Activities of Inactive Ingredients in Drugs

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Abstract. In this essay, I will talk about two papers that were published. In order to demonstrate the activities of inactive ingredients, these two papers reported the impact of inactive ingredients on biological targets through some experiments. Because as the development of pharmaceutical chemistry, more and more people pay more attention on medication safety. As a result, in this paper, I will use the Thimerosal, Glycyrrhizin and Butylparaben as the main experiment examples to help explain the discovery of the effect of inactive ingredients on biological targets. Because there was not systematic research, this article will discuss this topic about materials and methods in order to have a better understanding.

Keywords: Pharmaceutical Chemistry; Excipients; Inactive Ingredients; Interaction; Targets.

1. Introduction of Research of Inactive Ingredients in Drugs:

Inactive ingredients are common in pharmaceuticals. However, recent research based on computer-based prediction, biological tests, and intravital animal research indicates that some inactive ingredients may have biological activities. Although most inactive ingredients are inert, there is a lot of interaction between these inactive ingredients and biological targets, which could have an impact on physiological processes. We therefore attempt to conduct a study on the interaction of inactive ingredients and biological targets in order to ascertain the effects of this interaction.

2. Literature Review

Excipients may interact with some significant biological pathways, according to Joshua Pottel et al., the author of Science Concentrates Exploring Excipients (Joshua Pottel et al. 2020). They screened a large number of excipients and 28 toxicity-related targets before conducting additional research on twelve target-active excipients using the BioMAP Diversity PLUS panel in Joshua Pottel et al (2020).'s paper. Then I'll take thimerosal, glycyrrhizin, and butylparaben.

Shoichet, Urban, and colleagues used computational modeling, enzymatic assays, and in vitro tests to show how excipients and biological targets interact. This test allows us to draw the conclusion that 1-Cetylpyridinium chloride and thimerosal have shown potential biological activity in animal studies and have a concentration in rat blood that is high enough to interact with biological targets. It is crucial that we look into whether excipients will affect people's health, especially when it comes to medications that people must take on a regular basis. Excipients are frequently used, but little is known about how they interact with specific molecules.

Table 1. The data of excipients in vitro binding assays with marketed drugs, which the data is from the Handbook of Pharmaceutical Excipients (64) (Joshua Pottel et al. 2020)

Excipient	Function	Example Marketed drug	Highest excipient amount/dose	Predicted target	K_i/IC_{50} (μm)
Butylparaben	Antimicrobial preservative	Fexofenadine (Children's Allergy)	8mg/5ml	CHRM1	12
Glycyrrhizin	Flavoring agent	Junior ibuprofen	1.25mg/5ml	SLCO1B1	13

In order to learn about the activities of excipients, with regard to in vitro targets, they must forecast and test the activity. They use 3000 medically relevant proteins to screen 28 frequently used toxic relevant targets and predict the reasonable targets of excipients. Following that, they chose 69 excipients for in vitro functional testing (Joshua Pottel et al. 2020) in order to obtain a graph of motivation, which is an exercise that promotes concentration. These graphs show that 19 excipients will be active in at least one of the 12 targets, which they can infer (Joshua Pottel et al. 2020). Alternatively, they chose 73 common medical excipients to screen (Joshua Pottel et al. 2020). There are 38 "inactive ingredients" with 134 types of activities to 44 targets through these two methods. Although these activities differ from inactive ingredients, these excipients will not be active to the body's health.

In vitro binding assays, I will take Butylparaben and Glycyrrhizin (Joshua Pottel et al. 2020) for instance, Butylparaben is used as preservative in the food or drug. However, in animal models, Mohammad Shah and Masamichi Kurohmaru found that Butylparaben can make spermatogenic cells of preadolescent rats died (Mohammad Shah, Masamichi Kurohmaru 2014). They gave Sprague-Dawley which are three weeks old a single oral of dose of 1000mg/kg Butylparaben and killed with anesthetic after 3, 6 and 24 hours. After this, they collected testes for research, they found that Butylparaben will make Sertoli cell vimentin filaments collapse (Mohammad Shah, Masamichi Kurohmaru 2014). This means spermatogenic cells will have apoptosis so that this will effect the male reproductive system function (Mohammad Shah, Masamichi Kurohmaru 2014). There is a predicted target called CHRM1 (Joshua Pottel et al. 2020), which can exist in human, mouse and rats, therefore, if we assume that Butylparaben can also have the similar affect in human body, this will have the similar influence of spermatogenic cells in preadolescent male reproductive system function.

Another example is Glycyrrhizin (Joshua Pottel et al. 2020). As we can see in the table 1, the predicted target is SLCO1B1 (Joshua Pottel et al. 2020). SLCO1B1 is the gene of Organic aeon-transporting polypeptide 1B1 (OATP1B1) (Kalliokoski, Annikka et al. 2010). The gene SLCO1B1 is polymorphic so that this may influence the transport function of OATP1B1 (Kalliokoski, Annikka et al. 2010). Dong, Jiajia et al. found that Glycyrrhizin is a substrate of OATP1B1. Glycyrrhizin uses concentration-dependent manner with Ki values to inhibit the absorption of E217βG by OATP1B1 (Dong, Jiajia et al. 2018). SLCO1B1 SNPs have been proved that there is a relationship between SLCO1B1 and transport function of OATP1B1 in vitro. After the research of substrate of OATP1B1, SLCO1B1*5 has relationship with the decrease in transport function (Kalliokoski, Annikka et al. 2010). As a result, this means Glycyrrhizin has active action.

We also have animal models that have been exposed to excipients systemically. Targets in the gut epithelia are frequently exposed to excipients at high concentrations. They must cross the gut and metabolic barriers before reaching the general circulation in order to have an impact on the entire body. Studies using white mice have also shown that the blood has a quick metabolism. Aside from oral drugs, there are other ways for drugs to enter the systemic circulation, such as Thimerosal, which is used as an excipient in injectable drugs. Thimerosal is an antibacterial agent; however, it is a mercury derivative, and its use has been restricted, particularly in pediatric vaccines. As a result, in this article, I will investigate Thimerosal. An example of a commercially available drug is the packaging of the influenza vaccine in multiple doses; the highest excipient amount/dose is 0.03%. Thimerosal serves as an antimicrobial preservative. Thimerosal targets ADORA3, ADRA2A, SLC18A2, DRD1, DRD3, and 5HT2b** (Joshua Pottel et al. 2020). The amounts of Ki/IC50 or EC50(m) differ due to the different targets. Ki, short for "inhibition constant," measures how strongly an inhibitor inhibits a target. The lower the value, the stronger the inhibitor's influence. Sometimes it is the same as Kd; however, IC50 is unaffected by substrate and enzyme concentrations used in the study, whereas Ki is. The amount of medication or inhibitor required to block 50% of a particular biological process is known as the 50% inhibiting concentration (IC50). Thimerosal and dopamine D3 are found to have a 320nM Kd. As a result of pediatric vaccinations, mercury can be found in the blood of newborns and infants; however, mercury can be eliminated after 30 days. Although the amount of mercury in adults is lower than that in human babies, we use monkey babies to measure

the amount of mercury in the brain, and we estimate that the highest amount of mercury in a human baby's brain is 13-24 ng/g. This observation leads us to the conclusion that thimerosal and ethyl mercury are active in the gut and brain. The dopamine D3 receptor and the dopamine D5 receptor are crucial targets for ethyl mercury in the gut and brain as a result.

3. Discussion:

Additional study reveals that many inactive ingredients are active; in drug simulations, They will be active on enzymes, receptors, ion channels, and transporters that are important in biology. Excipients are used in greater quantities in many medicines than in bulk drugs. Taking Thimerosal, Glycyrrhizin, and Butylparaben as examples, the concentration of Thimerosal is sufficient to affect the protein, Glycyrrhizin will affect the SLCO1B1, and Butylparaben will also have an effect.

However, I believe there is insufficient research on excipients in these research papers. This is because, as we know from the Thimerosal experiment, the metabolism in the blood is fast. We don't have enough time to look into it further. Furthermore, we demonstrate that several excipients could have an effect on human biological targets; however, we lack adequate clinical experiments to demonstrate that excipients will have a negative influence on the human body. This does not, however, imply that the study has no significance; we must consider issues of medical ethics; there are a lot of debates about whether people should conduct experiments on the human body. We hope for species continuity so that we can know that life is valuable. As a result, the experiments do not involve the human body. Furthermore, it is unknown whether other impurities exist or whether only excipients affect human physiology. Therefore, at the moment, we can reduce or change the amount of excipients used if we believe they have biological targets and will have an effect on the human body.

4. Conclusion

According to this study, some excipients interact with inactive ingredients and biological targets. I'll use the excipients thimerosal, glycyrrhizin, and butylparaben as examples of potentially active excipients. This research may also assist us in focusing more on health. This idea is applicable to food, cosmetics, and medicine as well. To ensure that the impact of excipients is reduced, I hope that in the future we can learn more about excipients and carry out more research.

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