A Q&A

How To Ensure Reliable Drug Product Quality at Intermediate pH by Using Pre-Neutralized Kollicoat® MAE 100-55

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Nowadays, attributes such as product quality, reliable processing, and time to market are more important than ever before. Quality by Design (QbD) aspects or a global cost pressure onto health expenses have intensified the discussion of these attributes. To continuously expand the boundaries of quality and economical processing even further, a strong interconnection between various disciplines is required.

Manufacturers of pharmaceutical products need to rely on a strong relationship within leading academia, engineering companies, and excipient vendors for reaching the next level regarding the quality of pharmaceutical dosage forms and their manufacturing efficiency. Only an intensified interplay between these aforementioned elements can provide the full capability required for a successful step toward improving the future. Here, Thorsten Cech, manager of the European Application Lab (Pharma Solutions & Human Nutrition) at BASF, comments on this important issue.

Thorsten, you have more than 25 years of experience in the field of pharmaceutical product development. In your current position, you head the European Pharma Application Lab of Pharma Solutions at the BASF headquarters in Ludwigshafen, Germany. What are your main responsibilities in this role?

Indeed, I used to work in galenical development for different pharmaceutical companies before joining BASF some 10 years ago. Being responsible for the European Pharma Application Lab is a challenging, but an utmost interesting task. The team is taking care of customer projects dealing with feasibility studies, formulation development, scale-up, or process optimization. There is a long list of successful projects, indicating distinct quality or process improvements we are able to implement for our customers. Independent of actual projects requiring attention in our lab, we offer customized workshops addressing, for instance, process and product understanding, both essential components in the realm of QbD considerations. However, this is an overall description of our activities, which we in Europe share with our colleagues working in the application labs in all regions: Asia, North America, and South America.

BASF offers a vast portfolio of excipients, addressing numerous applications and dosage forms. Considering all the projects you are taking care of, what's the most surprising aspect from your point of view?

Offering one of the largest excipients portfolios there is, we saw the requirement to organize the products into five platforms, according to their main application or usage in the pharmaceutical industry: Instant & Modified Release, Solubilization, Skin Delivery, Soft Gels, and Biologics.

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Behind each platform is a matrix, simplifying the guidance to the functionality and excipient required by a formulator. It is much easier now for customers to find the product that most sufficiently serves their current needs.

Over the last years, the pharmaceutical industry has faced an increasing number of newly developed, but poorly soluble drugs. Consequently, projects addressing the improvement of solubility and bioavailability of poorly soluble active pharmaceutical ingredients are quite common. Considering the vast number of solubilizers in our portfolio, BASF is an inherently superior partner for formulators working in that field.

However, it is surprising that most requests are still for the Instant & Modified Release platform. One could consider that these dosage forms, well established in the market for decades, should hardly provide any major challenges during formulation development. Yet, the opposite holds true. Solid oral dosage forms still represent the largest segment of products being sold at pharmacies (considering the number of single doses). As a consequence, there are plenty of opportunities to run into formulation problems. One such challenge most frequently brought to our attention is the formulation of dosage forms providing enteric-release characteristics.

That is indeed surprising. Considering that the polymers used for this application were introduced about 40 years ago, one could assume that their handling and usage are well established in formulation development centers. What challenge do formulators face in this field?

It is less the handling and more that the formulation experiences unforeseen trouble. Over the last years, poly(methacrylic acid-co-ethyl acrylate) became the standard excipient to introduce enteric-release functionality to a dosage form. The polymer is insoluble in the acidic aqueous media provided by the gastric juice. Yet, it becomes soluble at the pH-value given in the intestine. Thus, one uses the difference in pH-value present within the gastrointestinal tract to trigger an immediate drug release immediately after the dosage form has been transferred from the stomach into the intestine.

Since the polymer is initially insoluble in water, the product is primarily available as an aqueous latex dispersion (Kollicoat® MAE 30 DP). Handling of the dispersion requires some heeding, though. For instance, the dispersion can only be handled at temperatures between 0 °C and 30 °C. Exposure to conditions outside this range leads to irreversible coagulation. If that happens, the dispersion must be disgarded.

Isn't it quite challenging then to handle such a product?

No, it's not. We do control the shipment and use data acquisition systems to log the environmental temperature during product transport. Eventually, we can guarantee that the product arrives at our customer's facility, meeting the high-quality standards they are used to. Nevertheless, considering variations in climatic conditions given, there needs to be an alternative approach.

This alternative is provided by the two powder grades: Kollicoat® MAE 100-55 and Kollicoat® MAE 100 P, which we also have in our portfolio. These grades are stable at low temperatures and at elevated temperatures, thus shipment as well as storage at the customer's warehouse are much easier and more convenient. Before using the product, it needs to be redispersed in water, but subsequently serves the same applications as the aqueous dispersion. Additionally, organic solvents could be employed as a liquid carrier, which is obviously not possible when using the aqueous dispersion.

Thorsten, you mentioned there are two powder grades in your portfolio. Why is that and how are they different?

Well, the spray-dried polymer cannot be readily redispersed in water. It requires partial neutralization to improve wettability to subsequently allow redispersion. Some alkaline material such as sodium hydroxide is required for this. To simplify the handling and to improve the safety situation for the operator, Kollicoat® MAE 100 P is partially neutralized during the manufacturing process, thus the powder can be directly redispersed in water without requiring additives.

Kollicoat® MAE 100-55 is not subjected to the same manufacturing procedure. It lacks the alkaline additive, requiring partial neutralization during the preparation of the aqueous film-coating dispersion at our customer's end. It is mainly a me-too product, addressing formulations employing alternative commercially available products offering the same chemistry and the same opening pH-value of 5.5.

Earlier, you mentioned that you are supporting your customers with formulation expertise such as product and process understanding. To my understanding, Kollicoat® MAE is a comparatively old and well-established pharmaceutical excipient. What features still require explanation?

You are right; most formulators have experience in handling this product or in formulating enteric-release functionality into a dosage form. Nevertheless, plenty of aspects require attention when starting formulation development. We've come out with several product developments and have seen and solved various challenges.

The feature most frequently overlooked is the effect of partial neutralization on the dissolution pattern. Considering the aqueous dispersion in the first place, which doesn't require alkaline additives: the opening pH-value (that's the pH-value allowing the polymer to dissolve) of poly(methacrylic acid-co-ethyl acrylate) is 5.5. Kollicoat® MAE 30 DP based coats tightly seal a substrate, unless the pH-value of 5.5 is reached, or exceeded, respectively. Consequently, the consumption of food that alters the pH-value in the stomach (the gastric juice becomes less acidic) has hardly any impact on the functionality. The likelihood that the pH-value exceeds the 5.5 threshold is rather low.

Over the last years, standard testing conditions to prove gastric-resistant functionality where conducted by exposing the dosage form to artificial gastric juice: hydrochloric acid of a pH-value of 1.1. After two hours, during which less than 10% of drug is allowed to be liberated, the pH-value is altered to 6.8, typically by adding a phosphate buffer. This testing method does not allow any differentiation between the polymer grades, though. Therefore, most formulators think there is no difference between the grades, but the varying preparation procedure of the film-coating dispersion.

Unfortunately, that's not the full picture. In contrast to the aqueous dispersion, a partially neutralization of 6 mol% of the functional groups shifts the opening pH-value, the polymer starts to become soluble in the range of 4 to 5 (depending on the buffer system employed). The risk of food effects increases dramatically, allowing drug liberation or acid uptake in the stomach.

But, this alteration of the opening pH-value appears to be a quality issue, doesn't it?

Yes, indeed it is. That's the crucial point. The regulatory bodies are aware of this effect. That's why they started to request dissolution data at intermediate pH-value. Eventually, one needs to put a warning onto the drug product, stating that it's not allowed to take the remedy in a fed state.

But, this is only relevant if one cannot prove functionality at intermediate pH-values, which is still possible, even for the powder grades. The trouble is that in the past, hardly anyone paid any attention to this effect. The amount of partial neutralization of 6 mol% was a value that established itself, because it worked. Nowadays, with years of experience in production and formulation optimization, it can be stated that the polymer can be produced reliably in a reproducible narrow quality range. Recently published case studies prove that a more moderate neutralization of scarcely 4 mol% provides the same redispersability, but an improved performance regarding intermediate pH-values.

Our clear recommendation is to redisperse Kollicoat® MAE 100-55 with a partially neutralization of merely 4 mol% by employing sodium hydroxide. This procedure hardly alters the opening pH-value of the polymer. Consequently, food effects are not to be expected and the dissolution characteristics of the dosage form are much more reliable, fostering product quality. It is important to know, though, that this safety feature is only available with Kollicoat® MAE 100-55. Other commercially available products still require the higher level of pre-neutralization, which means that our product can be used in formulations based on other products (me-too), but not the other way around.

This seems to be a small thing to remember, but not knowing it or overlooking it has a tremendous impact on product quality.

Often, these tiny, little things make the difference between an excellent product and an expensive failure. And, there are plenty of these obstacles scattered on the field of galenical development.

However, this brings me back to my initial statement: please get in contact with us. There are plenty of people in all regions that are happily willing to offer their support, not only with regard to questions on instant and modified-release delivery forms, but also on solubilization issues, skin delivery topics, or soft gel capsule formulations.