A text mining study on the utility of physiologically based pharmacokinetic/biopharmaceutics modeling (PBPK/PBBM) in formulation development

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Introduction

Physiologically based pharmacokinetic (PBPK) modeling is an evolving tool that has a profound impact on drug discovery and formulation development processes. A major advantage of PBPK models is that they have the ability to mechanistically explain how drug properties, product quality attributes and physiological factors influence the *in vivo* drug performance. To better specify the application field of these models and highlight the link between *in vitro* dissolution and drug's *in vivo* behavior, a novel term, physiologically based biopharmaceutics modeling (PBBM), was recently introduced.

The versatility of application of these models is perceived through the growth in the number of scientific publications that include the use of PBPK/PBBM (Krstevska et al, 2022). In the present study, the use of PBPK/PBBM across the publications from the past decade was analyzed, with the focus on the application of these models in pharmaceutical/formulation development.

Materials and methods

Text mining of the literature was performed using Orange 3.32.0 software (Demšar et al., 2013). Data were collected using the PubMed widget, a key component of the text mining section. PubMed search was conducted using the following key terms: "PBPK" or "Physiologically based pharmacokinetic" or "Physiologically based modeling" or "Physiologically based model" or "Physiologically based biopharmaceutics modeling" or "PBBM" within the abstract or title of the

manuscript. Only original research articles published in English between 2012 and 2022 were included for analysis. All original research articles which focused on the utilization of PBPK/PBBM in the area of formulation development were extracted using the topic modeling widget, which is an important text mining tool for the discovery of hidden semantic structures in a collection of documents. To limit the construction of tokens, only the article abstract was kept for analysis. Prior to the main analysis, necessary text preprocessing tools were applied to convert textual data into convenient numerical features. The 'word cloud' widget was used to determine the frequency of occurrence of specific words within the published papers, while statistically significant words were identified with the help of 'bag of words' and 'word enrichment' widgets.

Results and discussion

A total of 386 articles met the pre-defined eligibility criteria. As visible from Figure 1, the number of publications on the use of PBPK/PBBM in formulation development increased over the years, with marked incline in the last half of the decade, which may be related to the regulatory recognition of these methods within recently issued guidelines (EMA, 2018; FDA, 2020).
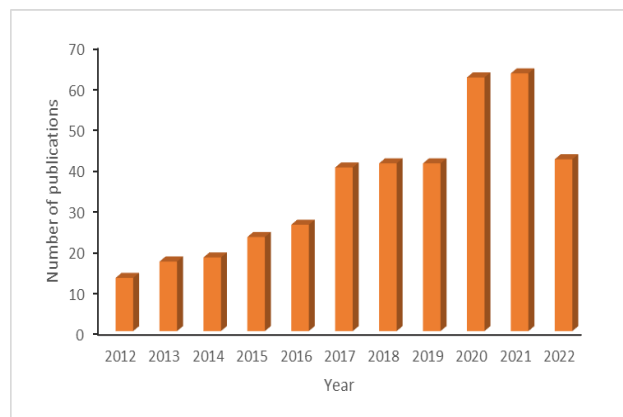
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Figure 1. Growth in the number of published papers on the use of PBPK/PBBM in formulation development (data for 2022 covered only first half of the year)

The results of the 'word cloud' widget revealed that the words "clinical" and "absorption" are encountered in 22% and 21% of the published articles, respectively. This suggests that PBPK/PBBM models are mostly used to identify clinically relevant drug/formulation attributes or to predict clinical outcomes, as well as for mechanistic interpretation of drug absorption pattern. The word "formulation" is mentioned in 19% of the published papers, which highlights the importance of PBPK/PBBM to guide formulation development. In addition, the occurrence of the words "bioavailability (BA)" (10%), "food" (6%), "bioequivalence (BE)" (5%), and "biowaiver" (1%) indicates that PBPK/PBBM tools are less frequently used to predict the outcome of BA/BE studies and support a waiver from clinical studies.

Frequency of the word "dissolution" revealed that 15% of the published articles addressed the use of PBPK/PBBM to assess the impact of drug dissolution on concomitant absorption. Also, there is an evident trend on the use of PBPK/PBBM tools to assess the impact on drug's properties, such as "solubility" (22%), "permeability" (18%) and "precipitation" (9%) on the *in vivo* drug performance.

Another annotation is that the word "oral" occurred in 48% of the analyzed articles, which demonstrates the chief role of PBPK/PBBM in the development of oral dosage forms. On the other hand, the words "pulmonary/inhalation", "intravenous/parenteral", "dermal/skin" "subcutaneous", "nasal", and "ocular/ophthalmic" were much less frequent (< 10%), indicating that PBPK/PBBM-supported development of dosage forms for other dosing routes is still rather limited.

Lastly, our analysis revealed that majority of the published PBPK models were developed for "tablet" formulations (18%), followed by "suspensions" (6%), and "capsules" (5%). The occurrence of the words "nanoparticle", "peptide" and "antibody" within the analyzed papers was less than 3%, signifying that PBPK modeling tools have been only sparingly used to support the development of advanced drug delivery systems and formulations for large molecules.

Conclusion

This work illustrates a successful application of text mining tools for the assessment and interpretation of research trends in PBPK/PBBM applications. According to the obtained results, there is an evident increase in the utilization of PBPK/PBBM tools in formulation development, although not uniformly distributed across the specific application areas within this subject. The majority of the published models have been designed for oral dosing route, and used to assess the effect of drug/dosage form properties on clinical drug performance. The models for alternative dosing routes and specific formulation types are still scarce, with a likelihood for increase in the following years.

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