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International Journal of Pharmaceutics 223 (2001) 81–87

international journal of pharmaceutics

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Note

Effect of salt form on chemical stability of an ester prodrug of a glycoprotein IIb/IIIa receptor antagonist in solid dosage forms

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Received 21 September 2000; received in revised form 4 January 2001; accepted 18 April 2001

Abstract

The effect of salt form on the stability of an ester prodrug of a IIb/IIIa receptor antagonist was investigated. The pH of maximum stability for the ester prodrug is approximately 4. The mesylate salt is thought to provide lower microenvironment pH, closer to the pH of maximum stability, than the acetate salt. Stability of drug product manufactured using the mesylate salt (DMP 755) was studied and compared with that for the acetate salt (DMP 754). Formulations contained disodium citrate as a pH modifier to control formulation pH, since solid state stability for this compound is dependent on the microenvironment pH. The pH modifier was not able to achieve adequate microenvironment pH control for the DMP 754 drug product when added using a dry manufacturing process. While DMP 754 required the use of a pH modifier added in solution during wet granulation in order to improve drug product stability, DMP 755 was able to achieve similar results using the dry granulation process. Stability of DMP 755 drug product was independent of effectiveness of the pH modifier. This study showed that the choice of the salt form may provide an alternative for maximizing drug product stability. © 2001 Dupont pharmaceuticals company.

Keywords: Salt form; DMP 754; Microenvironment PH; Stability

1. Introduction

DMP 754 and DMP 755 are the acetate and mesylate salts, respectively, of (R)-methyl 3-[[[3-[4-(aminoiminomethyl)phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]amino] - *N* - (butoxycarbonyl) - L - alanine, an ester prodrug of platelet IIb/IIIa glyco

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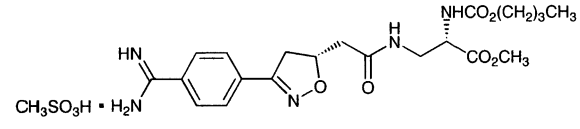
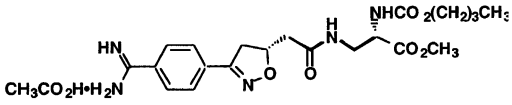
0378-5173/01/$ - see front matter © 2001 Dupont pharmaceuticals company.
PII: S0378-5173(01)00726-8

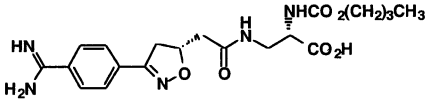
protein receptor antagonist (Mousa et al., 1996; Racanelli et al., 1996). DMP 754 drug substance was found to be crystalline and exhibited good stability in the solid state. However, it has been shown earlier that DMP 754 degradation in the solid state is significantly enhanced in the presence of common pharmaceutical excipients particularly at high excipient to drug ratios (Badawy et al., 1999a,b). The two main degradation products isolated in the solid state (Fig. 1) were the ester hydrolysis product (XV459) and the amidine hydrolysis product (SJ459). Hydrolysis rate of DMP 754 in the presence of lactose was dependent on the microenvironment pH. Lactose and DMP 754 have a saturated solution pH of approximately 6 and 6.8, respectively. Consequently, the pH of the microenvironment for the drug particles is expected to be in this range, which is approximately



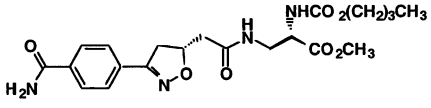
DMP 755



DMP 754



XV459



SJ459

Fig. 1. Structure of DMP 754, DMP 755 and degradation products, XV459 and SJ459.

Table 1
Physical properties of DMP 755 (mesylate salt) and DMP 754 (acetate salt)

	DMP 754	DMP 755
Solubility (mg/ml)	10	>100
Solution pH	6.8	2
Melting point (°C)	213	158

2–3 pH units higher than the pH of maximum stability for DMP 754 in solution (Rabel et al., 1997). Hydrolysis rates of the ester and amidine groups of DMP 754 in lactose blends were altered by incorporation of acidic components in the blend. Stability of DMP 754 in solid blends was improved by the use of an appropriate pH modifier, such as disodium citrate, that adjusts the microenvironmental pH to approximately 4.

Solid state hydrolysis rates of the ester and amidine groups can potentially be decreased by the use of a salt of a stronger acid. Although the pH of the microenvironment in a solid formulation has been implicated as an important factor for the stability of a compound (Brandl et al., 1995; Gu et al., 1990), very few reports, if any, have attempted to maximize stability by the use of a salt form that can provide optimum microenvironment pH. DMP 755 is a crystalline salt of methanesulfonic acid that has a lower pK_a than acetic acid (-1.2 vs. 4.76). As a result, the pH of a concentrated solution of DMP 755 is approximately 2 compared with 6.8 for a saturated solution of the acetate salt (DMP 754). The use of the methanesulfonic acid (mesylate) salt is, therefore, expected to provide a lower microenvironment pH than the acetate salt. This would enhance the stability of the amidine group since it showed continuous increase in stability with the decrease in microenvironment pH. The lower pH could also improve the stability of the ester group provided the microenvironment pH does not drop below 4, which is the pH of maximum stability for the ester group. Physical properties of DMP 755 and DMP 754 are summarized in Table 1. The purpose of this work is to evaluate the stability of the mesylate salt in binary blends with lactose and in solid dosage forms. Stability of the mesylate

salt (DMP 755) is compared with that of the acetate salt (DMP 754) in similar formulations manufactured by the same manufacturing processes.

2. Materials and methods

2.1. Materials

DMP 754 and DMP 755 were obtained from the Chemical Processing Research and Development Department of DuPont Pharmaceuticals Company and was used as received. Anhydrous lactose, NF was obtained from Quest International Inc. (Norwich, NY). Disodium citrate sesquihydrate was supplied by Aldrich Chemical Company (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).

2.2. Methods

2.2.1. Preparation of blends

A binary blend containing DMP 754 or DMP 755 (0.33% w/w) and anhydrous lactose (99.67% w/w), was prepared by a trituration process. DMP 754 or DMP 755 were triturated with anhydrous lactose in a mortar and pestle using a geometric dilution technique. The blend was hand-filled into size 1 hard gelatin capsules (150 mg per capsule).

2.2.2. Preparation of capsules by the dry granulation process

Capsules, 0.2 mg strength, containing 2.5% disodium citrate were prepared by the dry granulation process described earlier Badawy et al., 1999b). The final granulation was filled into size 3 hard gelatin capsules (Capsugel, Greenwood, SC) on a Zanasi capsule filling machine (60 mg per capsule). A batch of DMP 755 capsules without disodium citrate, 0.2 mg strength, was also manufactured using the same process.

2.2.3. Preparation of tablets by the wet granulation process

A formulation containing 2.5% disodium citrate was manufactured by a wet granulation process (Badawy et al., 1999b). The granulation was compressed into tablets (0.2 mg strength; 60 mg tablet weight).

Table 2 shows a summary of the different DMP 754 and DMP 755 formulations.

Table 2
Summary of DMP 754 and DMP 755 formulations

Ingredients	Composition (% w/w)[a]		
	Binary blend	Dry granulation	Wet granulation
DMP 754 or DMP 755	0.33	0.33	0.33
Disodium citrate	0	2.5[b]	2.5
Povidone	0	0	2.0
Magnesium stearate	0	1.0	1.0
Anhydrous lactose[c]	99.67	96.17	94.17
Tablet or capsule strength (mg)	0.5	0.2	0.2
Weight of tablet or capsule content (mg)	150	60	60

[a] Strength (or concentration) of the active in the various formulations represents that of the free base.

[b] An additional batch of DMP 755 capsules was manufactured without disodium citrate. Disodium citrate was replaced by anhydrous lactose.

[c] Theoretical amount of lactose based on free base. Actual amount was adjusted based on the use as value of the salt used in order to give the total tablet or capsule weight specified.

2.2.4. Stability of drug substance

Stability of drug substance was evaluated in an open dish at 40 °C/75% RH. Samples were removed at different time intervals and analyzed for degradation products by the HPLC method reported earlier (Badawy et al., 1999a).

2.2.5. Stability of tablets and capsules

Hand-filled capsules containing the binary blend were packaged into 40-cc high density polyethylene (HDPE) bottles capped with child-resistant caps. Two capsules were placed in the bottle without desiccant, and the bottle was capped, torqued, and induction sealed. Capsules and tablets manufactured by the dry and wet granulation processes were packaged into HDPE bottle in counts of ten or six, respectively, with desiccant (0.6 g silica gel). The packaged HDPE bottles were stored in stability chambers at 40 °C/75% RH and 50 °C (ambient humidity). The bottles were pulled at different time intervals, and the contents were analyzed for potency and degradation products by the HPLC method described earlier (Badawy et al., 1999a,b).

3. Results and discussion

Similar to DMP 754, DMP 755 drug substance showed minimal or no increase in degradant concentration when stored at 40 °C/75% RH in an open dish, which shows that the drug substance for both salt forms is stable at this condition (Table 3). Both salt forms are non-hygroscopic and neither one picks-up any appreciable quantity of moisture. The two salts showed higher degradant concentrations in their binary mixtures with lactose compared with the drug substance, despite the fact that these mixtures were stored in sealed HDPE bottles rather than an open dish (Table 3). In an earlier report, this increased degradation for the acetate salt was attributed, at least partly, to the catalytic effect of lactose, which provided concentration-dependent catalysis of DMP 754 hydrolysis in solution (Badawy et al., 1999a). It is noteworthy that the mesylate salt was more stable than the acetate salt in the binary blend after 4 weeks at 40 °C/75% RH and 50 °C.

Table 3
Degradant concentrations in drug substance and binary blend-filled hard gelatin capsules after storage for 4 weeks

	Moisture content (%)[a]	Degradation product (%)	
		XV459	SJ459
DMP 754 drug substance			
Time zero	0.0	<0.1	0.11
40°C/75% RH	0.2	0.11	0.13
DMP 754 binary blend			
Time zero	0.3	0.21	0.29
40°C/75% RH	1.3	1.08	0.70
50°C	0.6	1.25	0.99
DMP 755 drug substance			
Time zero	0.1	<0.1	<0.1
40°C/75% RH	0.0	<0.1	<0.1
DMP 755 binary blend			
Time zero	0.3	<0.10	<0.10
40°C/75% RH	0.4	0.42	0.29
50°C	0.2	0.41	0.34

[a] Moisture content determined by a Karl Fischer assay.

Stability of drug product for DMP 755 was compared with that of DMP 754 manufactured by the same process. In an earlier report, it was found that addition of the pH modifier (disodium citrate) in solution, during wet granulation process, maximized the stability of DMP 754 in the dosage form compared with a dry granulation process. The wet granulation process resulted in a more uniform distribution of the acid and, hence, better control of the microenvironment pH (Badawy et al., 1999b). In addition, tablets were more stable than capsules for the wet granulation process, while the reverse was true for the dry process. In this study, comparison was made between the two salt forms using the more stable dosage form for the given manufacturing process (tablets for wet granulation and capsules for the dry process) (Figs. 2 and 3). DMP 755 capsules manufactured by the dry granulation process and containing disodium citrate showed remarkably lower rate of degradation than DMP 754 capsules manufactured by the same process. Moisture content, determined by a Karl Fischer assay, was comparable for the two capsules (0.7% for the

DMP 755 capsules and 0.8% for the DMP 754 capsules). These results can be interpreted utilizing knowledge of the previously established effect of microenvironment pH on the stability of this molecule in the solid sate. The high degradation rate for DMP 754 capsules manufactured by dry granulation shows the inability of disodium citrate to lower the pH of the formulation in this case. On the other hand, the mesylate salt is expected to have a lower microenvironment pH in the solid state, regardless of the effectiveness of the pH modifier, and hence demonstrated improved stability of the drug product manufactured by the dry process. DMP 755 capsules manufactured by the dry granulation process without disodium citrate showed comparable degradation rate to those containing disodium citrate, confirming the minimal contribution of the pH modifying agent to the stability of DMP 755 capsules.

It is noteworthy that DMP 755 capsules manufactured by dry granulation showed similar degradation rates to the DMP 754 tablets manufactured by wet granulation. Knowing the sensitivity of this molecule to the microenvironment pH, these results suggest that both formulations have comparable microenvironment pH values. The uniform distribution of the buffer in the case of wet granulation makes the pH of the salt less critical for stability.

The effect of the counter ion on the microenvironment pH is the most plausible explanation for the observed differences in the stability of the two salt forms. This is particularly true since DMP 755 is more soluble in water than DMP 754 (>100 vs. 10 mg/ml) and has a lower melting

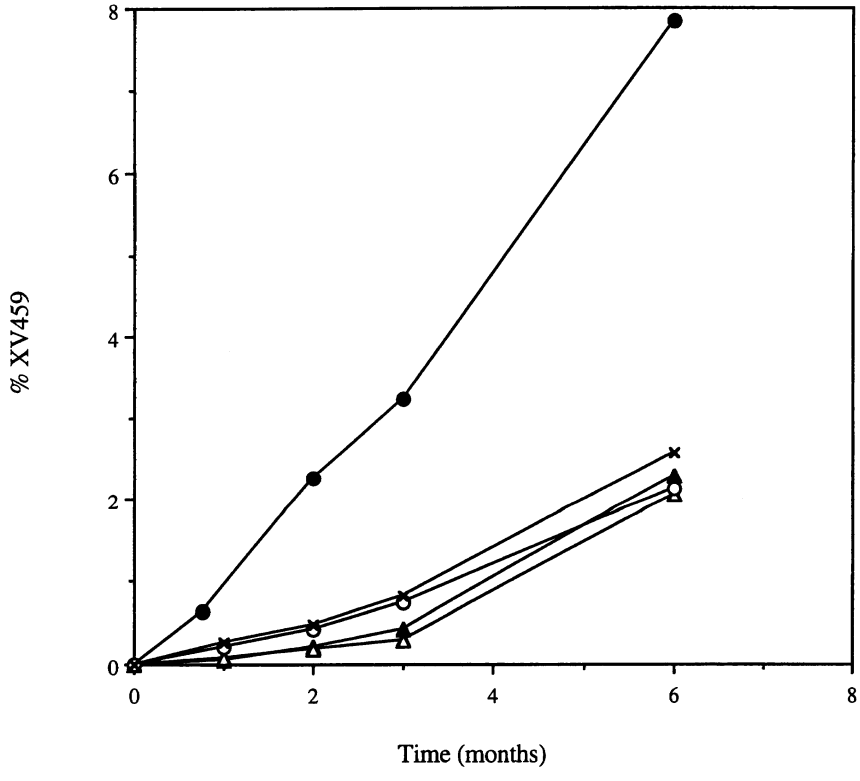


Fig. 2. Percent increase in XV459 in capsules and tablets packaged in HDPE bottles with desiccant and stored at 40 °C/75% RH. DMP 754 tablets manufactured by the wet granulation process, (▲); DMP 755 tablets manufactured by the wet granulation process, (△); DMP 754 capsules manufactured by the dry granulation process, (●); DMP 755 capsules manufactured by the dry granulation process, (○); DMP 755 capsules manufactured by the dry granulation process without disodium citrate, (x).

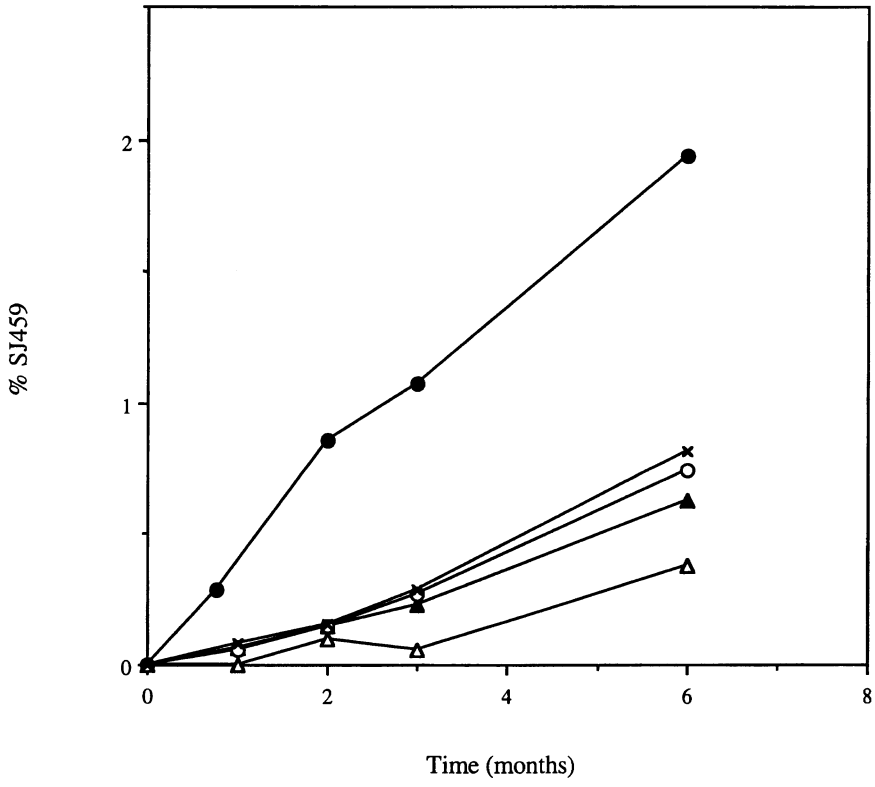


Fig. 3. Percent increase in SJ459 in capsules and tablets packaged in HDPE bottles with desiccant and stored at 40°C/75% RH. DMP 754 tablets manufactured by the wet granulation process, (▲); DMP 755 tablets manufactured by the wet granulation process, (△); DMP 754 capsules manufactured by the dry granulation process, (●); DMP 755 capsules manufactured by the dry granulation process, (○); DMP 755 capsules manufactured by the dry granulation process without disodium citrate, (x).

point (158 vs. 213 °C), factors that can negatively impact the stability of the mesylate salt (Gould, 1986).

Acknowledgements

The author is thankful to the Analytical R&D group of the DuPont Pharmaceuticals Company for assistance with the HPLC analysis and to Anthony J. Gawronski for his help with the manufacturing process. The author would also like to acknowledge the useful discussions and suggestions of Dr Munir A. Hussain.

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