

The suggestions and directions for future research on excipients-- A summary and review of a paper

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Abstract. Excipients, traditionally considered "inert ingredients" in drugs, often constitute the majority of the mass and play a vital role in pharmaceutical formulations, enabling effective drug delivery and product stability. The research and development process for excipients involves a multidisciplinary approach, encompassing various scientific disciplines and regulatory compliance. However, challenges related to safety assessment, limited understanding of excipient-drug and excipient-biological target interactions, and the absence of standardized characterization methods pose ongoing hurdles in excipient R&D. This paper as a summary and review of the latest research in the field of excipients, opens up a new avenue for researchers to overcome the current challenges. It highlights the growing understanding of potential biological activities of excipients and their clinical importance. The significances and limitations; pros and cons of the technique; future applications and attention regarding the research will be further discussed in this paper. By shedding light on the excipient research and development, this paper provides insights into optimizing drug formulations, enhancing patient safety, and improving therapeutic outcomes.

Keywords: Excipients, Pharmaceutical Chemistry, Drug Development.

1. Introduction

Excipients, widely known as "inert ingredients" in drug formulations, are used as antioxidants, preservatives, detergents and dyes to protect and maintain the stability of the active pharmaceutical ingredients (API) in drugs. Excipient research and development (R&D) employ diverse methodologies encompassing formulation science, material characterization, and regulatory compliance. Moreover, the identification of suitable excipients involves a thorough literature review, screening of existing excipient libraries, and innovative synthesis approaches (Ahmed et al., 2018). When it comes to production and application, excipient-based formulations undergo rigorous optimization, process development, and scale-up studies to ensure manufacturing feasibility and product quality (Chen et al., 2021).

Despite their importance, excipient R&D faces several challenges. Safety evaluation is a critical bottleneck, as excipients usually occupy the most part of a single drug formulation, but their pharmacological effects, potential risks, and how they could interact with the biological pathway have not been taken seriously and explored systematically. Although regulatory agencies, such as the US Food and Drug Administration (FDA), mandate comprehensive toxicological evaluations for excipient approval (Anderson et al., 2021), understanding the complex interactions between excipients and drugs remains limited, hindering rational formulation design (Mansourpour et al., 2022). Additionally, the lack of standardized methods for excipient characterization and evaluation poses challenges in comparing and selecting excipients across studies (Kesisoglou et al., 2019).

Previous studies about excipients that indicate their "inactive" property is by testing the gross tolerability studies in animals. However, the latest study from Joshua Pottel, Duncan Armstrong, et al., applying their newly developed methods to combine in vitro and in vivo tests demonstrates that a small portion of these "inactive" excipients might have activities against medically relevant targets, which opened up a new path for researchers to overcome the current challenges they are facing.

Pottel et al. tested the activities of excipients from three layers of screening; first is the inherent on-target activity in vitro. What they found were 134 activities for 38 excipients against 44 targets with crucial roles, and these activities covered a wide range from low-nanomolar to mid-micromolar (Pottel et al., 2020). Through further investigation on a dozen of selected target-active excipients with their cell-based toxicities and systemic exposure in animal models, researchers found that even

though many excipients tested reach the level of potent *in vitro*, only two of them thimerosal and cetylpyridinium chloride may reach relevant systemic exposure at maximum doses of drugs intake, which means that the majority of people were unable to achieve blood levels that were potent enough to regulate the biological targets when taking medication orally since most of them were rapidly metabolized. Nonetheless, not all individuals are likely to consume excipients solely from a single type of medication. For elderly populations, frequent and long-term consumption of several medications, occasionally containing overlapping excipients, may lead to the excessive intake of excipients that surpass the limit allowed for a single drug, resulting in elevated systemic levels. Additionally, most excipients are commonly used in food, drinks and cosmetic products, frequently in greater quantities than those found in drugs.

In summary, the research by Pottel et al. challenges the perception of excipients as inert substances by revealing their activities against medically relevant targets. This discovery creates novel pathways for researchers to explore the implications and risks associated with excipient intake, particularly for individuals consuming multiple medications or encountering overlapping excipients in food, drinks, and cosmetic products. This paper will further discuss the research by Pottel et al. from its significances and limitations; pros and cons of the technique; future applications and attention.

2. Significances and limitations

Despite being an initial investigation in the area of excipients, the study successfully drew the notice of scholars to the significant impact of excipients on biological targets. The findings of this study emphasized the need for further research to explore the effects of excipients in greater depth and to assess their potential risks to human health. This study also highlighted the importance of considering excipients in drug development and manufacturing to improve the efficacy and safety of medications. However, as a preliminary investigation, the study is not without limitations.

For example, although it demonstrated that the occurrence of thimerosal-D3 dopamine receptor activity is possible, the study lacks the verification that thimerosal leads to *in vivo* toxicities. A second limitation is that although the computational predictions and empirical assays revealed more than 100 activities for 38 excipients have potent *in vitro*, only seven excipients were studied for systemic circulation and most excipients lack the investigation of exposure in blood after oral dosing. Therefore, further investigation is required to address these limitations and enhance our comprehension of how excipients affect human well-being, which should primarily focus on the excipient *in vivo* activities, from the perspectives of cell-based toxicities and systemic circulation.

3. Pros and cons of the technique

As to the research approach this study applied to test the activities of excipients against molecular targets, Pottel et al. first screened 639 excipients against 3117 human targets based on the SEA (Similarity Ensemble Approach) E-value, in which SEA suggests that if a target has ligands that bear resemblance to a bait compound, such as an excipient in this case, there is a possibility that the target can also bind to that compound; and the E-value quantifies the probability of a prediction happening by chance or at random. Of the 20,000 excipient-target pairs that are plausible, 69 prioritized pairs were tested *in vitro*, and 19 excipients were revealed to be active. Meanwhile, they empirically screened 73 commonly used excipients against a panel of clinical safety targets, and 32 excipients were found to be active (Pottel et al., 2020). The advantage of this approach is that through two different assays there are overlapping active excipients and these are worthy to be further investigated *in vivo* to determine the cell-based toxicity and systemic exposure. Additionally, this approach is relatively all-sided since it computationally and empirically covers almost all commonly used excipients and targets relative to drug clinical safety.

Cell-based toxicity assay demonstrates the effects and toxicology of excipients on health or behavior changes of cell or tissue system in the human body. The excipients were evaluated at four

different concentrations, and their characteristics were compared to over 4000 drug reference profiles present in the database (Pottel et al., 2020). The merit of this assay is that it manifests the effects of excipients on a wide range of different human cells, and also implies the relationship between the concentration of the excipients and the behavior changes. Although the excipients are concentrated in the gut epithelia after consumption, in order to exert systemic effect, they need to traverse through metabolic and intestinal barriers. Systemic exposure of excipients after oral intake in animal models indicates whether the blood concentration is high enough to regulate the targets or not. It is the most helpful investigation to determine whether the regular dosing of medication can truly induce the excipient-target modulation in human body after metabolism.

Despite the advantages of *in vivo* tests, one of their drawbacks is the requirement for a relatively substantial number of resources to conduct them. Consequently, it is impractical to test every active excipient using these methods on a large scale. Moreover, there may be limitations in the extent to which these results can be extrapolated and applicable to humans. Therefore, there might be a need for the development of alternative methods or strategies that can efficiently and accurately assess the safety and efficacy of excipients in drug development.

4. Future applications and attention

As this study mentions, although there are several amounts of excipients might not be inert, 70% of the vast majority of them are inactive and have the fewest interactions with other medications. Therefore, one possible way to resolve the problem of active excipients is to replace the debatable ones with these inert excipients. For instance, thimerosal is an excipient present in injured drug formulations such as vaccines, and its primary metabolite and thimerosal are mercury derivatives. Due to the high concentrations of thimerosal observed in the gut and brain of human infants after vaccination, which makes it challenging to metabolize, this compound is no longer included in infant vaccines in developed nations. A second example of replacing problematic excipients in drugs to improve the absorptions of API is the removal of excipients in levothyroxine (Pottel et al., 2020). Consequently, the study of excipients has the potential to be applied in pharmaceutical industries to replace problematic excipients with inert ones, thereby enhancing the safety and efficacy of medications. By pointing out the fact that excipients can interact with biological targets, the research from Pottel et al. could facilitate the development of more effective and safer drugs.

Apart from drug intake, individuals may also consume excipients from other sources, such as food, beverages, and beauty products, often in larger quantities than those found in medications. Hence, it is imperative for manufacturers to disclose the presence of excipients to consumers and advise against the consumption of such sources of excipients in conjunction with medications.

5. Conclusion

This research paper emphasizes the crucial role of excipients in pharmaceutical formulations and the need for comprehensive understanding and evaluation of their properties. The study by Pottel et al. reveals the activities of excipients against medically relevant targets, challenging the notion of their inertness. The findings underscore the importance of reevaluating excipients safety, exploring their interactions with drugs and biological targets, and developing standardized methods for excipient characterization. Furthermore, this paper highlights the risks associated with cumulative excipient intake from multiple medications and other sources. The need for further investigation to explore the excipient activities or toxicities especially *in vivo*, and to improve our understanding of the impact of excipients on human health is mentioned in this paper. Future applications include replacing problematic excipients with inert alternatives to improve drug safety and efficacy. Overall, this research contributes to advancing the field of excipient research and emphasizes the significance of considering excipients in pharmaceutical formulations and patient safety.

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