SPI Pharma™
Making a Difference
An ABF Ingredients Company

MAKING MEDICINE EASIER TO TAKE

In this article, Graeme Macleod, PhD, Head of Global Research and Development, and Wayne Camarco, Global Head of Technical Development, both of SPI Pharma, discuss the rational design of excipients to meet the needs of patient-centric formulations.

Regulators are increasingly insisting that formulators consider patient centricity in the dose form they are developing. This means, in addition to normal factors such as stability, efficacy, content uniformity, robustness and manufacturability, the organoleptics of the dose form must be considered from the start of any project.

In solid dose form design, there has been a significant increase in the number of patient-centric dose forms coming onto the market to help meet these requirements. Orally disintegrating tablets (ODTs), chewable tablets, granules, resuspendable tablets or granules and orally dispersible powders are all examples of dose forms that help to improve patient adherence, particularly in patient groups – such as paediatrics and elderly patients – where this can be particularly challenging. Patient adherence can be enhanced with dosages that are easier and/or more pleasurable to take – e.g. orally disintegrating or chewable dosages with favourable taste and texture.

Despite the evolving requirements of patients and regulators alike, the introduction of excipients enabling formulators to meet these objectives has been minimal. Development of new excipients – or existing excipients with enhanced functionality – is time consuming and can be costly to excipient companies. Often the rewards do not meet the efforts expended. This conundrum requires excipient suppliers to think rationally about what the ideal "universal excipient" might look like to address these challenges.

> "In an ideal world, the formulator would have a monograph excipient with all the benefits of a co-processed system. With this in mind, SPI Pharma set about development of a universal excipient."

UNIQUE COMBINATION OF MATERIAL SCIENCE AND APPLICATION KNOW-HOW

SPI Pharma was the first company to launch a co-processed excipient specifically aimed at rational design of ODTs. Our Pharmaburst® platform, for the first time, enabled the formulation of a directly compressible blend of API, excipient and lubricant that could meet the competing requirements of ODT development.

An ODT formulation needs to be sufficiently robust to withstand downstream processing, such as packaging, but at the same time disintegrate within 30 seconds in the mouth and impart a positive patient experience. SPI Pharma used its knowledge of key excipients, such as mannitol, and its co-processing expertise to design a system that met these needs. Since then, many other companies have launched similar products that were designed with ODT in mind.

Despite the success of these types of products, there remained some limitations in that the multi-component nature of co-processed systems meant they were not suitable across the board for a range of development projects. In an ideal world, the formulator would have a monograph excipient with all the benefits of a co-processed system. With this in mind, SPI Pharma began development of a universal excipient.

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ENHANCED PERFORMANCE IN A FAMILIAR PACKAGE

Mannitol is widely used as an excipient in oral dose form development due to its low hygroscopicity and high stability or inertness. It does not undergo the Maillard reaction with amine APIs (unlike lactose) and has successfully been used to formulate some difficult actives in swallow tablets, such as levothyroxine. It has extremely pleasant organoleptics, with a mild sweetness and a minor cooling effect as it solubilises in saliva. This has made it the preferred excipient in ODT formulations and the base for most ODT platforms.

As more and more drugs are converted to patient-centric dose forms, it was clear that mannitol had many of the attributes required to fit the needs of a universal excipient, with all the requirements set out in Table 1. The main barrier to its ubiquitous use was its relatively low tabletability.

For a formulator, the ability of an excipient to form a robust compact is critical, particularly in ODTs which generally have higher porosity or superior solubility to enable rapid disintegration. Formulators measure the tabletability of a given formulation by producing tablets over a range of compression forces and measuring the strength of the resultant tablet using standard equipment, such as a hardness tester, and converting the result into a tensile strength which considers the tablet thickness and diameter (Figure 1).

Features	Requirement
Tabletability	medium to high; resultant tablets robust and low friability
Stability	inert, low hygroscopicity;
Organoleptics	sweet and cooling to the mouth; non gritty texture
Solubility	high
Disintegration	fast inherent, with minimal need for disintegrant
Flowability	high; suitable for direct compresion tableting processes

Table 1: What properties would a universal excipient possess?

By taking the slope of the tensile strength versus compression force (Figure 2), the formulator can compare different formulations or excipients to understand the relative tabletability. The greater the tabletability, the more robust the resultant tablet will be and the lower the friability it will have. These are critical quality attributes (CQAs) that are key to rational drug design. If one could combine a high tabletability with the inherent stability, inertness and pleasant organoleptics, one would be close to having the universal excipient desired for rational dose form design.

Knowing this, SPI Pharma scientists set about trying to design this universal excipient. The result of more than 18 months of development work is the Mannogem® XL technology. In March 2020, SPI Pharma launched the Precious Gem Collection, which includes two new grades of Mannogem XL mannitol – "Ruby" and "Opal" – that we believe offers formulators an excipient that meets existing monograph needs and has universal applicability.

- Tensile strength equation: $\sigma_x = (2 \cdot F) / (\pi \cdot t \cdot D)$

Where s_x is the tensile strength (MPa)
F is the crushing force (N), measured by diametral compression
t is the compact thickness (mm)
D is the compact diameter (mm)

- The linear region of the tensile strength versus pressure graph is known as the compactibility slope
- The compactibility slope describes the inter-particular cohesion in the compact or the tabletability

Figure 1: Calculation of tablet tensile strength and its use in determining tablet robustness.

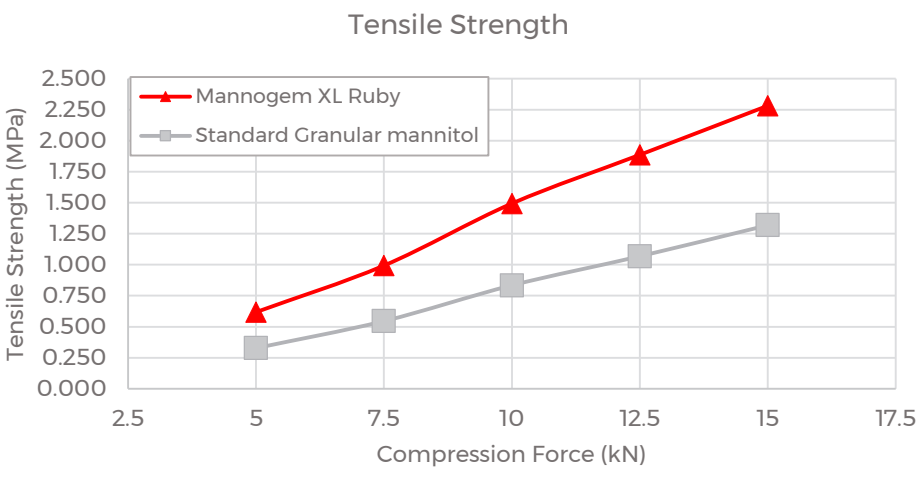

Figure 2: Comparing the tabletability of Mannogem XL Ruby to standard granular mannitol.

MANNOGEM XL RUBY

Earlier, we explained the challenges in developing a chewable tablet or ODT. These challenges are amplified when formulators are required to develop a formula that requires taste masking. Taste masking is an absolute must for certain APIs that can be bitter or astringent in nature. These attributes can be particularly off-putting for children, who already need encouragement to take their medicines.

Fortunately, taste-masking approaches exist, such as SPI Pharma's Actimask® technology, to help reduce the bad taste of a given API. In the majority of cases, the taste-masking approach requires application of a polymeric membrane to granules of the drug to help mask the bad taste. As a result of these taste-masking techniques, the resultant drug particles can be quite large (in pharmaceutical terms), easily greater than 300 microns.

Unfortunately, this causes another problem for the formulator. Blending a larger particle size API with a smaller particle excipient causes segregation of the active particles from the rest of the blend. A simple example of segregation is to think of granola. Anyone familiar with granola will know that the small particles – raisins and nuts – tend to settle at the bottom of

> "Segregation of a powder blend containing API will lead to content uniformity issues, which is unacceptable because the patient would receive either higher or lower amounts of the drug, leading to possible side effects or subtherapeutic doses."

the box, meaning the last few bowls are lacking in the larger particles. The same type of phenomenon occurs with direct compression blends with much more serious consequences.

Segregation of a powder blend containing APIs will lead to content uniformity issues, which is unacceptable because the patient would receive either higher or lower amounts of the drug, leading to possible side effects or subtherapeutic doses. Neither is acceptable. To overcome this issue, there are currently granular grades of mannitol on the market that have a larger particle size than the more common spray-dried grades.

By matching the taste-masked API particle with the larger particle size, it is possible to overcome the segregation described. However, until now, these grades of mannitol had even lower tabletability than the smaller particle size spray-dried grades. SPI Pharma's Mannogem XL Ruby, for the first time, combines the large particle size of a granular mannitol with tabletability approaching that of spray-dried material.

Mannogem XL Ruby is a uniquely designed excipient that enables formulators to do things they were unable to contemplate previously. They can now formulate an ODT with all the benefits of mannitol that make it patient centric, but with the added benefit of incorporating taste-masked APIs that can be blended with confidence that drug segregation will not be an issue. Additionally, Ruby's superior tabletability means there is less compaction force required, reducing the stress applied to pressure-sensitive formulation components, such as taste-masked APIs or multi-unit pellets systems (MUPS).

MANNOGEM XL OPAL

By extending this same functionality to a spray-dried product – Mannogem XL Opal – SPI Pharma can further extend the use of mannitol as a universal excipient, giving the most compressible grade of mannitol. As already described, the target for the formulation scientist is to have a rationally designed formulation that optimises the combination of high tabletability, low friability and rapid disintegration.

The superior tabletability of Opal enables the formulator to develop products that have high drug loading to a level that was not previously possible with mannitol. It also enables simplicity of formulation, negating the need to use other binders – such as microcrystalline cellulose and hydroxypropyl cellulose – which can undermine the organoleptics and accelerating development.

Additionally, smaller tablets are possible with Opal to enhance patient adherence by improving swallowability. An example of a simplified chewable tablet formulation is given in Table 2.

As formulations are transferred from development to manufacturing scale, the robustness of the formulation is key. The principles of quality by design require formulations to have a wide design space to minimise development time, particularly when it comes to technical transfers from development to production.

Mannogem XL Opal has been uniquely designed to optimise the key attributes described above to give this robustness and wide design space. Such formulations will transfer to production quickly and enable high yields and fast production speeds to be achieved. Table 3 compares the performance

Material	Quantity (mg)
Actimask® APAP 92M*	172.5
Mannogem XL Opal	989.1
Crospovidone	49.8
Magnesium Stearate	24.9
Colour	2.5
Flavour	6.2
Total	**1245.0**

Table 2: Typical direct compression Mannogem XL Ruby APAP (acetaminophen) chewable tablet formulation. *Actimask APAP 92M is SPI Pharma's taste-masked APAP, 172.5mg equivalent to 160mg of APAP

Mannogem XL Opal					
Compression Force (kN)	5	7.5	10	12.5	15
Tensile strength	0.63	1.06	1.64	2.15	2.43
Friability	0.9%	0.6%	0.0%	0.3%	0.2%
Disintegration time	33.4	54.6	102.2	141.2	182.2
Ejection force	100	140	180	210	250

Larger Design Space

Competitor 1					
Compression Force (kN)	5	7.5	10	12.5	15
Tensile strength	0.42	0.75	1.16	1.55	1.86
Friability	2.6%	1.3%	0.2%	0.8%	1.2%
Disintegration time	50	77.2	99.4	137.8	163.4
Ejection force	100	150	200	230	260

Failure Borderline Fail Success

Smaller Design Space

Table 3: Extending design space using Mannogem XL Opal.

"Regulatory requirements and patient demands have pushed dose design earlier in the drug development process."

of an Opal-based formulation with the same formulation that uses standard mannitol. As seen below, the Opal formulation is much more robust in terms of all the key CQAs.

CONCLUSION

Increasingly, the recent advances in regulatory expectations with respect to dose form patient centricity add to this challenge. With its Precious Gem Collection, SPI Pharma has taken the rational design approach and extended it to designing excipients that can significantly enhance patient-centric dose form functionality and formulation robustness.

Regulatory requirements and patient demands have pushed dose design earlier in the drug development process. Requirements for patient centricity in new drug development, and the need to match doses with consumer preferences in OTC development, have increased the importance of functional excipients that provide convenience and ease of administration. Mannitol is understood to be one of the best excipients to create easy-to-administer and aesthetically pleasing doses.

Simultaneously, drug delivery has become more sophisticated and dose development has become more complicated, requiring rational application of specifically functional excipients. In this respect, SPI Pharma has developed a collection of mannitol excipients that match targeted functionality, with the ability to make drugs easier to administer.

Product	Main Application	d50 (µm)	Bulk Density (g/mL)	Tapped Density (g/mL)
Mannogem XL Opal	Direct compression ODTs, swallow and chewable tablets	160	0.52	0.45
Mannogem XL Ruby	Direct compression ODTs and chewables with larger MUPS or taste-masked APIs where segregation is an issue	300	0.65	0.57

Table 4: Typical physical properties and applications for Mannogem XL Ruby and Opal grades

Excipients can no longer be generally applicable – they must provide specific functionality that can be applied to a rational design concept. Typical physical properties and applications of Mannogem XL Ruby and Opal grades are summarised in Table 4.

Mannogem XL Ruby addresses the emerging need to create orally dispersible doses with large-particle, multicomponent ingredients. Mannogem XL Opal can help make tablets more robust with fewer ingredients. These new grades are a demonstration of excipients that are developed with drug development and patient needs in mind. Rationally designed excipients from SPI Pharma match the rational approach of the industry and meet the increasing demands of developing safe and efficacious medicines.

ABOUT THE COMPANY

SPI Pharma provides the innovative solutions global pharmaceutical and nutritional customers need to succeed. The company helps solve the most challenging formulation problems efficiently, cost effectively and with a focus on service. Serving over 55 countries in the manufacture and marketing of antacid actives, excipients, drug delivery systems for tablets and powders, taste-masked actives and vaccine adjuvants, SPI Pharma employs more than 300 people globally and is backed by parent company Associated British Foods. It also specialises in drug development services, having participated in over 60 commercially launched and marketed drugs globally.

ABOUT THE AUTHORS

Graeme Macleod attained his PhD in pharmaceutical technology from the University of Manchester (UK). He has 25 years of industrial experience in the fields of formulation development, drug delivery, pharmaceutical solid form equipment and excipients. Dr Macleod joined SPI Pharma in June 2017. His areas of experience include oral dose form technologies and processes, novel soft capsule technologies and drug formulation.

Wayne Camarco joined SPI Pharma in 2019 as Global Head of Technical Development. He has broad-based excipient and API experience in the areas of formulation development and technical service. Mr Camarco has worked in a variety of technical, sales and business development roles at ACG Capsules in the US, Juniper Pharma (Catalent, UK), Ashland Specialty Ingredients (US) and Rhodia (US and France).

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Make Medicine Patients Want to Take

Mannogem® XL Ruby & Opal

Enhanced Performance
Better Patient Experience