INTERVIEW: ELIZABETH SHEN, COLORCON

Here, Elizabeth Shen, PhD, Technical Marketing Manager, Colorcon, talks taste-masking, from the positive impact on medication adherence, to technical approaches and technology selection, and regulatory considerations.

Q: Why is taste-masking important?
A: Many active pharmaceutical ingredients (API) inherently possess a bitter taste. Nearly 20% of American adults surveyed complained of bad aftertastes or struggling to swallow when trying to take medication.[1]

If a medication is not palatable, the patient may opt to discontinue it. In fact, one of our own colleagues admitted he would rather risk malaria than continue with the foul-tasting preventative regimen. Whilst that comment might sound flippant, in fact it illustrates a very serious problem. Failure to take medication as prescribed leads to increased morbidity, mortality, and potentially avoidable healthcare costs exceeding US$100 billion annually in the US alone.[2] While objectionable taste may be one of several reasons for poor adherence, every measure that minimises these reasons helps.

With a recognised impact on patient healthcare outcomes and costs, the European Medicines Agency (EMA) has released guidelines promoting the development of medicines for paediatric use.[3] The US FDA is promoting similar initiatives. As a result, Colorcon has seen an increased interest from the pharmaceutical industry in taste-masking technologies.

Q: Which populations are most commonly targeted for taste-masking?
A: As you would imagine, taste-masking is incredibly important for paediatric populations. Firstly, children are 3-4 times as sensitive to tastes as adults, with increasing tolerance to bitter tastes with age. Secondly, children, particularly infants, are unable to rationalise ingestion of an unpalatable medicine.

Geriatric patients also often have problems with adherence due to difficulty in handling and swallowing tablets. While crushing some immediate-release tablets may be allowable, it generally is not advisable or palatable, and so other dosage forms may be more desirable.

Q: What dosage forms are typically used for taste-masked formulations?
A: The most popular oral dosage forms include liquids, powders, granules, orally disintegrating tablets (ODT), and chewable tablets. Each one has pros and cons, depending on the target age group. Liquids, powders, and granules provide the greatest flexibility in dosing, provided there is a simple way to meter the powders. For solid oral dosage forms like ODTs and chewable tablets, break-lines can be included in the tablet design to adjust dosing.

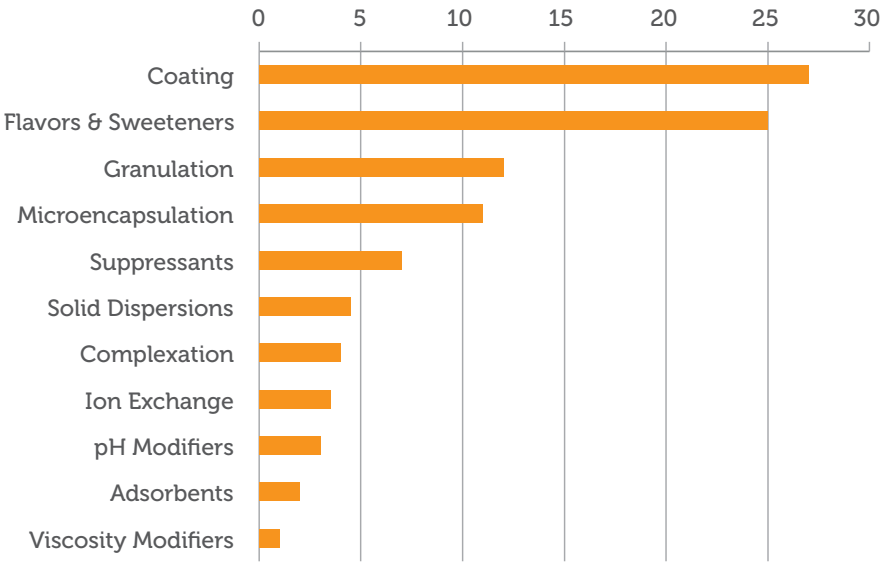

Figure 1: Breakdown of taste-masking technologies (from Bansal et al, "Trends in Pharmaceutical Taste Masking Technologies: A Patent Review". Recent Patents on Drug Delivery and Formulation, 2009, Vol 3, pp 26-39).

For infants and very young children, liquids, powders, and granules tend to be the dosage form of choice since these eliminate the need for chewing. The powders and granules can often be sprinkled onto baby foods and ingested simultaneously.

From the manufacturer's perspective, alternative dosage forms can also increase the product lifecycle and extend market exclusivity.

Q: What criteria are important for taste-masked formulations?
A: Both dissolution profile and taste profile contribute to the acceptability criteria for taste-masked formulations. However, each drug product will have different release profile requirements to meet an acceptable level of taste-masking depending on the dose strength and organoleptic response to the API. Ideally, the taste-masked dosage form should prevent release of the unacceptable tasting medicine until the API has left the mouth, then allow for immediate release once the dosage has been ingested.

To determine the taste profile, while electronic tongue technology is advancing, taste panels remain the preferred methodology for determining efficacy of taste-masking. Patients may be able to tolerate different levels of release in the mouth for different APIs depending on the drug solubility and other ingredients such as flavours and sweeteners in the formulation.

Some regulatory authorities have cautioned that the formulation cannot taste "too good" as a safeguard against mistaking the medication for candy. Taste profiles should aim for a neutral taste or one that is generally acceptable.

Mouthfeel can also contribute to the acceptability of a dosage form. If a drug particle or granule is tasteless but too large, it can give an unpleasant gritty sensation. Larger particles also become targets for chewing, eventually crushing the taste-mask coating, and causing release of the drug and bitter taste in the mouth.

Specifically in the case of paediatric dosage forms, the goal for taste-mask coating aims for the minimum weight gain necessary to achieve robust functionality. However, effective weight gains will be dependent on the properties of the substrate. For instance, if the drug particle is very fine or has a broad particle size distribution, higher weight gains of the

coating will be required for consistent taste-masking.[4] In short, when it comes to successful taste-masking, understanding the properties of your coating substrate or drug really matter.

Q: What kinds of strategies are available for taste-mask formulations?

A: For most solid oral dosage forms (SODs) or tablets, the API is blended with a number of excipients, and a well-designed film coating, such as Opadry® complete film coating system, often provides sufficient properties to adequately mask objectionable tastes for the brief residence time in the mouth before swallowing.

Alternative dosage forms such as sachets, ODTs, and chewable dosage forms pose additional challenges in taste-masking due to increased contact surface area as well as residence time in the mouth, enhancing any unpleasant taste and/or lingering aftertaste. In these cases it is often necessary to create a barrier, such as a specific taste-mask coating, between the API and the taste buds in order to improve palatability and aid compliance.

In a review of taste-masking technologies, coating was most highly rated, with inclusion of flavours and sweeteners a close second in terms of popularity (Figure 1).

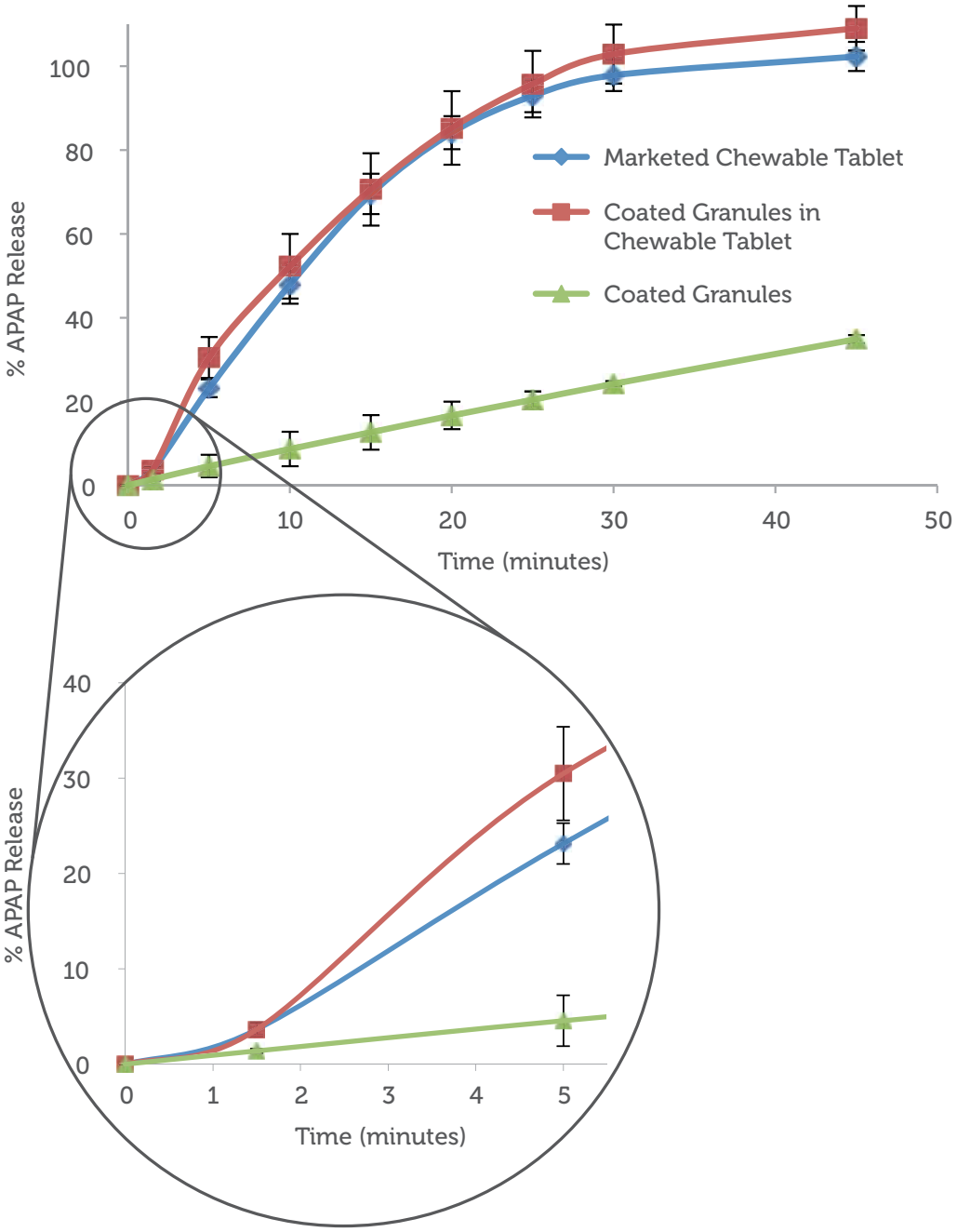

Figure 2: Drug release profiles of acetaminophen (APAP) granules coated with Surelease:Opadry (85:15) for the purposes of taste masking, formulated as granules and in a chewable tablet form, compared with a marketed chewable tablet. Top graph shows 50 minutes of data, with the first five minutes magnified in the lower graph.

Q: What types of coating technologies exist that provide taste-masking for oral dosage forms?

A: There are two main categories of coatings for taste-masking: pH-independent and pH-dependent.

As an example of a pH-independent taste-mask coating, Colorcon's customers have been successful when a combination of Surelease® and Opadry® is applied.[5] Surelease is an aqueous ethylcellulose dispersion and acts as the insoluble barrier membrane which prevents drug release in the mouth. Opadry acts as the soluble pore-former to promote immediate release in the stomach.

Recent work at Colorcon has demonstrated the use of this combination for taste-masking acetaminophen (APAP) granules. Surelease:Opadry (85:15) was applied to APAP granules in a Glatt GPCG-2 fluid bed. Granules were coated to 10% weight gain of the Surelease:Opadry and compressed into a chewable tablet formulation. The dissolution profiles are shown in Figure 2, demonstrating that by using Surelease and Opadry for taste-masking we were able to match the release profile of a commercially marketed product and meet requirements for immediate release (no less than 75% released in 45 minutes).

You may have noticed that the dissolution of the coated granules is quite different before and after compression into the chewable tablet. It is completely normal and expected for a partial rupture of the coating upon compaction pressure, and this can be accounted for in the design of the dosage form, as we have done here.

The second category of taste-mask coating technology is a pH-dependent coating based on reverse enteric polymers which are insoluble at the relatively neutral pH of the mouth and become soluble once in the lower pH of the stomach.

Included in this class of polymer are acrylic acid soluble polymers such as

Kollicoat® SmartSeal, an aqueous dispersion of methylmethacrylate and diethylaminoethyl-methacrylate copolymer from BASF (Ludwigshafen, Germany). The product was developed specifically for taste-masking applications for orally administered pharmaceutical products, and is considered a best-in-class reverse enteric polymer.

In 2014, Colorcon entered into a collaboration with BASF to develop a fully formulated coating system using Kollicoat SmartSeal. This relationship leverages BASF's expertise in polymer chemistry and Colorcon's long recognised leadership in fully formulated coating systems for pharmaceutical use. This collaboration aims to improve manufacturing speed and simplicity for the customer, enabling easy reconstitution of the film former while maintaining product functionality.

Colorcon is excited to have expanded its taste-masking product portfolio with Kollicoat SmartSeal. This allows us to better serve the industry in providing solutions to improve adherence, particularly in the more challenging paediatric and geriatric spaces.

Q: What is the regulatory status of these coatings?
A: Surelease and Opadry have been used for decades in the pharmaceutical industry including in immediate and extended release systems. Surelease has precedence of use in the US and EU for both adult and paediatric formulations.

In fact, the combination of Surelease and Opadry was selected by Merck, Sharpe, and Dohme (MSD) for a taste-masked version of ISENTRESS (raltegravir) for the treatment of HIV specifically for the paediatric segment.[7]

Kollicoat SmartSeal is a relatively new polymer in the marketplace, and its safety is supported by a comprehensive toxicological package including both in vitro and in vivo studies. There has been considerable interest from multinational pharmaceutical companies to explore SmartSeal for taste-masking development projects. Colorcon's regulatory team is also poised to assist any customer through the commercialisation process.

Q: What are the main concerns in the industry around taste-masking?
A: Some in the industry are concerned that a taste-mask coating could slow or completely arrest release, affecting bioavailability or efficacy of the drug.

Transit times in the gastrointestinal tract can vary greatly depending on the age of the patient, whether 90 days old or 90 years old, dose timing and patient instruction can be critical to achieving the desired release profile.

For pH-dependent coatings like SmartSeal, fluctuation in internal pH needs to be considered when designing the coating thickness and formulation. Internal pH can be affected by whether the medication was taken with or without food, what kind of food, or if the patient is taking other medications which may affect the stomach pH. Design of the coating thickness and formulation should allow pH-dependent coatings like SmartSeal to release at typical and elevated pH levels in the stomach.

Q: If I were developing a new taste-masking project tomorrow, how would I decide which coating is right for my project?
A: That's an excellent question, and harder to answer than you would think. Several factors go into the decision process for the formulation, including properties of the API, dose level, dosage form, desired release profile, etc, so there is no set answer.

The good news is that Colorcon's unparalleled Technical Services Group is available to guide customers through the decision process based on their formulation needs, beginning with initial product selection and continuing through development to scale-up and product launch. With access to Colorcon's technical experts, our customers can reduce development time and utilise any one of our Technical Service laboratories worldwide for trials, or Colorcon can provide expertise directly at our customers' sites.

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Dr Elizabeth Shen
Technical Marketing Manager,
Colorcon
T: +1 215 256 7700
E: eshen@colorcon.com

Colorcon, Inc
275 Ruth Road
Harleysville
PA 19438
United States

www.colorcon.com

Elizabeth Shen has more than a decade of pharmaceutical industry experience, with more than seven years at Colorcon as a Technical Manager focused on film coatings and formulation of solid oral dosage forms. Her experiences range from initial product recommendations to troubleshooting of commercial scale processes resulting in numerous marketed dosage forms.

Dr Shen holds a BS in Chemical Engineering from Case Western Reserve University and went on to complete her MS and PhD from Rutgers the State University of New Jersey's Department of Chemical and Biochemical Engineering. Dr Shen subsequently completed post-doctoral studies in Rutgers' Pharmaceutical Engineering Training Program under the direction of Fernando J Muzzio, PhD.