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Influence of hydrophilic excipients on the interaction of aspirin and water

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Summary

Photomicrographic evidence is presented which documents the existence of an apparent hydrophobic field generated by an aspirin crystal which prohibits the condensation of water from a high humidity environment in the vicinity of that crystal at 25°C. Water vapor sorption results on aspirin at the same temperature were found to be consistent with those expected for a solid which is not completely wetted by the condensed adsorbate (Type III).

Photomicrographic evidence is also presented which shows that when aspirin is combined with certain hydrophilic excipients, condensation in the vicinity of the aspirin crystals is found. In certain cases individual aspirin crystals become immersed in a pool of water when the powder blend is exposed to high humidity. Sodium starch glycolate, croscarmellose sodium, crospovidone, and colloidal silicon dioxide blends were studied. Since the amount and perhaps the state of water associated with aspirin influences hydrolytic degradation, it is suggested that the stability of aspirin formulations may correlate with these observed sorption results.

Introduction

Aspirin is the pre-eminent example of a moisture-sensitive drug, yet many fundamental aspects of the stability of the crystalline solid in the presence of moisture have not been articulated. Two important points in this regard are: (1) aspirin is not a particularly hygroscopic drug; and (2) water in condensed form must be present before hydrolysis becomes a serious problem. Consequently, the stability

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of aspirin in solid dosage forms depends upon the influence of formulation excipients on the net water sorption characteristics of the product.

In this paper, the influence of selected excipients on the water sorption characteristics of aspirin at 100% relative humidity has been studied by direct observation of solid particles in a controlled humidity chamber, through use of a photomicrograph.

Materials and methods

Photomicrographic apparatus

The system employed to photograph individual solid particles while maintaining them in a controlled humidity environment consisted basically of these components: a camera fitted to a microscope, a stage chamber, and a pump to circulate humidified air. The specically constructed 28 × 73 × 130 mm Plexiglas stage chamber, was designed with a 25.4 mm diameter hole in the top to accomodate the 10 × objective. A flexible latex sleeve was tightly fitted to the objective and the opening in the chamber to maintain the integrity of the chamber and permit focusing. The face of the chamber was removable so that the sample, distributed on a 25 × 50 mm glass slide, could be placed into the chamber and positioned for observation of selected particles. The glass microscope slides were all similarly treated prior to use. The procedure involved cleaning with a degreaser (Chlorothene NU), rinsing with isopropyl alcohol, and then drying at 100°C.

Controlled humidity conditions were generated and maintained by gas transpiration. Air in the closed system was continuously circulated by use of a Masterflex rotary peristaltic tubing pump. The pump head and variable-speed drive were selected and adjusted to provide a flow rate of approximately 100 ml/min, as verified by a liquid flow calibration. Air from the chamber was bubbled through distilled water or an aqueous sulfuric acid solution of selected concentration to achieve the desired degree of humidification (Stokes and Robinson, 1949). The gas saturator, pump, microscope stage chamber, and a trap to prevent small droplets from being swept into the chamber, were interconnected with 3.18 mm ID Tygon tubing.

Chemicals

Reagent grade concentrated H_2SO_4 (J.T. Baker Chemicals) was used in the preparation of all humidity-controlling solutions. The aspirin (Monsanto) was 80 mesh and met USP standards. Excipients employed in the study all conformed to NF standards: croscarmellose sodium (Ac-Di-Sol; FMC), sodium starch glycolate (Primojel; Generichem), colloidal fumed silicon dioxide (Cab-O-Sil; M-5, Cabot) and crospovidone (Polyplasdone XL; GAF). All powder samples except aspirin were preconditioned by drying at approximately 70°C for at least 48 h in a vacuum oven (Model 5831, National Appliance) attached to a two-stage vacuum pump (Dist-O-Pump; Welch Scientific). Pressure in the oven during the final stages of drying was approximately 50–100 μm Hg as measured by a McLeod gauge (Model A185, Research and Development Glass Products). To avoid sublimation, aspirin was dried

in a similar fashion without heating. All samples and blends were stored in an evacuated desiccator over Drierite at 25°C.

Sorption studies

Equilibrium water-vapor adsorption studies were conducted gravimetrically. Approximately 2 g of powder was placed in a previously weighed 35 × 10 mm plastic dish (Falcon tissue culture dish) and the initial weight was determined. All weighings were performed on a Mettler Analytical Balance whose sensitivity was 0.1 mg. Three such samples were placed in a 150 mm Nalgene desiccator containing an aqueous sulfuric acid solution of preselected concentration. The concentration of each sulfuric acid solution was chosen to provide a set of chambers with the following relative humidities at 25°C (Stokes and Robinson, 1949): 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90 and 95%. When a 100% RH was desired, distilled water was placed in the chamber. All chambers were stored in a Precision Model 815 Low Temperature Incubator, maintaining temperature at 25.0 ± 0.1°C. Equilibrium was assumed when subsequent weighings indicated a weight gain of less than 0.2 mg and moisture content was then determined by difference. Reported values represent the average moisture content of the 3 samples, on a dry weight basis.

Small blends of powders were prepared in 50 g quantities, using previously dried materials, by simply shaking the powder for a few minutes in a plastic vial. All excipients were added to aspirin at the 4% w/w level except the colloidal fumed silicon dioxide, which was prepared at the 1% level.

Samples for microscopic evaluation of water vapor sorption were prepared by distributing a small quantity of powder on a microscope slide and positioning the slide in the stage chamber so that a representative collection of particles was isolated in the field. After sealing the stage chamber, and placing distilled water in the saturator, the pump was activated and a photographic record of the sorption process was taken after a 24 h exposure period.

Results and discussion

It has been shown that decomposition of aspirin requires moisture (Leeson and Mattocks, 1958), so it is obvious that water vapor adsorption must precede hydrolysis. The progressive physical and chemical events associated with the hydrolytic degradation of solid aspirin stored in an environment containing water vapor may be considered in steps: the dry solid will first attract moisture from the environment and this adsorbed moisture will then participate in hydrolysis at a rate governed by the activity of the water and aspirin in the surface region.

Aspirin by itself is reasonably stable, even in the presence of relatively high humidity. In one study, crystalline aspirin stored at 100% RH at 40°C showed less than 10% degradation after 8 weeks (El-Banna et al., 1978), and the authors hypothesized that a low level of water sorption by the hydrophobic drug was responsible for this apparently unexpected stability. (Our analysis of the aspirin used in the adsorption study below indicated less than 0.2% decomposition for a sample

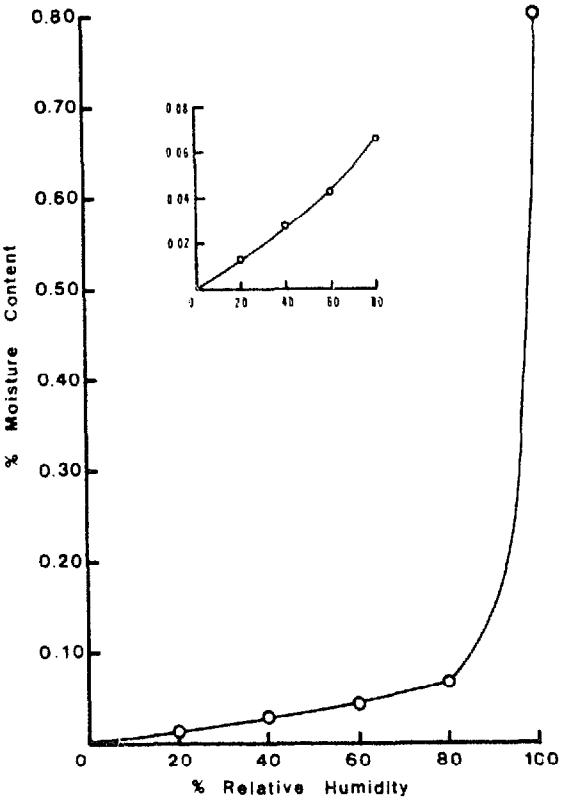

Fig. 1. Water vapor adsorption isotherm for aspirin at 25°C. Insert presents an expanded view of the low moisture content data.

maintained at 25°C and 100% RH for 120 days.) For comparative purposes the half-life of aspirin in aqueous solution at its most stable pH at 25°C is 14.3 days (Garrett, 1957). Clearly, when a moisture stability problem exists for aspirin in a solid dosage form, the problem may be directly associated with the influence of one or more hydrophilic excipients in the formulation on the water vapor sorption of the blend.

Adsorption results presented in Fig. 1 indicate that at 25°C the aspirin powder adsorbs less than 1% moisture at 100% RH. The adsorption isotherm appears to be nearly a Type III (Brunauer, 1945), which is consistent with the fact that water does not spontaneously spread on this solid. In that regard, a rather high contact angle of 73–75° has been reported for a saturated aqueous solution on an aspirin compact at 23° (Lerk et al., 1976). There is no evidence in the isotherm of condensation of the adsorbate on the apparently low energy surface of aspirin, and consequently the adsorbed water molecules possess considerable translational energy. Given these observations, the stability of aspirin at high humidity is not surprising.

A direct observation of the influence of aspirin on the condensation of water from a 100% RH environment was made by placing a sample of the crystalline material in the stage chamber of the photomicrograph and maintaining saturation of the air in the isolated system. The results of this study are presented in Fig. 2. In the absence

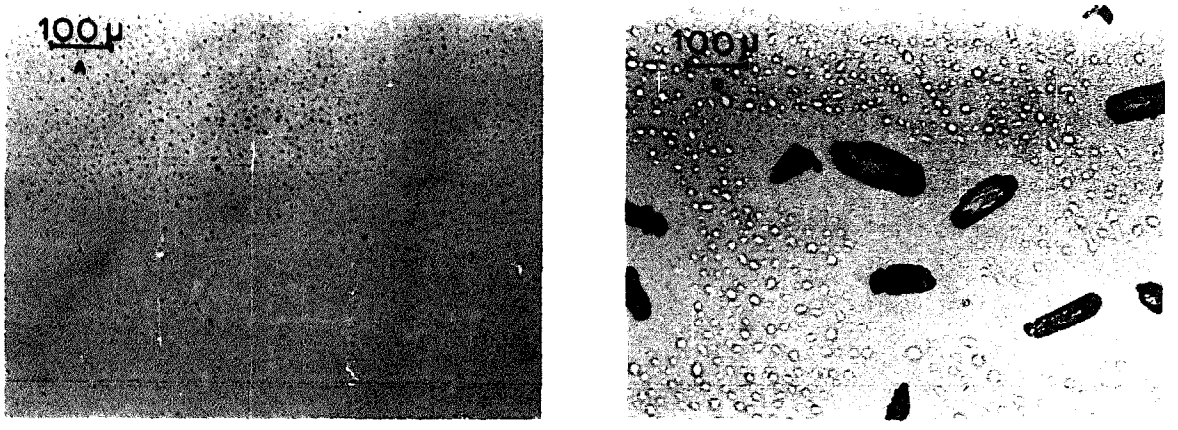

Fig. 2. Influence of aspirin on the condensation of water at 100% RH. A: condensation of water on a glass slide without any powder present. B: condensation of water on a glass slide in the presence of aspirin crystals.

of powder, moisture condenses in very fine droplets uniformly over the microscope slide. However, this condensation process is dramatically altered by the presence of aspirin. There is a clearly defined zone around each crystal where no condensation was seen and some coalescence has occurred in the areas where condensation was evident. There appears to be a hydrophobic field emanating from each aspirin crystal; not only does water not condense on the aspirin crystals, it does not condense in the immediate vicinity of the crystals.

The expression "hydrophobic field" is used here descriptively rather than casually. Although aspirin does adsorb water (Fig. 1), the behavior presented in Fig. 2 suggests that this solid does indeed have a phobia for water in the liquid state. The term "field" is used in its most general sense to simply identify the space in which the causative force operates.

When certain excipients are combined with aspirin, even at relatively low levels, the character of the excipient has a profound effect on the sorption of the blend.

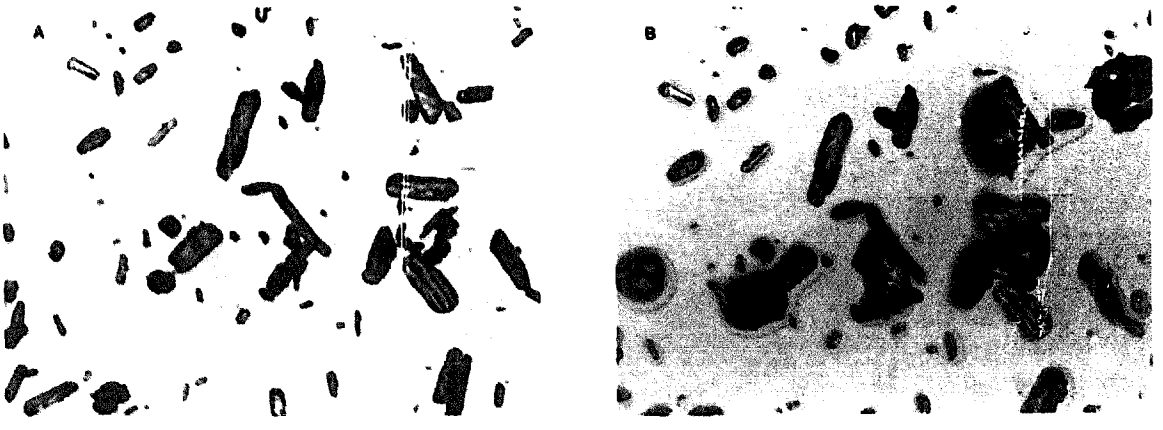

Fig. 3. Influence of sodium starch glycolate (4%) in an aspirin powder blend on the condensation of moisture at 100% RH. A: dry powder. B: condensation of water.

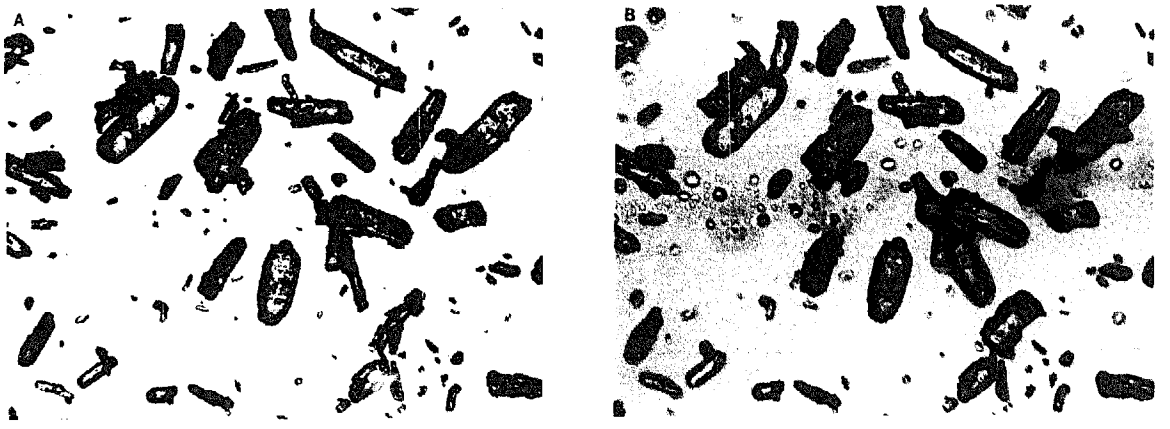

Fig. 4. Influence of croscarmellose sodium (4%) in an aspirin powder blend on the condensation of moisture at 100% RH. A: dry powder. B: condensation of water.

Figs. 3–6 demonstrate this principle for blends of aspirin and sodium starch glycolate (4%), croscarmellose sodium (4%), crospovidone (4%) and colloidal fumed silicon dioxide (1%), respectively. The first 3 of these materials were selected because of their utility as disintegrants, and the colloidal fumed silicon dioxide was included because it is often purported to be a moisture scavenger or preferential adsorbent.

Both sodium starch glycolate (Fig. 3) and croscarmellose sodium (Fig. 4) appear as remarkably hydrophilic substances which swell considerably with moisture uptake. There is no evidence of the hydrophobic effect, and in contrast to Fig. 2 all of the aspirin particles in these blends are engulfed in pools of water. In the case of sodium starch glycolate, this effect is so pronounced that condensation is restricted to areas surrounding the particles.

The influence of crospovidone on the condensation process is quite different from that of the other disintegrants. In Fig. 5 it can be seen that this material is less hydrophilic—there are even some stable droplets in contact with the crospovidone particles—and that it does not swell after 24 h exposure to 100% RH. There is

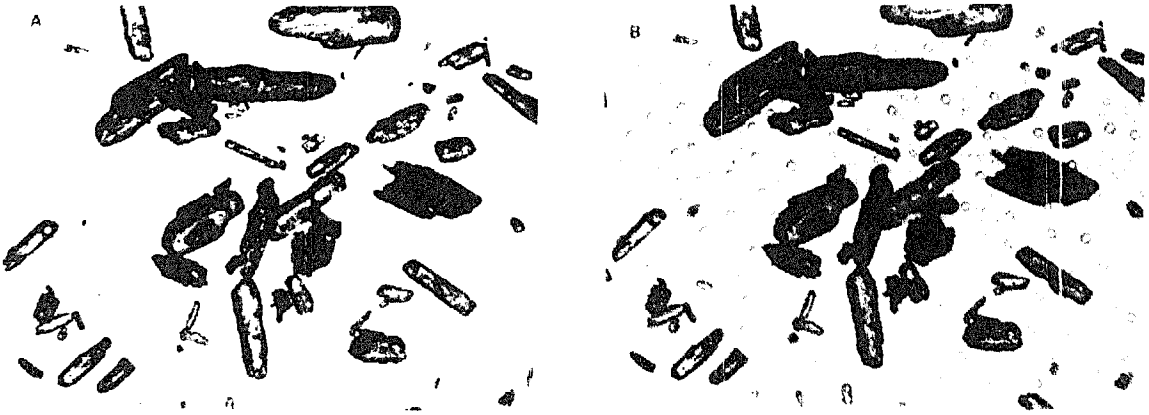

Fig. 5. Influence of crospovidone (4%) in an aspirin powder blend on the condensation of moisture at 100% RH. A: dry powder. B: condensation of water.

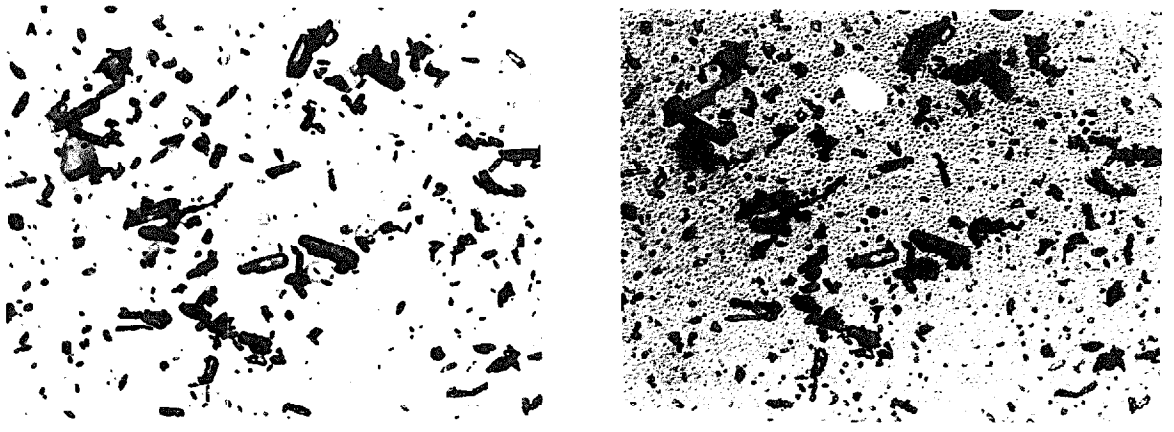

Fig. 6. Influence of colloidal fumed silicon dioxide (1%) in an aspirin powder blend on the condensation of moisture at 100% RH. A: dry powder. B: condensation of water.

evidence that some of the hydrophobic effect noted before still exists, particularly when there is a close association of several aspirin crystals.

Finally, it is evident that the colloidal fumed silicon dioxide (Fig. 6) does not "protect" aspirin from contact with water. In fact, the hydrophobic effect described previously is not apparent in this system and droplets of water may be seen in contact with aspirin crystals.

Perhaps the best way to approach an explanation for these observations is to consider the process of condensation of water on the glass slide itself. Initially, molecules of water are adsorbed onto the dry glass surface forming a "film" in which these molecules have considerable 2-dimensional freedom. As the density of this film increases, with further adsorption, simultaneous collisions of several molecules occur forming clusters, some of which exist long enough to serve as nuclei for condensation. The eventual result is a random pattern of droplets as depicted in Fig. 2A. The placement of solid particles on the glass slide produces a situation where developing water films interface; when the films are associated with solids whose surface energetics are different, the character of the films will be different. All of the results presented in Figs. 2–6 reflect the manifestation of these differences on the eventual condensation of water.

Two factors discussed here indicate that the "film" associated with aspirin does not progress to the nucleation and condensation stage. The existence of a contact angle in the previously cited work of Lerk et al. (1976) demonstrates that water in an adsorbed film on aspirin has a structure sufficiently different from bulk liquid to allow coexistence of these phases. Also, there is no evidence of a phase change in the adsorption isotherm (Fig. 1). The hypothesis put forward here for the hydrophobic field evident in Fig. 2 is that it is an extension of the influence of aspirin beyond the immediate vicinity of the solid. In essence, the structure of the adsorbate film on aspirin has an orientation effect on neighboring water molecules of the adsorbate film on glass. This effect is sufficient to prevent the normal nucleation process from occurring in the region through which its influence extends.

The excipients added in Figs. 3–6 perturb this orientation effect to different

degrees. Sodium starch glycolate and croscarmellose sodium are so hydrophilic that they overwhelm all other influences and, in fact, serve as particulate nuclei for condensation.

Some general conclusions may be drawn from these observations. First, the ultimate chemical stability of aspirin is never improved by combination of the drug with a hydrophilic excipient. However, there seems to be different degrees to which the adsorption process is influenced by the presence of an excipient. It can be anticipated that formulation-dependent stability differences will exist and perhaps correlate with differences observed in this work. A long-term stability study for these systems is currently underway and the results will determine whether or not this hypothesis is valid.

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