DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(1), 77-98 (1988)

THE EFFECT OF SELECTED DIRECT COMPRESSION EXCIPIENTS ON THE STABILITY OF ASPIRIN AS A MODEL HYDROLYZABLE DRUG

Nagin K. Patel*, Indravadan J. Patel*[X],
Anthony J. Cutie*, Deodatt A. Wadke**,
Donald C. Monkhouse**[XX] and George E. Reier**

*Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Division of Pharmaceutics and Industrial Pharmacy, Long Island University, Brooklyn, NY 11201

**The Squibb Institute for Medical Research, New Brunswick, NJ 08903

[X]Present address: Pharmacia, Inc., Piscataway, NJ 08854

[XX]Present address: Sterling-Winthrop Research Institute, Rensselaer, NY 12144

ABSTRACT

The stability of a moisture sensitive drug is normally studied in relation to packaging which prevents water vapor ingress or minimizes its effect by using dessicants in a container. However, excipients contain intrinsic water which may degrade the drug. This paper deals with the stability of aspirin, as a model hydrolyzable drug, in combination with excipients having either hydrate water (dibasic calcium phosphate

dihydrate and lactose) or variable adsorbed moisture depending upon environmental conditions (microcrystalline cellulose and pregelatinized starch). Tablets containing 10 and 50 per cent aspirin with these excipients were stored in open and closed bottles at various temperatures and humidities. Pregelatinized starch based tablets were stable in closed containers for 30 weeks while tablets containing microcrystalline cellulose or dibasic calcium phosphate dihydrate were unstable with respect to USP salicylic acid content. The stability of lactose based tablets was dependent on aspirin content. In some cases tablets in open bottles were more stable than those in closed bottles. This indicates that water liberated from excipients, if allowed to remain in a closed package, will affect the stability of hydrolyzable drugs. Product stability programs must be properly designed to detect instability from this source.

INTRODUCTION

The stability of a hydrolyzable drug in solid dosage forms is usually determined by studying the amount of water that can be adsorbed by the finished product before instability can be detected. Pope, in his review of stability testing, stated that the percentage of water in a product or the relative humidity at which the product is stored could influence its stability (1). Lee *et al*. reported that the stability of aspirin and ascorbic acid in various compressed solid matrices depended on the amount of water adsorbed by them (2). To prevent water adsorption,

proper packaging is necessary. Dukes in his article on developing a stability testing program placed emphasis on evaluating closures resistant to high humidities and temperatures (3).

One source of water associated with capsule formulations is the gelatin itself. Studies have described water transfer from hard gelatin capsule shells to the capsule contents (4,5). Another study found that water from a soft gelatin shell precipitated drug from a solution within the capsule (6).

There are no reports of water loss from solid dosage form excipients per se causing instability. However, Woolfe and Worthington have noted that moisture may transfer from one component of a solid dosage form to another (7). Carstensen has discussed excipient or active ingredient dehydration as a function of storage temperature and pressure (8). Water loss from tablets containing dicalcium phosphate dihydrate has been suggested even though storage was at elevated temperature and humidity (9,10).

Two types of excipients were selected for this study as potential sources of water leading to drug degradation. One type contains hydrate water. Of this type, dibasic calcium phosphate dihydrate unmilled and lactose were chosen for investigation. The stability of lactose hydrate has apparently not been determined while that of calcium phosphate dihydrate has previously been noted (9,10).

The second type of excipient has a variable water content depending on environment. Examples chosen for study were microcrystalline cellulose and pregelatinized starch. The stability of aspirin was reported to be satisfactory in combination with either excipient when the excipient/aspirin ratio was 20:80 (11). The inverse ratio would be applicable in the case of a low dose hydrolyzable drug.

Aspirin was selected as a model hydrolyzable drug because of ease of quantification of its degradation product, salicylic acid. Reports of factors affecting the hydrolysis of aspirin in the solid state are numerous (2, 12-22 for example).

The purpose of this research was to ascertain the influence of the chosen excipients on the hydrolysis of aspirin at 10 and 50 per cent levels in directly compressed tablets stored in open and closed containers under several temperature and humidity conditions. The two aspirin levels simulate the presence of low and high dose drugs and provide a means for comparing degradation as a function of concentration.

EXPERIMENTAL

The eight formulations studied contained either 10 or 50 per cent aspirin, 3 per cent lubricant and the remainder excipient as follows.

Aspirin	10% or 50%
Excipient	87% or 47%
Lubricant	3%

The lubricant used was stearic acid. It has been reported that stearic acid and alkaline stearates promote the degradation of aspirin in tablets (14,15). However, another study using a suspension technique showed that stearic acid had negligible effects on aspirin stability (13). Aspirin was found to be stable when mixed with stearic acid in a 15:4 ratio (22).

Materials

The aspirin[1] and the dibasic calcium phosphate dihydrate[2] were USP grade. The lactose[3], the microcrystalline cellulose[4], the pregelatinized starch[5] and the stearic acid[6] were NF grade. Glacial acetic acid[1], methanol[7], chloroform[7] and n-heptane[8] were used in the analyses of tablets for aspirin and salicylic acid. All were HPLC grade except the acetic acid which was ACS grade.

Methods

Formulation Manufacture. Powder blends of 10.4 kg were prepared using a planetary mixer[9]. All materials were screened through a #16 mesh screen except for the stearic acid which was passed through a #40 screen. The aspirin and excipient were mixed for five minutes. Stearic acid was added and mixing continued for an additional three minutes. Tablets weighing 650 mg were compressed using 7/16" flat face beveled edge tooling on a Colton 216 rotary tablet press[10] operated at about 800 tablets per minute. Tablets were compressed to approximately twice the final mixture fluff density by adjusting tablet thickness. Equal compression force would not result in tablets of equal hardness

or thickness (density) because of differences in compressibility of the excipient materials. Similarly, compression to the same tablet thickness would yield tablets of varying hardness and density.

Fluff Density. Fluff density was determined by allowing the powder to fall freely through a device[11] holding a series of glass plates such that the powder cascades into a collection vessel of known volume. The weight of the collected powder is determined and used to calculate the density.

Packaging and Storage. Amber glass bottles (3.5 oz. for all tablets except microcrystalline cellulose tablets which required 5 oz.) previously inspected for sealing surface imperfections were used for packaging. Metal caps containing pressure sensitive seals were applied using known torques. Silica gel capsules[12] (one per bottle) were used as desiccant. One-third of each tablet batch was packaged in open bottles, one-third in closed bottles with desiccant and one-third in closed bottles without desiccant. Storage of the open bottles at high humidity was in desiccators utilizing a saturated solution of sodium chloride (with excess solute) to obtain 75% relative humidity (23).

Analytical Methodology. The analytical method was based on that of Taguchi, et al. (24). Tablets were analyzed by first powdering five to ten in a mortar and then transferring 650 mg of the powder to a 100 ml volumetric Flask. Five ml of glacial

acetic acid were added to the flask followed by 5 minutes of moderate shaking. Fifty ml of n-heptane and 20 ml of chloroform were added. The flask was placed in an ultrasonic bath for 10 minutes and the volume made up to 100 ml with chloroform. The solution was filtered into HPLC injector vials to remove insoluble material. The use of n-heptane in preparing sample solutions and standard solutions was not a part of Taguchi's method but was found necessary to reduce viscosity and eliminate injector motor straining and vial breakage. Standard solutions of aspirin and salicylic acid were prepared as follows. Either 65 mg or 325 mg of aspirin were analytically weighed and transferred to a 100 ml volumetric flask depending on whether 10% or 50% aspirin tablets were being analyzed. In either case, the aspirin in the flask was treated as described for the tablet analysis. Salicylic acid (250 mg) analytically weighed was transferred to a 100 ml volumetric flask. As described above for the tablet analysis, glacical acetic acid, n-heptane and chloroform were added. The resulting solution was considered a stock solution and dilutions made as needed with 50:50 chloroform and n-heptane. Mobil phase consisted of 5% (v/v) glacial acetic acid in n-heptane. All mobile phase was filtered through a sintered glass filter and kept overnight to allow air to escape. System conditions included a mobile phase flow rate of 3.5 ml/min. Column temperature was maintained at 30°C for reproducibility of results by a constant flow of heated water through a column water jacket. UV detection was at 300 nm.

Sample and standard were usually alternated with 50:50 methanol and n-heptane to eliminate precipitation of material in the injector loops. System components consisted of a pump[13], an automatic injector with 50 µl loop[14], 10 µm microparticulate silica column[15], a variable wavelength spectrophotometer detector[16] and a dual pen recorder[17].

pH. Suspensions of aspirin or aspirin/excipient mixtures were made in distilled water (3% w/v) and the pH determined[18].

Excipient Weight Gain/Loss. The weight change of excipients was studied both at room temperature and known humidity and at 5°, RT, 33°, 40° and 50°C at ambient humidity. Solutions of salts yielding relative humidities from 11 to 83% at room temperature (23) were placed in desiccators. About one gram of each excipient was placed into open dishes in the desiccators. The ambient humidity study was carried out by placing one gram samples in open dishes at the various temperature conditions.

Differential Thermal Analysis (DTA). The technique and apparatus described by Jacobson and Reier (25) were used to obtain aspirin and excipient thermograms.

RESULTS AND DISCUSSION

Physical Data

The data in Table 1 reveal that mixtures of microcrystalline cellulose, lactose and pregelatinized starch containing stearic acid with either 10% or 50% aspirin have the same pH as aspirin

Table 1. pH Values of 3% Suspension of Materials Alone and of Mixtures of Composition A or B*

Material	Alone	Mixture A	Mixture B
Aspirin	2.7	---	---
Microcrystalline Cellulose	7.4	2.9	2.7
Dibasic Calcium Phosphate Dihydrate	8.0	4.4	3.8
Lactose	6.4	2.9	2.7
Pregelatinized Starch	5.0	2.8	2.7

*Composition A: 87% excipient, 10% aspirin, 3% stearic acid.
Composition B: 47% excipient, 50% aspirin, 3% stearic acid.

alone indicating that these excipients have no buffer capacity and would not be expected to effect aspirin stability on the basis of pH. The dibasic calcium phosphate-aspirin mixtures, however, do have higher pH values than aspirin alone. Because there is deviation from pH 2.5 where aspirin has maximum stability (26), there will be some contribution from this factor to any instability observed.

Changes in excipient weights after storage for one month at room temperature under various relative humidities are given in Table 2. Microcrystalline cellulose and pregelatinized starch had moisture contents which were humidity dependent. A minimal amount of water adsorbtion by lactose was observed at 75% and 85% relative humidity. Dibasic calcium phosphate dihydrate exhibited a tendency for weight loss over the entire range of humidities studied. These data are consistent with literature values (27).

This short term study did not indicate the total extent to which dibasic calcium phosphate dihydrate will lose water. In

Table 2. Weight Changes of Excipients in Open Containers After One Month at Various Relative Humidity (RH) Conditions at Room Temperature

	Per Cent Weight Change			
% RH	Micro-crystalline Cellulose	Dibasic Cal. Phos. Dihydrate	Lactose	Pre-gelatinized Starch
11	-1.7	-0.1	0.0	-4.4
23	-0.5	-0.2	-0.1	-2.0
33	+0.1	0.0	0.0	-0.6
43	+0.9	-0.3	0.0	+0.3
52	+1.9	-0.1	-0.1	+1.1
57	+2.1	0.0	0.0	+1.4
68	+3.5	0.0	-0.2	+3.3
75	+4.5	-0.4	+0.1	+5.1
83	+5.7	-0.2	+0.1	+7.3

addition, the two sharp endotherms at slightly above 100°C in the thermogram for this material (Figure 1) indicate a temperature specific moisture release. The data in Table 3 show that moisture lost from dibasic calcium phosphate dihydrate in open containers under ambient humidity conditions is both time and temperature dependent. Above room temperature the amount of water lost is quite surprising. Even at room temperature, moisture loss is significant. Lactose, on the other hand, lost only small amounts of water above room temperature. Microcrystalline cellulose and pregelatinized starch had variable moisture contents over the course of the study but clearly there was moisture adsorption at low temperature (high ambient humidity) and moisture loss at high temperature (low ambient humidity).

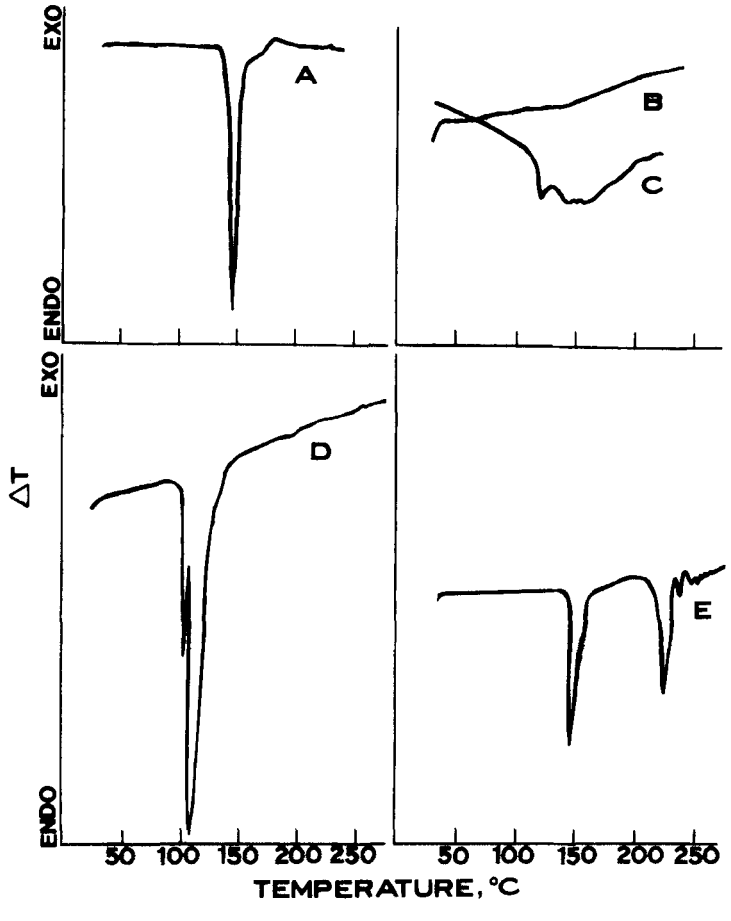

Figure 1 - Thermograms of Aspirin and Excipients. Key: A, Aspirin; B, Mirocrystalline Cellulose; C, Pregelatinized Starch; D, Dibasic Calcium Phosphate Dihydrate; E. Lactose

A comparison of final mixture fluff density and tablet density and thickness are given in Table 4.

Analytical Data

Analytical data for tablets are presented in Table 5 and 6. Also included in these tables are data on aspirin powder. The quantities of aspirin and salicylic acid should total a constant sum depending on tablet potency. However, especially in those

Table 3. Excipient Weight Changes in Open Containers at Ambient Humidity

Time, Months	Per Cent Weight Change at 5°C	RT	33°C	40°C	50°C
		Microcrystalline Cellulose			
1	+5.9	-0.8	-0.4	-1.4	-2.0
2	+5.3	+0.6	-0.1	-0.6	-2.3
3	+6.1	+1.7	+0.1	-0.9	-2.1
6	+3.4	+0.5	-0.9	-1.2	-3.1
		Dibasic Calcium Phosphate Dihydrate			
1	0.0	-0.2	-5.8	-13.7	-17.7
2	-0.9	-0.9	-14.9	-18.8	-19.5
3	-0.9	-2.1	-17.4	-19.9	-19.7
6	-0.9	-4.1	-18.4	-20.5	-20.4
		Lactose			
1	+0.2	0.0	-0.1	-0.1	-0.1
2	0.0	0.0	-0.4	-0.1	-0.3
3	0.0	0.0	-0.4	-0.1	-0.4
6	-0.5	0.0	-0.5	-0.2	-0.5
		Pregelatinized Starch			
1	+5.4	+0.5	-2.3	-3.8	-5.2
2	+6.2	+0.3	-2.0	-3.2	-5.6
3	+7.2	+1.6	-1.5	-3.2	-5.8
6	+6.6	+1.6	-3.3	-4.2	-7.8

cases where severe degradation took place, it was extremely difficult to handle tablets without dislodging salicylic acid crystals which had formed on the surfaces. There were also instances of salicylic acid accumulation on the insides of bottles and/or caps. It is not believed that these difficulties had any influence on the conclusions drawn because of the trends observed over time.

Table 4. Final Mixture and Tablet Densities

Excipient	Mix Fluff Density (g/cu.in.)	Tablet Density[a] (g/cu.in.)	Tablet Thickness (in.)
	10% Aspirin		
Microcryst. Cellulose	5.5	11.0	0.300
Dibasic Cal. Phos. Dihy.	13.2	28.8	0.150
Lactose	10.3	21.6	0.200
Pregelatinized Starch	9.4	19.2	0.225
	50% Aspirin		
Microcryst. Cellulose	6.6	13.8	0.240
Dibasic Cal. Phos. Dihy.	11.9	23.4	0.185
Lactose	10.4	21.6	0.200
Pregelatinized Starch	9.8	20.1	0.215

[a] Tablet Density = tablet weight/tablet volume. Tablet volume was calculated from tablet diameter and thickness.

Aspirin/Microcrystalline Cellulose Tablets

In open bottles poorer stability was observed at 75% relative humidity than at ambient humidity indicating that moisture adsorbed by the microcrystalline cellulose is available for reaction. Aspirin powder at 75% relative humidity showed no instability at RT. At higher temperatures the extent of aspirin powder degradation was less than that in microcrystalline cellulose tablets at the same time point. In closed bottles degradation was evident at temperatures of 33° through 50°C regardless of the presence or absence of desiccant, probably due to moisture loss from the microcrystalline cellulose (Table 3).

The 10% aspirin tablets failed the USP specification of not more than 0.3% free salicylic acid upon initial assay. The

Table 5. Aspirin, ASA, and Salicylic Acid, SA, Content (mg/tablet) - Open Bottles

t, °C	Wk	Aspirin Powder		Excipient A*				Excipient B*				Excipient C*				Excipient D*			
				I*		II*		I*		II*		I*		II*		I*		II*	
		ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA
								Ambient Relative Humidity											
5	12	330	0.1	62.6	0.9	320	0.6	64.5	1.2	329	0.6	66.6	0.1	324	0.1	65.6	0.1	329	0.1
	26	--	--	65.8	0.5	321	0.8	61.3	1.3	318	1.3	68.0	0.1	330	0.2	64.3	0.1	307	0.3
RT	0	329	0.1	66.7	0.4	325	0.3	65.7	1.1	326	0.6	68.2	0.1	325	0.1	67.5	0	332	0.2
	12	316	0	63.2	1.3	322	0.9	64.0	1.9	333	1.2	66.4	0.1	321	0.2	66.9	0.1	329	0.2
	26	--	--	60.9	1.6	317	1.0	59.7	2.9	324	2.3	65.5	0.2	318	0.3	64.9	0.1	326	0.4
33	12	312	0	61.0	1.1	327	0.7	49.8	3.7	324	3.6	67.6	0.1	322	0.2	65.3	0.1	334	0.2
	26	--	--	55.8	0.9	314	1.4	36.6	8.4	308	5.9	63.8	0.2	310	0.3	66.4	0.1	325	0.4
40	8	331	0.1	63.6	1.4	302	0.8	31.4	8.9	293	6.4	66.7	0.2	333	0.3	66.5	0.2	329	0.2
	12	331	0.1	57.4	1.2	324	0.8	27.3	10.4	286	9.2	65.2	0.2	328	0.3	68.0	0.1	332	0.2
	26			49.7	0.9	308	1.3	6.7	15.6	287	9.9	61.4	0.4	314	0.6	68.9	0.2	324	0.7
50	4	--	--	60.5	0.9	325	0.8	31.5	7.1	232	4.3	54.4	1.6	328	0.9	54.1	0.2	334	0.3
	12	333	0.1	53.8	1.2	329	0.8	2.2	12.9	268	10.6	37.2	2.3	321	2.5	64.4	1.6	318	0.2
	26	--	--	43.5	1.6	313	1.5	UD*	19.8	245	18.1	21.1	2.8	259	3.4	58.1	3.2	324	0.7
								75% Relative Humidity											
RT	16	334	0.1	61.0	3.2	325	2.0	68.2	3.2	336	1.8	64.2	0.1	326	0.3	60.8	0.1	338	0.3
	30	326	0.1	56.8	6.1	320	2.8	55.7	5.7	321	3.2	64.1	0.1	318	0.3	62.4	0.1	323	0.2
33	16	334	0.1	53.3	10.6	326	5.9	42.3	18.1	314	15.7	62.6	0.1	331	0.7	59.3	0.2	326	0.2
	30	330	0.2	38.7	16.2	310	9.1	20.5	23.5	279	21.9	64.8	0.1	320	0.3	58.2	0.1	324	0.3
40	8	324	0.1	45.1	15.3	330	11.3	15.7	41.4	253	56.0	63.9	0.4	325	0.3	61.9	0.3	329	0.3
	16	322	0.2	40.1	19.7	316	12.6	4.0	44.9	219	96.8	65.7	0.4	317	0.4	53.9	0.2	328	0.3
	30	329	0.6	14.8	30.0	295	17.2	--	--	3	169	62.0	0.5	322	0.5	53.0	0.8	320	0.6
50	1	330	0.1	57.4	4.2	316	2.8	34.3	19.6	311	15.5	--	--	--	--	66.0	0.1	328	0.1
	4	--	--	47.2	14.6	318	8.6	UD*	58.2	233	12.5	67.3	0.7	342	0.6	65.7	0.3	339	0.4
	16	340	0.6	15.9	14.0	298	21.7	--	--	2.4	287	64.4	0.8	317	0.6	46.2	2.8	311	1.8
	30	330	2.4	0.7	37.0	272	32.7	--	--	--	--	58.6	1.7	309	1.7	15.7	16.1	302	7.3

*KEY: A, Microcrystalline Cellulose; B, Dibasic Calcium Phosphate Dihydrate; C, Lactose, D, Pregelatinized Starch; I, 10% Aspirin; II, 50% Aspirin; UD, undetectable.

Table 6. Aspirin, ASA, and Salicylic Acid, SA, Content (mg/tablet) - Closed Bottles

t, °C	Wk	Aspirin Powder		Excipient A*				Excipient B*				Excipient C*				Excipient D*			
				I*		II*		I*		II*		I*		II*		I*		II*	
		ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA	ASA	SA
With Desiccant																			
5	16	--	--	65.3	0.3	340	0.4	61.1	1.3	324	0.6	67.6	0.1	336	0.7	67.5	0.1	330	0.1
	30	--	--	61.9	0.4	322	0.4	61.1	1.4	323	0.6	64.5	0.1	326	0.3	67.6	0.1	328	0.1
RT	16	--	--	63.7	1.0	327	0.7	63.2	1.3	324	2.4	65.1	0.1	328	0.4	65.4	0.1	330	0.1
33	8	--	--	--	--	--	--	51.7	10.0	334	1.7	--	--	--	--	--	--	--	--
	16	--	--	61.6	1.6	310	0.8	1.5	39.4	279	9.5	65.5	0.2	337	0.2	67.6	0.2	330	0.2
	30	--	--	59.9	2.5	319	1.5	1.0	38.6	271	25.3	63.3	0.3	321	0.3	65.5	0.1	324	0.2
40	8	--	--	--	--	--	--	UD*	55.0	310	23.0	--	--	--	--	--	--	--	--
	16	--	--	59.2	3.4	326	1.6	--	--	260	60.2	61.7	0.2	327	0.5	65.6	0.2	330	0.2
	30	--	--	55.1	3.1	306	3.4	--	--	90	155	62.5	0.4	325	0.6	66.9	0.1	323	0.4
50	8	--	--	--	--	--	--	UD*	51.4	232	78.0	--	--	--	--	--	--	--	--
	16	--	--	48.7	14.4	321	1.2	--	--	11	237	56.1	2.4	321	2.0	66.2	0.3	331	0.3
	30	--	--	19.4	29.0	303	11.2	--	--	--	--	50.9	2.8	310	1.8	62.2	0.1	324	0.5
Without Desiccant																			
5	12	329	0.1	65.2	0.3	330	0.3	65.6	1.0	330	0.5	67.5	0.1	322	0.2	69.3	0.1	321	0.2
	26	--	--	61.8	0.8	332	0.3	65.5	1.2	346	0.9	67.1	0.1	323	0.1	66.3	0	312	0.5
RT	12	328	0.1	64.5	1.2	324	0.7	56.2	0.6	321	4.6	64.2	0.2	340	0.3	66.1	0.1	321	0.2
	26	--	--	65.2	1.1	320	0.8	35.8	15.5	320	7.9	63.3	0.1	313	0.3	67.6	0	327	0.4
33	12	338	0.1	62.9	1.8	326	0.9	1.8	40.6	274	24.4	64.8	0.2	329	0.3	67.9	0.1	328	0.3
	26	--	--	59.7	1.6	312	1.2	3.1	38.5	248	52.0	63.9	0.2	313	0.3	70.1	0	327	0.4
40	8	338	0.1	60.1	2.5	324	1.7	UD*	55.0	294	22.7	--	--	--	--	--	--	329	0.1
	12	331	0.1	59.4	6.5	319	1.3	--	--	272	53.2	64.7	0.2	333	0.3	66.1	0.1	327	0.3
	26	--	--	47.8	8.4	311	2.9	--	--	56	132	61.4	0.4	332	0.7	65.7	0.1	318	1.0
50	4	--	--	60.8	4.4	326	2.5	UD*	56.5	303	36.9	62.8	2.3	333	1.4	--	--	--	--
	12	330	0.1	41.4	17.5	328	6.9	--	--	15	212	59.8	2.7	329	2.1	64.6	0.2	325	0.2
	26	--	--	10.7	34.1	316	16.7	--	--	UD*	141	57.4	3.6	316	2.5	63.3	0.1	316	0.8

*KEY: A, Microcrystalline Cellulose; B, Dibasic Calcium Phosphate Dihydrate; C, Lactose, D, Pregelatinized Starch; I, 10% Aspirin; II, 50% Aspirin; UD, undetectable.

salicylic acid level in the 50% tablets approached the limit after 26 weeks at RT in closed bottles without desiccant and would be expected to do so with desiccant present in a similar time period. Microcrystalline cellulose would appear to be unsuitable as an excipient for aspirin tablets in the ratios studied. Its suitability for use with other hydrolyzable drugs will depend on the amount of hydrolysis product that can be tolerated, the rate of hydrolysis and the ratio of excipient to drug. The presence of other excipients could also influence stability.

Aspirin/Dibasic Calcium Phosphate Dihydrate Tablets

A comparison of stability in open bottles (ambient relative humidity) with closed bottles without desiccant shows poorer stability in the latter case undoubtedly due to moisture liberation from the excipient (Table 3) and pH (Table 1). The use of desiccants in closed bottles improved stability at RT and 33°C. but not at higher temperatures. Only at 5°C storage in closed bottles did 50% aspirin tablets meet the USP limit for free salicylic acid. As with microcrystalline cellulose, free salicylic acid in 10% aspirin tablets exceeded the USP limit at the initial assay point. This excipient is extremely prone to water loss and should not be used in formulating tablets of hydrolyzable drugs.

Aspirin/Lactose Tablets

Tablets in open bottles were more stable than microcrystalline cellulose tablets in open bottles at all

conditions except 50°C. at ambient relative humidity. Only at 50°C. in closed bottles did 50% aspirin tablets reach salicylic acid levels in excess of the USP specification. For 10% aspirin tablets, a storage temperature of 33°C (with desiccant) appears to be the maximum satisfactory storage temperature in closed bottles based on salicylic acid generation. Lactose can contain surface moisture (28). It is this moisture and not hydrate water (which is about 5%) which causes aspirin degradation. Lactose appears to have utility in the formulation of high dose hydrolyzable compounds but use with low dose compounds will require caution.

Aspirin/Pregelatinized Starch Tablets

Tablets containing 10% aspirin were more stable in closed bottles at 50°C than in open bottles (ambient relative humidity. This observation is not understood since the opposite was found for both dibasic calcium phosphate dihydrate and microcrystalline cellulose tablets. Apparently, in this case, water was only desorbed when the bottles were open.

More water loss occurs from pregelatinized starch than from microcrystalline cellulose (Table 3, 33° - 50°C) and this would be expected to contribute to more instability. However, pregelatinized starch tablets in closed bottles were more stable almost without exception than microcrystalline cellulose tablets regardless of aspirin concentration. Pregelatinized starch tablets can be judged stable in closed bottles under any storage

condition including 50°C As a practical matter, however, continued storage above 33° would be expected to result in some instability from the slow release of surface moisture. Nevertheless, commercial tablet formulations of aspirin and starch confirm the results found. Pregelatinized starch can be expected to be an excellent excipient for use in formulations of hydrolyzable drugs.

Stability and Packaging

It is evident from Tables 5 and 6 that, in many instances, short term studies would not have indicated degradation or severity thereof. There can be no substitute for stability studies of longer duration to estimate true product stability. Poor control of packaging used in stability studies also can lead to erroneous conclusions. Products subject to hydrolysis which are in packages thought to be hermetically sealed, but which in fact are not, would appear stable since excipient moisture could escape. Conflicting data could be obtained during a stability study if a portion of the packages were sealed while others were not.

ACKNOWLEDGEMENTS

This paper is dedicated to the late Lloyd Kennon.

The work reported is based on a thesis submitted by Mr. Indravadan J. Patel to the Graduate Faculty, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island

University, in partial fulfillment of the M.S. in Industrial Pharmacy degree requirements.

A presentation of this material was made at the 33rd Academy of Pharmaceutical Sciences Meeting, Industrial Pharmaceutical Technology Section, San Diego, California, 1982.

Gratitude is expressed to the Squibb Institute for Medical Research and particularly to those in the Pharmaceutical Research and Development Department who facilitated this industry-university collaborative project. The authors are deeply indebted to Miss B. A. Sarsfield for her help in modifying and conducting analytical procedures.

FOOTNOTES

[1] J.T. Baker Chem. Co., Phillipsburg, NJ 08865

[2] Di-Tab®, Stauffer Chemical Co., Weston, CT 06880

[3] Fast-Flo Lactose®, Foremost Whey Products, Baraboo, WI 53913

[4] Avicel PH 101®, FMC Corporation, Philadelphia, PA 19103

[5] Starch 1500®, Colorcon, Inc., West Point, PA 19486

[6] A. Gross and Co., Newark, NJ 07101

[7] Fisher Scientific, Chem. Manufacturing Div., Fair Lawn, NJ 07410

[8] M.C.B. Manufacturing Chemical, Inc., Cincinnati, OH 45212

[9] Hobart Corp., Troy, OH 45374

[10] Vector Corporation, Marion, IA 52302

[11] Available at Squibb Institute for Medical Research, New Brunswick, NJ 08903

[12] Humicaps®, N.T. Gates Co., Pennsauken, NJ 08810

[13] Altex Model 110A, Altex Scientific Operation/Beckman Instruments, Berkeley, CA 94710

[14] Micromeritics 725, Micromeritics Instrument Corp., Norcross, GA 30093

[15] Whatman Partisil 10, Whatman Chemical Separation, Inc., Clifton, NJ 07014

[16] Perkin-Elmer LC-75 Spectrophotometer Detector, Perkin-Elmer Corporation, Ridgefield, CT 06877

[17] Fisher Recorder Series 5000, Fisher Scientific, Pittsburgh, PA 15219

[18] Accumet pH Meter Model 292, Fisher Scientific, Pittsburgh, PA 15219

REFERENCES

1. D.G. Pope, Drug Cosmetic Ind., 127, 48 (1980).

2. S. Lee, H.G. Dekay and G.S. Banker, J. Pharm. Sci., 54, 1153 (1965).

3. G.R. Dukes, Pharm. Tech., 6 (1), 80 (1982).

4. K. Ito, S. Kaga and Y. Takeya, Chem. Pharm. Bull., 17, 1134 (1969).

5. J.H. Bell, N.A. Stevenson and J.E. Taylor, J. Pharm. Pharmacol., 25, 96P (1973).

6. A.T.M. Serajuddin, P. Sheen and M.A. Augustine, J. Pharm. Sci., 75, 62 (1986).

7. A.J. Woolfe and H.E.C. Worthington, Drug Dev. Comm., 1, 185 (1974).

8. J.T. Carstensen, Pharm. Tech., 10 (9), 98 (1986).

9. J.M. Lausier, C. Chiang, H.A. Zompa and C.T. Rhodes, J. Pharm. Sci., 66, 1636 (1977).

10. E.M. Rudnic, J.M. Lausier and C.T. Rhodes, Drug Dev. and Ind. Pharm., 5, 589 (1979).

11. K.S. Manudhane, A.M. Contractor, H.Y. Kim and R.F. Shangraw, J. Pharm. Sci., 58, 616 (1969).

12. L.J. Leeson and A.M. Mattocks, J. Am. Pharm. Assoc., Sci. Ed., 47, 329 (1958).

13. S.S. Kornblum and M.A. Zoglio, J. Pharm. Sci., 56, 1569 (1967).

14. H.V. Maulding, M.A. Zoglio and E.J. Johnston, ibid., 57, 1873 (1968).

15. M.A. Zoglio, H.V. Maulding, R.M. Haller and S. Briggen, ibid., 57, 1877 (1968).

16. B.K. Martin in "Advances in Pharmaceutical Sciences", Vol. 3, H.S. Bean, A.H. Beckett, J.E. Carless, Eds., Academic Press, New York, NY, 1971, pp 107-171.

17. H.M. El-Banna, N.A. Daabis, and S.A. El-Fattah, J. Pharm. Sci., 67, 1631 (1978).

18. A.Y. Gore and G.S. Banker, ibid., 68, 197 (1979).

19. P.V. Mroso, A.L.W. Po and W.J. Irwin, ibid., 71, 1096 (1982).

20. A. Mitrevej and R.G. Hollenbeck, Int. J. Pharm., 14, 243 (1983).

21. J.T. Carstensen, F. Attarchi and X. Hou, J. Pharm. Sci., 74, 741 (1985).

22. D. J. Ager, K.S. Alexander, A.S. Bhatti, J.S. Blackburn, D. Dollimore, T.S. Koogan, K.A. Mooseman, G.M. Muhvic, B. Sims and V.J. Webb, ibid., 75, 97 (1986).

23. L.B. Rockland, Anal. Chem., 32, 1375 (1960).

24. V.Y. Taguchi, M.L. Cotton, C.H. Yates and J.F. Millar, J. Pharm. Sci., 70, 64 (1981).

25. H. Jacobson and G. Reier, ibid., 58, 631 (1969).

26. K.A. Conners, G.L. Amidon and L. Kennon, "Chemical Stability of Pharmaceuticals", John Wiley and Sons, New York, NY, 1979, pp. 151-155.

27. J.C. Callahan, G.W. Cleary, M. Elefant, G. Kaplan, T. Kensler and R.A. Nash, Drug. Dev. and Industrial Pharm., 8, 355 (1982).

28. J.T. Fell and J.M. Newton, Pharm. Acta. Helv., 45, 520 (1970).