

Reevaluating Excipients in Pharmaceuticals

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Abstract

Medications are extensively used in the present day. These medications primarily consist of two fundamental components: the active pharmaceutical ingredients (API) and the excipients. The API consists of an active element, and it's responsible for therapeutic effects. Excipients, the significant component by mass, are considered the "inactive" ingredient that stabilizes the API in most cases. Excipients are used to be thought of as "inert" or "inactive." However, recent research by Pottel et al. found that the excipients are active toward some targets. Thus, this review provides a summary of this research and explores its advantages and disadvantages.

Keywords: excipients, pharmaceutical chemistry, medicinal chemistry, toxicity of excipients, review

Introduction

Medication refers to a particular substance or drug, typically prescribed by a healthcare professional, to diagnose, treat, or prevent medical conditions or diseases in humans and animals. Medications are available in many forms, such as pills, tablets, liquids, etc. Regardless of their form, medications commonly consist of two main components: the active ingredient, which is active pharmaceutical ingredients (API), and the "inactive" ingredient, which is excipient¹. The Active Pharmaceutical Ingredient (API) constitutes the active element within a medication responsible for its therapeutic effects. In contrast, pharmaceutical excipients refer to the "inactive" components aside from the API^{2,3}. Even though the excipients don't directly contribute to the therapeutic action of the medication, their role is crucial. For instance, excipients can stabilize the API, especially in its pill form, allowing the maximum interactions between the API and body and absorption⁴.

Additionally, they can enhance the medication's shelf life, ensuring it remains effective over time. Furthermore, excipients can be used as color indicators to let pharmacists and patients easily tell the difference between medications or to confirm the presence of an active ingredient⁴. Their presence can also improve the taste, texture, and overall user experience, which is essential for ensuring patient compliance with their medication regimen⁵.

However, Pottel et al. recently researched the activities of drug "inactive" ingredients on biological targets³. Their findings challenged the conventional notion that these "inactive" excipients do not impact the intended targets. Therefore, this review provides a summary of this research and explores its advantages and disadvantages.

Summary of the Research

In the study conducted by Pottel et al., a comprehensive approach was used to assess the toxicity and activity of excipients toward targets. The researchers used several ways to ensure a thorough understanding of the toxicity of excipients. The researchers initially focused on in vitro predictions and testing of the excipients. Firstly, the Similarity Ensemble Approach (SEA) was used to predict plausible molecular targets for the excipients computationally. Subsequently, widely used excipients were empirically screened against a panel of 28 toxicity-related targets. This dual-pronged approach allowed for a robust assessment of the excipients' potential interactions and adverse effects at the molecular level. Using these two methodologies, the researchers realized that excipients are active against some targets.

Following the in vitro phase, the researchers used the BioMAP Diversity PLUS profile, a method renowned for its effectiveness in determining the safety, efficacy, and mechanism of action of candidate drugs, to test the activities of common "inactive" excipients. Using the BioMAP Diversity Plus profile, the researchers found that some excipients, traditionally considered inactive, exhibit various cellular activities, potentially raising questions about their impact when included in drug formulations. However, they also noted that being active does not mean excipients have activities on organs that will change one's health or behavior.

Finally, the researchers tested the toxicity of the excipients in vivo by using animal models. By testing the excipients in vivo, the researchers found that most excipients, although exhibiting activity against the target, did not reach significant blood levels that would cause health problems. However, indeed, there are still some common excipients, such as cetylpyridinium chloride in

mouthwash, which can reach significant blood levels and might affect overall health.

Discussion

Before the publication of the study conducted by Pottel et al. in 2020, there was barely any research addressing the toxicity of excipients, their interactions with molecular targets, and their overarching effects on general health because the excipients were thought as “inert” and “inactive.” Therefore, the significance of excipients has been largely overlooked within the scientific community. However, following the release of this paper, there was an increase in research related to topics such as the influence of excipients on gut microbiota and the potential toxicity and healing characteristics of excipients in ocular medications^{6,7}. Therefore, it cannot be denied that this study has played a crucial role in advancing the understanding of excipients in pharmaceutical formulations and could be used as a guide for future research.

Moreover, it is impressive that the researchers computationally predicted 3000 medically relevant proteins and tested 73 commonly used excipients against a panel of 28 targets. Also, notably, their inclusion of detailed findings in a tabular format enhances the overall quality of the study. Furthermore, it distinctly aligned with the primary objective of this study: to demonstrate that the “inactive” ingredients exhibit activity against specific targets.

While this study presents numerous advantages, it is essential to acknowledge the presence of certain limitations, and these areas of constraint might be considered for future research. First, the researchers examined excipient-target activities and observed potential toxicity; however, it would be beneficial if they could propose a mechanism of action. The researchers examined excipient-target activities and observed potential toxicity; however, it would be helpful to propose a mechanism of action to explain better how excipients interact with the biological molecular targets. Secondly, the study solely addressed interactions between individual excipients and their respective targets within a single medication without exploring potential interactions among excipients that may lead to toxicity, both in vitro and in vivo. Lastly, as the researchers mentioned, it would be advantageous to include an investigation into whether interactions among excipients could lead to toxicity when multiple medications are concurrently administered to elderly individuals or those with cancer.

In general, the study conducted by Pottel et al. in 2020 has significantly contributed to understanding excipients in

pharmaceutical formulations, challenging the traditional perception of these components as “inactive” or “inert.” Furthermore, this review has provided a summary of Potter et al.’s research and explored the advantages and disadvantages of the study.

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