European Journal of Pharmaceutics and Biopharmaceutics 111 (2017) 1–15

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

# Biopharmaceutical aspects and implications of excipient variability in drug product performance

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ARTICLE INFO

*Article history:*
Received 13 September 2016
Revised 2 November 2016
Accepted in revised form 7 November 2016
Available online 11 November 2016

*Keywords:*
Excipients
Dissolution
Solid dosage form
Solubility
Gastrointestinal
Polymers
Variability

ABSTRACT

Implementation of Quality by Design approaches in pharmaceutical industry requires a sound understanding of the parameters triggering final product variability. Excipients, although generally regarded as inert components, are of great significance in terms of solid dosage form development and any variation in the material attributes may impact drug product performance. Sourcing, production and processing are contributing factors to excipient variability. Interchange between different suppliers can lead to final products with different quality attributes. Identification of excipient critical material attributes is not straightforward, as criticality must be linked to functionality and it is well recognized that the mechanisms by which excipients exert their action are not fully understood. Investigating the impact of excipient variability on *in vitro* dissolution could enable scientists to get an insight on the *in vivo* behavior of drug products and potentially tolerate variability. A thorough understanding of excipient material properties, product components interactions and the effect of the gastrointestinal tract heterogeneity on excipients and drug release is recommended. This review aims to present current knowledge on excipient critical material attributes and their link to biopharmaceutical behavior and dissolution characteristics. Attempts to describe the impact of physiological conditions on excipient functionality are also addressed. Excipient properties that are considered crucial to drug product performance in a biorelevant perspective are elucidated.



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http://dx.doi.org/10.1016/j.ejpb.2016.11.004
0939-6411/

## 1. Introduction

Pharmaceutical development is now entering the new era of quality build. The traditional three batch validation is currently fading as batch failures, product recalls, drug shortages are still present in the pharmaceutical market. Regulatory agencies tend to impose more strict product specifications for new drug applications (NDAs), abbreviated new drug applications (ANDAs), biowaiver extensions and require a profound understanding of active pharmaceutical ingredient (API), excipient and product manufacturing, as well as, any interaction between these parameters that may affect final product safety and efficacy. In an attempt of amelioration, pharmaceutical industry is implementing the principles of Quality by Design (QbD). The aim is to build robust manufacturing processes in order to assure that the desirable product is constantly delivered to the patient through the establishment of a design space that defines the permissible area where variability and/or variations of input materials will not affect the outcome of the production process. Reducing or tolerating final product variation requires a profound understanding of all factors playing a crucial role in finished dosage forms. Controlling these crucial parameters will allow the design of products that will consistently meet final requirements, contribute to minimization of regulatory constraints and enable the safe passage from batch to continuous manufacturing, a beneficial production technique to address industrial deficiencies [1]. Excipients constitute a major component of final products and it is recognized that variability in their material properties can impact product processing, manufacturing and performance [2,3]. The exact mechanisms by which excipients exert their action are still to be discovered, especially when drug product performance is concerned [4,5]. The gastrointestinal heterogeneity and its effect on excipient functionality is an additional challenge in understanding and controlling the role of excipients in drug release.

A comprehensive overview of the current knowledge on excipient variability and its effect on solid dosage form performance is presented in this review. The biopharmaceutical parameters that impact the functional role of key excipients used in solid formulations is discussed. The aim is to gain a basic understanding of potential critical material attributes and their link to excipient and final drug product variability.

## 2. Excipient variability in drug development

As mentioned in the ICH Q8 "the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product" [6]. A final dosage form should meet a number of specifications to justify its efficacy and safe use. Deviation from these acceptance criteria indicates variability of final dosage forms. Variation is difficult to control since random distribution prevails in everything [7]. QbD aims towards controlling variability by (i) defining the final product attributes that will justify the intended use of final products and (ii) deliberately designing the production process and establishing the design space and control strategy to always meet these final attributes. Aspects whose variability can compromise product quality are characterized by high criticality. Critical quality attributes refer to aspects of the output product while critical material attributes to input materials [8]. In terms of pharmaceutical development, factors that may trigger final product variability include: active pharmaceutical ingredients (APIs), excipients and process parameters [8]. The physicochemical properties of the two former, any deviations or alterations in the latter and the complex interplay of process parameters and material attributes contribute to the incline in quality specifications. It becomes clear that in order to control the outcome we must have a fundamental understanding and control of all input materials. The required understanding of the reasons triggering product variability and batch failures is needed towards continuous pharmaceutical production and may not always be an easy task [9].

The impact of manufacturing processes on drug product quality has been addressed [10–12] but a more comprehensive approach towards drug product components is yet to be made. Examining the effect of input materials (e.g. APIs and excipients) on finished solid dosage forms requires a linkage of material properties to product quality attributes [13]. A thorough understanding of molecular, structural and particle properties of a substance is necessary. The limited knowledge on the role of physical and chemical properties of pharmaceutical components hinders the possibility to further optimize the behavior of oral solid dosage forms throughout manufacturing, but this gap is more pronounced in drug product performance. A change in a critical attribute for dissolution will not only cause production or regulatory failures, but it may strongly affect drug bioavailability. The complexity of the gastrointestinal environment adds a further challenge in investigating the effect of material attributes variability in drug dissolution. Although the API is considered the most substantial product component for disease treatment, it has to be noted that excipients can be more important in processes prior to oral drug absorption and also can induce even treatment failure if the drug is not appropriately released and dissolved according to product specifications. From manufacturing through to *in vivo* functional performance, excipients exert their action but their properties can affect drug dissolution, as it will be revealed by the critical analysis performed in this review. Since excipients constitute a large portion of a solid dosage form, comprising up to 99% of the total formulation mass [14], their impact on quality attributes can be statistically significant. The broad range of the excipient level used in solid dosage forms along with a possible alteration in excipient functionality by level variation, complicates further the excipient variability issue. *In vitro* and/or *in vivo* excipient effects on drug solubility, dissolution and permeability could impact oral bioavailability and bioequivalence. The use of a different type of excipient with the same intended functionality could also be problematic as the diversity of material properties may result in a change of the overall product performance. Understanding and integrating excipient variability in the production's design space and control strategy will pave the way for building robust production processes both in batch and continuous manufacturing [15].

## 3. Sources of excipient variability

Final product variability either preexists or is created during manufacturing. In this review, we are focusing on inherent excipient variability and its effect on final drug product. The main