Moisture adsorption and desorption properties of colloidal silicon dioxide and its impact on layer adhesion of a bilayer tablet formulation.

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ABSTRACT

A bilayer tablet formulation approach was used to develop a fixed dose combination tablet formulation of drugs Y & Z. The weight of Layer I containing Drug Y and the weight of Layer II A or II B containing Drug Z were 250 mg and 1280 mg, respectively. While Layer I was manufactured using dry granulation, Layer II A and II B were manufactured using a moisture activated dry granulation (MADG) process. Layer II A and Layer II B contained 3% w/w colloidal silicon dioxide with the surface area of 300 m^2/g (Aeroperl® 300) and 200 m^2/g (Aerosil® 200), respectively, for moisture scavenging, and otherwise common excipients. Both grades of silicon dioxide were amorphous. When exposed to an open relative humidity of 40°C/75% for 72 hours, the bilayer tablet consisting of Layers I/Layer II A (containing Aeroperl® 300) showed a clear layer separation while the tablet consisting of Layers I/Layer II B (containing Aerosil® 200) did not. If the individual layer is exposed to a similar condition, the projected change in the moisture content for Layer I, Layer II A, and Layer II B, could be 63% w/w, 107% w/w, and 109% w/w, respectively. Thus, the difference in moisture adsorption between Layer I/ Layer II A (containing Aeroperl® 300) than Layer I/Layer II B (containing Aerosil® 200) was similar. The comparison of the moisture adsorption-desorption isotherms for Aeroperl® 300 and Aerosil® 200 suggested that Aeroperl® 300 can adsorb relatively large amounts of moisture at any humidity level due to its greater surface area but it does not retain moisture when the humidity decreases. In contrast, Aerosil 200 adsorb relatively smaller amounts of moisture but it retains moisture due to its larger pore sizes. It is hypothesized that the moisture not retained by Aeroperl® 300 could be available for interaction with other Layer I excipients, such as, microcrystalline cellulose and crospovidone. Such interaction can generate significant shear stress at the layer interface triggering the delamination.

KEY WORDS: Bilayer tablet, layer adhesion, moisture adsorption, swelling, layer separation, silicon dioxide

INTRODUCTION

The technology for formulating bilayer or multilayer tablets is considered flexible for fixed

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dose combination (FDC) formulations (1, 2). The technology is considered flexible because it can provide both sustained and immediate release in a single dosage unit through two separate layers (3). It can also allow two incompatible drugs to coexist in a single dosage unit by, not only incorporating them into two separate layers, but by further separating these by another layer, to minimize interaction at the interface of the two layers. For example, an alkaline layer containing calcium carbonate, magnesium oxide, magnesium carbonate, or sodium phosphate monobasic was evaluated as a buffer layer to prevent chemical reactions between pravastatin and aspirin in two separate layers in a tri-layer tablet (4).

With these advantages in mind, the challenges when developing bilayer or multilayer tablet should not be underestimated. A major challenge is layer separation (delamination) during tablet compression or storage. Thermal stresses that develop during layer compression can result in delamination (5). The delamination process is further augmented by an elastic mismatch between the two layers (5). This elastic mismatch creates different degrees of relaxation of the layers post-compression thus increasing the risk for delamination. The relaxation at the interface decreases with the increase in interfacial strength because of plastic bonding (6). The lamination process has been further characterized by studying densification and relaxation behavior of commonly used excipients such as lactose and microcrystalline cellulose with 2% w/w silica (Prosolv®) in a powder bed as a function of their relative proportions. It has been reported that when lactose, a highly fragmenting material, was more than 50% w/w of a tablet composition, the mixtures favored transmission of load in an axial direction during tablet compression with some residual stress, resulting later in delamination. However, when microcrystalline cellulose, which is more plastic or ductile, was more than 50% w/w of the composition, the mixtures favored transmission of load in a radial direction during tablet compression releasing the stress prior to tablet ejection resulting in no lamination (7).

An FDC formulation containing an immediate release Drug Y and an extended release Drug Z was required. To maintain two different release profiles in a single dose unit, a bilayer tablet formulation approach was adopted. The first layer containing Drug Y for an immediate release was manufactured using dry granulation and the second layer, containing Drug Z, for an extended release was developed using a moisture activated dry granulation (MADG) process. The MADG process is similar to traditional wet granulation but the amount of water used for granulation is very limited. As the amount of water added is limited, water is distributed and adsorbed by the ingredients in the formulation. The resulting granules look quite dry and almost free-flowing. It is not necessary to dry the wet granulation using fluid bed or tray drying. Instead, silicon dioxide is added to the wet mass to further scavenge moisture from the wet granules and to re-distribute it within all the ingredients in the final mixture, which is dry and free flowing (8, 9).

In addition to Drug Y, the major components of the dry granulation formulation contained approximately 70% w/w of microcrystalline cellulose and 16% w/w of lactose. The second layer contained Drug Z, 18% w/w of hydroxypropylmethyl cellulose (HPMC) as a release controlling polymer, and 3 % w/w of colloidal silicon dioxide as a moisture scavenger. Based on the literature cited above, the formulation had the correct proportions of microcrystalline cellulose and lactose to avoid any delamination issues. The bilayer tablets did not show any delamination with Aerosil® 200 (colloidal silicon dioxide from Evonic) upon exposure to 40ºC/75% relative humidity (RH). However, replacement of this grade of colloidal silicon dioxide with another grade, Aeroperl® 300 from the same vendor resulted in severe delamination when the tablets were exposed to the same conditions. The alternate grade of

silicon dioxide was used in order to provide flexibility in the supply chain. The main difference in the two grades of colloidal silicon dioxide was surface area. Aeroperl® and Aerosil® have a surface area of 300 and 200 m^2/g, respectively. Despite the differences in their surface area, both colloidal silicon dioxides were used at a 3% w/w level in the second layer and their total amount in the tablet was about 2.5 % w/w. Based on their small amount in the tablet formulation, delamination due to interchangeability of colloidal silicon dioxide grade was unexpected. In order to understand the observed delamination phenomenon, a systemic study was undertaken and the results reported here.

MATERIALS AND METHODS

Materials

Drug Y and Z were provided by Bristol-Myers Squibb Company, Microcrystalline cellulose (NF, Avicel® PH102) was obtained from FMC BioPolymer, Philadelphia, Pennsylvania, anhydrous lactose (NF) from Sheffield Pharma Ingredients, New London, Connecticut, crospovidone (NF) and Hydroxypropyl methylcellulose (Hypromellose® K100M) from BASF Corporation, Florham Park, New Jersey, silicone dioxide (NF) Aeroperl® 300 and Aerosil® 200 from Evonik Degussa Corporation, Piscataway, New Jersey, and magnesium stearate (NF) from Mallinckrodt Inc, St. Louis, Missouri.

Manufacture of bilayer tablets

Two types of bilayer tablets, one consisting of Drug Y in Layer I and Drug Z in Layer IIA and the other consisting of Drug Y in Layer I and Drug Z Layer IIB, were manufactured. The compositions of the formulations of all three layers are listed in Table 1. The following process was used to manufacture the bi-layer tablets containing Layers I/IIA or I/IIB. Layer I, an immediate release formulation with a weight of 250 mg, comprised of Drug Y 4.1% w/w, microcrystal line cellulose 73.4% w/w, lactose anhydrous 16.0% w/w, crospovidone 4.0% w/w, silicone dioxide (hydrous) 1.5% w/w, and magnesium stearate 1.0% w/w. Layer IIA, an extended release formulation with a weight of 1280 mg, was comprised of Drug Z 78.2% w/w, hydroxypropyl methylcellulose (Hypromellose® K100M) 18.0% w/w, colloidal silicon dioxide, anhydrous lactose (Aeroperl® 300) 3.0% w/w, and water 0.8% or 2.5% w/w. The formula of the Layer IIB was the same as that of Layer IIA except that Aerosil® 200, another grade of anhydrous colloidal silicon dioxide, was used to replace Aeroperl® 300 at the same amount. The final blend of Layer I was made with a dry granulation process in a roller compactor (Alexanderwerk WP 120). The final blend of Layer IIA or IIB was made using the MADG process in a high shear granulator (Diosna), followed by drying, milling, and blending (Figure 1). The bilayer tablets consisting of Layers I/IIA or Layers I/IIB were compressed into tablets using a bilayer rotary tablet press (Piccola Bilayer Tablet Press, SMI,

Table 1 Bilayer tablet formulation

INGREDIENT	% w/w	FUNCTION OF THE INGREDIENT
Layer I -250 mg weight		
Drug Y	4.1	Active ingredient
Microcrystalline cellulose	73.4	Filler/diluent
Lactose anhydrous	16.0	Filler/diluent
Crospovidone	4.0	Disintegrant
Silicon dioxide, hydrous	1.5	Glidant
Magnesium stearate	1.0	Lubricant
Total	100.0	
Layer IIA -1280 mg weight		
Drug Z	78.2*	Active ingredient
Hydroxypropyl methylcellulose	18.0	Release controlling polymer
Aeroperl 300 (colloidal silicon dioxide-anhydrous)	3.0	Moisture scavenger
Purified water	0.8 or 2.5	Binder
Total	100.0	
OR Layer IIB -1280 mg weight		
Drug Z	78.2*	Active ingredient
Hydroxypropyl methylcellulose	18.0	Release controlling polymer
Aerosil 200 (colloidal silicon dioxide-anhydrous)	3.0	Moisture scavenger
Purified water	0.8 or 2.5	binder
Total	100.0	

*The amount of drug was proportionally reduced with the increase in water amount

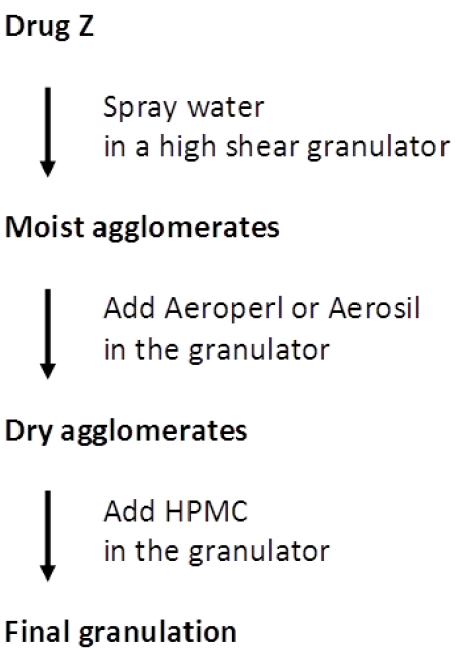

Figure 1 Manufacturing process flow for Layer II using a moisture activated dry granulation process (MADG)

serial number -044) equipped with an oval shaped tooling, 0.748 in x 0.400 in. The Layer II (A or B) was compressed first using a 3 kN tamping force. Layer I was compressed second with the compression force in the range of 40 to 50 kN to obtain a tablet hardness of about 604 N. The tablet friability was less than 0.5% for all the formulations. Two tablet batches each with Aeroperl® 300 and Aerosil® 200 in Layer II were manufactured. Efforts were made to optimize the water level for Layer IIA and Layer IIB. It was also noted that for Layer IIA containing Aeroperl® 300, no delamination was observed after tablet compression and storage at room temperature when 0.8% w/w water had been used in the batch. However, in a separate batch made using 2.5% w/w water, the tablet delaminated after compression, even when storing at room temperature. On the other hand, for Layer IIB containing Aerosil® 200, the tablets did not delaminate after compression when storing at room temperature irrespective of whether 0.8% w/w or 2.5% w/w water used for the manufacture.

Moisture adsorption/desorption measurement

The moisture adsorption/desorption versus relative humidity curves at room temperature of each individual ingredient used for Layers I, IIA, and IIB were determined using an automated VTI Moisture System. Vapor thermal isotherm (VTI) curves were generated using an IGASorp dynamic vapor sorption analyzer (Hiden Isochema, Warrington, UK). Samples of approximately 45 mg were loaded onto the IGASorp microbalance with a 5 g capacity, a resolution of 0.1 μg and stability of ± 1 μg. Sample temperature was maintained at 25°C with stability of 0.3°C/min. Relative humidity was lowered to below 0.5% and then ramped up in relative humidity steps ranging from 10% to 90%. Sorption data was collected at 10% RH intervals. Equilibrium target was 99.5% with a minimum wait time of 30 minutes and a maximum of 180 minutes. Air flow rate was 250 ml/min. Desorption data was collected under the same conditions with decreasing % RH steps. Since results were interpreted as being dependent on relative (rather than absolute) values of water absorption/ desorption, the experiments were preformed only once if comparable results had been published literature.

Expansion and delamination of the bilayer tablets

Since the bilayer tablets, at the addition of 0.8% w/w water, did not delaminate after compression when stored at room temperature, whether they included Aeroperl® 300 in Layer IIA or Aerosil® 200 in Layer IIB, they were selected for further evaluation at a stressed condition of 40ºC/75% RH. They were subjected to 40°C at relative humidity of 75% environment for 72 hours in an open Petri dish. The tablet dimensions, including length, width, and height, before and after the exposure, were measured. The physical integrity of the individual tablets was observed as well.

Manufacture of the physical mixtures of individual layers

The physical mixtures of the Layers I, IIA, and IIB of the same compositions as described in the section above "manufacture of the bi-layer tablets" were made by mixing all ingredients in a diffusion mixer (Turbula) at 45 RPM for 20 minutes. No water was added to the physical mixture of Layer I. The water was sprayed in fine mist onto the mixture of Layer II (as shown in Figure 1) after dry mixing, followed by mixing for three additional minutes.

Compaction behavior characterization of each layer

A uniaxial compaction simulator (Stylcam model 200R, Medel'Pharm, France,) equipped with an instrumented upper punch, lower punch, and die was used. The axial upper and lower compression forces and displacements, as well as radial die wall pressure, were measured during compaction. A set of flat-faced tablet tooling with the diameter of 11.28 mm was used. On the suggestion of previous reports, the die wall was lubricated with magnesium stearate powder between each compaction in order to minimize the impact of die wall friction on powder property measurement (10).

Mercury Intrusion Porosimetry

Pore-volume distributions of Aerosil® 200 and Aeroperl® 300 were determined by mercury intrusion porosimetry using an AutoPore IV 9500 (Serial No. 1106, Micromeritics, Norcross, Georgia). A powder penetrometer with 5 cc bulb and 1.131 cc stem (s/n 10-0539) was used for testing a 53 mg sample of Aerosil® 200. The penetrometer assembly with sample was evacuated down to a pressure of 50 μm Hg before mercury was introduced at low pressure. Incremental pore volume was determined at 50 different pressure steps ranging from 0.5 psi to 33,000 psi corresponding to pore diameters between 352 μm to 0.005 μm. Equilibrium time was 10 seconds at each pressure. The same test method and penetrometer size were used for testing a 154 mg sample of Aeroperl® 300.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy, SEM, images were collected of the samples mounted on aluminum stubs to which adhesive carbon conductive tabs had been applied. They were sputter coated using a Cressington 208 HR Auto Sputter Coater equipped with a platinum target (Ted Pella, Inc., Redding, California). Secondary electron images were acquired at 2 kV using a field emission FEI XL30 ESEM (FEI Company, Hillsboro, Oregon, 97124 USA).

Powder X-ray Diffraction (PXRD)

Powder X-ray diffraction (PXRD) patterns were generated using an Empyrean (PANalytical, Ea Almelo, Netherlands) X-ray powder diffractometer with Cu $K\alpha 1$ radiation: λ = 1.54059 Å. The diffractometer was equipped with a rotating-anode generator, which was set at a power level of 40 kV and 40 mA, and a PIXcel 1D real time multiple strip (RTMS) detector. Incident optics consisted of a primary Göbel mirror, primary soller slit of 2.29°, and divergence slit of 10 mm. Diffracted optics consisted of Nickel Beta-filter, secondary soller slit of 2.29°. Data were collected in reflectance geometry over a 2θ range of 2-32°, with a step size of 0.0394°, and counting time 7.8 seconds/ step in continuous mode.

RESULTS AND DISCUSSION

As shown in Table 1, the only difference in Layer IIA and Layer IIB was the grade of colloidal silicon dioxide. Layer IIA contained Aeroperl® 300 and Layer IIB contained Aerosil® 200. As described under the manufacture of the bilayer tablets, no delamination was observed after tablet compression and storage at room temperature when 0.8% w/w water had been added. However, in a separate batch with Aeroperl® 300, when 2.5% w/w water was added, the

tablet delaminated after compression even when storing at room temperature. On the other hand, the tablets in Layer IIB containing Aerosil® 200, did not delaminate after the addition of 2.5% w/w water when stored at room temperature. Therefore, the tablets containing 0.8% w/w water were evaluated at 40ºC/75% RH.

The bilayer tablets containing Aeroperl® 300 made with 0.8% water showed clear layer separation after 72 hours of exposure at 40ºC/75% RH, but the tablets with Aerosil® 200 did not, under the same conditions. Although both Aeroperl® 300 and Aerosil® 200 are anhydrous colloidal silicon dioxide and constituted just 3% w/w of the Layer II formulation, they influenced the physical integrity of the tablet when exposed to high humidity. Exposure of a bilayer tablet formulation to high humidity followed by visual observations of possible layer delamination is a commonly used method to determine whether a bilayer tablet will maintain its physical integrity throughout the product shelf-life.

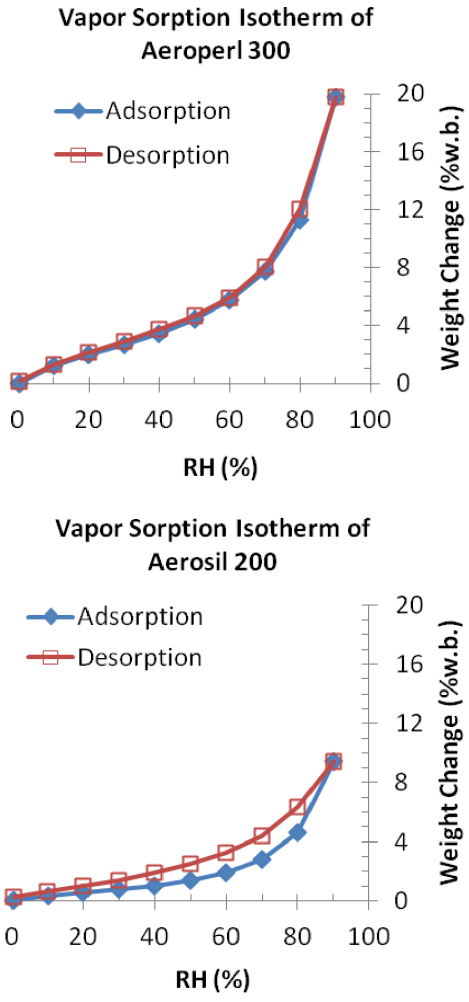

Figure 2 Water sorption isotherms, Aerosil® 200 versus Aeroperl® 300.

Since the layer separation was triggered by moisture, the investigation focused on the behavior of Aeroperl® 300 and Aerosil® 200 on exposure to high humidity. Moisture adsorption isotherms were obtained for Aeroperl® 300 and Aerosil® 200 using VTI Moisture System (Figure 2). Both excipients picked up moisture when exposed to higher humidity as shown by the adsorption isotherm curves. However, when the humidity was decreased during the moisture desorption stage Aeroperl® 300 retained little moisture, while Aerosil® 200 retained some moisture. Given the greater surface area of Aeroperl® 300, it as expected, picked up more moisture than Aerosil® 200 (20% vs. 9.5%) (Figure 2). It was also noted that Aerosil® 200 showed moisture-desorption hysteresis, indicating that Aerosil® 200 had a different desorption behavior than Aeroperl® 300. The moisture adsorption-desorption isotherm behaviors of the APIs and other excipients in the formulations of the three layers were also experimentally measured in the same manner as for Aeroperl® 300 and Aerosil® 200. As summarized in Table 2, experimentally obtained moisture adsorption isotherm curves for all individual ingredients were retrofitted into polynomial equations.

Taking Aeroperl® 300 as an example, the percent of weight change by moisture adsorption, versus the relative humidity, x, was curve fitted and expressed using the exponential function shown in Equation 1:

$$Y = 311.6x^5 - 576.5x^4 + 403.5x^3 - 123.6x^2 + 23.0x - 0.08 \quad \text{Eq. 1}$$

Table 2 The base numbers of the exponential equations for various excipients those provided the best fit

EXCIPIENT	x^5	x^4	x^3	x^2	x	CONSTANT	R^2
Aerosil® 200	163.29	-285.23	183.83	-49.94	7.43	-0.0403	0.9995
Aeroperl® 300	311.57	-576.46	403.49	-123.64	23.03	-0.0802	0.9998
Silicon dioxide	793.14	-1468.20	1004.50	-299.65	45.28	-0.1753	0.9995
Drug Y	0.49	-0.62	0.32	-0.04	0.03	-0.0006	0.9943
Lactose Anhydrous	-41.74	100.06	-77.10	23.02	-2.11	0.0201	0.9843
Mag Stearate	27.67	-41.70	25.15	-11.83	5.16	-0.028	0.9977
Drug Z	3.68	-7.04	4.81	-1.37	0.21	-0.0009	0.9990
MCC PH102	145.83	-323.91	288.24	-121.79	31.04	-0.0753	0.9999
Corspovidone	294.90	-517.41	353.88	-101.26	46.35	-0.0419	0.9999
HPMCK100M	271.08	-533.96	407.53	-129.05	26.36	-0.0954	0.9999

Table 3 Moisture, Y, based on the curve for each excipient in the formulation at various humidity conditions using the exponential equation

EXCIPIENT	75% RH	50% RH	45% RH	40% RH	35% RH	30% RH	20% RH	15% RH	10% RH	4.6% RH	0.25% RH
Aerosil® 200	3.49	1.44	1.26	1.08	0.90	0.74	0.51	0.44	0.36	0.21	-0.02
Aeroperl® 300	9.41	4.67	4.13	3.61	3.12	2.68	1.99	1.69	1.34	0.75	-0.02
Silicon dioxide	12.67	6.14	5.49	4.82	4.17	3.60	2.84	2.58	2.22	1.36	-0.06
Drug Y	0.05	0.02	0.02	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00
Lactose Anhydrous	0.61	0.03	0.04	0.06	0.08	0.09	0.05	0.01	-0.03	-0.04	0.01
Mag Stearate	1.17	1.00	0.99	0.97	0.93	0.86	0.67	0.55	0.39	0.19	-0.02
Drug Z	0.06	0.0365	0.03	0.03	0.02	0.02	0.01	0.01	0.01	0.01	0.00
MCC PH102	8.42	5.34	4.90	4.50	4.13	3.79	3.10	2.66	2.07	1.12	0.00
Corspovidone	33.32	18.93	16.78	14.72	12.73	10.83	7.28	5.59	3.89	1.91	0.07
HPMCK100M	14.39	6.86	5.88	4.99	4.20	3.53	2.51	2.08	1.61	0.88	-0.03

The regression coefficient of curve fitting, *R*, is 0.9998, indicating a good fit between the experimental isotherm curve and the corresponding equation. Furthermore, the moisture content of each ingredient at various relative humidity values were then calculated and are listed in Table 3. The advantage of this approach is that the total amount of moisture adsorbed by a mixture of various ingredients can be calculated for various humidity conditions. The results are shown in Table 4.

Assuming the relative humidity in a GMP compliant manufacturing or material storage facility would be 50%, the moisture content of each layer at the end of the manufacturing process was determined. As a result, the final moisture content of Layer I, II A, and II B at the completion of manufacture were 4.7845 g, 1.412 g, and 1.3145 g per 100 g of layer weight, respectively (Table 4). When these bilayer tablets were exposed to a 75% relative humidity environment for 72 hours, the maximum or equilibrium moisture of all individual layers reached 7.8144 g, 2.928 g, and 2.7498 g per 100 g of layer weight, respectively (Table 4). As shown in Table 5, the maximum changes in moisture content for all layers from 50% RH to 75% RH for 72 hours were projected to be 63%, 107%, and 109%, for Layers I, IIA, and IIB, respectively.

Thus, the projected increase in the moisture content of Layer IIA (with Aeroperl® 300) or Layer IIB (with Aerosil® 200) is similar, but greater than for Layer I. Layer I contains about 73% w/w of microcrystalline cellulose, which can absorb moisture even at 50% RH, so the relative change in moisture content after exposure to 75% RH is not as high for Aeroperl® 300, Aerosil® 200, or HPMC K100 (Table 3).

Aeroperl® 300 and Aerosil® 200 are anhydrous colloidal silicon dioxides. Based on vendor information, which was confirmed

Table 4 Calculation of the amount of moisture adsorbed by Layer IIA (with Aeroperl® 300) and Layer IIB (with Aerosil® 200) under various humidity conditions.

LAYER II A	75% RH	50% RH	35% RH
Drug Z	78.2 x 0.06	78.2 x 0.0365	78.2x0.02
HPMC	18.0 x 14.39	18.0 x 6.86	18.0 x 4.20
Aeroperl® 300	3.0 x 9.41	3.0 x 4.67	3.0 x 3.12
0.8% water added in MADG	0.8	0.8	0.8
Total moisture adsorb(g)	292.74/100= 2.928	141.2/100 = 1.412	87.34/100 =0.8734
LAYER II B	**75% RH**	**50% RH**	**35% RH**
Drug Z	78.2 x 0.06	78.2 x 0.0365	78.2 x 0.02
HPMC	18.0 x 14.39	18.0 x 6.86	18.0 x 4.20
Aerosil® 200	3.0 x 3.49	3.0 x1.44	3.0 x 0.90
0.8% water added in MADG	0.8	0.8	0.8
Total moisture adsorbed	274.98/100= 2.7498 g	131.45/100= 1.3145 g	80.66/100 =0.8066 g

Table 5 Projected moisture adsorption for each layer when exposed to 40ºC/75% RH for 72 hours

LAYER	MOISTURE CONTENT AT THE END OF MANUFACTURE (ASSUMES 50% RH)	MOISTURE CONTENT AT THE AND OF MANUFACTURE (ASSUMES 75% RH)	CHANGE IN MOISTURE CONTENT (%)
Layer I	4.7845 g	7.8144 g	63
Layer II A (with Aeroperl 300)	1.412 g	2.928 g	107
Layer II B (with Aerosil 200)	1.3145 g	2.7498	109

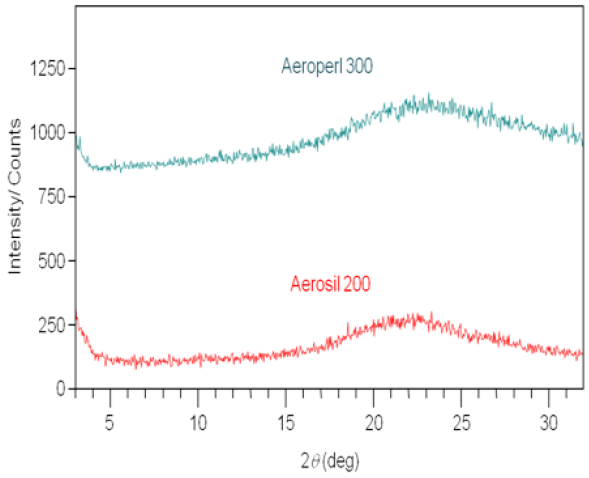

Figure 3 Powder X-ray patterns for Aeroperl® 300 and Aerosil® 200

experimentally, the surface area for Aeroperl® 300 and Aerosil® 200 are 300 m^2/g and 200 m^2/g, respectively. The larger surface area of Aeroperl® 300 should allow more moisture adsorption as is shown in Figure 2. However, the difference in surface area alone cannot explain the difference in moisture retention capacity of these two grades. Powder X-ray patterns for Aeroperl® 300 and Aerosil® 200 are shown in Figure 3. It can be seen that the PXRD pattern for both excipients reveal no peaks indicating an amorphous state for both grades. If both grades are amorphous then they would be expected to behave similarly when exposed to high humidity. Since they were not behaving similarly, they were characterized further.

As shown in Figure 4, the morphology of the different silicon dioxide excipients is substantially different as determined by SEM and qualitative interpretation of images at a magnification of 250 x and 2000 x. Aeroperl® 300 appears to have a bimodal particle size distribution (PSD) of spherical particles, which is consistent with the literature on PSD of this granulated colloidal silicon dioxide. On the other hand, Aerosil® 200 has irregularly shaped particles of different sizes with irregular, porous or sponge-like surfaces. Both grades were compared at 10,000 x using SEM, shown in Figure 5. Aerosil® 200 is viewed as a much more complex material composed of irregular, branched structures. At the higher magnification, Aeroperl® 300 surface texture is shown. The image shows aggregates/

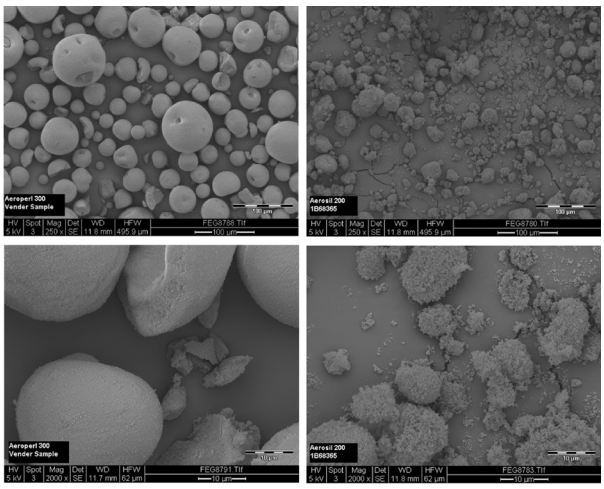

Figure 4 Comparison of Aeroperl® 300 (left) and Aerosil® 200 by SEM at x250 and x2000 magnification

agglomerates of the colloidal silicon dioxide that construct the spherical particle.

To elucidate structural differences, pore sizes and pore volume distributions for Aeroperl® 300 and Aerosil® 200 were studied using mercury intrusion porosimetry (MIP). Figure 6 shows the total cumulative intrusion volume for Aerosil® 200 as two and a half times greater than for Aeroperl® 300. A summary of key material properties evaluated during the characterization of Aeroperl®-300 and Aerosil®-200 has been provided in Table 6. As shown in the table, the key parameters are total intrusion volume, average pore diameter, porosity and bulk density. The porosity as well as pore diameter of Aeroperl® 300 and Aerosil® 200 is substantially different. The data shows that both materials have a mesopore network. This

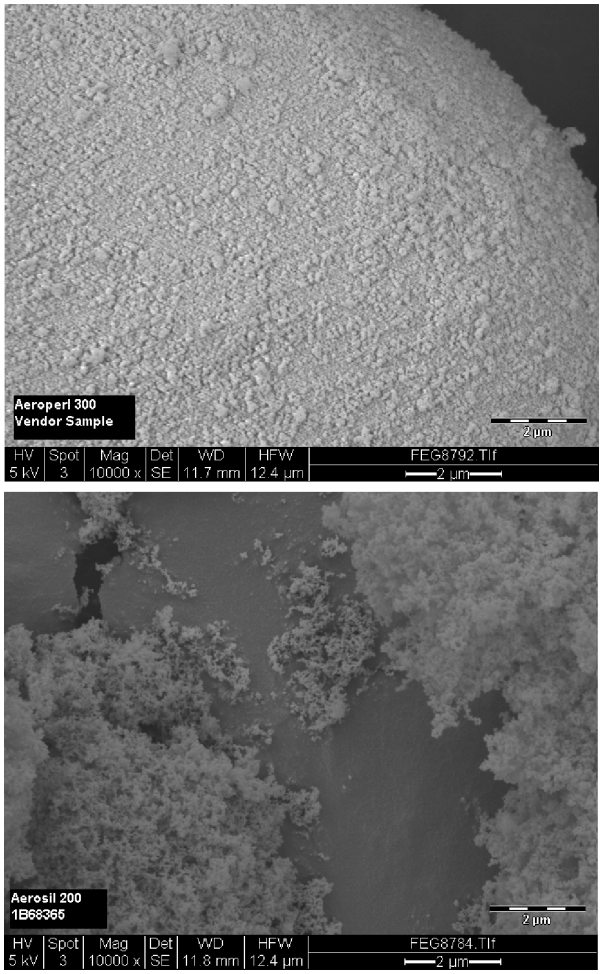

Figure 5 Comparison of Aeroperl® 300 (top) and Aerosil® 200 by SEM at x1000 magnification

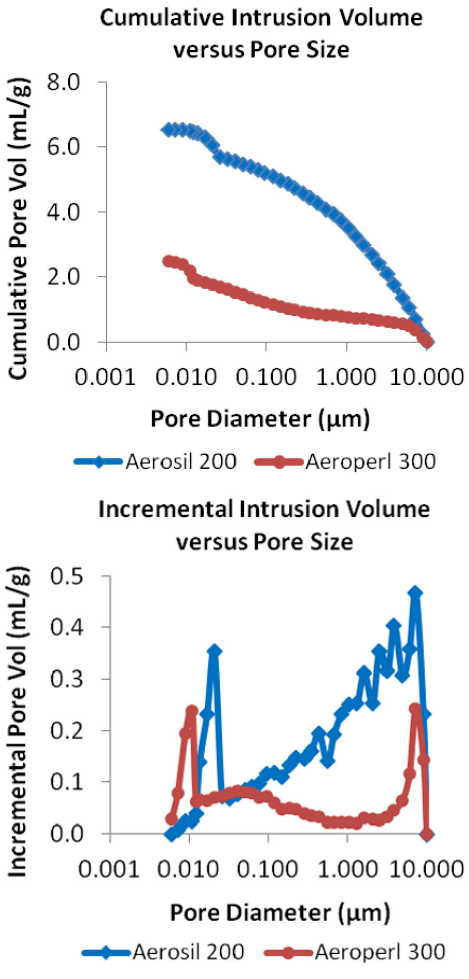

Figure 6 Pore size and pore volume of Aeroperl® 300 and Aerosil® 200 by mercury porosimetry (MIP)

implies an inter-particle network of pores.

Table 6 Comparison of key properties of Aerosil® 200 and Aeroperl® 300

INTRUSION DATA SUMMARY	UNIT	AEROSIL® 200	AEROPERL® 300
Total Intrusion Volume	ml/g	6.5	2.5
Average Pore Diameter	µm	0.11	0.03
Porosity	%	40	65
Bulk Density (at 0.51 psia)	g/ml	0.08	0.26

Bilayer tablet compression and commonly encountered issues have been previously summarized by Kottala *et al.* (11, 12). There are three main reasons for layer separation. First, when using a material which has a more deformable capacity, such as microcrystalline cellulose, in the first layer. This was not the case here since the layer containing approximately 73% microcrystalline cellulose was used in the second layer (i.e. compressed second). Second, using a higher tamping force in the first layer that would smooth out the layer surface so much that it would have difficulty to interlock with the particles in the second layer resulting in layer separation. The 3 kN tamping force used here for the first layer was on the low side of the normally used tamping force range of 2 to 18 kN. Thirdly, a mismatch in moisture adsorption could trigger interfacial stress resulting in layer separation. It is believed that this was the reason for the layer separation observed in this study. As Figure 2 shows, Aeroperl® 300 can adsorb more moisture than Aerosil® 200 due to its greater surface area. Further, the vapor sorption isotherm for Aeroperl® 300 shows that it does not retain moisture with decreasing humidity. In contrast, Aerosil® 200 adsorbs relatively less moisture than Aeroperl® 300 due to its smaller surface area, but it retains some moisture at decreasing humidity due to its larger pore sizes. Thus, Aeroperl® 300, makes moisture available for interactions with other excipients in Layer I of the tablet formulation, such as, microcrystalline cellulose and cropovidone. Crospovidone which is a disintegrant and, microcrystalline cellulose can swell significantly in the presence of moisture resulting in considerable stress at the layer interface triggering layer separation. As noted, during the tablet manufacture when 2.5% w/w water was added, tablets containing Aeroperl® 300 delaminated after compression for this reason even when stored at room temperature/ambient humidity.

Such impact of any commonly used excipient has not been reported previously. As stated above, both grades of silicon dioxide behaved differently when exposed to external moisture. These interactions were surprising since no compendial or vendor specifications are available which may alert formulation scientists for such a possibility. Thus there are two lessons to be learned i.e., (1) the compendial or vendor specifications may not provide sufficient information to interchange an excipient grade in a formulation, (2) replacing an excipient grade with another grade exhibiting dissimilar adsorption/desorption when exposed to high humidity can result in more significant shear at the layer interface triggering layer separation.

CONCLUSION

A bilayer tablet formulation containing two different grades of colloidal silicon dioxide exhibited significantly different layer separation/delamination behavior when exposed to increased humidity. Aeroperl® 300 and Aerosil® 200 are both amorphous but Aeroperl® 300 has a relative surface area larger than Aerosil® 200. When exposed to increased humidity levels, Aeroperl® 300 demonstrated a greater moisture adsorption capacity due to its larger surface area but did not retain the moisture content with decreasing humidity. Aerosil® 200 showed better moisture retention capacity due to its larger pore sizes. The moisture which was not retained by Aeroperl® 300 in Layer II A was available for interaction with other excipients in Layer I such as microcrystalline cellulose and crospovidone which is a disintegrant. It was hypothesized that such interactions result in considerable stress at

the layer interface triggering the layer separation.

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