Issue: June 2015, **Posted Date:** 6/1/2015

SPECIAL FEATURE - Excipients: Enhancing the New, Poorly Soluble APIs

Close to 40% of the currently marketed drugs fall into the two low solubility Biopharmaceutical Classification System (BCS) categories; furthermore, if looking at the pipeline of drug entities under discovery or in development, this number increases to 80%. This trend towards low solubility will see the market for solubility enhancement excipients grow at a compound annual growth rate of nearly 13% in the period from 2014 to 2024.[1] And the overall pharmaceutical excipients market is expected to be valued at $8.43 billion by 2019, up from $5.76 billion in 2013.[2]

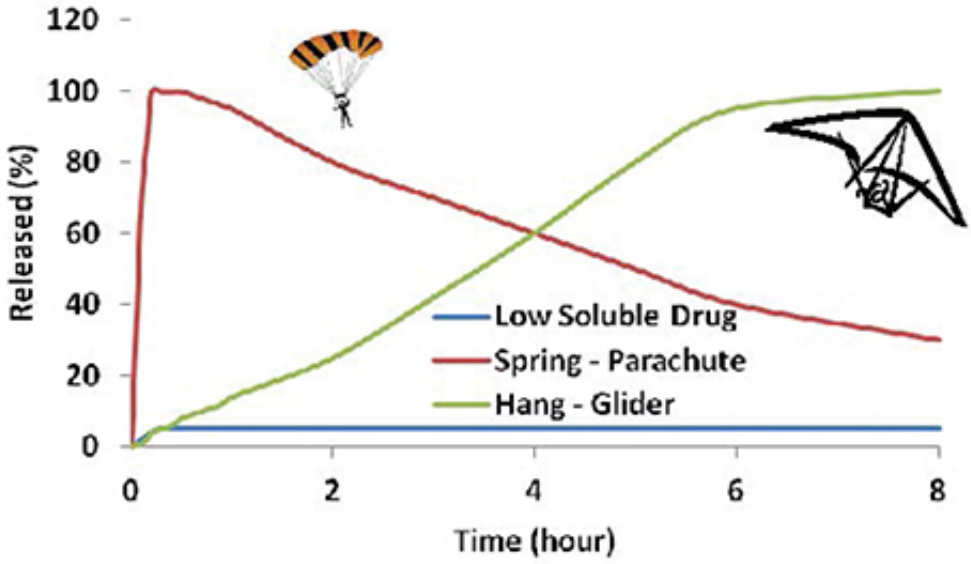
Various techniques are being followed to achieve increased solubility of the drug compounds depending upon active pharmaceutical ingredients (API) characteristics, formulator's capabilities, and relative cost effectiveness of the strategies. Among advanced solubility enhancement technologies, the most important ones are solid dispersions and lipid solubilization. In fact, lipid excipients are the largest category of solubility enhancement excipients because of their large levels of use in drug formulations and their ability to increase the solubility of lipophilic active ingredients. Polymers come in second due to the increasing use of solid dispersion technologies.

In addition to solving solubility challenges, other issues driving the excipient market are an increasing demand for new excipients in drug manufacturing procedures, technological advancement in drug delivery systems, and the emergence of innovative drugs for the treatment of chronic diseases. Moreover, the growing generics market has increased the demand of excipients.[3]

In this exclusive *Drug Development & Delivery* report, excipient manufacturers share their insights about the role excipients play in formulating and manufacturing drugs for improved bioavailability, solubility, and delivery.

Ashland Specialty Ingredients - Bringing Bioavailability Enhancement to a Broader Range of APIs

It is well known that the majority of active pharmaceutical ingredients (APIs) currently in development are poorly soluble. Amorphous solid-dispersion technology has tremendous potential to increase bioavailability and absorption for APIs with poor solubility because it offers improved solubility with limited or no impact on permeability. Over the last decade, Ashland has made significant investments in understanding and developing this technology, particularly through hot-melt extrusion and spray drying.



Hang-glider effect for controlled release of a poorly soluble drug (Ashland Specialty Ingredients).

Vivian Bi, Technical Director, Solubilization and Contract Services at Ashland explains: “A key component of a solid dispersion is the polymer system. Polymeric excipients stabilize the amorphous API in solid state then maintain its supersaturation in aqueous media. Excipients can also be used to control the release once the API is solubilized.”

Ashland has experience with solid-dispersion polymers, such as copovidone and hypromellose acetate succinate, as part of a broad range of cellulose and vinyl pyrrolidone polymers. Over the years, Ashland has developed and characterized hundreds of amorphous solid dispersions. In more than 90% of the studies, a prototype with desirable stability and increased solubility was achieved.

“No one polymer system is a solution for all APIs,” says Dr. Bi. “Ashland provides know-how on polymer selection and expertise to support R&D programs focused on improving solubility. In our Wilmington, Delaware, Center of Excellence, resources are available to conduct proof-of-concept studies to assess solid dispersions and determine if solid dispersion is the right approach for increasing API solubility and bioavailability.”

Initial studies can be conducted with small amounts of API (~10 g) to develop several formulations and select an effective combination of drug and polymer. The study can then be expanded with a design-of-experiments model to optimize the drug load and polymer level. Once the optimum formulation is selected, Ashland scientists can provide scale-up, process development, final dosage form development, and non-GMP manufacturing services for animal toxicology or additional studies.

To demonstrate how controlled release of a poorly water-soluble drug can be achieved with solid-dispersion technology, Ashland performed a study with nifedipine. As with any formulation involving an insoluble drug, the primary challenge was to achieve enhanced bioavailability through solubility improvement, says Dr. Bi. However, in this case there was the additional challenge of sustaining that solubility for 6 hours or more. An amorphous solid dispersion (ASD) of nifedipine in pellet form was developed, resulting in extended release over 8 hours by

combining copovidone and typical controlled release grades of hydroxypropylmethylcellulose (HPMC). This combination was processed with nifedipine in a hot-melt extruder.

Copovidone has excellent extrudability due to its thermoplasticity and HPMC is known for its ability as a crystallinity inhibitor, as well as a controlled-release polymer, Dr. Bi says.

“The aim for this type of formulation is to achieve a hang-glider effect, where the drug is not only solubilized in the immediate term, but also achieves continued release and sustained supersaturation for an extended time,” explains Dr. Bi. “Stable ASDs were achieved at 20% drug loads. In the next phase of the case study, nifedipine release rate was effectively controlled while maintaining supersaturation by varying the HPMC molecular weight.”

BASF - A Focus on Highly-Functional Excipients

BASF offers a range of excipients for immediate and modified release, polymers and solubilizers, as well as excipients and solvents for skin delivery applications. Examples of immediate-release excipients include binders and disintegrants (e.g. water soluble Povidones or Kollidon® grades), water insoluble Crospovidone or Kollidon® CL grades and Copovidone or Kollidon® VA64 and VA64 Fine), and the Kollicoat® IR-based coating systems. Modified-release excipients are derived from a range of chemistries and properties such as Kollicoat® SR30 and Kollidon® SR for controlled release, Kollicoat® MAE30DP/100P for enteric, and Kollicoat® Smartseal for taste-masking as coating polymers for matrix tablets, granules and soft gel capsules, and mannitol-based Ludiflash® for orally dispersive tablets.

Solubilizers are also derived from a range of structures with some having the lipophilic hydrophilic balance (HLB) values 12 or higher. For example, Soluplus® with HLB value of 14 is derived from PEG, which is grafted with vinylcaprolactame and vinylacetate, while Kollidon VA64 (HLB 0) is a random copolymer comprised of vinylpyrrolidone and vinylacetate (60:40). Both these excipients are used as solubilizers for poorly soluble compounds offering unique advantages over many existing polymers in solid dispersions.

“Excipients play an important role in the formulation and manufacturing of pharmaceutical dosages, functionally required either as fillers, binders, coatings, or solubilizers to improve the solubility and enhance the bioavailability of drugs,” says Shaukat Ali, PhD, Technical Support Manager, BASF.

Several excipients have “high functional” roles, meaning if used as binders, they could also be used as solubilizers or vice versa. For instance, Copovidone (Kollidon VA64), which is used as a wet/dry binder, can also be used as a solubilizer for poorly soluble compounds in solid dispersions. “These unique interchangeable characteristics are critical in selecting the appropriate excipients to design and develop the desired formulations to alleviate API-excipient interactions and enhance shelf life while maintaining the integrity and efficacy of pharmaceutical dosages.”

The use of BASF excipients can be best demonstrated in a marketed HIV drug, comprised of two individual APIs, Lopinavir and Ritonavir (Kaletra®). Both are poorly soluble drugs and are marketed in soft-gel capsules and tablets. The patients have to take 6 capsules per day while the solid dispersion formulation requires only 4 tablets per day. Consequently, the pill burden on a patient is less with tablets than soft-gel capsules. Kaletra contains Polyoxyl 35 castor oil in soft gel as self-emulsifying system (SEDDS) while the tablet formulation contains Copovidone as solid dispersion/solution. Another example is Norvir® soft gel, which contains Polyoxyl 35 castor oil, while the tablet contains Copovidone.

“These examples demonstrate the applicability of two high functional excipients as good

solubilizers not only in tableting but also in soft-gel formulations," says Dr. Ali.

Colorcon - Creating Economical, Low Friability Tablets for Film Coating & Packaging

In solid oral dose development, API compatibility will drive the selection of the excipient. Tablets are still the most common solid oral dosage form for many reasons, including ease of manufacturing, convenience for the patient, accurate dose administration, and good stability.

Excipient choices for a formulation are typically driven by functionality requirements and compatibility with the API. For more than 50 years, Starch 1500® partially pre-gelatinized maize starch has had marketed product success in innovator, generic, and OTC market segments across more than 80 countries. When used as secondary excipient, typically alongside microcrystalline cellulose (MCC), Starch 1500 delivers low-moisture activity with good tablet hardness and low friability, which are critical for film coating and packaging of the final tablet, says Deborah Taylor, Global Market Communications, Colorcon.

Film coating of tablets provides benefits for both product development and manufacturing. For the formulator, film coating is included to improve product stability and final product quality, while attaining in-use shelf life. For the manufacturer, film coating strengthens the dosage form, enables improved packaging efficiency, and prevents cross contamination. For the patient, a film coating improves compliance through enhanced swallowability and palatability, and allows for better product differentiation and minimizes medication errors through color and appearance.

"Starch 1500 is manufactured exclusively for the global pharmaceutical industry and provides the formulator with an economical binder and disintegrant option for direct compression, stability for moisture-sensitive drugs through low-water activity, effectiveness for low-dose drugs, and process flexibility for granulation, says Ms. Taylor.

SIDEBAR

NSF International—A New Standard for Pharmaceutical Excipients

NSF International recently published the first American National Standard for pharmaceutical excipients: NSF/IPEC/ANSI 363 Good Manufacturing Practices (GMP) for Pharmaceutical Excipients. This consensus-based standard incorporates multiple regulatory and industry requirements into a single, rigorous standard for the manufacturing and distribution of pharmaceutical excipients. The new standard is designed to help pharmaceutical companies verify GMP compliance and strengthen safety and quality throughout the supply chain.

"It's an important advancement for an industry that once virtually ignored excipients, even though they typically make up 70 to 90% of the volume of most pharmaceutical formulations," says Maxine Fritz, Executive Vice President of Pharma Biotech, NSF Health Sciences.

The new standard raises the bar for excipient manufacturers. Pharmaceutical manufacturers should now require all of their excipient manufacturers to meet or exceed the NSF/IPEC/ANSI 363 standard. Manufacturers of finished pharmaceutical products can do this by auditing their individual excipient manufacturers annually – a daunting task when you consider the number of excipients used in any given formulation. It should be noted that auditing is equally challenging for excipient manufacturers, who may need to host hundreds of audit teams a year.

Auditing excipient manufacturers presents a special challenge because most excipients are manufactured in bulk and sold to many industries, not just the

pharmaceutical industry. The pharmaceutical industry will need to work closely with its excipient manufacturers to ensure they are manufacturing ingredients with the appropriate GMPs in mind.

Fortunately, there is a better way, says Ms. Fritz. In addition to collaborating on the development of the new standard, NSF International developed an excipient certification program. Instead of hosting hundreds of audits a year, excipient manufacturers can now apply for certification from NSF International. Manufacturers certified to the NSF/IPEC/ANSI 363 standard demonstrate that their excipients are manufactured to the appropriate GMPs for pharmaceutical use. "We believe certification will become a competitive advantage for excipient manufacturers and should help eliminate the nearly continuous audit process many excipient manufacturers endure annually."

"This will be an interesting development for excipient manufacturers," says Christopher Wilcox, PhD, Vice President, Sales & Marketing, Pfanstiehl, Inc. "It can only be good for pharma in the long term, as higher quality standards will inevitably translate to safer products for patients. Pfanstiehl has been manufacturing cGMP, injectable-grade excipients for decades in an ICH Q7 compliant environment. We have expected and prepared for these changes for many years and see the industry moving towards treating excipients more and more like APIs, as they should be. The days of sourcing food-grade excipients for pharma applications is coming to an end."

And Shaukat Ali, PhD, Technical Support Manager, BASF, says: "Implementation of recent NSF international guidelines means more empowerment of regulatory authorities and drug manufacturers. The NSF international guidelines also provide increased transparency with excipient manufacturers while minimizing adverse health effects and protect human health, and safety of the drug products worldwide. BASF is committed to adherence to stringent controlled policy by the regulators and other auditing agencies by implementing the validated method standards and protocols to test and qualify the excipients to meet current monographs and follow the guidelines concurrent with the changes in monographs."

Pharmaceutical companies purchasing excipients certified to the NSF/IPEC/ANSI 363 standard can elect to purchase Certification Audit reports. The NSF Excipient Certification Program offers the report purchaser the benefit of initial GMP certification and annual surveillance by expert auditors against the NSF/IPEC/ANSI 363. "Certification combined with an independent audit report provides additional assurance of excipient quality," says Ms. Fritz.

Evonik - Software Screens Polymers to Identify the Best

Partly due to the use of high-throughput screening methods in the drug discovery stage, there has been a recent surge in the number of poorly water-soluble drug substances under evaluation (more than 70% of newly discovered actives). As a result, pharmaceutical formulation development scientists have adopted hot-melt extrusion (HME) and spray-dried dispersion (SDD) techniques in combination with polymeric excipients as the main approaches to improve the aqueous solubility of these APIs. HME and SDD techniques break the strong crystal lattices of poorly soluble drugs under high temperature/shear or through solvation of the API in a highly polar solvent, respectively. The amorphous active is then stabilized in the glassy polymeric excipient matrix through polar, dispersive, and/or ionic interactions, as well as possible hydrogen bonding between the functional groups on the polymer and the active.

When selecting excipients for solubility enhancement through amorphous solid dispersion stabilization, the desired strong interaction between the polymer and the active is often undermined by the random mixing of these components.

Solubility parameters have been used since the early 1900s to identify good solvents for small solutes and polymers. When forming solid dispersions, the solvent and solute roles are inversed as the smaller solute molecule (API) is dissolved in the larger macromolecular polymeric solvent. It is essential to build selection quality into the polymeric excipient-drug combination screening studies by considering the individual molecular structures and potential interactions. Similar to crystalline molecules like table salt and sugar that dissolve in water through ionic interactions and hydrogen bonds, when polymer and active are capable of such bonds, the formation and stabilization of amorphous solid dispersions are enhanced. Hence, pharmaceutical-grade excipient polymers like poly(meth)acrylates (EUDRAGIT®), cellulosics (HPMC, HPC, HPMCAS, HPMCP), vinylpyrolydones (povidones and copovidones) and others should be included in the initial screening studies.

Evonik has been manufacturing EUDRAGIT poly(meth)acrylate polymers (anionic, cationic and neutral) for more than 60 years. This family of polymers has been used extensively in thousands of pharmaceutical product formulations for controlled-release coatings or in matrix applications.

“In addition to hydrogen bonding, polar attraction, and dispersive force potential, EUDRAGIT polymers offer ionic interactions with free-base and free-acid drugs or salts, allowing unique possibilities for solubility enhancement of poorly water soluble actives,” explains Dr. Firouz Asgarzadeh, Director Technical Services, Pharma Polymers and Services, Health Care Business Line, Evonik.

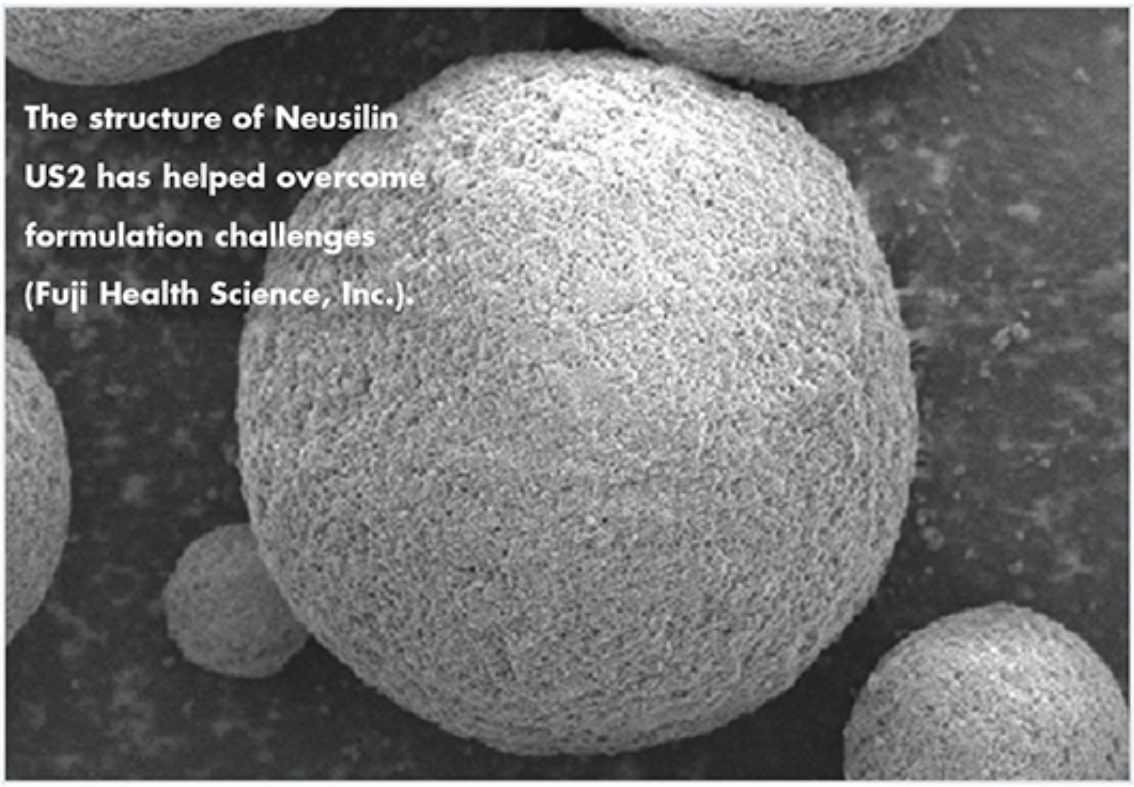
Evonik has developed a platform called Melt Extrusion Modeling and Formulation Information System (MemFis^{TM}) that uses solubility parameter calculations and hydrogen bond formation probabilities to screen 30 different excipient polymers to identify the best 2-3 first experiments for developing solid dispersions.

Evonik has applied MemFis to numerous customer projects. In one recent case study, the customer initiated the screening studies with random mixing of polymers and the active with no success in improving the solubility of a poorly soluble active. The contract research organization that the customer was using referred the client to Evonik to evaluate the MemFis tool. The results from MemFis identified a cationic polymer that was overlooked in the initial random mixture study. The use of the identified polymer resulted in the successful enhancement of API solubility. “The strength of this platform is the unbiased screening of all commercial polymers and not just Evonik polymers,” says Dr. Asgarzadeh.

Fuji Health Science, Inc. - Developing Unique Excipients to Overcome New Challenges

In light of recent solubility and bioavailability challenges, formulators are turning away from conventional fillers or binders and utilizing novel and unique excipients that offer enhanced functionality. A lipid-based delivery system, such as self-micro emulsifying drug delivery systems (SMEDDS), is a promising approach to enhance bioavailability of poorly water-soluble drugs, says Xi Han, PhD, Technical Sales and Support, Excipients, Fuji Health Science, Inc.

One challenge in commercializing this delivery system, however, is that it requires the product to be in a liquid form, such as a liquid-filled capsule or solution. This limitation could result in poor patient compliance or, in the case of liquid-filled capsules, the potential for incompatibilities between the active and the capsule shell.



There is a need for inert carriers to solidize lipid-based delivery systems or convert them to a powder and ultimately tablet form. Two of Fuji's specialty excipients, Neusilin® and Fujicalin®, are made through a proprietary powdering technology, resulting in a high specific surface area with a mesoporous structure. This unique structure provides a high oil adsorption capacity and can convert the lipid-based delivery system into a freely flowing and compressible powder that maintains enhanced bioavailability.

In one example, explains Dr. Han, a customer was looking for an alternate dosage form for a lipid-based delivery system. Their initial trials with a liquid-filled soft gel had stability failures due to an incompatibility between the drug and capsule shell. Various carriers were evaluated to solidize the lipid and Neusilin was determined to offer the best performance in terms of drug loading, dissolution, and tablet hardness without the need for additional binders.

Gattefossé USA - Lipid Excipients for Oral Bioavailability Enhancement

Among the fast-developing approaches that address the challenges presented by the vast number of existing and emerging drug entities is lipid-based drug delivery (LBDD). The field

surrounds novel excipients and formulation technologies based primarily on the function of fatty acids, fatty acid esters, and their assemblies. In recent years, the field has witnessed significant development of methods and predictive tools resulting from industry/academia-wide collaborations that help the design, characterization, and evaluation of LBDD systems in ways that may not have seemed possible a decade ago.

Successful design of LBDD systems requires a clear understanding of two sets of factors: the properties and challenges unique to the drug candidate; and the physico-chemical and biopharmaceutical role of lipids in the formulation, says Jasmine Musakhanian, Scientific & Marketing Director, Pharmaceutical Division of Gattefossé USA.

Lipid excipients are generally considered for their ability to solubilize/disperse the drug molecule in the dose, but more importantly for their impact on the processes that follow *in-vivo*. The primary mechanism for lipid formulation is micellization in the gut milieu by self-emulsification of surface-active lipids and or by digestion of the oily components by bile salts and pancreatic enzymes.

The micellization process leads to formation of lamellar/multi-lamellar micelles with even greater solubilizing properties preventing the active drug from falling out of solution; ameliorating the drug's affinity for the aqueous monolayer lining the intestinal enterocytes; and facilitating the subsequent passage across the lumen due to enhanced membrane fluidity.

Examples of Gattefossé self-emulsifying excipients are Labrasol®, Labrafil® M1944, and Gelucire® 44/14, which form fine dispersions (20-300 nm) once in contact with aqueous media. “A key aspect of excipients like Labrasol and Gelucire 44/14 is their ability to solubilize/disperse the active in the GI milieu and to improve drug permeability by inhibiting/saturating the enterocyte-based transporters,” says Ms. Musakhanian. “This is particularly useful for drugs that have permeability issues.”

Other products like Gelucire® 50/13 and 48/16, due to their solid-state characteristics, are suitable for preparation of solid dispersions by melt extrusion or spray atomization for preparation of self-emulsifying solid dosage forms.

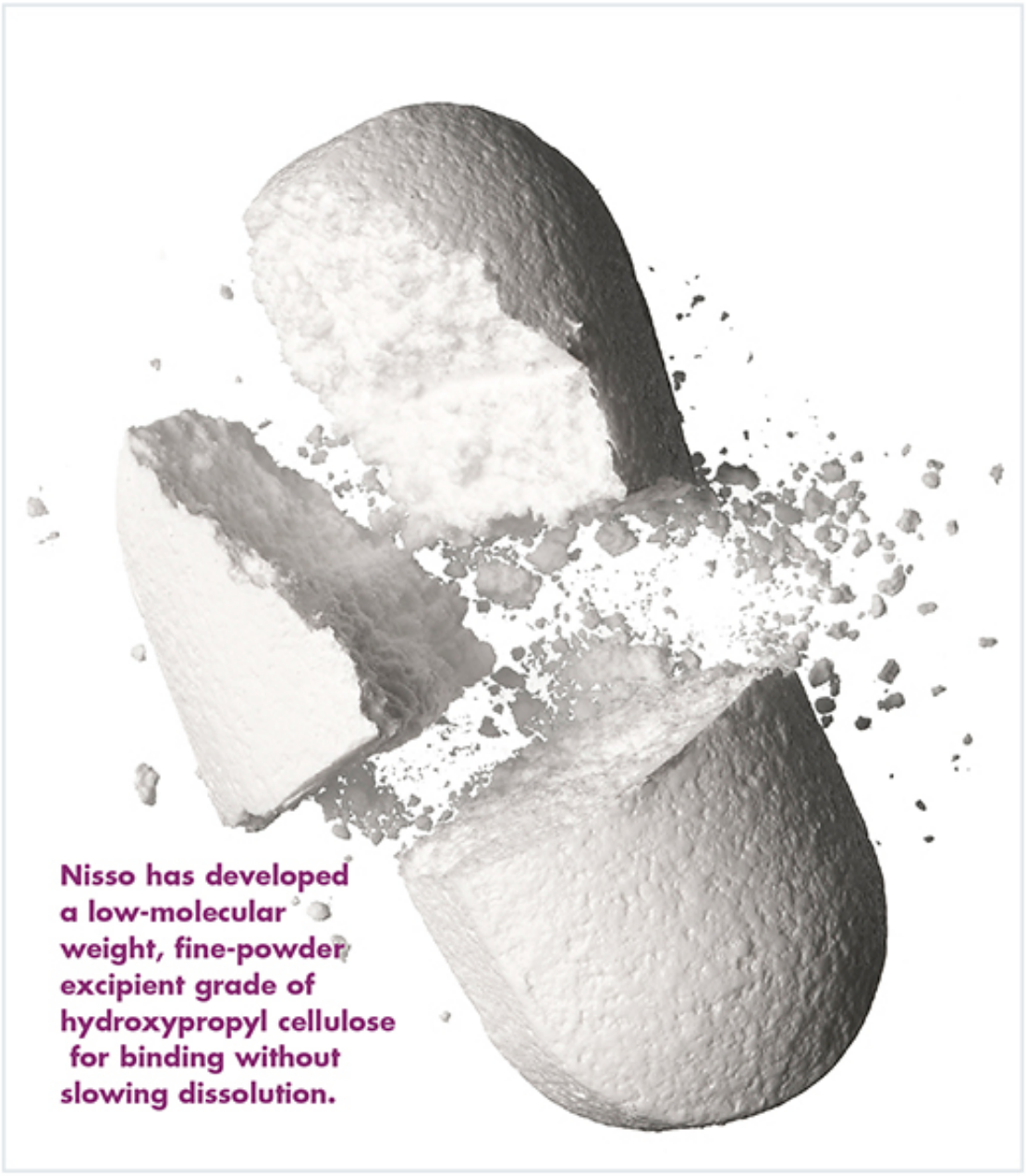
Another important bioavailability enhancing mechanism associated with lipid formulations pertains to the biopharmaceutical role of excipients comprised of long-chain fatty acids (LCFA) like oleate and linoleate. The latter associate themselves with chylomichron synthesis and lipoprotein transport via the lymph, and therefore, are helpful for promoting lymphatic absorption of highly lipophilic drugs that would otherwise be eliminated pre-systemically in the liver. The approach is most effective for delivery of drug actives with log P>5 and solubility of >50 mg/L in triglycerides. Examples of Gattefossé excipients with LCFA’s are Maisine™ and Peceol™.

As excipient choices are often linked to a processing technology, Gattefossé supports its products with application data and guidelines, including direct compression, spray atomization, melt-granulation, fluidized bed coating, and melt-extrusion processes.

Nisso - Manufacturing a Unique Grade of HPC

Nisso has recently announced completion of a hydroxypropyl cellulose (HPC) manufacturing capacity expansion at its facility in Nihongi, Japan. The expansion was completed to respond to the growth in worldwide demand for NISSO HPC. The production facility has multiple lines that operate independently to provide increased supply security.

“Customers appreciate the 5-year shelf life and low lot-to-lot variability of NISSO HPC, while a robust global warehouse and distribution network provides responsive supply to customers with short lead times,” says Mr. Kenji Sugisawa, Global Manager of NISSO HPC.



NISSO HPC is a highly efficient excipient, traditionally used as a tablet binder in pharmaceutical and nutraceutical products, but with growing application in spray drying, hot-melt extrusion, and film formation.

A particular focus of the expansion was to support growth of the new grade called NISSO HPC SSL-SFP, which stands for Super Special Low viscosity, Super Fine Powder hydroxypropyl cellulose. “This grade is unique in the market, as Nisso technology was developed to create the lowest molecular weight of HPC (approximately 40,000 Daltons) for binding without slowing dissolution,” explains Mr. Sugisawa.

The SFP grinding technology is also used to produce an extremely fine powder (d50 approximately 20 microns) for high binding efficiency, while maintaining adequate power flow. SSL-SFP utilizes this combination of low molecular weight and super fine powder to create a new level of performance in HPC.

One customer recently reported using SSL-SFP to rescue a product launch. They found capping problems on scale up and adding 1% SSL-SFP to the formulation resolved this issue without costly and lengthy reformulation,” says Mr. Sugisawa. “Other customers have reported using

SSL-SFP to reduce tablet size for reformulation projects by replacing 15% MCC with 3% HPC.”

A harmonized standard for hydroxypropyl cellulose has been formally approved by the USP Monographs, European Pharmacopeia, and the Japanese Pharmacopeia on December 1, 2014. NISSO HPC produced after that date will conform to the harmonized standard and will make it easier for customers to develop a single product formulation that meets global regulatory requirements, he says.

Pfansthiehl - Carbohydrate-Based Excipients Stabilize & Protectthe API

Carbohydrate-based excipients such as trehalose, sucrose, and mannitol enable formulation scientists to stabilize large and small molecule injectable therapeutics that would otherwise not make it to the clinic due to low solubility and/or bioavailability. The majority of commercialized injectable drugs depend on this class of excipients as stabilizers, tonicifying agents, or bulking agents.

Complex large molecules and cells are often prone to aggregation, denaturation, and/or oxidation. A key function of carbohydrate-based excipients is to stabilize and protect the active ingredient to make sure it reaches the patient, having the same molecular conformation, the same bioavailability, and the same potency every time. In injectable formulations, this means that the manufacturing process used to produce these critical excipients must be exceptionally robust, free of contaminants, low in elemental impurities, and strictly monitored and controlled. High-quality excipients are essential for consistent formulations, as they are almost always present at much higher concentrations than the active itself.

Pfanstiehl manufactures parenteral-grade excipients such as trehalose, sucrose, mannitol, sorbitol, and maltose for use in liquid and lyophilized applications where high quality, cGMP-produced components are required. “Trehalose is particularly effective as a stabilizer for complex molecules and cells under the high stress conditions that most formulations must endure,” explains Christopher Wilcox, PhD, Vice President, Sales & Marketing, Pfanstiehl, Inc.

Trehalose and sucrose are each widely used in commercial monoclonal antibody (mAb) formulations and have also proved beneficial for ADCs, vaccines, and cell therapy applications. Mannitol is widely used as a lyoprotectant and bulking agent in injectable applications. Sorbitol has unique properties that make it an interesting choice for protein and vaccine stabilization.

For one client, an ADC formulation was stabilized best with sorbitol. However, the impurity profile and lot-to-lot inconsistency of the sorbitol excipients available were not suitable for the injectable application. Therefore, the team was going to have to completely reformulate the product or put the program on hold. “We assured the client that this would not be an issue with a cGMP-produced sorbitol excipient, which will be delivered to the client shortly,” says Dr. Wilcox.

Another client was having difficulty developing a platform formulation for stabilizing a range of monoclonal antibodies. Dr. Wilcox says: “As soon as the formulation team became familiar with Pfanstiehl’s cGMP-produced trehalose excipient, they were able to use it across the board as a stabilizer of choice, and gained great peace of mind after seeing their quality issues decrease as a result.”

To view this issue and all back issues online, please visit www.drug-dev.com.

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