Chemical Stability of an Ester Prodrug of a Glycoprotein IIb/IIIa Receptor Antagonist in Solid Dosage Forms

SHERIF I. FARAG BADAWY,* REED C. WILLIAMS, AND DONNA L. GILBERT

Contribution from *Pharmaceutical R&D, DuPont Pharmaceuticals Company, Experimental Station, P.O. Box 80400, Wilmington, Delaware 19880-0400.*

Received August 12, 1998. Accepted for publication January 21, 1999.

Abstract □ DMP 754 is an ester prodrug of a glycoprotein IIb/IIIa receptor antagonist that undergoes ester and amidine hydrolysis in the presence of excipients. A means for the stabilization of DMP 754 was needed for the formulation of a stable drug product. Incorporation of a pH modifier in the formulation was used to control the microenvironment pH to coincide with that of maximum stability for DMP 754. Stability of tablets and capsules manufactured by (a) trituration process, (b) dry granulation process, and (c) wet granulation process was evaluated in HDPE bottles. Formulations manufactured by the dry and wet granulation processes contained disodium citrate as the pH modifier. Although aqueous wet granulation of a hydrolyzable drug is usually avoided, tablets and capsules manufactured by wet granulation were more stable in this case than those manufactured by the dry granulation process. This was attributed to the more uniform distribution of the pH modifier. Although the compression process resulted in enhanced degradation of the binary blend of DMP 754 and anhydrous lactose, tablets manufactured by the wet granulation process were more stable than capsules manufactured by the same process. Decreasing excipient-to-drug ratio enhanced the stability of tablets manufactured by the wet granulation process.

Introduction

DMP 754, the acetate salt of (*R*)-methyl 3-[[[3-[4-(aminoiminomethyl)phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino]-*N*-(butoxycarbonyl)-L-alanine, is an ester prodrug of platelet IIb/IIIa glycoprotein receptor antagonist.[1,2] DMP 754 drug substance is crystalline and was found to exhibit good stability in the solid state. DMP 754 degradation in the solid state was significantly enhanced in the presence of different excipients, and the rate of degradation was proportional to the excipient:drug ratio. Among all the fillers tested, anhydrous lactose showed the lowest rate of DMP 754 degradation. However, DMP 754 showed significant degradation in the presence of anhydrous lactose at high excipient-to-drug ratios. A means for the stabilization of DMP 754 in solid dosage forms was needed since it is a potent drug that is present at low concentration in the drug product. The two main degradation products isolated in the solid state (Figure 1) were the ester hydrolysis product (XV459) and the amidine hydrolysis product (SJ459). Enhanced hydrolysis of DMP 754 in the presence of lactose was attributed, at least partly, to lactose catalysis, since lactose was shown to provide concentration-dependent catalysis of ester and amidine degradation in solution.[3] While catalysis of esters by sugars and polyhydric alcohols in aqueous solutions was reported,[4] this effect was not previously shown for the amidine group.

* Corresponding author. Phone: 302-695-9116. Fax: 302-695-7592. E-mail: sherif.i.badawy@dupontpharma.com.

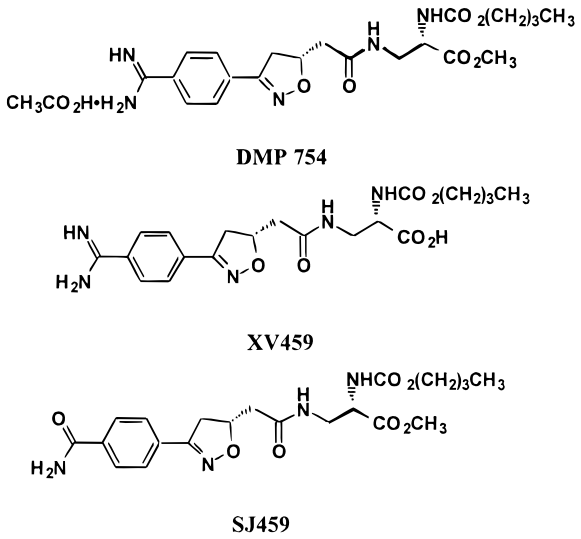

Figure 1—Structure of DMP 754 and degradation products, XV459 and SJ459.

Hydrolysis rate of DMP 754 in the presence of lactose was found to be dependent on the microenvironment pH. The hydrolysis rates of the ester and amidine groups of DMP 754 in lactose blends were altered by incorporation of acidic components in the blend. The use of pH modifiers to decrease the degradation rate in the solid state was previously reported.[5,6] However, the rationale for the choice of particular pH modifier was generally lacking. The effect of an acid on the microenvironment pH of DMP 754 was predicted by the saturated solution pH of the acid.[3] The ester group attained maximum stability with acids having saturated solution pH of approximately 4. On the other hand, the amidine group showed increased stability with the more acidic modifiers having saturated solution pH values as low as 0.4. Hydrolysis rate of amidines was reported to decrease as the acidity of the reaction medium increased.[7] Disodium citrate (saturated solution pH of 4.6) was the only acid tested that improved the stability of both groups. Stability of DMP 754 in the solid state can, therefore, be improved by the use of an appropriate acid that adjusts the microenvironmental pH to approximately 4.

The purpose of this study was to develop a stable oral solid dosage form for DMP 754. The formulation and manufacturing process were selected to maximize DMP 754 stability. Disodium citrate was included in the formulation as a pH modifying agent, in an attempt to control the microenvironment pH to that of maximum stability for DMP 754 as mentioned earlier. The effect of the manufacturing process on DMP 754 stability was also evaluated. Although aqueous wet granulation is usually avoided for a hydrolyzable drug,[8] both dry and wet processes were evaluated for the manufacture of DMP 754 drug product. Method of incorporation of a pH modifier can affect the

10.1021/js9803297 CCC: $18.00
Published on Web 03/02/1999

Table 1. Summary of DMP 754 Formulations

ingredients	concentration (% w/w)						
	physical blends		dry granulation	wet granulation			
DMP 754	0.33	0.33	0.33	0.33	0.8	1.7	0.33
disodium citrate	0	2.5	2.5	2.5	2.5	2.5	0
povidone	0	0	0	2.0	2.0	2.0	2.0
lactic acid	0	0	0	0	0	0	0.0083
magnesium stearate	0	0	1.0	1.0	1.0	1.0	1.0
anhydrous lactose	99.67	97.17	96.17	94.17	93.7	92.8	96.66
tablet or capsule strength (mg)	0.1	0.1	0.2	0.2	0.5	1.0	0.1
weight of tablet or capsule content (mg)	30	30	60	60	60	60	30

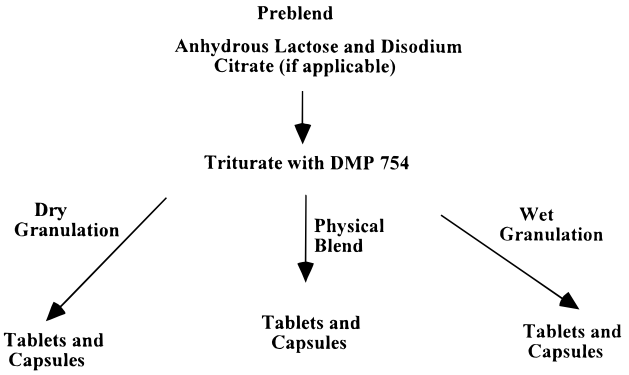

Figure 2—Summary of the manufacturing processes for DMP 754.

stability of the drug product.[6] Initially, the effect of compression and encapsulation on DMP 754 stability was examined for binary blends with anhydrous lactose. The effect of processing on the stability of drug product containing disodium citrate was then evaluated. Thus, stability of DMP 754 tablets and capsules containing disodium citrate and manufactured by a dry granulation (slugging) process or a wet granulation process was assessed.

Materials and Methods

Materials—DMP 754 was obtained from the Chemical Processing Research and Development Department of DuPont Pharmaceuticals Company and used as received. Mean particle size of DMP 754 was 11.5 μm. Anhydrous lactose, NF (Quest International Inc., Norwich, NY), was used as the filler. Disodium citrate sesquihydrate was supplied by Aldrich Chemical Co. (Milwaukee, WI). Other excipients used were magnesium stearate, NF (Mallinckrodt, St. Louis, MO), and povidone, USP (ISP, Wayne, NJ). HPLC grade trifluoroacetic acid (TFA) and glacial acetic acid were obtained from J. T. Baker, Phillipsburgh, NJ. HPLC grade acetonitrile (ACN) was obtained from EM Science (Gibbstown, NJ).

Equipment—Turbula T2C mixer (Willy A. Bachofen AG, Basel, Switzerland); Carver press (Fred S. Carver Inc., Menomonee Falls, WI); V-blender (Patterson-Kelley, East Stroudsburg, PA); Stokes single station press (Pennwalt Corporation, Warminster, PA); Key KG-5 high shear granulator (Key International, Englishtown, NJ); Zanasi AZ5 capsule filling machine (IMA, Fairfield, CT).

Methods—Table 1 summarizes the different DMP 754 formulations. Figure 2 shows a summary of the different manufacturing processes. Strength (or concentration) of DMP 754 in the various formulations represents that of the free base. Potency of DMP 754 was corrected for the assay value of the free base in the drug substance (use as value).

1. Preparation of Blends—A blend containing DMP 754 (0.33% w/w), disodium citrate (2.5% w/w), and anhydrous lactose (97.17% w/w), was prepared by a trituration process. DMP 754 was triturated with anhydrous lactose/disodium citrate preblend in a mortar and pestle using a geometric dilution technique. Another blend of DMP 754 (0.33% w/w) and anhydrous lactose (99.67% w/w) without disodium citrate was also prepared by a similar trituration process.

2. Preparation of Capsules and Tablets from the Binary Blend with Anhydrous Lactose—A binary blend of DMP 754 and anhydrous lactose, prepared by the above-mentioned method, was hand-filled into size 1 hard gelatin capsules (Capsugel, Greenwood, SC). Tablets were also manufactured by direct compression of the binary blend (no magnesium stearate) using the Carver press.

3. Preparation of Capsules and Tablets by the Dry Granulation Process—Capsules and tablets, 0.2 mg strength, containing 2.5% disodium citrate were prepared by a dry granulation process. Disodium citrate, DMP 754, and anhydrous lactose were blended with three-fourths the quantity of magnesium stearate using a V-blender with I-bar. The discharged blend from the V-blender was compressed into tablets (slugs) with a target weight of 200 mg on a Stokes single station press. The slugs were hand-screened through a 25-mesh screen and blended with the remaining amount of magnesium stearate in the V-blender. The resulting granulation was filled into size 3 hard gelatin capsules on the Zanasi capsule filling machine, or compressed into tablets on the Stokes single station press.

4. Preparation of Capsules and Tablets by the Wet Granulation Process—A formulation containing 2.5% disodium citrate was also manufactured by a wet granulation process. DMP 754 was blended with anhydrous lactose in the bowl of the high shear granulator. The blend was then granulated with an aqueous solution containing disodium citrate and povidone (pH of granulating solution was adjusted to 4 with 1 N hydrochloric acid). The wet granulation was screened through 8-mesh screen and dried in a vacuum oven at 40 °C to a moisture NMT 1.0% (determined by loss on drying at 105 °C). The dried granulation was screened through a 25-mesh screen and blended with magnesium stearate in a V-blender. The granulation was filled into hard gelatin capsules, or compressed into tablets similar to the dry granulation formulation. Various tablet strengths (0.2, 0.5, and 1.0 mg) were manufactured by the wet granulation process. Tablet weight was kept constant and the different strengths were obtained by changing the excipient-to-drug ratio.

In addition, DMP 754 tablets were manufactured by the above wet granulation process without disodium citrate. The formulation contained 0.0083% lactic acid added to the granulating solution. The pH of granulating solution was adjusted to 4 with 0.1 N sodium hydroxide. The formulation was similar to that mentioned above for the 0.2 mg tablets except for the substitution of lactic acid for disodium citrate.

5. Stability of Blends, Tablets and Capsules—Blends, tablets, and capsules were packaged into 40-cc high density polyethylene (HDPE) bottles capped with child-resistant caps. A 180 mg amount of the blend was accurately weighed into a bottle without desiccant, and the bottle was capped, torqued, and induction sealed. Capsules and tablets were packaged into the HDPE bottle in counts of ten or six, respectively, with or without desiccant (0.6 g silica gel). The packaged HDPE bottles were stored in stability chambers at 30 °C/60% RH and/or 40 °C/75% RH. The bottles were pulled at different time intervals, and the contents were analyzed for DMP 754 and degradation products by the HPLC method described below.

6. Analytical Method—An HPLC system equipped with automatic sampler, heated column compartment, gradient elution pump, and variable wavelength UV detector set at 280 nm (Model 1050/Hewlett Packard) was used for analysis of the blend, capsule, and tablet samples. The reverse phase HPLC assay method utilized a Waters Symmetry C-18 column (15 × 0.4 cm, 5 μm packing) with a mobile phase of 18:82 ACN/0.05% TFA in water

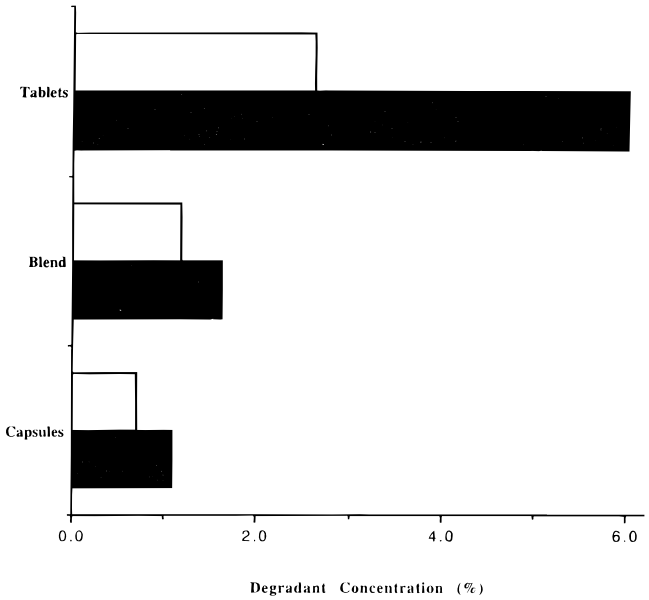

Figure 3—Percent degradation products of DMP 754 in binary blends (without magnesium stearate) after four weeks at 40 °C/75% RH. SJ459, (□); XV459, (■).

delivered at a flow rate of 1.5 mL/min and column temperature of 35 °C. The degradation products method also used a Waters Symmetry C-18 column with gradient elution of the mobile phase from 10:90 to 60:40 ACN/0.05% TFA in water over 30 min at a flow rate of 1.5 mL/min and a column temperature of 35 °C.

The blend samples were prepared by adding 30 mL of 14:86 ACN/0.05% glacial acetic acid in water to the HDPE bottles containing the blends and shaking for 30 min. The solution was then filtered as needed through 0.45 μm syringeless filter (Whatman, Clifton, NJ). In the case of tablets and capsules, 10 dosage units were dissolved in 14:86 ACN/0.05% glacial acetic acid in water, and the solution was filtered through the 0.45 μm syringeless filter. An external standard method was used for the assay and degradation products analysis.

The HPLC method was validated for linearity, accuracy, precision, limit of quantitation, and specificity. Studies with spiked placebo samples showed recoveries of 99.5% with method repeatability of 0.6% RSD. Specificity was determined by stressing samples with heat and light and by chromatographing known impurities; no peaks were found to coelute with the known degradants. Studies with degraded samples showed mass balance of drug substance and degradation products. Methods were linear over the range of study, and limit of quantitation of degradants was measured to be 4 ng/mL which was equivalent to 0.02% of drug substance in blends. Samples showed no degradation in the extraction solvent for up to 4 days.

7. X-ray Microanalysis—Citrate distribution in the tablets manufactured by the dry and wet granulation processes was evaluated by determining the sodium distribution on the tablet surface using X-ray analysis in the electron microscope. Citrate exists as sodium salt in the formulation, and therefore sodium distribution is expected to reflect the extent of citrate distribution in the sample. Intact tablet samples were mounted on aluminum stubs, carbon-coated, and examined using a Cameca electron microprobe fitted with a Wavelegth Dispersive Spectrometry (WDS) detector.

8. Moisture Uptake Studies—Moisture uptake by the granulation was determined at 25 °C using VTI MB 300G Integrated Microbalance System (VTI Corporation) from 40% RH to 90% RH with desorption to 10% RH. All transitions were in incremental steps of 10% RH.

Results and Discussion

1. Stability of DMP 754 Binary Blends with Anhydrous Lactose—Encapsulation and compression affected the stability of DMP 754 in the binary blend with anhydrous lactose. The encapsulation of the lactose/DMP 754 blend into hard gelatin capsules decreased drug degradation. The stabilizing effect of encapsulation was comparable for the ester and the amidine groups. The encapsulation of the blend reduces the surface area of the blend exposed to the environment and can decrease the rate of penetration of water vapor into the powder bed. The capsule shell can also act as a barrier that water vapor has to penetrate before it reaches the blend. This is particularly true if the gelatin shell is more hygroscopic than the blend and can consequently act as a "desiccant". Thus, encapsulation can prolong the time that it takes the moisture content of powder bed to equilibrate with water vapor pressure at 75% RH, which may be the reason for the improved stability of blends encapsulated into hard gelatin shells. To the contrary, tableting of the DMP 754/lactose blend enhanced drug degradation (Figure 3). Tableting increases the number of contact points between lactose and DMP 754. This would possibly enhance lactose catalysis and also increase the rate of moisture transfer between lactose and the drug, thus resulting in an increased rate of drug degradation in the tablets as compared to the blends. Despite the low concentration of moisture associated with anhydrous lactose (approximately 0.5% at 75% RH), this moisture corresponds to high water:drug molar ratio due to the small amount of DMP 754 in the blend and the low

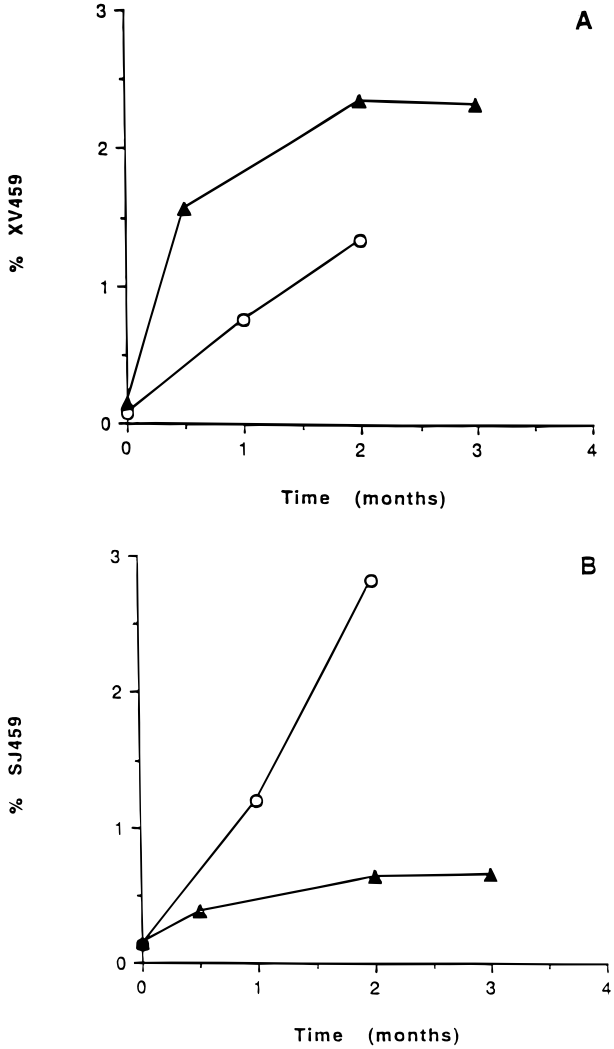

Figure 4—Percent degradation products of DMP 754: (a) XV459 and (b) SJ459 in blend with 2.5% disodium citrate, (○); and capsules with 2.5% disodium citrate manufactured by the dry granulation process, (▲); packaged in HDPE bottles without desiccant and stored at 40 °C/75% RH.

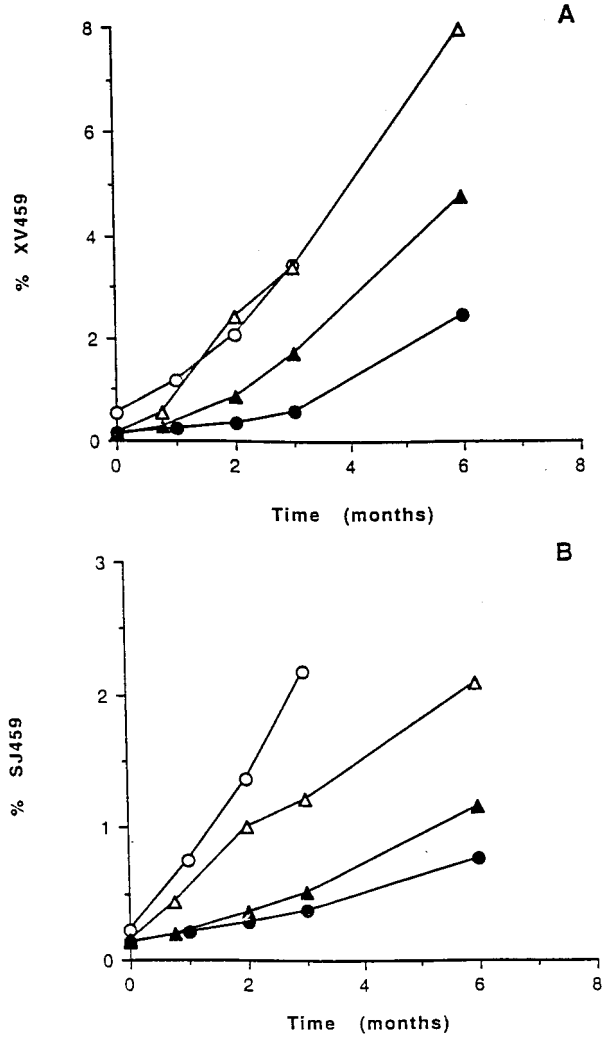

Figure 5—Percent degradation products of DMP 754: (a) XV459 and (b) SJ459 in capsules and tablets packaged in HDPE bottles with desiccant and stored at 40 °C/75% RH. Capsules manufactured by wet granulation process, (▲); capsules manufactured by dry granulation process, (△); tablets manufactured by wet granulation process, (●); tablets manufactured by dry granulation process, (○).

molecular weight of water. The destabilizing effect of tableting appeared to be more pronounced for ester hydrolysis than amidine hydrolysis. Thus, processing influences the stability of DMP 754.

2. Stability of DMP 754 Drug Product Manufactured by Dry Granulation Process—Capsules containing disodium citrate manufactured by dry granulation showed enhanced ester hydrolysis compared to the corresponding blend with disodium citrate in the same packaging configuration at 40 °C/75% RH. On the other hand, the dry granulation process resulted in diminished amidine hydrolysis compared to the blend (Figure 4). The dry granulation process for capsules involves the destabilizing effect of slugging (compression) and the stabilizing effect of encapsulation as mentioned above. On the basis of results from the binary blends, capsules manufactured by the dry granulation process would be expected to have higher ester and amidine degradation rates since the destabilizing effect of tableting was shown to be more pronounced than the stabilizing effect of encapsulation for both groups. The same effect of the dry granulation process on stability was also observed for a similar formulation without disodium citrate. Thus, the effect of the dry granulation process on amidine hydrolysis was not predicted by the blend studies. It is possible that this discrepancy may be due to magnesium stearate, which is not present in the binary blend. Magnesium stearate is known to have the ability to coat individual particles in a pharmaceutical formulation.[9] This can act as a barrier that protects DMP 754 from lactose catalysis, which is an important factor in the solid-state hydrolysis of the amidine group.[3]

Tablets manufactured by the dry granulation process showed comparable ester stability to the corresponding capsule formulation manufactured by the same process in the same packaging configuration at 40 °C/75% RH. However, the amidine group appeared to be even less stable in the tablet formulation (Figure 5).

3. Stability of DMP 754 Drug Product Manufactured by the Wet Granulation Process—DMP 754 capsules, 0.2 mg, manufactured by wet granulation process were more stable when stored at 40 °C/75% RH compared to capsules manufactured by the dry granulation process in the same packaging configuration (Figure 5). A similar trend was also observed at 30 °C/60% RH. The rates of

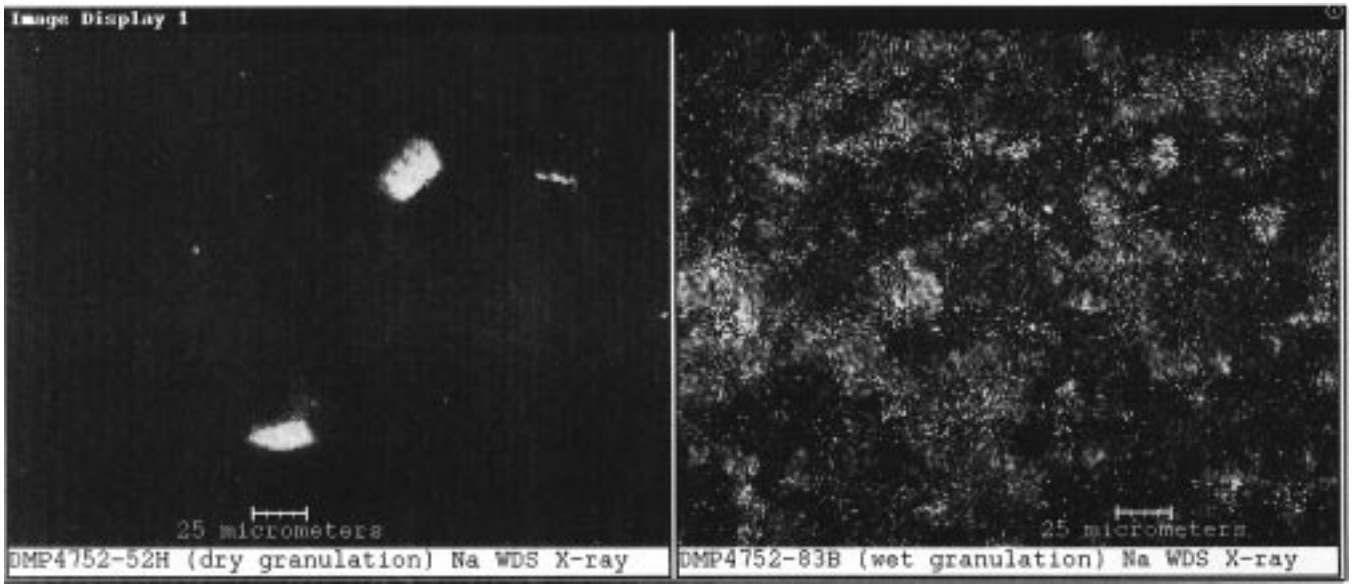

Figure 6—Distribution of sodium in DMP 754 tablets manufactured by dry granulation (left) and wet granulation (right). The intensity of the white areas is proportional to sodium concentration.

Table 2. Degradation of DMP 754 in Tablets and Capsules after 3 Months at 40 °C/75% RH

	disodium citrate concentration (%)	strength (mg)	moisture content (%)[a]	degradation product	
				XV459	SJ459
capsules/dry granulation	2.5	0.2	0.7	3.41	1.22
tablets/dry granulation	2.5	0.2	0.7	3.44	2.18
capsules/wet granulation	2.5	0.2	2.5	1.72	0.51
tablets/wet granulation	2.5	0.2	1.5	0.59	0.37
tablets/wet granulation	2.5	0.5	1.2	0.46	0.32
tablets/wet granulation	2.5	1.0	1.4	0.28	0.25
tablets/wet granulation	0[b]	0.1	1.5[c]	1.36[c]	2.00[c]

[a] Moisture of tablet or capsule content determined by Karl Fischer assay after 3 months at 40 °C/75% RH. [b] Contains 0.0083% lactic acid. [c] Two months timepoint.

degradation of the ester and amidine groups were lower for the wet granulation capsules than for the dry granulation capsules. The higher stability of capsules manufactured by wet granulation may be explained by the more uniform distribution of the citrate in this formulation. Adding the citrate to the granulating solution leads to intimate contact of this acidic component with the drug and other formulation components, resulting in a better control of the microenvironment pH. The granulating solution wets the particles, and when the water evaporates, the citrate is in close contact with the formulation constituents. Sodium distribution was found to be more diffuse in the wet granulation sample compared to localized distribution in the dry granulation sample, thus suggesting a more uniform distribution of the citrate in the former formulation (Figure 6).

Moisture content of capsules manufactured by the wet granulation process was higher than those manufactured by the dry granulation process. Capsule moisture content at time zero, determined by a Karl-Fisher titration, was found to be 0.6% and 2.0% for the dry and wet formulations, respectively. The moisture content of capsules manufactured by wet granulation was also higher than those manufactured by dry granulation after 3 months of storage at 40 °C/75% RH (Table 2). The higher moisture content of the wet granulation formulation is attributed to two reasons. First, partial conversion to lactose monohydrate during the wet granulation process was observed by X-ray diffraction of the granulation manufactured by the wet process. Second, the formulation manufactured by the wet granulation process was found to be more hygroscopic than the dry granulation formulation as determined by moisture sorption−desorption isotherms for the two formulations. Percent weight gain of the granulation upon the increase of relative humidity from 40% to 90% was 1.7% and 6.5% for the dry and wet formulations, respectively. Although the increased hygroscopicity of a formulation is generally expected to increase the degradation rate of a moisture sensitive drug, the effective microenvironment pH control in the case of the wet granulation formulation was a key factor for the stability of this formulation. The microenvironment pH control in the case of the wet granulation formulation was probably able to compensate for the increased hygroscopicity, resulting in a more stable dosage form than the less hygroscopic dry granulation formulation, which lacked effective pH control.

DMP 754 tablets, 0.2 mg, compressed from the granulation manufactured by the wet process were more stable than the capsules filled with the same granulation at 40 °C/75% RH (Figure 5). DMP 754 degradation was more pronounced at 40 °C/75% RH than at 30 °C/60% RH. At both conditions, ester and amidine hydrolysis rates were lower in the tablet dosage form. The higher degradation rate in the case of capsules may be due to the moisture associated with capsule shell. Due to the hygroscopic nature of the formulation manufactured by wet granulation, moisture may be transferred from the capsule shell to the granulation, which is in direct contact with the gelatin shell. Capsules manufactured by wet granulation showed higher moisture content than tablets (Table 2). In the case of the wet granulation formulation, compression did not demonstrate the destabilizing effect observed for the dry blends. Increasing the number of contact points in the case of granulation manufactured by the wet process did not result in enhanced degradation, probably due to the control of microenvironment pH. Stability of tablets manufactured by the wet granulation process increased with the decrease of the excipient-to-drug ratio. Thus, the

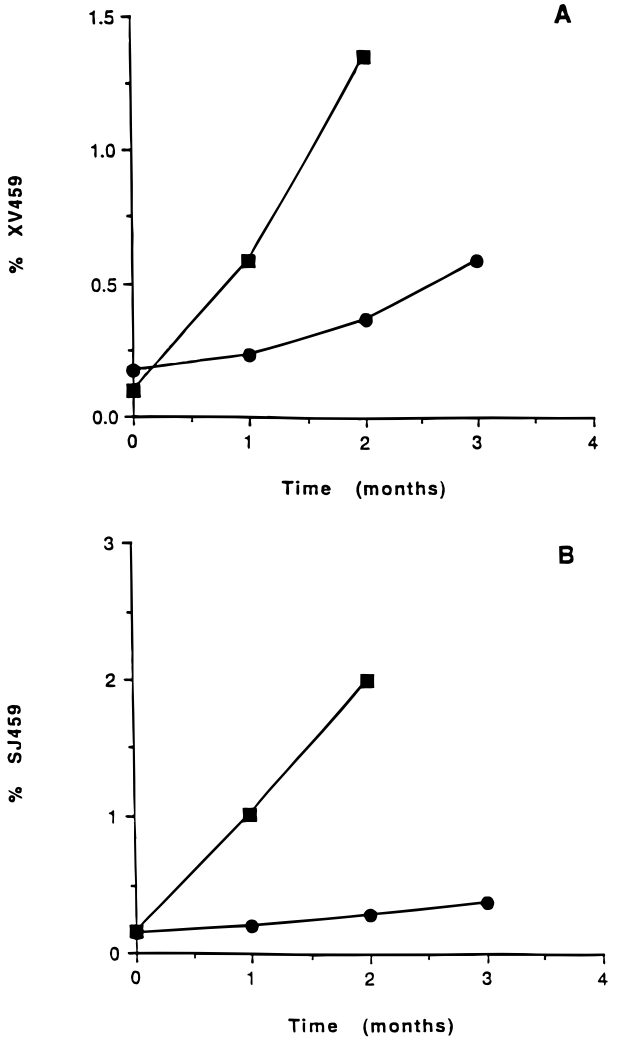

Figure 7—Percent degradation products of DMP 754: (a) XV459 and (b) SJ459 in tablets manufactured by the wet granulation process. Tablets are packaged in HDPE bottles with desiccant and stored at 40 °C/75% RH. Tablets containing 2.5% disodium citrate, (●); tablets without disodium citrate, (■).

1.0 mg tablet showed the least degradation among the three strengths followed by the 0.5 mg tablet, while the 0.2 mg tablet demonstrated the highest rate of degradation (Table 2).

The stabilizing effect of disodium citrate was further demonstrated by the instability of tablets without disodium citrate. Although this formulation was manufactured using a granulating solution buffered to pH 4 with lactate, these tablets showed a higher degradation rate than for the tablets with disodium citrate (Figure 7). The very low concentration of lactate (0.0083% of the total weight of the formulation) was probably insufficient to control the microenvironment pH in the tablets. This was shown by measuring the pH of a slurry prepared by mixing 0.5 g of the granulation with 0.5 g of water. The pH values of the slurries prepared from the granulations with disodium citrate and lactate were found to be 4.4 and 7.7, respectively.

Conclusions

A stable solid dosage form containing a pH modifying agent was developed for DMP 754. The choice of the manufacturing process was critical to the stability of the drug product. The stability of DMP 754 in the dosage form was maximized by the inclusion of the pH modifying agent and the selection of the appropriate manufacturing process. Method of incorporation of an acidic ingredient affects its ability to control the microenvironment pH of a hydrolyzable drug such as DMP 754 and, hence, the stability of the drug product. Depending on the nature of the moisture-sensitive drug and the formulation, the dry granulation process may not be the process of choice. The wet granulation process can yield a more stable drug product for a hydrolyzable drug if the formulation contains a pH modifying agent that controls the pH of the microenvironment. Excipient-to-drug ratio can also be modified in order to maximize drug product stability.

References and Notes

1. Mousa, S. A.; Bozarth, J.; Forsythe, M.; Xue, C. B.; Wityak, J.; Olson, R.; Thoolen M. J.; Reilly, T. M. Discovery of a Novel Non Peptide Antiplatelet GPIIb/IIIa Receptor Antagonist, DMP 754: Receptor Binding Afffinity and Specificity. *Circulation* **1996**, *94(8)*, I-513.
2. Racanelli, A. L.; Kapil, R. P.; Mousa, S. A.; Reilly T. M.; Thoolen, M. J. Oral Antiplatelet Effects of DMP 754 in Dogs and Nonhuman Primates. *Circulation* **1996**, *94(8)*, I-98.
3. Badawy, S. I. F.; Williams, R. C.; Gilbert, D. L. Effect of Different Acids on Solid State Stability of an Ester Prodrug of a Glycoprotein IIb/IIIa Receptor Antagonist. Accepted for publication in *Pharm. Dev. Technol.*, in press.
4. Kallion, R. B.; Stella, V. J. The Nucleophilicity of Dextrose, Sucrose, Sorbitol and Mannitol with *p*-Nitrophenyl Esters in Aqueous Solution. *Int. J. Pharm*. **1990**, *66*, 149−155.
5. Brandl, M.; Magill, A.; Rudraraju, V.; Gordon, M. S. Approaches for Improving the Stability of Ketorolac in Powder Blends. *J. Pharm. Sci*. **1995**, *84(10)*, 1151−1153.
6. Gu, L.; Strickley, R. G.; Chi L. H.; Chowhan, Z. T. Drug-Excipient Incompatibility Studies of the Dipeptide Angiotensin-Converting Enzyme Inhibitor, Moexipril Hydrochloride: Dry Powder vs Wet Granulation. *Pharm. Res*. **1990,** *7(4)*, 379−383.
7. De Wolfe, R. H. Kinetics and Mechanisms of Reactions of Amidines. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; John Wiley & Sons Ltd.: New York, 1975; p 354.
8. Carstensen, J. T. *Drug Stability: Principles and Practice*; Marcel Dekker Inc.: New York, 1990; p 165.
9. Peck, G. E.; Baley, G. J.; McCurdy, V. E. Tablet Formulation and Design. In *Pharmaceutical Dosage Forms: Tablets*; Liberman, H. A., Lachman, L., Schwartz, J. B., Eds.; Marcel Dekker Inc.: New York, 1989; Vol. 1, p 111.

Acknowledgments

The authors are thankful to Janet F. Edwards and Kathleen L. Reilly for their assistance in the HPLC analysis and to James L. Long and Anthony J. Gawronski for their help with the manufacturing process. The authors also thank C. Michel for performing the X-ray microanalysis and R. Vickery for his help with the moisture uptake studies.

JS9803297