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Short review

# Introduction to the OrBiTo decision tree to select the most appropriate *in vitro* methodology for release testing of solid oral dosage forms during development

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ABSTRACT

The EU research initiative OrBiTo (oral biopharmaceutics tools) involving partners from academia, pharmaceutical industry, small medium enterprises and a regulatory agency was launched with the goal of improving tools to predict the absorption of drugs in humans and thereby accelerating the formulation development process. The OrBiTo project was divided into four work packages (WP), with WP2 focusing on characterization of drug formulations. The present work introduces the OrBiTo WP2 Decision Tree, which is designed to assist the investigator in choosing the most appropriate *in vitro* methods for optimizing the oral formulation design and development process. The WP2 Decision Tree consists of four stages to guide the investigator. At the first stage, the investigator is asked to choose the formulation type of interest. At the second stage, the investigator is asked to identify which type of equipment (compendial/modified/noncompendial) is preferred/available. At the third stage, characteristics of the active pharmaceutical ingredient (API) are evaluated and in the fourth stage of the decision tree, suitable experimental protocols are recommended. A link to the living Decision Tree document is provided, and we now invite the pharmaceutical sciences community to apply it to current research and development projects and offer suggestions for improvement and expansion.

## 1. Introduction

Over the past two decades, the importance of predictive dissolution testing during formulation development has greatly increased. Since the introduction of biorelevant dissolution media as a milestone in the late 90s, a variety of predictive *in vitro* methods have been developed. Today, numerous publications demonstrating the usefulness of such dissolution methods for predictive investigations can be found in the literature [1–15].

In 2012, the EU research initiative OrBiTo (innovative tools for oral biopharmaceutics, www.orbitoproject.eu/) involving partners from academia, pharmaceutical industry, small medium enterprises and a regulatory agency was launched with the goal of improving tools to predict the absorption of drugs in humans and thereby accelerating the formulation development process. The OrBiTo project was divided into four work packages (WP) focusing on tools regarding the characterization of the API (WP 1) and formulations (WP 2), *in vivo* studies to address gaps in our knowledge of the gastrointestinal tract (WP 3) and the utilization of *in silico* tools (WP 4) (please refer to Fig. 1 for an overview). For WP 2, in addition to the eleven tasks which evaluated various dissolution methodologies to address specific drug formulation challenges, a key task was to generate a decision tree to assist investigators in identifying the most appropriate *in vitro* methodology for a given drug/formulation combination.

The aim of this publication is to introduce the web-based decision tree to the scientific community and to invite investigators in the pharmaceutical development to use and participate in revising and extending the decision tree. The current version can be accessed[2] via

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[2] To open the decision tree document, the free software yEd graph editor is required, which can be downloaded at the following link: https://www.yworks.com/products/yed.

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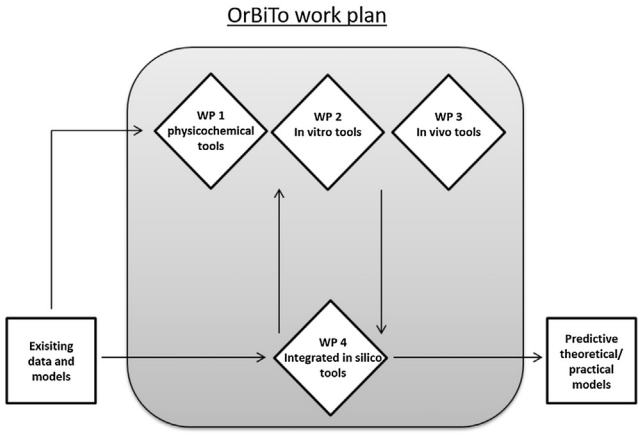


**Fig. 1.** Structure of the Work Packages in OrBiTo, the Oral Biopharmaceutical Tools Project (www.orbitoproject.eu).

www.orbito-dissolution.eu. At the moment, the decision tree focuses on the *in vitro* methods which were included in the OrBiTo WP 2 task list as a platform to identify gaps and innovation needs in predictive dissolution testing. However, given the availability of numerous other *in vitro* methods in the literature, the decision tree may serve as a springboard to extensions in areas not specifically investigated in OrBiTo and thus provide a more comprehensive guide to method selection.

## 2. OrBiTo partners and methods

The proposed decision tree represents input from six academic partners, thirteen pharmaceutical companies and one small medium enterprise who all participated in WP 2 of the OrBiTo project (Table 1).

The focus of WP 2 was to develop and optimize *in vitro* release methods. In this context, a variety of different dissolution approaches was developed and optimized for immediate (IR), delayed (DR) and extended release (ER) formulations. The investigations included the use of dissolution media with different levels of complexity in terms of their composition, the use of single- vs. multi-compartmental methods such as United State Pharmacopiea (USP) apparatus II-IV or test systems aimed at a more physiological representation of the hydrodynamic forces such as the stress tester or the TIM (Total gastro-Intestinal Model) systems. Where applicable, ring studies were conducted to investigate the reproducibility of the experimental conditions as part of the method validation. An overview of the methods investigated, along with references to associated literature, can be found in Table 2.

At this point, the decision tree encompasses the methods investigated in WP 2 of the OrBiTo project. However, the decision tree is intended to be regarded as a living document guiding investigators in the decision process to select the most appropriate *in vitro* test during formulation development and it is anticipated that further methods will be added over time.

## 3. The general structure of the decision tree

The general structure of the decision tree is depicted in Fig. 2. In the first stage, the decision tree offers three branches: immediate, extended

**Table 1**
Overview partners who participated in establishing the decision tree.

| Academic partners | Pharmaceutical industry | Small medium enterprises (SME) |
|---|---|---|
| Goethe University, Frankfurt, Germany | Abbvie | Triskelion |
| National and Kapodistrian University of Athens, Greece | AstraZeneca | |
| Ernst Moritz Arndt Universität Greifswald, Germany | Bayer | |
| Johannes Gutenberg University Mainz, Germany | Bristol-Myers Squibb | |
| KU Leuven, Belgium | Boehringer Ingelheim | |
| University of Copenhagen, Denmark | GlaxoSmithKline (GSK) | |
| | H. Lundbeck | |
| | Janssen | |
| | Merck Sharp & Dohme | |
| | Novartis | |
| | Orion | |
| | Pfizer | |
| | Sanofi-Aventis | |

**Table 2**
Overview of dissolution method protocols generated in WP2 of the OrBiTo project according to formulation type.

| Immediate release (IR) | Extended release (ER) | Delayed release (DR) |
|---|---|---|
| TNO systems [16,17] | TNO systems [16,19] | TNO systems [19] |
| Artificial stomach duodenum (ASD) model [18] | Dissolution stress test apparatus tester [14,20,21] | Dissolution stress test apparatus [22] |
| BioGit model [23–25] | USP apparatus II | USP apparatus II |
| Biorelevant dissolution[a] [7] | | |
| Biphasic dissolution apparatus [26,27] | USP apparatus III[a] [12,13,28] | USP apparatus II (mini paddle) [29,30] |
| Artificial membrane insert (AMI) system [31] | USP apparatus IV[a] [12,13,28] | USP apparatus III [28] |
| Transfer model [2,6] | | USP apparatus IV [28] |
| Two stage test[a] [7] | | |
| GastroDuo [32,33] | | |
| USP apparatus II[a] | | |

[a] Comparative ring studies with at least 6 participating partners were conducted as part of the method validation.