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From Core to Coating

The right formulation choices can dramatically improve development and manufacturing efficiency; with good tablet design positively impacting patient experience.

Here, Colorcon experts discuss some of the latest regulatory and manufacturing trends relating to excipient choice, tablet design and formulation, and the solutions available for delivering your perfectly finished tablet.

Speed and Simplicity – A Formulator's Best Friend in Development

From core to coating, there is a lot to consider when it comes to developing and optimizing a solid dosage formulation. Simple best practices can offer an edge that allows formulators to reduce potential problems that could occur in later stage commercial manufacturing.

By Jayesh Parmar

Formulators are faced with many choices during the early phase of development, and they must focus on the project milestones they need to deliver. Examining formulation strategy early can deliver key benefits and having an end goal in mind early on leads to greater efficiency, as everyone will understand what they are working towards. Understanding the molecule is the first step, then exploring the needs and options for formulation enables development to progress faster and smoother.

Solubility is one issue that is often encountered with new molecules in development. Many technologies are available to help solubilize an API; however, if a robust formulation and process is not developed then it can impact the subsequent manufacturing of a consistent product. Using the right technology and choice of excipients, it's possible to develop a stable formulation with reduced complexity. Partnership with key suppliers of ingredients and equipment is critical during development phase. For example, formulators need to ensure that the process parameters for equipment used during development are transferrable to commercial-scale equipment. Similarly, formulators should partner with suppliers before putting in place any particular specifications for ingredients; thus avoiding future supply issues.

Formulation simplification

Designing the formulation for your next new product involves many decisions. What is the desired drug release profile? What excipients should be used? Do they interact with the API? Which film coating should be used? And how should the tablet design look? Drug developers also need to consider what will work at the commercial manufacturing scale. Generally, I recommend formulators keep their strategy simple; by reducing ingredients and process steps this is less likely to cause problems and results in the most cost-effective option. From a regulatory standpoint, complex processes are also more likely to lead to complex questions from regulators and may extend the approval process.

Process efficiency

In the very early stage of formulation, a capsule is generally the preferred oral dosage form, due to its binding capability for clinical trials. However, due to economic, ease of manufacturing and marketing considerations, most oral solid dosage forms on the market today are tablets. There can be a great opportunity for cost and time savings, as formulators can develop a dosage that works both in a capsule and as a final tablet form.

Direct compression is considered by many in the industry to be one of the simplest methods for manufacturing tablets and works well at large manufacturing scales. In comparison, wet granulation involves multiple steps and the use of moisture, which can introduce the risk that the API may degrade. With industry preference leaning towards direct compression, several excipients have been developed that excel in this area. As one example, consider our newest excipient, StarTab directly compressible starch. StarTab is designed specifically for direct compression and offers benefits in terms of both simplifying the formulation and processing. Starch excipients are commonplace in the industry, but many require additional ingredients to be fully effective in the formulation – such as an excipient to improve flow, an excipient to improve compressibility, as well as superdisintegrants. This can complicate the formulation and process, given that you need to examine how all of the excipients interact with one another, as well as interact with the API; lactose, for example, is one common formulation ingredient that can interact with certain types of API, so it is best avoided. StarTab is a single excipient which, because of its particle shape and size, is directly compressible and provides improved flow during manufacture. It can also avoid the use of superdisintegrants – and be used at both small scale and large scale, as well as with the latest technology such as continuous processing. Excipients like this offer manufacturers significant flexibility in terms of how they manufacture their product.

Other excipients can help with productivity, such as METHOCEL DC2, which also enables manufacturers to replace costly wet granulation in matrix tablet production with more cost-effective dry granulation and direct compression techniques. It is a pure, compendial HPMC and the most flowable direct compression grade of HPMC available today. It exhibits better flow in formulation blends compared to traditional hypromellose-based formulations, and uniform die-fill during tablet manufacturing provides tighter tablet weight control. Overall, it can improve process capability.

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"Another important formulation decision revolves around API stability, which can be improved through the correct choice of film coating."

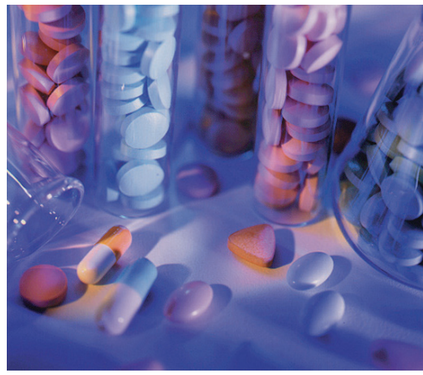
Another important formulation decision revolves around API stability, which can be improved through the correct choice of film coating. Whilst film coatings have an important role to play for aesthetic purposes by giving the tablet a perfect finish, they also play a part in defining branding strategies. They also fulfil more practical roles; a good coating protects the tablet during storage from moisture, light and oxygen, for example, and helps to stabilize the API. The right coating choice also enables ease of transition of drug production between manufacturing sites; in early stage development the final site(s) for manufacture is not usually a consideration. Colorcon's Opadry QX has a wide processing latitude which means it is suitable for use across a range of coating equipment – which is imperative if you don't know where the final product will ultimately be manufactured. Specialist film coatings also provide a barrier that reduces the ingress of moisture to the tablet core, helping to support stability for sensitive actives. And let's not forget, film coating also helps tablets to run smoother in tabletting equipment and protects them from damage during the manufacturing process.

Right first time

Failing to consider core and coating formulation early on can lead to delays, added costs and, in the worst-case scenario, project termination. Often, big pharma companies understand the benefits of investing in early formulation and will have large departments dedicated to this role, but many others, particularly small and medium-size companies, may not have the resources and, understandably, will be prioritizing proving efficacy and safety of the API. In many instances, rather than developing an optimized formulation strategy, a company will simply resort to the same tried and tested approach that they have used for their previous products, even though it might not be best matched with the newest molecule. At other times, a company may want to take a new approach to optimize the formulation but struggle to find a starting point, since there are many options!

Companies do not need to go through the formulation process alone; Colorcon offers its HyperStart starting formulation service globally to help bench scientists understand the options available for delivering their API to the patient. We simply take basic information (confidentially, of course) related to the API, such as solubility, the dosage, and the technology being considered for the final dosage form, and then deliver back a starting formulation. Some companies already have good starting guidelines in this area, but what worked for one formulation may not be the best starting point for the next. Our service supports scientists to make decisions early, giving them an informed starting point.

In my view, vendors have an obligation to support on the regulatory side too with documentation. When it comes to excipients and ingredients, it can be surprising how regulations across the world differ; what is allowed in the US may not be allowed in Japan, for example. This can also apply to certain pigments – and it wouldn't be the first time I've come across a company shocked to learn that their manufactured tablet in one country can't be marketed in another without changing the ingredients! Having this information early allows you to plan early and choose ingredients accepted in all the countries you are targeting for market launch.



Although attrition in drug development is high, considering the formulation in the early development stages will definitely lay the foundations to support clinical success, and good formulation expertise can make all the difference.

Jayesh Parmar is General Manager at Colorcon.

The Power of Productivity

Tablet coating is not just about aesthetics; a good coat will improve stability, aid patient adherence, and enhance productivity in manufacturing equipment.

By Kelly Boyer

Why is coating important? Aesthetically, a coated tablet looks more appealing, which can impact how a patient feels about their medicine. A well-presented coated tablet, free from defects, gives patients confidence that it's high quality and a trusted product from a reputable company. A coated tablet also provides many important advantages directly to the consumer. Consider patient compliance as one example. An uncoated tablet will often be chalky and, for some patients, unpalatable, since there is nothing to mask the texture or taste. There is also a high chance that the tablet will stick during the swallowing process. If a patient finds taking their medicine difficult or unpleasant, then they are less likely to adhere to the prescribed regimen. Coatings can help overcome this issue. For example, we have developed Opadry EZ, easy swallow coating, which provides exceptional slip when the coating becomes wet, making the tablet easier to swallow. This can be particularly important where a large tablet size is unavoidable.

A coating also provides the opportunity for differentiation and prevention of medication mix ups. Some companies choose a simple white coating, but when all tablets look the same there is a higher risk of errors, particularly where patients must take multiple medications. The FDA encourages companies to consider differentiation – especially amongst various dosage levels. Application of a pigmented coating can help to avoid dispensing and administration of the wrong dosage or other look-alike errors. Going back to aesthetics, including color can also make a tablet look more attractive and impart stronger brand recognition.

In addition, coating can convey specific functional properties on to a tablet, such as moisture barrier protection or light protection; and modified release coatings allow the drug release to be delayed or targeted to a specific site.

Reaching for higher productivity

Over the years, film coatings have evolved significantly. The standard coating system traditionally used HPMC as the main polymer, which is still widely used. HMPC-based coatings provide adequate performance, but there is room for improvement. HPMC coatings may not adhere well to the tablet and are typically slow to apply, resulting in low production speeds. The subsequent introduction of PVA-based coatings gives greater flexibility with improved functionality, providing an opportunity for faster production which in turn means less potential for defects. Most recently, Opadry QX, a quick and flexible coating system, has been developed. Based on a PVA-PEG copolymer system, this coating formulation allows for the highest solids dispersion level, resulting in the greatest process efficiency – some of our customers have reported a 40 to 50 percent boost in productivity by switching to Opadry QX. Buying back machine time can make a huge difference in reducing bottlenecks in production and providing an opportunity to increase coating operations.

We have also evolved from art to science in the area of sugar film coating. Sugar-coated products are very aesthetically pleasing because they have a smooth, glossy surface, with a sweet taste that can mask bitter-tasting ingredients. But the biggest challenge with a sugar coat is productivity and reproducibility. Sugar-coating is a very labor intensive and time-consuming manual process – and the finish, from batch-to-batch, can vary depending on the person performing the coating operation.

Bringing in science to bridge the gap, Opadry SGR has been developed. This product is designed to deliver a high gloss, aqueous sugar film coating system that can be used in automated processes (fully perforated or conventional coating pans retrofitted with spray capability), allowing for significant time savings; down from days to a couple of hours.

Ultimately, the coating you choose for your tablet will depend on your requirements. For some companies, high productivity is not possible or necessary, particularly if they are using older equipment, or if labor cost is not a factor. But for others who are running at full capacity, a move to a higher solids and higher productivity coating may allow them to achieve a greater throughput with their existing assets and delay the need to invest in additional coating equipment.

"If you purchase a ready formulated coating system then you are buying one material from one vendor, which makes for a much simpler supply chain!"

Coating equipment and geographic location can also dictate choice of coating. It is not uncommon for companies to develop a drug in one region, where equipment and conditions are spot-on, before moving commercial production to another region, where coating equipment may not be as reliable, or where there are issues with airflow, temperature or humidity that present production problems. Choosing a coating which is flexible enough to be used across a range of different conditions while still giving consistent defect-free, flawless coating is a must.

Clean label appeal

A more recent trend that may affect coating decisions is the increasing consumer interest in cleaner labels. Most of this activity is coming from the nutraceuticals industry; in France, for instance, the use of titanium dioxide has recently been suspended for use in food and nutritional supplements, and companies are wary of similar moves in pharmaceuticals and want to get ahead of the curve. In response, we are now actively promoting titanium-free coatings and are getting interest from customers wanting to move to alternative coatings.

Overcome the dangers of "DIY"

Some pharmaceutical manufacturers design and manufacture their own coating, but the majority will buy a ready formulated coating system because it is a simpler, more efficient process than a DIY (do it yourself) approach. Using an in-house coating necessitates the sourcing and associated quality testing of various raw materials from several vendors who may need to be audited and approved.

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Additionally, inventory will be required for all of these materials, along with dispensing and dispersion preparation operations. Dispensing your own coating materials introduces cleaning considerations and risk for cross-contamination. Creating a stable, consistent coating is not always the easiest process either, especially if you're not a coating expert. Color consistency and uniformity can be significant challenges, as color is contingent on the particle size distribution of pigments and, therefore, any batch-to-batch inconsistency will result in color variation.

If you purchase a ready formulated coating system then you are buying one material from one vendor, which makes for a much simpler supply chain! Plus, the vendor will perform the quality audits of its own suppliers, have second sources of supply and provide regulatory support. It is, however, important to choose a trusted and reputable company. Looking at a company's business continuity plans (BCP) is crucial to ensure reliable supply. Regional manufacturing is becoming an important trend in the pharma industry. At Colorcon, we have seven manufacturing plants located strategically across the globe, which means they can meet the needs of the local market. Importantly, all of our plants are operating with the same raw materials, same equipment and the same processes – and we have done a lot of work to validate the interchangeability of products from all of the sites. If there is an issue getting material from one plant then we can simply supply it from another. We also have technical support laboratories worldwide to help customers through the coating process; enabling them to run trials in our coating labs (they may not have the equipment spare in their own company to run trials), seeking advice from us in terms of troubleshooting, or participating in our "Coating School" training sessions, which cover how best to manage and optimize the coating system.

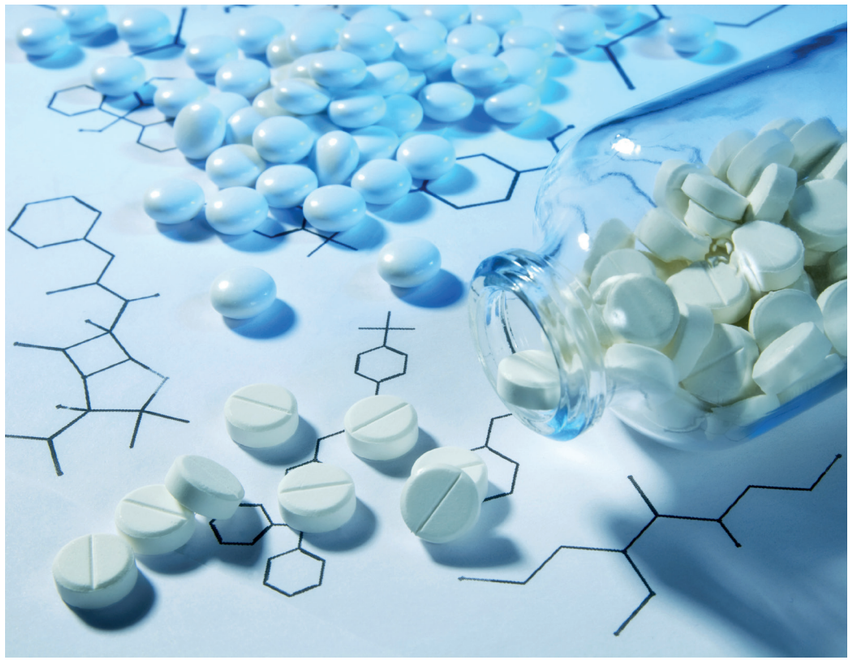
By partnering with a reputable and trusted company with plans in place to ensure supply, you reap the rewards of a consistent finish developed by coating experts that can also aid productivity!

Kelly Boyer is Film Coating General Manager at Colorcon.

Staying On Trend

From patient-centric design to speciality excipients and security of supply; what are the latest trends in formulation strategies?

By Ali Rajabi-Siahboomi



If you want to create a patient-centric medicine with the best chances of compliance, then paying attention to the design of your tablet is crucial. But as well as keeping patients in mind, it's also important to consider manufacturing – decisions made about a tablet and its formulation, including its coating finish, can have a significant impact on production efficiency (1, 2). In short, your formulation strategy matters for many different reasons.

Over the past two decades with Colorcon, I have seen a lot of change in terms of formulation needs as companies strive to be more efficient and deliver better medicines. Importantly, our customers' requirements need solutions to match their business challenges and production needs, as well as the needs of patients. Colorcon is a unique company in that it is extremely innovative and agile, even though we operate within a tightly regulated market. This is important, as it means we can respond as market needs change, providing exceptional products, local technical support and regional production capabilities. Today, for example, many pharma companies have regional manufacturing facilities and require the same raw materials at the same consistency and quality for use across these different geographical territories. Through expansion of our global footprint, Colorcon now has capabilities in strategic locations around the world to enable easy, local access and supply for our customers. Our industry expertise has continued to deepen over the years. While Colorcon's focus has always been in film coating and speciality excipients, through our alliance with DuPont we also represent an extensive line of excipients for modified release applications. This is important expertise that pharma companies are looking for in a long-term partner.

Patient-centricity combined with safety

One topic that is becoming increasingly recognized by healthcare providers and brand owners is patient-centricity. When developing a new product, manufacturers want to meet the treatment goals but they are now increasingly looking to improve patient experience and adherence.

Making it easier for patients to take their medicine is one of the best things you can do! There are a number of solutions out there to help with this. Tablet shape, size and color should all be considered from the patient's perspective. Tablets that are too large, for example, can impede swallowability, while tablets that are too small can also be a problem since they may be difficult to handle. Colorcon's Brand Enhancement service helps to visualize what a dosage will look like as a tablet. We have also developed coating formulations (Opadry EZ) that improve swallowability, through making the tablet very slippery when in contact with just a small amount of water. A positive patient experience is key to improving medication adherence.

Another key trend that companies should not ignore is product authentication. Fake and diverted medicines are a huge problem (and cost) around the world, and many countries now mandate the use of serialization or other on-packaging security measures to ensure the authenticity of medicines. With anything on the packaging, however, there is still a risk that it can be copied. Now, there is also growing interest in physical chemical identifiers (PCIDs) that can be incorporated into a tablet coating to enable individual tablets to be authenticated. The FDA is very interested in this technology because it will be almost impossible for counterfeiters to copy. The agency is currently conducting a review process for on-dose identifiers.

"The marketplace is changing. The large centralized R&D model has changed, with innovation instead being led by smaller start-ups and CROs."

Keeping pace with market trends

All companies want to reduce their development times, get to market as quickly as possible and manufacture efficiently. In addition, it is important to mitigate potential risks, both from regulatory registration as well as product robustness – no one wants to put something on the market that they then must call back! In terms of registration, we offer directly accessible online regulatory documentation to support dossier submission. Delays often occur when information is missing from dossiers – and when manufacturing, packaging and other areas are ready to get moving, the last thing you want is a delay caused by regulators asking questions. We also help customers to de-risk with our business continuity plans for security of supply; we have manufacturing plants in multiple locations around the globe, and the materials and products are interchangeable from one facility to another – so if there is ever an interruption at one plant we simply manufacture and ship from an alternative site.

To reduce development time and help with product robustness, we provide R&D with access to HyperStart, a starting formulation service. Through this confidential service, we collate information about the properties of the API, drug, solubility, dose, particle size, shape and so on – and then we present the customer with a start-up formulation. We aim to get it first time right – this can be challenging to do but it certainly helps to reduce the number of iterations that the customer would otherwise have to do.

And for the future?

The marketplace is changing. The large centralized R&D model has changed, with innovation instead being led by smaller start-ups and CROs, which often don't have significant experience in formulation or commercial production. Through our global network, we're able to actively support development with these smaller companies; providing formulation and excipient expertise, access to facilities and regulatory support.

When designing new products and services, we focus on our customer's challenges – what's holding them up? As always, manufacturers are seeking to reduce costs and increase productivity, so looking at how we can help our customers to improve the efficiency of their manufacturing operations – while still being patient-centric – is key for us. For example, we developed the first high solids level dispersion, Opadry QX, a PVA-PEG copolymer based coating system that delivers significant process efficiencies. Our sugar coating system, Opadry SGR, reduces production time from days to hours by allowing for the use of automation (traditionally, sugar coating is a manual process). Recently launched, StarTab, directly compressible starch, is proving to be game changer, slashing the number of excipients needed for tableting and making direct compression even easier. Choosing your excipients to streamline or buy back production time can be significantly more cost effective than upgrading to more high-capacity equipment.

We also aim to keep up to speed with the new and emerging technologies our customers are using so that we can provide the right support for them. Key topics that people are currently talking about are continuous manufacturing and 3D printing. We've been active in the area of continuous processing for some time, leading the development of excipients and coating formulations that provide unique benefits in this area. With 3D printing, we continue to investigate and have partnered with universities and other experts to learn more in terms of what excipients are suitable for this technology. It's all about supporting customers both now and in the future as their needs continue to evolve.

Ali Rajabi-Siahboomi is Vice President and Chief Scientific Officer at Colorcon

Continuing education

For over 30 years, Colorcon has run Coating and Formulation Schools, which combine theoretical and hands-on training, plus regulatory understanding in the areas of film coating, core formulation, excipient selection and controlled release of solid dosage forms. The courses come with a certificate of attendance and we find many customers send their staff as part of their continuous training and professional development.

Now together with the Innovation Program, these educational events are under the umbrella of the Colorcon Academy.

References

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