Evaluation of Moisture Sorption by Tablet Cores Containing Superdisintegrants During the Aqueous Film Coating Process

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A physical-chemical analysis of the extent of sorption of water by tablets containing superdisintegrants was carried out following the aqueous film coating of formulated tablets. Characterization of the uncoated and coated tablet properties was conducted using thermogravimetric analysis, differential scanning calorimetry, mercury intrusion porosimetry, and measurement of the tablet tensile strength. Tablet residual moisture content, pore system characteristics, tensile strength, and glass transition temperature of the amorphous polymer components of the tablet matrix were significantly affected after the coating operation. These findings were attributed to the penetration of water from the aqueous film coating solution into the tablet matrix.

KEY WORDS: aqueous film coating; superdisintegrants; moisture sorption; glass transition temperature; tensile strength; mercury porosimetry.

INTRODUCTION

The aqueous film coating technology has been widely utilized for the application of polymer film coating to pharmaceutical dosage forms. Aqueous based polymeric solutions and dispersions are commonly employed for product identification and taste masking purposes as well as for the preparation of controlled-release dosage forms through the application of a rate-controlling polymer membrane to crystalline drug particles, pellets, granules, and pharmaceutical tablet dosage forms (1,2).

However, an important area of concern in aqueous film coating relates to the exposure of tablets to an aqueous environment and elevated temperatures. In many cases, the impact of these conditions on the physical integrity and the chemical stability of the active ingredient remains speculative and undetermined. In the coating process, the coating liquid is sprayed onto tablet surfaces which contain pores leading into the internal structure of the solid mass. The question of whether the aqueous film coating process achieves instantaneous drying, or there is some penetration of moisture from the applied polymer solution into tablet cores, has not been addressed in a quantitative manner.

Fast-acting disintegrating agents are most useful in the formulation of low-water-soluble drugs to ensure appropriate liberation of the drug. Superdisintegrants may be employed in some tablet formulations at concentration levels of up to 20% (w/w). These compounds have the capacity to absorb water and achieve a maximum swelling of several hundred times their original volume (3,4).

This study examined the extent of penetration of water from the applied aqueous film coating solution into formulated tablets containing superdisintegrants following the film coating process. The effects of retention of residual moisture on the physical and chemical properties of the coated tablet cores were investigated.

MATERIALS AND METHODS

The formulated tablets consisted of the following components: dibasic calcium phosphate, dihydrate, USP (Di-Tab), from Rhone-Poulenc (Westport, Connecticut); microcrystalline cellulose, NF (Avicel PH 101), and croscarmellose sodium, type A, NF (Ac-Di-Sol), from FMC Corporation (Philadelphia, Pennsylvania); sodium starch glycolate, NF (Primojel), from Generichem Corporation (Little Falls, New Jersey); crospovidone, NF (Polyplasdone-XL), from ISP Chemicals Corporation (Wayne, New Jersey); and magnesium stearate and cobalt chloride hexahydrate from Mallinckrodt Inc. (Paris, Kentucky). The aqueous film coating solution consisted of hydroxypropyl methylcellulose 2910, USP (Methocel E-5), from Dow Chemical Company (Midland, Michigan); polyethylene glycol 3350 NF from Ruger Chemical Company (Irvington, New Jersey); and polyethylene glycol 8000 from Union Carbide Corporation (Danbury, Connecticut). All excipients were used as received from the suppliers, with the exception of Avicel PH 101 and cobalt chloride hexahydrate, which were predried for 21 hr at 80°C.

Tablet Formulation and Preparation

Table I shows the percentages of excipients used in the manufacture of the various tablet formulations, each denoted by an appropriate code name. Tablets were prepared by using a standardized blending procedure and compression of the powdered ingredients. The powder mixture was blended for 13 min in a small laboratory-size V-blender. Five hundred-milligram samples of the mixed powder ingredients were weighed and directly placed in a 12.7-mm flat-faced punch and die set and compressed at a compression load of 6000 lb (211 MPa) at a constant rate of loading using a standard hydraulic laboratory press (Carver press, Menomonee Falls, Wisconsin).

Coating Solution Composition

The polymer coating solution consisted of the following ingredients: (a) Methocel E-5 (6%, w/w), (b) polyethylene glycol 3350 (1%, w/w), (c) polyethylene glycol 8000 (1%, w/w), and (d) distilled water (q.s. 100%, w/w).

Coating Procedure

The aqueous film coating of tablets was performed using a 24-in. Accela-Cota (Thomas Engineering, Hoffman Es-

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Table I. Tablet Formulation Composition

Tablet ingredient	Formulation code (%, w/w)										
	A_I[a]	A_{II}	A_{III}	P_I[b]	P_{II}	P_{III}	CP_I[c]	CP_{II}	CP_{III}	AC	C
Ac-Di-Sol	5	10	20								
Primojel				5	10	20					
Polyplasdone-XL							5	10	20		
Avicel PH 101[d]	20	20	20	20	20	20	20	20	20	20	
Di-Tab[e]	73	68	58	73	68	58	73	68	58	78	98
Cobalt chloride	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1

[a] A_I, A_{II}, and A_{III}—Ac-Di-Sol at 5, 10, 20% (w/w), respectively.
[b] P_I, P_{II}, and P_{III}—Primojel at 5, 10, and 20% (w/w), respectively.
[c] CP_I, CP_{II}, and CP_{III}—Polyplasdone-XL at 5, 10, and 20% (w/w), respectively.
[d] Avicel PH 101 was not present in a similar set of tablets containing the same concentration levels of each disintegrant.
[e] The percentage (w/w) of Di-Tab was increased by 20% for tablets without Avicel PH 101.

tates, Illinois). The coating equipment instrumentation consisted of the following indicators: (a) inlet and exhaust air temperature (°C), (b) pan rotational speed (rpm), and (c) pressure drop across the tablet bed (inches of water). The temperature of the inlet drying air was controlled and maintained at the desired level by a separate custom air heating unit (Teko, Hoffman Estates, Illinois). The exhaust air temperature was continuously monitored using a Solomat 455 thermohygrometer (Solomat Partners LP, Stamford, Connecticut). The thermohygrometer probe was inserted into the exhaust air stream through an opening (0.5 in. wide) in the exhaust air duct. The amount of air flow through the pan was measured using an air velocity meter (Model 1650, TSI Inc., St. Paul, Minnesota). An ultrasonic spray nozzle system was used to deliver the coating solution onto the tablet bed. The Sonicore spray nozzle, Model 052H (Parsippany, New Jersey), consisted of a narrow circular air gap, a central orifice for the liquid jet stream entry, and a snap-on resonating metal pin located directly above the liquid entry orifice. The spray nozzle was attached to separate stainless-steel liquid and air feed lines. The coating solution was delivered to the spray nozzle assembly via a peristaltic flow meter (Cole Parmer Instrument Co., Chicago, Illinois) with an adjustable pumping speed. This arrangement allowed the pressurized air (35 psi) and the liquid stream to mix and impact upon the metal pin. The resulting pin vibrations caused atomization of the coating solution producing a wide spray fan with a uniform spray pattern (maximum droplet size, ≅5 μm). Preliminary investigations showed that the Sonicore spray nozzle system enabled the use of faster spray rates as compared with conventional air atomized spray guns and resulted in visually satisfactory tablet film coatings.

Tablets from each formulation type, both with and without Avicel PH 101 (i.e., A_I through CP_{III}, AC, and C, given in Table I), were mixed with 2.0 kg of standard convex, red-colored, lactose tablets precoated with hydroxypropyl methylcellulose. The tablet mixtures were placed in the coating pan and coating was performed under the conditions stated in Table II. The process parameters and conditions inside the pan were closely monitored throughout the coating run.

Evaluation of Physical and Chemical Properties of Formulated Tablets Before and After the Aqueous Film Coating Operation

Prior to all testing procedures and evaluations, the polymer film layer was carefully peeled from the edges and surfaces of each coated tablet, with the aid of a sharp razor blade.

Moisture Content Determination

A Thelco vacuum oven, Model 19 (Precision oven, Chicago, Illinois), was used to conduct routine moisture analysis. Five uncoated and coated tablets from each formulation type (Table I) were heated, at 102°C and a vacuum of 30 in. of mercury, to constant weight for a period of 7 days. The results were calculated as the average of five values and expressed as the percentage weight loss on the basis of initial sample weight.

A Perkin-Elmer TGS-2 thermogravimetric system (Norwalk, Connecticut) connected to a system 4 microprocessor and a strip-chart recorder was used to conduct thermogravimetric analysis of uncoated and aqueous film coated tablets as well as the individual tablet components. Fifteen-milligram powder samples from a crushed tablet mass or excipient were placed in a platinum sample pan (5.8 mm in ID × 1.8 mm deep) and heated in a furnace under dry nitro-

Table II. Process Parameters and Levels for the 24-in. Accela-Cota

Tablet load	2.1 kg
Inlet air temperature	60°C
Exhaust air temperature	50°C
Exhaust air flow rate	423 cu ft/min
Pan rotational speed	10 rpm
Air pressure to the spray nozzle	35 psig
Solution spray rate[a]	73 g/min
Tablet bed warming	15 min (jugging)
Total coating time	53 min
Tablet weight gain	7.41% (w/w)

[a] Intermittent spraying with 0.67 min of spraying/min.

gen purge (20 cm^3/min) at a rate of 10°C/min from 40 to 230°C and a chart speed of 5 mm/min. All determinations were carried out in duplicate. From the thermograms the percentages (%, w/w) of weakly bound-unbound water and bound water were evaluated. Bound water refers to the water of hydration (due to the dihydrate in the diluent) and weakly bound-unbound water refers to all types and forms of water other than tightly bound water in accordance with the classification described by Berendsen (5).

A moisture distribution study was carried out to determine the depth and the extent of moisture penetration into the tablet substrate. Powder samples of 100 mg each from the surface layer and the core of a tablet were obtained with the aid of a sharp razor blade. Powder samples from the surface layer and the core of two individual tablets were combined and analyzed for their respective moisture contents using the Perkin-Elmer thermogravimetric system described above. The results were reported as the percentage (%, w/w) of weakly bound or unbound water and bound water for the surface and core layers of each coated and uncoated tablet formulation without Avicel PH 101 (shown in Table I).

Differential Scanning Calorimetry

Differential thermal analysis of uncoated and aqueous film-coated tablet formulations A_{II}, P_{II}, and CP_{II} (containing 20%, w/w, Avicel PH 101) as well as individual tablet components was conducted using a Perkin-Elmer DSC-4 differential scanning calorimeter (Norwalk, Connecticut) connected to a strip-chart recorder. Powder samples of about 5 mg from either a crushed tablet mass or an excipient were encapsulated in flat-bottom aluminum pans with crimped-on lids. The reference used consisted of an empty sealed aluminum pan. The sample holder assembly was heated under dry nitrogen purge (10 cm^3/min) at a constant heating rate of 5°C/min, from 50 to 380°C. The change in specific heat capacity associated with the glass transition was measured directly from the height of the displacement from the baseline. The ordinate scale of the recorder was expressed as units of heat capacity (mcal/°C) by dividing the full-scale sensitivity or the range (mcal/sec) by the scanning rate (°C/sec), as follows:

$$\Delta C_p = \frac{(\Delta H)/(dt)}{(dT/dt)} \quad (1)$$

where, ΔC_p is the change in heat capacity, $(\Delta H)/(dt)$ is the rate of heat flow, and $(dH)/(dt)$ is the constant heating rate. The magnitude of actual step in specific heat amounted to 2.5 cal/g°C in each case. At least two replicates were made for each DSC thermogram.

Tensile Strength Determination

The tensile strength of tables was determined using a testing instrument previously developed in these laboratories (6). At least five tablets were tested from each uncoated and coated formulation type to obtain a mean value for the breaking strength. Tensile strength was calculated from the following formula:

$$\tau = \frac{2P}{\pi \cdot D \cdot t} \quad (2)$$

where τ is tensile strength (kg/cm^2), P is breaking load (kg), D is diameter (cm), and t is thickness (cm).

Mercury Intrusion Porosimetry

A microprocessor-controlled Micromeritics Autopore II, Model 9220 (Norcross, Georgia) mercury intrusion instrument was used to measure tablet pore-volume and pore volume-size distribution. Tablets were predried to remove adsorbed moisture and were placed in a penetrometer cell, which was first evacuated and then filled with mercury. The low-pressure measurement ranged from 0.5 up to 30 psia where pore volumes corresponding to a maximum pore diameter of ≅360 μm were measured. The high-pressure chambers attained a maximum pressure of 60,000 psia whereby intraparticle pores in the submicron range were determined by measuring the volume of mercury forced into the pores by the applied pressure. All determinations were carried out in duplicate for each aqueous film coated and uncoated tablet formulation type (containing Avicel PH 101).

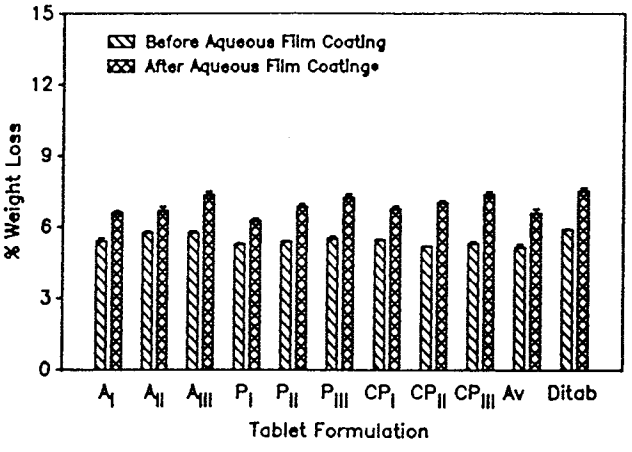
The mean geometric pore diameter was determined by plotting the percentage cumulative pore volume oversize against the pore diameter on a log probability paper. This plot yielded the pore diameter at 50% probability. Tablet porosity was calculated from the apparent solid densities obtained from mercury penetration data and also from the tablet bulk and true volumes obtained from the tablet dimension, weight, and true solid densities of the individual tablet components.

RESULTS AND DISCUSSION

Determination of Tablet Residual Moisture Content

Tablet moisture content determinations were usually carried out within 24 hr of the completion of the aqueous film coating process, during which time coated tablet cores were placed in screw capped glass containers and stored in a desiccator.

Figures 1 and 2 present the results of the percentage weight loss on vacuum oven drying for both uncoated and coated tablet formulations. From these data it was deter-



• polymer film removed

Fig. 1. Percentage weight loss on vacuum oven drying of coated and uncoated tablet formulations with Avicel PH 101.

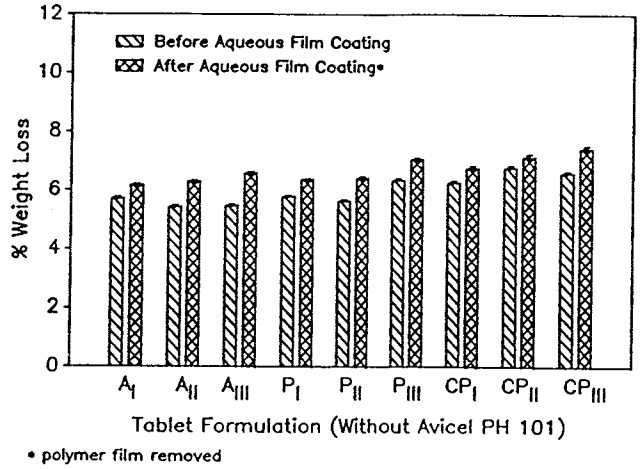


Fig. 2. Percentage weight loss on vacuum oven drying of coated and uncoated tablet formulations without Avicel PH 101.

mined that following the coating operation, tablet residual moisture content significantly increased for all formulation types ($P < 0.05$). These results led to the conclusion that the increased tablet moisture content was due to the penetration of some of the water from the aqueous film coating solution into the tablet matrix during the coating process. This was attributed to the moisture adsorptive capacity of the disintegrant and microcrystalline cellulose particles present in the tablet formulation.

Figure 3 shows that there was no difference in the moisture content (determined by thermogravimetric analysis) of the surface and the core layers of the coated tablet cores. An obvious interpretation of this finding was that penetration of the aqueous solvent into the tablet core had taken place and was not restricted to the tablet surface. In addition, it was observed that following the coating operation, cobalt chloride particles exhibited the same degree of color change (dark purple to light blue) irrespective of their distribution within the tablet matrix, that is, whether present in the core or on the tablet surface. Since these particles acted as a hygroscopic indicator, this color change was attributed to the contact of these particles with moisture from the applied polymer coating solution.

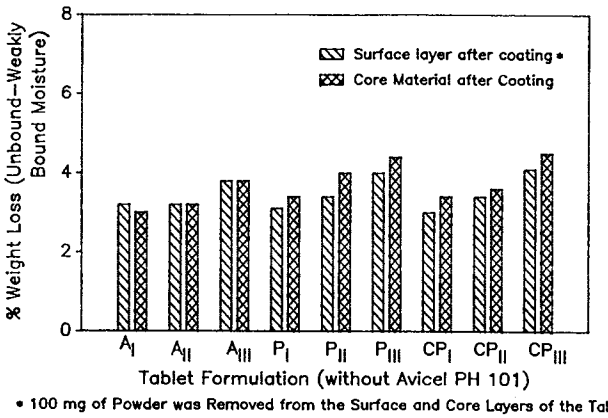


Fig. 3. Thermogravimetric analysis of percentage weakly bound-unbound water content of the tablet core and surface layers (without Avicel PH 101), after the aqueous film coating process.

Table III. Determination of Glass Transition Temperature and the Change in Specific Heat for the Transition from the Glassy to the Rubbery State Obtained from Differential Scanning Calorimetry[a]

Sample	T_g (°C)	ΔC_p (cal/deg · g)
Excipients		
Avicel PH 101	304.33 ± 4.04	7.36 ± 1.82
Primojel	251.66 ± 7.64	7.2 ± 2.2
Ac-Di-Sol	275	7.44
Tablet formulation code[b]		
Aqueous film coated[c]		
A_{II}	290.35 ± 10.05	7.14 ± 0.97
P_{II}	262.25 ± 17.78	8.71 ± 0.98
CP_{II}	233.95 ± 23.531	7.92 ± 0.86
Uncoated		
A_{II}	305	7.44
P_{II}	301	9.36
CP_{II}	260.5	6.96

[a] Heating rate, 5°C/min; heat flow rate, 10 mcal/sec.
[b] Tablets contain 10% (w/w) of the following disintegrants: (A_{II}) Ac-Di-Sol, (P_{II}) Primojel, and (CP_{II}) Polyplasdone-XI.
[c] The mean value for all coating combinations.

Differential Scanning Calorimetry

The results of the differential scanning calorimetry of powder samples from the uncoated and coated tablet formulations A_{II}, P_{II}, and CP_{II} (containing Avicel PH 101; Table I), as well as from the pure excipient components, are shown in Table III. From these data it can be seen that microcrystalline cellulose powder had the highest glass transition temperature (T_g, °C) followed by that of Ac-Di-Sol and Primojel powder samples, respectively. Microcrystalline cellulose consists of the highly crystalline regions of the original cellulose which remain after the more accessible material has been hydrolyzed (7,8); its degree of crystallinity has been reported to be about 63% (9). An increase in polymer crystallinity generally leads to an increase in the value of the glass transition temperature (10). This has been attributed to the stiffening effect of the dispersed microcrystalline cross-links, which leads to decreased mobility of the chain seg-

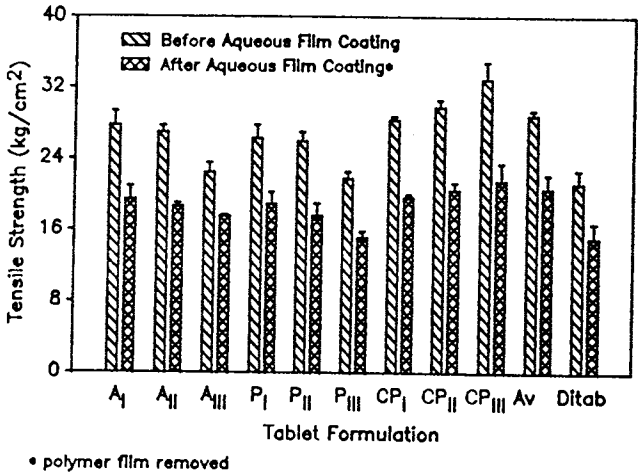


Fig. 4. Determination of the tensile strength of tablet cores (containing Avicel PH 101), before and after the aqueous film coating process.

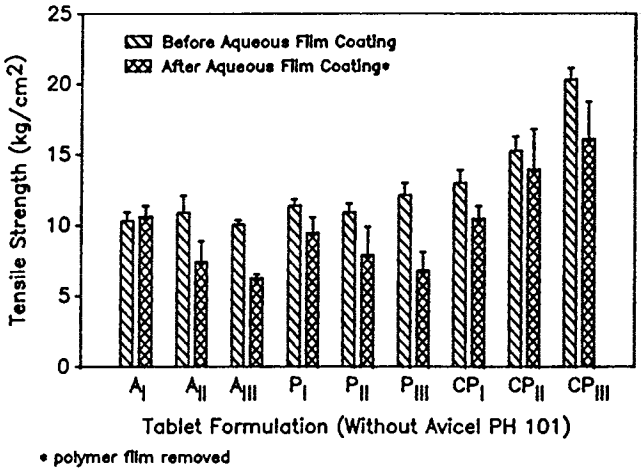


Fig. 5. Determination of the tensile strength of tablet cores (without Avicel PH 101), before and after the aqueous film coating process.

ments in the interconnected amorphous regions. Such factors may account for the relatively high value of T_g for microcrystalline cellulose. The determination of the glass transition temperature for Polyplasdone-XL powder samples was not possible with any great degree of accuracy but was generally observed to be less than 250°C. The relatively low value of T_g for Polyplasdone-XL was attributed to its highly amorphous and cross-linked nature.

The determination of the glass transition temperature (°C) for the uncoated tablets represented the value for the polymeric components of the tablet matrix. Polyplasdone-XL tablets had the lowest T_g (°C). The values of T_g for the aqueous film coated tablets were significantly lower as compared to the corresponding values for the uncoated tablets.

It has been widely recognized that plasticization by water molecules affects the glass-to-rubber transition temperatures of many synthetic and natural amorphous polymers, particularly at low moisture contents (10–12). The plasticizing effect of increased moisture content leads to increased

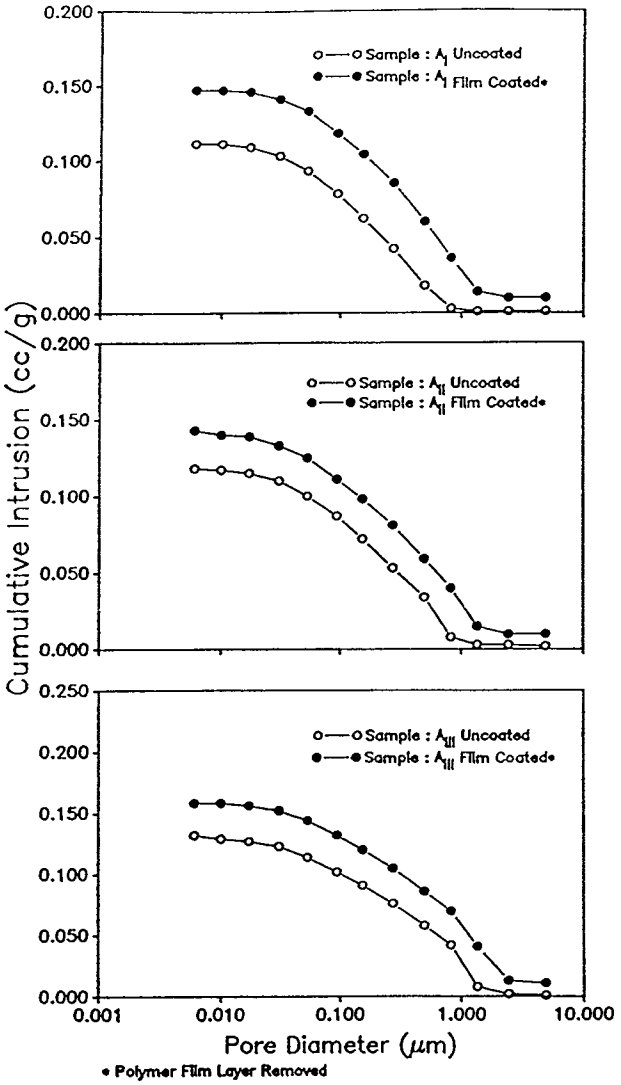


Fig. 6. Cumulative pore volume as a function of the logarithm of pore diameter for coated and uncoated tablets containing Ac-Di-Sol, determined by mercury intrusion.

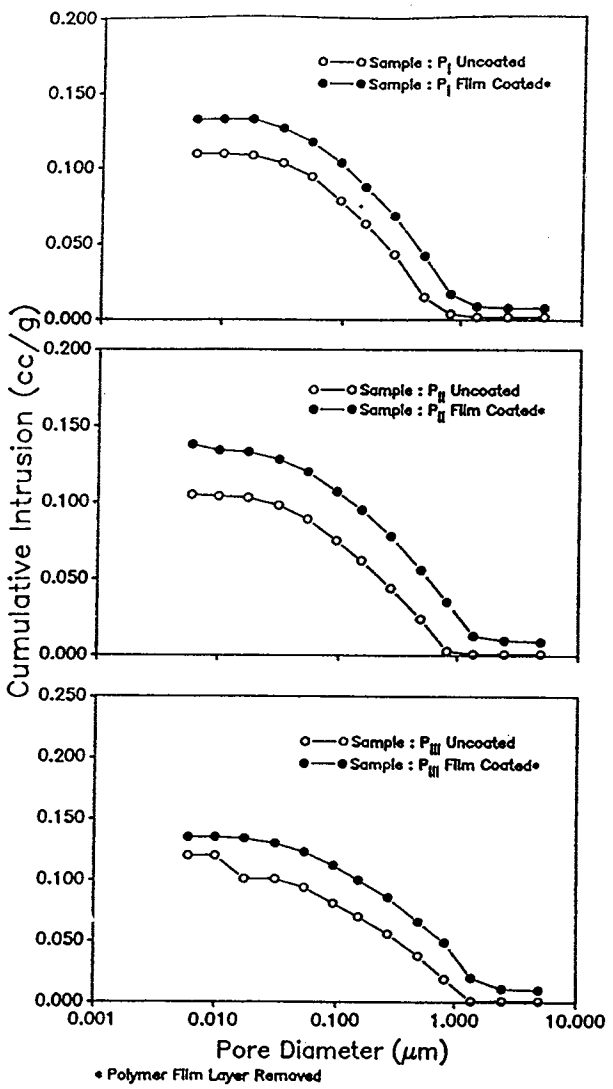


Fig. 7. Cumulative pore volume as a function of the logarithm of pore diameter for coated and uncoated tablets containing Primojel, determined by mercury intrusion.

segmental mobility of the chains in the amorphous regions of glassy and partially crystalline polymer, which, in turn, produces a glass-to-rubber transition at a decreased temperature (13). This finding was attributed to the plasticizing effect of water molecules as a result of the penetration of moisture from the applied aqueous film coating solution into the tablet matrices.

Evaluation of Tablet Tensile Strength

Figures 4 and 5 show that following the aqueous film coating operation, the coated tablet core tensile strength was significantly reduced ($P < 0.05$) for all formulation types. This was attributed to the hydration and the swelling of disintegrant particles within the tablet matrix and a reduction in tablet cohesion due to disruption of bonds between powder particles. However, the tensile strength of the two control tablet formulations, which consisted of Di-Tab alone and its combination with 20% (w/w) Avicel PH 101 (i.e., Di-Tab and AC), also showed a significant reduction after the coating operation. Since the control tablet formulation AC contained no superdisintegrant, the reduction in coated tablet cohesion was attributed to the effect of penetration of the aqueous film coating solution into the tablet, leading to breakage of hydrogen bonds between microcrystalline cellulose particles. The reduction in tensile strength of coated tablet cores containing Di-Tab alone was caused by the mechanical weakening of the tablet microstructure. This was attributed to attrition during the coating process, and the penetration of the polymer coating solution into the tablet by virtue of capillary forces, since crystalline solids (such as dibasic calcium phosphate, dihydrate) consolidate under load by fragmentation and brittle fracture, creating a large tablet void volume.

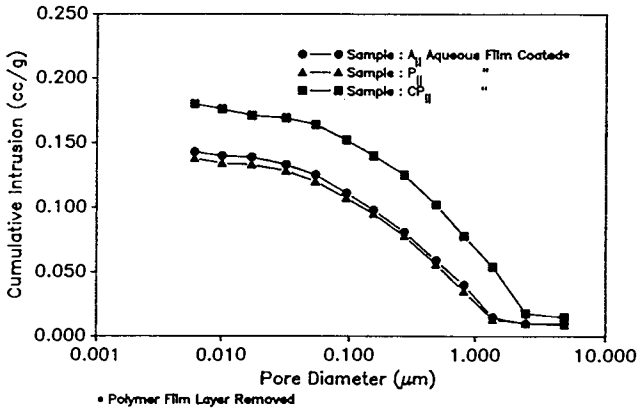


Fig. 9. Cumulative pore volume as a function of the logarithm of pore diameter for coated tablets containing each superdisintegrant at a 10% (w/w) level, determined by mercury intrusion.

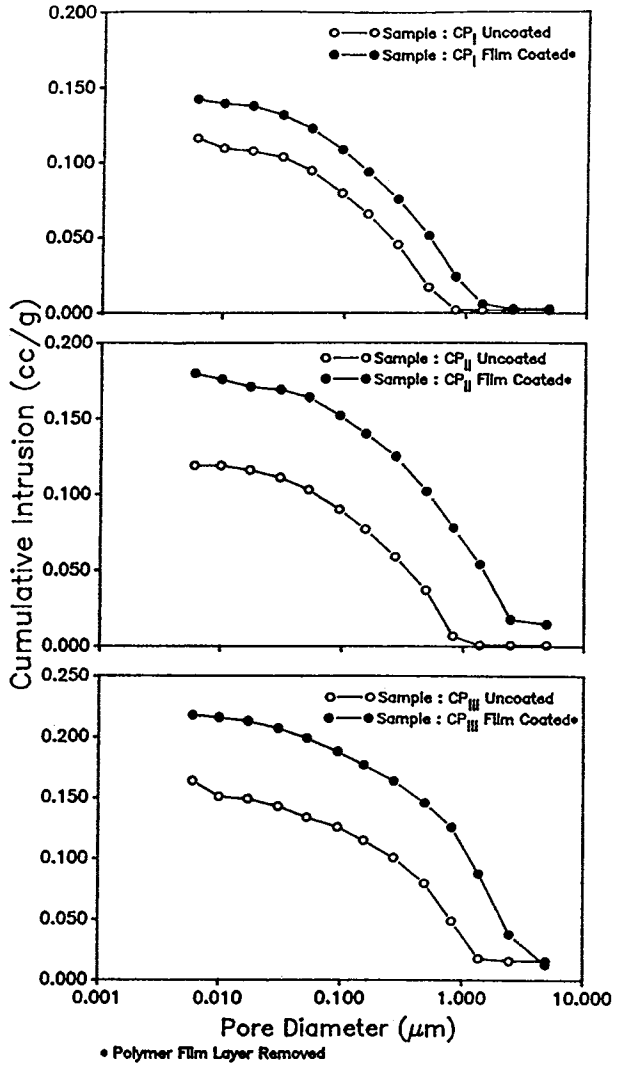


Fig. 8. Cumulative pore volume as a function of the logarithm of pore diameter for coated and uncoated tablets containing polyplasdone-X1, determined by mercury intrusion.

Evaluation of Tablet Pore System Characteristics

Tablet porosity and pore volume-size distribution were determined to evaluate the microstructural changes that may occur as a result of exposure to water vapor in an aqueous film coating environment.

Pore Volume-Size Distribution Curves. The mercury intrusion curves obtained for each uncoated and coated tablet formulation (containing Avicel PH 101) are shown in Figs. 6–8. Without exception, the pore volume-size distribution curves of tablet formulations showed a significant increase in

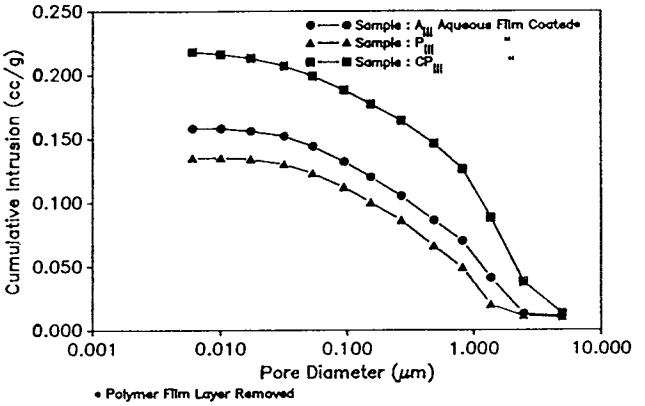


Fig. 10. Cumulative pore volume as a function of the logarithm of pore diameter for coated tablets containing each superdisintegrant at a 20% (w/w) level, determined by mercury intrusion.

Table IV. Pore System Characteristics of Aqueous Film-Coated and Uncoated Tablet Formulations

Sample	Uncoated			Aqueous film coated[a]		
	Porosity (%)	Mean pore diameter (μm)	Total intrusion volume (cm^3/g)	Porosity (%)	Mean Pore diameter (μm)	Total intrusion volume (cm^3/g)
A_I	16.68	0.19	0.111	23.45	0.33	0.147
A_{II}	17.35	0.23	0.118	24.01	0.34	0.143
A_{III}	18.53	0.37	0.132	26.37	0.58	0.158
P_I	19.32	0.19	0.109	22.16	0.28	0.132
P_{II}	18.34	0.24	0.105	21.05	0.35	0.138
P_{III}	—	0.21	—	21.9	0.47	0.135
CP_I	17.66	0.19	0.116	19.39	0.30	0.142
CP_{II}	17.66	0.27	0.119	30.05	0.60	0.180
CP_{III}	17.66	0.45	0.164	31.10	1.05	0.218

[a] Polymer film layer was removed.

larger pores after the aqueous film coating operation. The difference between the distribution of coated and that of uncoated tablet pore sizes was greater for Polyplasdone-XL tablets at both 10 and 20% (w/w). This indicated that, following the coating operation, there was a widening or enlarging of the tablet pore structure due to the expansion of disintegrant particles and the exertion of a swelling pressure on the surrounding tablet components. The resultant tablet swelling and expansion were attributed to the hydration of disintegrant particles as a result of penetration of water from the applied coating solution into the tablet matrix.

Comparison of coated tablet pore size distribution curves containing each of the disintegrants at comparable concentration levels showed that while similar profiles were obtained at 5% (w/w), there was a significant increase in the distribution of pore sizes for coated tablets containing 10 and 20% (w/w) of Polyplasdone-XL compared to similar concentrations of either Ac-Di-Sol or Primojel (Figs. 9 and 10). Since uncoated tablets had showed similar pore size distributions at all concentration levels, these findings were interpreted to mean that, following the coating operation, the increase in tablet pore size was much more pronounced for tablets containing Polyplasdone-XL than for either Ac-Di-Sol or Primojel.

Tablet Percentage Porosity and Mean Pore Diameter. From data shown in Table IV it was apparent that the coated tablet mean geometric pore diameter was significantly greater than the value for the corresponding uncoated tablet. This demonstrated that the arrangement and the size distribution of the tablet internal pore structure were significantly altered after the coating process. Tablet porosity (%) was increased for coated tablets containing 10 and 20% (w/w) of Polyplasdone-XL. This indicated that for these tablets the total tablet void volume was increased after the coating operation.

SUMMARY

It was established that following the aqueous film coating of formulated tablets containing superdisintegrants (Ac-Di-Sol, Primojel, and Polyplasdone-XL, at 5, 10, and 20%, w/w), penetration of the aqueous solvent into the tablet core had taken place and was not restricted to the tablet surface. The findings indicate that the extent of moisture sorption by tablets, coated under normal operating conditions, was sufficient to result in significant changes in tablet physical characteristics such as residual moisture content, glass transition temperature of the tablet matrix, tensile strength, and tablet pore volume-size distribution. It was apparent that the high capillary activity of tablets containing Polyplasdone-XL resulted in marked changes in the tablet microstructure and its pore system characteristics following the film coating operation.

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