Seeing is Believing: Innovative Use of Raman Microscopy to Visualize the Integrity of a Barrier Membrane Coating for Taste-Masking of Acetaminophen Granules in Chewable Tablets

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Purpose

Effective taste-masking of particles for incorporation into chewable dosage forms is influenced by the consistency and integrity of the applied barrier membrane (BM) coating. During the tablet compression process, the coating around drug particles may fracture leading to an adverse taste profile from the final dosage form. In addition to the barrier coating composition and application levels, the substrate morphology, film strength, and particle size also influence the final integrity of the coated particles.[1,2] In this study, Raman microscopy was used to generate images and visualize the integrity of barrier membrane coatings on two different grades of acetaminophen (APAP) granules with differing morphologies. Raman imaging was used to evaluate granule characteristics from two stages of the manufacturing process; after coating and after compression of the coated granules. Further, the observations from the Raman image analysis were correlated with in vitro drug release.

Experimental Methods

Coating of APAP Granules

For taste-masking purposes, two grades of APAP, Compap (amorphous, spray dried, d(50): 181 µm) and Special granular (crystalline d(50): 332 µm) (Covidien, USA) were coated using Surelease® Ethylcellulose Dispersion Type B NF, combined with a hypromellose-based Opadry® complete film coating system (Colorcon Inc., West Point, USA) used as a pore-former at a ratio of 85:15 w/w. The coating was applied to the granules using a top spray fluid bed coater (Glatt GPCG-2, USA) up to 30% weight gain (WG).

Chewable Tablet Formulation

The coated APAP granules were passed through a 20 mesh sieve, then blended with the Parteck ODT blend (Merck Millipore, DE) plus a sweetener, disintegrant and colloidal silica. Magnesium stearate and FD&C blue #1 aluminum lake were passed through a 60 mesh sieve, then added to the chewable tablet blend as lubricant and colorant. The chewable tablet blend was compressed using a single station manual compression press (Globe Pharma, USA) with 12.5 mm flat-faced beveled edge tools at a compression pressure of 1200 psi. The target tablet weight was kept constant at 770 mg. The composition of the chewable tablet formulation is shown in Table 1.

Table 1. APAP Chewable Tablet Formulation

Ingredients	Supplier	(%)
Coated APAP granules	--	13.9
Parteck ODT blend	EMD Millipore, USA	76.8
NutraSweet (Aspartame)	NutraSweet, USA	0.8
Kollidon® CL-F (Crospovidone)	BASF, DE	5.0
Cab-o-Sil M5-P (Colloidal silica)	Cabot Corp., USA	1.5
Magnesium stearate	Peter Greven GmbH, DE	1.8
FD&C Blue #1	Colorcon, USA	0.2
Total		100.0

Raman Spectroscopy Studies

The Raman maps of coated APAP granules and chewable tablets were acquired using a Horiba LabRam HR at laser excitation wavelength of 785 nm and power <40 mW. For Raman microscopic analysis, samples of the coated APAP granules were entrapped in UV cure epoxy resin and the cross-section obtained using microtome knife; whilst cross-section for the chewable tablets was directly obtained using the microtome knife.

Dissolution Studies

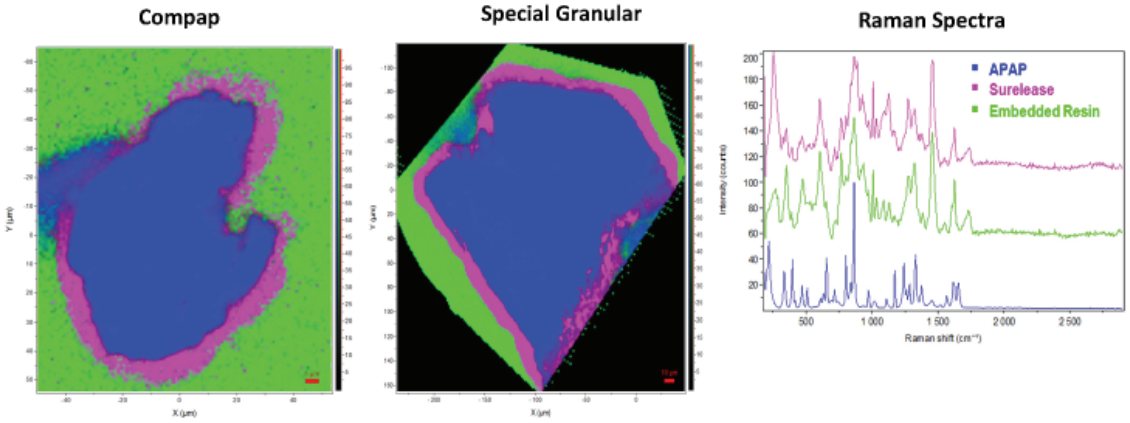
In vitro dissolution testing of the coated granules and chewable tablets was carried out using USP Apparatus II (paddles) at 75 rpm in 900 ml of pH5.8 phosphate buffer. Drug release was determined spectrophotometrically at a wavelength of 243 nm.

Results

Raman Microscopy of Coated Granules

Raman images of the coated granules confirmed the presence of the coating surrounding the particle surfaces for both grades of APAP (Figure 1). However, non-uniformity of the coating around the edges of the irregularly shaped Compap granules was clearly observed. Compared to the Compap granules, the coating on the more regular shaped Special granular grade appeared more uniform in thickness, continuity, and integrity.

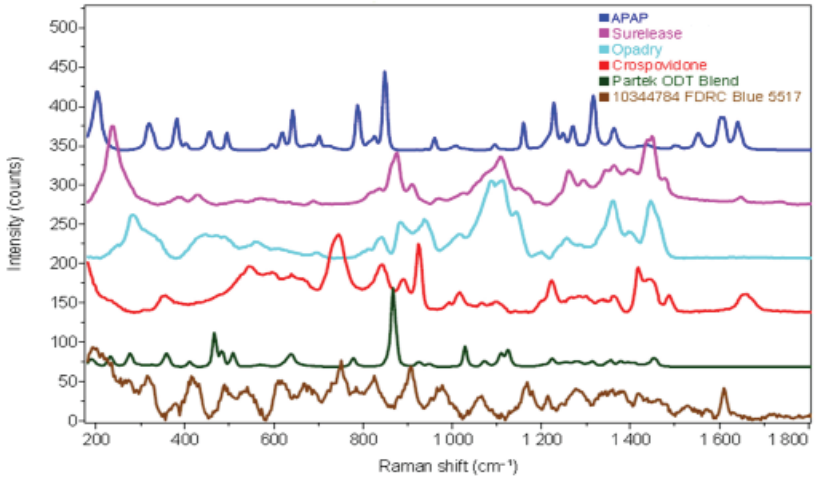
Figure 1. Raman Imaging of Coated APAP Granules prior to Compression



Raman Microscopy of Compressed Chewable Tablets

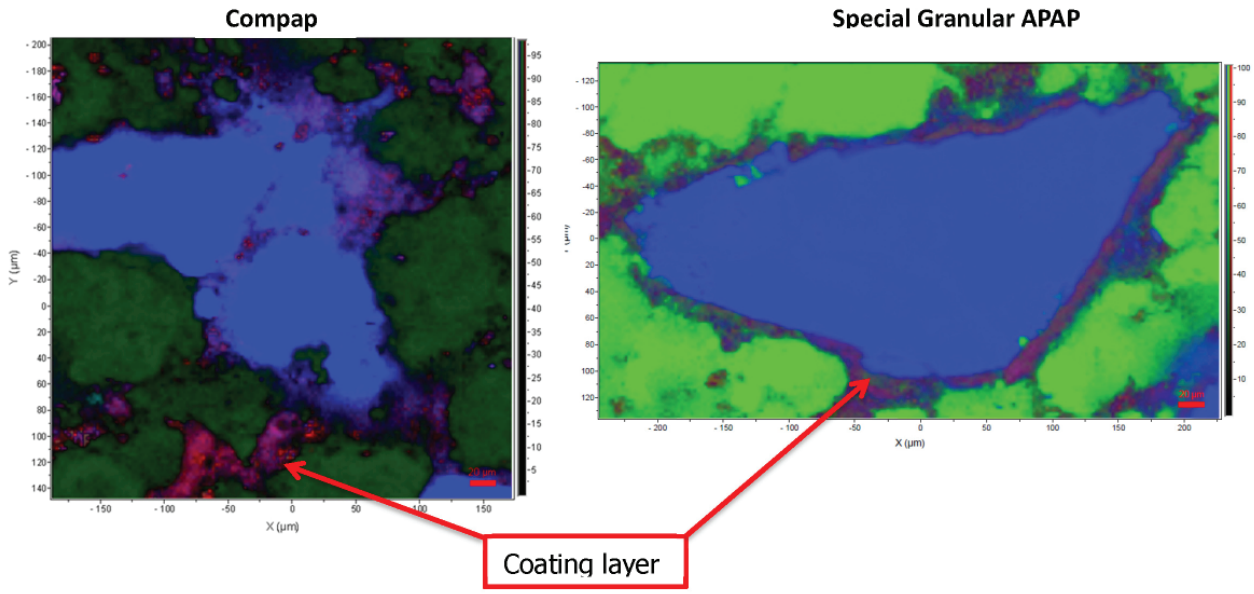
The Raman spectra of the compressed tablets indicate clear differentiation of the individual formulation components (Figure 2).

Figure 2. Raman Spectra of APAP Compressed Chewable Tablets



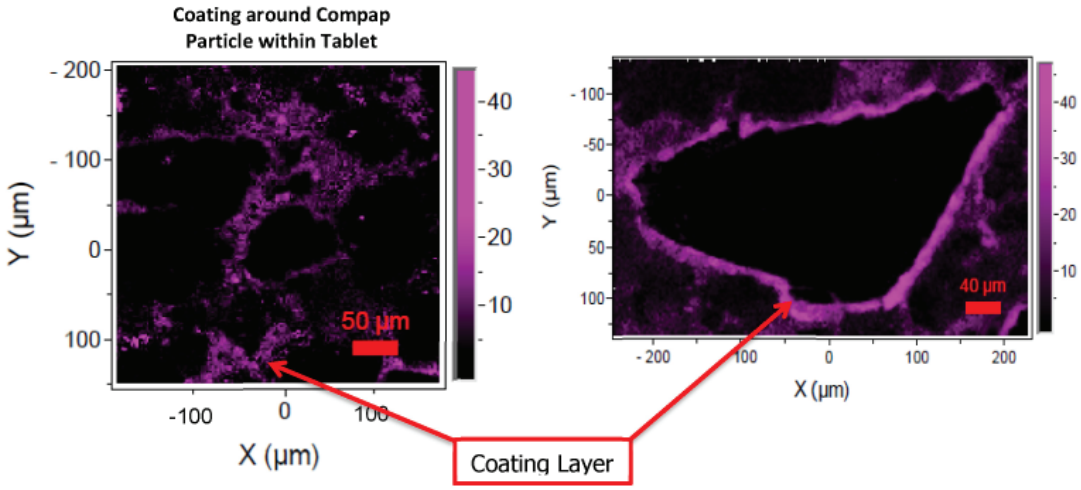
In chewable tablets, the integrity of BM coating layer around the Compap particle was further disrupted, probably due to the effect of compression force. The coating layer (highlighted in purple) was diffused into the other regions of the tablet leaving the Compap particle unprotected. Conversely, the Special granular particles coating layer was found to be intact and adhered uniformly (Figure 3).

Figure 3. Raman Imaging of Single APAP Particle after Compression



Further individual component spectral analysis was carried out by retaining the coating layer (Surelease) component spectra (purple) and eliminating all other component spectra from the analysis. This highlighted the differences in coating layer integrity between the particles of different morphology (Figure 4).

Figure 4. Raman Imaging of Surelease Coating around APAP Particle within Chewable Tablet



Drug Release Analysis

The observed differences in coating layer integrity after compression of the coated granules was further illustrated by dissolution testing. Slower initial drug release, in the first 5 mins, is necessary to attain efficient taste-masking of acetaminophen granules. The drug release from coated Compap granules was significantly faster than Special granular grades, primarily due to non-uniformity of coating around the irregular particle shape. Further, the compression of the Compap granules into chewable tablets resulted in a 41% increase in drug release in the first 5 mins. Whereas, compression of Special granular grades resulted in only a 5% rise in drug release after 5 mins of dissolution (Figures 5 and 6).

Figure 5. Coated Granule Drug Release Before and After Compression

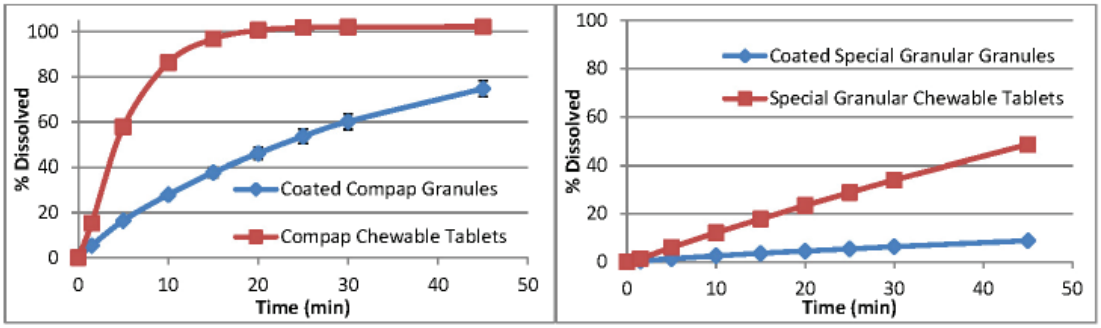
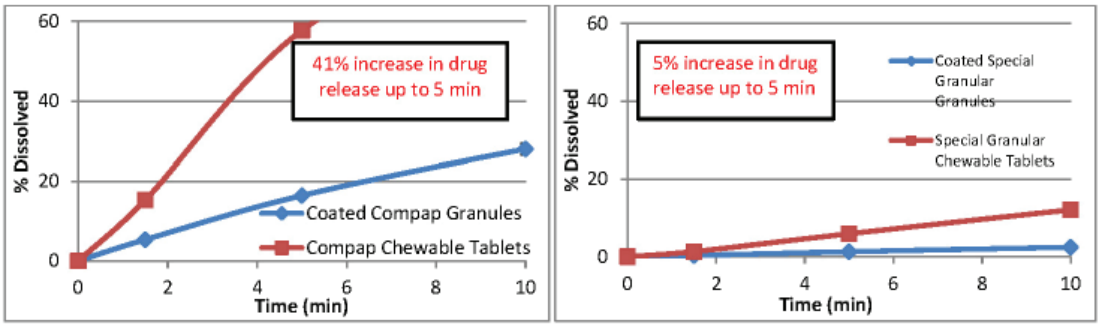


Figure 6. Expanded View of Coated Granule Drug Release Before and After Compression



Once substrate considerations are understood, the drug release profile can be tailored to achieve either greater lag times or faster release by varying the coating weight gain and Surelease:Opadry ratios.[3]

Conclusions

In this study, drug particles were successfully coated with Surelease:Opadry giving a reduced initial drug release that may provide desirable taste-masking characteristics when compressed into chewable tablets. The effect of substrate morphology and particle characteristics were found to be important in maintaining the integrity of the coating throughout the process of manufacturing chewable tablets. Raman microscopy was a useful technique to visualize the integrity of the coating layer at various stages of chewable tablets development and provided evidence for APAP release profile patterns seen from their compressed chewable tablets.

References

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