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Methodology of oral formulation selection in the pharmaceutical industry

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ABSTRACT

Pharmaceutical formulations have to fulfil various requirements with respect to their intended use, either in the development phase or as a commercial product. New drug candidates with their specific properties confront the formulation scientist with industrial challenges for which a strategy is needed to cope with limited resources, stretched timelines as well as regulatory requirements. This paper aims at reviewing different methodologies to select a suitable formulation approach for oral delivery. Exclusively small-molecular drugs are considered and the review is written from an industrial perspective. Specific cases are discussed starting with an emphasis on poorly soluble compounds, then the topics of chemically labile drugs, low-dose compounds, and modified release are reviewed. Due to the broad scope of this work, a primary focus is on explaining basic concepts as well as recent trends. Different strategies are discussed to approach industrial formulation selection, which includes a structured product development. Examples for such structured development aim to provide guidance to formulators and finally, the recent topic of a manufacturing classification system is presented. It can be concluded that the field of oral formulation selection is particularly complex due to both multiple challenges as well as opportunities so that industrial scientists have to employ tailored approaches to design formulations successfully.

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1. Introduction

The number of FDA novel new drug approvals was 41 in 2014 (CDER's, 2014 reports) and a comparison of the different routes of administration shows that 19 (46%) of the new drug approvals were for oral delivery as either capsules or tablets. Oral delivery has since the early days of pharmaceutics been the most important route of administration. This clear dominance has changed in recent years due to the rise of biopharmaceuticals that are generally administered by injections. However, it is likely that oral formulations will continue to play a crucial role in the future because of their ease of administration, good stability, established manufacturing processes, and low costs of goods.

While the reasons for favouring oral administration are typically straightforward and part of the target product profile (TPP), it is more difficult to decide on a formulation strategy or on a process technology. Companies often show marked differences in their decision making approach towards the formulation strategy. Scientific arguments are important, but strategic aspects (such as outsourcing) and company traditions also play a significant role. For new drug candidates, the results of pharmaceutical profiling and biopharmaceutical modelling provide an initial basis for decision making. Once a drug candidate has reached phase I clinical trials, the availability of human pharmacokinetic data helps define the formulation strategy for later development phases. The final drug product has other requirements to fulfil compared to preclinical or early clinical delivery approaches. Preclinical formulations are for example needed for toxicological studies and the focus is here typically on high drug exposure to cover safety margins. Lower drug exposure is generally needed for clinical formulations at the lower therapeutic doses, but aspects of for example long-term stability, regulatory excipient status, or process scale-up are playing an increasing role during later stage development. The strategy of formulation selection can therefore have a different focus depending on characteristics and indication of the drug molecule as well as on the type of formulation that is being developed as part of the drug life-cycle.

The present work aims to review methodologies for oral formulation selection from an industrial viewpoint. First the specific industrial challenges are highlighted and the next section is dedicated to case-specific formulation strategies. The formulation selection is outlined for drugs that exhibit biopharmaceutical constraints as well as for compounds that are either chemically labile or that have a low dose. The formulation strategy is then discussed for drugs that require controlled release delivery.

Once a formulation approach has been selected, the final drug product should be developed in a structured way. This topic together with the emerging manufacturing classification system is discussed in a last section of this article. This review finally aims to provide an overview and some guidance to pharmaceutical scientists in their selection of formulations for oral delivery.

2. Industrial challenges in selecting oral formulations

The very high attrition rate of clinical candidates has impacted significantly on oral formulation strategies within the pharmaceutical industry. A recent assessment of attrition rates in three therapeutic areas; HCV (hepatitis C virus), Alzheimer's Disease (AD) and MRSA (methicillin-resistant *Staphylococcus* aureus) versus the industry average paints a depressing picture (Table 1). The attrition statistics can be further broken down into the reasons for termination, i.e. efficacy (51%), strategic (29%) and safety (19%) considerations (Arrowsmith, 2010).

As a result, more focus has been placed on safety and efficacy during discovery and early development to address these issues. These high attrition rates are typically ascribed to poor physicochemical and biopharmaceutical attributes. However, several expert opinions (Kwong, 2015; Fotouhi et al., 2008) have raised concerns about rigidly imposing 'drug likeness' rules as it must be recognised that many commercial drugs were developed 'at the margins or even outside the boundaries of these proposed drug's rigid properties' (Kwong, 2015). For example, although increased lipophilicity does decrease solubility and enhance metabolic clearance, it can also enhance permeability, particularly into the target compartment (Kwong, 2015).

Historically, many organisations (but principally small, virtual companies) have deliberately focused on speed to clinical decision making with commensurate minimization of cost expenditure and mostly ignored early phase physicochemical and formulation optimisation. Typically, they utilised the active pharmaceutical ingredient (API) 'as is' and used simple formulations, i.e. API powder in bottle (PIB), API powder in capsule (PIC) or extemporaneous compounding approaches. However, these approaches often resulted in non-linear pharmacokinetics and consequently an inability to fully explore the clinical pharmacology in preclinical/clinical species due to inadequate in vivo exposure. More recently, biopharmaceutical approaches have proved useful in assessing a candidate's 'fitness for purpose' and its ability to deliver adequate exposure (Amidon et al., 1995; Buckley et al., 2013; Butler and Dressman, 2010). There are two reported strategies for addressing poor dissolution/solubility properties of a candidate molecule; either, (i) developing a 'candidate quality' approach, whereby the physicochemical properties of the drug candidate are viewed as being of equal importance to potency and specificity, and/or (ii) addressing the issues with an optional prodrug or salt/polymorph approach and appropriate choice of the formulation strategy (Kwong et al., 2011). The most common strategy is trying to enhance absorption by solubilising the drug in a suitable aqueous vehicle and/or maintaining the drug in the solution state by reducing the potential for precipitation. This is particularly important for those compounds that show differential solubility in different gastrointestinal compartments; i.e. good solubility in the gastric compartment and poor solubility in the intestinal compartment (Kawakami, 2012).

At the current time, a balanced approach is favoured, where the molecule is appropriately optimised (even though it may not be optimal),

Table 1
Percentage of attrition rates by clinical phase of development.
Adapted from Calcoen et al. (2015).

Development phase	% attrition rates (HCV)[a]	% attrition rates (AD)[b]	% attrition rates (MRSA)[c]	% attrition rates (industry average)
Pre-clinical	97	99	92	93
Phase I	90	97	79	88
Phase II	83	96	66	78
Phase III	41	83	44	38
Registration	10	0	10	10
Overall success rate	2.0	0.5	4.6	4.1

[a] Hepatitis C virus.
[b] Alzheimer's Disease.
[c] Methicillin-resistant *Staphylococcus* aureus.