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RESEARCH PAPER

Characterization of Excipient and Tableting Factors That Influence Folic Acid Dissolution, Friability, and Breaking Strength of Oil- and Water-Soluble Multivitamin with Minerals Tablets

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ABSTRACT

The goal of this study is to characterize the formulation and processing factors that influence folic acid dissolution from oil- and water-soluble multivitamin with minerals tablet formulations for direct compression. The following parameters were studied: bulk filler solubility, soluble to insoluble bulk filler ratio, triturating agent (preblending carrier) solubility, disintegrant usage, compression pressure, and folic acid particle size. Folic acid particle size was determined by using light microscopy, and surface area was measured by using BET adsorption. The tablets were compressed on an instrumented Stokes B2 tablet press, and the friability, weight variation, and dissolution were measured according to USP methods, along with tablet breaking strength. In summary, we found the following factors to be critical to folic acid dissolution: bulk filler solubility (soluble fillers, such as maltose, increase folic acid dissolution); disintegrant amount (levels less than 0.4% (w/w) are ineffectual, whereas levels greater than 1.2% (w/w) did not further increase dissolution); and compression force (generally, maltose produce harder tablets). In addition, folic acid dissolution was less affected by changes in compaction pressure when a ''super'' disintegrant and maltose, as a bulk filler, were used. It was determined that the trituration agent did not play a significant role in folic acid dissolution. In the range of parameters studied, statistical analysis found no significant interactions between the parameters studied, which means they act independently in an additive manner. The results also show that no one factor is completely responsible for dissolution failure. Thus, it is the combination of formulation factors and processing conditions that collectively add up to produce dissolution failure; however, the use of a disintegrant and a soluble filler such as maltose can make a formulation more robust to the inevitable changes that can occur during commercial production.

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Key Words: Folic acid; Dissolution; Excipient solubility; Oil- and water-soluble multivitamin tablets and multivitamin formulation.

INTRODUCTION

In the United States, Europe, and Asia, large quantities of vitamin and mineral supplements are consumed each day. For the most part, diets in these areas have an adequate supply of essential nutrients, and vitamin or mineral deficiencies are rare.[1] Thus, supplementing the diet is a personal decision for those who believe this will improve their health and for certain population groups who may be at risk of a deficiency in certain nutrients. One of the most important populations needing nutritional supplements are women of childbearing age[2]; for this population, folic acid is a critical nutrient that can play a significant role in the prevention of neural tube birth defects.[3,4] Folic acid also has been shown to lower the risk of arteriosclerotic vascular disease.[5] These special populations require high-quality supplements designed to ensure folic acid bioavailability. However, this is not always the case; for example, Hoag, Ramachandruni, and Shangraw[6] found that 66% of the prenatal vitamin products tested failed to meet the USP folic acid dissolution standard, which raises serious concerns about folic acid bioavailability from these nutritional supplements. Similar problems were also found with nutritional supplement disintegration,[7] further indicating that efficacious formulation and manufacturing strategies must be developed and made available to formulators to address this issue.

On the basis of our previous research, the authors have identified several factors that could explain why so many multivitamin products fail to meet USP dissolution specifications. The complex nature of folic acid dissolution suggests that these factors and the interactions between them could act together to influence folic acid dissolution.

The first factor that the authors believe could influence folic acid dissolution is excipient solubility; because the amount of folic acid in a formulation is so low, most manufacturers use some type of preblending procedure to achieve a uniform mix. The carrier for these preblends varies considerably from manufacturer to manufacturer; many manufacturers use insoluble carriers, such as dibasic calcium phosphate (dical), which is known to impede dissolution.[8–11] In addition, insoluble excipients, such as dical, are also commonly used as bulk fillers to increase the calcium content of a product. Here again, insoluble fillers are known to impede disintegration and dissolution.[12–14] Preliminary studies have shown that a soluble filler like maltose can improve folic acid dissolution,[15] but more study is needed to better understand the properties maltose can impart to a formulation. The second factor involves the use of a disintegrant, and the third factor involves the interaction between peak compression force, tablet-breaking strength, and folic acid dissolution. Based on the above factors, the objective of this study is to determine if these factors influence folic acid dissolution, tablet-breaking strength and tablet friability. This information will help to produce guidelines for developing efficacious oil- and water-soluble multivitamin with minerals tablet formulations for direct compression.

EXPERIMENTAL

Materials

Three different sources of USP grade folic acid were used: EM Science (Gibbstown, NJ), Seltzer Chemicals, Inc. (Carlsbad, CA) and AnMar International Ltd. (Bethel, CT). A mixture of multivitamins BC-3320 was obtained from B&C Nutritional Products Inc. (Vista, CA); see Table 1. The mixture of minerals CB1273 was obtained from Watson Food Co., Inc. (West Haven, CT); see Table 2. Dibasic calcium phosphate (dical), Emcompress® grade, was obtained from Mendell Inc. (Patterson, NY); anhydrous lactose was obtained from Sheffield Products Norwitch, NY; maltose, Advantose® grade, was supplied by SPI Polyols, Inc. New Castle, DE; mannitol Pearlitol SD200 grade was obtained from Roquette, Keokuk, IA; microcrystalline cellulose (MCC) Avicel PH101 grade was obtained from FMC Corporation, Newark, DE; pregelatinized starch, Starch 1500 grade was obtained from Colorcon Inc., West Point, PA; magnesium stearate was obtained from Mallinckrodt (St. Louis, MO).

Tablet Preparation

To manufacture the direct compression formulations, the appropriate quantities were weighed and

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Table 1. Oil- and water-soluble vitamin blend used for tablet formulations.

Ingredients	Amount
Biotin	15 mg
Folic acid	0.4 mg
Niacin (niacinamide)	100 mg
Pantothenic acid (calcium pantothenate)	50 mg
Vitamin B-1 (thiamin hydrochloride)	7.5 mg
Vitamin B-2 (riboflavin)	8.5 mg
Vitamin B-6 (pyridoxine hydrochloride)	10 mg
Vitamin B-12	0.03 mg
Vitamin-D	2,000 IU
Vitamin-A (palmitate)	25,000 IU
Vitamin-C (ascorbic acid)	300 mg
Vitamin-E (dl-alpha tocopheryl acetate)	150 IU
Vitamin-K (phytonadione)	0.125 mg
Maltodextrin[a]	*Q.S.* to make 1.0 g

[a]Note maltodextrin is the major excipient, but other excipients such as gelatin, lactose, and cellulose were also added in minute quantities as trituration agents for some of the micronutrients.

Table 2. Mineral blend used for tablet formulations.

Ingredients	Amount
Chromium (chromium chloride)	3.2 mg
Selenium (sodium selenate)	1.0 mg
Molybdenum (sodium molybdate)	8.0 mg
Vanadium (sodium metavandate)	0.5 mg
Nickel (nickelous sulfate)	0.25 mg
Silicon (sodium metasilicate)	0.5 mg
Boron (sodium borate)	7.5 mg
Tin (stannous chloride)	0.5 mg
Dibasic calcium phosphate	*Q.S.* to make 1.0 g

mixed thoroughly in a twin shell blender for 15 min; then Mg stearate was added and mixed for 2 additional min. The formulations were compressed on an instrumented Stokes® B2 tablet press running at 32 RPM. To compress the tablets, 7.9375 mm (0.3125 inch) concave or 15.875 mm (0.6250 inch) flat faced punches were used for the folic acid single ingredient and multivitamin tablets, respectively. Tablet-breaking strength was measured by using KEY® HT-300 hardness tester (Englishtown, NJ); friability and weight variation were measured according to USP methods <1216> and <905>, respectively.

Folic Acid Dissolution

Folic acid dissolution was measured by using USP Apparatus II (paddles) according to the USP methods <711> and <2040> (75 RPM with 900 mL water at 37°C). Dissolution studies were done with six replicates. Great care was taken to ensure the samples did not degrade before HPLC analysis; most samples were analyzed immediately after dissolution. If samples had to be stored, they were protected from light and stored at 4°C before analysis.

Folic Acid Assay and Methods Validation

Using HPLC, the official USP 23 (1995) methods were used for the folic acid assays. The methods were validated by using standard procedures. Folic acid analysis conditions were UV detection at 280 nm, 3.9 mm × 30 cm column (C-18, 10 μm, by Phenomenex Inc., Torrancc, CA), flow rate 1.5 mL per minute. For the mobile phase, 1 L contained 2 g of monobasic potassium phosphate, 12 mL 25% tetrabutylammonium hydroxide in methanol, 7 mL of 3 N phosphoric acid and 240 mL of methanol; this solution was diluted to 1 L with water, and the final pH was adjusted to pH = 7.15.

The HPLC standard curve for folic acid was linear with a correlation of $r^2 = 0.9999$. The intraday and interday assay precision for folic acid in the formulation solution, (%RSD = SD/mean × 100) and the intraday and interday assay accuracy for folic acid in the formulation solution, (%RE = (mean − spiked)/spiked × 100) were monitored and kept within acceptable limits (less than 6% variability).

Particle Size Analysis

Feret's diameter was measured by using a Leitz (Wetzlar, Germany) microscope. Surface area was measured by using FlowSorb 2300 Micromeritics (Norcross, CA). The test conditions were 30% nitrogen and 70% helium mixture, the flow rate was 65 cm^3/min, and liquid nitrogen was used as a coolant. After calibration, each sample was run in triplicate.

RESULTS AND DISCUSSION

As described above, the authors have identified several factors that could influence folic

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acid dissolution. Given the tremendous number of possible factors that can affect folic acid dissolution, experimental design procedures that reduce the total number of experiments to a manageable number must be used. Thus, we chose a sequential experimental design strategy.[16] With this strategy, a series of smaller scale experiments are done before doing the final study. The goal of these initial studies is to screen out unimportant factors and suggest better formulations and production conditions for the next study. With this strategy, the factors believed to be most important are studied first; then these data are used to design the next study. This process continues until there are enough data to design the final multifactorial study.

The particle size and surface area for the three folic acid samples obtained for this study are given in Table 3. Unless otherwise stated, the 18.3-μm samples were used.

Trituration Excipients and Folic Acid Dissolution

Because folic acid is a micro ingredient, it must be preblended to ensure content uniformity. Therefore, soluble and insoluble excipients can be added either as a trituration agent or as a bulk filler/direct compression binder. Using folic acid-only tablets to study the effect of excipient solubility on folic acid dissolution, eight formulations were developed; see Table 4. To study the effect of the bulk filler/direct compression binder solubility, tablets were made with either a mixture of 1 part MCC and 2 parts lactose or 100% (w/w) dical. To study the effects of the trituration material, folic acid in a 10% (w/w) mixture was triturated either with dical, starch, mannitol, or maltose. These excipients were chosen because they are commonly used in many of the vitamin and mineral formulations on the market today. Each tablet weighed 250 mg with 0.4 mg of folic acid. The trituration was done in a mortar and pestle using geometric dilution techniques; only gentle mixing was used.

Table 3. Particle size and surface area data from three different folic acid sources.

Folic acid lot #	Mean horizontal diameter (μm)	Surface area (m^2/g)
169072(EM)	24.44	2.96
970726(AnMar)	18.3	6.454
72080(Seltzer)	9.04	12.357

Table 4. Formulations used for folic acid dissolution study; all tablets were 250 mg and contained 0.4 mg of folic acid.

Formulation number	Bulk filler	Trituration material
1A	Dical	Dical
1B	1/3 MCC + 2/3 lactose	Dical
2A	Dical	Starch
2B	1/3 MCC + 2/3 lactose	Starch
3A	Dical	Mannitol
3B	1/3 MCC + 2/3 lactose	Mannitol
4A	Dical	Maltose
4B	1/3 MCC + 2/3 lactose	Maltose

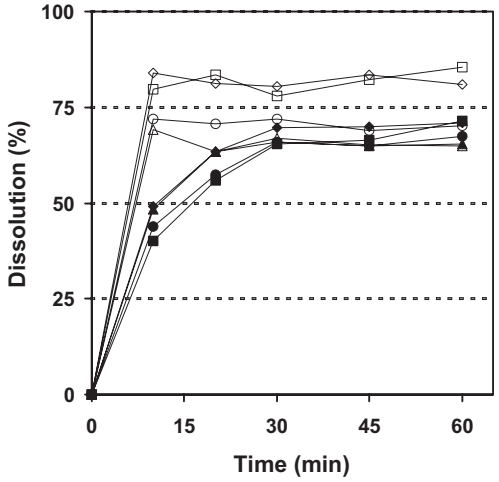

Figure 1. Folic acid dissolution from formulations shown in Table 4 (bulk filler:trituration agent): (■) dical:dical, (▲) dical:starch, (●) dical:mannitol, (◆) dical:maltose, (□) 1/3 MCC + 2/3 Lactose:dical, (△) 1/3 MCC + 2/3 Lactose:starch, (○) 1/3 MCC + 2/3 Lactose:mannitol, (◇) 1/3 MCC + 2/3 Lactose:maltose, each tablet weighed 250 mg with 0.4 mg of folic acid.

The dissolution results, (Fig. 1) show that all preblends with soluble bulk filler reached the maximum amount released in 10 min, whereas all the preblends with insoluble bulk filler took 30 min to reach the maximum amount released. It is worth noting that none of the formulations with insoluble bulk fillers met the USP specification for folic acid dissolution, which is at least 75% of label claim amount released in 1 hr. These results show that the bulk filler has a

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greater influence on folic acid dissolution, although the nature of the trituration agent has some influence, this effect is much less than the bulk filler. These results are reasonable because the trituration agent comprises only a small percentage of the tablet weight and the primary factors affecting dissolution are the properties of the tablet matrix (i.e., the bulk filler). Thus, only the effect of the tablet matrix and processing conditions on folic acid dissolution will be examined in subsequent studies (i.e., no further studies were done on the effect of a trituration agent).

Critical Formulation and Tableting Factors

The goal of this part of the study is to identify the critical formulation factors that affect multivitamin tablet dissolution, breaking strength, and friability. The total number of factors affecting multivitamin properties is very large especially when considering composition effects. Therefore, to narrow the scope of the study and to produce results relevant to the vitamin industry, the study was based on the composition of a recognized industry standard Centrum® (Lederle Consumer Health Division, Pearl River, NY), which is a popular oil- and water-soluble multivitamin with minerals product. Popular commercial vitamin and mineral premixes also will be used in the multivitamin studies. Presently, many manufacturers use these vitamin and mineral premixes when formulating their products. In other words, for many manufacturers, the multivitamin and mineral composition is fixed; thus, the remaining factors that must be assessed are the excipient composition and processing conditions. With excipients, there are many different types of soluble and insoluble bulk fillers that could be used. For the insoluble fillers, we chose to study dical because of its widespread use in the nutritional supplement industry. Dical is probably used to increase the calcium content of the tablets and for cost efficiency. For the purpose of this study, the components of the formulation can be categorized into three groups: minerals, vitamins (oil- and water-soluble), and excipients. Based on Centrum®, the vitamin and mineral compositions are given in Tables 1 and 2, respectively. Table 5 shows the formulations used to study the effect of maltose and dical on folic acid dissolution.

In addition to formulation effects, processing conditions, such as compression pressure, can also affect dissolution via tablet-breaking strength and hence disintegration time. The breaking strength vs. peak compression force curves for maltose and dical formulations 1 and 2 from Table 5 are shown in Fig. 2. In the range of peak compression forces studied from 10 to 23 kN, these data show that for a given tablet-breaking strength, the formulations containing maltose required less compression force to achieve the desired breaking strength, and this effect was more pronounced at higher pressures. It should be noted that the correct way to determine tablet-breaking strength or tensile strength is to normalize the fracture load by tablet thickness and diameter (i.e., fracture surface area). However, this procedure is not always done. Thus, given the fact that the die diameter was constant for all multivitamin tablets and our measurements of tablet height showed that even with the variations in composition, the different tablet-processing conditions tablet height did not change to a significant degree. Thus, only the peak fracture force was reported.

Table 5. Multivitamins with mineral tablets formulations, all weights in mg.

	Formulation number	
Ingredient	1	2
Vitamin premix BC-3320	200	200
Mineral triturate CB-1273	1000	1000
Maltose	300	0
Dical	0	300
Ac-Di-Sol	15	15
Mg stearate	15	15

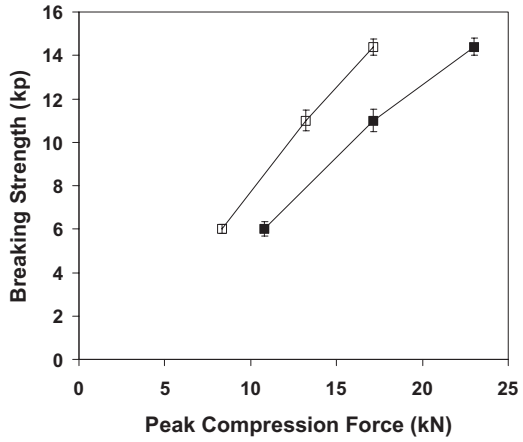

Figure 2. Breaking strength of the multivitamin tablets with maltose or dical made to different peak compression forces: (■) dical, (□) maltose. See Table 5 for composition.

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To study the effect of excipient solubility and tablet-breaking strength on folic acid dissolution, formulations 1 and 2 from Table 5 were compressed to produce tablets with a hardness of 6, 11, or 14.5 kP. Figure 3 shows the folic acid dissolution profiles for the multivitamin tablets made with either maltose or dical. Like the previous results, these data show that soluble bulk fillers have better dissolution than insoluble bulk fillers. It should be noted that all the formulations that contained soluble fillers met the USP dissolution specifications. These data also show that tablet-breaking strength (i.e., manufacturing conditions) can have a pronounced effect on folic acid dissolution, and it should be noted that dissolution from dical formulations was more sensitive to peak-compression force and that overcompression can cause dissolution problems. This fact creates a difficult balancing act because to manufacture and coat large batch sizes requires the tablets to have sufficient breaking strength yet still maintain their dissolution properties; however, the use of maltose can minimize these problems by aiding folic acid dissolution while maintaining acceptable tablet breaking strength.

In summary, from the preliminary studies we found the following factors to be critical to folic acid dissolution: bulk filler type (soluble or insoluble) and tablet-breaking strength. It was also determined that for the type of systems studied, the trituration agent did not play a significant role in folic acid dissolution. Finally, these results show that when making comparisons between two formulations, controlling all the variables such as tablet-breaking strength is very important to the validity of the conclusions. It should be noted also that the use of a super disintegrant is not always sufficient to ensure a multivitamin will meet USP dissolution specifications; see Fig. 3.

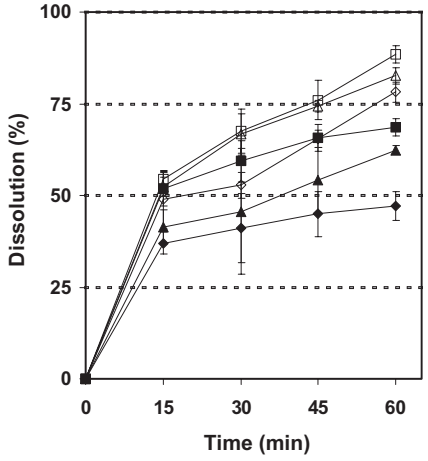

Figure 3. Folic acid dissolution from multivitamin formulations 1 and 2 given in Table 5. Tablets made with maltose to a crushing strength of (◇) 14.5 kP, (△) 11 kP, (□) 6 kP and tablets made with dical to a crushing strength of (◆) 14.5 kP, (▲) 11 kP, and (■) 6 kP.

Mixture and Treatment Level Effects

To better understand the above critical variables, a multifactorial experimental design was used. In addition, many vitamin manufacturers may want to use dical in their formulations to increase the calcium content and for cost efficiency. Thus, the experimental design will also include the ratio of dical to maltose and the total amount of filler (i.e., maltose plus dical) to be added, rather than just a binary inclusion of either dical or maltose. By using the method developed by Fang,[17] this study was done with use of the $U_{10}(10^4)$ even experimental design, which uses 4 factors with 10 levels of treatment. Based upon this design, the 10 studies to be done are given in Table 6; italicized numbers indicate the treatments used. As before, Centrum® was used as the basis for the vitamins and minerals; 200 mg of the vitamins given in Table 1, 1000 mg of minerals given in Table 2, and 1.0% (w/w) Mg stearate were used in every formulation. The four factors to be studied are total filler amount, ratio of maltose to dical (i.e., filler composition), peak compression force, and disintegrant amount. For these 10 formations, the dependent variables measured were dissolution, tablet friability, tablet-breaking strength and tablet weight variation. At each of the 10 levels studied, at least 6 replications were done for each variable studied.

The dissolution results for the 10 formulations are graphed in Fig. 4; Table 6 gives the numerical values for the percent dissolution in 60 min (Q_{60}), tablet-breaking strength, tablet friability, and their standard deviation. It should be noted that even though the friability levels given in Table 6 are higher than what is typically encountered, flat faced tooling was used, which produces tablets with sharp edges. These sharp edges naturally have a higher friability than concave or rounded caplet shaped tablets. Thus, if standard tooling were used, the friability would be significantly lower. This tablet shape was chosen because it gives the most accurate determination of tablet-breaking strength. Multiple linear regression was used to analyze the

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Table 6. The $U_{10}(10^4)$ even experiment design according to the method of Fang.[17]

No.	Filler (mg)	M/D (%)	P_{max} (kgf)	Ac-Di-Sol (%)	Q_{60} (%)	Friability (%)	Breaking strength (kP)	Wt. Var[a]
1	*50*	*20*	*1000*	*1.2*	102.9 ± 7.2	67.7 ± 2.27	2.9 ± 0.40	1.5
2	*100*	*40*	*1500*	*0.4*	90.8 ± 27.8	1.2 ± 0.05	7.3 ± 0.61	6.6
3	*150*	*60*	*900*	*1.8*	101.7 ± 12.7	42.0 ± 1.51	3.4 ± 0.47	1.2
4	*200*	*80*	*1400*	*1*	96.8 ± 3.9	1.52 ± 0.10	6.4 ± 0.58	2.4
5	*250*	*100*	*800*	*0.2*	73.6 ± 12.1	28.8 ± 0.62	3.2 ± 0.47	0.7
6	*300*	*10*	*1300*	*1.6*	108.4 ± 12.5	1.61 ± 0.15	6.1 ± 0.76	5.1
7	*350*	*30*	*700*	*0.8*	98.7 ± 22.0	86.3 ± 3.42	1.8 ± 0.26	1.1
8	*400*	*50*	*1200*	*0*	57.6 ± 10.5	1.81 ± 0.11	5.7 ± 0.70	1.4
9	*450*	*70*	*600*	*1.4*	107.9 ± 24.0	100 ± 0.00	1.9 ± 0.20	1.2
10	*500*	*90*	*1100*	*0.6*	97.2 ± 21.8	1.59 ± 0.12	7.3 ± 0.29	0.6

The *italicized* number is the value of the treatment level; the standard text is the mean ± SD. Each formulation includes multivitamins (200 mg), minerals (1000 mg), magnesium stearate (1% w/w), and the fillers listed below.
[a]%STD, $n = 10$.

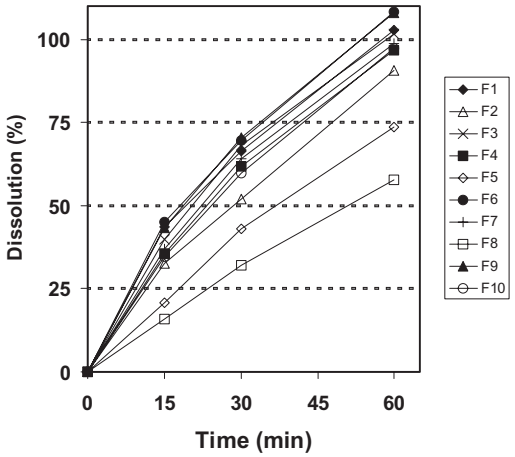

Figure 4. Folic acid dissolution from multivitamin tablets given in Table 6; the final amount released ±SD at 60 min is given in Table 6.

data in Table 6. The data were fit to the following model:

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3} + \beta_4 x_{i4} + \varepsilon_i \quad (1)$$

where y_i is either Q_{60}, tablet-breaking strength, tablet friability, or weight variation. The β_j coefficients correspond to the following parameters: β_0 is the intercept, β_1 is the amount of total filler in the formulation, β_2 is the ratio of maltose to dical in percent, β_3 is the peak compression force, and β_4 is the amount of disintegrant. In addition, x_{ij} is the variable corresponding to the level of each of the four treatments, amount of filler (x_{i1}), ratio of maltose to dical (x_{i2}), compression pressure (x_{i3}), and amount of disintegrant (x_{i4}); ε_i is the random error associated with each measurement. It should be noted that interaction terms were initially included in Eq. (1), but they were not statistically significant and hence dropped.

For tablet-breaking strength, Eq. (1) was found to have excellent fit with a $r^2 = 0.95$, and based on the F-value the overall model p value was 0.00173, indicating the model has a good fit to tablet-breaking strength data. However, careful analysis of sums of squares for the individual parameters shows that only the total amount of filler and peak compression pressure, (p value = 0.0038 and p value = 0.00023, respectively) are statistically significant. For tablet friability, Eq. (1) has good fit with an $r^2 = 0.86$, and based on the F-value, the overall p value of 0.024. Again, analysis of sums of squares for the individual parameters indicates that only the compaction pressure, p value = 0.043, has a significant effect on tablet friability. For tablet weight variation, Eq. (1) does not have a reasonable fit; therefore, no conclusion can be made on the influence of these formulation factors on tablet weight variation; in addition, none of the subsets of the Eq. (1) showed a statistically significant difference.

For analysis of dissolution based on Q_{60}, statistical analysis showed Eq. (1) did not fit the data with an r^2 of 0.72 and overall model p value of 0.12, which indicates the model does not adequately describe dissolution. However, when the Q_{60} dissolution data is fit to the model:

$$y_i = \beta_0 + \beta_4 x_{i4} + \beta'_4 x_{i4}^2 + \varepsilon_i \quad (2)$$

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where the term x_{i4}^2 is the amount of disintegrant squared and β_2' is its coefficient, the fit becomes much better with an $r^2 = 0.94$ and the overall model p value < 0.001, and the parameters y intercept, x_{i4}, and x_{i4}^2, were all significant. This model fits better because the dependence of Q_{60} on the amount of disintegrant is non-linear. A plot Q_{60} vs. percent of disintegrant shows that increasing the disintegrant level above 1.2% (w/w) does not increase Q_{60}. The addition of the term x_{i4}^2, which had a negative coefficient, better fits to the data because this model can better accommodate the plateauing of the disintegrant effect.

In summary, three general trends emerged; first, the use of a disintegrant improves folic acid dissolution, and levels less than 0.4% (w/w) are ineffectual, whereas levels greater than 1.2% (w/w) did not increase dissolution. Second, to produce tablets with sufficient breaking strength and friability for large-scale production, at least 1000 kgf of compression force is needed for these formulations. Third, the more filler, the better tablet breaking strength; however, increasing tablet size must be balanced against consumer preference, which favors smaller tablets. One limitation of treatment levels used in this study was the low breaking strength and high friability values of some formulations. This leads to rapid tablet disintegration, which is a prerequisite to dissolution. In other words, these formulations are not representative of tablets produced in the vitamin industry and the poor tablet mechanical integrity leads to rapid disintegration, which tends to obscure formulation and processing differences that influence dissolution. Thus, more study is needed to better understand the role excipients play in tablet dissolution.

Multivitamin Multifactorial Study

Given the constraints patient compliance adds to tablet size, it was decided to fix the filler amount, and based on previous results, the disintegrant amount was also fixed. Thus, in this section the effects of tablet-breaking strength and filler composition on dissolution and friability will be further examined. This study was done using a factorial type design with two factors with three levels for breaking strength and four levels for composition, see Table 7; italicized numbers indicate the independent variables. The dependent variables measured were dissolution and tablet friability. As before, Centrum® was used as the basis for the vitamins and minerals; each tablet contained 200 mg of the vitamins given in Table 1, 1000 mg of minerals given in Table 2, 1.0% (w/w) disintegrant, 1.0% (w/w) Mg stearate and 500 mg of total filler. For all the levels studied, at least six replications were done for each variable.

The dissolution results for the 15 formulations are graphed in Fig. 5; Table 7 gives the numerical values for Q_{60} dissolution, tablet friability, and their standard deviations. Multiple-linear regression was

Table 7. The factorial design for multivitamin study.

% Maltose	Breaking strength (kP)	Q_{60} (%)	Friability (%)
0	*14.5*	66.5 ± 3.99	1.0
0	*11*	72.2 ± 1.16	1.2
0	*6*	84.2 ± 2.43	2.1
25	*14.5*	72.7 ± 2.30	0.9
25	*11*	91.6 ± 1.01	1.1
25	*6*	90.4 ± 6.52	1.8
50	*14.5*	87.7 ± 3.64	0.9
50	*11*	85.9 ± 2.88	1.0
50	*6*	94.6 ± 4.05	1.8
75	*14.5*	88.4 ± 4.60	0.8
75	*11*	90.5 ± 3.74	1.0
75	*6*	92.9 ± 2.38	1.7
100	*14.5*	96.7 ± 2.74	0.7
100	*11*	96.5 ± 2.31	0.9
100	*6*	100.5 ± 2.30	1.3

The *italicized* numbers are the values for the treatment level; the standard text is the mean ± SD. Each formulation includes multivitamins (200 mg), minerals (1000 mg), 1.0% (w/w) disintegrant, and 1% (w/w) magnesium stearate.

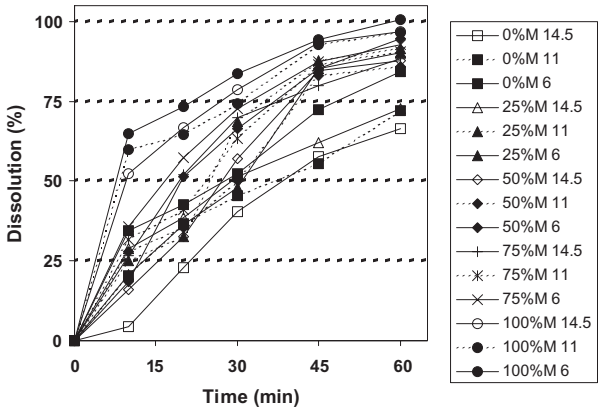

Figure 5. Folic acid dissolution from formulations tablets given in Table 7; the final amount released ± the SD at 60 min is given in Table 7.

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used to analyze the data in Table 7. The data were fit to the following model:

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \varepsilon_i \quad (3)$$

where y_i is either Q_{60} amount released in 60 min or tablet friability, β_0 is the intercept, β_1 is the ratio of maltose to dical, and β_2 is tablet-breaking strength. In addition, x_{ij} is the variable corresponding to the ratio of maltose to dical (x_{i1}) and tablet-breaking strength (x_{i2}), and ε_i is the random error associated with each measurement. As with Eq. (1), the interaction action terms were not statistically significant in Eq. (3), and hence omitted.

For tablet friability, Eq. (3) has good fit with an r^2 of 0.92, and based on the *F*-value, the overall p value $\ll$0.001. Again, careful analysis of sums of squares for the individual parameters indicates that as the percentage maltose and tablet-breaking strength p value = 0.0015 and p value $\ll$0.001, respectively, had a significant effect on tablet friability. The regression coefficients β_1 and β_2 also were −0.00397 and −0.107, respectively. This means as the percentage of maltose increases, the friability is reduced, and as expected, tablets with greater breaking strength were less friable.

For dissolution based on Q_{60} statistical analysis showed that the equation had a good fit to Eq. (3) with a r^2 of 0.81 and based on the *F*-value the overall p value $<$ 0.0001. Analysis of sums of squares for the individual factors shows that maltose ratio and tablet-breaking strength had a significant effect on dissolution, p value $\ll$0.001 and p value = 0.0049, respectively. The final regression model was

$$y = 89.445 + 0.21336x_1 + -1.1982x_2 \quad (4)$$

showing that as tablet-breaking strength decreases and as the percent maltose goes up, the dissolution rate increases. Interaction plots[16] for both friability and dissolution rate showed very little interaction with breaking strength and the effect of maltose percentage; in other words, breaking strength and maltose percentage influence friability and tablet dissolution independently.

Figure 6 summarizes the dissolution data presented in Fig. 5; please note the standard deviations are given in Table 7. The Q_{60} data show that for the 100% dical formulations as the breaking strength increases, the Q_{60} dissolution decreased from 84% to 67%, whereas the 100% maltose decreased from 101% to 97% and the 25%, 50%, and 75% formulations showed behavior in between these two limits. This indicates that one must be careful when making tablets because the poor control over compression could retard dissolution to the point of failing to meet USP specifications. The data also show that the addition of maltose can minimize the effect of compression pressure on the retardation of dissolution.

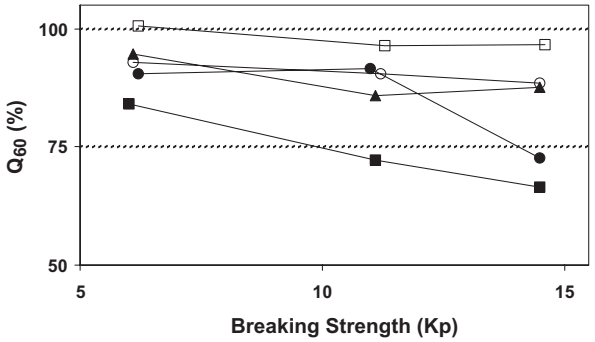

Figure 6. Folic acid dissolution, Q_{60} vs. tablet breaking strength, for multivitamin formulations given in Table 7 and Fig. 6: maltose to dical percentage (□) 100%, (○) 75%, (▲) 50%, (●) 25%, and (■) 0% maltose.

Particle Size and Folic Acid Dissolution

A formulation containing multivitamins (200 mg), minerals (1000 mg), 500 mg of filler (80% maltose/dical), Mg stearate (1% w/w), and (1% w/w) Ac-Di-Sol were used to study the effect of folic acid particle size on dissolution. The particle sizes and surface areas of the folic acid studied are given in Table 3. These tablets were made as before with compression forces of 500 and 1500 kgf, which produced tablets with hardness of 3.0 and 20 kP, respectively. The Ferret's diameters for the folic acid particles used were 24.4 and 9.0 μm. The dissolution results are shown in Fig. 7. Although the formulations made with the 9.0-μm particles had a slightly higher amount released at 60 min, the difference was not statistically significant from the 24.2-μm particles; this trend was observed for both pressures. These results show that in the range of particle sizes studied the matrix has more influence than the particle size, indicating, once again, the exposure to folic acid to the solvent (i.e., disintegration) can be the rate-limiting step in dissolution. These results do not mean that folic acid particle size is not important, but formulations of the type studied that use particles with a Ferret's diameter less than about 25-μm should meet USP dissolution standards for folic acid.

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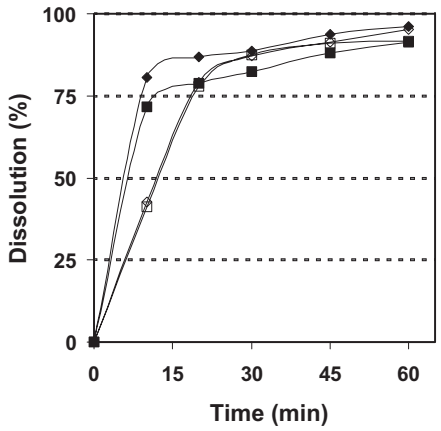

Figure 7. Folic acid dissolution from the optimization of multivitamin tablet formulations given in Table 7 where (◆) 9.04 μm and 500 kgf, (■) 24.4 μm and 500 kgf, (◇) 9.04 μm and 1500 kgf, and (□) 24.4 μm and 1500 kgf.

Conclusion

The goal of this study was not to come up with the definitive formulation but to identify and characterize some common formulation and processing parameters that could lead to dissolution failure. Statistical analysis found no significant interactions between the parameters studied, which means they act independently and in an additive manner. The results also show that no one factor is completely responsible for dissolution failure. Thus, it is the combination of formulation factors and processing conditions that collectively add up to produce dissolution failure. In addition, our results show that certain excipients can make a formulation more robust (i.e., less sensitive) to factors that can adversely affect dissolution, tablet-breaking strength, and friability. For example, the addition of maltose increased the dissolution rate and made the formulation less sensitive to compaction pressure (see Fig. 4), and maltose had the added benefit of improving tablet-crushing strength and friability. Thus, the use of excipients, such as maltose and a "super" disintegrant, can make a more robust system that can better withstand the inevitable variations that will occur during commercial manufacturing.

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