

In-vitro Dissolution Testing of Delayed Release Multi-Particulate Systems

ABSTRACT SUMMARY

Enteric coated multi-particulate systems may soften and agglomerate on the outer surface when in acidic media, affecting drug release profiles when tested in buffer. In this study the efficacy of fumed silica as an anti-adherent agent on the surface of enteric coated multi-particulates was investigated. Spraying of silicon dioxide dispersion affected discrete multi-particulate units in acid media and resultant consistent dissolution profiles in buffer media.

INTRODUCTION

There is a growing interest in the area of multi-particulate (MP) delayed release systems. Aqueous acrylic enteric systems have been extensively studied for coating of MPs (1). Enteric coated dosage forms are tested for their gastro-resistance performance in HCl acid media (pH 1.2) for up to 2 hours prior to being assessed for drug release in a buffer media (phosphate buffer pH 6.8 or above) (2). During the gastro-resistance testing, the enteric membrane on MPs may soften and cause agglomeration of the units. This may lead to slow and variable drug release profiles, when transferred to the buffer media (3). The objective of this study was to investigate the use of fumed silica as an anti-adherent agent to prevent potential agglomeration of multi-particulates in acid media.

EXPERIMENTAL METHODS

Fumed silica (CAB-O-SIL[®] M-5P, Cabot Corporation, USA) and a formulated methacrylic acid co-polymer (Acryl-EZE[®], Colorcon, Inc., USA) were used in this study. Chlorpheniramine maleate (CPM) was coated onto 18/20 mesh (850-1000 μ m) sugar spheres (Colorcon, Inc.) to a target drug load of 37 mg/g using a Vector fluidized bed coater (FL-M-60 equipped with Wurster column) using Hypromellose 2910 (METHOCEL[™] E6 Premium, Dow-Wolff Cellulosics, USA) as a binder. The drug layering was carried out at an inlet temperature of 58-60°C, fluid delivery rate of 118 mL/minute, atomizing air pressure of 20 pounds per square inch (psi) and an air volume of 900 cubic feet per minute (cfm).

The CPM beads were coated with Acryl-EZE[®] to a 30.0% weight gain (WG) in an Aeromatic Strea-1 (Niro, USA). Fumed silica dispersion (5.0% w/w in water) was then sprayed to the surface of the enteric coated MPs up to a 1.0% WG. In a comparative study, dry fumed silica powder was added to the enteric coated MPs and blended in the Aeromatic Strea-1. The process parameters for the fumed silica applications are shown in Table 1.

Table 1: Parameters- Method of Silica Addition

Parameters	Aqueous Coating	Dry Blending
Nozzle size (mm)	1	-
Charge (g)	750	750
Fluid delivery rate (g/min)	4.0 – 5.0	-
Inlet air temperature (°C)	45	RT*
Exhaust air temperature (°C)	38 – 41	RT*
Atomization air pressure (bar)	1.5	-
Air volume (cfm)	100 – 200	100 – 200
Weight gain (%)	1	1

* RT: room temperature.

The Acryl-EZE coated MPs (1.0 g) with or without fumed silica applications, were placed in baskets of a USP, apparatus I dissolution unit (SOTAX, Switzerland) and immersed in acid dissolution media pH 1.2 HCl or pH 4.5 acetate buffer for 2.0 hours. The MPs were then removed and dried at room temperature for at least 48 hours. The surface and cross-sections of the MPs, before and after 2.0 hours in acidic media, were observed using an optical microscope (Miller Optical, USA) or a scanning electron microscope (SEM) (Micron Inc, USA).

The CPM release from the enteric coated beads was evaluated in the USP, apparatus I at 100 rpm, for 2.0 hours in pH 1.2 (1000 ml), followed by 60 minutes in pH 6.8 phosphate buffer (1000 ml). An on-line dual beam spectrophotometer (Perkin-Elmer, USA) was used for the detection of CPM at a wavelength of 262 nm.

RESULTS AND DISCUSSION

The surface and cross-sectional SEM images of the enteric coated MPs with 1.0% WG of fumed silica applied by spraying and dry blending are shown in Figures 1 & 2, respectively. Spraying provided a smooth uniform finish over the entire surface of the pellets. Dry blending resulted in silica agglomeration on the surface and non-uniform surface coverage. Figures 3 & 4 indicate that the application of 1.0% WG of fumed silica (by spraying) provided sufficient anti-adherence to prevent agglomeration of MPs after 2.0 hours in acid media pH 1.2 (HCl) or pH 4.5 (acetate buffer).

Figure 1: SEM Images of a Pellet with 1.0% WG Fumed Silica by Spraying (A) Surface; (B) Cross-Section.

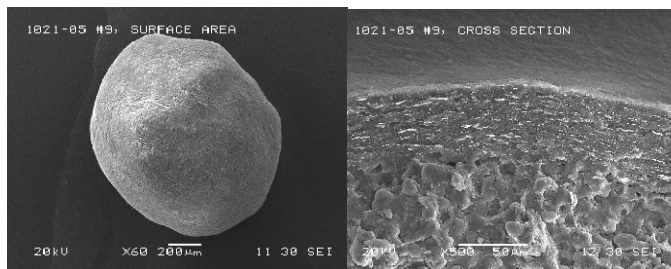


Figure 2: SEM Images of a Pellet with 1.0% WG Fumed Silica by Dry Blending (A) Surface; (B) Cross-Section

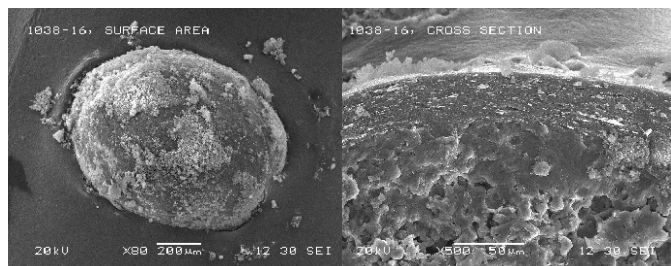


Figure 3: Optical Microscope Images of Pellets Before (MPs on the Left) and After Exposure to pH 1.2 (MPs on the Right): (A) without Fumed Silica; (B) with 1.0% Fumed Silica Sprayed



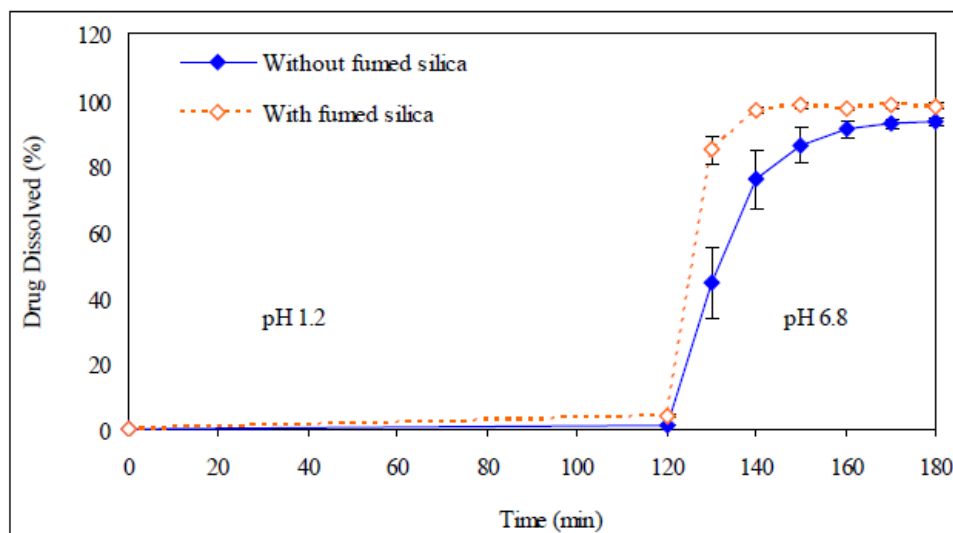
Figure 4: Optical Microscope Images of Pellets before (MPs on the Left) and After Exposure to pH 4.5 (MPs on the Right): (A) without Fumed Silica; (B) with 1.0% Fumed Silica Sprayed.



Further studies revealed that fumed silica sprayed on the surface of MPs exhibited good anti-adherence at levels as low as 0.25% WG in pH 1.2 or pH 4.5 buffer. The MPs with 1.0% WG of fumed silica retained their anti-adherence properties after friability stress testing (25 rpm, 2 minutes; Varian, USA) or after 2 weeks open dish 40°C / 75% relative humidity.

Figure 5 shows the dissolution profiles of CPM from Acryl-EZE® enteric coated MPs with and without 1.0% fumed silica application. The results show consistent and immediate release of CPM in pH 6.8 buffer from pellets sprayed with fumed silica (1.0% WG), compared to MPs without fumed silica. This is mainly due to anti-adherence of fumed silica preventing MP agglomeration in the acid media.

Figure 5: Drug Release Profiles of Acryl-EZE® Coated MPs with and without Top Coat, (n=6).



CONCLUSIONS:

Fumed silica adhered and remained to the surface of enteric coated multi-particulates when applied via aqueous dispersion spraying. The use of fumed silica resulted in consistent and immediate release of CPM in buffer, without agglomeration of the multi-particulates in acid media. It is therefore recommended to apply up to 1.0% fumed silica, by spraying to the surface of enteric coated MPs to avoid pellet agglomeration.

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3. Colorcon internal document, 2007

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