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Potassium carbonate as a desiccant in effervescent tablets

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Abstract

A central composite study design was used to determine the moisture scavenging effect of 0–2% w/w potassium carbonate in an effervescent dosage form containing 0.2–1.3% w/w total moisture. Total moisture content of the tablets was calculated by adding the water contribution of each ingredient based on loss on drying or Karl Fischer data. Tablets were directly compressed on a rotary tablet press, packaged in cold form foil/foil blisters, and then thermally stressed by exposure to 75°C for 3 h. In this study, exposure of effervescence in such a manner has been shown to release water of hydration from dextrose monohydrate, thus giving a convenient means of adding water and then 'activating' it to perform rapid moisture stability studies. After thermal stressing, tablets were given a rating from 0–7 (least to most) as to the degree of tablet mottling due to effervescent base degradation. Response surface regression of the data resulted in a quadratic equation with an adjusted R^2 of 0.92 and no evidence of lack of fit ($P = 0.85$). Analysis of the data showed the optimal level of potassium carbonate to be 1.3% w/w for the formulations tested. This level of potassium carbonate will accommodate total moisture levels up to 0.4% w/w and still prevent effervescent base degradation. © 1997 Elsevier Science B.V.

Keywords: Potassium carbonate; Effervescent tablets; Moisture; Stability; Hydrates

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1. Introduction

Moisture is a fundamental concern in the formulation of pharmaceutical dosage forms. This concern is magnified when formulating an effervescent tablet. Excessive moisture in an effervescent tablet will prematurely react with the effervescent system, which will release carbon dioxide leading to puffing of blisters or pouches, mottling of tablets, a change in tablet hardness, and a change in tablet disintegration and dissolution time.

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Many methods of achieving effervescent stability have been reviewed by Mohrle (1989). Foremost among these, the formulator must eliminate or minimize the amount of free water available to prevent premature reaction of the effervescent system. This may be accomplished by purchasing equivalent materials with lower moisture specifications or by drying materials to the desired moisture level. Another method of improving effervescent stability is to always use anhydrous materials because hydrates exhibit varying degrees of stability. Surface passivation is another technique to improve effervescent stability. This essentially involves pre-reacting the effervescent system in a closed vessel with heat to form a non-reactive coating around the effervescent granules. Another common technique to improve effervescent stability is to add finely divided anhydrous sodium carbonate to the formulation. This can either be purchased ready for addition or can be produced by heating sodium bicarbonate to form sodium carbonate. Other methods of improving effervescent stability include encapsulating the acid or base components of the formulation in an effort to provide a barrier to the reaction and producing a core tablet containing the effervescent system covered by a protective coating of a sugar alcohol.

Although there are a number of methods above for achieving a stable effervescent system, most of them involve additional processing steps before tableting and, therefore, are not convenient or cost-effective means of producing a stable product. Therefore, it would be useful to have additional methods of accommodating higher levels of moisture which may provide more flexibility when formulating an effervescent product.

Anhydrous potassium carbonate is a hygroscopic salt capable of forming a sesquihydrate (The Merck Index, 1989). Although its use as a carbonate source in effervescent systems has been discussed (Mohrle, 1989), description of its use as a desiccant is extremely limited (Takaichi et al., 1992a,b). Therefore, the objective of this study was to quantitatively determine the moisture scavenging effects of potassium carbonate through statistical experimental design.

2. Materials and methods

2.1. Materials

2.1.1. Tablet excipients

The following excipients were used in the preparation of tablets: mannitol, U.S.P. from Roquette America Inc. (Mannitol 60, U.S.P.); sodium bicarbonate, U.S.P. from Church and Dwight (Sodium bicarbonate, No. 1, U.S.P.); citric acid, U.S.P. from Ashland Chemical Fine Ingredients Distribution (Citric acid, anhydrous, fine granular, U.S.P.); magnesium stearate, N.F. from Mallinckrodt (Product code 2256); Natural Prosweet Powder® from Virginia Dare Inc.; potassium carbonate, U.S.P. from E. Merck (Potassium carbonate, anhydrous, U.S.P.); Pink lake blend from Colorcon (Pink LB-1355); and silicon dioxide, N.F. from Cabot Corp., Cab-O-Sil Division (Cab-O-Sil M5).

2.1.2. Packaging materials

All packaging materials were received from A and L Packaging (Lawson Mardon/Neher). The forming material used was Formpack (OPA 25/Al 45/PVC 60). The peelable lidding material used was Peelable Lid (Pap 50/PET 12/HSC LA 754).

2.1.3. Analytical reagents

Karl Fischer analyses utilized HydraPoint Comp 2 (9774-02) reagent supplied by J.T. Baker, as well as HPLC grade Methanol from Burdick and Jackson.

2.2. Methods

2.2.1. Milling of potassium carbonate

All excipients, except anhydrous potassium carbonate, were used as received. Anhydrous potassium carbonate comes as crystalline material with some aggregation having occurred after bulk packaging. These aggregates are too difficult to break apart by simple sieving. In addition, some particle size reduction of the material is desired for the material to be comparable in size with the other in the formulation. Therefore, anhydrous potassium carbonate was milled using a Frewitt Hammer Mill (Model MGH J1-2271, Key International) using a US Std. No. 60 mesh screen, run at 5080 rpm and knives forward. This process was carried out under controlled temperature and humidity conditions (temperature: not more than (NMT) 25°C; relative humidity: NMT 20%). Temperature and relative humidity were monitored during milling via a temperature/relative humidity probe (Vaisala Model HMI 36 with HMP 36 probe).

2.2.2. Particle size determination of milled potassium carbonate

The particle size of milled potassium carbonate was determined by microscopy method. A Zeiss Axioscope was used to view the milled potassium carbonate dispersed in mineral oil on a microscope slide. The microscope was connected to a Sony CA325B video camera which interfaced with a VIDAS computer. The Roche Image Analysis System VIDAS version 2.1 was used to collect the long axis lengths of 200 milled potassium carbonate particles and perform statistical analysis of the data. Particles were randomly selected for particle size determination. Miscellaneous equipments associated with this procedure were a Sony VO-9600 VHS VCR recorder, Sony Trinitron PVM1343MD VCR monitor, Sony UP-5000 video printer, Hewlett Packard LaserJet III printer, and two Mitsubishi color monitors.

2.2.3. Surface area determination of milled potassium carbonate

The surface area of milled potassium carbonate was determined by nitrogen gas adsorption with liquid nitrogen as the coolant using a Quantachrome Corp. Autosorb-1 interfaced with a Compaq DeskPro 386/20e computer, color monitor, keyboard, and Epson FX-850 dot matrix printer. Approximately 2 g of milled potassium carbonate was outgassed in a glass sample tube at 25°C until no increase in pressure was observed when vacuum was terminated. The sample tube was then placed in the sample port of the unit. A multi-point BET analysis was then performed using the Quantachrome Autosorb Automated Gas Adsorption System Report ASORB2PC version 1.10.

2.2.4. Moisture sorption isotherm determination for potassium carbonate

A moisture sorption isotherm was determined for potassium carbonate at 25°C using the VTI Corporation's MB-300G Moisture Sorption System. Equipment associated with this system includes: NEC Multi-Sync 5FG Monitor Lens, Compaq Presario 660 computer, Cahn Digital Recording Balance D-200, Hewlett Packard DeskJet 500 Printer, Neslab RTE-210 Circulating Water Bath, Edwards Model E2M2 High Vacuum Pump, and a Laud Brinkmann RMG Circulating Water Bath.

2.2.5. Thermogravimetric analysis of dextrose monohydrate

Approximately 13.5 mg of dextrose monohydrate (E. Merck) was placed in the sample pan of a Perkin-Elmer TGA 7 Thermogravimetric Analyzer. The sample was heated from 30°C to 75°C at a rate of 10°C/min and then maintained at 75°C to determine the length of time required for the release of the hydrated moisture. Equipments associated with this system are PE Gas Selector, PE Thermal Analysis Controller TAC 7/DX, PE Graphics Plotter 7, and a Digital DECstation 425c with color monitor.

2.2.6. Moisture determination of excipients

Moisture determinations for mannitol, sodium bicarbonate, citric acid, magnesium stearate, potassium carbonate, and silicon dioxide were carried out by their respective U.S.P. XXIII and/or N.F. XVIII methods (US Pharmacopeia XXIII/NF XVIII (1995). Loss on drying for compendial methods was performed in a Baxter Convection Oven Model DN-63. Karl Fischer analyses were performed on an Orion Model AF8 Volumetric Karl Fischer unit. Moisture determination of Natural Prosweet Powder was performed by Karl Fischer analysis. The moisture content of pink lake blend (LB-1355) was determined by a loss on drying method developed by Colorcon (Schwartz, 1996).

2.2.7. Tablet production

All tablet formulations contained 5.1% sodium bicarbonate, 3.7% citric acid, 2.0% magnesium stearate, 0.2% pink lake blend, and 0.5% silicon dioxide. Table 1 describes how different tablet formulations in the central composite design differ with respect to the amounts of the remaining ingredients. Table 1 also lists the calculated moisture contents of the formulations based on the moisture determinations of individual excipients and their % w/w in a formula. Batch sizes of 937.5 g were manufactured for each formula. The center point formula in this design (Formula no. 1 in Table 1) was done in triplicate to assess reproducibility, resulting in 11 tablet batches being manufactured.

All steps in tablet production were carried out under controlled temperature and humidity. Temperature and relative humidity were monitored during different steps in tablet production via a temperature/relative humidity probe.

All excipients, except magnesium stearate, were weighed and then screened through a US Std. No. 20 mesh sieve. These materials were then placed into a 4 quart V-blender (Patterson-Kelley) and mixed for 30 min. Magnesium stearate was then weighed and also screened through a US Std. No. 20 mesh sieve. The screened magnesium stearate was added to the other excipients in the V-blender and these materials were mixed for an additional 5 min. The powder blend was compressed on a rotary station tablet press (Cadmach DC-16 Rotary Tablet Press, Key International Inc.) tooled with two stations of 1/2 inch round, flat-faced, standard bevel, D-size tablet punches (Thomas Engineering Inc.) with isometric coating (Isometric Micro Finishing Co.). The tablet hardness that was targeted and achieved was approximately 12 N. The target tablet weight for each formula was 625 mg.

2.2.8. Tablet packaging

Tablets were packaged in cold form foil/foil blisters using a Sepha EZ Blister Packaging Machine (Sepha Inc.) at a sealing plate temperature of 191°C, dwell time of 2 seconds, and a force of 30 psi. The blister cards formed were in a 2 × 4-configuration. All packaging was done under controlled temperature and humidity. Temperature and relative humidity were monitored, while packaging tablets, via a temperature/relative humidity probe.

2.2.9. Seal integrity assessment of packaged tablets

The seal integrity of the packaged tablets was verified by submersing up to 4 blister cards in water in a vacuum desiccator; pulling a vacuum of 20″. Hg and maintaining that vacuum for 1 min; releasing the vacuum and leaving the blister cards submersed for 1 min; then carefully opening each blister and checking for ingress of water. One blister card (8 tablets total) from each batch was tested. No leaking blisters were found.

2.2.10. Thermal stressing of packaged tablets

Two blister cards (16 tablets in total) from each batch were placed in a 75°C convection oven (Baxter Scientific Products Model DN-63) for 3 h. The blister cards were then pulled and allowed to cool to room temperature. Once at room temperature, each of the blisters was opened under controlled temperature and humidity conditions and assessed for the degree of tablet mottling. Because the tablets were colored, any effervescent reaction that occurred could easily be seen as darker spots or mottling on the tablet.

2.2.11. Mottling assessment of stressed tablets

Tablets were given a rating from 0–7 (least to most) for the degree of tablet mottling. Packaged tablets of each formula that had not been thermally stressed acted as controls. These controls were given a mottling rating of zero. One analyst graded all stressed tablets in a blinded fashion in an effort to minimize the variability and bias in this assessment.

2.2.12. Statistical analysis of data

Data were statistically analyzed in JMP® version 3.1.5 for the Macintosh (SAS Institute, Inc.).

3. Results and discussion

Fig. 1 gives the particle size distribution of the milled potassium carbonate as determined by microscopy. The 95% confidence interval for the mean particle size is 15.9 ± 1.1 μ. range of particle sizes observed was from 2.8 to 46.1 μ.

Table 1
Tablet formulas, design placement, calculated moisture contents, and mottling assessment after thermal stressing

Formula no.	% w/w			Design placement	Calculated water content (% w/w)	Mottling (0–7 scale)
	Mannitol	Potassium carbonate	Natural Prosweet Powder			
1	81.4	1.0	6.1	Center	0.77	2, 3, 2
2	78.0	0.3	10.2	Vertex	1.17	5
3	86.3	0.3	1.9	Vertex	0.38	2
4	76.6	1.7	10.2	Vertex	1.17	4
5	84.9	1.7	1.9	Vertex	0.38	0
6	75.7	1.0	11.8	Star	1.32	4
7	87.2	1.0	0.3	Star	0.23	0
8	82.4	0.0	6.1	Star	0.77	4
9	80.4	2.0	6.1	Star	0.78	3

Multi-point BET analysis determined a surface area of 0.33 m^2/g for the milled potassium carbonate with a correlation coefficient of 0.9999.

The moisture sorption isotherm at 25°C for potassium carbonate is given in Fig. 2. Only an adsorption isotherm was performed since it deliquesces at $>40\%$ relative humidity. Note that potassium carbonate can absorb 18–19% moisture to form the sesquihydrate at very low relative humidities (10–40%) before deliquescing. Therefore, the anhydrous form is very hygroscopic and explains why it can be used as a desiccant in an effervescent dosage form. It should be noted that the failure to obtain a vertical line from the anhydrous to the sesquihydrate in the isotherm indicates that the instrument's relative humidity change setting was not set sufficiently sensitive enough to obtain true equilibrium values.

Natural Prosweet Powder is a flavor enhancer and improver. It contains dextrose monohydrate and other flavor ingredients. In this study, Natural Prosweet Powder was used solely as a convenient means of incorporating water into the

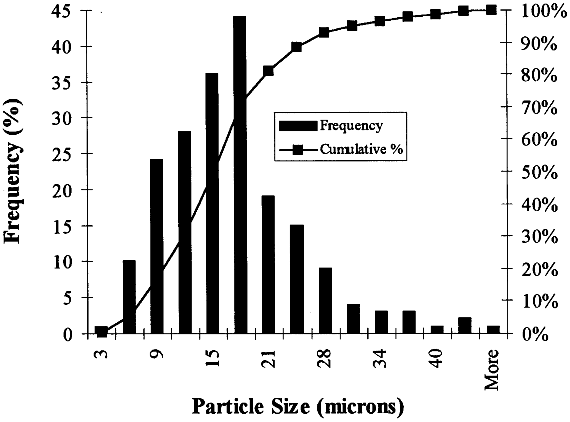

Fig. 1. Particle size distribution for milled, anhydrous potassium carbonate.

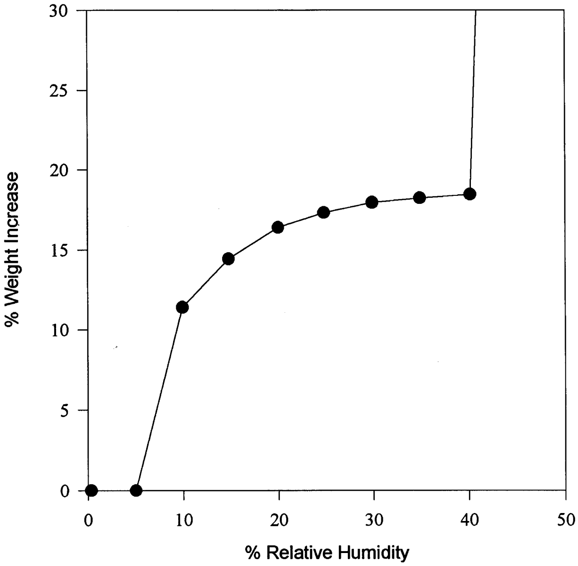

Fig. 2. Moisture sorption isotherm 25°C for potassium carbonate.

formulation. Moisture sorption isotherm for dextrose (Wade and Weller, 1994) shows that the hydrate form is very stable, even at low relative humidities. However, this study used heat (75°C for 3 h) to force the hydrated form of dextrose to release its water in the tablet in the sealed blister. Evidence of this 'activation' of water in the tablet is supported by thermogravimetic analysis (TGA) of dextrose monohydrate. Upon heating dextrose monohydrate to 75°C and holding it at that temperature, all its water of hydration is released within 5 min of achieving 75°C. Understandably, this is not a true reproduction of what is occurring in the blister cavity under the conditions of these experiments. However, it is a fair assumption that this is occurring in this study when one considers that the tablets were held at 75°C for 3 h in a package that was sealed at very low relative humidity (< 20%).

It is easy to understand why hydrates can cause stability problems for effervescent products. The material, arrives as a hydrate, is incorporated with other powders and compressed and packaged under low percent relative humidity conditions (< 20%). This is the environment within the hermetically sealed product. Therefore, if the true equilibrium state under those conditions is the anhydrous form, the hydrate must give up its water of hydration. If no desiccant is incorporated into the formula this will result in dissolution of the effervescent components, which will react to form carbon dioxide. This will result in puffed blisters or pouches, mottling and/or pitting of tablets, a change in tablet hardness, and a subsequent change in disintegration and dissolution time.

However, if a desiccant, such as anhydrous potassium carbonate is incorporated into the effervescent formula, moisture present may preferentially be taken up into the crystalline hydrate (see Fig. 2) as long as the amount of moisture isn't enough to overwhelm the desiccant present or the kinetics of the process of converting the free water into crystalline bound water. Potassium carbonate is purchased as the anhydrous form and is processed, i.e., mixing, compression, and packaging under low relative humidity. At these low relative humidities (10–20%), it has a significant affinity for moisture so it can form its equilibrium state, the sesquihydrate. Therefore, it has the ability to take up moisture being freed by a hydrate, such as dextrose, and incorporate the water into its hydrate so the water cannot cause reaction of the effervescent system.

Table 2
Statistical parameter estimates for central composite study

Term	Estimate	S.E.[a]	*t* Ratio	*P*
Intercept	1.074	0.496286	2.16	0.0671
K_2CO_3	−3.314	0.798451	−4.15	0.0043
H_2O	4.072	0.430754	9.45	<0.0001
$(K_2CO_3)^2$	1.262	0.380758	3.32	0.0128

$R^2 = 0.940774$; adj. $R^2 = 0.915391$

[a] S.E. = Standard error.

One might want to take this one step further and ask why not use anhydrous potassium carbonate as a desiccant in a normal tablet with standard packaging, i.e., plastic bottle or thermoformed plastic blisters. This would not work because these packaging designs are not closed systems like the foil/foil packaging of an effervescent product. These packaging designs would allow the ingress of moisture. In this case anhydrous potassium carbonate would do more harm than good with respect to moisture stability since it would attract water from the environment.

Table 1 gives the mottling scores after thermal stress testing for the different formulations studied.

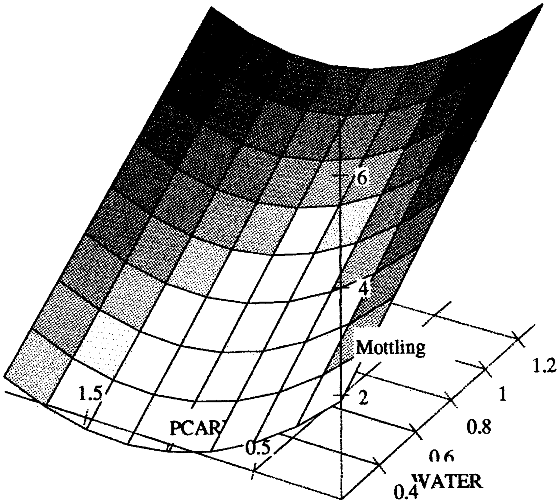

Fig. 3. Response surface plot relating % w/w anhydrous potassium parbonate (PCARB) and % w/w moisture (WATER) to Mottling.

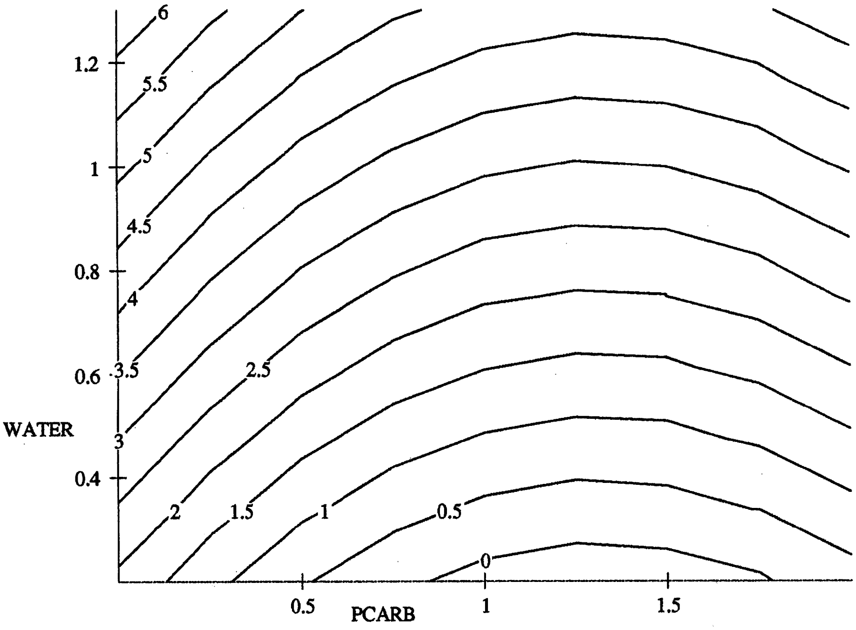

Fig. 4. Contour plot relating % w/w anhydrous potassium carbonate (PCARB) and % w/w moisture (WATER) to Mottling (contour lines).

Three scores are given for formulation # 1 since it was done in triplicate to assess reproducibility. The estimated standard deviation for reproducibility is 0.577.

Table 2 gives the parameter estimates determined from statistical analysis of the data. An excellent fit was obtained (adj.-$R^2 = 0.92$) and there was no evidence of lack of fit ($P = 0.85$) for this model. Therefore, the equation relating mottling to these independent variables is:

$$\begin{aligned} \textit{Mottling} &= 1.074 - 3.314\,(\%\ \mathrm{w/w}\ K_2CO_3) \\ &\quad + 4.072\,(\%\ \mathrm{w/w}\ H_2O) \\ &\quad + 1.262\,(\%\ \mathrm{w/w}\ K_2CO_3)^2 \end{aligned} \tag{1}$$

Table 3
ANOVA for central composite study

Source	df	Sum of squares	Mean square	F ratio
Model	3	24.973261	8.32442	37.0635
Error	7	1.572193	0.22460	Prob > F
C Total	10	26.545455		0.0001

Figs. 3 and 4 give the response surface and contour plots, respectively for Eq. (1). From Figs. 3 and 4, the optimal level of potassium carbonate

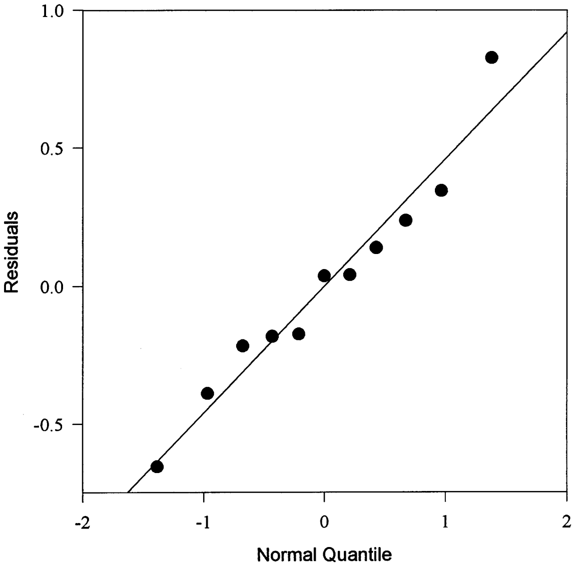

Fig. 5. Normal Probability Plot for Residuals from Statistical Analysis.

is determined to be approximately 1.3% w/w. If one assumes that for an acceptable product the mottling score should be ≤ 0.5, the maximum total moisture content the 1.3% w/w potassium carbonate can accommodate is 0.4%.

These results agree very well with Takaichi et al. (1992b) in U.S. Patent No. 5 087 442 where, in legal jargon, the amount of potassium carbonate to be used in effervescent tablets is given as 0.2–13%, preferably 0.3–3%, but more preferably 0.4–1%. This agreement is in spite of a number of experimental differences in how these numbers were determined.

Table 3 gives the ANOVA for the system studied. The F ratio has a value of 37.06. For a model to be a good predictor of future observations this value should be at least ten times the critical F value for 3 and 7 degrees of freedom in this case. The 5% critical $F_{3,7}$ value is 4.35. Therefore, the F ratio should be at least 43.5. However, the residuals do appear to be normally distributed: the normal probability plot for residuals in Fig. 5 looks quite good and the Shapiro-Wilk test for normality failed to reject the model ($P = 0.89$). Note that one point in Fig. 5 falls off the straight line. This is one of the center points of the design with a mottling score of 3 instead of 2. If this observation is removed, the F ratio jumps well above ten times the critical F value. One must also remember that the response here is not continuous, but an ordered categorical variable. Therefore, it should not be surprising to see this kind of variation. This variation also likely explains the slight increase in mottling ($+0.5$) depicted by the model in Figs. 3 and 4 at 2% potassium carbonate for a given moisture content.

As nicely as the data fit the model, there are a number of caveats that must be remembered about this study. The milled material used for this study had a moisture content of 0.3%. Since moisture content of the potassium carbonate remained constant in this study, the same amount of effervescent base protection cannot be assumed at a different level of moisture in the potassium carbonate. Another caveat is that even though all processing was done under low relative humidity ($< 20\%$), based on Fig. 2, the humidity was still high enough for potassium carbonate to have the ability to acquire moisture during processing. In this study, exposure of anhydrous potassium carbonate to the environment was minimized by keeping it double-bagged in a sealed container. Even so, there is no way to tell how much moisture it acquired during processing of the tablets. Therefore, it is imperative to be extremely protective of the anhydrous potassium carbonate when doing any processing. One must also remember that the thermal stressing occurred at 75°C whereas the moisture sorption isotherm was conducted at 25°C. It is likely that at the elevated temperature the isotherm would be shifted to the right, presenting a much different environment for the potassium carbonate to act as a desiccant. Therefore, although it is a useful worst case check for activity as a desiccant, the actual relationship between level of potassium carbonate, amount of formulation moisture, and mottling on long term storage at standard conditions may be different. Lastly, this study was essentially based on potassium carbonate's ability to prevent effervescent base degradation by its ability to take up moisture given off by dextrose monohydrate. Different hydrates with different moisture sorption isotherms, i.e., different affinities for acquiring or releasing water and the kinetics of these processes, may have a different effect on anhydrous potassium carbonate's ability to act as a desiccant in effervescent tablets.

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References

The Merck Index, 1989. 11th edn., Merck and Co., Inc., Rahway, NJ, pp. 1212–1213.

Mohrle, R., 1989. Effervescent Tablets. In: Lieberman, H.A., Lachman, L., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 1, chapter 6, 2nd edn., Marcel Dekker, Inc., New York, NY.

Schwartz, C.J. (Manager), 1996. Quality Control at Colorcon, Personal Communication via fax, June 11.

Takaichi, A., Okamoto, T., Matsumoto, T., 1992a. Preparation for iron supply, preparation for vitamin supply and method for stabilizing a foam preparation. US Patent Number 5 160 728, November 3.

Takaichi, A., Okamoto, T., Matsumoto, T., 1992b. Preparation for iron supply, preparation for vitamin supply and method for stabilizing a foam preparation. US Patent Number 5 087 442, February 11.

US Pharmacopeia XXIII/NF XVIII, 1995. US Pharmacopeial Convention, Rockville, MD, p. 382, p. 929, p. 1253, p. 1414, p. 2262, p. 2300.

Wade, A., Weller, P.J. (Eds.), 1994. Handbook of Pharmaceutical Excipients, 2nd Edn., Pharmaceutical Association, The Pharmaceutical Press, London, pp. 154–157.