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Interaction of omapatrilat with FD&C Blue No. 2 lake during dissolution of modified release tablets

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Abstract

The purpose of this study was to identify the mechanism(s) of omapatrilat degradation observed during dissolution from modified release (MR) tablet formulations containing colorants. The tablets were manufactured by a dry granulation process employing roller compaction. The colorants were added intragranularly and included red and yellow iron oxides and FD&C Blue No. 2 lake and dye. Dissolution studies in pH 6 or 6.8 media do not indicate any omapatrilat degradation in the absence of colorants. In the presence of colorants the degradation rate of omapatrilat in pH 6.8 media was in the following order: blue lake > blue lake + yellow iron oxide > yellow and red iron oxides. Higher degradation was observed with MR tablets formulated with indigo carmine (dye) as opposed to tablets formulated with aluminum oxide or aluminum hydroxide (dye substrate portion of lake). The inclusion of tartaric acid and the photostabilizer, uric acid, in omapatrilat MR tablets containing the blue lake reduced the degradation significantly. The dissolution instability observed at pH 6.8 in the MR tablet formulated with FD&C Blue No. 2 Lake was attributed to the dye component of the lake. The instability was more pronounced at higher pH and in the absence of a photostabilizer.

Keywords: Omapatrilat; Dissolution; Modified release; Blue No. 2 lake; Stability; Photostabilizers; Indigo carmine

1. Introduction

Omapatrilat (BMS-186716-01), a vasopeptidase inhibitor, was investigated for the treatment of high blood pressure and heart failure. An immediate release formulation had been developed for use in clinical trials. A controlled release formulation was developed to provide a more favorable blood plasma peak to trough ratio of omapatrilat. Colorants were primarily used to differentiate between different tablet potencies. FD&C Blue No. 2 lake and yellow and red iron oxides are among the few colorants that are accepted in major international markets. Since these colors can also be mixed in different proportions to yield new colors/shades, they were evaluated during formulation development. Eventually the different strength tablets were differentiated using pink, yellow, light blue and light green shades. The pink, yellow and blue shades were obtained by using low levels of red iron oxide, yellow iron oxide and FD&C Blue No. 2 lake, respectively. The light green shade was obtained by using a combination of yellow iron oxide and FD&C Blue No. 2 lake.

Whilst some colors, notably the inorganic pigments (e.g. iron oxides), show excellent stability, other coloring agents, such as some organic colors (e.g. FD&C Blue No. 2 lake), have poor stability properties but are used in formulations because of their lower toxicity. There are also some technical restrictions on the use of iron oxides, e.g. dullness and limitation of shade, and abrasiveness to processing equipment. The stability of certified organic dyes has been studied by various authors. Indigo carmine (FD&C Blue No. 2 dye) has been shown to be poorly compatible with citric acid, saccharose, ascorbic acid, gelatin, glucose, lactose, oxidizing agents, and saturated sodium bicarbonate solution. It has also been shown to be sensitive to light (Handbook of Pharmaceutical Excipients, 1994). Jones et al. (1955) showed that solutions of FD&C Blue No. 2 dye exposed to ordinary diffuse laboratory light underwent oxidative degradation. Asker and Collier (1981) and Lachman et al. (1962) have tried to improve the photostability of colorants by using UV absorbers such as uric acid and 2,4-dihydroxybenzophenone, respectively. The photostability of FD&C Red No. 3 color coated tablets was improved with 2-ethoxyethyl *p*-methoxycinnamate,

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a sun-screening agent (Hajratwala, 1974). Brownley and Lachman (1963) found that FD&C Blue No. 2 dye was very unstable in the presence of lactose and spray-processed lactose and their primary hydrolysis products (D-glucose and D-galactose). According to these authors the blue dye seems to have degraded by reduction to a semiquinone followed by oxidation.

Very little information is published on the incompatibilities of the lake colorants with either excipients or drugs. The water insoluble lakes are made by adsorbing the soluble dyes onto inert substrates such as alumina. This makes the lakes more stable and less prone to surface migration during the drying of wet granulated formulations. As a result, the lakes have been widely used and the use of soluble dyes has fallen out of favor in pharmaceutical dosage forms. However, the incompatibilities of the soluble dye portion of the lake with drugs or excipients under the right conditions is still a concern.

The objective of this study was to investigate the cause of omapatrilat degradation observed during dissolution testing of modified release (MR) tablets containing colorants.

2. Materials and methods

2.1. Materials

Omapatrilat (vasopeptidase inhibitor, Bristol-Myers Squibb), FD&C Blue No. 2 HT aluminum lake, red and yellow iron oxides (colorant; Colorcon Inc., PA, USA), indigo carmine (indigotine/blue #2 dye; J.T. Baker, NJ, USA), alumina/aluminum hydroxide (substrates for indigo carmine dye; J.T. Baker, NJ, USA), lactose anhydrous, microcrystalline cellulose (diluents/fillers; to check manufacturers), hydroxypropyl methylcellulose premium grades (controlled release aids; The Dow Chemical Company, MI, USA), tartaric acid (acidifying agent), stearic acid (lubricant), disodium salt of ethylenediamine tetraacetic acid (disodium EDTA) a chelating agent (J.T. Baker, NJ, USA), uric acid and 2,4-dihydroxybenzophenone (2,4-DHBP) (photostabilizers; J.T. Baker, NJ, USA).

2.2. Tablet manufacturing

The drug, lactose anhydrous (deaggregated) and colorant(s) were mixed in a V-blender (A&M Corporation, Canada). Dye substrates, ethylene diamine tetraacetic acid disodium salt (disodium EDTA), tartaric acid and photostabilizers when included in the formulation, were processed in the same fashion as the colorants. The mixed blend was passed through a Comil (Quadro) equipped with a 1.0 mm screen for enhancing color distribution. Microcrystalline cellulose (Avicel PH 101®), hydroxypropyl methylcellulose (K100LVPCR and K4MPCR) and stearic acid were then added and further blended. This blended pre-mix was then dry granulated by roller compaction using the Freund TF Mini™ roller compactor (Vector Corporation). The compacted ribbons were sized using an oscillator (Erweka) equipped with a 4.0 mm pre-screen and a 1.0 mm final screen. The sized granulation was then mixed with silicon dioxide and stearic acid. Capsule shaped tablets, containing 5 mg of omapatrilat per tablet were then compressed on a rotary tablet press (Korsch™ PH 100).

2.3. Tablet dissolution

Dissolution studies ($N = 6$) were carried out in 1000 mL of pH 6.0, 6.5 or 6.8 phosphate buffers containing 0.006% disodium EDTA using the USP 1 apparatus (baskets) at 100 rpm and 37 °C. Quantification of omapatrilat and the disulfide degradant were done by reverse phase HPLC at 220 nm. The column used was a 15 cm × 3 mm Zorbax® C_{18} column with a 3.5 μm particle size. The mobile phases were as follows—mobile phase A: 35% acetonitrile/65% water containing 0.1% phosphoric acid. Mobile phase B: 90% acetonitrile/10% water.

2.4. Solid state stability testing

The solid state stability testing of tablets was carried out at 5 °C and 40 °C/75% RH storage conditions in open and closed packages. In the open condition the tablets were placed in a petri dish. For the closed condition, the tablets were placed in 95 cm^3 white, opaque (high density polyethylene) HDPE bottles closed with a child resistant cap without any cotton or desiccant.

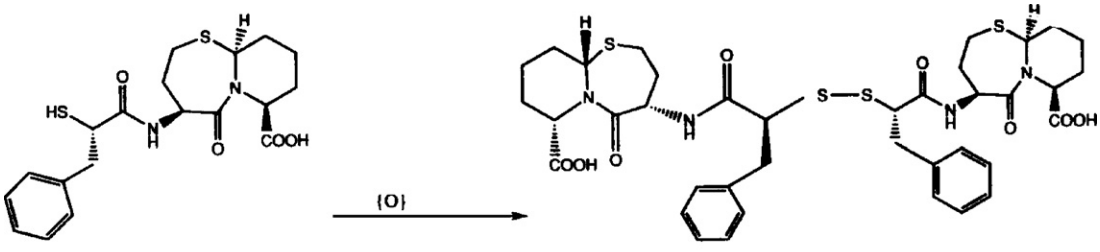
2.5. Impurity analysis of tablets (stored under accelerated stability)

Omapatrilat was extracted in a mixture of acetonitrile and 0.02 M ammonium phosphate (50:50) buffer system. The pH of the system was adjusted to 2.0 with phosphoric acid, and 0.005% EDTA disodium was added to prevent oxidation. Impurity analysis (peak area percent) was conducted by reverse phase HPLC at 220 nm. The column and mobile phases are as described in Section 2.3.

3. Results and discussion

3.1. Solid state stability of omapatrilat tablets

In the solid state, omapatrilat primarily degrades via oxidation to form the disulfide dimer as shown below:



BMS-186716-01 Disulfide Dimer

Table 1
Solid state stability profile (19 weeks data) of 5 mg omapatrilat MR tablets in the presence and absence of colorants

Formulation	Condition	Area %		
		Omapatrilat	Disulfide degradant	Total impurities
Neat drug	Initial	99.5	0.09	0.48
	5 °C	99.5	0.08	0.44
	40 °C/75% RH open	99.5	0.16	0.50
	40 °C/75% RH closed	99.5	0.14	0.50
Tablets with no colorant	Initial	99.5	0.18	0.55
	5 °C	99.5	0.20	0.52
	40 °C/75% RH open	98.6	1.01	1.36
	40 °C/75% RH closed	98.7	1.02	1.29
Tablets with FD&C Blue No. 2 lake	Initial	99.5	0.18	0.55
	5 °C	99.5	0.18	0.40
	40 °C/75% RH open	98.3	1.33	1.75
	40 °C/75% RH closed	98.7	1.04	1.26
Tablets with indigo carmine dye	Initial	99.5	0.18	0.54
	5 °C	99.5	0.17	0.45
	40 °C/75% RH open	98.7	1.06	1.34
	40 °C/75% RH closed	98.6	1.21	1.41

Open condition: tablets as well as neat drug was placed in a petri dish; closed condition: tablets as well as neat drug were placed in a 95 cm^3 white, opaque HDPE bottle closed with a child resistant cap without induction sealing.

The thiol functionality of omapatrilat is prone to free radical-initiated oxidative degradation. The rates of such degradation depend on the pH, the amount of dissolved oxygen and the presence of metal ions in solution (Jain, 1986). Omapatrilat was shown to be more stable at low pH. At 37 °C, a 0.03 mM solution of omapatrilat exhibited an 11% decrease in potency at pH 2 and 4 after 16 h. The stability of omapatrilat decreased as the pH was raised and at pH 7 there was a loss of 71% potency in a 0.03 mM solution after 16 h at 37 °C (Thakur and Chen, Internal Communication, 1993). The drug exhibited good solid state stability when formulated as MR tablets with the colorants FD&C Blue No. 2 lake and indigo carmine (FD&C Blue No. 2 dye) as shown in Table 1. For comparison, the stability of the API and MR tablets formulated without the colorants are also shown. In general, higher disulfide levels were observed at the 40 °C/75% RH condition for all tablets. The neat API exhibited better stability as compared to the formulated dosage forms. However, the stability of tablets formulated with and without colorants was similar. From this it was concluded that omapatrilat was compatible with the colorants in the solid state.

3.2. Stability of omapatrilat in MR tablets during dissolution testing

The dissolution data of omapatrilat tablets formulated with and without colorants in pH 6.8 media containing 0.006% disodium EDTA is shown in Fig. 1. There was no degradation observed in the absence of any colorants. However, moderate degradation (as determined by decrease in % dissolved) was observed in the presence of the blue lake. Relatively lower amounts of degradation was observed from green omapatrilat tablets formulated with a mixture of yellow iron oxide and the blue lake. This was attributed to the lower amount of blue lake in the mix. Finally, minimal degradation was observed when the MR tablets were formulated with either yellow or red iron oxides. Since the oxidative degradation of omapatrilat could be catalyzed by trace metal ions, the effect of adding additional disodium EDTA to the dissolution medium was investigated. The results in Fig. 2 shows that increasing the amount of disodium EDTA had no effect on reducing the degradation. Similarly, formulating the MR tablets with disodium EDTA intragranularly had no beneficial effect on the degradation profile (Fig. 3). Thus, it was concluded that trace metal ions did not contribute to the degradation of omapatrilat in the presence of the blue lake or dye.

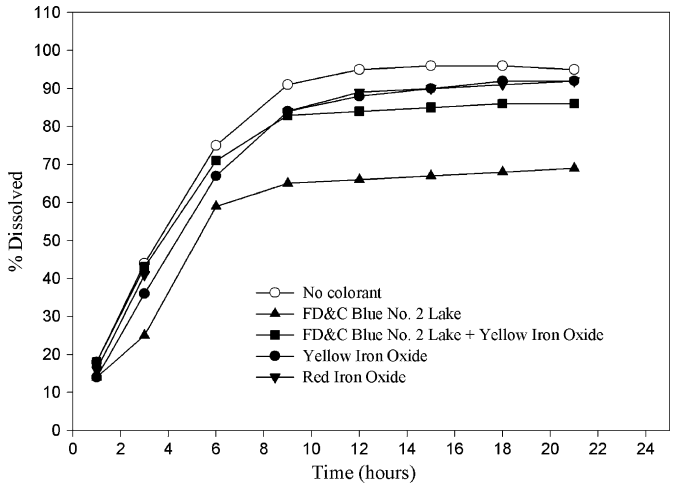


Fig. 1. Dissolution of 5 mg omapatrilat MR tablets containing different colorants in pH 6.8 phosphate buffer.

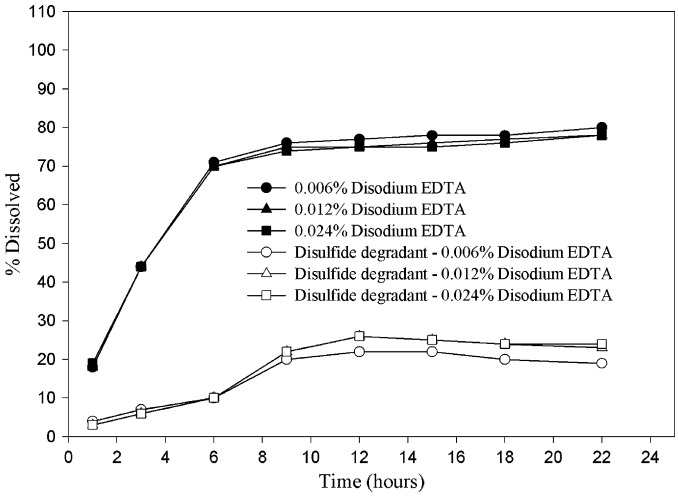


Fig. 2. Dissolution/degradation of 5 mg omapatrilat MR tablets in pH 6.8 media containing varying levels of disodium EDTA.

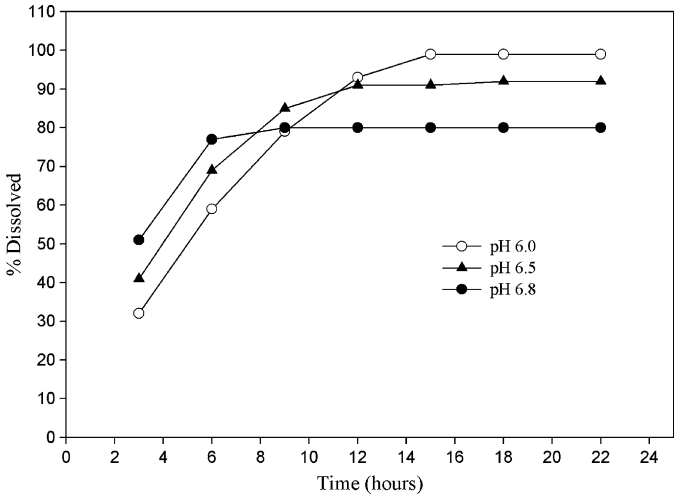


Fig. 4. Dissolution of 5 mg omapatrilat MR tablets containing FD&C Blue No. 2 lake as a colorant in different pH media.

3.3. Effect of dissolution media pH on omapatrilat stability

The dissolution of omapatrilat tablets containing FD&C Blue No. 2 lake at different pH is shown in Fig. 4. The initial dissolution rate tends to increase with increasing pH. This is probably due to the pH solubility profile of the weak acid, omapatrilat. At pH 5.6 the equilibrium solubility of omapatrilat is 0.33 mg/mL at 24 ± 3 °C. The solubility increases to 2.38 mg/mL at pH 6.8. The higher dissolution rate with increasing pH is then probably due to the higher concentration gradient across the diffusion layer. From the figure it can also be seen that the amount of drug dissolved/recovered decreases as the pH of the dissolution medium increases, an indirect indicator of higher instability at higher pH. This data is in agreement with the solution state stability data that was reported in Section 3.1. The absence of degradation in tablets without the blue lake suggests that the tablet microenvironment during dissolution plays a role in omapatrilat degradation. A possible role is that the tablet microenvironment contributed to the instability of the blue lake, which in turn leads to the degradation of omapatrilat. To study this hypothesis, omapatrilat was formulated with intragranular tartaric acid as an acidifying agent to see if reduction in the microenvironmental pH would improve drug stability. The results indicated that the incorporation of tartaric acid significantly reduced the degradation (Fig. 5) in pH 6.8 media. Thus, it appears that tartaric acid may have lowered the microenvironmental pH to a level where the blue lake may have been more stable, thereby, reducing the degradation of omapatrilat. To approximate the microenvironmental pH, a 10% (w/w) slurry of the tartaric acid containing omapatrilat granulation in pH 6.8 phosphate buffer was prepared. The omapatrilat granulation was stirred for about 24 h resulting in the formation of a smooth gel. A more concentrated system (>10% (w/w)) resulted in the formation of an extremely viscous system that led to the formation of lumps that were hard to disperse. The pH of the gel was found to be 5.99. This lower pH further supports the role played by tartaric acid in stabilizing the drug by creating a low pH milieu.

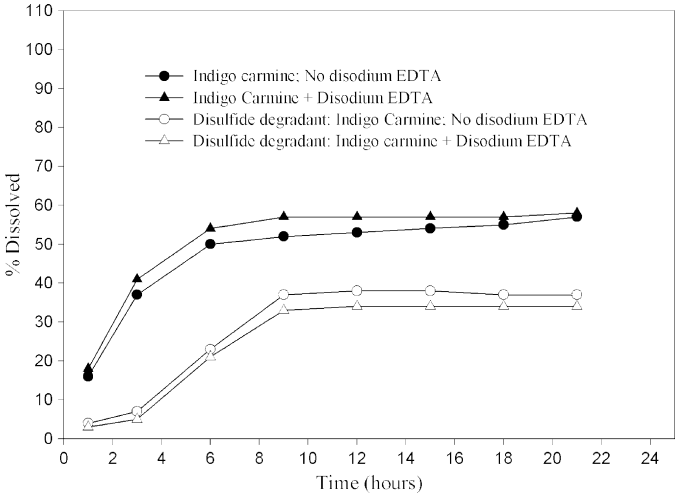


Fig. 3. Dissolution/degradation of 5 mg omapatrilat MR tablets in pH 6.8 media formulated with and without the chelator, disodium EDTA. Both prototypes contain the colorant, indigo carmine.

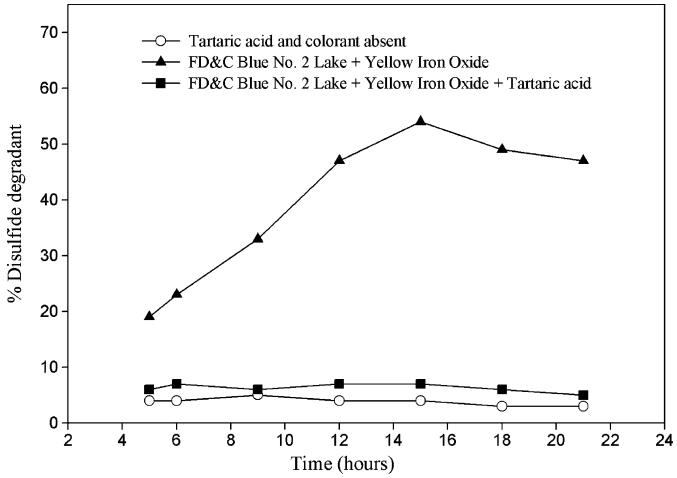


Fig. 5. Formation of disulfide degradant in pH 6.8 media of 20 mg omapatrilat MR tablets formulated with and without tartaric acid.

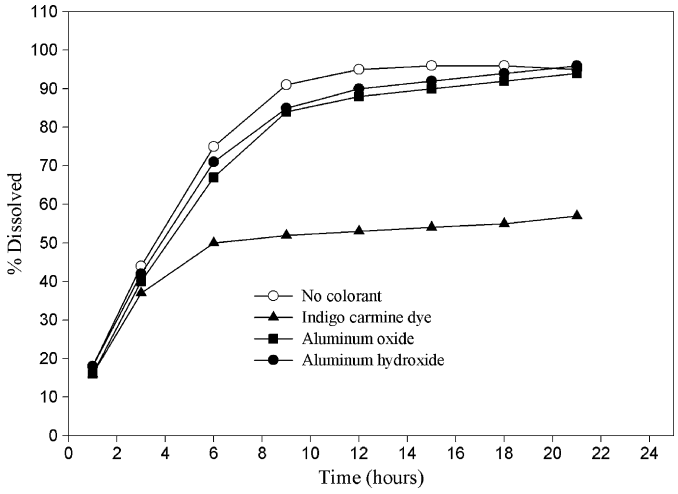


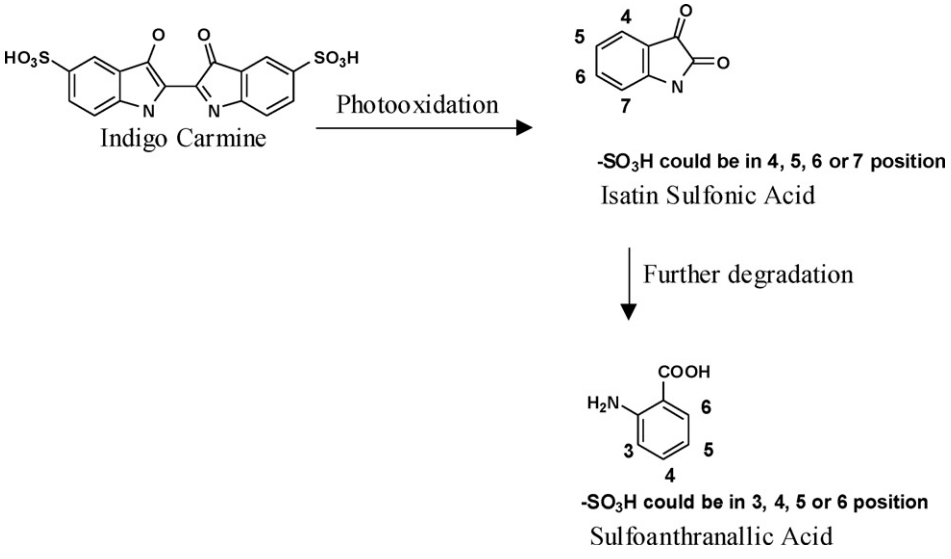
Fig. 6. Dissolution of 5 mg omapatrilat MR tablets formulated in the presence and absence of colorants and aluminum lake substrates in pH 6.8 media.

3.4. Effect of alumina hydrate/hydroxide on omapatrilat stability

FD&C Blue No. 2 lake is manufactured by adsorbing indigo carmine dye onto an alumina substrate. The alumina may exist as alumina hydrate, therefore, it is possible that alumina may have produced a higher microenvironmental pH via the formation of aluminum hydroxide in presence of the dissolution medium. This higher microenvironmental pH could lead to enhanced degradation of omapatrilat as discussed above. To test this hypothesis omapatrilat tablets were formulated separately with the alumina, aluminum hydroxide and the dye at 0.1% (w/w) and then tested for dissolution stability. The dissolution results indicate that the dye component of the lake was responsible for degradation of the drug as indicated by the lower recovery of drug in tablets formulated with the dye (Fig. 6). The results also indicate that the microenvironmental pH change induced by aluminum hydroxide at the concentration used was not enough to cause significant degradation. This is important to note since the concentration of alumina in commercial tablets formulated with the blue lake (<0.1% (w/w)) will be lower than tested in this experiment. The pH of a 10% (w/w) slurry of the alumina and aluminum hydroxide containing granulations was found to be 6.62 and 6.60, respectively. For comparison, an indigo carmine colored granulation slurry not containing these additives was found to have a pH of 6.70. These results show that the alumina and aluminum hydroxide do not raise the pH sufficiently to cause appreciable degradation of omapatrilat.

3.5. Effect of indigo carmine on omapatrilat stability

From the experimental data discussed previously, it seems that the indigo carmine contributed to the degradation of omapatrilat at higher pH values. One possible explanation is that at the higher pH values of 6.5 and 6.8 the –SH group of omapatrilat loses its –H to the dye (pK_{a1} for –COOH = 4.4, pK_{a2} for –SH = 8.3). This may lead to the reduction of the dye to form a semiquinone which is then further oxidized (Brownley and Lachman, 1963). The loss of the H atom in the –SH group may lead to the dimerization of omapatrilat. FD&C Blue No. 2 dye (indigo carmine) solutions are also known to be sensitive to ordinary and diffuse laboratory light (Brownley and Lachman, 1963). These authors found that the fading of FD&C Blue No. 2 dye solutions when exposed to light was primarily due to the oxidation of the colorant to isatinsulfonic acid and finally to sulfonated anthranilic acid. This was also reported by Jones et al. (1955). The probable degradation scheme has been shown in the schematic below:



It is possible that at the higher pH values of 6.5 and 6.8 the oxidative decomposition products of indigo carmine may interact with omapatrilat to cause increased formation of the disulfide degradant. To test this hypothesis dissolution testing in pH 6.8 phosphate buffer of the tablets with and without the Blue No. 2 lake was performed in clear and amber colored vessels under ordinary laboratory lighting conditions. The results suggest better dissolution stability of the blue lake containing tablets was obtained in amber vessels (Fig. 7). Tablets containing no colorant had similar stability regardless of vessel type.

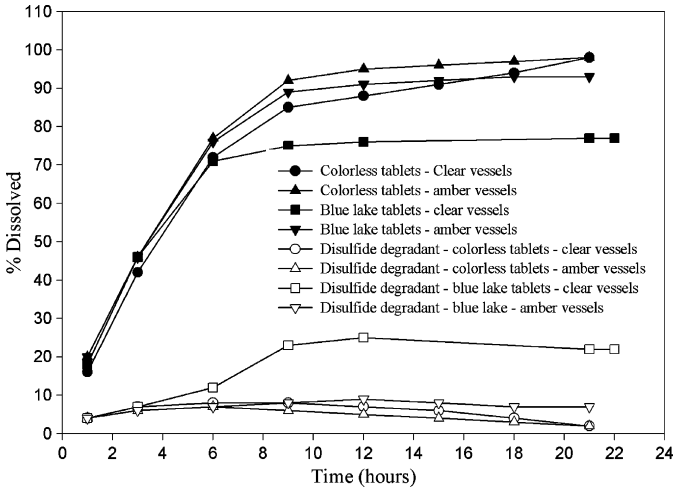


Fig. 7. Dissolution/degradation of 5 mg omapatrilat MR tablets in pH 6.8 media using clear vs. amber colored vessels. Tablets were formulated with and without the blue lake.

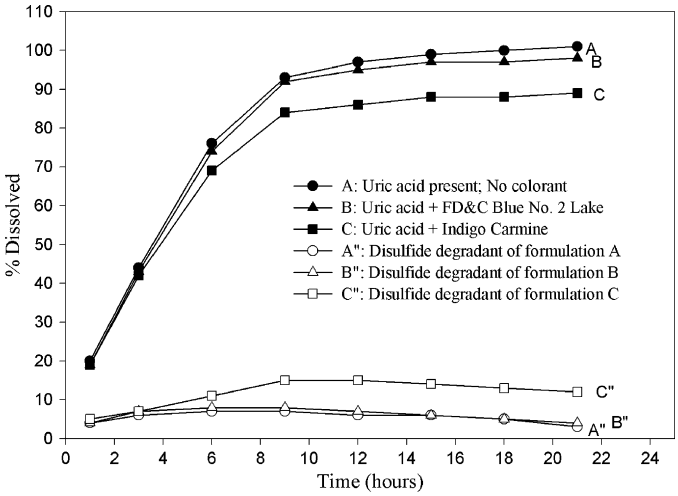


Fig. 9. Dissolution/degradation of 5 mg omapatrilat MR tablets in pH 6.8 media formulated with the photostabilizer, uric acid.

This experiment confirms that the solution state photoinstability of the dye at higher pH may contribute to the degradation of omapatrilat.

3.6. Effect of photostabilizers on omapatrilat stability

The photoinstability mediated degradation of omapatrilat by the blue lake further investigated by the inclusion of photostabilizers in the tablets. 2,4-DHBP and uric acid were evaluated as photostabilizers. The dissolution stability of omapatrilat tablets formulated with the photostabilizers 2,4-DHBP and uric acid at 2.5% (w/w) is shown in Figs. 8 and 9, respectively. The results suggest that 2,4-DHBP had no photostabilizing effect whereas; uric acid significantly improved dissolution stability. The photostabilization of FD&C Blue No. 2 dye solutions by uric acid has been demonstrated by Asker and Colbert (1982). Interestingly, the authors found that tartaric acid enhanced the photodegradation of FD&C Blue No. 2 dye solutions. According to the authors, the acceleration of fading of the dye by such hydroxy acids may be attributed to the OH– groups acting as electron donors in the degradation mechanism of the dye. In our study the tartaric acid actually helped in minimizing the degradation of omapatrilat. The mechanism by which this was achieved requires future investigation.

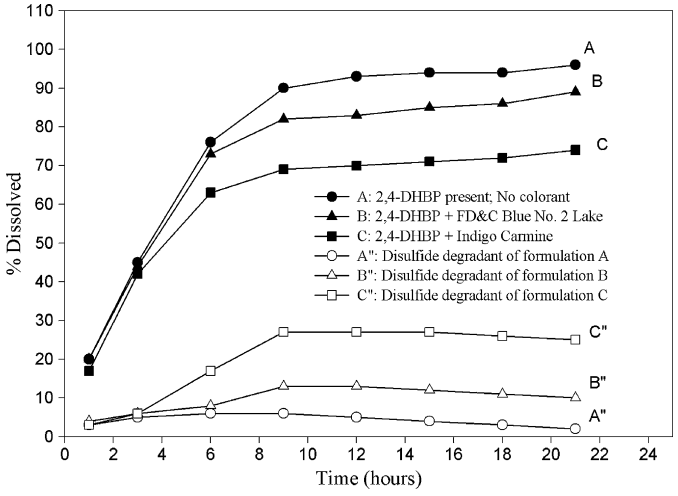


Fig. 8. Dissolution/degradation of 5 mg omapatrilat MR tablets in pH 6.8 media formulated with the photostabilizer, 2,4-DHBP.

4. Summary

Omapatrilat MR tablets containing colorants exhibited good solid state stability under stress conditions. The dissolution instability in pH 6.8 of omapatrilat MR tablets formulated with colorants was in the order: FD&C Blue No. 2 dye (indigo carmine) > FD&C Blue No. 2 lake > FD&C Blue No. 2 lake and yellow iron oxide combination > yellow and red iron oxides. This instability could be attributed to the dye portion (indigo carmine) of the lake. A lower microenvironmental pH was found to be more effective for stabilizing or preventing the formation of the disulfide degradant during dissolution in the presence of the blue lake. The photoprotective effect of uric acid in the tablet and the photoprotection offered by the amber colored dissolution vessels suggests that the sensitivity of the blue dye to light may play an important role in catalyzing the degradation of omapatrilat in addition to the influence of higher microenvironmental pH.

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