DRUG FORMULATION

The secret life of excipients

> These findings uncover potential activities of many so-called inactive substances in drug formulations at biologically and medically important targets

In addition to the active pharmaceutical ingredient, drug formulations contain excipients such as stabilizers, colourants and antioxidants, which are designated as 'inactive'. However, writing in *Science*, researchers from academia and industry now report that many commonly used excipients are active at physiologically relevant targets, suggesting more attention should be paid to these often-overlooked drug components.

The FDA's Inactive Ingredients Database (IID) lists more than 3,000 excipients, which are considered inactive largely on the basis of historical precedent and whole-animal toxicity studies. In the current study, Josh Pottel, Brian Shoichet, Laszlo Urban and co-authors sought to systematically investigate the activity of excipients at molecular targets.

The researchers used a chemoinformatics approach to predict plausible excipient–target pairs. They focused on the 639 well-defined, monomeric excipients in the IID, and ran an in silico screen against 3,117 human targets in the ChEMBL database. Activity predictions were based on chemical similarity between excipients and known ligands of the protein targets. From this screen, 69 excipient–target pairs were prioritized for in vitro functional testing; these studies identified 19 excipients with activity against at least 1 of 12 receptors, including muscarinic acetylcholine receptors and the intestinal organic anion transporter 2B1 (OATP2B1).

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In parallel to these computational studies, the investigators experimentally screened 73 commonly used excipients against 28 targets associated with drug safety and important biological functions, including the vesicular monoamine transporter VMAT2, sodium channel $Na_V1.5$ and OATP2B1. They detected activity for 32 excipients at one or more targets, most of which had half-maximal inhibitory concentration (IC_{50}) values of 30 μM or less.

Overall, the researchers identified 38 excipients with 134 activities against 44 targets. Approximately half of these activities were in the nanomolar to low-micromolar range, which indicates greater potency for these excipients than the on-target activity of some small-molecule drugs.

Next, the authors sought to examine whether these excipient–target interactions would be seen in tissues and organs. They used the BioMap Diversity PLUS panel — a set of cell-based systems that generates a 148-biomarker readout for each compound and compares this to more than 4,000 chemical reference profiles — to investigate 12 selected excipients. These excipients were selected on the basis of their frequency of use in formulations and to cover a range of excipient functions. Although several did not produce a BioMap activity profile (suggesting they would indeed be inactive in vivo), some did. For example, the BioMap fingerprint of the widely used excipient butylparaben overlapped with that of the anti-inflammatory drug nabumetone.

Last, the researchers tested systemic exposure of seven of the more active and commonly used excipients after oral dosing in rats. Most did not reach sufficient blood concentrations to modulate their target, presumably because they were sequestered in the gut or rapidly metabolized after absorption. However, cetylpyridinium chloride, an excipient in oral mouthwash, reached a maximum concentration in the blood that was in the range of its activity against the dopamine D3 receptor. In the context of non-oral formulations, injection of the excipient thimerosal, which is used in some vaccine preparations, was found to reach systemic concentrations that overlap with the compound's affinity for the dopamine D3 receptor.

These findings uncover potential activities of many so-called inactive substances in drug formulations at biologically and medically important targets. The approaches outlined lay the groundwork for further study. "It'd be great to see a more comprehensive attack on excipients — we have only scratched the surface," says Shoichet. More broadly, the research could help to reinvigorate the excipients field. "Getting new excipients approved is difficult, owing to regulatory hurdles. This leaves formulation scientists with a static and even shrinking toolbox," notes Shoichet. "It would be great to find a way to innovate in this field; few drugs would work without being formulated," he notes.

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