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

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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.[1, 2]

For taste-masking applications, a drug particle size range of 0.2-0.8 mm is recommended.[1] 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
Formulation Variables	
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
Process Variables	
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^3/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
Parteck® 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
Total		100.0	100.0

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

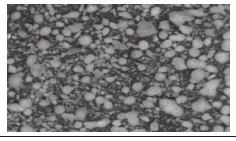
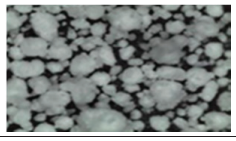
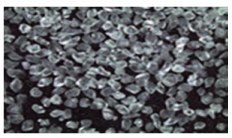
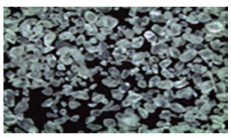
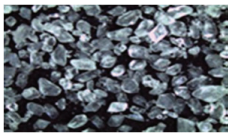
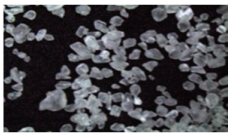
	Uncoated	Coated
Compap grade		
Special granular (SG)		
USP granular		

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

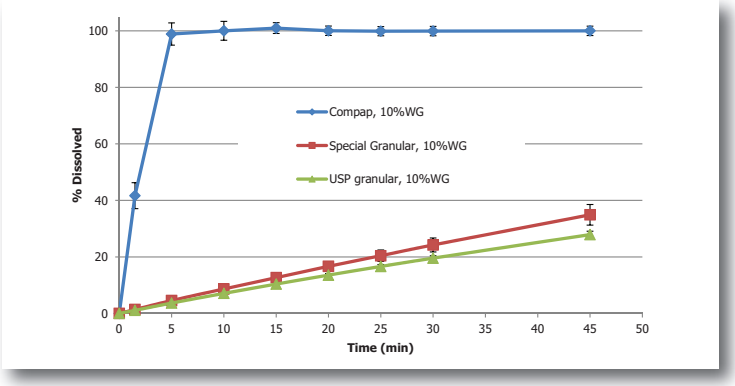


Figure 3: Drug Release from Coated Compap Granules at 30% WG and Compressed Chewable Tablets

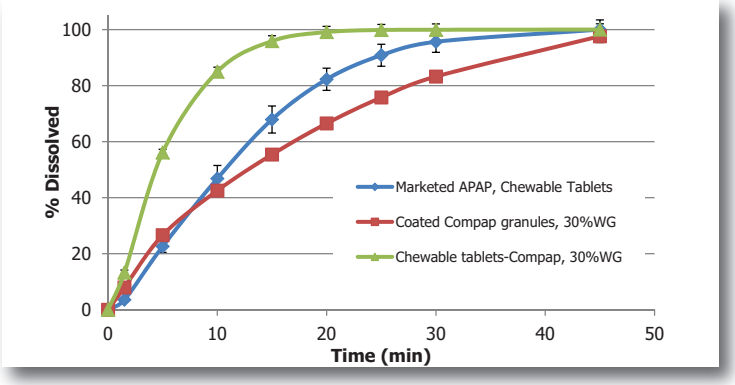
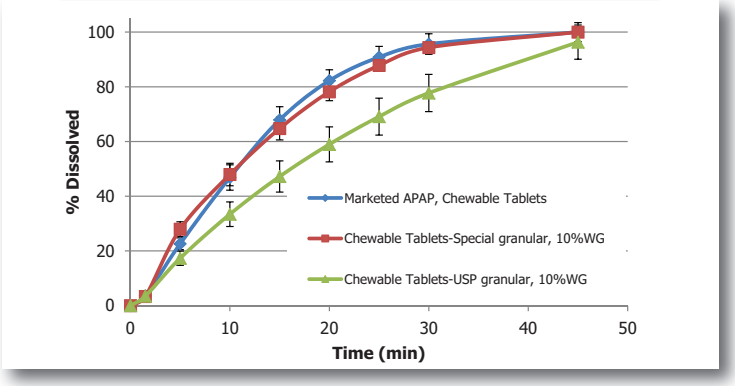


Figure 4: Drug Release from APAP Chewable Tablets from Coated SG and USP Granular Grades at 10% WG



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

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