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Research Paper

Formulation of Solid Dosage Forms to Overcome Gastric pH Interaction of the Factor Xa Inhibitor, BMS-561389

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Purpose. The purpose of the study was to investigate the specific mechanism by which elevated gastric pH reduces the absorption of BMS-561389, a factor Xa inhibitor, and to develop a solid formulation strategy to overcome this gastric pH interaction.
Methods. A dissolution method in an acetate buffer at pH 5.5 was used to evaluate the dissolution behavior of the tablet formulation. A precipitation model was used to screen different excipients for their potential to minimize the pH-dependent absorption of BMS-561389. Excipients that showed promise in the precipitation model were incorporated in modified tablet formulations. Dissolution rate of the modified tablets was also determined by the acetate buffer method. A canine model for pH-dependent absorption was subsequently used to evaluate the tablet formulations.
Results. Dissolution studies suggested that the reduced absorption of the original formulation was the result of the precipitation of the poorly water-soluble free base during the initial dissolution of the salt. Modified tablets containing organic acids, sulfobutylether-β-cyclodextrin, or povidone showed enhanced dissolution as compared with the original formulation. Drug absorption from the tablet containing tartaric acid was substantially independent of gastric pH in the canine model.
Conclusion. A multitier approach was successful in identifying a solid dosage form that minimizes the pH-dependent absorption of this drug candidate.

KEY WORDS: absorption; factor Xa; free base; gastric pH; precipitation; tablet formulation.

INTRODUCTION

The dependence of drug absorption on gastric pH has been reported for many drugs (1–4). Reduction in bioavailability of many weakly basic compounds has been observed during concurrent therapy with agents that increase gastric pH, such as antacids, H2 antagonists, or proton pump inhibitors. In some cases, the reduction in bioavailability can be substantial and results in subtherapeutic exposure to the active drug. In those cases, the concomitant intake of the gastric pH modifiers is contraindicated to allow for sufficient absorption of the active drug. This restriction complicates drug therapy and carries the risk of inadequate therapy in case of patient noncompliance with the restriction. For those drugs, oral formulations that minimize interaction with gastric pH modifiers would be highly desirable.

BMS-561389 (razaxaban) is a novel, potent, selective, and orally bioavailable direct factor Xa inhibitor (5). The free base form of BMS-561389 is a weak base with very low intrinsic solubility. It has two basic pK_a values of 2.2 and 7.4 and exhibits pH-dependent solubility, which decreases as the pH is increased. The hydrochloride salt has been selected for development. At normal gastric pH condition, BMS-561389 seemed to be well absorbed in fasted humans, and the plasma area under the curve (AUC) was proportional to the dose when administered in a suspension form, suggesting that absorption is not limited by incomplete dissolution within the tested dose range (10–160 mg). Also, traditional immediate release tablets showed identical pharmacokinetic profile to the suspension. However, preliminary studies in dogs showed significant reduction in plasma AUC and C_{max} when the immediate release tablets were coadministered with H2 receptor antagonists. The purpose of this work is to study the mechanism of reduced absorption of BMS-561389 under elevated gastric pH conditions and to evaluate solid dosage formulation approaches that would minimize gastric pH interaction.

MATERIALS AND METHODS

Materials

BMS-561389 drug substance was obtained from the Process R&D department of Bristol Myers Squibb Co. Excipients used include microcrystalline cellulose (Emcocel® 90M, JRS Pharma, Patterson, NY, USA), croscarmellose sodium (Ac-Di-Sol®, FMC Corporation, Philadelphia, PA,

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USA), tartaric acid (J.T. Baker, Phillipsburgh, NJ, USA), povidone (PVP; Kollidon®, BASF, Florham Park, NJ, USA), hydroxypropyl cellulose (Klucel® LF, Aqualon, Wilmington, DE, USA), sulfobutylether-β-cyclodextrin (SBE-β-CD; Captisol®, CyDex, Overland Park, KS, USA), polyoxyl 40 hydrogenated castor oil (Cremophor® EL, BASF), copovidone (Kollidon® VA 64, BASF), poloxamer 188 (Pluronic® F-68, BASF), polyvinyl alcohol–polyethylene glycol (Kollicoat® IR, BASF), polysorbate 80 (Tween® 80, Merck KGaA, Darmstadt, Germany), and cetyltrimethylammonium bromide (CTAB, Eastman Kodak Rochester, NY, USA).

Methods

Solubility of BMS-561389

Solubility studies were conducted by placing excess BMS-561389 into glass vials with deionized water and adding varying amounts of sodium hydroxide or hydrochloric acid to adjust the pH. Vials were rotated at room temperature and were sampled at various intervals. The samples were filtered, and the filtrate was employed for pH determination and high-performance liquid chromatographic (HPLC) analysis, as described below. Sampling was continued until equilibrium was achieved, and equilibrium solubility values were plotted against the corresponding pH.

Solubility samples were analyzed by an HPLC method using a system equipped with autosampler, elution pump (Alliance Separation Module 2695, Waters Corp., Milford, MA, USA), reversed-phase Zorbax® Eclipse XDB C18 (250 × 4.6 mm ID; 5 μm) column (Agilent Technologies, Palo Alto, CA, USA), heated column compartment set at 40°C, and a variable wavelength UV detector set at 280 nm (Waters 2487 Absorbance Detector). An isocratic elution was performed using a mobile phase consisting of 0.1% trifluroacetic acid in water/tetrahydrofuran, 72.6:27.4 v/v, at flow rate of 1.2 mL/min.

Dissolution Studies

Composition of the original tablet formulation is shown in Table I. Dissolution rate of this formulation (prepared by the method described below) was evaluated in 500 mL of 50 mM acetate buffer, pH 5.5, at 37°C using USP Apparatus 2 (paddle) at agitation rates of 60, 80, or 100 rpm and USP Apparatus 1 (basket) at an agitation rate of 75 rpm. Dissolution rate of the tablets was also determined in 900 mL of 0.01 N HCl at 37°C using the paddle method at 60 rpm. Dissolution samples were analyzed by an on-line UV spectrophotometric method at 246 nm.

In a separate experiment, 400 mg of BMS-561389 drug substance was mixed with 125 mL of 50 mM acetate buffer, pH 5.5, at room temperature in a flask using a magnetic stir bar. Stirring was continued for 100 min. The solid residue was then filtered, dried, and analyzed by powder X-ray diffraction.

Precipitation Studies

The effect of excipients on crystallization kinetics of BMS-561389 free base was examined by dissolving the excipient in deionized water at 0.2% w/v concentration. BMS-561389 was then dissolved in the excipient solution at a concentration of 1 mg/mL. An equal volume of 50 mM acetate buffer at pH 5.5 was added to the drug/excipient solution while stirring at room temperature. A measurement of pH indicated that the resulting solution pH is ~5.5. At predetermined time points, aliquots were withdrawn from the solution and filtered. The filtrate was diluted immediately and assayed by the HPLC method previously described. A control experiment was also conducted similarly without including the excipient in the drug solution. For PVP K30, drug solutions containing 2 and 10% w/v of the polymer were prepared in addition to the above 0.2% w/v solution and used similarly.

Preparation of Tablets

BMS-561389 original and modified tablets were manufactured by a wet granulation method. The drug substance was blended with the intragranular components in a high shear granulator. The blend was granulated with water in the high shear mixer, and the wet granulation was dried in an oven at 50°C to a moisture content of not more than 3%. The dried granulation was screened using a 20-mesh screen, blended with the extragranular components including magnesium stearate, and compressed into tablets. Table I shows the composition of the various tablet formulations manufactured. Dissolution rate of the modified tablet formulations was determined in the acetate buffer, pH 5.5, by the paddle method at 60 rpm and/or by the basket method at 75 rpm, as described above.

Dog Biovailability Studies

BMS-561389 formulations were evaluated *in vivo* in a canine model for their pH-dependent absorption (6). Formulations were administered to a group of three to four dogs pretreated with either pentagastrin (6 μg/kg), given intramuscularly 30 min before dosing of the formulation, or famotidine (40 mg/dog), given orally 3 h before dosing. A crossover design was used so that each formulation tested was administered to the same group of dogs following each pretreatment after an appropriate washout period. Because canine gastric pH is higher and more variable than that of human (7,8), the purpose of pentagastrin pretreatment is to lower the dogs' gastric pH to ~2 for 1 h to simulate human gastric pH. On the other hand, famotidine maintains the canine gastric pH at 5–7.5 for more than several hours to mimic human gastric pH after treatment with an acid-reducing drug. Animals were fasted overnight until 4 h post dosing and denied free access to water for 1 h prior to and post dosing. After tablet administration, a total of 50 mL water was given by gavage to control the gastric fluid volume. Blood samples were obtained at specified time intervals after dosing, and plasma BMS-561389 concentrations were determined using a validated liquid chromatography/mass spectrometry (LC/MS) analytical method described below.

Analysis of Dog Plasma Samples

An LC/MS/MS method has been developed and validated for the quantitation of BMS-561389 in dog plasma. The

Table I. Composition of BMS-561389 Formulations

Ingredient	Percentage of total weight				
	Formulation #1 (control tablet, original formulation)	Formulation #2	Formulation #3	Formulation #4	Formulation #5
BMS-561389	35.6	29.7	29.7	29.7	30.0
Microcrystalline cellulose	60.4	50.3	50.3	50.3	49.3
Hydroxpropyl cellulose (Klucel LF)	3.0	2.5	2.5	2.5	3.0
Croscarmellose sodium	0.5	0.4	0.4	0.4	3.5
Magnesium stearate	0.5	0.4	0.4	0.4	0.5
Tartaric acid (extragranular)	–	16.7	–	–	–
Tartaric acid (intragranular)	–	–	–	–	16.7
Citric acid (extragranular)	–	–	16.7	–	–
Succinic acid (extragranular)	–	–		16.7	–
Tablet weight (mg)	300	360	360	360	360

	Formulation #6	Formulation #7	Formulation #8	Formulation #9	Formulation #10	Formulation #11
BMS-561389	30.0	32.4	30.0	29.7	30.0	24.9
Microcrystalline cellulose	53.5	54.8	56.0	50.3	30.5	42.3
Hydroxpropyl cellulose (Klucel LF)	–	2.7	–	2.5	3.0	2.1
Croscarmellose sodium (intragranular)	3.0	0.5	3.0	0.4	3.0	0.4
Croscarmellose sodium (extragranular)	3.0	–	3.0	–	3.0	–
SBE-β-CD (intragranular)	–		–	–	30.0	–
SBE-β-CD (extragranular)	–		–	16.7	–	30.0
PVP K12 (intragranular)	10.0		–	–	–	–
PVP K12 (extragranular)	–	9.1	–	–	–	–
Cremophor EL (intragranular)	–		7.5	–	–	–
Magnesium stearate	0.5	0.5	0.5	0.4	0.5	0.4
Tablet weight (mg)	360	330	360	360	360	428

SBE-β-CD = sulfobutylether-β-cyclodextrin; PVP = povidone.

method utilized DPC-A80662-ZO as the internal standard. After the addition of internal standard and 2 mM ammonium acetate solution to 0.1 mL of each quality control sample, calibration standard, and study sample, the samples were loaded onto a conditioned 3M Empore C8 solid-phase extraction column. As a cleanup step, the samples were washed with water and a 30% methanol/water solution before elution. The compound was eluted with methanol, and the eluate evaporated to dryness. The residue was reconstituted and injected into the LC/MS/MS system. Chromatographic separation was achieved isocratically on a Supelco Discovery RP-Amide C16 analytical column (2.1 × 50 mm, 5 μm). The mobile phase contained 0.1% formic acid in water and in acetonitrile. Detection was by positive ion electrospray tandem mass spectrometry. The standard curve, which ranged from 2.00 to 2000 ng/mL for BMS-561389, was fitted to a $1/x$ weighted quadratic regression model.

RESULTS AND DISCUSSION

Solubility

The pH–solubility profile of BMS-561389 is shown in Fig. 1. Intrinsic solubility of the unionized drug was very low (~0.2 μg/mL). Solubility increased as the pH was lowered below 6.5, reaching ~2 mg/mL at pH 3. Further decrease in pH below 3 did not result in any further increase in solubility, suggesting a pH_{max} value around 3.

Dissolution Studies of Original Formulation

The dissolution rate of the original tablet formulation, 50 mg potency, showed rapid and complete dissolution in 0.01 N HCl using the paddle method at 60 rpm (Fig. 2A). On the other hand, dissolution testing of this tablet formulation (50 and 100 mg strengths) in the acetate buffer at pH 5.5, using the paddle method at 60 rpm, showed rapid dissolution rate initially, where approximately 40–45% of the dose dissolved in 10 min (Fig. 2A and B). However, there was no further increase in the fraction dissolved beyond the 10-min time point, and the percentage dissolved remained constant after 3 h. A similar profile was obtained for the 100-mg tablet in the acetate buffer, pH 5.5, with the basket method at 75 rpm. For the two methods, BMS-561389 concentration in the dissolution medium was more than 10-fold higher than its saturation solubility at this pH, indicating that drug can exist in a supersaturated state in the bulk solution for a relatively extended time period under these conditions. The lack of complete dissolution is likely to be caused by the conversion

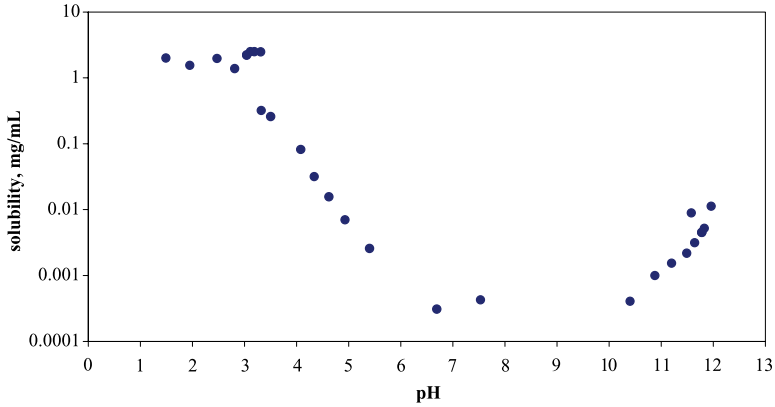


Fig. 1. pH–solubility profile of BMS-561389.

of the undissolved fraction to the free base as the hydrochloride salt is initially dissolving. Thus, whereas BMS-561389 showed the ability to maintain a supersaturated solution in the bulk dissolution medium for a relatively long time period, the significantly higher degree of supersaturation in the local environment of the dissolving tablet may have resulted in rapid precipitation of the free base.

If this is the case, then the fraction of the hydrochloride salt precipitating as the free base during dissolution seems to be dependent on the experimental conditions. Increasing impeller speed to 80 or 100 rpm increased the extent of dissolution to ~72 and ~95% for the two stirring speeds, respectively (Fig. 2A). The rapid dissolution at the higher impeller speed has probably resulted in a decrease in the fraction converted to the free base as the dissolving drug quickly diffused into the bulk medium, hence reducing the extent and duration of supersaturation in the local environment of the dissolving tablet. The choice of dissolution stirring speed is therefore critical to the outcome of the dissolution study in this case. Lower paddle speed (60 rpm) seems to correlate with reduced absorption observed *in vivo*, whereas high impeller speeds (particularly 100 rpm) result in more complete dissolution, which is not consistent with the incomplete absorption at the elevated gastric pH.

Mixing of BMS-561389 drug substance with the acetate buffer, pH 5.5, in a ratio that substantially exceeds the solubility limit resulted in complete dissolution initially. However, precipitation started to appear within several minutes. After the precipitate was isolated by filtration and dried, it was analyzed by X-ray diffraction analysis to confirm that the isolated precipitate is the free base (data not shown). In this case, no precipitation of the free base seemed to have occurred during initial dissolution. Again, this is probably caused by the fast stirring under those experimental conditions. Interestingly, precipitation from the supersaturated bulk was faster than in the dissolution studies. This could be attributed to the higher degree of supersaturation of the bulk solution in this case and/or to the absence of tablet excipients that could act as nucleation inhibitors.

Based on the above data, a mechanism for reduced absorption of BMS-561389 at elevated gastric pH condition was proposed and contrasted to the absorption under normal gastric pH conditions (Schemes 1 and 2). To minimize gastric pH interaction for solid dosage forms, precipitation of the free base during initial dosage form dissolution should be minimized. Slowing down free base nucleation/crystallization kinetics would provide more time for the drug to diffuse into the bulk medium without precipitation. This may be accomplished by the use of excipients that would act as nucleation inhibitors by decreasing the diffusion coefficient of the molecule in the solution. Another mechanism by which

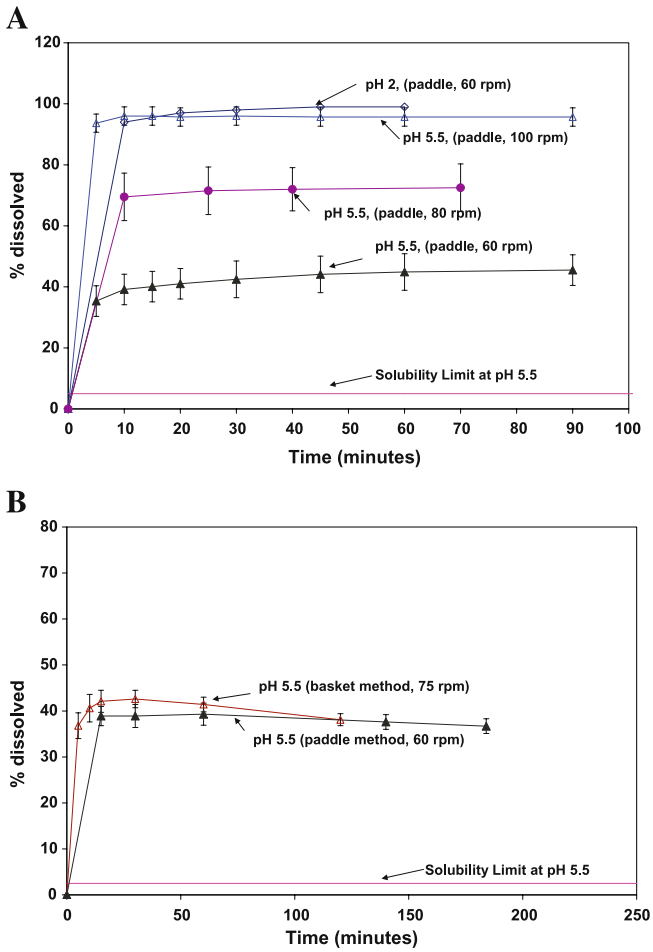
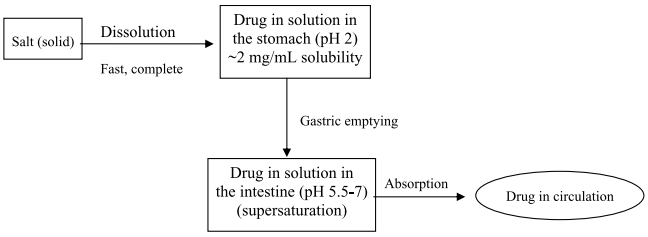


Fig. 2. Dissolution profile of BMS-561389 original tablet formulation (formulation #1). (A) 50 mg. (B) 100 mg.



Scheme 1. Absorption of BMS-561389 under normal gastric pH conditions.

nucleation can be slowed down is through the decrease of supersaturation (the driving force for nucleation) in the local environment (9). Agents that modify pH, and possibly other excipients, can increase solubility of the drug in the local environment and hence decrease nucleation rate.

Excipient Screening using Precipitation Model

Polymers, surfactants, and complexing agent tested in the precipitation model showed a wide range in their ability to slow down crystallization of the free base. Generally, polymers were more effective in slowing down free base crystallization compared with other excipients tested. Kollidon VA 64 and PVP at 0.1% concentration showed remarkable decrease in the free base precipitation rate, with initial drug concentration in the solution (500 μg/mL) still maintained after 120 min (Fig. 3A). In contrast, control experiment without excipients showed significant precipitation which resulted in the decrease in drug concentration to 3.7 μg/mL in 45 min. The effect of PVP was concentration dependent, and higher PVP concentration was more effective in retarding precipitation (Fig. 4). Complexing agent, SBE-β-CD, also showed good ability to retard crystallization, and there was only a small decrease in drug concentration after 160 min. Surfactants, while showing a retarding effect on precipitation rate compared with the control sample, were all less effective than the polymers and SBE-β-CD (Fig. 3B).

Dissolution Studies of Modified Formulations

Dissolution of modified formulations was tested in the acetate buffer, pH 5.5, with the basket at 75 rpm or the paddle at 60 rpm. Those methods predicted the reduced bioavailability of the original tablet formulation at the elevated gastric pH and hence could be useful in forecasting

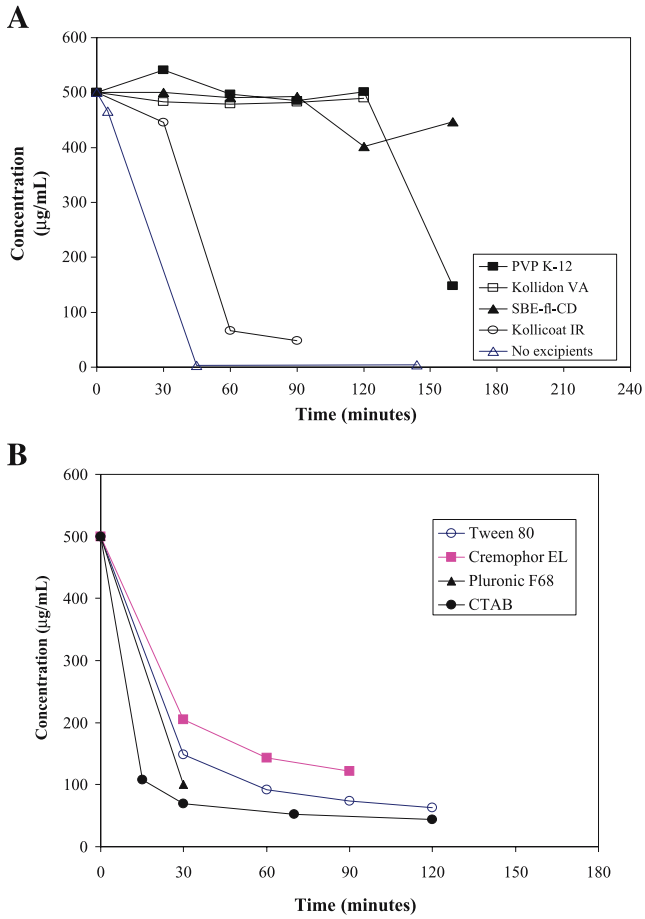
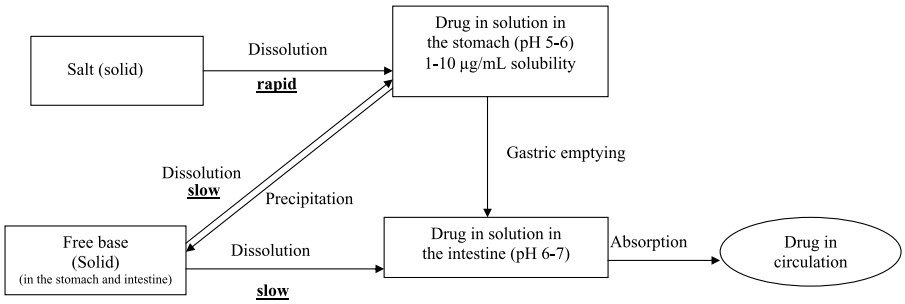


Fig. 3. Effect of excipients (0.1% w/v) on precipitation rate of the free base at pH 5.5. (A) Polymers and SBE-β-CD. (B) Surfactants.

the performance of the modified formulations. Because the precipitation model, by design, was not suitable for screening acids, they were selected instead based on their physical-chemical properties. For an acid to be effective in retarding free base precipitation, it should have sufficiently low pK_a value and be available at an adequate concentration in the local environment of the dissolving drug, so that local environment pH is sufficiently lowered, preferably below the pH_{max} (~3). Therefore, acids with pK_a at or less than ~4 and with high water solubility were selected. The high water solubility is desirable so that dissolution rate of the acid would match the rapid dissolution of the hydrochloride salt



Scheme 2. Absorption of BMS-561389 at elevated gastric pH conditions.

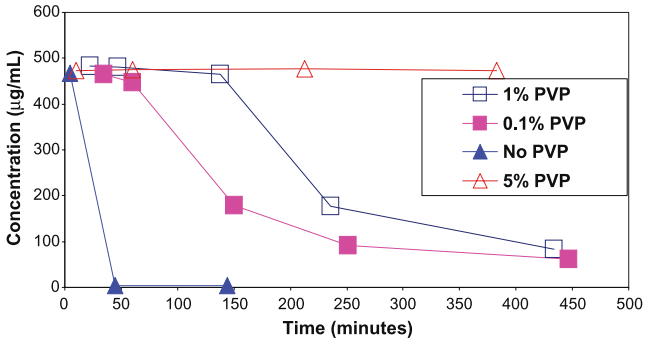


Fig. 4. Effect of PVP K30 concentration on precipitation rate of the free base at pH 5.5.

of the drug. The acids that were chosen also have established and acceptable safety profile after oral administration and hence are appropriate for use in oral dosage forms. Compositions of tablets containing acids are shown in Table I. In addition to those containing an acid, formulations containing selected excipients based on the data from the precipitation model were also prepared and tested using the same dissolution method(s) (Table I).

In vitro dissolution profile of the tablets containing 16.7% extragranular tartaric acid (formulation #2) showed a rapid dissolution rate in the pH 5.5 buffer, and the fraction dissolved was ~90%, in contrast to ~40% for the control tablets without tartaric acid (formulation #1) under the same experimental conditions (Fig. 5A). The pH of the dissolution medium remained substantially constant at ~5.5 until the end of the test. Thus, tartaric acid does not enhance the dissolution behavior of BMS-561389 by increasing its solubility in the bulk medium. Instead, tartaric acid probably increases the solubility in the local environment of the dissolving dosage form, resulting in a lower degree of supersaturation in such an environment, hence minimizing free base precipitation during dissolution of the hydrochloride salt. Once diluted into the bulk medium, the drug is capable of remaining in supersaturated solution for an extended time period at those conditions providing an opportunity for drug absorption to take place. Addition of tartaric acid in the intragranular composition (formulation #5) showed similar results, where the fraction dissolved after 60 min was ~90% (Fig. 5B). Initially, those tablets showed slower dissolution rates, which can be attributed to slower tablet and/or granule disintegration when tartaric acid is incorporated intragranularly. The extragranular incorporation of tartaric acid may be preferred from a chemical stability perspective, as it protects the drug from exposure to the low microenvironment pH provided by tartaric acid during wet granulation. The addition of the same amount of tartaric acid to the dissolution medium, however, did not result in any significant increase in the dissolution behavior of the control tablets. This supports the argument that mechanism of action of tartaric acid is mediated through its effect on the local environment rather than on the bulk solution. The use of other organic acids, such as citric and succinic acids (formulations #3 and #4, respectively), also resulted in similar enhancement of BMS-561389 *in vitro* dissolution profile at pH 5.5 (Fig. 5A).

The effect of PVP on the extent of BMS-561389 dissolution was generally less pronounced than the acids and appeared to be dependent on the method of incorporation of PVP (Fig. 6A). Intragranular incorporation of PVP appeared to be more effective than the extragranular method of addition. Fraction dissolved from the formulation containing 10% intragranular PVP 12 (formulation #6) was 70%. In contrast, formulation #7 with extragranular PVP K12 showed essentially similar fraction dissolved as the control tablet (~40–45%). On the other hand, addition of PVP to the dissolution medium (instead of incorporation into the tablets) increased fraction dissolved somewhat to ~55%. As shown in the precipitation experiment, crystallization rate of the free base was inversely related to PVP concentration in the solution. Differences in the fraction dissolved from tested formulations may be related to difference in the effective concentration of PVP in the local environment of dissolving drug particles. Such concentration is expected to depend on PVP concentration in the formulation, its dissolution rate, and proximity of PVP and drug particles in the tablet. Whereas incorporation of PVP in the dissolution medium results in its immediate availability in the local environment of drug particles, the concentration used (1%) may not be sufficient to effectively impede crystallization from the highly supersaturated drug solution in the local environment. The superior performance resulting from intragranular incorporation of PVP can be attributed to the intimate contact of PVP and drug particles in the formulation.

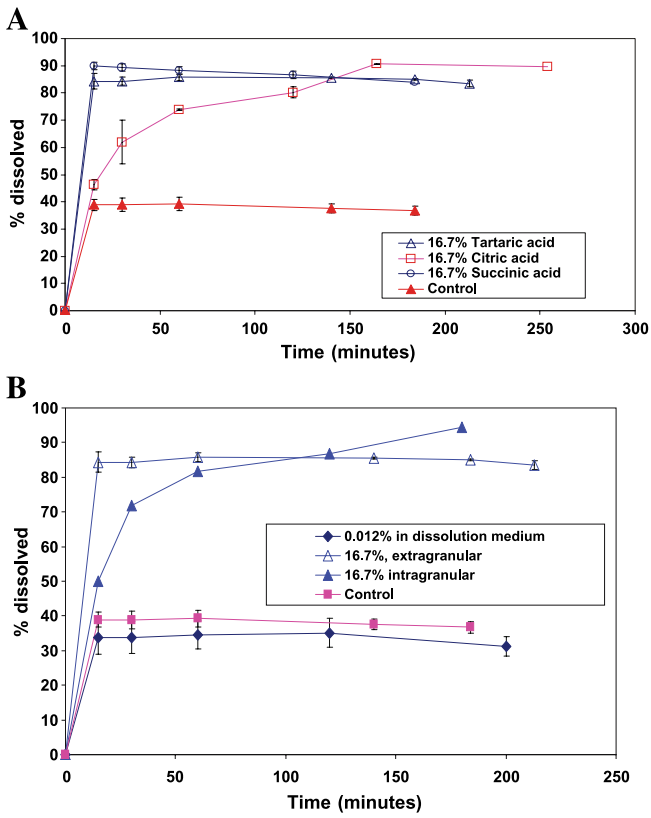


Fig. 5. Effects of acids on dissolution profile of BMS-561389 tablets in the acetate buffer, pH 5.5 (paddle method, 60 rpm). (A) Different acids added extragranularly. (B) Tartaric acid incorporated by different methods.

The formulation containing 7.5% Cremophor EL (formulation #8) showed marginal improvement in the fraction of drug dissolved compared with the control tablet (50.0 and 39.3% dissolved at 60 min for the two formulations, respectively). This was expected given the limited effect of Cremophor EL and other surfactants exhibited in the precipitation experiments.

Incorporation of 16.7% SBE-β-CD extragranularly resulted in moderate increase in fraction dissolved to ~60% (formulation #9) (Fig. 6B). Further increase in SBE-β-CD concentration to 30% resulted in additional increase in fraction dissolved (Fig. 6C). Results were comparable for the two formulations containing 30% SBE-β-CD, regardless of whether SBE-β-CD is incorporated as intragranular (formulation #10) or extragranular component (formulation #11). Formulations containing 30% SBE-β-CD showed enhancement of BMS-561389 dissolution comparable to that exhibited by the tartaric acid formulation (formulation #2).

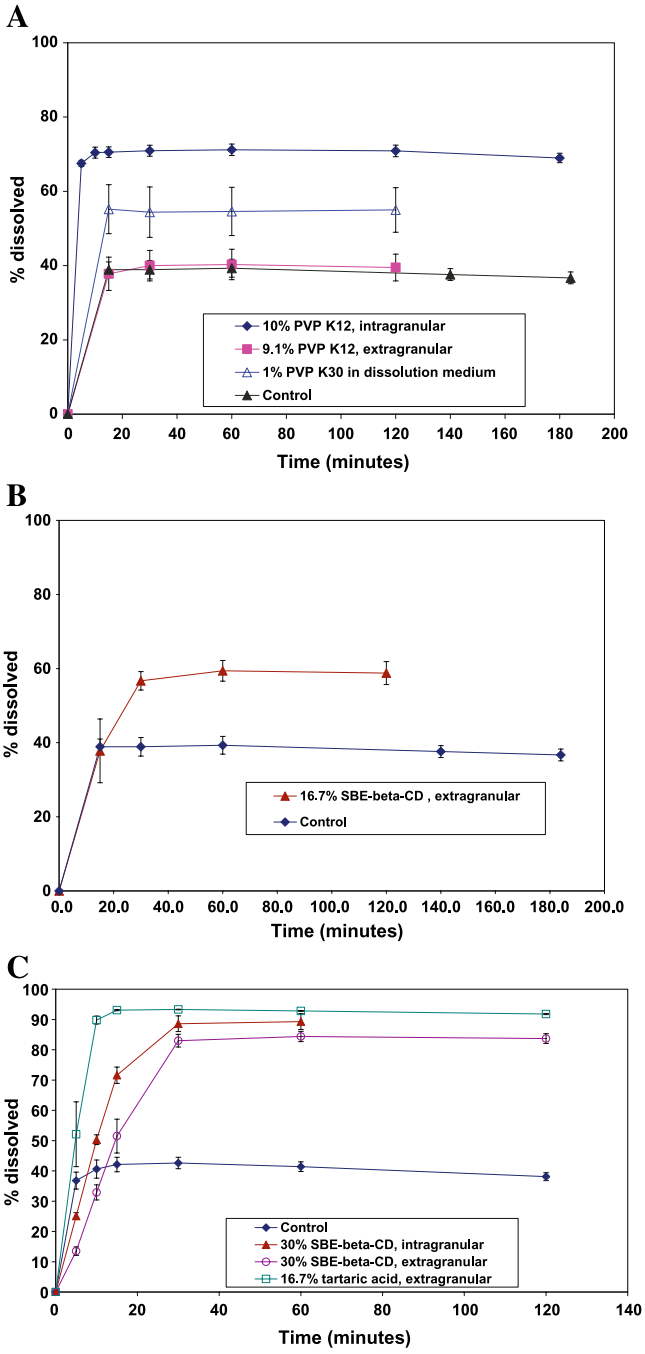


Fig. 6. Dissolution profiles of BMS-561389 tablet, 100 mg, in the acetate buffer, pH 5.5. (A) Formulations #6 and #7 using paddle at 60 rpm. (B) Formulation #9 using paddle at 60 rpm. (C) Formulations #2, #10, and #11 using baskets at 75 rpm.

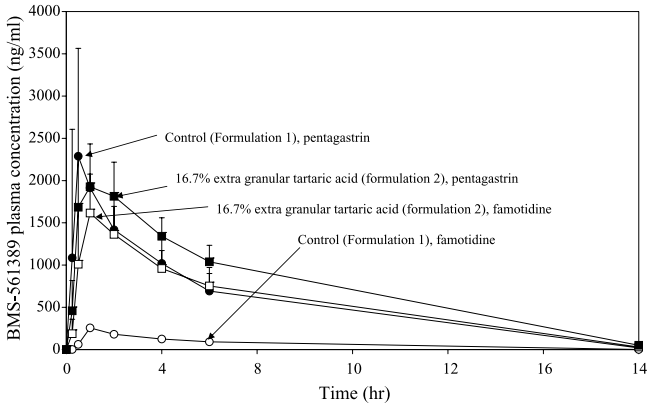


Fig. 7. Plasma profiles of BMS-561389 in dogs after administration of 100-mg tablets.

Dog Biovailability Studies

Formulation #2 (16.7% extragranular tartaric acid) was selected based on the above *in vitro* dissolution studies for further evaluation in a canine model for pH-dependent absorption. Plasma profiles of BMS-561389 in dogs after administration of control tablets are shown in Fig. 7. Compared with pentagastrin treatment, famotidine (40 mg) treatment decreased the C_{max} of formulation #1 by 85%, from 2413 to 257 ng/mL, and decreased its AUC_{0-24} by 88%, from 10,716 to 1143 ng/mL h, in dogs. However, famotidine (40 mg) treatment did not significantly decrease the C_{max} and AUC_{0-24} of the tartaric acid formulation compared with pentagastrin treatment in dogs. Although the C_{max} of tartaric acid tablets decreased by 19.5%, from 2136 to 1720 ng/mL, and the AUC_{0-24} decreased by 28.7%, from 14,408 h to 10,270 ng/mL h, after famotidine treatment, these differences are not statistically significant from the values obtained in pentagastrin-treated dogs. This indicates that tartaric acid formulation overcomes the pH-dependent absorption of BMS-561389 in the employed canine model as predicted by the dissolution studies.

CONCLUSIONS

A multitier approach was utilized to formulate BMS-561389 into a solid dosage form that minimizes the interaction of this factor Xa inhibitor with agents that raise gastric pH. The initial step was to elucidate specific mechanism by which elevated gastric pH reduces BMS-561389 absorption. A precipitation model was then used to screen and select

individual excipients based on their ability to retard precipitation of the free base at the elevated pH. A dissolution method was subsequently used to test formulated tablets and select a promising candidate for *in vivo* studies. Finally, a dog model for the pH interaction was used to evaluate the ability of the selected formulation containing tartaric acid to overcome the pH-dependent absorption of BMS-561389.

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