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Research Article

Effect of Counterion on the Solid State Photodegradation Behavior of Prazosin Salts

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Abstract. The effect of counterion was evaluated on the photodegradation behavior of six prazosin salts, *viz*., prazosin hydrochloride anhydrous, prazosin hydrochloride polyhydrate, prazosin tosylate anhydrous, prazosin tosylate monohydrate, prazosin oxalate dihydrate, and prazosin camsylate anhydrous. The salts were subjected to UV–Visible irradiation in a photostability test chamber for 10 days. The samples were analyzed for chemical changes by a specific stability-indicating high-performance liquid chromatography method. pH of the microenvironment was determined in 10% *w*/*v* aqueous slurry of the salts. The observed order of photostability was: prazosin hydrochloride anhydrous>prazosin camsylate anhydrous~prazosin-free base>prazosin hydrochloride polyhydrate>prazosin tosylate anhydrous>prazosin oxalate dihydrate~prazosin tosylate monohydrate. Multivariate analysis of the photodegradation behavior suggested predominant contribution of the state of hydration and also intrinsic photosensitivity of the counterion. Overall, hydrated salts showed higher photodegradation compared to their anhydrous counterparts. Within the anhydrous salts, aromatic and carbonyl counterion-containing salts showed higher susceptibility to light. The pH of microenvironment furthermore contributed to photodegradation of prazosin salts, especially for drug counterions with inherent higher pH. The study reveals importance of selection of a suitable drug salt form for photosensitive drugs during preformulation stage of drug development.

KEYWORDS: anhydrous; counterion; hydrate; photodegradation; prazosin; salt.

INTRODUCTION

During preformulation development, screening of a suitable salt form for ionizable drug candidates is a common strategy. This is because diverse salt forms at times possess different physicochemical and/or biopharmaceutical properties, namely, solubility, hygroscopicity, stability, and/or bioavailability (1–6). The screening protocols also include evaluation of the photosensitivity of the salt forms in both solid as well as solution state, as significant photodegradation of the salt form may compromise its therapeutic efficacy and/or potentially toxic products may be generated during the shelf life (7–9).

The photodegradation potential of a drug substance emerges from sensitivity of functional groups in the molecule to the light (7), *e.g.*, groups like carbonyl, nitro-aromatic, aryl, vinyl, thiol, halogens, *etc.*, are susceptible to photodegradation (10). However, apart from this inherent sensitivity, susceptibility of drug salt to light may be affected additionally by the nature and type of counterion. Among the reported examples, photodegradation of salts of an experimental compound B in solid state followed the order: piperazine salt > free acid > ethylenediamine salt > disodium salt (11). Similarly, solid-state photodegradation of amlodipine camsylate was lower compared to that of amlodipine besylate (12).

In literature, several reports exist on the effect of ionization on solution state photostability of various drugs. Examples of drugs include chloroquine (9), mefloquine (13), and ciprofloxacin (14). However, a systematic study analyzing the underlying factors in the solid-state photodegradation of drug salts has been lacking.

The purpose of this investigation was to make a comparative assessment of photo lability of drug salt forms in a solid state. Prazosin (Fig. 1) was chosen as a model drug, and the study was extended to its six salts existing in either anhydrous and hydrated forms. The drug possesses α_1 adrenergic blocking properties, and is useful in the treatment of hypertension and benign prostatic hyperplasia (15). It is weakly basic in nature (pK_a, 6.8). Currently, anhydrous and polyhydrate forms of hydrochloride salts are used commercially, which have a water content of <2% and 8–15%, respectively (16). The marketed anhydrous hydrochloride form is photostable, however, the polyhydrate hydrochloride form, which is formed from anhydrous hydrochloride form on exposure to high humidity, is sensitive to light (17). The selection of this molecule allowed us to study the effect of a range of parameters on photodegradation, including the

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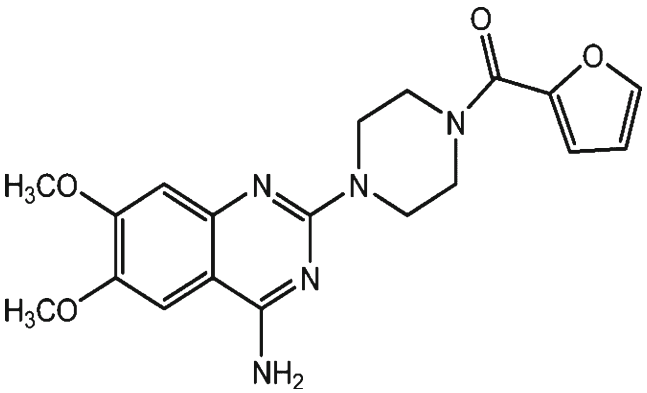


Fig. 1. Structure of prazosin

hydration state and counterion type. Moreover, preparation of different salts of prazosin allowed study of these factors further, along with a study of effect of inherent photosensitivity of the counterion.

MATERIALS AND METHODS

Materials

Prazosin hydrochloride anhydrous (PRB HCl AN) and prazosin hydrochloride polyhydrate (PRB HCl P) were purchased from Synthokem Laboratories, India and used as supplied (chemical purity >99.9%). All other chemicals used were analytical grade.

High-Performance Liquid Chromatography Method

High-performance liquid chromatography (HPLC) analysis was performed on LC1200 system (Agilent, Waldbronn, Germany), equipped with an on-line degasser (G1379A), high-pressure binary pump (G1312A), autoinjector (G1329A), thermostated column compartment (G1316A) and photodiode array detector (G1315B). Chromatographic separations were achieved on a Pursuit XRs C18 (250×4.6 mm, 5 μm) column. Data processing and acquisition was performed using Chemstation® software. The mobile phase consisted of methanol and potassium dihydrogen phosphate (10 mM, pH 4.0; Table I). The flow rate was 1 ml/min. Analysis was performed at a detection wavelength of 254 nm, using an injection volume of 5 μl.

Preparation of Salts of Prazosin

Prazosin salts were prepared by reaction crystallization method. First, prazosin-free base (PRB) was generated by dissolving the hydrochloride salt in water, followed by alkalinization with 2.5 M sodium hydroxide. The obtained precipitate was collected by filtration, and characterized by DSC, TGA, ^{1}H NMR and elemental analysis. Prazosin salts were then prepared by dispersing PRB in acetonitrile/water (4:1), followed by addition of counterion (in 1:1.5 stoichiometric ratio) dissolved in acetonitrile/water (4:1). In all the cases, white precipitate of the corresponding salt was formed immediately, which was filtered, dried and characterized by elemental analysis, ^{1}H NMR, PXRD, and DSC/TGA.

Photostability Study

As photodegradation in solid state is affected by the particle properties, including particle size and surface area of the drug (18), therefore, to ensure similar particle properties, samples were ground so as to reduce their particle size to <5 μm. The powders were then exposed to light in a photostability chamber (KBF 240, WTC Binder, Germany) set at 30±1°C/65±3% RH. The chamber was equipped with an illumination bank on the inside top, consisting of a combination of two black light UV lamps (OSRAM L18 W/73) and four white fluorescent lamps (Philips, Trulite), in accordance with option 2 of the ICH guideline Q1B (19). Both fluorescent and UV lamps were put on simultaneously. Samples of prazosin salts were spread in clean glass petri plates to 1 mm thickness and exposed to UV–Visible radiations for 10 days, and analyzed subsequently. In addition, moisture gain of the samples was evaluated at respective time points by gravimetric analysis. DSC, PXRD, and HPLC analyses were also performed on the samples at each pull point. Solution state photodegradation was assessed in mild acidic (0.01 N HCl), alkaline (0.01 N NaOH), and neutral (H_2O) conditions for 10 days. Suitable control samples were maintained under dark condition through appropriate external wrapping.

Statistical analysis of data was performed by Student–Neuman–Keuls method, using Sigmastat® software version 2.03 (Systat Software Inc., USA). Differences were considered to be significant at a level of $P<0.05$.

Microenvironment pH

Microenvironment pH was measured using the method proposed by Serajuddin *et al.* (20–22). A 10% *w/v* aqueous slurry of drug and salts was prepared and pH was determined using a calibrated pH meter (Hanna pH 210 microprocessor, USA).

Solubility Analysis

Solubility of prazosin salts was determined by shake flask method. Briefly, excess of prazosin salt was suspended in water, followed by equilibration in shaker bath for 24 h (37°C; 200 rpm).

Table I. Gradient HPLC Method for Analysis of Prazosin and its Salts

Time (min)	MeOH (%)	Buffer (%)	Elution
0.01→1.00	10	90	Isocratic
1.00→25.00	10→70	90→30	Linear gradient
25.00→30.00	70→10	30→90	Switch to initial eluent composition
30.00→37.00	10	90	Re-equilibration

Analysis was performed by high-performance liquid chromatography method, as mentioned in the High-Performance Liquid Chromatography Method section. Residual solids were assessed for any solid-state transitions by DSC and PXRD.

Activation Energy for Dehydration

Activation energy (E_a) of dehydration of hydrates was determined by DSC. Samples were heated in DSC aluminum pans at heating rates of 1, 2, 5, 10 and 20°C/min. Peak temperature (T_{max}) of dehydration was obtained at each heating rate (β). E_a was determined by Kissinger analysis as (23,24):

$$\frac{d\ln\left\{\frac{\beta}{T_{max}^2}\right\}}{d\left\{\frac{1}{T_{max}}\right\}} = -\left\{\frac{E_a}{R}\right\}$$

RESULTS AND DISCUSSION

Characterization of Prazosin Salts

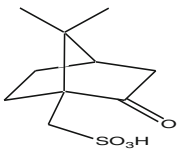
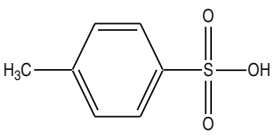
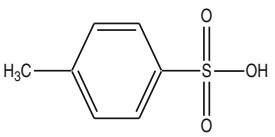
Table II enlists the physicochemical properties of prepared salt forms of prazosin. The detailed physicochemical properties of prepared salts of prazosin have been reported elsewhere (25). TGA analysis showed that prazosin, PRB HCl AN, PRB CSA AN, and PRB TSA AN were all anhydrous in nature. In contrast, PRB HCl P, PRB OA DI, and PRB TSA MH existed as hydrates. Earlier, we have reported that PRB HCl P is a non-stoichiometric channel hydrate, containing channel-bound water, in addition to the free interstitial water in the unit cell (26).

Photodegradation of Prazosin Salts

Table III shows the photodegradation pattern of prazosin salts after 10 days followed the order: PRB HCl AN>PRB CSA AN~PRB>PRB HCl P>PRB TSA AN>PRB OA DI~PRB TSA MH. This data has been reported in our previous work (25). In this work, we envisaged a thorough understanding of the factors affecting the observed photodegradation behavior.

In general, creamish yellow to reddish brown surface discoloration of samples was observed, except for PRB CSA AN and PRB HCl AN, which retained off-white color even after photodegradation. Chemical degradation of prazosin salts was high initially, but slowed down subsequently. This could be attributed to the initial surface photodegradation and

Table II. Physicochemical Characterization of Salt Forms of Prazosin

Compound	Melting point [a] (onset °C)	TGA[a] (% weight loss)	Nature of solid form[a]	Solubility (mg/ml)[a,b]	pH[c]	Counterion structure
PRB	264	0.2	Anhydrous	0.15	8.50	–
PRB HCl AN	284	0.2	Anhydrous	0.99	2.98	HCl
PRB HCl P	272	10.0	Polyhydrate[d]	0.93	3.20	HCl
PRB CSA AN	332	0.2	Anhydrous	0.22	5.32	
PRB OA DI	254	8.3	Dihydrate	0.16	1.98	
PRB TSA AN	300	0.2	Anhydrous	0.40	5.33	
PRB TSA MH	310	3.0	Monohydrate	0.30	4.80	

[a] Data reproduced from Ref. (25)
[b] Aqueous solubility, as determined by 'shake flask' method after 24 h
[c] pH of the microenvironment (20,21)
[d] Polyhydrate form, consisting of dihydrate and free interstitial water

Table III. Percent Drug Remaining for Prazosin Salts, After 10 days

Sample	% remaining[a]
PRB	93.96 (0.08)[b]
PRB HCl AN	99.55 (0.15)
PRB HCl P	91.04 (0.06)
PRB CSA AN	94.24 (0.08)
PRB OA DI	76.84 (0.02)
PRB TSA AN	87.10 (0.04)
PRB TSA MH	76.04 (0.11)

[a] Data reproduced from Ref. (25)
[b] Parentheses indicate the standard deviation

subsequent inability of the photodegradation reaction to percolate to the bulk sample (27,28). An additional contributor could be the shielding of bulk material by colored photodegradation products formed on the surface (27). In contrast, lesser surface discoloration was observed in PRB HCl AN, thus providing weaker shielding of bulk molecules. In a study on solid-state photostability of nifedipine, it was observed that some photodegradants absorbed light strongly and thus had a photoprotective effect on the bulk of the solid sample (8). It is similarly reported that the drug molecules present in the core of a tablet formulation are shielded by the photodegradation products formed near the surface (28). This also becomes important during the photodegradation of prazosin, which generated creamish yellow to reddish brown photodegradation products.

Effect of Hydrate Water on Photodegradation

PRB HCl AN exhibited lesser photodegradation compared to PRB HCl P, thus indicating contribution of water of hydration towards photodegradation. A similar behavior was observed for PRB TSA AN and PRB TSA MH, wherein the latter showed higher overall photodegradation. In a reported study also, faster photodegradation of lanthanum nitrate hexahydrate and calcium nitrate tetrahydrate was observed, compared to their anhydrous counterparts (29). In still another study, photostability of different solid forms of cianidanol followed the order: monohydrate II (most stable) > monohydrate I > tetrahydrate I (least stable) (30,31).

The explanation is that water of hydration provides different strength of interaction in the crystal lattice of a salt, thus contributing to differential photodegradation behavior. It is reported that hydrate molecules with a weaker binding of water in the crystal lattice show higher photodegradation, compared to the hydrate molecules having stronger water binding in the crystal lattice (30,31). Also, binding strength of hydrate water in the crystal lattice may be correlated to the dehydration activation energy of hydrate molecule. Higher activation energy is required for removal of hydrate water from crystal lattice having stronger interactions within the crystal lattice. Figure 2 shows the Kissinger plots for dehydration of PRB HCl P (showing least photodegradation in hydrate class) and PRB TSA MH (showing highest photodegradation in hydrate class). Kissinger plot is based on the assumption that the rate of reaction is maximal at the temperature at which endotherm reaches a maximum, and indicates activation energy for dehydration of a hydrate (24,32). Plots with regression of 0.97–0.99 were obtained. E_a (in kilojoule per mole) for dehydration gave the values: PRB HCl P (50.6) and PRB TSA MH (42.2). This suggests easier dehydration of lattice water from PRB TSA MH (and in turn weaker binding in the crystal lattice), compared to that from PRB HCl P. This may contribute to the observed lower photodegradation of PRB HCl P, in spite of its higher water content, compared to PRB TSA MH.

Effect of Microenvironment pH

It is a known fact that photodegradation of an ionizable drug in solution state is affected by pH of the solution. For example, photodegradation of ciprofloxacin hydrochloride was dependent on the solution pH (14). Ciprofloxacin is an amphoteric compound, with pK_a values of 6.09 (carboxylic group) and 8.74 (piperazinyl ring nitrogen) (33). The zwitterion has an isoelectric pH of 7.4. The drug is most sensitive to photodegradation in zwitterionic form at slightly basic pH. Conversely, it is most stable at pH 3.0 to 4.0, wherein the COOH group is not ionized and the basic nitrogen group is completely protonated. Similarly, in another study, photodegradation of amiloride (weakly basic drug) was observed to be dependent on the solution pH, with neutral molecule being more reactive than the ionized form (34).

The concept of pH-dependent solution photodegradation has been extended to solid state in terms of the microenvironment pH, which refers to hydrogen ion activity in water layers or water plasticized amorphous domains, and has been implicated as a factor influencing drug degradation in the solid state (35). During photodegradation, loss of surface hydrate molecules may furthermore generate a supersaturated drug solution in the microenvironment, amenable to higher photodegradation. Moisture uptake during photodegradation could also contribute to an increased activity in the microenvironment, thus simulating solution state photodegradation.

The values of microenvironment pH for prazosin and its salts are included in Table II. The pH of prazosin-free base microslurry was 8.5, while the same for prazosin salts was acidic, with values dependent upon the strength of the counterion and the solubility of corresponding salt. Solubility of PRB HCl AN and PRB HCl P was reasonably higher (~1 mg/ml),

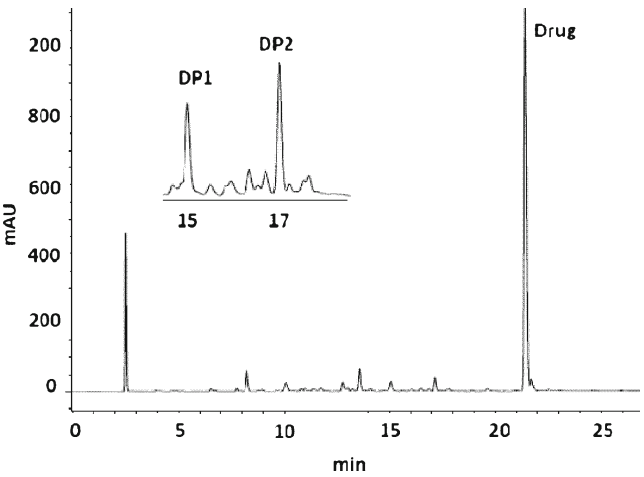


Fig. 2. HPLC chromatogram of prazosin, showing the photodegradation products. DP1 and DP2 denote the major photodegradation product formed in solid state

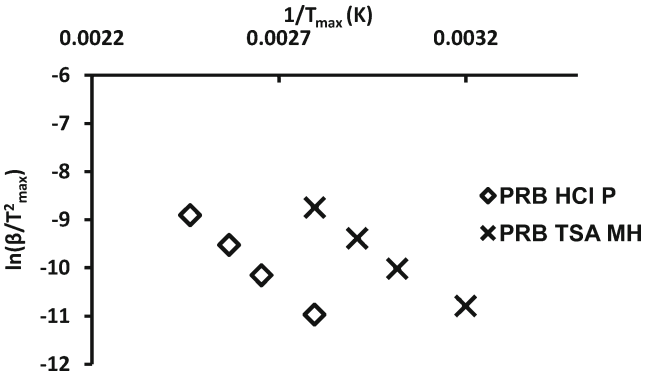


Fig. 3. Kissinger plot for PRB HCl P and PRB TSA MH (n=2). *Error bars* indicate standard deviation

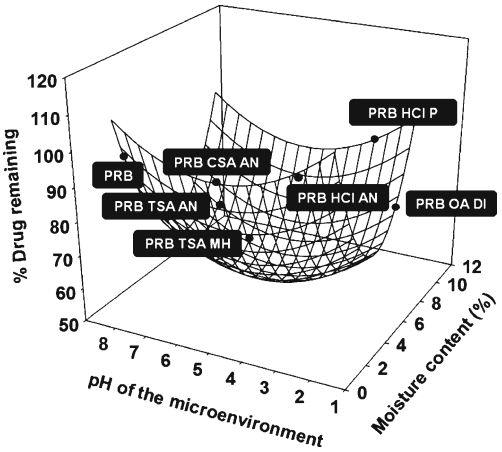


Fig. 5. Plot showing the effect of pH of the microenvironment and hydration state on drug photodegradation (till 10 days). Moisture content includes the moisture gained till 10 days

resulting in lower microenvironment pH. Conversely, solubility of PRB CSA AN, PRB TSA AN, and PRB TSA MH salts was lower (0.2–0.4 mg/ml), thus leading to relatively higher microenvironment pH. PRB OA DI provided an extremely acidic microenvironment (pH 1.98), possibly due to two carboxylic groups in the counterion structure. Prazosin salts showing higher pH of the micorenvironment showed higher photodegradation, due to an increased tendency to disproportionate to the unionized free base.

Analysis of photodegradation samples by LC-MS (Fig. 3) in solid as well as solution state was performed, to mechanistically understand the observed photodegradation behavior. Two major photodegradation products *viz*., DP1 (*m*/*z* 221) and DP2 (*m*/*z* 318) were formed in the solid state. In solution state, DP1 was predominantly formed at basic pH, while DP2 was observed in both acidic and neutral pH. The absence of DP2 in alkaline pH could be correlated to its complete further fragmentation to DP1, as elimination of piperazine ring could be catalyzed in alkaline pH (Fig. 4).

The generation of DP-1 may be directly from the parent drug through heterocyclic piperazine ring cleavage. It may be formed through *N*-dealkylation photodegradation process pathway, which is a well-documented reaction (36). DP-2 is most likely formed due to homolytic cleavage of carbon bond α to carbonyl between C=O and furanyl group thus leading to a carbonyl radical, which further abstracts a hydrogen from surrounding molecules, *e.g.*, solvent. This is further favored if the departing alkyl part has a stabilized hydroxy group (ring oxygen may serve the purpose in the present case or an intermediate formed after hydrolytic opening of furan ring may in fact have a −OH group at the C-bearing radical).

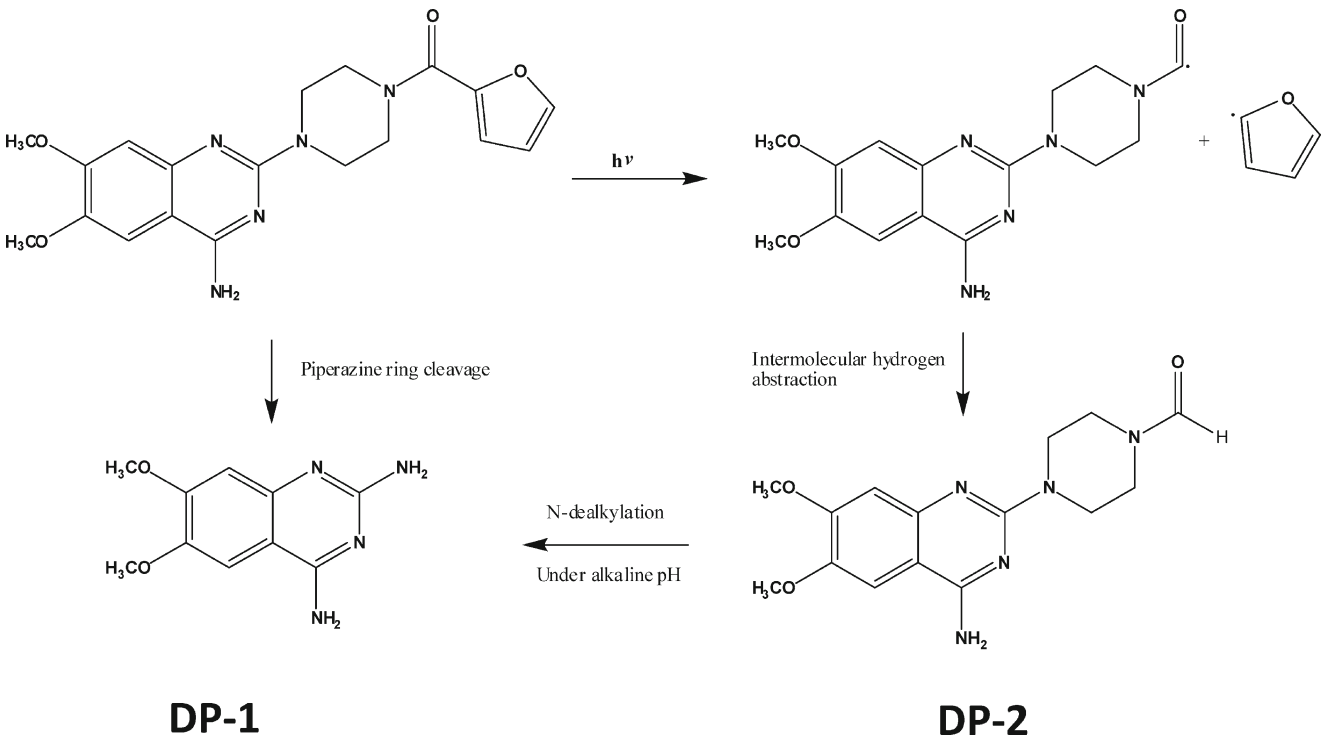


Fig. 4. Possible photodegradation pattern of prazosin

Effect of Intrinsic Photosensitivity of the Counterion

Intrinsic photosensitivity of the counterion affects the photodegradation behavior of drug salts. Aromatic and/or carbonyl counterions do show higher photodegradation, compared to the non-aromatic counterions (37). This is further correlated to the fact that carbonyl counterions like oxalic acid and aromatic toluenesulfonic acid have an inherently higher tendency towards photodegradation (38,39). A similar behavior is reported for the photodegradation of amlodipine salts, wherein, amlodipine besylate showed higher photodegradation in comparison to amlodipine camsylate (12). Aromatic counterions absorb light and act as potential photosensitizers, thus catalyzing photodegradation reactions. This reasoning explains higher photodegradation of prazosin salts prepared with aromatic (PRB TSA AN and PRB TSA MH) or carbonyl counterion (PRB OA DI).

Multivariate Analysis of the Factors Affecting Photodegradation

Figure 5 shows the effect of pH of the microenvironment and water content on extent of drug loss upon photodegradation till 10 days. The percent drug remaining could be represented by the following equation:

$$\begin{aligned}\%\ \text{drug remaining} = {} & 168.37(\pm 6.54) - 25.21(\pm 1.63) \\ & \times \text{moisture content} - 13.57(\pm 1.69) \\ & \times \text{pH} + 2.03(\pm 0.14) \\ & \times \text{pH}^2 + 1.26(\pm 0.15) \\ & \times \text{moisture content}^2; r^2 = 0.99.\end{aligned}$$

Multivariate analysis suggested that % photodegradation increased with an increase in moisture content and pH of the micoenvironment. The effect of moisture content on photodegradation was relatively higher as compared to the effect of pH of the microenvironment.

Comparison of photodegradation of PRB HCl AN (0.2% moisture content) with other anhydrous salts of prazosin, namely, PRB CSA AN (0.2% moisture content) and PRB TSA AN (0.2% moisture content) suggested predominant effect of the type of counterion and thus its inherent photosensitivity. Inorganic hydrochloride counterion showed lesser tendency to photodegradation, as compared to aromatic PRB TSA AN, as well as PRB CSA AN. Comparison of PRB CSA AN and PRB TSA AN furthermore demonstrated the role of the intrinsic photosensitivity of counterion, wherein, in spite of a similar pH of the microenvironment and moisture content, photodegradation of PRB TSA AN (aromatic counterion) was higher compared to PRB CSA AN (non-aromatic counterion).

Comparison of PRB HCl AN and PRB HCl P suggested catalyzing effect of water of hydration on photodegradation. A similar behavior could be observed for PRB TSA AN and PRB TSA MH, wherein degradation of PRB TSA MH was higher due to its hydrate nature. Similarly, pH of the microenvironment contributed towards photodegradation of prazosin salts, and was more important for low soluble salts (PRB CSA AN, PRB TSA AN, and PRB TSA MH), having high microenvironment pH. However, as discussed earlier, overall contribution of pH was limited in solid state, compared to the effect of type of counterion, and their hydration state.

Comparison of prazosin and its salts did not establish any correlation between the photodegradation and ionization of prazosin, possibly due to concomitant contribution of other factors.

CONCLUSION

This study evaluated the effect of counterion on the photodegradation behavior of prazosin.

Photodegradation of prazosin salts was affected by the hydration state of salt form inherent photosensitivity of the counterion, and to a limited extent by the pH of the microenvironment of the drug salt. This study thus highlights the importance of photostability evaluation of drug salts in solid state during preformulation stage of drug development.

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