Feasibility of Taste-Masking a Highly Soluble Drug via Powder Layering with Fine Particle Ethylcellulose

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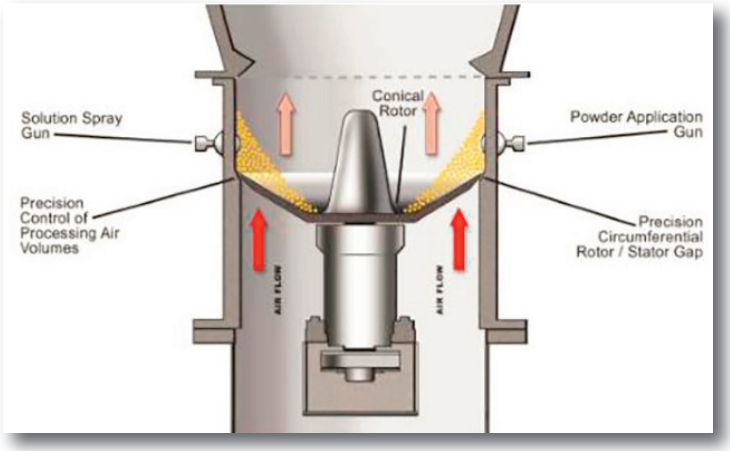
Purpose

The objective of this work was to evaluate rotor granulation and powder layering for the purpose of taste-masking a very bitter and highly soluble model drug for a pediatric dosage form. Previous attempts, using other methods to mask the taste, proved insufficient due to the high aqueous solubility of the model drug.[1] In this study ETHOCEL™ Standard 7 FP Premium (ETHOCEL 7 FP), fine particle ethylcellulose, (IFF, USA) was chosen as a barrier membrane for taste-masking.

Rotor granulation and powder layering were selected for investigation as these methods are reported to produce dense, round, and evenly sized granules at a faster coating rate than typically achieved with Wurster.[2] As opposed to top or bottom spray, rotor granulation uses a rapidly rotating plate to spheronize the material within the powder bed (Figure 1). Generally a liquid binder is applied in a granulation process, or a powder is fed in the presence of a binder, to act as a dry coating on the substrate within the rotor granulator. The film produced by powder layering is coalesced via application of an aqueous binder along with high tangential forces.

Figure 1. Cross-sectional Schematic of GRANUREX Rotor Granulator (Courtesy of Vector-Freund Corporation)

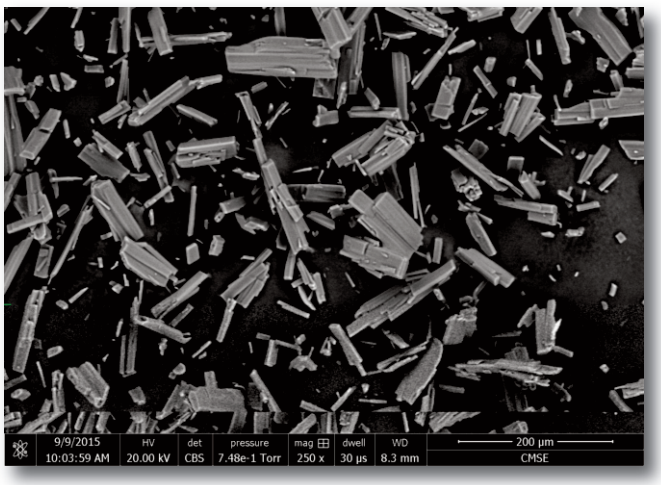


Methods

The model drug is highly water-soluble (50 mg/ml) with a D_{50} of 50 µm. In the scanning electron microscopic (SEM) image shown in Figure 2, the needle-shaped morphology and broad particle size distribution (PSD) of the model drug is evident.

A Vector VFC-LAB 3 Flo-Coater System fitted with a GXR-35 Granurex rotor insert (Vector-Freund Corporation) was used to enable rotor granulation and powder drug layering. A loss-in-weight powder feeder (K-Tron) was employed to meter the powder application.

Figure 2. Scanning Electron Micrograph of the Model Drug



Three strategies for creating a robust coating substrate were investigated (Figure 3), and process parameters are detailed in Table 1.

In the first part of the study, the model drug was layered onto Suglet® sugar spheres (60/80 mesh) using an Opadry® Clear coating as the binder. This process created round, uniform substrates for taste-mask coating. Opadry, at 5% w/w solids solution, was applied to 1 kg Suglets at a rate of 7 g/min, creating a "tacky" substrate. Drug was fed into the powder bed at a rate of 25 g/min, continuing until 1 kg of model drug had been layered onto the beads. To create a barrier membrane for taste-masking, 1.5 kg batch of the layered beads were placed back into the Granurex for ETHOCEL 7 FP powder layering. ETHOCEL 7 FP was fed at a rate of 15 g/min while applying a binder of triethyl citrate, polysorbate 80, and deionized water at a rate of 6-9 g/min. At the end of the run, a 75 g quantity of talc was added to prevent layered beads from sticking to one another.

In the second trial, Starch 1500® partially pregelatinized maize starch was blended with the drug using a 4:1 drug to starch ratio, to examine the impact of drug adherence to the Suglet. The free-flowing blend was fed at a rate of 30 g/min, layering 1.7 kg of the blend onto 1 kg of Suglets in under 90 minutes. The Suglets layered with drug:starch were further layered with ETHOCEL FP at a rate of 12 g/min. The barrier membrane layering process was completed in under 40 minutes.

For the third trial, the model drug was blended with microcrystalline cellulose (MCC) (Avicel PH-101, FMC) in a 95:5 ratio and rotor granulated with a METHOCEL™ E5LV (hypromellose) solution (10% w/w solids) as a binder. Granules were dried in the Granurex for 15 minutes at 40ºC. These granules were sieved to obtain particles ranging between 100 and 425 µm diameter, discarding coarse and fine particles.

Manufactured coating substrates were powder layered with ETHOCEL 7 FP and sampled at various weight gains up to 70% weight gain (WG). ETHOCEL FP layered granules were cured in the Granurex for one hour at 70ºC, 50 cfm, to achieve a final product temperature of 35ºC.

Figure 3. Formulation Strategies for Taste-Masking of Model Drug
(i) Powder Drug Layer using Opadry Clear onto Suglets (60/80 mesh)
(ii) Powder Drug Layer using Starch 1500 onto Suglets (60/80 mesh)
(iii) Rotor Granulation of Drug with MCC

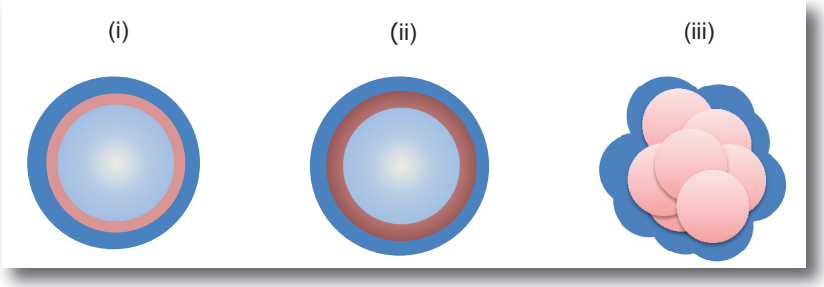


Table 1. Process Parameters for Drug Layering, Rotor Granulation, and ETHOCEL 7 FP Powder Layering

	Drug Layering on Suglets	Rotor Granulation	ETHOCEL 7FP Powder Layering
Starting Batch Size	1.0 kg	1 kg 95:5, API:MCC	1.0-1.5 kg
Binder	Opadry Clear @ 5% solids in DI water	METHOCEL E5LV @ 10% solids in DI water	69.9% DI water 30.0% triethyl citrate 0.1% polysorbate 80
Powder Feed Rate (g/min)	25-30	n/a	12
Binder Spray Rate (g/min)	8-12	6-9	6-9
Rotor Speed (rpm)	250	250-300	250
Product Temperature	16-18°C	15°C	15°C
Exhaust Temperature	17-18°C	16° C	17°C
Slit Air (cfm)	15	12	12
Total Process Time (min)	70	110	70

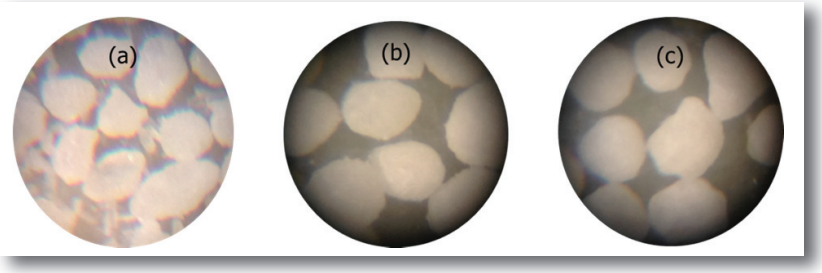
Particle size analysis was conducted on the powder layered particles using a Malvern Mastersizer. Coated substrates were evaluated for drug release using a small-volume biorelevant dissolution method developed at Colorcon. The method consists of a two-stage process beginning with 5 ml of simulated saliva for five minutes, followed by transfer to a 250 ml vessel of simulated gastric fluid to mimic a fasted stomach after intake of water.

Results

Drug layering onto Suglets was successful, although this model drug included long needle-shaped particles which did not adhere well to the sugar sphere. Only small particles appeared bound to the spheres with large particles remaining free (Figure 4a).

The formula including Starch 1500 improved adhesion to the sugar spheres (Figure 4b). These drug-layered spheres were then powder layered with up to 30% WG of ETHOCEL 7 FP in under 40 minutes. Rotor granulation of the model drug with MCC produced uniform and free-flowing particles. From a 1.7 kg granulation batch, 1.3 kg of granules were retained between 100 and 425 µm. These sieved granules were then powder layered with ETHOCEL 7 FP up to 70% WG in under 1 hour. Two separate batches of ETHOCEL 7 FP layered granules were manufactured and cured at 70ºC to achieve a final product temperature of 35ºC. Optical micrographs of each formulation approach are shown in Figure 4.

Figure 4. Optical Micrograph of (a) Suglets Powder Layered with Model Drug (b) Suglets Powder Layered with a Blend of Model Drug and Starch 1500 (c) Rotor Granulated Model Drug Powder Layered with ETHOCEL 7 FP



Due to the particle size of the extragranular material to be used in the final dosage form, the overall powder layered Suglets were not selected for further analysis. Particle size distribution, SEM, and dissolution analysis were completed for the rotor granulated drug, powder layered with ETHOCEL 7 FP (70% WG).

Particle size analysis was conducted using a Malvern Mastersizer (Figure 5). The PSD for both trials was very similar indicating good reproducibility on the lab scale, as well as consistency of granule size (Table 2).

Figure 5. Particle Size Distribution of Drug Granules Powder Layered with ETHOCEL (70% WG)

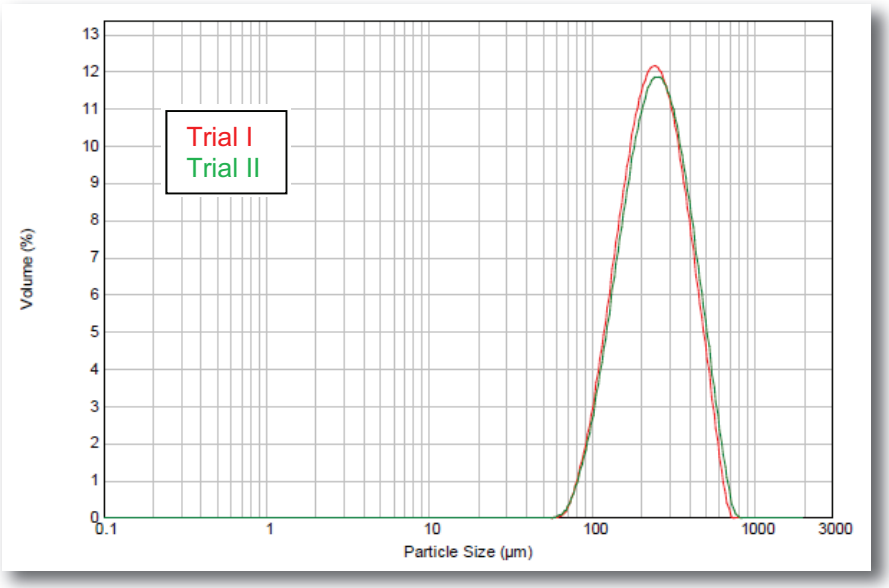
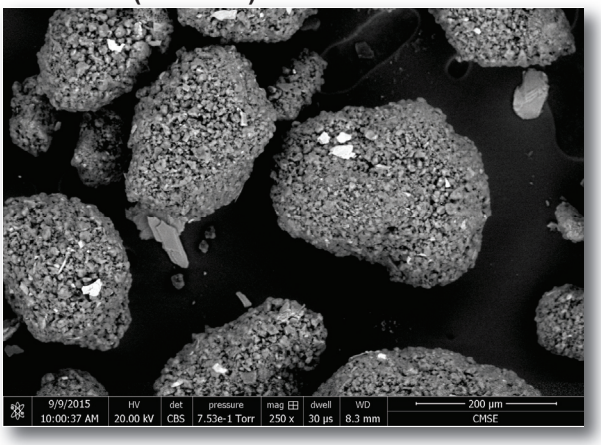


Table 2. Average Particle Size of ETHOCEL 7 FP Layered Drug Granules

	Trial #1	Trial #2
D_{90}	434.1 µm	456.9 µm
D_{50}	238.8 µm	248.4 µm
D_{10}	127.8 µm	130.5 µm

The SEM image of the cured and powder layered granules, clearly shows the structure and morphology (Figure 6). The granules appear to be uniform in size, fairly round, and evenly coated with ETHOCEL 7 FP particles.

Figure 6. Scanning Electron Microscopic Image of Rotor Granulated Model Drug, Powder Layered with ETHOCEL 7 FP (70% WG)



In vitro dissolution testing demonstrated that powder layering of ETHOCEL 7 FP resulted in some initial delay of release, with approximately 10% release in 30 seconds in simulated saliva (Figure 7). Immediate release was achieved once the granules were transferred to the simulated gastric fluid.

No other taste-masking methodology had yet been successful in providing any significant change in release profile. Uncoated granules demonstrated 99% drug release in less than one minute. Even the slightest delay in initial release was considered successful given the challenges in taste-masking using both bottom-spray and tangential-spray fluid bed coating.[1]

Figure 7a. Two-Stage Dissolution of ETHOCEL 7 FP Layered Granules (70% WG). (a) Dissolution in Simulated Saliva Followed by Simulated Gastric Fluid

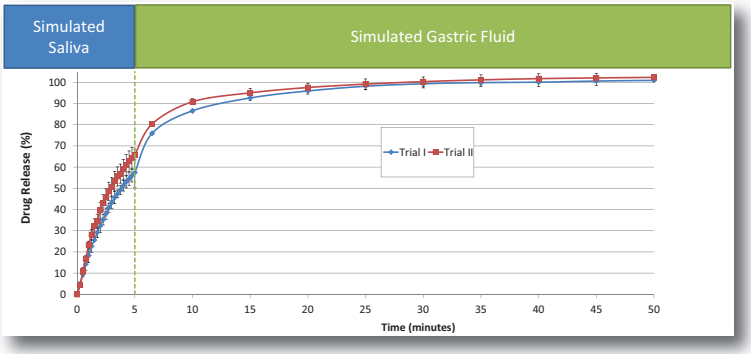
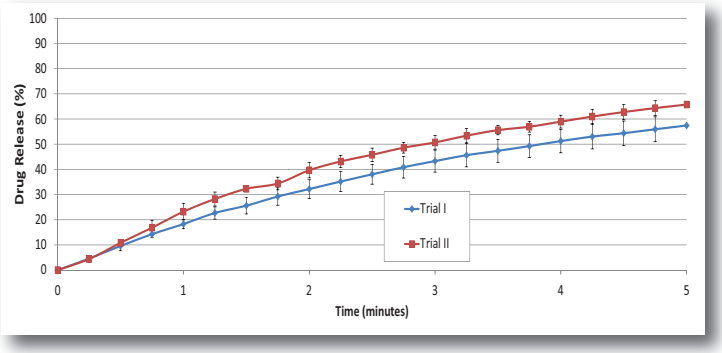


Figure 7b. Two-Stage Dissolution of ETHOCEL 7 FP Layered Granules (70% WG). (b) Focus on First Stage of Release in Simulated Saliva.



Conclusions

This work demonstrates the feasibility of ETHOCEL 7 FP powder layering as a highly efficient taste-masking technology. A significant advantage of rotor granulation and powder layering is the reduced process times, compared to traditional fluid bed processes. Weight gains of the barrier membrane polymer ETHOCEL 7FP were successfully applied at a rapid rate, in this trial at 1% WG per minute. Additionally, the method requires low process temperatures and low moisture allowing for use with heat and/or moisture sensitive compounds.

While drug-layered Suglets were not evaluated for dissolution, due to segregation potential in this research, it remains a feasible alternative taste-masking technology for evaluation with other drugs and formulations.

Rotor granulation and powder layering produced uniform, free-flowing particles with sufficient delay of release to demonstrate potential for taste-masking of a very soluble model drug. Powder-layered granules exhibited taste-masking delay, excellent flow properties, and matched powder properties of the extragranular excipients intended for compression into an orally disintegrating tablet.

REFERENCES

1. S. Forster, "Comparing Process Efficiency and Capability of Fluid bed Technology for Taste Masking," Solid Dose Drug Delivery Workshop, Quebec, Canada, September 3, 2014.
2. Characteristics of Rotor Granulation (Spheronization) Accessed September 2015, http://www.freund-vector.comtechnology/granmeth.asp

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