How sharing compound solubility data can advance drug discovery

Gathering compound solubility data is a key step during drug discovery that helps ensure cost-effective screening, yet it is a long process and is often underestimated in terms of difficulty. Global sharing of such data can help pharmaceutical companies minimise unnecessary expenditures in terms of time, money and resources. This collaborative initiative between research laboratories helps diversify research in the long run and enhances the drug discovery process overall.

By Andrii Lozoniuk

A recent metadata analysis published in 2019 showed that 13.8% of drug development programmes successfully pass clinical trials[1]. This shows a positive trend, having risen from 10.4% in 2014[2]. These numbers are vital for clinical researchers and biopharma investors when making scientific and economic decisions[1] – innovative drug discovery is on the rise and will attain huge commercial benefits in the near future.

One of the reasons for this rise could be that more information is being made publicly available, leading to the development of new and diverse research methods and shortened timelines. This article looks specifically at solubility data, which is an important factor to consider when selecting compounds for screening assays[3].

It is often necessary for researchers to assess solubility for each individual compound before each screening experiment. This can be a time-consuming and expensive process as well as requiring a lot of resources[4]. In some cases, to avoid these expenditures, laboratories might even screen new compounds without gathering any solubility data at all. Tests on these compounds might then fail due to solubility issues, wasting time and resources needlessly[5].

Is this soluble?

An early stage of the drug discovery pipeline involves identifying compounds that interact with the target protein and, therefore, could represent potential drug candidates. There are an almost endless number of compounds available and critical decisions must be made about the compounds chosen, bought and tested, and which of those show the most and least promise.

Knowing compound solubility is an important part of this process since it serves to predict the way compounds react both *in vitro* in terms of drug dissolution as well as *in vivo* to predict bioavailability levels[5]. Potential complications of low solubility compounds affect the entire drug discovery pipeline, from initial screening to the pre-clinical stages. These complications include: precipitation by using the wrong solvent, reduced target specificity, and low bioavailability in animal studies[6]. These compounds, therefore, have a lower chance of passing clinical trials[6] and must be further researched/adapted.

Figure 1
Compound solubility levels
(image courtesy of MolPort)

Assessing the solubility of compounds prior to screening could provide valuable information for adapting the research method, such as the correct solvent for optimal compound dissolution.

For instance, rifaximin is a poorly-absorbed antibiotic that targets the gastrointestinal tract. Small amounts of the more soluble form can significantly alter its bioavailability and pharmacological properties[7]. By adapting the research to the compound, taking into account its poor solubility, the drug now acts as a successful, efficacious treatment providing the intended therapeutic effect.

Solubility should therefore be a key characteristic when choosing compounds, yet it is often overlooked during compound selection and purchasing because there is not enough information available[8]. This essentially forces researchers to assess solubility prior to each screening assay, wasting time and impacting greatly on the efficiency of pharma/biopharma laboratories.

Solubility assessments

There are a number of known methods for determining compound solubility, with some of the main procedures outlined here. There is no 'one size fits all' solubility assay due to various factors such as compound quantity, speed and workflow, which complicates the decision process[9,10]. Different methods are also often used at different stages of drug discovery. Reviewing these methods provides insight into the difficulties associated with determining compound solubility.

The shake-flask method is the current 'gold-standard'[10]. As the name suggests, this method involves shaking a flask containing solute in a chosen solvent and measuring when this saturates.

Advantage

- Known as the most reliable method to date.

Disadvantage

- Extremely time-consuming and labour-intensive for single solubility experiments, sometimes taking several days or even weeks.
- Requires large quantities of the potential drug compound, which can be difficult or impossible to obtain during the early stages of drug discovery.

Another approach uses the solvent evaporation method with an equilibrium 96-well microtiter plate. Solubility is determined through high-performance liquid chromatography (HPLC) analysis[10].

Advantage

- Compared to others, this method removes the need for excessive weighing tasks[10].

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- Suitable for high-throughput laboratories.

Disadvantage

- Accurate dispensing of low levels is difficult.
- Generally, only suitable for low viscosity compounds.
- The equipment required is costly, and so a great portion of costs will go towards the compound selection before compound screening takes place.

Miniature devices are also used where the compound is added to a tube that is later filtered continuously to determine solubility[10].

Advantage

- Small quantities can be tested.
- Results are reliable since the drug slurry is continuously filtered through the tube.

Disadvantage

- Solid dispensing is very slow and therefore time-consuming.
- Expensive equipment is needed with high-level training due to the equipment's complexity, affecting laboratory efficiency.

Reviewing these compound solubility assays highlights the type of difficulties faced by researchers prior to compound screening. To avoid these issues, a collaborative effort is proposed to share solubility data from early testing as a pre-competitive benefit to all.

Some laboratories have already performed solubility assays for specific compounds that they are/have been working with. This existing data can be easily shared with suppliers of the compounds in a collaborative effort to help the research industry as a whole.

Sharing science

In the drug discovery industry, it is a race against time to identify promising leads that can be developed into potential therapeutic drugs. This highly-competitive and lucrative industry often pits researchers from both academia and pharma against each other, competing to forge intellectual property (IP) space and develop the next blockbuster drug[11]. As a result, pharma/biopharma companies, academic and research institutions, and suppliers are understandably protective of their data.

In some situations, however, it can be hugely beneficial to share findings and data. A key example is solubility data, which can help provide information into drug bioavailability and how well it is likely to bind to a target.

Companies that share or make available their experimental data are effectively taking part in the 'open-science' initiative; a relatively novel concept whereby data is shared freely and made available to anyone regardless of organisation background[9]. The initiative benefits the research industry by further expanding specific research fields, increasing the likelihood of discovering and developing novel drugs that tackle major diseases. In addition, overall drug discovery timelines are shortened significantly since data gathering is made more efficient, improving laboratory productivity and saving costs[8,9].

Sharing compound solubility data is the latest request from suppliers and researchers alike[11] to help improve compound screening – a vital step in the drug discovery timeline – for everyone associated with drug discovery. As Dr David Koes, Assistant Professor in Computational & Systems Biology at the University of Pittsburgh, and creator of the Pharmit interactive screening tool[12], stated: "Compound solubility is critical information and companies that have existing solubility data should be urged to share this information to compound suppliers. This collaborative act benefits everyone in the industry since knowing this information in advance makes screening significantly more cost-effective and productive."

For instance, biopharmaceutical companies needing to screen potential cancer drug targets can filter out any compounds with known issues using data shared by other companies. Previously, the unavailability of this information likely contributed to the unnecessary use of resources during many studies as they were likely carried out with compounds that reacted indiscriminately and broadly as a result of insolubility[8].

This approach therefore provides an improvement in efficiency and productivity in the search for novel treatments for some of the world's most serious diseases, such as cancer. This is all through sharing data that otherwise would be generated separately and evaluated repeatedly by each company – wasting a lot of resources and expending costs needlessly, all to obtain the same conclusion[11].

Companies might initially be hesitant to share data due to wanting to protect IP or even exhibiting competitive behaviour that aims to prevent other companies benefiting from their data. However, the reality is that initiating a pre-competitive open-science type initiative, such as the sharing of solubility data, provides opportunities for improvements in efficiency and reduction of unnecessary expenditure. This approach helps diversify research and

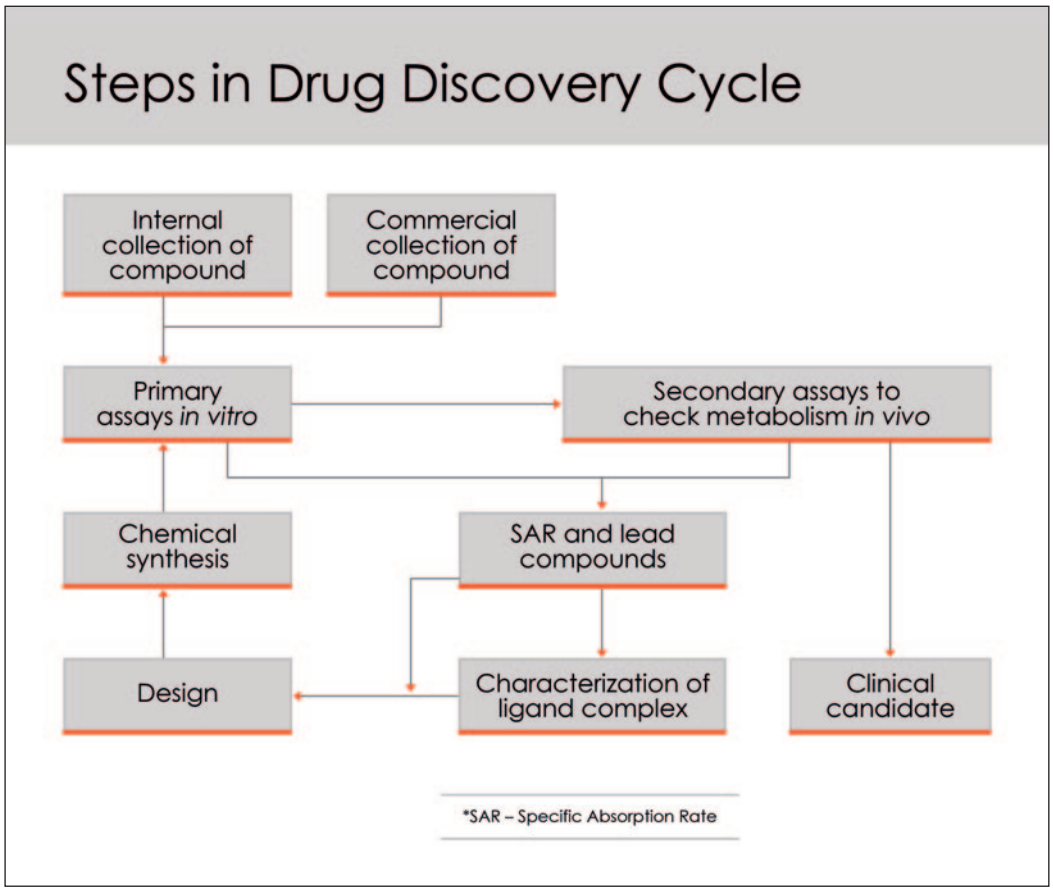

Figure 2
Drug discovery cycle

thereby enhances research fields, raising the potential for more successful drug discoveries in the near future[11].

Supporting the collaborative efforts

A collaborative effort, therefore, has the potential to greatly improve laboratory efficiency when compared to each lab repeating the same time-consuming experiments to gather data for themselves, or even some just buying and testing the compounds via trial and error during compound screening. The initiative can increase the overall pace of drug discovery for all scientists since it saves researchers from needless efforts that might delay the entire drug discovery process.

Some market-leading companies have already begun sharing data, including both compound suppliers and compound consumers.

An advocate for open-science, MolPort, is a platform for compound suppliers that gathers solubility data from its customers to label its products with any solubility issues, if present. Suppliers like this aim to make poor-solubility molecules labelled as such to ensure the most appropriate products are ordered by consumers performing compound screens, thereby avoiding any potential delays to a drug discovery process[8].

Aiming to continuously update and expand compound information, compound suppliers make sure researchers can order the best available compounds for their specific laboratory and study. This builds trust between the suppliers and scientists, and supports the industry in shortening drug discovery timelines and building customer confidence in their products.

The use of these types of compound suppliers is supported in a 2019 study by Antolin, Workman and Al-Lazikani, who suggested that researchers should avoid general search engines and vendor catalogue information as they are likely to provide incorrect data regarding their products[8].

Professional compound suppliers, therefore, become the best option for scientists to obtain compounds with accurate product information – saving laboratories time, cost and resources that would be otherwise spent on ordering and testing unsuitable or unreliable compounds.

GlaxoSmithKline (GSK) is one example of a major pharmaceutical company that also supports the open-science initiative. For instance, a recent

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investigation into the less-studied protein kinases as potential cancer drugs is being openly shared to expand the research fields. Scientists all over the world now have the chance to develop various approaches to tackle this deadly disease. The CEO of GSK, Sir Andrew Witty, stated: "I want my scientists to be exposed to as many great and diverse ideas as possible"[11].

With both suppliers and consumers collaboratively sharing science with each other to better the research industry, many long-term benefits are coming their way. For instance, diversifying the research fields through sharing science will lead to a large return on investment from novel drug developments, as well as adding substantial value to society[11].

Overview

Obtaining accurate and pharmaceutically-relevant drug solubility data is a necessity in the drug discovery pipeline, but is also challenging and should not be underestimated. The costs to research laboratories can be great and potentially unnecessary, with many labs performing solubility tests on numerous, and potentially the same, compounds prior to screening.

Sharing solubility data early provides a pre-competitive benefit to all and can therefore help alter the way research is done, making the industry as a whole more collaborative and, ultimately, productive and profitable. Overall, through the combined efforts, scientists can shorten timelines, reduce expenditure and save resources, thereby boosting productivity and efficiency. So far, only a few companies are already sharing these data, including various compound supplier platforms and consumers that buy and study specific compounds for their discovery pipeline.

If taken up by drug discovery laboratories around the world, this collaborative effort could help expand numerous research fields – shortening library-to-lead timelines, creating more novel drugs, and potentially finding solutions to diseases that heavily impact society today. DDW

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