COMMENTARY

A Molecular Basis for Innovation in Drug Excipients

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Excipients are ubiquitous in drug formulation, ensuring that active ingredient drugs are properly released on dosing, retain their properties over time, and are palatable, among other roles. Despite their crucial roles, surprisingly little is known about their systemic availability and activities on molecular targets. Here we review key excipient properties, introduce a public-accessible database that enumerates and categorizes them, and sketch a strategy for exploring their possible direct actions on molecular targets.

Excipients are used ubiquitously to formulate drugs. Ranging from detergents like stearoyl phosphocholines, to wetting agents like benzalkonium chloride, to stabilizers like cellulose, to dyes like acid blue, to sweeteners like aspartame, excipients are crucial to drug solubility and permeability, stability, palatability, and delivery. Whereas it is the active ingredient that is responsible for drug pharmacodynamics, without excipients few drugs would achieve the exposure needed for efficacy.

Despite their importance, it is difficult to search for the molecular structures of excipients that are used in approved drugs, and hence to understand their relationships and chemical properties. It is harder still to interrogate molecular excipients for possible biological roles. Excipients used in approved drugs are generally considered pharmacodynamically inert, but this has rarely been explicitly tested, and it is conceivable that some excipients have direct, on-target pharmacology.[1] Indeed, a cursory inspection of excipients used in approved drug products reveals molecules similar to nonexcipients known to have direct on-target effects.

With funding from the Office of Generic Drugs provided by Generic Drug User fee Amendments (GDUFA), we sought to develop a new resource for the community that brings molecular excipients together in a single place, enabling their searching, representation, and analoging by simple graphical interfaces and large-scale chemoinformatics. Further, we have begun to explore whether certain excipients have direct on-target pharmacology of their own, which would have to be considered in their future use. For reasons of statute as well as science, introducing new excipients is now difficult and expensive, and this has limited innovation in this crucial, if sometimes underappreciated, area of drug development. Excipient selection is a critical part of the development of generic drug products and therefore GDUFA support of research in this area can enable more efficient product development with a better understanding of potential risks of using a particular excipient in a drug product. Better understanding of the pharmacological risk of current excipients could also inform the US Food and Drug Administration's (FDA's) review of requests to use these excipients at higher levels than in currently approved products.

AN OPEN ACCESS DATABASE FOR CATALOGING EXCIPIENTS AND THEIR MOLECULAR PROPERTIES

Perhaps the most useful excipients compendium is the FDA inactive ingredients database (IID, http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm). The IID is a list of the excipients that have been used in FDA-approved new drug applications and abbreviated new drug applications. The database provides the routes of administration and dosage forms of the approved drugs in which the excipient was used. It also includes the maximum amount of each excipient in a unit dose that has been used in approved drugs for a particular route of administration and dosage form.

The IID has the virtue of being publicly available and comprehensive. It has the drawbacks of being challenging to search, mixing true molecules like α-tocopherol with mixtures like canola oil and polymers like povidone, and lacking molecular properties. In the IID, most excipients are

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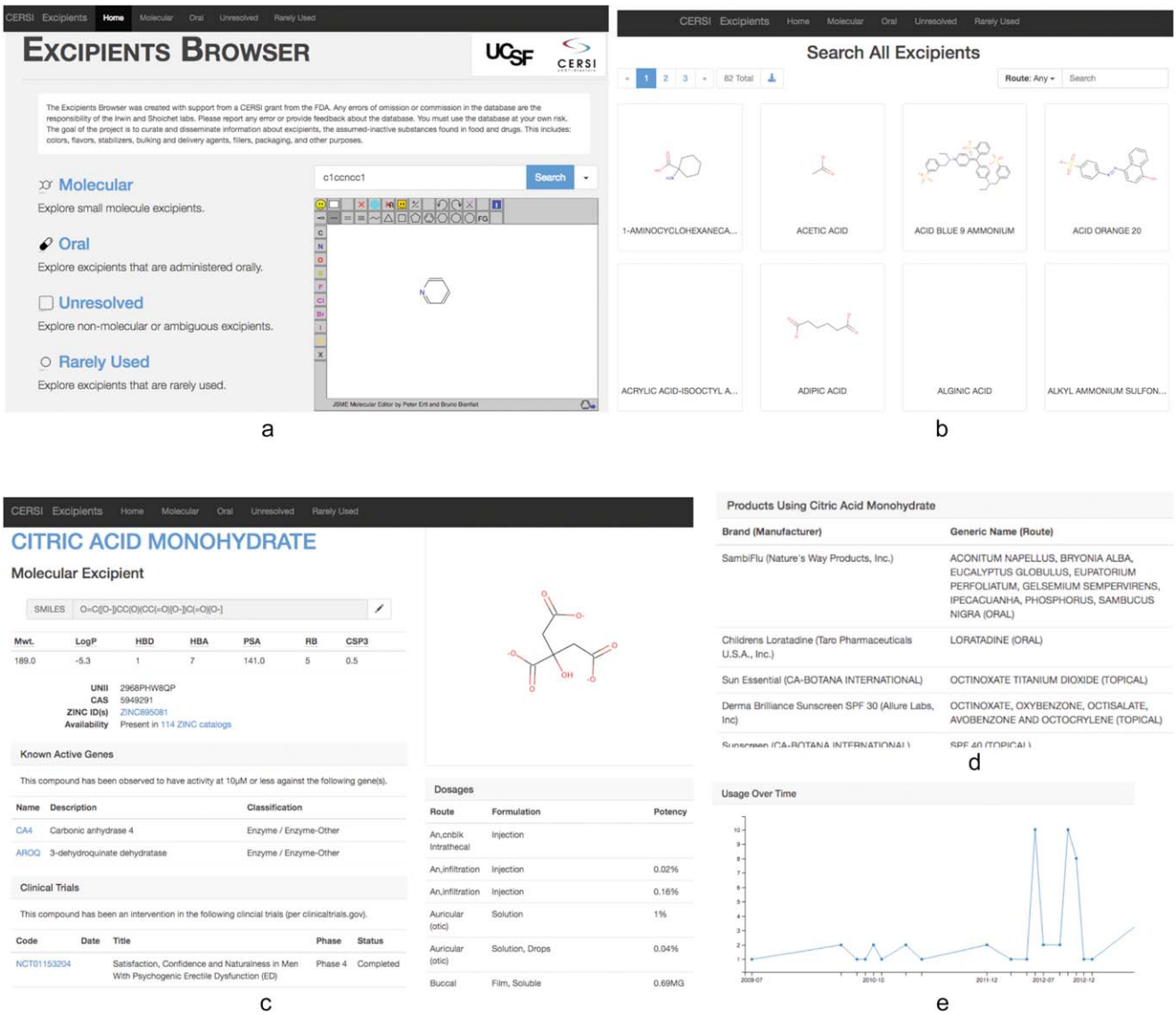

Figure 1 A public access browser for molecular excipients and their properties. **a**: Landing page (http://excipients.ucsf.bkslab.org/) allowing browsing and searching, here by structure using pyridine. **b**: The first 8 of 82 FDA-approved molecular excipients containing the word "acid" in the name. **c**: Detail page for one excipient, citric acid. **d**: Continuation of detail page: FDA-approved products using citric acid monohydrate (truncated). **e**: Continuation of detail page: number of formulations approved by the FDA incorporating citric acid monohydrate (truncated, showing July 2009 to December 2012).

represented by multiple dosage forms, and for 539 unique molecular excipients there are over 5,100 records. The chemical structures are not readily displayed in the tool, nor readily drawn into it, making them difficult to search or to cross-reference to other excipients or to other molecules. The IID does not provide physical or chemical properties of excipients, toxicology data, or other relevant information that may be used to judge the suitability of excipients for use in a particular drug. Taken together, this has reduced the utility of the IID as a chemistry-oriented research tool for formulating drug products.

Drawing on the IID, we developed a public access, graphically driven database for interrogating molecular excipients (http://excipients.ucsf.bkslab.org/). From the main landing page (**Figure 1a**) the user can browse by major category or search by excipient name or structure. The browsing entry points are *molecular*, for those excipients mapped to a single molecular species, *oral*, for those excipients in oral formulations, and *unresolved*, containing those excipients that cannot be or have not yet been resolved to a single small molecule structure. To use the search tool, the user may simply enter a name or part of a name. For instance, searching on "acid" reveals 82 excipients, both molecular, with structures, and unresolved, without structures. To search for excipients containing a pyridine ring, the user would draw that ring in the drawing tool and click "Search" to find three excipients.

The user may access a detail page for each excipient by clicking on a displayed excipient (**Figure 1b**). The detail page (**Figure 1c**) begins with descriptive information including name, a 2D depiction, a computer representation (SMILES), physical properties, identifiers such as CAS and UNII, and a ZINC ID[2] which links to purchasing and other information. The

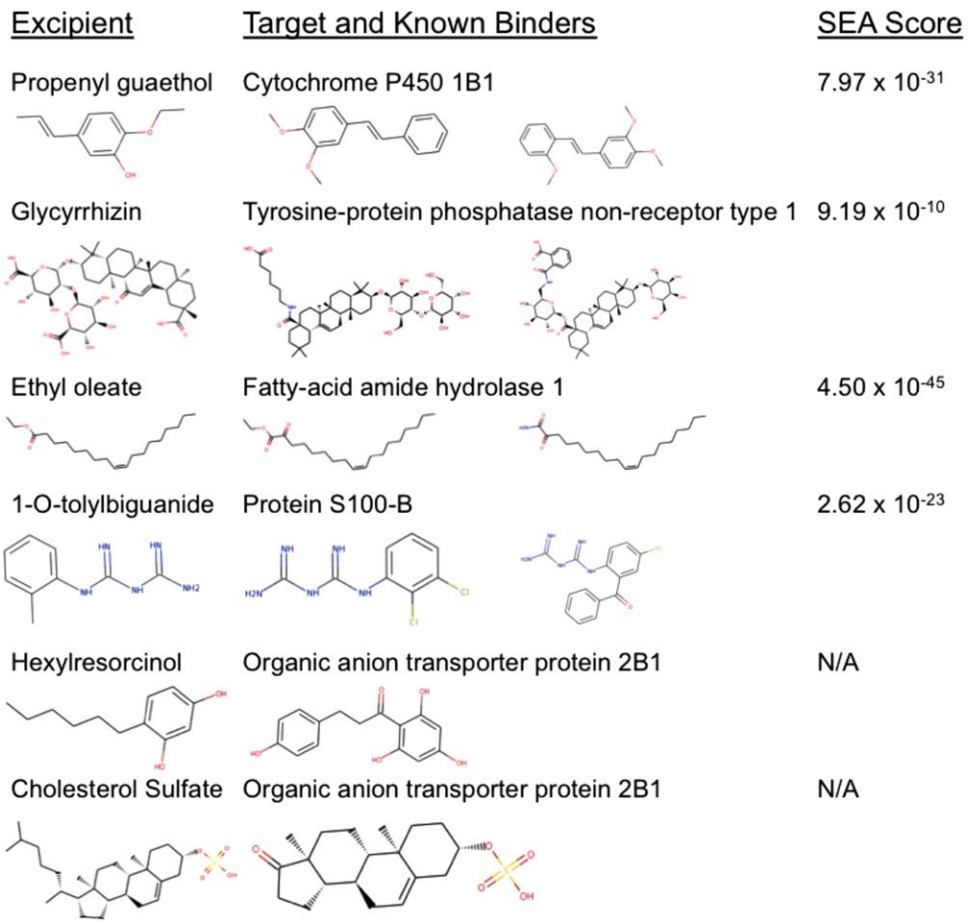

Figure 2 Excipients similar to ligands known for several representative targets.

following additional information may also be available: 1) Dosage information from the FDA IID file, gene targets hit by the compound according to the ChEMBL database (www.ebi.ac.uk/chembl); 2) clinical trials involving this compound (clinicaltrials.gov); 3) products that incorporate this excipient and its usage over time according to OpenFDA (api.openfda.gov). These data enable detailed interrogation of the uses to which the excipients are put, and of their chemical and physical properties and how these relate to other molecules and other excipients.

HOW INACTIVE ARE THEY?

The "inactive ingredients database" reflects an aspect of excipients that is assumed but rarely tested—that they are inactive. Several studies have suggested that at least some excipients do have direct on-target effects, especially on transporters and P450 enzymes.[3–5] With the molecular interrogation enabled by the new excipients browser, we can begin to investigate this systematically. Simple comparison reveals that at least some excipients are closely related to bioactive molecules (**Figure 2**), including drugs, and may share their on-target activities. Comparing excipients to ligands annotated to targets chemoinformatically suggests that over 300 excipients may have activities against hundreds of targets. A systematic and comprehensive investigation of excipient action on targets, which is now computationally feasible,[6] may change our ideas of the direct pharmacology of these molecules. With the ability to pair excipients with the drugs with which they are used, it should also be possible to investigate how the two modulate one another's activity, via the targets that they individually act upon. As excipient targets are developed and enumerated through this resource, cross reactions between drugs and excipients may become apparent.

EXCIPIENTS IN BIOEQUIVALENCE OF GENERIC DRUGS

Generic drug products may use different excipients with the same active ingredient as the branded product, and that may result in bio-inequivalence issues between the generic and the brand name product. That is, the rate or extent of absorption of the active ingredient may differ between formulations. Understanding and predicting excipient effects on bioavailability and bioequivalence would be a critical tool for the generic drug industry to use in their excipient selection and formulation development processes.[7] This is a particular problem for BCS (Biopharmaceutical Class System) class III drugs, which rely on transporters for permeability, and for which excipient activity could have a profound effect on rate and extent of drug absorption. One organic anion transporter highly expressed in the intestine, OATP2B1, mediates the absorption of many BCS Class III drugs. This transporter may be among the first to investigate as a direct target of excipients; any excipient that did modulate it might be reconsidered for the formulation of BCS Class III drugs (**Supporting Information Table 1**). Further, such excipients would not be optimal for

formulations of Class III generic drug products for which the developers have requested that *in vivo* bioequivalence studies be waived. We note that several excipients used with BCS Class III drugs, such as hexylresorcinol, cholesterol sulfate, and metanil yellow, resemble known OATP2B1 inhibitors (**Figure 2**). This similarity suggests a general chemoinformatic approach to the question of what proteins might be modulated by what excipients, an enterprise that may be undertaken at scale by the community using one of several public-access tools (e.g., http://sea.bkslab.org) and the new excipients database (http://excipients.ucsf.bkslab.org).

PROSPECTS FOR INNOVATION IN EXCIPIENTS

If investigating the on-target activities of excipients may illuminate their hidden pharmacology and guide drugs pairing, it will be a restrictive guidance. Almost all the excipients used today have been grandfathered-in from earlier studies. Developing a new excipient requires an evaluation of preclinical data not much different from that used for active ingredient drugs, at least from the standpoint of safety. Any new excipient would be evaluated when it was first included in the formulation of a proposed new drug product. This means that any issue identified with the excipient could jeopardize the entire drug product clinical program and possible approval.

This leaves the field in an awkward state. We know that excipients can make the difference between an effective drug and one that is not exposed at relevant concentrations. We are stuck, however, with a small, static, and aging set of molecules. Worse, we expect the experiments and calculations now beginning to reveal that some of these excipients should no longer be used, or be used only with certain drugs.

Still, we can now interrogate established excipients for chemical similarity, physical properties, and even suppliers, and can bring modern methods to the discovery of new ones. Scientifically, there is much room for innovation, not least because the bar is low. From an economic and a regulatory standpoint, the situation is entangled by the high costs of establishing the safety of a new excipient. Here, it is innovative policies that are required, perhaps involving public–private partnerships, although the path forward remains uncertain.

Goodman and Gilman famously argued that without drug exposure there was no drug efficacy, and that remains as true today as it was 75 years ago. Excipients play a crucial role in modulating drug pharmacokinetics, and formulation can completely transform drug permeability and exposure. Scientifically, we have opportunities for innovation in excipients that we have never previously had. A key will be to match the scientific opportunities with policies that allow them to have the impact on patient health that is so needed.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Additional Supporting Information may be found in the online version of this article.

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Clopidogrel Pharmacogenetics: Beyond Candidate Genes and Genome-Wide Association Studies

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While it is well established that genetic variation is a significant contributor to interindividual variability in clopidogrel efficacy, candidate gene and genome-wide approaches have failed to

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