INTRODUCTION

Oral drug delivery is generally considered to be the most common route of drug administration, due in large part to the fact that it offers major advantages, such as self-administration, non-invasiveness and cost-effective production. Oral delivery constitutes about half of the total drug dosage forms in use today. In 2017, the US FDA approved 46 drugs, of which 24 were oral dosage forms. As a drug traverses the gut, it encounters various environments, enzymes, pH media, microflora, etc. The drug dissolves, solubilises and then permeates through cellular membranes to impart its action. This seemingly simple process is jeopardised when a drug undergoes first-pass metabolism, does not dissolve or has permeability issues, and such cases are not rare. About 17% of clinical attrition is attributed to pharmacokinetic and bioavailability issues.

The biopharmaceutical classification system (BCS) was introduced in 1995 and continues to be a reference for preliminary evaluation and categorisation of drugs as soluble, permeable or otherwise. In vitro and in silico tools have added advanced predictability to the drug discovery and development process. Yet still the challenge of poorly soluble drugs with bioavailability issues remains under resolved.

"Ideally, a holistic plan to evaluate and address bioavailability challenges should be devised at the initial drug development stage."

One major reason attributable here is the way in which drug development is currently happening. The focus of lead selection and optimisation is to show pharmacological activity at target sites/receptors (biological selectivity and specificity). For this, lipophilic ligands are added to drug structures, which in turn generate highly lipophilic drugs that present challenges of solubility in biological fluids. This problem is usually only identified in late clinical stages, while during preclinical in vivo and in silico testing the early formulations are either solutions in solvents, surfactants, etc, or the issue is masked by a low drug dose. To a large extent, enabling formulation interventions can address solubility and bioavailability challenges of drugs. Time to evaluate the need for such interventions is critical.

Ideally, a holistic plan to evaluate and address bioavailability challenges should be devised at the initial drug development stage. It is easier to make process changes when the product is in the drug substance development stage than in the drug product. Two examples of processes which could potentially benefit the drug development process are the use of crystallisation models for small size crystals, which could avoid micronisation, or the evaluation of various solid forms, which could help select more soluble forms, such as an amorphous form. "Formulate-ability" can be better assessed if an integrated approach is followed from drug discovery to drug product development.

THE SCIENCE OF SOLUBILITY

A combination of prognostic and diagnostic tools would be required for assessing the solubility and bioavailability challenges of a drug. One of the first steps is to determine solubility. It is important that the solubility testing is performed in the relevant media, representing the physiological environment that a drug is likely to encounter in vivo. Intrinsic dissolution testing, pH solubility
profile and solubility in simulated fluids (gastric, intestinal, etc.) can provide valuable information as to whether a drug has a solubility and/or bioavailability challenge and, if so, what the cause may be.

The possible causes include solvation-limited solubility (grease ball drugs that have high log P/log D values, i.e. >3) and solid state-limited solubility (brick dust drugs that have a high melting point, i.e. >200°C), both of which need to be addressed with enabling formulation strategies. Few drugs have characteristics of both classes, i.e. high log P values and high melting point like levothyroxine (log P 4.6 and \( T_m = 235^\circ C \)) and are therefore difficult to formulate. Increasingly the role of in silico tools, in vitro tests and computational predictions have to play is being recognised.

Bioavailability is an important pharmacokinetic parameter that defines the fraction of drug reaching systemic circulation. Various factors, physiological and physicochemical, affect bioavailability. When devising a strategy for enhancing bioavailability, it is important to identify the reason bioavailability is low in the first place. Formulation interventions are better suited to situations where bioavailability is a function of drug’s dissolution and solubility. Permeability modulations, though possible, are not very easy to achieve because of the multiple factors that exert influence in this area.

FORMULATION INTERVENTIONS FOR SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

As per the BCS, class II and class IV drugs are amenable to formulation interventions for solubility and bioavailability enhancement (Figure 1). Selection of appropriate formulation strategy would depend on the following considerations:

- **Stage of drug development where formulation is required:** At the early stages of drug development (preclinical and before), availability of limited drug quantities and constraint of time and money necessitate that a simple, reproducible and physico-chemically stable formulation is developed. From Phase I onwards, a more in-depth study is possible and various formulation strategies could be evaluated. However, if a solubility enhancement is applied at later stages, it calls for a bridging study between the early- and late-phase formulations, which would obviously result in additional work and cost.

- **Purpose of formulation:** It is important to understand the purpose of a formulation development, e.g. a toxicology study requires the maximum exposure of a drug, a Phase I study is for dose ranging, Phase II requires a composition that is closer to the market product, etc. Each phase has clear objectives and a fit-for-purpose formulation should be designed. Accordingly, the approach that is utilised for enabling formulation development needs to be considered.

It would be appropriate at this juncture to state that any enabling formulation approach needs to distinguish itself as discovery formulation, preclinical formulation or clinical formulation. Until late-stage clinical study, it is preferable to keep the formulation as simple as possible, mainly for the following reasons:

- Addition of many additives/excipients would require extensive drug excipient compatibility studies.
- Complex technologies would require a lot of work on the process, its optimisation, scale-up, etc. This would delay the drug to dosing stage.
- Until Phase I/IIa, formulation development is an iterative process which could involve various changes to the target in vivo profile of the drug. Therefore, investing in sophisticated product design/process would not be appropriate.

There are various tools that are utilised to support the decision of which enabling formulation approach should be selected for a poorly water-soluble drug. Formulation scientists are moving towards a more

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**Figure 1:** The BCS system of drug classification.
structured and predictive model. A few important tools are:

- High throughput screening (HTS) of physicochemical and biological properties
- Mini-scale preparation, in vitro testing and ex vivo studies
- Guidance maps
- Decision trees
- Computer modelling and simulations.

Drug classification systems are also evolving from the BCS to the developability classification system (DCS). The DCS was devised by Butler and Dressman and it subdivides class 2 into 2a (dissolution rate limited) and 2b (solubility limited), further guiding the decisions for appropriate enabling formulations.

Thoroughly knowing the drug molecule is the best way to identify and resolve solubility and bioavailability challenge.

AMORPHOUS SOLID DISPERSIONS

In recent years there has been a surge in the utilisation of amorphous solid dispersion technology. In spite of the challenges of solid state stability, it is continuing to garner the attention of researchers...

"In recent years there has been a surge in the utilisation of amorphous solid dispersion technology. In spite of the challenges of solid state stability, it is continuing to garner the attention of researchers..."
From laboratory-scale screening to clinical and commercial production, this approach requires a sound understanding of factors such as chemistry, polymer science, analytical characterisation and engineering. Also, the characterisation requirements (Table 1) require a deep scientific understanding. Therefore, integrated organisations that have the necessary capabilities for development, manufacturing and analytical characterisations in-house are well suited to take on such products.

**CONCLUSION**

Most technology-based products add some complexity in development but have the potential to provide enormous benefits in terms of product intellectual property and limited competition. It is worthwhile to assess and utilise technologies like ASDs, which could be used as early as the preclinical phase and eventually transform into commercial products. Regulatory authorities are encouraging well-controlled, process-based products through initiatives supporting continuous manufacturing and application of process analytical technology (PAT) tools.

In the next few years, amorphous solid dispersion technology is likely to see greater technical advancements.

The views and opinions expressed in this article are solely those of the author and are not necessarily shared by Dr Reddy’s Laboratories or any other organisations with which the author is affiliated.

**REFERENCES**


**ABOUT THE COMPANY**

Dr Reddy’s Laboratories Ltd is an integrated pharmaceutical company, committed to providing affordable and innovative medicines for healthier lives. Through its three businesses – Pharmaceutical Services & Active Ingredients, Global Generics, and Proprietary Products – Dr Reddy’s offers a portfolio of products and services including APIs, custom pharmaceutical services, generics, biosimilars and differentiated formulations. The company’s major therapeutic areas of focus are gastrointestinal, cardiovascular, diabetes, oncology, pain management and dermatology. Dr Reddy’s operates in markets across the globe, including the US, India, Russia & CIS countries and Europe.

**Table 1: Typical analytical testing parameters and methods for ASDs.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Analytical Method</th>
<th>Test Information</th>
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<tbody>
<tr>
<td>Preliminary Screening</td>
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<tr>
<td>Glass forming ability (GFA)</td>
<td>DSC</td>
<td>Glass transition temp. (T&lt;sub&gt;g&lt;/sub&gt;)</td>
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<tr>
<td></td>
<td></td>
<td>Onset temp. of crystallisation (T&lt;sub&gt;c&lt;/sub&gt;)</td>
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<td></td>
<td></td>
<td>Onset temp. of melting (T&lt;sub&gt;m&lt;/sub&gt;)</td>
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<tr>
<td></td>
<td></td>
<td>Enthalpy of melt ΔH</td>
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<tr>
<td>Thermal stability</td>
<td>TGA/DSC</td>
<td>Decomposition temperature</td>
</tr>
<tr>
<td>Solid state</td>
<td>PLM</td>
<td>Amorphous/crystalline</td>
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<td></td>
<td>XRD</td>
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<tr>
<td>Moisture sorption</td>
<td>DVS</td>
<td>Moisture sorption</td>
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<tr>
<td>Stability in aqueous pH solutions</td>
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<tr>
<td>Stability in organic solvents/co-solvents</td>
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<td>Related substances/stability</td>
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<tr>
<td>Miscibility in polymers</td>
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<tr>
<td>Dissolution in simulated media</td>
<td>HPLC/UV</td>
<td>Assay</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Related substances/stability</td>
</tr>
<tr>
<td>Stability (shelf life)</td>
<td>Mouthfeel</td>
<td>A drying, puckering and shrinking sensation in the oral cavity causing contraction of body tissues.</td>
</tr>
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<td>Advanced Characterisation</td>
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<td>Thermodynamics of drug-polymer interaction</td>
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<td>Relative interactions of prototypes</td>
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Rashmi Nair is Senior Scientist (Pharmaceutical Product Development) at Dr Reddy’s Laboratories Ltd. She is a qualified pharmaceutical professional with supplementary roles of lead technical associate to business and certified in intellectual property/patents.

In the last decade of her work at the Custom Pharmaceutical Services (CPS) division of Dr Reddy’s, she and her team have worked with various innovator companies from the US, Europe and Asia Pacific for development of proprietary technologies and have specialised in bioavailability enhancement techniques for new chemical entities and repurposed drugs in clinical studies.

The focus of her work, as reflected in her international papers and presentations, has been to highlight importance of simplified innovation and integrated development between chemistry, pre-formulation, formulation and manufacturing teams.