# RESEARCH ARTICLES

# Degradation Kinetics and Mechanism of an Oxadiazole Derivative, Design of a Stable Drug Product for BMS-708163, a γ-Secretase Inhibitor Drug Candidate

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**ABSTRACT:** The stability of a 1,2,4-oxadiazole derivative, BMS-708163, A, was studied in the cosolvent mixture of acetonitrile–water at various pH values, in the solid state and in the presence of various excipients. The objective of this study was to develop a deep understanding of the stability of compound A based on its degradation kinetics and mechanism to enable design of a robust drug product. A series of isotopically $^{13}C$- and $^{15}N$-labeled compounds were synthesized and their degradation was studied by liquid chromatography–mass spectrometry and nuclear magnetic resonance to prove the degradation mechanism. Compound A exhibited maximum stability at a pH range of 3–5. In forced degradation studies, higher or lower pH resulted in an increase in degradation rate. At low pH, the N-4 atom on the 1,2,4-oxadiazole ring is protonated, followed by nucleophilic attack on the activated methine carbon to cause ring opening to form aryl nitrile degradation product, compound B. At high pH, the nucleophilic attack occurs on the methine carbon to generate an anion on N-4. Subsequent proton capture from a proton donor, such as ambient water, facilitates ring opening to generate compound B. In the absence of a proton donor, such as in dry acetonitrile, anion on N-4 will go back to compound A. Therefore, compound A is stable in absence of proton donor. This study defines the package condition and microenvironmental pH under which compound A can be formulated into a stable product. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

**Keywords:** chemical stability; degradation products; mechanism; oxadiazole; kinetics; formulation; solid dispersion

## INTRODUCTION

The 1,2,4-oxadiazole (isoxadiazole) ring system has been used extensively in medicinal chemistry. This structural motif is found in several commercially marketed drugs[1–4] such as Picovir,[5] Proxodolol,[6–8] Etiracetam, Memolog,[9] Rolipram,[10] Pidotimod, and other drug products.[11,12] The oxadiazole ring serves as a bioisostere of carboxylic esters and amides, and has contributed to increased pharmacological activities by participating in hydrogen-bonding interactions with biological receptors.[4] Derivatized oxadiazole ring systems were found to decompose under high temperature conditions, through ring cleavage, to afford nitrile and isocyanate derivatives.[13,14]

BMS-708163 (Compound A in Fig. 1) is being developed for the inhibition of γ-secretase to reduce the amyloid-β aggregation that is believed to have a role in the progression of Alzheimer's disease.[15,16] Compound A has a solubility of less than 1 μg/mL, and is nonionizable under physiologically relevant pH range. Owing to its low solubility, BMS-708163 is being developed as an amorphous solid dispersion in cellulose-based polymers. Preliminary studies showed that compound A was physically and chemically stable for at least 3 months in accelerated stability studies [40°C/75% relative humidity (RH) open and 50°C close conditions] in the solid state. However, it was found that compound A was much less stable in solution. In solution at both low and high pH and in drug–excipient compatibility studies, the main degradant was found to be a nitrile degradation product (compound B in Fig. 1), which increased with time during storage at elevated temperature.

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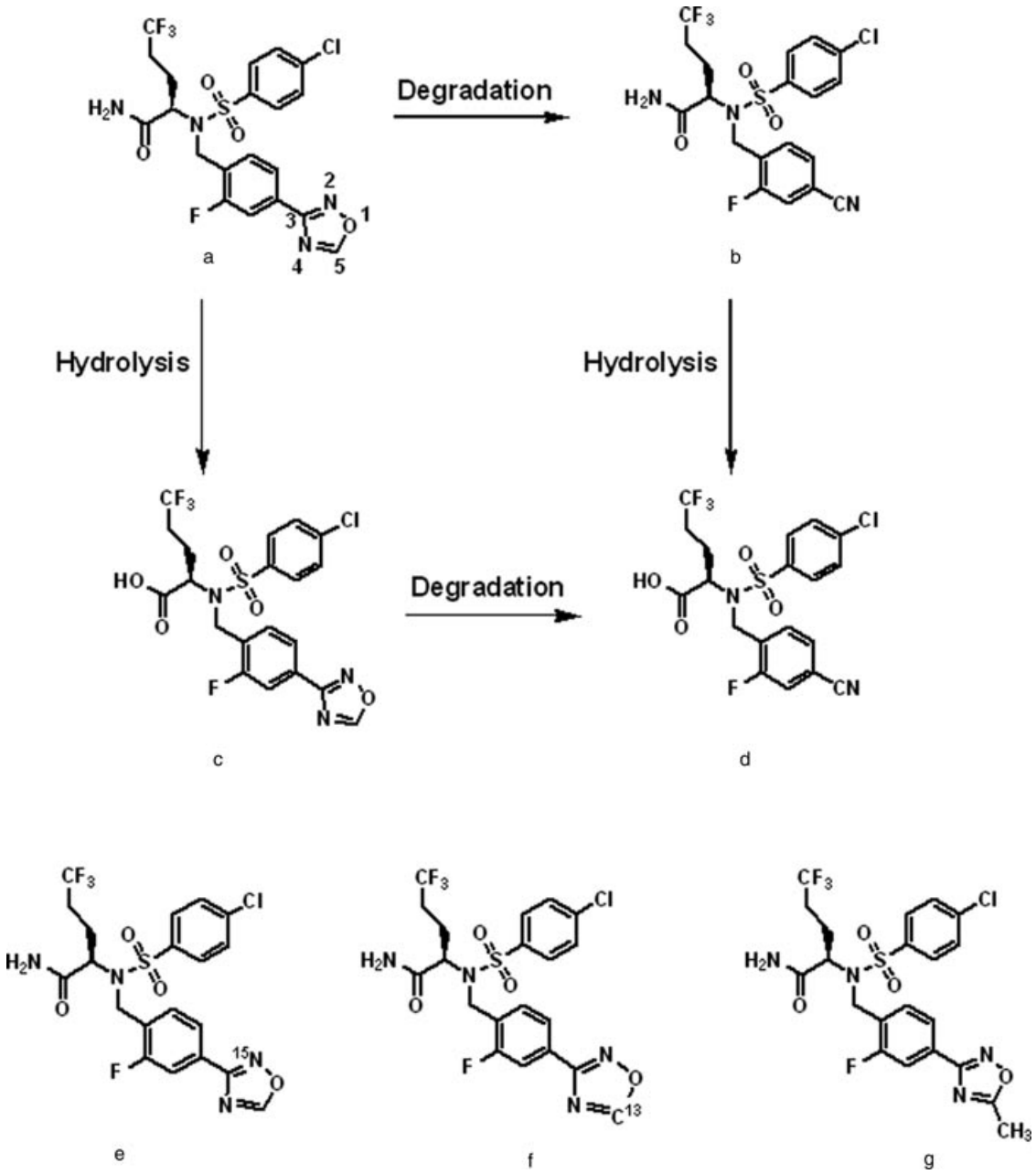


**Figure 1.** Structures of compound A, compound B (aryl nitrile degradation product of compound A), compound C (amide hydrolysis of compound A), and compound D (amide hydrolysis of aryl nitrile degradant compound B), $^{15}$N-labeled compound E, $^{13}$C-labeled compound F, and methylated compound G.

In the presence of nucleophilic groups, Claisse et al.[17] proposed that the degradation of the oxadiazole moiety likely follows a pathway wherein ring opening occurs through a concerted reaction (Fig. 2), leading to a nitrile and isocyanate ion. The current stability study was conducted to investigate the degradation kinetics and mechanism, both in solution and in the proposed solid dosage form to mitigate the degradation risks in drug product.

## MATERIALS AND METHODS

### Chemicals

Compounds A–G (Fig. 1) were prepared by the Chemical Development group at Bristol–Myers Squibb, Company, New Brunswick, New Jersey. Hydroxypropyl methylcellulose acetate succinate (HPMC-AS) was obtained from Shin-Etsu Chemical Company Ltd. (Chiyoda-ku, Tokyo, Japan), HPMC

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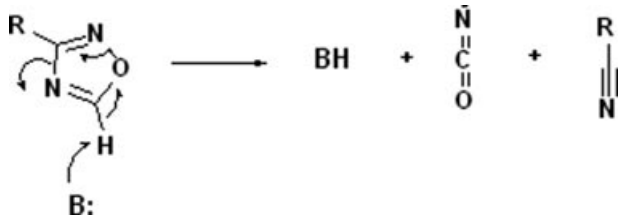


**Figure 2.** Basic degradation mechanism of the 1,2,4-oxadiazole ring proposed by Claisse et al.[17]

and polyvinylpyrrolidone–vinyl acetate (PVP–VA) were obtained from Dow Chemical Company (Midland, Michigan). Acetic acid, sodium acetate, citric acid, sodium citrate, and deuterated solvents were purchased from Sigma–Aldrich Chemical Company (St. Louis, Missouri).

### Compound A Chemical Stability Studies

#### *Chemical Stability in Solution*

The degradation rate of compound A was determined at various pH values ranging from 0.25 to 9. Compound A solutions were prepared at apparent pH values of 0.25 (1 N HCl), 1 (0.1 N HCl), 2 (0.01 N HCl), 3 (0.02 M citrate buffer), 4 (0.02 M citrate buffer), 5 (0.02 M citrate buffer), 7 (0.02 M phosphate buffer), and 9 (0.02 M Tris buffer) and stored at a temperature of 40°C. For all buffers, the ionic strength ($\mu$) was adjusted to 0.1 M using sodium chloride. Compound A was practically insoluble in water (<1 $\mu$g/mL); therefore, it was dissolved in acetonitrile and added to the buffers to make 25:75 acetonitrile–aqueous buffer solutions. The final concentration of compound A was 0.05 mg/mL. The samples were filled into serum vials, sealed with metal caps, tested at predetermined time points, and analyzed by a gradient reversed-phase high-performance liquid chromatography (RP-HPLC).

Solution chemical stabilities for the isotopically labeled (E and F) and methylated (G) compounds were followed at apparent pH values of 1.44 (0.1 N HCl), 5.40 (0.02 M acetate buffer), and 8.53 (0.02 M acetate solution). Compounds were dissolved in 25:75 acetonitrile–aqueous solutions (v/v) with a final concentration of 0.25 mg/mL. Samples were filled into serum vials, sealed with metal caps, and stored in a 60°C oven. Samples were tested at predetermined time points and analyzed by a gradient RP-HPLC and liquid chromatography–mass spectrometry (LC–MS).

### Solid Dispersions Stability and Microenvironmental pH Measurement

A mixture of compound A and polymer (HPMC, HPMC-AS, or PVP–VA; 40:60 by weight) was dissolved in acetone and spray dried to make amorphous solid dispersion. Each spray-dried powder was analyzed at time zero and stored in stability chambers under differential conditions. Samples were withdrawn at predetermined time points, extracted using methanol and analyzed by a gradient RP-HPLC.

Roughly about 1 mL distilled water was added into 1 g of each solid dispersion formulation, and then stirred for 1–2 h to prepare a concentrated slurry of the formulation. The pH of the slurry was determined using a pH meter and designated as the microenvironmental pH of the solid formulation.

### RP-HPLC Analysis

A Waters Alliance 2695 HPLC system equipped with a Waters 2487 ultraviolet–visible dual wavelength detector (Milford, Massachusetts) was used to follow the stability of compound A. A YMC-Pack Pro C18 column [150 × 3.0 mm internal diameter (i.d.), 3 $\mu$m particle size; Kyoto, Japan] was used to separate the compounds at 30°C. The sample chamber temperature was set as 5°C. Mobile phase A was 0.05% trifluoroacetic acid (TFA) in water and mobile phase B was 0.05% TFA in acetonitrile. The gradient elution profile was linear ramp from 75% A initially to 85% B at 35 min. The flow rate was 1.0 mL/min and the detection wavelength was 244 nm.

### HPLC–MS Studies

The isotopically labeled compounds solution stability samples were characterized by HPLC–MS. The HPLC analysis conditions were the same as the aforementioned. The mass spectra were obtained on Waters ZQTM 4000 (Single Quadrupole Mass Spectrometer) equipped with an electrospray ion source. The source temperature was held at 125°C and the desolvation temperature was 350°C. The capillary voltage was 3.20 kV; cone voltage was 25.00 V; cone gas flows was 25 L/h; desolvation gas flow was 750 L/h. Magnet scans were performed over the mass–charge range of 18–1000 Da.

### Nuclear Magnetic Resonance Studies

$^{1}$H NMR spectra were obtained on a Bruker Avance DRX 500 NMR instrument (Billerica, Massachusetts) at 25°C or 60°C using a Nalorac 3-mm $^{1}$H–$^{13}$C dual probe or a Bruker CPTXI 5-mm probe. $^{13}$C NMR spectra were obtained on a Bruker Avance DRX 500 NMR instrument at 25°C using a Nalorac 3-mm $^{1}$H–$^{13}$C dual probe. $^{1}$H and $^{13}$C chemical shifts were referenced to the residual nuclear magnetic resonance (NMR) solvent ($CD_3CN$: 1.94 and 1.30 ppm). The NMR samples were heated either inside the NMR instrument for data acquisition or in an oil bath and then transferred to the NMR instrument for data acquisition.

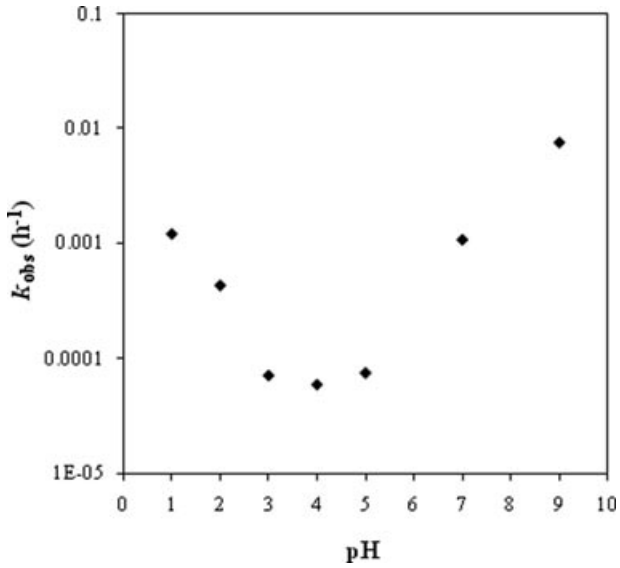


**Figure 3.** pH-rate profile for the degradation of compound A at 40°C. The observed first-order degradation rate constants were not determined at zero buffer concentration.

## RESULTS AND DISCUSSION

### Degradation Behavior

The stability of compound A in the pH range 0.25–9 was studied at 40°C with different buffers. The pH versus degradation rate profile of compound A is shown in Figure 3. The first-order reaction rate was obtained using the equation: $\ln [A]_t = -k_{obs}t + \ln[A]_0$, where [A] is compound **A** concentration and $k_{obs}$is the observed first-order rate constant. Compound A was maximally stable in a pH range of 3–5.

The molecular weight of the major degradant was found to be 477 by MS and corresponds to compound B. Figure 4 shows a typical HPLC chromatogram of partially degraded compound A under acidic conditions. In addition to the disappearance of compound A, each of the degradant peaks increased with time and temperature. Chromatogram peaks from left to right in Figure 4 were identified as compound B (aryl nitrile degradation product), compound A, compound D (amide hydrolysis products of compound B), and compound C (amide hydrolysis products of compound A), respectively. Under neutral or fairly basic condition, no amide hydrolysis was observed and peaks corresponding to compounds C and D were not detected in the chromatogram.

### Degradation Mechanism Studies

Isotopically labeled compound E and F and methylated compound G solutions were prepared at pH values of 1.44, 5.40, and 8.53, and stored at 60°C. Table 1 shows the HPLC results of the solution stability. The response factors for the compounds B, C, and D relative to compound A were found to be 0.85, 1.00, and 0.83, respectively. The concentrations of the degradants were determined from the peak areas corrected for the response factors. $^{15}$N- and $^{13}$C-labeled compound E and F showed similar degradation kinetics to that of compound A. The methylated compound G showed no degradation over the study period except for the hydrolysis of the side chain amide moiety under strongly acidic conditions, supporting the proposal that the oxadiazole ring hydrogen is involved in the degradation mechanism.

The stability samples were also subjected to LC–MS studies. Figure 5a shows the HPLC chromatogram for the stability of $^{15}$N-labeled compound E with the insert showing the mass spectrum corresponding to the nitrile product peak. The mass spectrum gives a protonated molecular ion $[M + H]^+$ at $m/z$ 478.75, indicating the isotope $^{15}$N has been retained in the degradant of compound E. The mass spectrum in Figure 5b shows that the degradant of $^{13}$C-labeled compound F corresponds to a molecular ion $[M + H]^+$

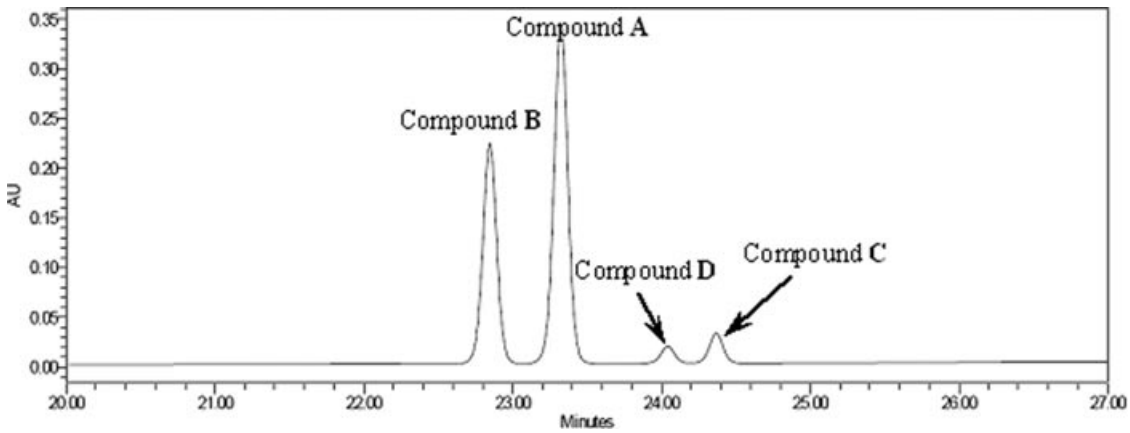


**Figure 4.** Typical HPLC chromatogram of compound A stability sample. Peaks from left to right are compound B (aryl nitrile degradation product), compound A, compound D (amide hydrolysis of compound B), and compound C (amide hydrolysis product of compound A).

**Table 1.** Percentage of Degradants from Solution Stability Studies at Different pH Values for Compounds E, F, and G After Storage at 60°C for 7 Days

| | N15 Label Compound **E** | | | | C13 Label Compound **F** | | | | Methylated Compound **G** | |
|---|---|---|---|---|---|---|---|---|---|---|
| pH | Aryl nitrile product | Compound E | Amide hydrolysis of nitrile product | Amide hydrolysis of compound E | Aryl nitrile product | Compound F | Amide hydrolysis of nitrile product | Amide hydrolysis of compound F | Compound G | Amide hydrolysis of compound G |
| 1.44 | 40% | 50% | 3% | 5% | 41% | 54% | 3% | 6% | 91% | 9% |
| 5.40 | 1% | 97% | Not detectable | | 1% | 99% | Not detectable | | 99% | Not detectable |
| 8.53 | 69% | 29% | Not detectable | | 70% | 30% | Not detectable | | 99% | Not detectable |

at $m/z$ 477.76, the same mass as compound B, indicating that the label has been lost during the degradation. From the MS studies of $^{15}N-$ and $^{13}C$-labeled compound E and F degradation products, the 1,2,4-oxadiazole ring cleavage appears to occur at both the $^{15}N-O$ and C—N bond.

Once the position of the atoms involved in ring cleavage was established, NMR studies were conducted to investigate the mechanism of the degradation process. Compound F ($^{13}C$ labeled, 11.4 mg) was dissolved in 0.5 mL of $CD_3CN$ and transferred into a 5-mm i.d. NMR tube. The resulting anhydrous sample was subjected to $^1H$ and $^{13}C$ NMR data acquisition. Benzylamine (10 μL) was then added to the sample for $^1H$ NMR data acquisition under three different conditions: time zero at room temperature (RT), overnight at RT, and 6 h at 60°C. On the basis of the mechanism proposed in Figure 2, the formed isocyanate could be trapped as benzylurea and easily observed by various spectroscopic or chromatographic techniques. However, no indication of degradation was observed in any of the resulting $^1H$ NMR spectra. $D_2O$ (0.1 mL) was then added to the same NMR sample and $^1H$ NMR spectrum was collected after overnight storage at RT. A small amount of benzylurea was observed that substantially increased when the sample was heated at 60°C for 6.5 h, as shown in Figure 6 (reaction is shown in Fig. 7).

Figure 6 shows the overlay of $^1H$ NMR spectra at different conditions. The peak at $\delta$ 4.25 is assigned to the methylene protons on benzylurea. The NMR experiments show that benzylamine does not react with compound F under anhydrous conditions, but $D_2O$ significantly accelerates the reaction. The sequence of this experiment clearly demonstrates that without the presence of a proton donor, a weak base nucleophile alone does not facilitate the oxadiazole ring opening. In accordance with these findings, a mechanism is proposed, which involves nucleophilic attack on the methine carbon followed by protonation on the resulting N-4 negative charge to form an unstable intermediate, as shown in Figure 8. The methine proton in this intermediate becomes very acidic and prone to facilitate the ring opening process. When the methine proton was replaced by the methyl group (Compound G), such ring opening pathway was eliminated and no ring opening degradation was observed. At neutral or weakly basic conditions, the degradation is likely proceeded with the same mechanism shown in Figure 8.

At low pH, the higher p*K*a N-4 nitrogen of the 1,2,4-oxadiazole ring could become protonated and thus facilitate the degradation process. As a result, the methine carbon is activated and susceptible to the nucleophilic attack, such as from $H_2O$, to form a similar unstable intermediate and facilitate the concerted ring opening degradation process (Fig. 9).

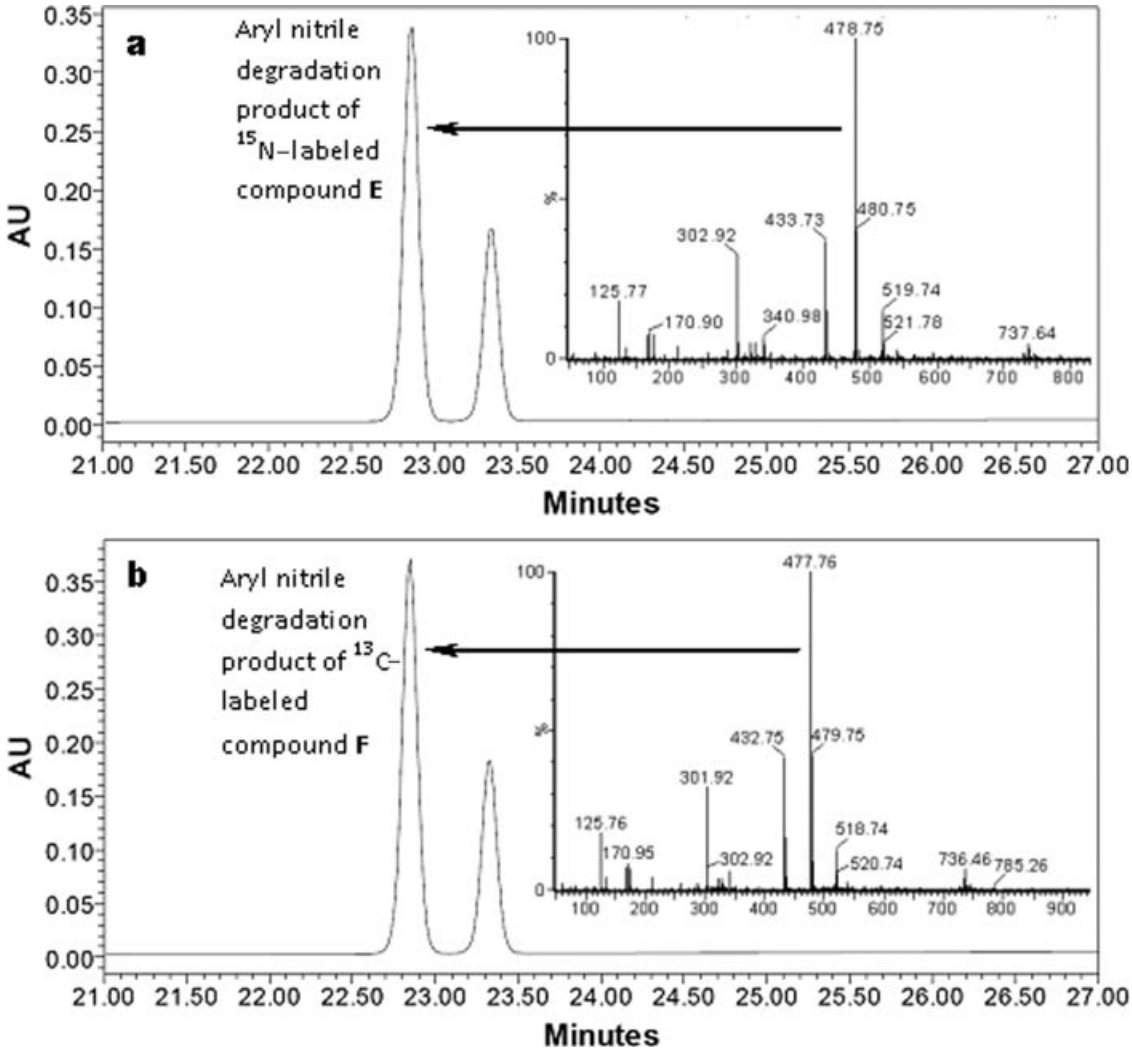


**Figure 5.** LC–MS results of stability samples for compound E (a) and compound F (b) in sodium acetate solution stored at 60°C for 7 days, indicating that $^{15}$N atom is retained on the nitrile group (*m/z* 478).

The dependence of the oxadiazole ring opening on the presence of proton donor under basic conditions and the observed acid catalysis are in disagreement with the mechanism previously proposed by Claisse et al.[17] (Fig. 2). The concerted mechanism initiated by proton abstraction by the base would be expected to result only in reduction in degradation rate as the pH is lowered and is not consistent with the *U*-shaped rate—pH profile shown in Figure 3. The profile is more consistent with our proposed mechanism where the nucleophilic attack on the methine carbon (which is both base and acid catalyzed) is the rate-limiting step.

During the NMR studies, it was found that the methine proton on the oxadiazole ring is exchangeable with deuterium under neutral or basic conditions as evidenced by the disappearance of the doublet peak ($\delta$-9.05, $J_{HC}$ = 230 Hz). Figure 10b showed that the methine proton almost completely exchanged with deuterium ($CD_3CN/D_2O$) in the presence of benzylamine at ambient temperature overnight. The mechanism of H/D exchange is proposed in Figure 11. The H/D exchange phenomenon implies that the methine carbon of the oxadiazole ring rapidly undergoes hybridization changes from $sp^2$ to $sp^3$ like and back to $sp^2$ like. Although the H/D exchange occurred rapidly through free base form, it would not likely proceed under acidic conditions as the protonated N-4 bearing a positive charge would become a highly energetic doubly charged intermediate. Figure 10c illustrates that the H/D exchange activity slows down dramatically at pD ~1, indicating that the protonated N-4 atom hurdle the H/D exchange. Figure 10d revealed the H/D exchange was almost complete in $CD_3CN/D_2O$ without the presence of deuterium chloride.

At a pH range of 3–5, the protonation of the N-4 would be minimal. In addition, the concentration of the nucleophile is too low, as compared with that at

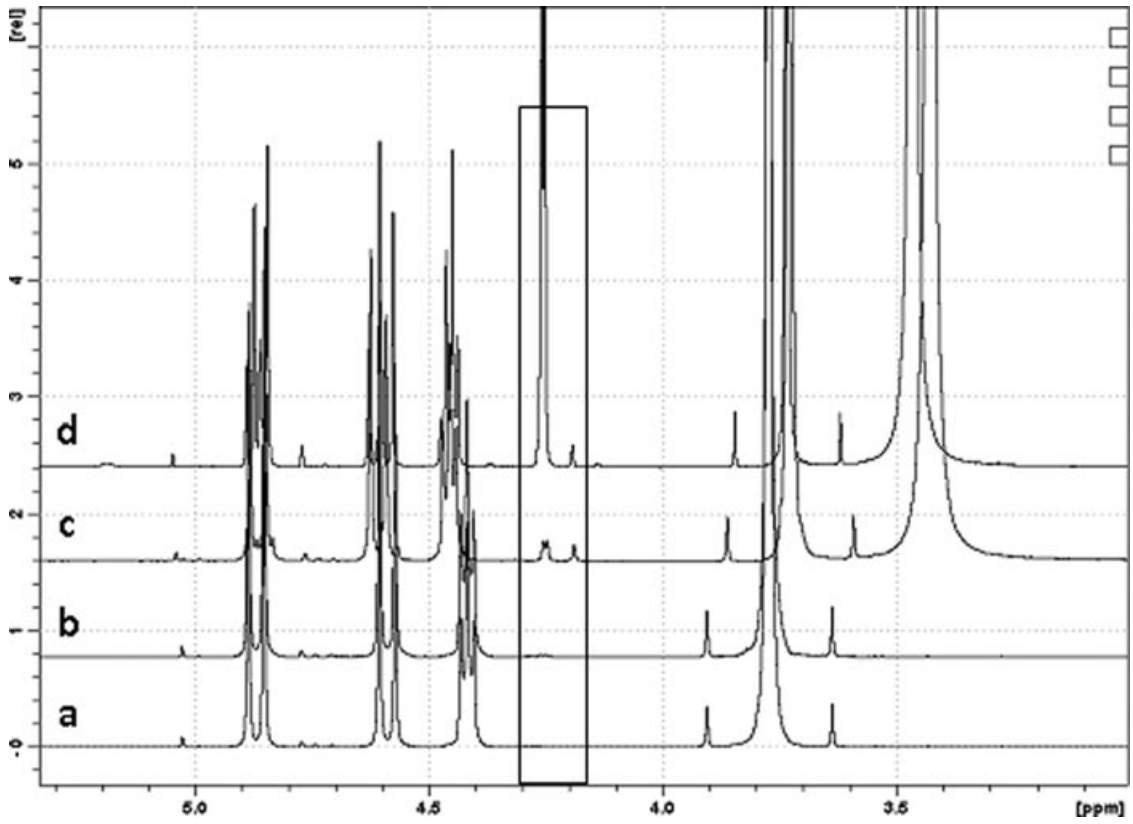


**Figure 6.** Overlay of partial $^{1}H$ NMR spectra (a) compound F + benzylamine in $CD_3CN$ at time 0, (b) compound F + benzylamine in $CD_3CN$ at 60°C after 6 h, no degradation observed, (c) compound F + benzylamine in $CD_3CN/D_2O$ at RT overnight, degradation proceeded, and (d) compound F + benzylamine in $CD_3CN/D_2O$ at 60°C after 6.5 h, degradation proceeded significantly.

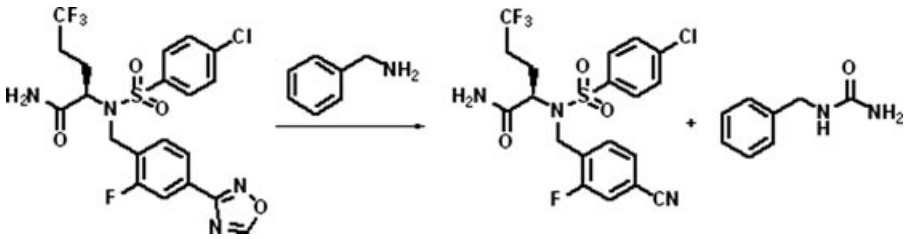

**Figure 7.** The reaction of compound A with benzylamine to form compound B and benzylurea.

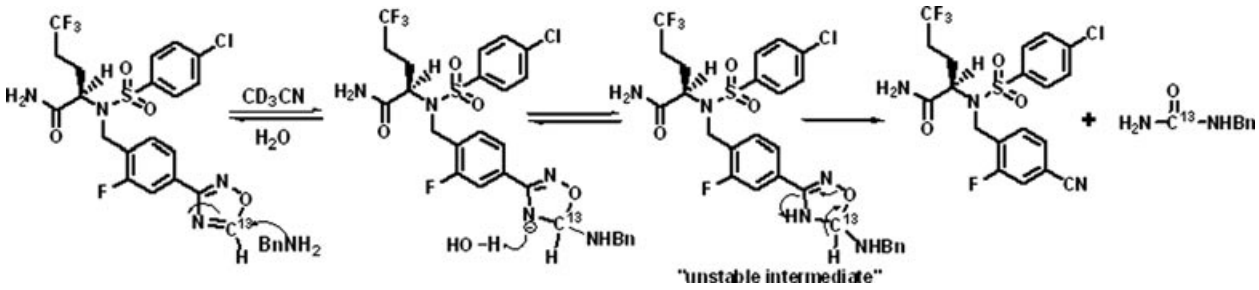


**Figure 8.** Proposed mechanism for compound F ($^{13}C$-labeled compound A) degradation process in the presence of benzylamine and water.

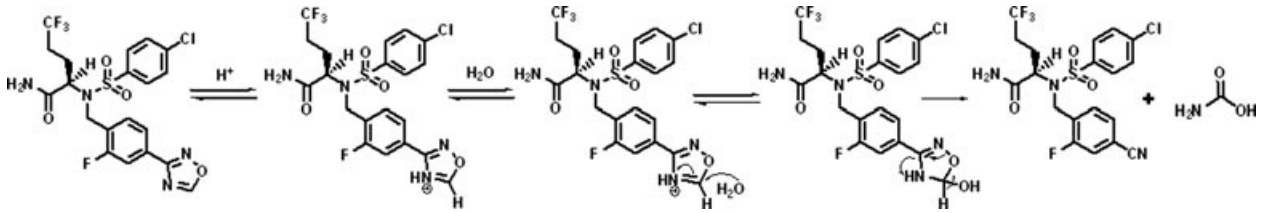

**Figure 9.** Proposed mechanism for compound A degradation under acidic conditions.

pH > 6, to produce the unstable intermediate that leads to ring opening. As a result, the degradation of compound A was the slowest. It was clear that at higher pH, the degradation of compound A was facilitated by a strong nucleophile in conjunction with a proton donor, and at lower pH, the protonation of the N-4 activated the methine carbon for nucleophilic attack to form a similar unstable intermediate.

Additional solution stability studies on compound A in the pH range of 3–5 in acetate buffers were carried out to investigate the degradation process in this relatively stable pH range. The degradation kinetics were compared under the same concentration at pH 3.8 and pH 5 acetate buffers, respectively. The observed first-order rate constant was faster at pH 3.8. There are two mechanisms operating simultaneously in acetate buffer at this pH range. One is nucleophilic attack by the acetate ion, and the other is N-4 protonation. The nucleophilic attack is more predominant at pH 5 (higher concentration of carboxylate) than at pH 3.8. On the contrary, the protonation at N-4 is relatively favored at pH 3.8 than at pH 5. Overall, the degradation rate was higher at pH 3.8 than pH 5 even though the actual concentration of the ionized acetate nucleophile is lower at pH 3.8 than at pH 5.

### Stability of Drug Product

Although HPMC-AS was selected as the polymer for solid dispersion of compound A based on its superior bio-performance, the stability of compound A in solid dispersions with HPMC and PVP–VA was studied

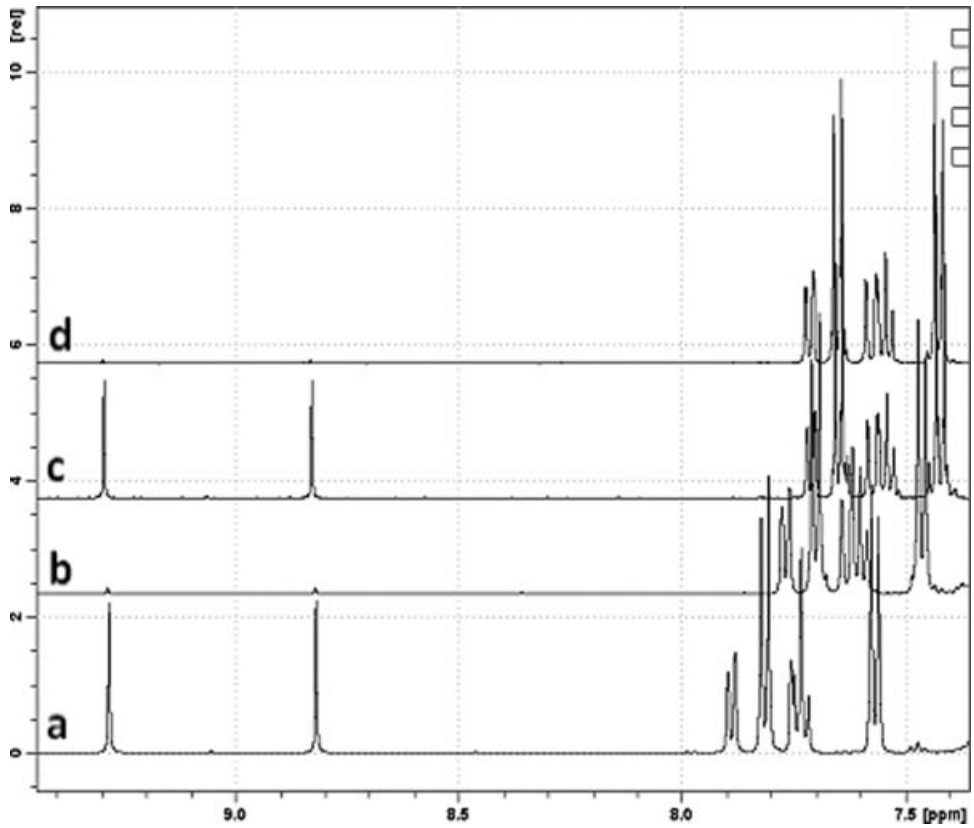


**Figure 10.** Overlay of partial $^1$H NMR spectra (a) compound F + benzylamine in $CD_3CN$ at 60°C for 6 h, (b) compound F + benzylamine in $CD_3CN/D_2O$ at RT overnight, (c) Compound F in $CD_3CN/D_2O$/DCl (pD-1) at RT overnight, then at 60°C for 18 h, and (d) Compound F in $CD_3CN/D_2O$ at RT overnight, then at 60°C for 18 h.

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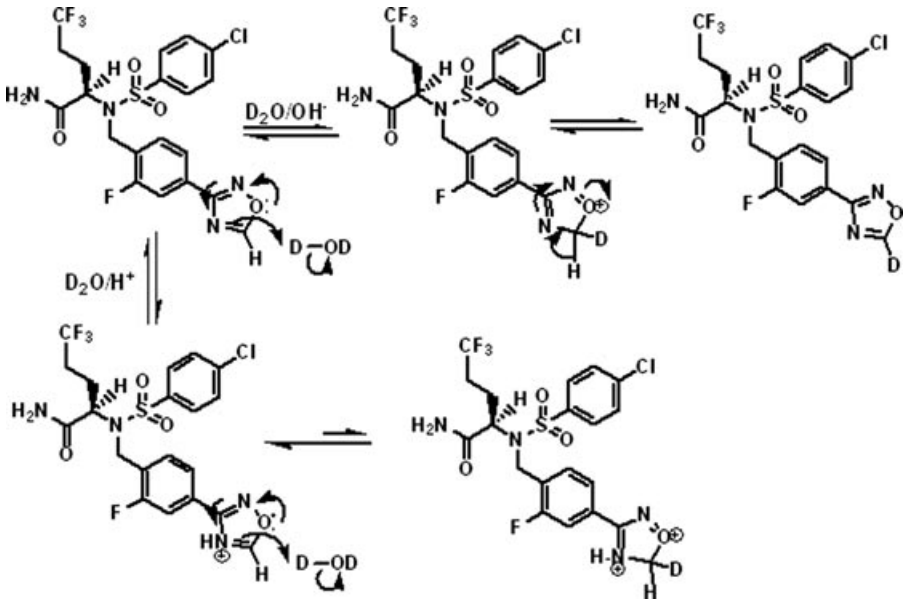


**Figure 11.** The H/D exchange of the methine proton on oxadiazole ring in basic and acidic condition.

to help understand the degradation in the dosage form. The microenvironmental pH values for HPMC-AS-, PVP–VA-, and HPMC-based solid dispersion estimated using a slurry method[18] were 4.2, 6.6, and 6.9, respectively. In the solid dispersion of compound A and HPMC, there was an increase of 0.8% compound B in the 40°C/75% RH closed condition, and 0.5% compound B in 25°C/60% RH open condition after 4 weeks. Under similar conditions, solid dispersion of compound A and HPMC-AS showed relatively lower degradant level (0.4% and 0.2% compound B in the 40°C/75% RH closed and 25°C/60% RH open conditions, respectively, after 4 weeks). These data agree with the estimated microenvironmental pH for the two solid dispersions. However, there was no degradation found in the solid dispersion of compound A and PVP–VA, although the moisture uptake in PVP–VA-based solid dispersion was the highest among all the formulations. This finding suggests that in the solid dispersion, available moisture amount alone is not critical and the presence/absence of a nucleophilic group (such as–OH) in the polymer chain in combination with moisture plays a role in the degradation. This is in accordance with our proposed mechanism (Fig. 8), that is, the combination of nucleophilic groups contained within cellulose, such as–OH, attacks the methine carbon and moisture protonating the N-4 nitrogen, leading to compound A degradation. It is worth noting that all three solid dispersions remained amorphous and no phase separation during the period of the stability study was observed. The microenvironmental pH of compound A and HPMC-AS solid dispersion is around 4, which places the drug in the most stable pH range, and the desiccant and induction sealed package reduces the risk of protonating N-4 nitrogen. Overall, understanding the degradation kinetics and mechanism helped designing a stable drug product.

## CONCLUSION

Our studies have shown that nitrogen protonation and nucleophilic reaction were the key factors in the degradation process of compound A. The pH-degradation rate profile showed that compound A was relatively stable in a pH range from 3 to 5. However, compound A degraded more rapidly outside of pH 3–5. Isotopically labeled and methylated compounds were employed in conjunction with LC–MS to investigate the bond cleavage positions on the oxadiazole ring. Once the cleavage positions were established, NMR studies verified that compound A did not degrade in dry nonnucleophilic solvents, and also helped elucidate the degradation mechanisms. Nucleophilic attack and protonation of the N-4 nitrogen are two important factors to initiate the degradation process. Because of the understanding of the kinetics and mechanism of degradation, the nature of the excipients in terms of their nucleophilic group, microenvironmental pH, and protection from moisture were all found to be critical in developing a stable drug product.

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