DRUG SOLUBILITY
Utilising a high throughput screening platform to determine the optimum pharmaceutical excipients in the development of liquid formulations

EXECUTIVE SUMMARY
Drugs are small molecules or macromolecules with their own characteristics and properties. The aim of dosage form design is to achieve the satisfactory performance of the molecules, in terms of safety, quality and efficacy, in a formulation under physiologic conditions. Some molecules introduced to the portfolio have very challenging properties and a major hurdle faced by many companies today is the very low aqueous solubility. Despite the superior pharmacological properties of these molecules, they risk withdrawal from drug development because of their poor aqueous solubility. The principle strategies for improving the solubility of these compounds include either solid form manipulation using amorphous, salt or cocrystal form, or solvation methods using excipients that can solubilise the drug compound, for instance co-solvents, surfactants and cyclodextrins.

At early phase development, testing the toxicological profile, bioavailability and pharmacokinetic (PK) of drug molecule relies on using liquid formulations. Traditionally selection of solubilising excipients involved an empirical experiment i.e. a trial and error based method. Developers formulate candidate compounds into liquid formulations by doing a solubility test for the molecule with an excipient to find its solubilisation capacity. Such experiments are expensive and time consuming. Furthermore, the risk of missing the best possible formulation is high.
Recipharm has developed a fully-automated, high throughput screening process that can assess the solubility of candidate compounds and identify the most effective excipients with which to prepare liquid formulations in just two to three days.

OVERVIEW OF CURRENT APPROACHES TO ENHANCING SOLUBILITY

According to the US Food and Drug Administration’s biopharmaceutics classification system (BSC), chemical compounds can be classified according to their fundamental parameters, aqueous solubility and intestinal permeation\(^1\).

The ideal drug ingredient has good permeability, the ability to cross membranes, combined with the solubility required to achieve the desired therapeutic efficacy. However, in practice ideal compounds are rare. According to widely cited research, around 40% of approved drugs are poorly soluble\(^2\). The study also suggests 90% of drugs in development pipelines are poorly soluble.

A variety of factors favour the selection of poorly soluble candidates during drug discovery, from industry’s focus on larger more complex molecules that are less likely to face generic competition through to its desire for lower dose, higher potency compounds.

A range of methods can be used to enhance drug solubility. Chemical modifications, like the creation of pro-drug or salt versions of a candidate compound, are common approaches\(^3\).

Another approach is to enhance solubility by making physical modifications to the candidate compound. Combining an insoluble API with a soluble material allows the active to enter solution\(^4\). Similarly, creating a solid dispersion – a mixture of drug particle and a hydrophilic matrix that dissolves in liquid – has been used to make solutions of insoluble compounds\(^5\).

Other solubility enhancement methods include the use of carrier systems that encapsulate the insoluble compound or the use of solvents that force it to move into solution.

The problem is that, while various methods are available, selecting the most effective excipient for a particular compound is time consuming and costly. What works for one candidate may not be as effective for another, which means developers are forced to try a range of different approaches.

Another challenge is that candidate drugs are usually costly to produce, which means the API is often in short supply. This is an issue because any additional formulation developed requires the use of more material. Furthermore, creating and analysing multiple liquid formulations takes time, at least three to four weeks, which increases staff-related and reagent costs.

Current estimates suggest it takes 15 years and $1.5bn to create a new medicinal product so, at face value, taking an extra four weeks to identify the correct excipient may not seem significant. However, delays during early phase development are amplified. In addition, selecting molecules with optimum properties among a selection of structures is necessary at this stage.

And because drug companies rely on the revenue they generate, anything that delays launch impacts revenue, and is a significant risk for future R&D efforts especially at the early stage.
HIGH THROUGHPUT SCREENING FOR EXCIPIENT SELECTION

Automating excipient selection using high throughput screening (HTS) has the potential to significantly cut costs and timelines. Also reducing the number of experiments needed to identify the most effective solubility enhancing excipient means less API is required.

Similarly, a high throughput approach allows for different liquid formulations of a compound to be tested in parallel, thereby reducing the time taken to complete the analysis. Furthermore, the use of automated liquid handling technologies can shorten the duration of such research considerably and eliminate manual handling errors.

In addition, automated HTS has the potential to provide more complete information on the candidate molecule than an unconnected series of experiments selected on the basis of trial and error.

Ultimately, automation can cut development time and allow the compound to get to the next stage and market fast, which is beneficial for patients and allows developers to derive greater returns from their R&D investment. This could impact the drug development market in the long run and has potential to reduce the cost of medicines.

ESTABLISHING A NEW METHODOLOGY

Developing a robust HTS platform for excipient selection required considerable effort and experimentation. The primary goal was to prove the approach was at least as effective as traditional methodologies, with the ultimate aim being to demonstrate it is faster and cheaper.

The approach was used to examine the solubilisation capacity of 30 different excipients – from water soluble organic solvents and non-ionic surfactants to cyclodextrins and phospholipids – for six chemically diverse drugs.

The experiments were run in parallel in 96 well-plates with each test formulation being dispensed using a Tecan automatic dispenser. Each plate was shaken for 48 hours to ensure the solution was at equilibrium.

The research established the solubilisation capacity of each excipient when combined with a range of different types of active ingredient. These results were compared with solubility measurements performed using a manual shake flask method where 15mg of powder and 2mL of excipient were added.

In addition, the samples were shaken for 48 hours, centrifuged and then analysed by high-performance liquid chromatography (HPLC) to determine whether the solubility of the compounds in the excipient had changed.
EXPERIMENTAL FINDINGS

The results showed the automated HTS approach identified the best excipient, in terms of solubility enhancement of insoluble drugs with diverse properties, at least as effectively as manual methods.

The high throughput approach also generated data much faster than manual methods. It took between three and five days to generate results for each set of compounds tested, which is a significant improvement on the three to four weeks seen with manual methods.

As expected, it was noted that the drug’s properties have an impact on the solubility. The solubility of compounds with strong lattice (high melting) properties appear to improve dramatically if they are converted to an amorphous form. Also, properties like logP (partition coefficient) and pKa (acid dissociation constant) have a pronounced impact on the solubility of the compound.

CONCLUSIONS

Knowledge of the candidate compound’s solubility is vital for it to be turned into an effective drug. Excipients can be used to enhance the solubility of an insoluble compound, however, current methods used to select these excipients are imprecise, time consuming and costly.

HTS using automated technology is as effective at identifying the best excipient as manual methods. It is also faster, less materials intensive and provides a more detailed range of information.

The approach has the potential to help drug companies to further reduce development times and to make candidate selection decisions faster. Ultimately the method could help bring drugs to market fast.
ABOUT RECIPHARM
Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 5,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 20 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, we conduct our business as we always have and continue to deliver value for money with each customer’s needs firmly at the heart of all that we do. That’s the Recipharm way.

REFERENCES

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