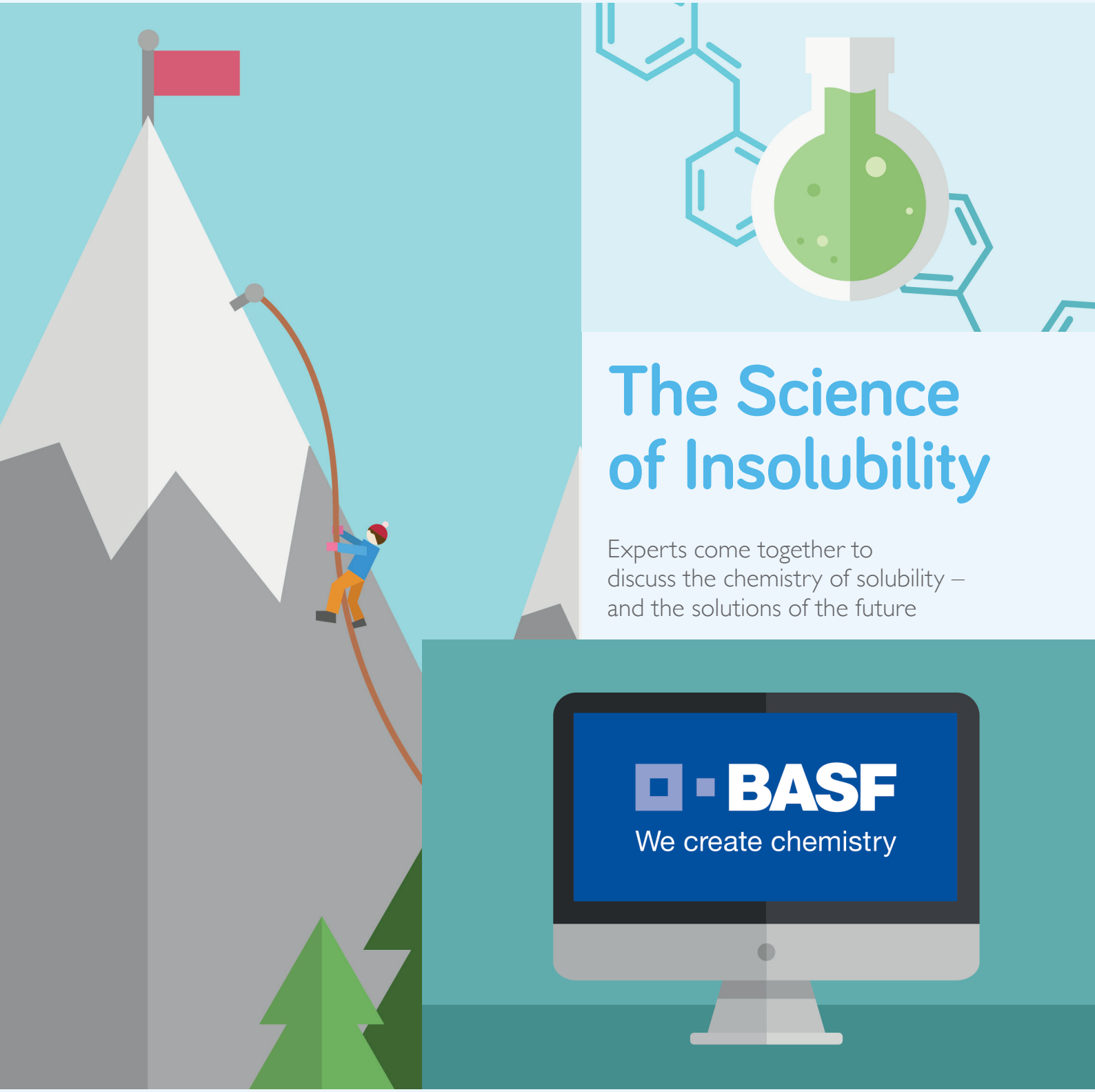


The Science of Insolubility

Experts come together to discuss the chemistry of solubility – and the solutions of the future

The Scientific Approach to Insolubility

Experts continue to unravel the science of solubilization – and their efforts are leading to improved formulations for previously insoluble compounds

Insolubility is a problem that has plagued drug manufacturers since the industry began. If a drug is not soluble then it cannot be absorbed by the body. Traditionally, companies avoided insoluble drugs, but now they are approaching the problem of insolubility with fresh eyes.Today, it is estimated that around 80 percent of compounds in development face solubility issues – and in some cases are almost like brick dust.

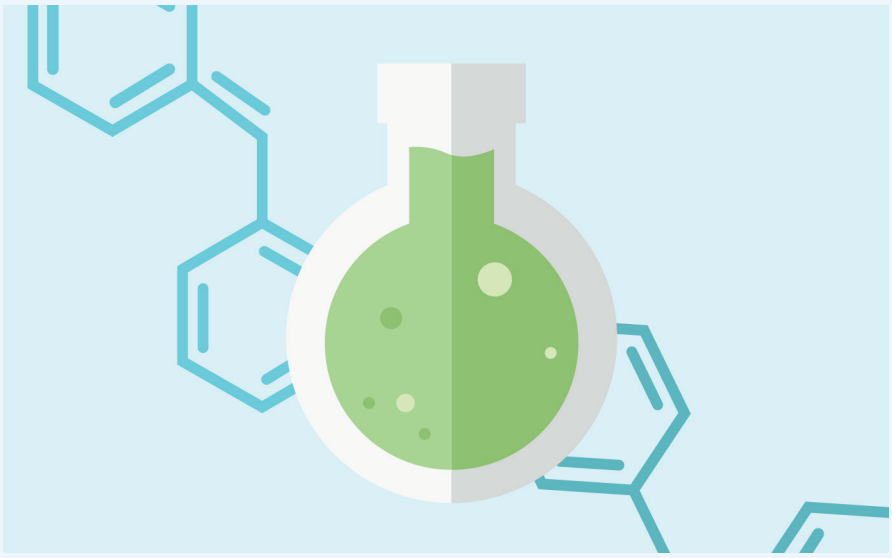
Over the decades, a number of techniques have emerged for tackling insolubility. Popular nontraditional techniques include co-crystallization, amorphous solid dispersion techniques and lipid-based drug delivery systems. These approaches are not just relevant to drugs in development today; a large number of already approved drugs have some form of insolubility or bioavailablility problem, which presents an opportunity for reformulation using newer excipients and solutions to improve efficacy, safety and patient compliance.

The Medicine Maker is delighted to partner with BASF to publish this supplement dedicated to the challenges and opportunities arising from poor drug solubility. Solubility can be considered a well-trodden topic, but on the coming pages experts from BASF and elsewhere in the industry show that this is a vibrant area of research. By delving deep into the chemistry of solubility, it is possible to come up with new, tailored solutions and innovative predictive models that can help during development.

Stephanie Sutton
Editor

Tackling an Insoluble Problem with Chemistry

Managing common solubilization problems requires rare - and sophisticated - formulation expertise



By Shaukat Ali, Andreas Gryczke, Anette Müllertz and Martin Viertelhaus

Aqueous solubility is critical to drug bioavailability and yet the majority of molecules in the discovery pipeline suffer from some form of solubility or bioavailability issue. BASF's own analysis of around 6,000 poorly soluble drugs in the DrugBank open access database suggests that more than 80 percent of drugs are poorly soluble, by FDA definitions. How did this situation arise?

Part of the explanation lies in the drug discovery process, which tends to focus on targets found in lipophilic environments, such as receptors on the cell surface. Hence, lead discovery groups generate molecules that bind lipophilic targets with high affinity, but which are also poorly soluble in aqueous media. Absent effective solubilization technology, compensating for this hydrophobicity may require higher doses, which can come with the risk of adverse effects, variability of absorption, and increased unit costs.

Ensuring that promising drug candidates actually live up to the expectations requires sophisticated chemistry and solubilization strategies. With good formulation, it is possible to control parameters such as re-crystallization (both on the shelf and during gastrointestinal (GI) transit), degradation, and speed/timing of release from the dosage form. Each technology, however, has a different risk–benefit profile. For example, a formulation that provides excellent solubilization may be associated with sub-optimal stability, which may make it more suitable for some applications than others. Picking the right solution demands knowledge of the pros and cons of different technologies, which requires a combination of different types of specialist expertise.

Choose your chemistry

For some active pharmaceutical ingredients (APIs), such as those efficacious at low doses, conventional excipient and granulation technology may be adequate to aid solubility. The vast majority of APIs, however, have properties that demand more sophisticated thinking. In these cases, most companies tend to first consider technologies with a significant track record, since this will generally lead to smoother regulatory approval process and marketing. Established solubilization strategies include amorphous solid dispersion (ASD) techniques, lipid-based drug delivery systems (LBDDS) and modification of the crystalline form of the API, e.g. co-crystallization approaches.

Amorphous solid dispersion

In amorphous solid dispersions (ASDs), the drug is dissolved in a polymer that stabilizes the free energy difference between crystalline and the amorphous states, thereby preventing re-crystallization. ASDs are useful for enhancing the bioavailability of highly crystalline compounds, but may risk some kinetic (shelf-life) instability. Hence, ASD formulations often require additives that inhibit re-crystallization.

The most widely used ASD approaches are spray drying and hot melt extrusion (HME). Spray drying can be used with a range of solubilizers, including Kollidon VA64, Soluplus, PVP (i.e. Kollidon 30) or certain cellulose derivatives. Its scalability makes it applicable both to very small amounts of sample (e.g., for early clinical studies or formulation testing) and to high volume manufacture. Spray drying, however, requires significant solvent use, which adds to materials and process costs, particularly with regard to solvent removal.

HME is a relatively simple process that has the added advantage of being solvent-free. Although the heat required to melt the polymer can potentially degrade the API, formulation expertise can help by exploiting polymers that melt and dissolve the crystalline

Thoughts on Formulating for the Future

ASD

"It may be possible to synergistically use two or more formulation methods in one product; in particular, there is interest in combining methods that improve drug stability in the ASD and keep it in solution, once the ASD polymer has dissolved in the GI tract." *Anette Mullertz*

LBDDS

"One drawback of LBDDS products is their limited shelf-life. Because of this, there is interest in making emulsified systems into tablets. Approaches include the use of microcrystalline cellulose and Aerosil as matrices where self-emulsifying liquids can be absorbed prior to compression into tablets." *Shaukat Ali*

Co-crystallization

"Bioavailability can be increased using a co-crystal of the API. I look forward to the marketing of the first co-crystal product that is made of an old compound, but with lower API content, higher safety and equivalent efficacy." *Martin Viertelhaus*

Models for the future

"Another key trend in terms of solubilization is the development of better in vitro systems to mimic the GI system. New biorelevant media will better reflect the physicochemical constitution of GI fluids, including viscosity, leading to improved tests, reduced use of animals, and improved formulations. Eventually these tests may become automated, thus improving throughput and accuracy. The nearer term is likely to see increased use of algorithms and in silico models to predict how formulation components will behave." *Andreas Gryczke*

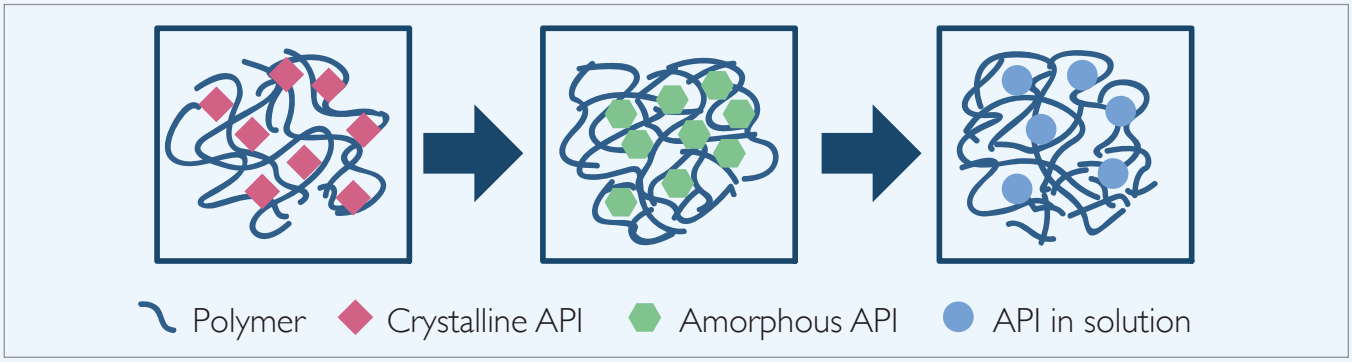
drug below the drug's own melting point. Another potential disadvantage of HME is tablet size constraints. If a formulation requires a high proportion of polymer to stabilize the API in an amorphous form, and if the API must be dosed at high levels, then the resulting formulation volume/dose may be unfeasibly large.

Excipient choice is critical to successful HME formulation, and should be considered from the perspectives of both chemistry and manufacturing processes. Excipient chemistry, such as the number and type of functional groups on the polymer, determines the exact properties of a formulation, including the precise mechanism of interaction with the API. Choosing a polymer with a high glass transition temperature may result in a drug that is kinetically stabilized; nevertheless, the drug remains potentially susceptible to shelf-life issues due to environmental factors that can increase mobility of API within the matrix. This can, however, be avoided by opting for polymers such as Soluplus or the copovidone Kollidon VA64, which support the formation of hydrogen bonds with the API, resulting in stable drug immobilization. In fact, VA64 has become the polymer of choice for many HME formulations because of its melting point of 140–150°C. Drugs with melting points of 200–300°C or more can easily dissolve in the melted VA64 without thermal degradation of either polymer or API. For drugs with low melting points (~ 150°C), Soluplus (melting point 120°C) is more suitable; furthermore, its high molecular weight (118,000) favors stability (increased molecular weight is associated with slower solubilization). Soluplus is also amphiphilic, so it acts as a surfactant; it both stabilizes the API as a solid dispersion and helps to keep the drug in solution, preventing re-crystallization, once the dispersion has dissolved in the GI fluid. By contrast, other formulations require additional surfactants to ensure the drug remains in supersaturated solution until absorbed.

Excipient chemistry also needs to be chosen with reference to ASD manufacturing processes. Although process technology cannot change the potential for a given polymer to dissolve a drug, it can affect the extent to which that potential is realized. For example, insufficient mixing will result in incomplete solubilization of API in the polymer melt, whereas over-mixing can cause shear-related degradation of the formulation. The shear stress experienced by the product is a function both of process (e.g., screw speed and geometry) and chemistry. For example, the higher the polymer glass transition temperature (T_g), the higher its viscosity, and hence the greater the shear stress. Choosing a more viscous polymer will be associated with higher shear stress and higher viscous heat generation in the extruder barrel – and the excessive temperatures can generate impurities that may catalyse drug degradation. Successful formulation therefore relies on striking a fine balance between different parameters, which requires broad experience and know-how.

Lipid-based drug delivery systems

LBDDS are especially suitable for poorly soluble drugs that are lipophilic in the log P range 2-10. As lipids are a natural part of the diet – easily digested and absorbed across the gut wall – LBDDSs are thought to benefit from existing GI processes. Furthermore, LBDDS essentially comprise only four components: API, surfactant/co-surfactant, solvent/co-solvent and lipid,



As the ASD is exposed to water and the hydrophilic polymers are dissolved, the amorphous drug is exposed to media that sooner or later could lead to precipitation, the rate of which will be affected by the polymer'schemistry. This also illustrates the maintenance of supersaturation by the virtue of polymer's ability to avoid API precipitation due to immediate solvation in water.

which is often triglyceride. This simplicity can be a big help in controlling costs.

For a company with a number of pipeline drugs, developing a LBDDS for one drug can have broader benefits, as the formulation may also be suitable for a proportion of the other drug candidates. Nevertheless, the chemistry of LBDDS formulations must be chosen with care. Achieving a two-year shelf-life is a particular issue; avoiding drug precipitation or hydrolysis-mediated drug degradation over this period demands advanced formulation expertise.

Developing the most effective LBDDS for a given API requires broad and deep knowledge of formulation chemistry, particularly the nature and concentration of the surfactant. Furthermore, maintaining the drug in solution as it travels through the various compartments of the GI tract also necessitates sophisticated understanding of excipient qualities, as the formulation must cope with enzymes and dramatic changes in pH or bile salt concentration. Sustained and predictable bioavailability, independent of the exact constitution of the GI environment, is essential to minimize the dose and variability of drug uptake. Again, as with HME, excipients are key; for example, surfactants can absorb at the surface of the lipid carrier and reduce surface tension, assist emulsification and help prevent drug re-crystallization.

Today, Kolliphor RH40 is the gold standard surfactant used in S(N)EDDS because of its stability. It is resistant to lipolysis and hydrolysis, and pancreatic lipases only break it down slowly. As a consequence, it remains intact for much longer than competing products.

Co-crystallization techniques

In some cases, it may be possible to directly modulate the solid-state properties of the drug such that spray-drying, HME and similar procedures are unnecessary. Solubilization strategies aiming at the solid state are well-known; different crystalline forms of an API (polymorphs) have different solubility characteristics, and salts tend to show higher kinetic solubility than neutral forms. Unfortunately, all polymorphs except the thermodynamic crystalline form are meta-stable (and therefore prone to re-crystallize into the stable form) and salts can only be made with ionizable compounds. Co-crystallization, however, which involves two different compounds participating in the formation of a lattice, can provide stable crystal alternatives.

Co-crystallization works with both ionizable and non-ionizable compounds – and this theoretical applicability to every API is a key advantage. Additional plus points include the potential to improve parameters other than solubility or dissolution rate, such as chemical stability, melting point, and hygroscopicity. Such modulations can have knock-on effects in manufacturing too. For example, reduction of hygroscopicity may reduce the need for water-resistant coatings or packaging, and increased photostability may simplify the production process and obviate the need for light-blocking coatings.

The end-product, being a crystal, is usually thermodynamically stable in the solid formulation and does not show re-crystallization. By contrast, methods of increasing solubility that rely on meta-stable solid state forms (meta-stable polymorphs or amorphous forms) are always at risk of re-crystallizing in the formulation during storage and can exhibit reduced shelf life.

That said, finding a co-crystal with the properties needed for a given API requires experimentation and accurate evaluation. Screening for pharmaceutical co-crystals takes about one month, but this is only the first part of the process as it is not yet possible to exactly predict the properties of a given co-crystal. Therefore, once a promising co-crystal is found, it needs to be scaled up and its properties must be analyzed empirically.

Drivers of safety and success

Elegant formulation chemistry is only useful to manufacturers if it supports a safe and cost-effective product that meets a market need. Solubilization expertise, therefore,

should not only be broad and deep, but also rooted in the real world. For instance, when it comes to ASDs, spray drying has theoretical safety concerns in the manufacturing facility, as intensive solvent use carries a risk of explosion. There can also be residual solvent in the product. On the economic side, solvent use is a significant cost-driver, especially if the solvent cannot be recycled. In addition, scaled-up spray drying requires a large machinery footprint, and may even need a new building to accommodate high-volume manufacture. By contrast, HME is very safe and has only a small footprint at large scale. Interestingly, the cost of materials (excipient and API) are much more significant cost drivers than energy use. Given that materials costs are related to process efficiency and wastage rates, this implies that HME costs are a function of operator expertise.

Inappropriate ASD choices may also lead to significant downstream costs; it is not easy to change systems at a late stage in drug development. This is partly because spray-drying and HME produce rather different solid dispersions; spray-dried polymers are relaxed in a different way compared with HME polymers. Also, particle size is established early in the formulation process (if the particles are too small, they form a gel; if too large, they dissolve too slowly) but the optimal size differs between HME and spray-dried polymers. Both ASD and HME can benefit from the economies associated with continuous processing; in practice, however, this requires considerable process expertise.

Looking at the big picture, many HME-processed drugs have successfully reached the market. For example, after launching the Kaletra® capsule, AbbVie developed a second-generation product in the form of a tablet, which used a Kollidon VA64 in Meltrex® technology. This provided several commercial advantages: in particular, room temperature storage instead of refrigeration, and a reduction in pill burden from 6 capsules to 4 tablets.

LBDDSs are largely based on normal dietary components, which means they are generally held to be safe, simplifying regulatory approval and marketing. LBDDSs have cost advantages related to scalability, are straightforward to manufacture and compatible with continuous processing. Most importantly, they are fast to develop; companies with relevant expertise can develop an LBDDS for a small lipophilic drug within a month.

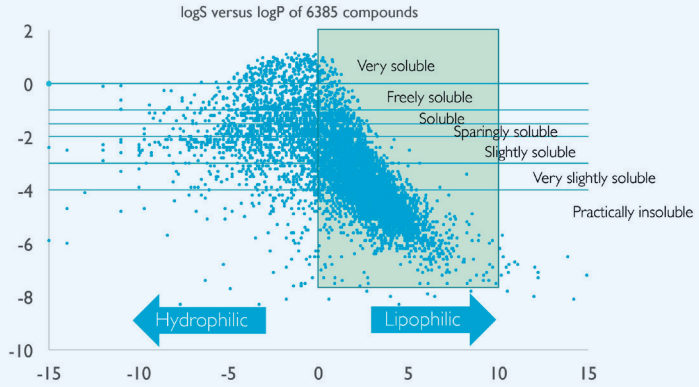
"Looking at the big picture, many HME-processed drugs have successfully reached the market."

Co-crystallization is not associated with particular safety issues; solvents tend to be standard chemicals used in normal API manufacture and are therefore well-understood from a hazard perspective. Monitoring the end-product by NMR, HPLC, powder X-ray diffraction, particle size distribution and dissolution rate measurements is sufficient to ensure that the co-crystal is uncontaminated by previous components of the process. Co-crystallization can be used both at large-scale (either with milling or with a high-volume crystallization system), or at small scale. In the former case, the machinery footprint is no different from the normal scaled-up process (the same vessels are used to make the API). In the latter case, crystallization systems of lower efficiencies are adequate. Co-crystallization therefore may be cost-effective even when only small amounts of material are required. In theory, co-crystallization is compatible with continuous processing; however, there are no current examples of co-crystallization being integrated into continuous processing systems.

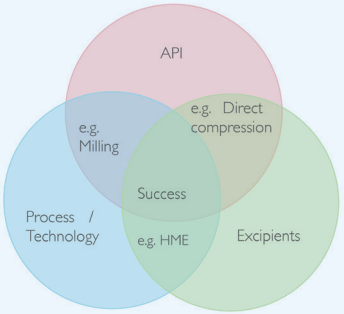
Co-crystallization used for a new API is no different from using a salt. When using a co-crystal approach to make a second-generation drug product, however, the registration pathway is still somewhat unclear, especially as the FDA and EMEA have published white papers specifying different approaches. The EMEA regards co-crystals as being similar to polymorphs and salts (thus, co-crystals are covered under the Drug Substance section of EMEA registration documents), whereas the FDA defines the co-crystal as a molecular association of API and excipient (such that co-crystals are covered under the Drug Product section of FDA registration documents). Also, the process is not dissimilar to making a new salt from a marketed API, and could be subject to similar regulatory requirements. Co-crystals are successfully marketed for agrochemical applications, and the first co-crystal products for clinical applications are now approaching the medical market.

Shaukat Ali is Technical Support Manager for Pharma Ingredients & Services at BASF; Andreas Gryczke is Global Development and Technical Marketing Manager of Pharmaceutical Ingredients at BASF; Anette Müllertz is Professor of Oral Drug Delivery and Industrial Relations at the University of Copenhagen, Denmark; and Martin Viertelhaus is a Research Scientist at BASF.

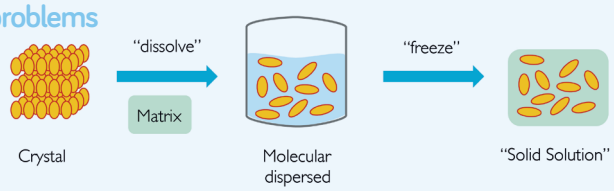
More than 80% of drugs in development are poorly soluble

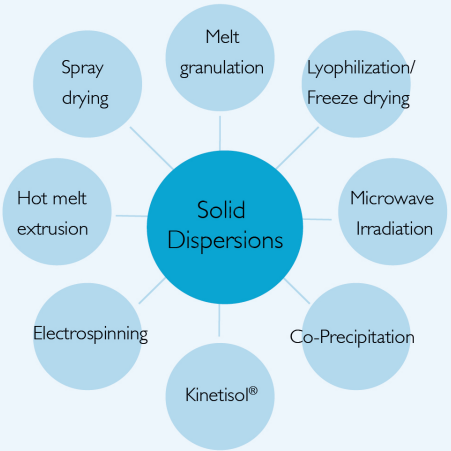


Success lies in finding the right excipients and process for a given API. The challenge is to decide which combination to test, given limited time and resources.

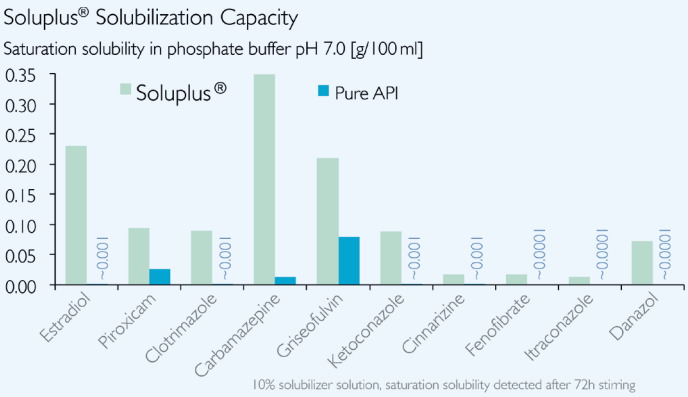


One popular approach to solubilization problems is to use solid dispersion technologies

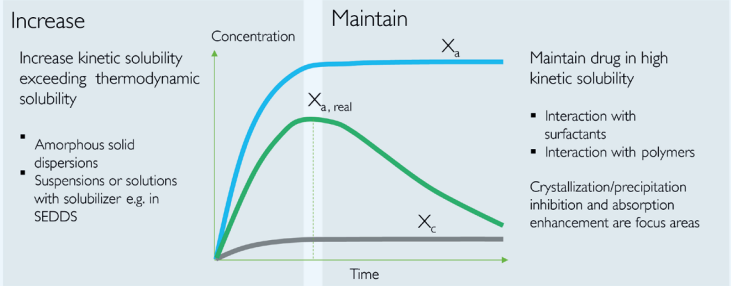




Solid Dispersion Technologies



Excipients bring APIs into higher kinetic energy state and reduce precipitation.



K Kawakami, "Modification of physicochemical characteristics of active pharmaceutical ingredients and application of supersaturatable dosage forms for improving bioavailability of poorly absorbed drugs", Adv. Drug Deliv. Rev., 64, 480-495 (2012). PMID: 22265844

Other successful solubilization techniques include:

- lipid-based drug delivery systems
- co-crystallization approaches.

When working with lipids or amorphous solid dispersion, excipients can make a big difference.

Rising to the Challenge

Competing demands in formulation and manufacturing necessitate a finely balanced approach

By Andreas Gryczke

Andreas Gryczke has over 16 years of experience in engineering and pharmaceutical technology. Today, he is Global Development and Technical Marketing Manager of Pharmaceutical Ingredients at BASF. As an engineer, Andreas finds great satisfaction in solving problems, particularly when it comes to the complex challenges of poorly soluble drugs. Here, Andreas offers an overview of how technologies are evolving and how BASF is helping to lead the way with its solubilization expertise.

How have solubilization technologies and techniques evolved over the years?

The issue of poor solubility has always been a problem in the industry but in the last two or three decades we have seen increasing implementation of solubilization platforms, as well as changes in the organizational structures of pharma companies; these developments allow scientists to focus on the issue of solubility and to identify solutions. Lipid-based systems, solid dispersions, nanocrystals and amorphization are some of the approaches that have seen a lot of attention in recent years.

Most of these drug delivery technologies have existed for a long time, but were perhaps not fully understood until more recently. For example, lipid-based drug delivery systems (LBDDS) are simple to prepare but have required (and still require) a lot of testing to find the composition that best solubilizes a drug. In 1971, Chiou and Riegelman published the first review on ASDs, where they also discussed a griseofulvin-PEG8000 solid dispersion, (which was the first ASD to reach the market) and in the 1980s, BASF began developing pharmaceutical melt extrusion processes. Since then, interest in solid dispersions has continuously grown. From the early 2000s – and especially after AbbVie's launch of Kaletra tablets – people expected a boom of amorphous solid dispersions (ASD); this has not yet happened, but the ASD market share is clearly growing faster than than other solubilization technologies.

What parameters are of importance in formulating a poorly soluble drug?

You have to consider both physical parameters (including aspects of the manufacturing process) and chemical parameters (such as API–excipient interactions). Each formulation process has particular advantages and disadvantages, and a corresponding risk–benefit mix. For example, in hot-melt extrusion (HME), modulation of physical parameters such as extruder screw geometry, screw speed, applied shear stress and temperature can affect the extent to which an API dissolves in a polymer. Extruder screw configuration has a critical effect on the process, and yet I know of cases where companies have never changed it from the factory setting. Poor process optimization can also affect the quality of the extruded product. For instance, inappropriate mixing may leave or generate impurities that then act as catalysts for drug degradation, which can reduce shelf life.

Process optimization must be achieved in the context of a given chemical formulation. Shear stress and process temperatures can be affected by polymer selection; polymers with higher glass transition temperatures generate higher temperatures in the extruder barrel. The operator can set the extruder barrel temperature, but that setting doesn't necessarily reflect the actual melt temperature inside the barrel. Many people do not really understand how to control the process temperature. For example, the viscosity of the melt, and corresponding shear stress and temperatures, can be reduced by addition of plasticizers. If the shear stress is reduced too far, however, the API will be inadequately dispersed. It is a very fine balance.

> *"We have developed an algorithm to calculate the expected range of API solubility in excipients."*

Excipient choice is also critically important, as the drug–excipient combination will influence all downstream steps. For ASD, polymer choice should be made with due reference to the API in question. Melting point is a key parameter. A low melting point API, such as ibuprofen (74°C), will require a polymer of low glass transition temperature, so that the polymer is softened by temperatures below those that would degrade the API. APIs that melt at high temperatures, however, are compatible with polymers of high glass transition temperatures. The ideal glass transition temperature for the polymer is 50-60° Kelvin below the required processing temperature, as this gives reasonable viscosity and torque conditions.

Finally, the chemistry of the formulation should be designed to promote stability in the gastrointestinal (GI) tract to avoid issues with food effects and re-crystallization. Surfactants may be required to maintain solubilization and enhance absorption.

So, both physical and chemical parameters must be well-balanced. At BASF, we often have to optimize client formulation and manufacturing process hand-in-hand by tweaking the fine details of each. This requires significant experience.

How have BASF's products contributed to drug solubilization?

BASF has made significant advances in a number of solubilization technologies, including ASD and LBDDS. We pioneered HME technology in the 1980s, and it's gratifying to see the continually growing market share of ASD-formulated drugs. Early successes included the AbbVie product Kaletra, which used Kollidon VA64-HME to overcome the problems of the previous softgel formulation.

Many competitor ASDs rely on polymers that stabilize drugs kinetically, but this approach is not optimal because moisture uptake or temperature changes will increase API mobility within the matrix and reduce stability. At BASF, we prefer to employ polymers such as Soluplus or the copovidone Kollidon VA64, which form hydrogen bonds with the API. This immobilizes the drug at the molecular level and makes for more stable formulations.

How is BASF responding to new challenges in the pharma industry?

My experience over the last 16 years tells me that the success of a formulation approach depends on know-how regarding both the technology and the precise technology–excipient combination. BASF recognizes this by continually developing and adding to its technical knowledge and expertise, not only in ASD but also in LBDDS and self-nanoemulsifying drug delivery systems. We are helped in this by collaborations with researchers such as Anette Müllertz and Thomas Rades at the University of Copenhagen, Duncan Craig from University College London, and Karl Wagner from the University of Bonn. One of the major questions we are trying to address with our collaborators relates to the respective contributions of the excipient and of the process technology in enhancing solubility.

Also, we are developing predictive models to assess the potential of experimental approaches in advance of empirical testing. For example, we have developed an algorithm to calculate the expected range of API solubility in excipients. The model permits separate assessment of hydrogen bonding between API and matrix; consideration of all possible van der Waals interactions individually; and analysis of novel (as yet unsynthesized) monomer units. It is particularly useful in cases where limited quantities of API make an empirical approach unattractive, and its predictions fit published data (on various hydroconazole-polymer combinations, for example).

What changes do you anticipate for the future?

Novel technologies are appearing in the fields of nanocrystals, electrospinning, and pressurized nanogyration, and alternatives to standard HME are being developed, such as Kinetisol. However, it is not clear if these technologies will ever address anything more than niche applications. Electro-spinning and fused deposition modelling (3D printing) might be amenable to scale-up, but questions remain regarding their potential for high throughput and processing into final dosage forms.

I expect, however, to see biorelevant media that better reflect the physicochemical constitution of GI fluids. These will permit better in vitro testing, which will reduce product variability. And that is important for solubilization because it will allow faster and better screening of new formulations. My personal vision is one of increased automation for in vitro sample preparation and testing, using a broad range of biorelevant media. In addition, there will be increasing reliance on computerized systems, not only for the prediction of physicochemical parameters, but also for the in silico modelling of suitable dosage forms and drug release kinetics.

Finally, we may see attempts to combine technologies in synergistic ways, but I fear that as long as the individual technologies are imperfectly understood, technology combinations have little chance of success.

The Solutions of Today and Tomorrow

Formulation advances come from synergies between theoretical models and real-world experience

Compounds of poor aqueous solubility represent an increasing proportion of the pharmaceutical pipeline. According to Bo Lian, Formulation Scientist at BASF, Tarrytown, USA, solubility is one of the most important physicochemical property of a drug, but as Sam Yalkowsky, Professor of Pharmacy Practice and Science at the University of Arizona, points out, "New drugs are becoming more lipid soluble and less water soluble each year."

Naturally, the industry has responded to the trend by developing advanced solubilization technologies. "Ironically, however, the success of new technologies may actually have contributed to the pipeline solubility crisis by encouraging companies to pursue more poorly soluble molecules," explains Yalkowsky. "Compounds that previously were too difficult to develop into drugs have now become feasible drug candidates."

Nevertheless, over the years, different solutions to the solubility problem have been developed, each with particular advantages and disadvantages. "I believe that an ideal approach is to enhance thermodynamic solubility," says Lian. "It is a true end-point and it can be maintained almost forever since optimizing thermodynamic solubility can, theoretically, provide drug forms which re-crystallize only slowly, or not at all."

Some of the first solubilization advances were in lipid-based drug delivery systems (LBDDSs). "LBDDSs were simple to prepare, but were limited to liquid forms; furthermore, finding the optimal LBDDS formulation for a given API was often challenging," says Andreas Gryczke, Global Technical Marketing Solubilization at BASF, Ludwigshafen am Rhein, Germany. "Alternative avenues of research gave rise to amorphous solid dispersion (ASD) technology, and the first ASD product, griseofulvin-PEG8000, reached the market in the 1960s. Since then, progressively more refined ASD techniques – in particular, hot melt extrusion (HME) and spray-drying – have steadily grown in importance."

Critical to this growth was BASF's pioneering research on pharmaceutical melt extrusion processes in the 1980s, which led to poorly soluble drugs, such as Kaletra® and Isoptin®, being released successfully onto the market. Since then, ASDs have been capturing a growing share of the market.

Formulation innovation

Formulation choices are guided by the precise nature of the solubilization problem. "With a highly crystalline drug, we disrupt the lattice structure to lower the melting point so that it goes into solution more easily," says Lian. "This can be achieved with, for example, HME solid dispersion technology. But with a highly lipophilic drug, solubilization is perhaps best achieved by making its environment even more lipophilic with organic solvents and appropriate surfactants or polymers. For example, cyclodextrins have a non-polar cavity that can accommodate non-polar drugs."

Since many formulation approaches essentially convert the stable, crystalline API into a high-energy state (such as an ASD), the problem then becomes how to maintain solubility over time. Ensuring that a given API remains solubilized from the point of manufacture to the point of absorption in the body requires broad and deep experience with different technologies, excipients and drugs. Diverse knowledge can help in this regard. For example, Lian has a background that includes human genetics, pharmacology and physical pharmacy, which gives him both theoretical and real-world experience. "I firmly believe that knowledge of physiology and of physical pharmacy complement each other in formulation design," he says.

"In silico models can also have advantages beyond guiding choice of solubilization method."

Gryczke shares this belief. "Know-how is crucial for successful development," he adds. Gryczke has over 16 years in engineering and pharmaceutical technology, which he says have given him a valuable perspective on the interplay between formulation chemistry and manufacturing processes.

Where absorption is limited by drug permeability, sophisticated formulation expertise can provide answers. In this context, Gryczke reminds us of the importance of absorption-enhancing

surfactants to overcome permeability issues. More specifically, Lian cites the example of a bifunctional excipient that both acts as a surfactant and also inhibits the drug-efflux activity of the Pgp transporter, thus enhancing net absorption. "In other cases, we use LBDDSs to bypass the circulation and affect absorption via the lymphatic and portal systems," says Lian.

These are just some examples of how industry has met the demand for tailored excipients to solubilize specific APIs. This type of R&D, however, is not easy. "Unfortunately, development of new excipients is expensive, partly due to high regulatory hurdles," says Gryczke. "This situation is driving research into new combinations of approved excipients. Such research, however, although less risky than developing entirely new formulation additives, can be an expensive and time-consuming endeavor. In particular, the empirical approach risks consuming valuable stocks of a new API before finding the right excipient combination."

Prediction paradigm

Gryczke, Lian and Yalkowsky have all put significant effort into developing predictive algorithms relevant to drug solubilization. In silico methods that predict the behavior of new API–excipient combinations can be crucial when it comes to improving the efficiency of formulation development. But how does one design a predictive algorithm and what are the critical aspects of an API that contribute to solubility?

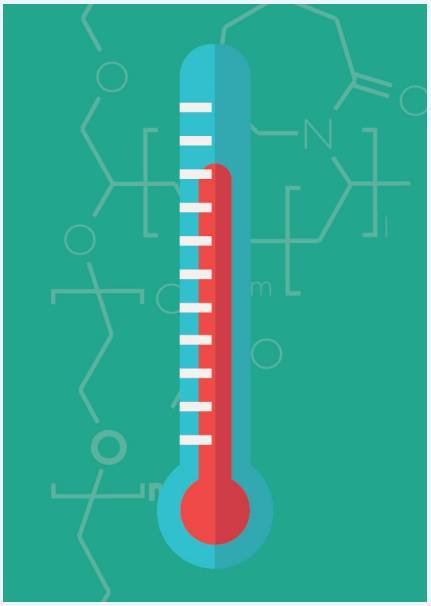
"All the physicochemical parameters of an API are connected. For example, as molecular weight increases, polarity is reduced and the melting point raised," says Yalkowsky.

"Gryczke, Lian and Yalkowsky have all put significant effort into developing predictive algorithms relevant to drug solubilization."

A model being used by Lian correlates drug structures with classic thermodynamic principles by using chemical structure. "This model can generate about 20 important physicochemical properties," he says.

That said, Yalkowsky and Lian believe that lipophilicity and melting point alone are sufficient to provide good solubility predictions for uncharged compounds. Hence, these two measurements are the basis for Yalkowsky's General Solubility Equation (GSE):

the logarithm of the aqueous solubility of a non-ionized species = 0.5 - (0.01 *(melting point -25) - 1 log P)



The equation suggests that for every 100°C increase in melting point, there is a ten-fold decrease in solubility; equally, a ten-fold decrease in solubility follows every log P unit increase in lipophilicity. "This could have significant real-world implications," says Yalkowsky. "With a compound of melting point 285°C and log P of 1, lipophilicity is insignificant – it is the melting point that is critical for solubilization. In this case, it is pointless attempting to improve solubility with co-solvents and surfactants." Conversely, for an API of melting point 120°C and log P of 5–6, solubilization efforts should focus on the solvent, not the crystal.

Similarly, Gryczke has developed a model that predicts API solubility in polymers. "I wanted to know the potential of an HME approach before embarking on it and I didn't like proceeding empirically when the client had only a small amount of API," he says. Gryczke's algorithm is based on Flory-Huggins theory and the Hansen Solubility Parameter, but with additional advantages, including:

- Assessment of the contribution of important hydrogen bonds to immobilization of drug in polymer.
- Evaluation of polymers as monomer units.
- Individual assessment of all possible van der Waals interactions – of which there can be thousands for each drug–monomer combination.

Gryczke's model does not explicitly incorporate estimations of other factors, such as steric hindrance, but its predictions allow for such parameters and fit well with published data. In addition, the algorithm is very fast. "It will screen a huge set of excipients in only 15 to 30 minutes," says Gryczke. "It also permits virtual screening of new polymers by evaluation of new, as yet unsynthesized, monomers. We can combine monomers into new polymers in silico, predict the optimal solubilization excipient for a given API, and run virtual experiments."

And the real-life importance of this model? Gryczke asserts that having a precise miscibility prediction increases the chance of success of a project because you know upfront whether your excipient is likely to dissolve the drug. "For example, I once worked on a client project where the model showed, surprisingly, that the client's API would dissolve in a combination of polymer and plasticizer, although both the polymer alone and the plasticizer alone were non-solvents for the API. That was a striking demonstration of the model's utility," he says.

In silico models can also have advantages beyond guiding choice of solubilization method. Lian points out that a good model can optimize compound synthesis strategy. "Our model is a screening tool. It allows us to focus on compounds with optimal properties." However, he also notes that some models are more useful than others. "For instance, algorithms based on sophisticated machine-learning software are most applicable to well-understood drug structures." By contrast, Lian's models are based on universally relevant principles.

Technologies to watch

How might drug solubilization evolve in the next few years? Gryczke is unambiguous. "The pharmaceutical industry will increasingly adopt computerized tools to predict physicochemical parameters and to support in silico development of dosage forms, such as controlled release systems," he says.

"Formulation choices are guided by the precise nature of the solubilization problem."

Meanwhile, Yalkowsky suggests that this "virtual" approach will be assisted by the massive amounts of data now available to researchers. "You can quickly test new theories against one database or another," he says. "Indeed, my current work – the development of algorithms to predict melting point – benefits from the availability of reference data."

That said, using models can still be challenging. According to Yalkowsky, the three most significant parameters are solubility, partition coefficient and melting point. "The easiest to predict is log P, which involves 3 species: water, octanol and the drug. Solubility involves 2 species - solvent and drug - but is more difficult to predict. Melting point, which involves only the API itself, should be the easiest to predict, but it's the hardest," he explains.

Gryczke also identifies challenges for developers of predictive algorithms. "We still can't predict the stability of an ASD formulation. We can determine if it's thermodynamically unstable, but we can't predict the time course for re-crystallization."

In addition to software development, formulation advances are also inevitable. "Anti-solvent precipitation is interesting, as are new grinding technologies for generating nanocrystal particles," says Gryczke. He cites the pressurized nanogyration technology for making nanofibres, developed at University College London; the Kinetisol® system, an HME alternative high-shear dispersive technology in the US; and other approaches including electro-spinning/electro-spraying and fused deposition modelling 3D printing as being projects to watch in the future.

"Developing a good understanding of the relative usefulness of different excipients used to maintain apparent solubility will be very important."

"I've also noted interesting developments in nanotechnology-based formulation, and the advent of liposomes and niosomes and other novel polymer-based drug delivery systems," says Lian. "If these technologies pass clinical trials, they'll have a significant impact on enhancing the bioavailability of poorly soluble drugs."

Nevertheless, Gryczke is realistic about the potential of early stage technology. "Collecting nanofibres and processing them into a final dosage form may be problematic and scale-up of 3D printing techniques could be challenging," he says. "We don't know if these methods will succeed commercially, or remain as academic ideas or niche applications."

And Lian agrees: "The pharmaceutical sector is highly regulated and relatively conservative. Technologies don't advance overnight and it takes time for new products to get accepted, even when they are of excellent quality."

Looking ahead to the future, Gryczke suggests that solubility enhancement will always remain a challenging discipline in drug development, but expects to see continued significant progress in ASD and LBDDS. Taking a broader view, Yalkowsky suggests that the big challenge of the future is to develop methods of predicting biological activity and toxicity.

Lian points to the enduring problems of enhancing true thermodynamic solubility and maintaining apparent solubility. "True solubility can be sustained, but apparent solubility is a dynamic system likely driven by selecting the right excipients. Developing a good understanding of the relative usefulness of different excipients used to maintain apparent solubility will be very important," says Lian. "Formulation know-how will accelerate development and help us to find many new solutions in the future."

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Solubility Problem Solver

Sitting Down With... Anette Müllertz, Professor of Oral Drug Delivery and Industrial Relations at the university of Copenhagen, Denmark.

How did you get involved in formulation research?

I've always been interested in digestion and in how the gastrointestinal (GI) tract absorbs nutrients and drugs. My career started with a PhD on lipid digestion at the Danish Technical University, and then continued with 9 years at Novo Nordisk, where I worked on lipases. Now, at the University of Copenhagen, I focus on lipid-based drug solubilization systems. But throughout this time, I have also investigated the development of in vitro models that simulate conditions in human or animal GI tracts – and these models have obvious applications in screening new formulations. So I think that my career has had a clear theme throughout.

Why are drug solubilization methods important?

Many of the molecular targets relevant to disease intervention, such as the active sites of cell surface receptors, are found in a lipophilic environment, so drug screening processes tend to identify lipophilic leads that won't easily dissolve in water. But drugs won't be taken up from the GI tract unless they are in solution, so if you want oral formulations of these drug candidates you have to address the solubility issue. And that means having the right chemical tricks to get the API stably solubilized and then efficiently absorbed.

How should drug developers choose a solubilization method for a given API?

That's a good question, but unfortunately I don't think we have the perfect answer yet! This is why defining the optimal formulation method for a particular drug is a major focus of our current research. In particular, we're working with BASF to define the circumstances that would point to a lipid formulation, or an amorphous solid dispersion (ASD), or perhaps some other formulation; however, we are not yet in a position to give clear guidance on this point. In any case, companies will often choose a solubilization technology using criteria beyond those pertaining to the technology itself. For instance, they will take into account their existing manufacturing set-up, their in-house formulation expertise, and so on. So, for any given API, the precise choice of formulation technology will vary between companies according to organization-specific factors.

What are the advantages of lipid-based systems?

Lipid-based drug delivery systems (LBDDSs) simulate food; they exploit natural components of the diet and normal digestion processes, so they are more natural than other approaches. Obviously, when you use them for drug delivery, you add some synthetic components, such as surfactants, but in general it's a very natural approach. In addition, the GI tract is perfectly equipped to handle lipids; it absorbs them with an efficiency of around 95 percent. Of course, there is the potential for drug precipitation when enzymes start to break down the lipid carrier, but our experience is that re-crystallization is rare. In fact, the GI tract appears to provide a good solubilization environment – certainly much better than that represented by our in vitro models. Even when we see precipitation in our in vitro models, we often don't find any interference with in vivo drug absorption.

What are you working on at present?

As well as working to determine which formulations are best for which drugs, we are also working on LBDDSs for oral delivery of peptides and proteins, and on in vitro models that simulate digestion and hydrodynamics in the GI tract. Effective models are especially important when developing controlled release or gastric-retention tablets, as it is vital to understand how the GI environment affects formulation performance. You can't just use simple media in your models, you have to simulate a dynamic environment, which changes continuously due to digestive enzymes, pH modulation, bile salt fluctuations and so on. You also have to consider exactly what you are trying to simulate, such as whether it is the human GI tract or that of an animal model.

As an independent researcher, how do you view BASF's products for drug solubilization?

BASF has some excellent products, both for solubilization and stabilization of amorphous forms. In particular, I have high expectations for Soluplus – I think it has a lot of potential as a polymer that both supports stable solid dispersions and acts as a solubilizing agent by virtue of its surfactant properties. We've successfully used both Soluplus and Kollidon VA64 to stabilize amorphous compounds, and we've also found Kolliphor RH40 and Kolliphor EL very useful as surfactants in lipid formulations. I think BASF is doing a good job in providing excipients to the pharma industry. They are also reacting to the changing demands of the industry by developing new technologies, but of course, getting a new formulation additive to market is a long-term project. It is difficult to get novel excipients through FDA approval.

What changes do you anticipate in the field of drug solubilization?

I believe we will see better decision trees to guide formulation choices for APIs in the context of a desired clinical product. In parallel, I expect improvements in the way we define the optimal product profile for an API, for example in terms of plasma profile. Predictive algorithms and in silico models will be increasingly used, both for simulating the GI lumen and for understanding the interactions of formulation components – with one another and with the environment. Finally, I think we will see attempts to combine LBDDSs with other approaches, such as ASD, to provide formulations with superior characteristics of stability and solubility in the GI tract.

Poorly soluble drugs are one of the major challenges pharmaceutical manufacturers are facing. More and more drugs in development exhibit low solubility. At BASF, we offer a comprehensive range of cutting-edge solubilization polymers, and have an unparalleled understanding of the corresponding process technologies. This unique combination means that we can make sure you achieve effective solubilization across a range of dosage forms – particularly in solid dispersions. Furthermore, BASF is a highly successful pioneer in the application of hot-melt extrusion technology in pharmaceutical production, which helps you combine effectiveness with cost efficiency.

"Selecting the right solubilization product and technology for a poorly soluble API often involves a lot of trial and error. By partnering with our experts, you tap into their extensive solubilization expertise with all key technologies, such as hot-melt extrusion, spray drying, and drug layering."

Andreas Gryczke, Global Development and Technical Marketing Manager, BASF Pharma

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