new technique to accelerate the drug development process and to reduce attrition rate on drug candidates. Now a day human microdosing show significant promise as an analytical tool. It also helps in the drug repurposing and pharmacogenomics activity by expediting the initial work. The fundamental strengths of microdosing are improved safety, reduced cost, and time for drug development. Microdosing studies involve systematic validation in large-scale, government-sponsored trials for universal adoption to take place.

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