Quantitative Evaluation of Pharmaceutical Effervescent Systems II: Stability Monitoring by Reactivity and Porosity Measurements

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Abstract □ The stability of selected effervescent tablet systems was monitored by means of mercury intrusion porosimetry and by a cantilever beam/proximity transducer balance. The porosity measurements proved to be useful in elucidating tablet pore structure changes over time. The measured parameter, percent pores greater than the experimental range, was a useful measure of porosity for statistical evaluations. The study showed that compression pressure and manufacturing conditions are not significant factors in the stability of an effervescent tablet system when nonhygroscopic materials are used.

Keyphrases □ Effervescent pharmaceuticals—quantitative evaluation, monitoring of stability by reactivity and porosity measurements □ Stability—of effervescent pharmaceuticals, monitoring by reactivity and porosity measurements □ Tablets—effervescent, measurement of stability by reactivity and porosity measurements

Accelerated stability tests are used in the systematic design of solid dosage forms to examine the changes in physical characteristics brought about by environmental stress conditions. To use any stability test successfully, the characteristics being monitored must be quantitatively measured.

The greatest problem with effervescent tablet products is their loss of reactivity with time, particularly from contact with moisture. Methods of quantitatively characterizing effervescent tablet systems are limited and do not lend themselves to direct measurement. However, a balance device utilizing a double-cantilever beam with a proximity transducer was recently developed to allow continuous recording of carbon dioxide weight loss from rapidly reacting effervescent systems (1). That study also described treatment of the data obtained, including calculation of an index of reactivity (I_R) to quantify the effervescent reactions.

A previous study (2) investigated the stability of a hydrolizable drug, aspirin, in relation to the porosity characteristics of the dosage form by means of mercury intrusion porosity measurements. Since effervescent tablets based on citric acid and sodium bicarbonate react prematurely, with carbon dioxide being generated and liberated, the porosity characteristics of such a tablet might be expected to change as the premature reaction proceeds. Therefore, mercury intrusion porosity data might provide useful information on the physical changes in effervescent systems with aging or decomposition, as well as data that might be correlated with other tablet reactivity measurements, resulting in a more quantitative method of stability assessment.

The present studies were undertaken to determine the stability of several experimental effervescent tablets. An index of reactivity (1) was developed as a stability indicator. The mercury intrusion measurement of the porosity of the effervescent tablets, used to monitor structural changes in the effervescent tablets with time under the influence of water vapor and high temperature, was also developed as a stability indicator.

EXPERIMENTAL

Materials—The compositions of the effervescent tablets used are listed in Table I. All materials were passed through a number 30 screen and then through a number 80 screen, mixed, and compressed at room temperature with a relative humidity (RH) of either 20 or 60%. The effervescent tablets contained a stoichiometric ratio of acid to base, with the tablets containing a base other than sodium bicarbonate equivalent to 1.9 g of sodium bicarbonate. Because of the large amount of sodium glycine carbonate and sodium dihydrogen citrate required in such formulations, the total weight of these tablets (Table I) was reduced by 63.5 and 25%, respectively. Corrections were later made so that the carbon dioxide loss data were reported as equivalent to a 1.9-g sodium bicarbonate formula.

Experimental Design—The stability study was designed as a factorial experiment to investigate the effects of the tablet manufacturing conditions (I), tablet formulations (J), tablet compression pressures (K), storage conditions (L), and storage times (M). The dependent variables measured were the index of reactivity, I_R, and a measure of the tablet porosity.

Large 25.4-mm, flat-faced, beveled-edge tablets were compressed at two different compression pressures, 897 or 1077 kg/cm^2, using a motorized hydraulic press[1]. Similar 12.7-mm tablets were also compressed to densities equal to the 25.4-mm tablets. The densities were measured on a commercial air comparison pycnometer[2] (Table II). The 12.7-mm tablets were required to accommodate the porosity measuring device used in the study. Prior to compression, the raw materials were oven dried at 120° for 24 hr, weighed out, mixed, and exposed to the manufacturing environment for 1 hr. The effervescent tablets were either compressed at an ambient relative humidity of ≤20% or at 60% RH. The relative humidity was monitored by means of a sling psychrometer[3].

During the high humidity stability test, the tablets were stored in glass bottles[4] without caps in a sealed rigid plastic case, equipped with a small fan for air circulation, containing a saturated salt solution of sodium chloride to produce 75% RH at 25°. The humidity was monitored by a hygrometer[5] placed inside the case. The second storage condition of the stability test was 50°, achieved in an oven[6]; tablets were stored in the oven in capped glass bottles[4].

The tablets were stored in the glass bottles in an alternating stack of 25.4- and 12.7-mm tablets with a polystyrene plastic disk[7] as filler on the top and bottom of each stack. Enough tablets were placed in a bottle to complete the necessary samplings at 0, 2, and 4 weeks of storage at each condition. For each bottle of sample tablets, a backup bottle containing one tablet of each size, along with the disks, was stored.

The general procedure for setting up and running the stability test started with the establishment of the 20 or 60% RH manufacturing conditions. The compression equipment was then moved to the location providing that condition. The five different effervescent tablet formulations to be compressed at two different compression pressures were coded and assigned an order of compression using a random number table. The raw materials for each of the 10 combinations (five formula-

[1] Motorized conver press, Fred S. Carver, Menomonee Falls, Wis.
[2] Model 930, Beckman Instruments, Fullerton, Calif.
[3] Taylor Instrument Co., Rochester, N.Y.
[4] Glass bottles for Alka-Seltzer 8's, Miles Laboratories, Elkhart, Ind.
[5] Model R560, Abrax Instrument Corp., Jamaica, N.Y.
[6] Thelco model 18, Precision Scientific Co., Chicago, Ill.
[7] Styrofoam filler plugs for Alka-Seltzer bottles, Miles Laboratories, Elkhart, Ind.

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Table I—Effervescent Tablet Formulations Used in the Effervescent Tablet Stability Study

Ingredient	Tablet Formulations, g				
	A	B	C	D	E
Citric acid anhydrous	1.45	1.08	—	—	—
Sodium dihydrogen citrate	—	—	1.82	—	—
Glutaric acid	—	—	—	1.49	—
Sodium bicarbonate	1.90	—	1.43	—	—
Sodium glycine carbonate	—	2.02	—	1.90	—
Total tablet weight	3.35	3.10	3.25	3.39	3.696[a]

[a] Experimental effervescent tablet. Granulation supplied by project sponsor.

Table II—Densities of Effervescent Tablets Compressed at Pressures[a] to Produce Equivalent Densities

Tablet Composition	Tablet Size, mm	Applied Compression Pressure, kg	Density
Citric acid–sodium bicarbonate	25.4	5455	1.912
	12.7	909	1.946
Citric acid–sodium glycine carbonate	25.4	5455	1.784
	12.7	909	1.790
Sodium dihydrogen citrate–sodium bicarbonate	25.4	5455	1.912
	12.7	909	1.910
Glutaric acid–sodium bicarbonate	25.4	5455	1.782
	12.7	909	1.726

[a] Pressure calculated by geometric and force transmission considerations for 12.7 mm tablets.

tions × two pressures) were then weighed out, and enough of both of the 25.4- and 12.7-mm tablets were compressed to meet the sampling and backup requirements of the stability test.

The tablets were then randomly placed in the glass bottles, labeled, and placed in the appropriate storage condition. Initial values of the reactivity and porosity measurements were taken. This procedure was repeated until all 20 combinations (five formulations × two pressures × two manufacturing conditions) were compressed and stored and initial values were taken.

At the appropriate times, the top 25.4- and 12.7-mm tablets in each sample bottle were removed from storage and their reactivities and porosities were determined. The tablets were sampled and measured in the same order as they were made, using one tablet per measurement.

The total stability study was replicated a second time in the described manner. The second replication was needed to provide some measure of the error between test measurements and between the manufacture of the tablets to make statistical tests on the major factors after the study.

The data collected in the study was analyzed statistically by analysis of variance. The experimental design contained three inherent restrictions on randomization, which were accounted for in the design of the statistical analysis model (3–5). The first restriction occurred when all tablet compression work was done under one manufacturing condition prior to the second condition. Second, each tablet formulation was compressed in turn at the high or low compression pressure prior to the other pressure being used. Third, the tablets were assigned storage conditions and had to be sampled at the specified storage times in the same order that they were made. With these errors accounted for in the model, property tests could be run on the dependent variables after the study was concluded.

The analysis of variance for the study design is shown in Table III. This design was used for the analysis of each dependent variable of reactivity and porosity measured at both storage conditions for 0, 2, and 4 weeks of storage. Analysis of variance was done by computer using a statistical library program[8].

Pooling of the error terms was performed to determine the mean square error (MS_{error}) to facilitate F testing by having a single MS_{error} with greater degrees of freedom (6). Pooling was performed as indicated in Table III.

[8] Purdue University, Computer Center, West Lafayette, Ind.

Table III—Analysis of Variance for One Dependent Variable in Two Storage Conditions[a]

Source	Degrees of Freedom	E.M.S.[c]
I	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + \sigma_\delta^2 + 60\sigma_{N(I)}^2 + 120\sigma_I^2$
$N(I)$	2	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + \sigma_\delta^2 + 60\sigma_{N(I)}^2}$
δ[d]	0	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + \sigma_\delta^2$
J	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 12\sigma_{N(I)J}^2 + 48\sigma_J^2$
IJ	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 12\sigma_{N(I)J}^2 + 24\sigma_{IJ}^2$
$N(I)J$	8	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 12\sigma_{N(I)J}^2}$
K	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 30\sigma_{N(I)K}^2 + 120\sigma_K^2$
IK	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 30\sigma_{N(I)K}^2 + 60\sigma_{IK}^2$
$N(I)K$	2	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 30\sigma_{N(I)K}^2}$
JK	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 6\sigma_{N(I)JK}^2 + 24\sigma_{JK}^2$
IJK	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 6\sigma_{N(I)JK}^2 + 12\sigma_{IJK}^2$
$N(I)JK$	8	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2 + 6\sigma_{N(I)JK}^2}$
ω[e]	0	$\sigma_\epsilon^2 + \sigma_\eta^2 + \sigma_\omega^2$
L	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + 30\sigma_{N(I)L}^2 + 120\sigma_L^2$
IL	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + 30\sigma_{N(I)L}^2 + 60\sigma_{IL}^2$
$N(I)L$	2	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + 30\sigma_{N(I)L}^2}$
JL	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + 60_{N(I)JL} + 24\sigma_{IL}^2$
IJL	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + 60_{N(I)JL} + 12\sigma_{IJL}^2$
$N(I)JL$	8	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + 60_{N(I)JL}}$
KL	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + 15\sigma_{N(I)KL}^2 + 60\sigma_{KL}^2$
IKL	1	$\sigma_\epsilon^2 + \sigma_\eta^2 + 15\sigma_{N(I)KL}^2 + 30\sigma_{IKL}^2$
$N(I)KL$	2	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + 15\sigma_{N(I)KL}^2}$
JKL	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + 3\sigma_{N(I)JKL}^2 + 12\sigma_{JKL}^2$
$IJKL$	4	$\sigma_\epsilon^2 + \sigma_\eta^2 + 3\sigma_{N(I)JKL}^2 + 6\sigma_{IJKL}^2$
$N(I)JKL$	8	$\underline{\sigma_\epsilon^2 + \sigma_\eta^2 + 3\sigma_{N(I)JKL}^2}$
η[f]	0	$\sigma_\epsilon^2 + \sigma_\eta^2$
M	2	$\sigma_\epsilon^2 + 20\sigma_{N(I)M}^2 + 80\sigma_M^2$
IM	2	$\sigma_\epsilon^2 + 20\sigma_{N(I)M}^2 + 40\sigma_{IM}^2$
$N(I)M$	4	$\underline{\sigma_\epsilon^2 + 20\sigma_{N(I)M}^2}$
JM	8	$\sigma_\epsilon^2 + 4\sigma_{N(I)JM}^2 + 16\sigma_{JM}^2$
IJM	8	$\sigma_\epsilon^2 4\sigma_{N(I)JM}^2 + 8\sigma_{IJM}^2$
$N(I)JM$	16	$\underline{\sigma_\epsilon^2 + 4\sigma_{N(I)JM}^2}$
KM	2	$\sigma_\epsilon^2 + 10\sigma_{N(I)KM}^2 + 40\sigma_{KM}^2$
IKM	2	$\sigma_\epsilon^2 + 10\sigma_{N(I)KM}^2 + 20\sigma_{IKM}^2$
$N(I)KM$	4	$\underline{\sigma_\epsilon^2 + 10\sigma_{N(I)KM}^2}$
JKM	8	$\sigma_\epsilon^2 + 2\sigma_{N(I)JKM}^2 + 8\sigma_{JKM}^2$
$IJKM$	8	$\sigma^2 + 2\sigma_{N(I)JKM}^2 + 4\sigma_{IJKM}^2$
$N(I)JKM$	16	$\underline{\sigma_\epsilon^2 + 2\sigma_{N(I)JKM}^2}$
LM	2	$\sigma_\epsilon^2 + 10\sigma_{N(I)LM}^2 + 40\sigma_{LM}^2$
ILM	2	$\sigma_\epsilon^2 + 10\sigma_{N(I)LM}^2 + 20\sigma_{ILM}^2$
$N(I)LM$	4	$\underline{\sigma_\epsilon^2 + 10\sigma_{N(I)LM}^2}$
JLM	8	$\sigma_\epsilon^2 + 2\sigma_{N(I)JLM}^2 + 8\sigma_{JLM}^2$
$IJLM$	8	$\sigma_\epsilon^2 + 2\sigma_{N(I)JLM}^2 + 4\sigma_{IJLM}^2$
$N(I)JLM$	16	$\underline{\sigma_\epsilon^2 + 2\sigma_{N(I)JLM}^2}$
KLM	2	$\sigma_\epsilon^2 + 5\sigma_{N(I)KLM}^2 + 20\sigma_{KLM}^2$
$IKLM$	2	$\sigma_\epsilon^2 + 5\sigma_{N(I)KLM}^2 + 10\sigma_{IKLM}^2$
$N(I)KLM$	4	$\underline{\sigma_\epsilon^2 + 5\sigma_{N(I)KLM}^2}$
$JKLM$	8	$\sigma_\epsilon^2 + \sigma_{N(I)JKLM}^2 + 4\sigma_{JKLM}^2$
$IJKLM$	8	$\sigma_\epsilon^2 + \sigma_{N(I)JKLM}^2 + 2\sigma_{IJKLM}^2$
$N(I)JKLM$	16	$\underline{\sigma_\epsilon^2 + \sigma_{N(I)JKLM}^2}$
ϵ	0	σ_ϵ^2

[a] Measured at 0, 2, and 4 weeks. [b] Key: I, manufacturing condition; N, replicate; J, tablet formulation; K, tablet compression pressure; L, storage condition; and M, storage time. [c] The error terms were pooled within the various sections as indicated by underlining. The pooled errors were then used to test the significance of those factors and interactions within the respective sections. [d] First restriction of randomization error. [e] Second restriction of randomization error. [f] Third restriction of randomization error.

In the case of significant two-way interactions from analysis of variance of a dependent variable, a Newman–Keuls sequential range test (6) was performed on the means involved to determine significant differences.

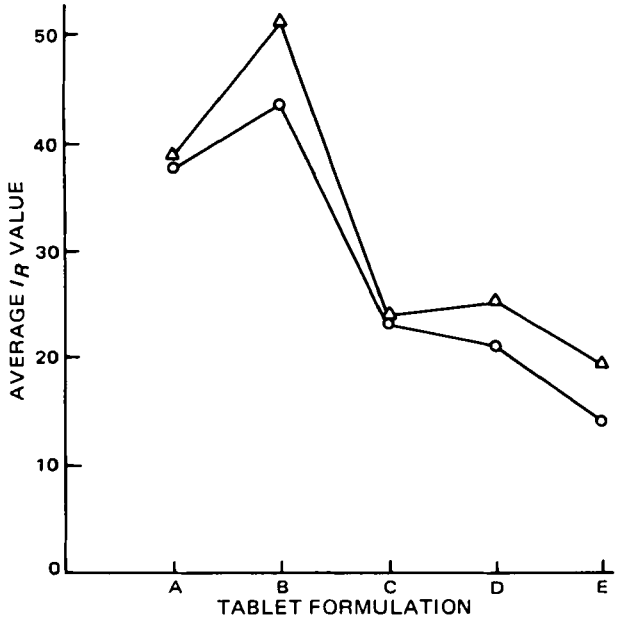

Figure 1—*Index of reactivity (I_R) analysis for J × I interaction. Key: △, 20% RH manufacture; ○, 60% RH manufacture; A, citric acid–sodium bicarbonate; B, sodium glycine carbonate–citric acid; C, sodium dihydrogen citrate–sodium bicarbonate; D, glutaric acid–sodium bicarbonate; and E, Tablet E.*

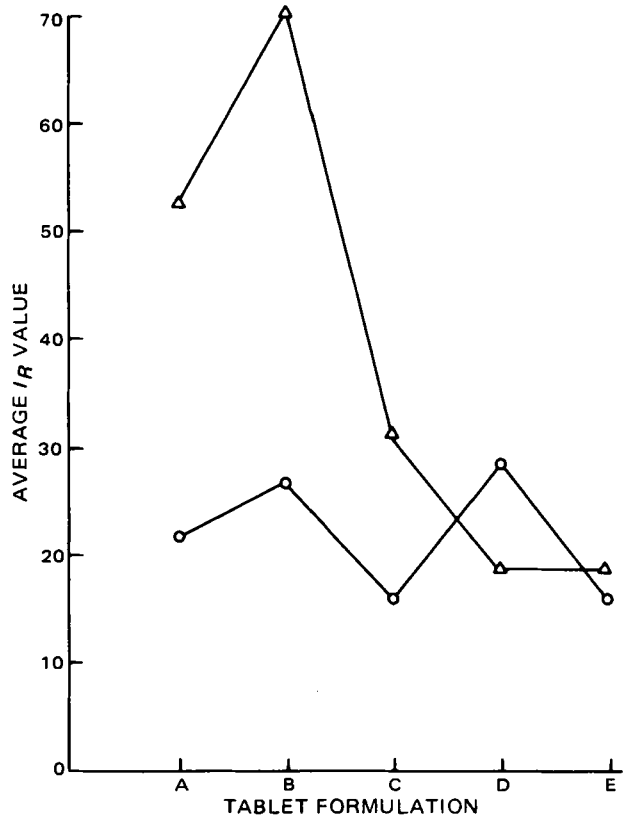

Figure 2—*Index of reactivity analysis for J × L interaction. Key: △, 50° storage condition; ○, 75% RH storage condition; A, citric acid–sodium bicarbonate; B, sodium glycine carbonate–citric acid; C, sodium dihydrogen citrate–sodium bicarbonate; D, glutaric acid–sodium bicarbonate; and E, Tablet E.*

The effervescent tablet porosity measurements were performed on a commercial mercury intrusion porosimeter using a method described previously (2, 7). In this procedure, several characteristics of a tablet's pore structure were calculated and could be used to express tablet porosity. However, statistical evaluation requires that a single dependent variable value be used. In this study, the calculated value of the percent pores greater than the experimental range (PPGTER) was used as the dependent variable value for porosity. The selection of the PPGTER values was based on the fact that moisture can interfere with mercury intrusion in pore-size distribution determinations within the experimental range (8, 9). Even though each tablet was pretreated by drying at room temperature under vacuum[9] for 15 hr as part of the mercury intrusion determinations, the effervescent reaction, however slow it may be, would not have ceased; therefore, water would still have been produced and been available to interfere with the measurements. The PPGTER value is not significantly influenced by moisture.

The true densities of the tablets required for the porosity calculations were determined by an air comparison technique using a commercial pycnometer[3]. Room air was used as the gas. Before each determination, a zero measurement check was made to correct for possible zero offset. Measurements were carried out by starting at an initial pressure of 1 atm and compressing the gas to 2 atm.

The reactivity of the 25.4-mm effervescent tablets at the selected storage times was determined by means of the beam/proximitor (b/p) balance previously described (1).

RESULTS AND DISCUSSION

As already mentioned, tablets containing sodium glycine carbonate and sodium dihydrogen citrate required weight reductions of 63.5 and 25%, respectively, and did not contain base equivalent to the 1.9 g of sodium bicarbonate in the standard tablet. From the standpoint of density and porosity, the weight reduction was not a factor. However, in trying to relate the reduced weight tablets to the standard tablet by means of the index of reactivity, I_R, the weight reduction is very crucial because:

$$I_R = kW_F \qquad \text{(Eq. 1)}$$

where W_F is the final weight loss of carbon dioxide from the effervescent solution and k is the rate constant of the effervescent reaction (1). Therefore, the data collected for the reduced tablets were multiplied by a correction factor. This factor was determined by measuring W_F on the b/p balance from tablets containing the full 1.9 g of sodium bicarbonate equivalent and from the reduced tablets. Dividing W_F for the full-base tablets by W_F for the reduced-base tablets gave a factor by which each data point generated on the b/p balance by the reduced tablets could be multiplied to yield data representative of tablets containing base equivalent to 1.9 g of sodium bicarbonate.

Analysis of variance of the adjusted I_R means revealed, at the 0.01 level, significant differences in I_R values with the following factors:

J = tablet formulation
L = storage condition
M = storage time
$J \times I$ = interaction
$J \times L$ = interaction
$J \times M$ = interaction
$L \times M$ = interaction
$I \times J \times M$ = interaction
$I \times K \times M$ = interaction
$J \times K \times M$ = interaction
$J \times L \times M$ = interaction
$I \times J \times K \times M$ = interaction

The individual factors of compression pressure (K) and manufacturing conditions (I) were not significant.

Analysis of variance showed that I_R appears to be a function not only of J but also of L and M. The single effects are supported by examination of the four significant two-way interactions involving the factors. Newman–Keuls (NK) tests were run, and the means were plotted for each interaction (Figs. 1–4).

Figure 1 shows the I_R means plotted for the interaction of tablet formulation and manufacturing conditions ($J \times I$). Figure 1 clearly shows the difference in I_R values according to the different formulas and supports the analysis of variance finding that manufacturing conditions did not have any significant effect on I_R values in that only the citric acid–sodium glycine carbonate tablet showed any significant difference, 0.01 level, between the two manufacturing conditions. With only this one difference, the total interaction is of doubtful significance.

[9] Thelco model 19 vacuum oven, Precision Scientific Co., Chicago, Ill.

Table IV—General Physical Observations

Tablet	Storage	Observations
A	75% RH	Some swelling, surface rough
A	50°	No change
B	75% RH	Surface rough, some swelling
B	50°	No change
C	75% RH/50°	No change
D	75% RH	Some swelling
D	50°	Very enlarged and porous ("sponge")
E	75% RH	Enlarged
E	50°	Very enlarged and porous ("sponge")

Investigation of the $J \times L$ interaction (Fig. 2) shows significant differences in the I_R means caused by storage conditions, with the citric acid–sodium bicarbonate and citric acid–sodium glycine carbonate tablets recording the largest I_R losses. The I_R values of the glutaric acid–sodium bicarbonate tablet support the observation (Table IV) that this composition was better, or was more stable, at 75% RH storage than at 50° storage in that its I_R value was greater after the former. Tablet E appeared to be equally low in I_R value in either storage condition.

A study of the $J \times M$ interaction in Fig. 3 shows that the I_R definitely decreased with storage time for all tablets. Moreover, there were no significant differences between the 2- and 4-week values of I_R for each tablet. The loss of stability appeared to take place during the first 2 weeks of storage.

The obvious relationship between L and M is supported by the interaction in Fig. 4. There was a significant loss of I_R at 50° between 0, 2, and 4 weeks. There was also a significant loss of I_R between 0, 2, and 4 weeks at 75% RH storage. The losses at 50° were significantly less than the losses at 75% RH storage. This result can be explained by the fact that only the glutaric acid–sodium bicarbonate and Tablet E lost a significant amount of reactivity at 50° storage whereas all tablets lost reactivity at the 75% RH storage condition.

The three-way and four-way interactions, calculated by analysis of variance to be statistically significant, were ignored since the significance

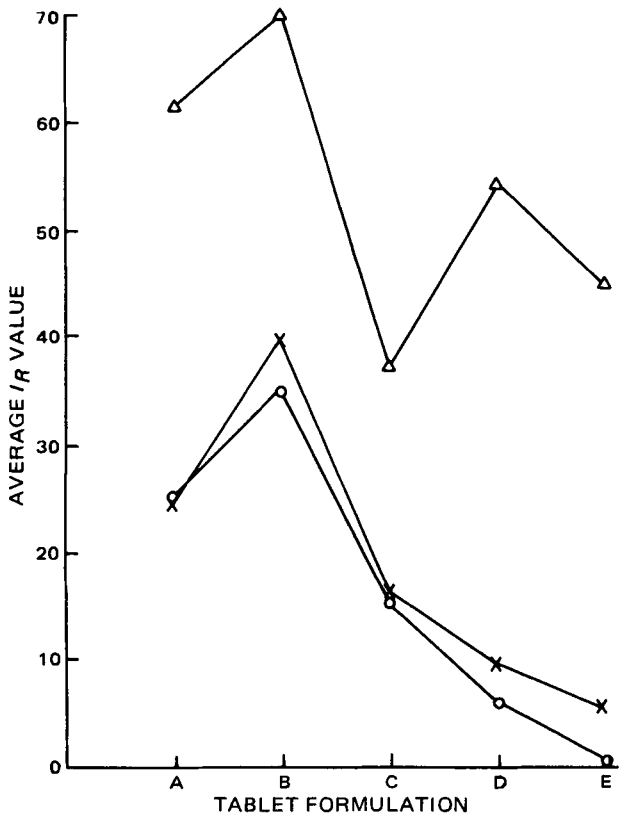

Figure 3—*Index of reactivity analysis for* J × M *interaction. Key:* △, *initial (0 week);* ×, *2 weeks of storage;* ○, *4 weeks of storage; A, citric acid–sodium bicarbonate; B, sodium glycine carbonate–citric acid; C, sodium dihydrogen citrate–sodium bicarbonate; D, glutaric acid–sodium bicarbonate; and E, Tablet E.*

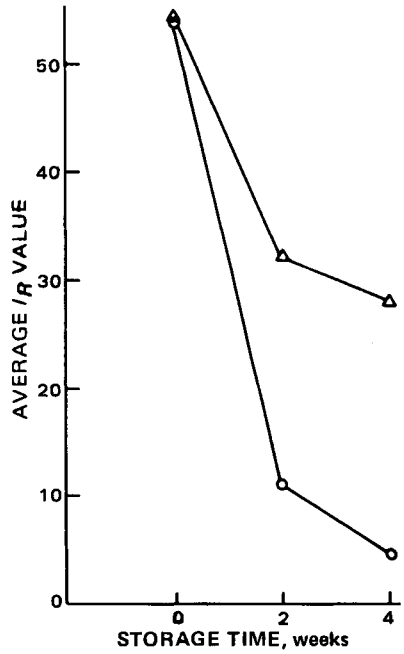

Figure 4—*Index of reactivity analysis for* L × M *interaction. Key:* ○, *75% RH storage condition; and* △, *50° storage condition.*

in the higher order interactions was probably caused by the strong common factor of storage time (M).

Analsis of Tablet Porosity Using PPGTER—Analysis of variance shows four significant differences in PPGTER values, at the 0.01 level, caused by the factors of J, M, $J \times M$, and $J \times L$. None of the other factors and interactions were significant. In a plot of both interactions (Figs. 5 and 6), the sodium dihydrogen citrate–sodium bicarbonate tablet values of PPGTER remain approximately constant.

Analysis of $J \times L$ by NK testing and plotting (Fig. 5) shows significant differences within tablets at the two storage conditions with the exception of the sodium dihydrogen citrate–sodium bicarbonate tablet formulation. The citric acid–sodium bicarbonate and citric acid–sodium glycine carbonate tablets appeared to have low PPGTER values at 50° and high values at 75% RH. The reverse was true for glutaric acid–sodium bicarbonate and Tablet E where the PPGTER values at 75% RH storage were lower than those at 50° storage. This interchange of values, causing the differences to perhaps cancel each other, probably eliminated the significance of L from the analysis of variance. Analysis of the $J \times M$ interaction (Fig. 6) shows that there was no significant difference between the citric acid–sodium bicarbonate and citric acid–sodium glycine carbonate tablets. The sodium dihydrogen citrate–sodium bicarbonate

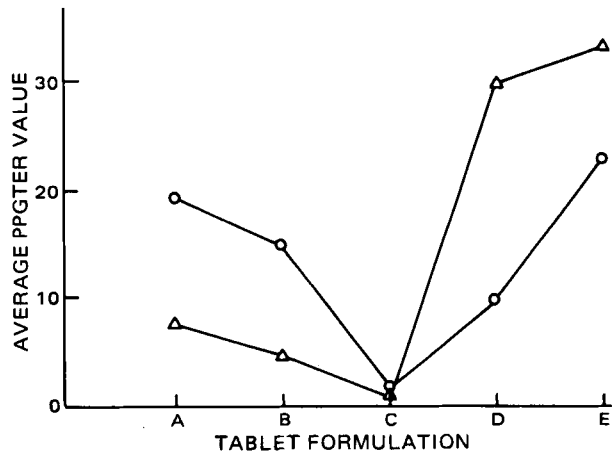

Figure 5—*Percent pores greater than experimental range (PPGTER) analysis for* J × L *interaction. Key:* ○, *75% RH storage condition;* △, *50° storage condition; A, citric acid–sodium bicarbonate; B, sodium glycine carbonate–citric acid; C, sodium dihydrogen citrate–sodium bicarbonate; D, glutaric acid–sodium bicarbonate; and E, Tablet E.*

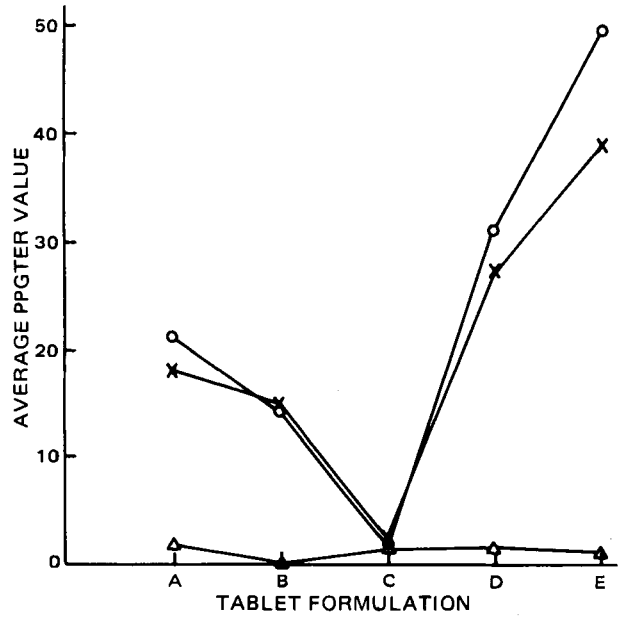

Figure 6—*PPGTER analysis for J × M interaction. Key: △, initial (0 week); ×, 2 weeks of storage; ○, 4 weeks of storage; A, citric acid–sodium bicarbonate; B, sodium glycine carbonate–citric acid; C, sodium dihydrogen citrate–sodium bicarbonate; D, glutaric acid–sodium bicarbonate; and E, Tablet E.*

tablets appeared to be lower in value and remained unchanged. As already shown, most of the significance came from the glutaric acid–sodium bicarbonate and Tablet E alone being greatly different from their initial values compared with the other tablets. The values at 2 and 4 weeks showed no significant differences, indicating that the loss in PPGTER stability occurred within the first 2 weeks of storage.

Analysis of variance of I_R values shows the sodium glycine carbonate–citric acid tablet to be good in comparison with the standard tablet (citric acid–sodium bicarbonate). There is also an indication that while

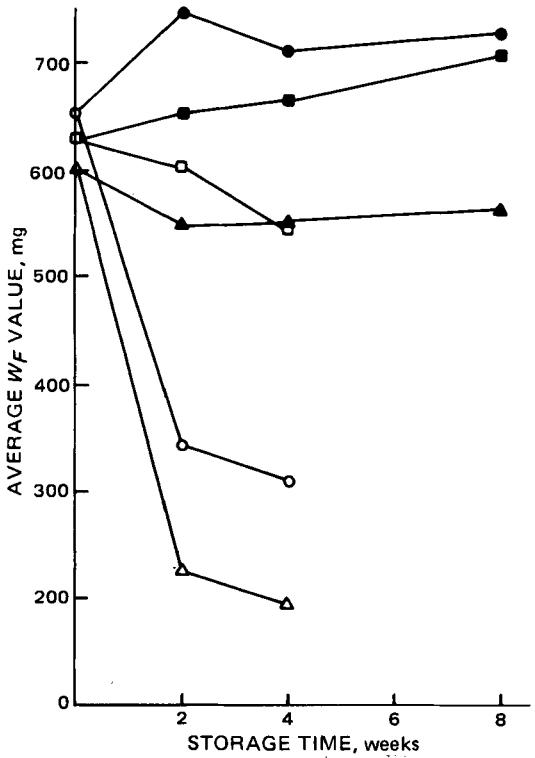

Figure 7—*Average final weight loss of carbon dioxide (W_F) at each storage condition and time for Tablets A (△), B (○), and C (□). Open figures represent the 75% RH storage condition; closed figures represent the 50° storage condition.*

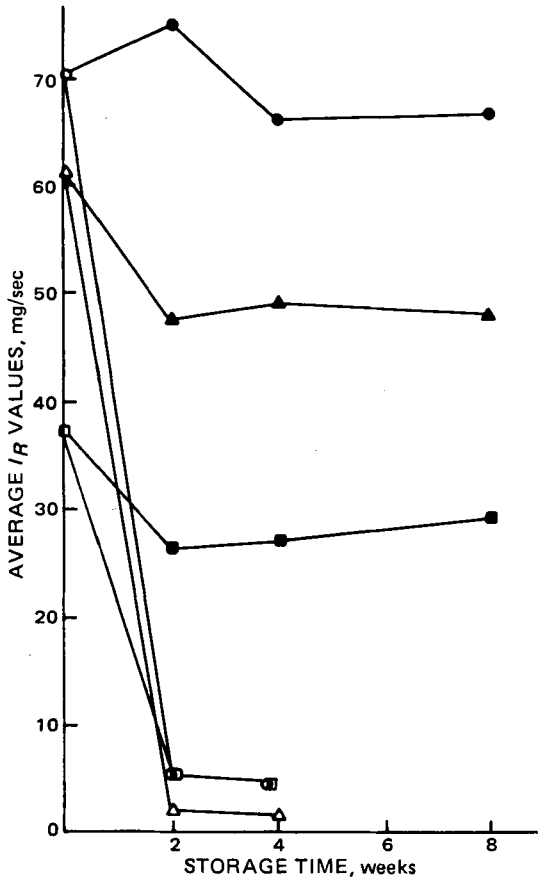

Figure 8—*Average index of reactivity (I_R) at each storage condition and time for Tablets A (△), B (○), and C (□). Open figures represent the 75% RH storage condition; closed figures represent the 50° storage condition.*

low in its I_R value, the sodium dihydrogen citrate–sodium bicarbonate tablet is quite stable. When restricting the discussion to these three formulations, analysis of variance of PPGTER shows that the sodium

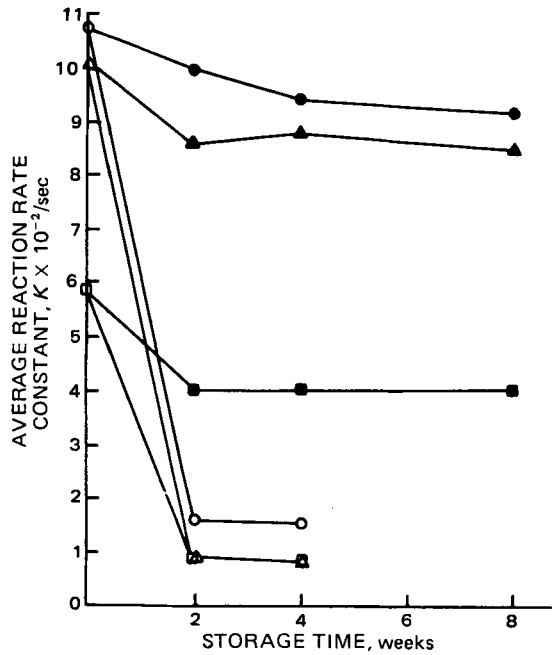

Figure 9—*Average reaction rate constant (k) at each storage condition and time for Tablets A (△), B (○), and C (□). Open figures represent the 75% RH storage condition; closed figures represent the 50° storage condition.*

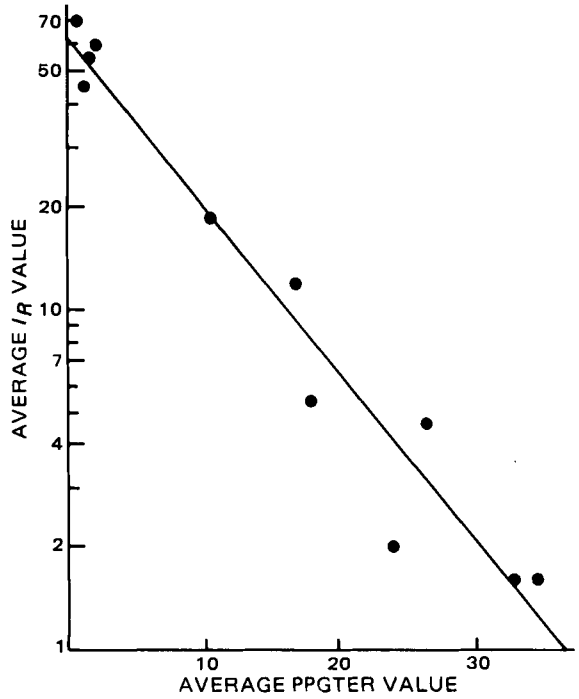

Figure 10—*Relationship between* I_R *and PPGTER.*

dihydrogen citrate composition underwent the least amount of internal structural changes, with the sodium glycine carbonate composition being second best. In addition, plots of the different reactivity data parameters (k, W_F, and I_R) in Figs. 7–9 show that the sodium glycine carbonate–citric acid tablet and the standard tablet were quite similar in initial reaction rate (Fig. 9); but on storage at 75% RH, the standard tablet lost ~67% of its carbon dioxide-producing capacity (W_F) compared with a 50% loss for the sodium glycine carbonate composition tablet (Fig. 7). The sodium dihydrogen citrate–sodium bicarbonate tablet retained its carbon dioxide-producing capacity at both storage conditions (Fig. 7); therefore, the low I_R values of the tablet (Fig. 8) were caused by low reaction rates (k) alone and not a combination of both W_F and k losses over time as would be indicated by Eq. 1.

It was shown that both the I_R PPGTER values are significantly affected by storage time. It appears that a correlation should exist between PPGTER and I_R. If it is assumed that the loss of reactivity is caused by the slow premature reaction of the tablets, then the loss of the reacting compounds to form the escaping carbon dioxide could alter the pore structure of the tablet by causing new pores to be formed and old pores to become larger.

A correlation does exist between PPGTER and I_R and is shown when the average PPGTER values for 0, 2, and 4 weeks in 75% RH storage are plotted against the log of the average I_R values at 0, 2, and 4 weeks of storage at 75% RH for the standard tablet, citric acid–sodium glycine carbonate, glutaric acid–sodium bicarbonate, and Tablet E (Fig. 10). For those tablets whose stability decreases in the 75% storage condition, the log of I_R decreases as the PPGTER increases.

Thus far, porosity has been limited to a discussion of PPGTER only.

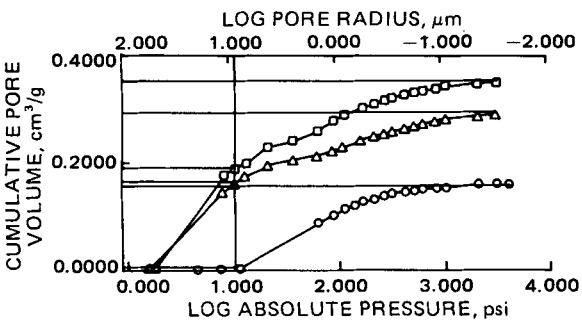

Figure 11—*Cumulative pore volume of the citric acid–sodium bicarbonate tablet in the 75% RH, 25° storage condition. Key: ○, initial (0 week); △, 2 weeks of storage; and □, 4 weeks of storage.*

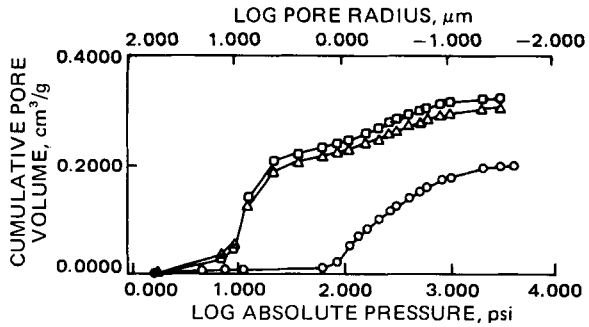

Figure 12—*Cumulative pore volume of the sodium glycine carbonate–citric acid tablet in the 75% RH 25° storage condition. Key: ○, initial (0 week); △, 2 weeks of storage; and □, 4 weeks of storage.*

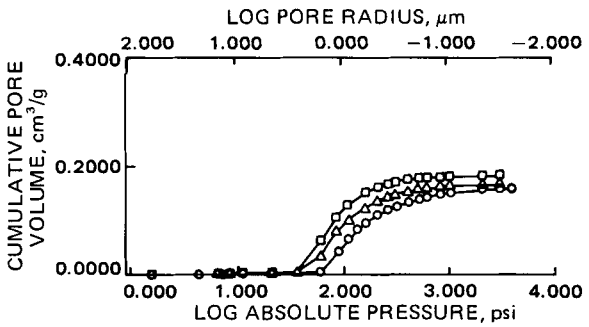

Figure 13—*Cumulative pore volume of the sodium dihydrogen citrate–sodium bicarbonate tablet in the 75%, RH, 25° storage condition. Key: ○, initial (0 week); △, 2 weeks of storage; and □, 4 weeks of storage.*

Mercury intrusion measurements can be presented graphically to illustrate the changes that occur in the tablet pore structure.

Examination of the mercury intrusion data[10] for the standard tablet stored in the 75% RH condition (Fig. 11) shows that at 10 psi, the smallest pore intruded by mercury was ~9 μm in radius. In the initial porosity determination, a negligible amount of mercury was intruded at pressures of <10 psi when compared to the total amount intruded. However, at the 2- and 4-week determinations, the amount of mercury intruded into pores ~≥9 μm in radius amounted to ~50% of the total mercury intrusion. In addition, the 2- and 4-week determinations revealed a greater total amount of mercury intruded compared to the initial determination. This finding indicates that as the tablet is exposed to the relative humidity of the storage condition, the pore structure of the tablet increases in total

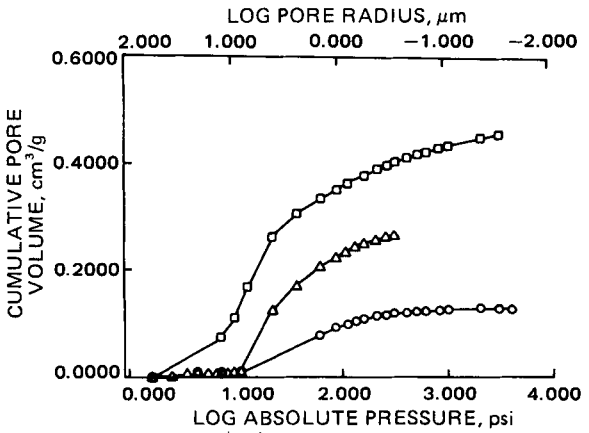

Figure 14—*Cumulative pore volume of the glutaric acid–sodium bicarbonate tablet in the 75% RH, 25° storage condition. Key: ○, initial (0 week); △, 2 weeks of storage; and □, 4 weeks of storage.*

[10] Although mercury intrusion measurements were made up through 15,000 psi, there was no significant intrusion beyond 4000 psi, and the mercury intrusion data plots are therefore not plotted beyond 4000 psi.

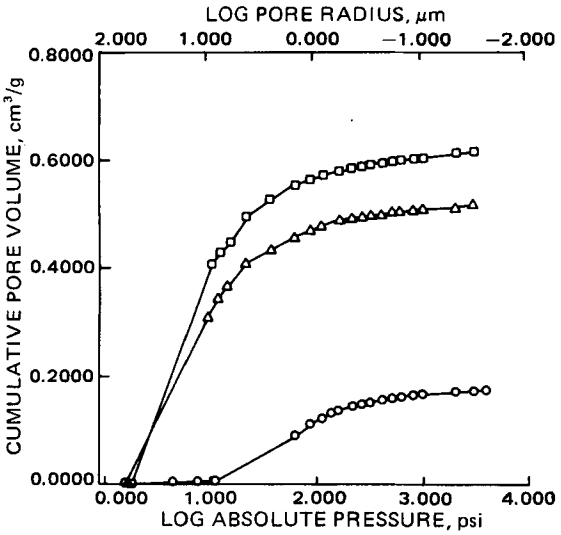

Figure 15—*Cumulative pore volume of Tablet E in the 75% RH, 25° storage condition. Key:* ○, *initial (0 week);* △, *2 weeks of storage; and* □, *4 weeks of storage.*

volume and the larger pores become a larger part of the pore-size distribution.

The use of the PPGTER values as a porosity indicator is supported by the distribution plots (Figs. 11–15). Tablets with storage time and storage condition combinations that produced large PPGTER values show up in the plots as having increased total mercury intrusion, with the distribution shifted toward the large pore sizes. For example, the $J \times M$ interaction in the PPGTER analysis in Fig. 6 shows that the glutaric acid–sodium bicarbonate and Tablet E had very high PPGTER values after 2 and 4 weeks. Figures 14 and 15 dramatically show the shift to larger pore sizes and the increased total mercury intrusion volume.

With the mercury intrusion plots, the differences in tablet pore structure caused by the different storage conditions for the standard, sodium glycine carbonate, glutaric acid, and sponsor composition tablets can be visualized as well as the stability of the sodium dihydrogen citrate composition tablet. Some resistance to higher humidity storage can be seen in the glutaric acid tablet (Fig. 14), supporting the earlier I_R data, in that a dramatic shift in pore distribution to large pore sizes occurred at the 4-week point and not at the 2-week point, as was seen with some other formulations (Figs. 11, 12, and 15).

SUMMARY

1. Mercury intrusion porosimetry was shown to be a useful tool in helping to elucidate pore structure changes in effervescent tablets.

2. The use of the index of reactivity (I_R) proved to be a successful indicator of effervescent tablet reactivity, combining both the amount of carbon dioxide generation and the reaction rate of the effervescent reaction.

3. The stability study of the selected experimental effervescent systems appeared to show that the manufacturing condition factor had little effect on the stability of the effervescent tablets studied, including the standard tablet of citric acid–sodium bicarbonate, which is well known as being sensitive to manufacturing conditions. This lack of effect on the standard tablet could be due to the materials used to make the tablets not having been exposed to the different manufacturing conditions long enough to influence stability significantly.

4. Statistical analysis did not demonstrate a statistically significant compression pressure factor (K). The stability of effervescent tablets apparently was not affected by the pressure at which the tablets were manufactured.

5. The study of effervescent systems showed that the stability of the effervescent tablet was dependent on the tablet formulation, storage conditions, and length of time the tablet was stored.

6. The citric acid–sodium glycine carbonate tablet appears to have better reaction properties and reaction property stability than does the standard citric acid–sodium bicarbonate tablet. The sodium dihydrogen citrate–sodium bicarbonate tablet appears to be inferior in reaction properties and reaction property stability to the standard tablet. However, the sodium dihydrogen citrate composition tablet was the only system to retain high W_F values in the 75% RH storage condition (Fig. 8), although its reaction rate (K) was lower than the other tablets and did decrease with time (Fig. 10).

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