On the role of excipients and their future development

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Abstract. Excipients are inactive substances that are included in pharmaceutical formulations alongside active ingredients. These substances are added to pharmaceutical products for various purposes, including improving stability, enhancing bioavailability, aiding in the manufacturing process, enhancing the appearance or taste, and facilitating administration or delivery of the active ingredient. We summarized a recent study published in science. This work suggests a systematic method to identify such active “inactive ingredients,” including the detection of allergenic and immunogenic properties. The examined excipient activity by combining large-scale computational screening with targeted experimental testing. They identified 38 excipients with activities against 44 targets. Although most excipients deserve their status as inert, many approved excipients may directly modulate physiologically relevant targets. This review increases our understanding of the relationship between drug excipients and active sites and provides more comprehensive theoretical support for future excipient selection.

Keywords: excipient, biological targets, drug development.

1. Introduction

The drug consists of the active pharmaceutical ingredient and the excipients. Excipients are inactive substances that are included in pharmaceutical formulations alongside active ingredients. These substances are added to pharmaceutical products for various purposes, such as improving stability, enhancing bioavailability, aiding in the manufacturing process, enhancing the appearance or taste, and facilitating administration or delivery of the active ingredient. Excipients are typically pharmacologically inert and do not have any therapeutic effect on their own. Instead, they serve to support the formulation and delivery of the active pharmaceutical ingredient (API) to the patient. Excipients can be classified into different categories based on their functions. Some common examples include: 1. Fillers and Diluents: These excipients add bulk to the formulation to ensure proper tablet or capsule size and aid in the uniform distribution of the active ingredient. 2. Binders: Binders are used to hold the ingredients together and provide the necessary cohesive properties for tablet formulations. 3. Disintegrants: These excipients promote the breakup of tablets or capsules in the gastrointestinal tract, facilitating the release and absorption of the active ingredient. 4. Lubricants: Lubricants reduce friction during tablet compression and ejection from molds, preventing sticking and ensuring smooth production processes. 5. Coatings: Coatings can be applied to tablets or capsules to improve appearance, protect the active ingredient from moisture or light, control release, or enhance swallowability. 6. Preservatives: Preservatives are added to prevent microbial growth and ensure the stability and shelf life of the pharmaceutical product. 7. Flavoring Agents: These excipients are used to mask the unpleasant taste of certain medications, making them more palatable. 8. Colorants: Colorants are added to provide an aesthetic appeal or to differentiate between different formulations or strengths of a product.

For example, we commonly see examples of binders, fillers, disintegrants, lubricants in tablets; Chinese medicine pills in wine, vinegar, juice; semi-solid preparations of ointments, creams in the matrix part; liquid preparations of preservatives, antioxidants, corrective agents, aromatics, co-solvents, emulsifiers, solubilizers, osmotic pressure regulators, coloring agents can be called excipients. Take lactose, pectin, and xanthan gum as an example. However, in fact, excipients are not completely inactive. Such as bithionol and amaranth have been eliminated from use. It was cancelled due to concerns about photosensitivity and tumorigenicity, respectively. It's important to note that excipients are carefully chosen and undergo extensive testing to ensure their safety and compatibility with the active ingredient. They play a crucial role in pharmaceutical formulations, contributing to the overall effectiveness, stability, and patient acceptability of the medication. In Halford, B., C&EN, 2020, 98(30), that doesn't imply these excipients are toxic, the researcher suggested, but they might not be inert. According to a survey, roughly 70% of excipients are inert, giving pharmaceutical companies a wide range of...
alternatives to those that could pose problems. Moreover, the activity of excipients on the target has not been systematically discussed. To further explore the excipients field, Pottel, J. et al, Science, 2020, 369, 403-413 and other experimenters calculated the probability that approved excipients will bind to molecular targets in the research ‘The activities of drug inactive ingredients on biological targets’

2. Predicting and testing excipient activity on in vitro targets

To rigorously examine the activity of authorized inactive substances against biologically significant molecular targets, authors employed a two-part technique. Using chemoinformatic inference, they first computationally suggested probable targets for excipients from a pool of 3000 therapeutically relevant proteins. The chemoinformatic Similarity Ensemble Approach (SEA; http://sea16.ucsf.bkslab.org) proposes that when a target has ligands resembling a bait compound, such as an excipient, it is likely to bind to that compound. This method has been utilized to anticipate drug side effects and identify potential targets for the mechanism of action. Second, they empirically screened a panel of 28 toxicity-related targets frequently used to identify probable clinical adverse events of drug candidates, as well as numerous other targets with significant roles in drug toxicity or pharmacological activity, against a variety of commonly used excipients. During the data collection, researchers found out some interesting examples. Thimerosal, an antibacterial agent with a mercury derivative that is frequently used as an excipient in medications. Despite efforts to restrict its use because it is a mercury derivative, thimerosal is nevertheless a component of vaccine industry formulations. As a result, people's blood now contains more mercury. This shows that the supposedly "inactive ingredients" do have direct actions in vitro against enzymes, receptors, ion channels, and transporters. In vitro testing for the ultimate research goal identified 25 excipient actions, ranging in concentration from low nanomole to high micromole. By comparing the activities to clinical safety goals, an additional 109 were found. Five excipients had signatures that indicated system-level toxicity in cellular models. Seven excipient exposures were examined; two of them, thimerosal and its main metabolite, which had brain and gut exposure and dopamine D3 receptor dissociation constant Kd values of 320 and 210 nM, respectively, may reach levels of in vitro target potency in some individuals. Several licensed excipients may directly influence physiologically relevant targets, despite the fact that the majority of excipients merit their position as inactive.

3. Computer predict the targets that could be encountered by excipients

The pros of the technique is by using the computer predict the targets that may be encountered by excipients. For example, by prioritizing 69 excipient-target pairs based on a visual comparison of the excipient and target ligands, those were removed. This method is much more efficient than traditional experiments in the laboratory to collect data. Moreover, it can be screened in advance to avoid unnecessary experiments. The cons of the method is the researcher was based on experience and thus the choice of excipients and there was sample bias. Therefore, the excipients used in the experiments were not sufficiently representative.

4. Ernie coefficient could as an indicator to analyze the frequency of distribution

In the research, Biologic excipients: Importance of clinical awareness of inactive ingredients, the authors suggests: although the average number of excipients used in biologics is half that of additives in small molecule drugs, the distribution of 120 unique excipients in 230 drugs with 1 to 14 ingredients per formulation suggests a high degree of variability. Using the Ernie coefficient as an indicator to analyze the frequency of distribution, the study showed that the distribution was skewed towards the most common ingredients. The Gini coefficient is a well-known economic indicator used to quantify income inequality by looking at the distribution of income in the population. However, it has been used to describe variation in other contexts, including the distribution of excipients in orally administered drugs. Findings also confirm that manufacturers largely do not report concentrations of inactive ingredients in biological formulations.
5. Conclusion and Discussion

Those researches are significant because this is a point that most people don't notice, but it does affect people's lives. Excipients are necessary to ensure the safety of the drug as the main component of the drug. For example, excipient interactions may lead to incompatibility, which has a substantial impact on the quality of the final product. Physical or chemical interactions are to blame for such incompatibility [1]. Also, the effects of excipients on specific populations cannot be ignored. Examples include the elderly and those who require long-term medication. The metabolic rate of the elderly is low, so excipients can accumulate in the body of the elderly, if the excipients have side effects. That will have a negative impact on the elderly. This is also true for people who need to take medication for a long time and ingest excipients for years and years. The fact that excipients have such a strong influence demonstrates the importance of conducting specific activity studies on them.

The potential applications of the research are improved drug delivery, enhanced drug stability, identification of new drug targets, and personalized medicine. Scientists could improve drug delivery [2], by understanding how excipients interact with drug targets, it may be possible to design delivery systems that more effectively target specific cells or tissues, resulting in better drug efficacy and fewer side effects. For enhanced drug stability [3], excipients can help stabilize drugs and prevent degradation, but it is important to understand their interaction with drug targets to ensure that they do not interfere with drug activity or cause toxicity. Identification of new drug targets [4]. Excipients may have their own biological activity and could potentially be used to modulate specific targets. Studying their interactions with targets could lead to the identification of new therapeutic targets or the development of new drugs. Personalized medicine, excipient-target interaction studies could help identify patient-specific responses to specific drugs, allowing for personalized treatment plans that are tailored to an individual's unique. Thus, there is a lot of potential for future work in the field of excipients, including the development of new excipients, targeted drug delivery systems, and personalized medicine based on patient-specific response to excipients. In addition, the use of computer technology to simulate experiments instead of real experiments is also a major trend. Traditional experiments are dependent on real-existing objects, and when the structure of the research object is complex and not easy to manipulate, it will consume a lot of human and material resources, but it is not enough to ensure that the experiment is carried out smoothly. Computer numerical simulation can make traditional experiments no longer constrained by the real physical world and no longer limited by time and physics.

Knowledge of the concentrations of inactive ingredients in formulations may help to uncover their potential role in producing adverse effects, although even small amounts of allergens in a drug may induce severe allergic reactions. The variability of biologics based on excipient selection and use is of clinical importance to identify patient groups that may be more susceptible to certain adverse effects. [5]
References


