

# Evaluation of Acetaminophen Particle Size and Crystal Morphology on Taste-Masking Performance from Coated Granules and Chewable Tablets

Raxit Y. Mehta, Charles R. Cunningham and Ali R. Rajabi-Siahboomi

CRS Poster Reprint  
2015

## Abstract Summary

The taste-masking of a bitter drug, acetaminophen (APAP) was achieved by application of a fully formulated aqueous ethylcellulose dispersion (Surelease®) and HPMC-based Opadry® combination coating. Three different grades of APAP with average particle size from 181 to 473 µm were selected to evaluate the effect of particle size and crystal morphology on taste-masking performance. The coated granules were characterized for in vitro drug release and then compressed into chewable tablets. Compap represents spray dried granules of APAP, while Special granular (SG) and USP granular represent a crystalline grade. The objective of this investigation was to evaluate the effect of initial particle size and crystal morphology on the drug release from coated granules and chewable tablets.

## Introduction

Taste-masking of unpleasant and bitter drugs is desired to improve patient compliance for pediatrics and geriatric patients. From the available taste-masking options, an insoluble polymer coating of the drug has been the most cost effective and preferred option.<sup>1,2</sup>

For taste-masking applications, a drug particle size range of 0.2-0.8 mm is recommended.<sup>1</sup> The initial drug particle size can affect the coating process efficiency, coating weight gain (WG) required, and drug release profile from resulting coated granules and chewable tablets. Hence, to evaluate the effect of particle size and crystal morphology, various APAP grades were selected and coated with an aqueous dispersion of ethylcellulose (Surelease E-7-19040) and a soluble pore-former (Opadry YS-1) combination.

The pore-former facilitates media penetration and drug release from the coated granules to conform to immediate release monograph specifications. The coated granules and compressed chewable tablets were characterized for drug release performance.

## Experimental Methods

### Coating of APAP Granules

Three grades of APAP: Compap; Special granular (SG) and USP granular (Covidien, USA) were coated using Surelease E-7-19040 and HPMC-based Opadry (YS-1) as a pore-former, at the weight ratio of 85:15 w/w (Table 1). Prior to the coating application the dispersion was prepared at 12% w/w solids concentration.

The coating was applied to the granules using a top spray fluid bed coating (Glatt GPCG-2) process. The coating process parameters are shown in Table 1. Samples were collected at 10% and 30% WG.

### Physical Characterization of Granules

Particle size (uncoated and coated granules) was measured using Malvern Mastersizer 2000. The microscopic images of the granules were taken using a Leica Microscope Camera.

### Chewable Tablets Formulations

The chewable tablet formulations are shown in Table 2. Coated APAP granules were blended with the Parteck ODT blend (Merck Millipore, DE), a sweetener, a disintegrant and colloidal silica after passing through a #20 mesh sieve. Magnesium stearate and FD&C blue #1 aluminum lake were passed through a #60 mesh sieve and used to lubricate the blend.

The chewable tablet blend was compressed using a single station manual compression press (Globe Pharma, USA) and 12.5 mm flat-faced beveled edge tooling at compression pressure of 1200 psi. The tablet weight was kept constant at 770 mg.

### Dissolution Studies

In vitro dissolution studies for the coated granules and compressed chewable tablets were carried out using USP Apparatus II (paddles) at 75 rpm in 900 ml of pH 5.8 phosphate buffer. Drug release was determined spectrophotometrically at a wavelength of 243 nm.

**Table 1. Coating Formulation and Process Parameters**

Parameters	Value
<b>Formulation Variables</b>	
Coating Substrates: APAP Grades	Compap, SG, USP granular
Coating formulation	Surelease: Opadry 85:15 ratio
Coating solution solids (w/w)	12%
Coating solution viscosity (cP)	70-80
<b>Process Variables</b>	
Coating Process	Top spray- Glatt
Batch size (g)	1000
Inlet temperature (°C)	75-85
Product temperature (°C)	42-45
Exhaust temperature (°C)	35-38
Atomizing air (bar)	2.0
Air volume (m <sup>3</sup> /hr)	40-50
Solution flow rate (g/m)	6-8

**Table 2. APAP Chewable Tablet Formulations**

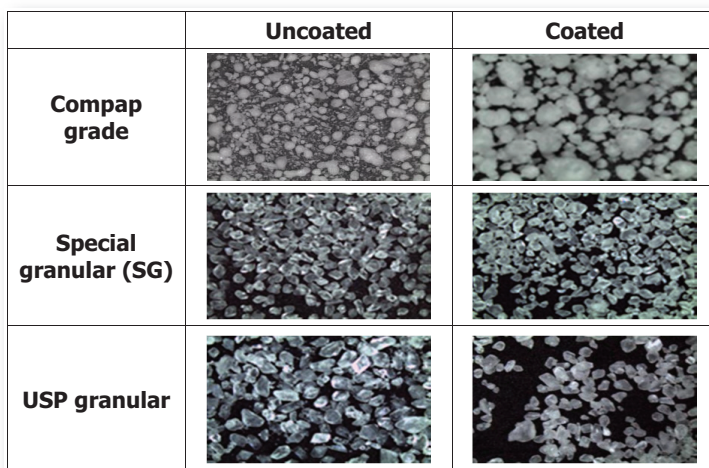
Ingredients	Supplier	10%WG Granules (%w/w)	30%WG Granules (%w/w)
Coated APAP Granules	--	11.8	13.9
Parateck® ODT blend	EMD Millipore, USA	78.9	76.8
NutraSweet® (aspartame)	NutraSweet, USA	0.8	0.8
Kollidon®CL-F (crospovidone)	BASF, DE	5.0	5.0
Cab-o-Sil M5-P (colloidal silica)	Cabot Corp., USA	1.5	1.5
Magnesium Stearate	Peter Greven GmbH, DE	1.8	1.8
FD & C Blue #1	Colorcon, USA	0.2	0.2
<b>Total</b>		<b>100.0</b>	<b>100.0</b>

## Results and Discussion

Microscopic examination of the coated granules clearly shows that the SG and USP granular grades of APAP were coated with little or no agglomeration and remained as discrete particles. The Compap grade with its high level of fines resulted in excessive levels of agglomeration (Figure 1).

These observations were further confirmed by particle size analysis where there were minimal differences in particle size growth between coated and uncoated granular grades and a large increase in particle size for the Compap grade (Table 3).

**Figure 1: Comparison of Uncoated and Coated APAP granules**



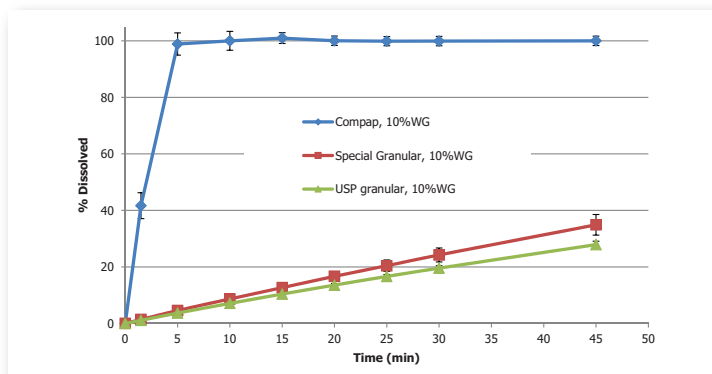
**Table 3. Particle Size Comparison of APAP Granules**

APAP grades	Processing Stage	Particle Size		
		D10 (µm)	D50 (µm)	D90 (µm)
Compap	Uncoated	75.3	181.2	332.3
	Coated	123.6	222.7	382.1
Special granular (SG)	Uncoated	209.2	332.2	525.0
	Coated	243.4	360.0	531.4
USP granular	Uncoated	280.0	473.4	773.7
	Coated	294.6	480.2	764.1

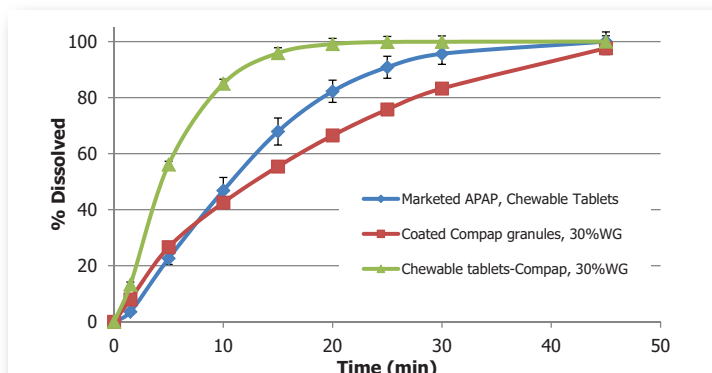
The drug release from Compap was significantly faster than SG and USP granular grades at 10% WG, due to the smaller particle size of Compap. Hence, Compap granules were coated up to 30% WG to achieve the desired rate of drug release for taste-masking and then compressed into the chewable tablets. However, the drug release from these tablets was still found to be faster than the marketed formulation, suggesting failure of taste-masking functionality even at 30% WG. This was related to breakage of friable agglomerates generated during coating of Compap granules.

On the other hand, SG and USP granular were coated at 10% WG and compressed into chewable tablets. The drug release from these tablets was comparable to the marketed APAP chewable tablets, as shown in Figure 4. The crystalline nature of SG and USP granular grades resisted compression force and retained taste-masking functionality.

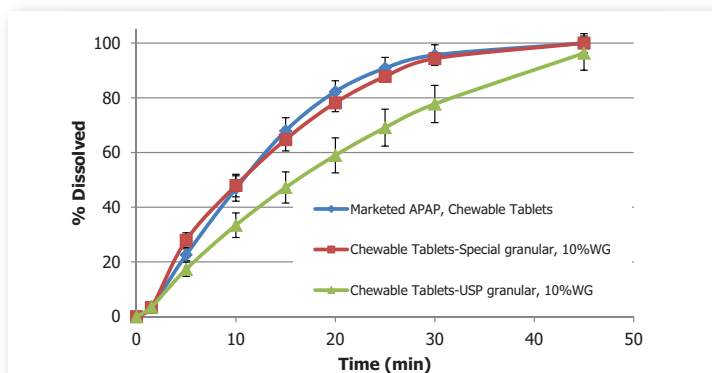
**Figure 2: Drug Release from Coated APAP Granules at 10% WG**



**Figure 3: Drug Release from Coated Compap Granules at 30% WG and Compressed Chewable Tablets**



**Figure 4: Drug Release from APAP Chewable Tablets from Coated SG and USP Granular Grades at 10% WG**



## Conclusions

This study successfully demonstrates the utility of aqueous ethylcellulose dispersion (Surelease) in combination with Opadry, as the pore-former, to develop APAP taste-masked chewable tablets comparable to marketed formulations. The initial particle size of the APAP granules significantly affects the coating weight gain and drug release profiles. Additionally, the strength of coated granules and morphology was also found to be critical for developing taste-masked APAP chewable tablets.

## References

1. Yourong Fu, et. al., Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies. *Critical Review in Therapeutic Drug Carrier Systems*, 2004; 21(6):433–475
2. Zelalem Ayenew, et. al., Trends in Pharmaceutical Taste Masking Technologies: A Patent Review. *Recent Patents on Drug Delivery & Formulation* 2009, 3, 26-39

---

The information contained herein, to the best of Colorcon, Inc.'s knowledge is true and accurate. Any recommendations or suggestions of Colorcon, Inc. with regard to the products provided by Colorcon, Inc. are made without warranty, either implied or expressed, because of the variations in methods, conditions and equipment which may be used in commercially processing the products, and no such warranties are made for the suitability of the products for any applications that you may have disclosed. Colorcon, Inc. shall not be liable for loss of profit or for incidental, special or consequential loss or damages.

Colorcon, Inc. makes no warranty, either expressed or implied, that the use of the products provided by Colorcon, Inc., will not infringe any trademark, trade name, copyright, patent or other rights held by any third person or entity when used in the customer's application.

For more information, contact your Colorcon representative or call:

North America  
+1-215-699-7733

Europe/Middle East/Africa  
+44-(0)-1322-293000

Asia Pacific  
+65-6438-0318

Latin America  
+54-1-5556-7700



All trademarks, except where noted, are property of BPSI Holdings LLC. The information contained in this document is proprietary to Colorcon, Inc. and may not be used or disseminated inappropriately.  
©BPSI Holdings LLC 2015