THE SCIENCE OF SOLUBILITY AND THE SUCCESS OF AMORPHOUS SOLID DISPERSIONS

In this article, Rashmi Nair, Senior Scientist, Formulation R&D, Dr Reddy's Laboratories, discusses the persistent challenge presented by poorly soluble drug formulations in oral drug delivery. Furthermore, she goes on to highlight the promise shown by amorphous solid dispersions, despite the difficulties they present.

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.[1]

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.[2]

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.[3] Yet still the challenge of poorly soluble drugs with bioavailability issues remains under resolved.

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.[4] To a large extent, enabling formulation interventions can address solubility and bioavailability challenges of drugs.[5] 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."

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.[6]

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

Rashmi Nair
Senior Scientist, Formulation R&D
T: +91 95 5055 7976
E: rashmin@drreddys.com

Dr Reddy's Laboratories Ltd,
Custom Pharmaceutical Services
JP Nagar, Miyapur
Telangana, 500049
India

www.drreddys.com

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.[7] 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°C) and are therefore difficult to formulate.[8] Increasingly the role of *in silico* tools, *in vitro* tests and computational predictions have to play is being recognised.[9]

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.[10] 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).[11] Selection of appropriate formulation strategy would depend on 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,[12] which would obviously result in additional work and cost.

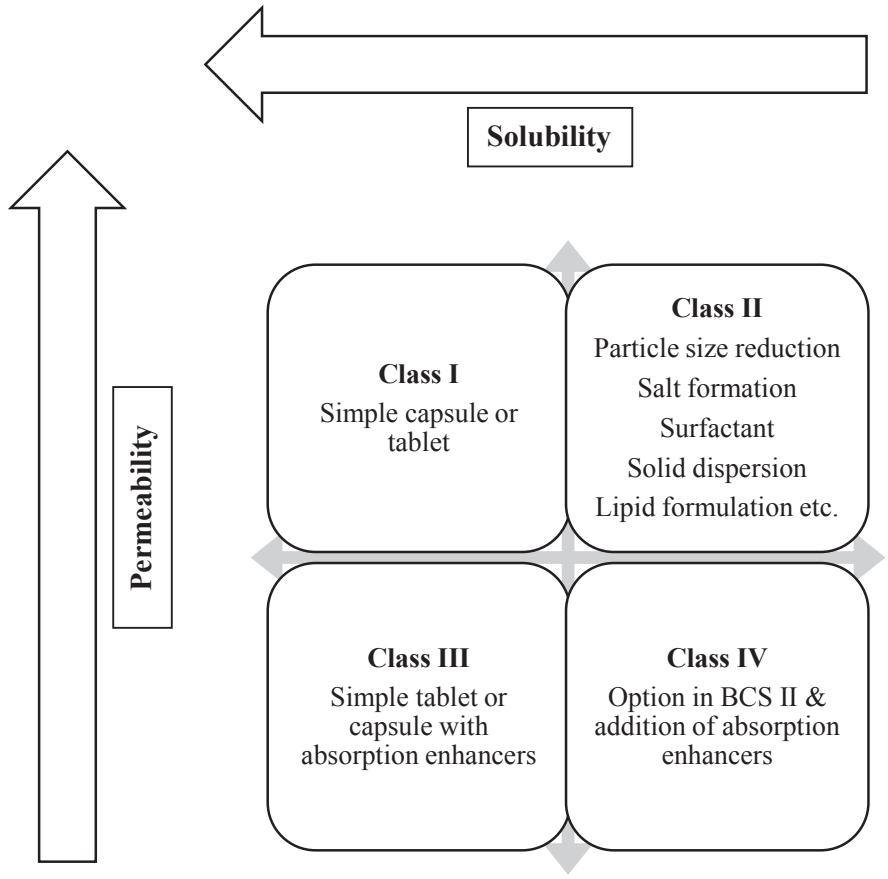

Figure 1: The BCS system of drug classification.

> "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..."

- **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,[13] preclinical formulation[14] or clinical formulation.[15] 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.[17] Formulation scientists are moving towards a more

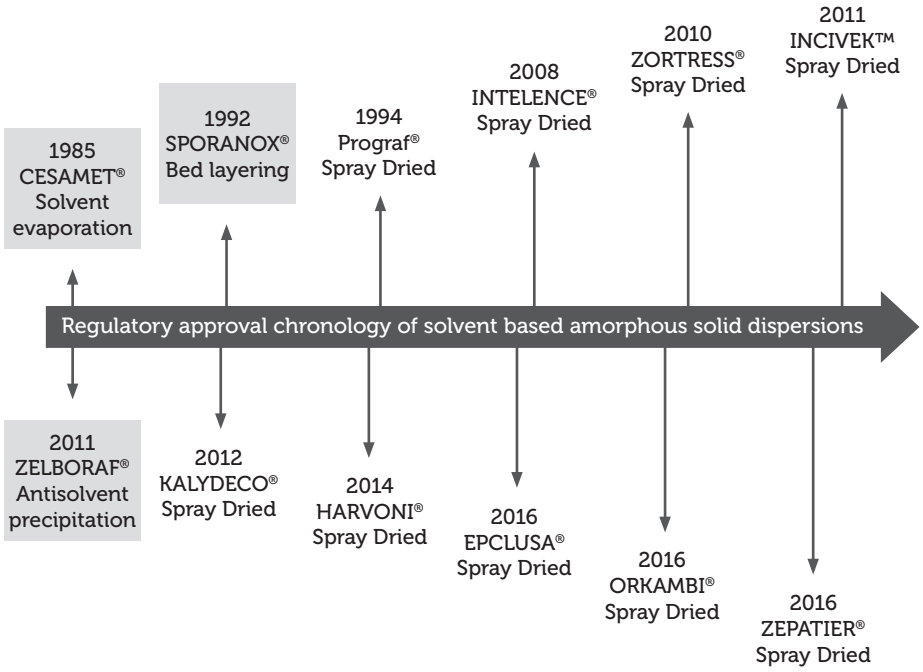

Figure 2: Chronology of product approvals for solvent-based ASDs.

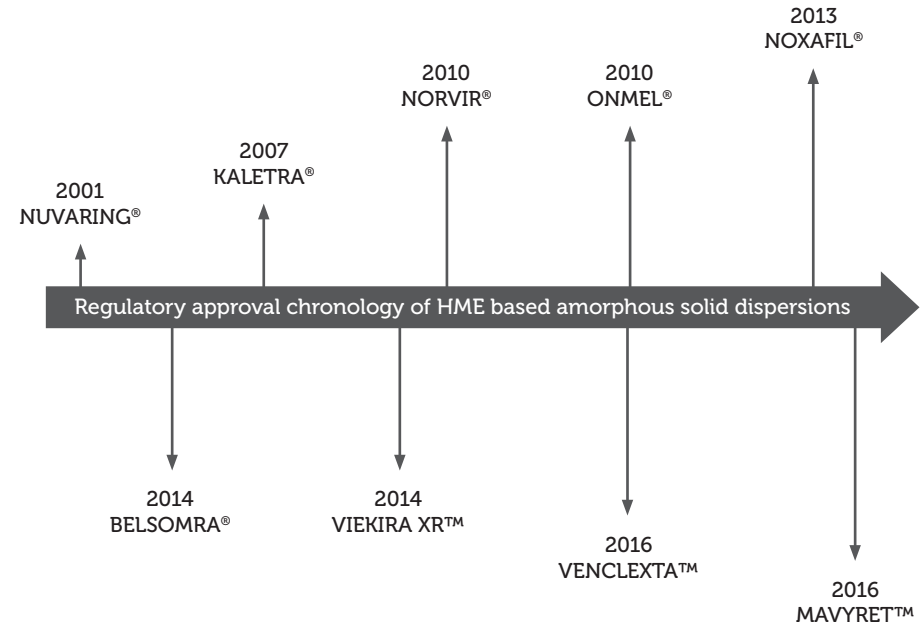

Figure 3: Chronology of product approvals for hot melt extrusion-based ASDs.

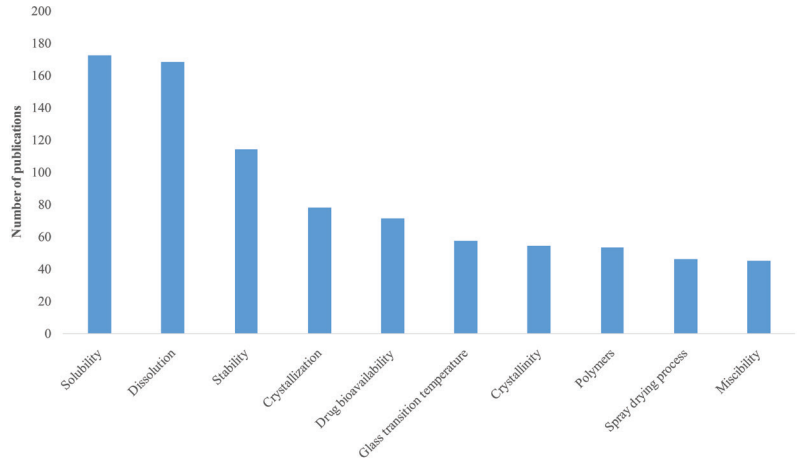

Figure 4: Top ten areas of research in ASDs.

> "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..."

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[18] 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 (ASD) technology. In spite of the challenges of solid state stability, it is continuing to garner the attention of researchers, a fact which is evident from the success of products that are majorly produced by solvent-based methods (Figure 2) or using hot melt extrusion (Figure 3).

An interesting point to note here is that a lot of research is directed towards certain particular areas which are process oriented (Figure 4), using ASDs as an intervention to the challenge of poor drug solubility and bioavailability. Particularly, hot melt extrusion is drawing lot of attention considering its ability to offer continuous manufacturing and in-line analysis.

Parameter	Analytical Method	Test Information
Preliminary Screening		
Glass forming ability (GFA)	DSC	Glass transition temp. (T_g)
		Onset temp. of crystallisation (T_{cr})
		Onset temp. of melting (T_m)
		Enthalpy of melt ΔH
Thermal stability	TGA/DSC	Decomposition temperature
Solid state	PLM	Amorphous/crystalline
	XRD	
Moisture sorption	DVS	Moisture sorption
Stability in aqueous pH solutions	HPLC/UV/HSM	Assay
Stability in organic solvents/co-solvents		Related substances/stability
Miscibility in polymers		
Dissolution in simulated media	HPLC/UV	Assay
		Related substances/stability
Stability (shelf life)	Mouthfeel	A drying, puckering and shrinking sensation in the oral cavity causing contraction of body tissues.
Advanced Characterisation		
Thermodynamics of drug-polymer interaction	FTIR	Chemical mapping
Relative interactions of prototypes	FTIR/NMR/Raman	Spectral imaging

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

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.

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.

REFERENCES

1. *Mullard A, "2017 FDA drug approvals". Nat Rev Drug Discov, Feb 2018, Vol 17(2), pp 81–85.*
2. *Aungst BJ, "Optimizing Oral Bioavailability in Drug Discovery: An Overview of Design and Testing Strategies and Formulation Options". J Pharm Sci, Apr 2017, Vol 106(4), pp 921–929.*
3. *Ayad MH, "Rational formulation strategy from drug discovery profiling to human proof of concept". Drug Deliv, 2015, Vol 22(6), pp 877–884.*
4. *Bergström CAS, Charman WN, Porter CJH, "Computational prediction of formulation strategies for beyond-rule-of-5 compounds". Adv Drug Deliv Rev, Jun 2016, Vol 101, pp 6–21.*
5. *Buckley ST et al, "Biopharmaceutical classification of poorly soluble drugs with respect to "enabling formulations"". Eur J Pharm Sci, Sep 2013, Vol 50(1), pp 8–16.*
6. *Butler JM, Dressman JB, "The developability classification system: Application of biopharmaceutics concepts to formulation development". J Pharm Sci, Dec 2010, Vol 99(12), pp 4940–4954.*
7. *DeBoyace K, Wildfong PLD, "The Application of Modeling and Prediction to the Formation and Stability of Amorphous Solid Dispersions". J Pharm Sci, Jan 2018, Vol 107(1), pp 57–74.*

8. *Di L, Fish PV, Mano T, "Bridging solubility between drug discovery and development". Drug Discov Today, May 2012, Vol 17(9–10), pp 486–495.*
9. *Fridgeirsdottir GA et al, "Support Tools in Formulation Development for Poorly Soluble Drugs". J Pharm Sci, Aug 2016, vol 105(8), pp 2260–2269.*
10. *Göke K et al, "Novel strategies for the formulation and processing of poorly water-soluble drugs". Eur J Pharm Biopharm, May 2018, Vol 126, pp 40–56.*
11. *Kawabata Y et al, "Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications". Int J Pharm, Nov 2011, Vol 420(1), pp 1–10.*
12. *Kostewicz ES et al, "In vitro models for the prediction of in vivo performance of oral dosage forms". Eur J Pharm Sci, Jun 2014, Vol 57, pp 342–366.*
13. *Ku MS, Dulin W, "A biopharmaceutical classification-based Right-First-Time formulation approach to reduce human pharmacokinetic variability and project cycle time from First-In-Human to clinical Proof-Of-Concept". Pharm Dev Technol, May-Jun 2012, Vol 17(3), pp 285–302.*
14. *Leucuta SE, "Selecting oral bioavailability enhancing formulations during drug discovery and development". Expert Opin Drug Discov, Feb 2014, Vol 9(2), pp 139–150.*
15. *Neervannan S. "Preclinical formulations for discovery and toxicology: physicochemical challenges". Expert Opin Drug Metab Toxicol, Oct 2006, Vol 2(5), pp 715–731.*
16. *Shah SM et al, "Preclinical Formulations: Insight, Strategies, and Practical Considerations". AAPS PharmSciTech, Oct 2014, Vol 15(5), pp 1307–1323.*
17. *Waring MJ et al, "An analysis of the attrition of drug candidates from four major pharmaceutical companies". Nat Rev Drug Discov, Jul 2015, Vol 14(7), pp 475–486.*
18. *Zheng W et al, "Selection of oral bioavailability enhancing formulations during drug discovery". Drug Dev Ind Pharm, Feb 2012, Vol 38(2), pp 235–247.*

ABOUT THE AUTHOR

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.