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N,N-Dimethylaniline and Zno nanoparticles mediated photochemical transformation of metronidazole

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A B S T R A C T

The present study evaluates the photochemical behavior of a nitroimidazole derivative drug metronidazole in presence of N,N dimethylaniline and ZnO nanoparticles. The photochemical behavior was examined in a photochemical reactor by irradiating with a light of 254 and 310 nm. After completion of reaction one photoproduct was obtained. The photoproduct was isolated by using column chromatography and the structure of the isolated photoproduct was established by different spectroscopic techniques. This study provides the probable mechanism of the photochemical transformation of metronidazole in presence of an electron donor and in presence of ZnO NPs. During the photochemical transformation the nitro group of metronidazole was reduced in the amine group by a series of electron transfer processes. The ZnO nanoparticles are very efficient catalysts, and they degrade almost 90% metronidazole in the 60 min of UV irradiation. The photocatalytic mechanism of the ZnO nanoparticles is also discussed.

1. Introduction

Many photosensitizing drugs are known; they are light sensitive and may decompose on exposure to light. The light induced degradation of drugs may cause loss of their efficacy and potency.[1] The photodegradation of drugs may cause phototoxicity.[2] It is therefore very useful to gain the knowledge of the photochemical behavior of drugs.[3] This knowledge is very useful in the production and storage of drugs. The behavior of drugs with respect to light may vary.[4] The variation of drug molecules with respect to light is basically due to their different structure.[5] The photodegradation of drugs may generate some phototoxic products also. The photochemical behavior of drugs also depends upon the wavelength of light. The photodegradation of drugs follows different mechanisms.[6,7] There are generally two types of photodegradation mechanisms discussed. These mechanisms give some insight regarding the formation of different reaction intermediates and the course of photochemical transformation.[8,9] Generally the highly reactive reaction intermediate like singlet oxygen, hydroxyl free radical superoxide anion and proxy free radical are formed during the photochemical transformation of drug molecules.[10] Depending upon the formation reaction intermediates of the photodegradation mechanism is divided into two categories. The type I mechanism of phototoxicity and the type-II mechanism of phototoxicity.[11] In type I mechanism the phototoxicity of drugs generally arises due to the formation of a free radical reaction intermediate and the type II mechanism of the phototoxicity is basically associated with the formation of singlet oxygen due to the energy transfer. [12,13]

During the last few decades, the use of antibiotics has increased tremendously due to the awareness among human beings.[14,15] Metronidazole is a kind of nitroimidazole antibiotic which is generally used to overcome the various health related issues caused by the anaerobic bacteria.[16] These drugs are easily soluble in water and have very low biodegradability and also exhibit some adverse phototoxic effects.[17] The pharmaceutical products are one of the most toxic non biodegradable waste and creating serious environmental threat.[18,19] The existing waste water treatment plan and procedure are not well

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equipped to remove these pollutants from the waste water.[20] During the last few decades tremendous amount of research is carried out to develop a new eco-friendly efficient procedure to remove these pollutants from waste water. Advanced oxidation procedure is one of the most attractive techniques to remove these pharmaceutical and organic pollutants from the waste water.[21,22] In the advanced oxidation procedure the highly reactive reaction intermediate free radicals are generated and it play prominent role in the photodegradation of the pharmaceutical product.[23] Advanced oxidation procedure generally adapted three basic techniques ozonolysis, fenton method and the UV visible initiated photocatalysis.[24]

UV-Visible initiated photo catalysis is one of the most adaptive methods of the advanced oxidation procedure.[25] UV visible initiated photocatalysis is a low cost eco-friendly approach and in this procedure low energy required and the generation waste product is almost nominal. In organic metal and metal oxide catalyzed degradation of the pharmaceutical product is one of the most innovative and promising fields of research. Intensive research work is carried out to explore the photocatalytic efficiency of the ZnO nanoparticles during the last few years.[26] ZnO NPs is a semiconductor hexagonal nanoparticle with remarkable photocatalytic efficiency. It plays vital role in the treatment of waste water by advanced oxidation process as a photocatalyst.[27]

The phototoxicity of drugs is basically due to the four different regions. Sometimes the photo toxicity is produced due to the generation of highly reactive short lived reaction intermediates.[28] Some drugs may react with endogenous substances and produce phototoxicity.[29] It is very important to know about the reason behind the phototoxicity of the drug molecules because it is helpful to control the possible phototoxic effect of the drug molecules.[30] In order to establish the mechanism of the photodegradation of drugs and to correlate the reason behind its adverse photobiological effects here we investigate the photochemical behavior of a most popular nitroimidazole derivative antibiotic Metronidazole under different conditions. In this research work we also highlighted the ZnO NPs mediated photocatalytic degradation of metronidazole in order to provide an alternative route for the treatment of waste water contaminated with the residue of the metronidazole.

2. Results and discussion:

2.1 Irradiation of metronidazole in presence of N, N dimethyl aniline

The photochemical transformation of metronidazole in presence of N,N dimethylaniline was examined by irradiating it with a light of 254 nm. After completion of reaction: 2-(5-amino-2-methyl-imidazol-1-yl)-ethanol was obtained as a major photodegradation product (**Fig. 1**). The formation of photoproducts can be elaborated in **Fig. 2**. In the photoproduct formation basically the nitro group of metronidazole is reduced in the amine group. This reduction involves the electron transfer process. In this study the N, N dimethyl aniline was used as an electron donor and the nitro group of metronidazole acted as an electron acceptor (**Fig. 2**).

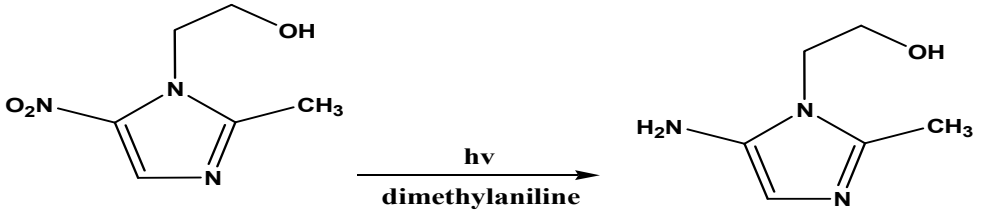

Fig. 1. Photochemical transformation of metronidazole.

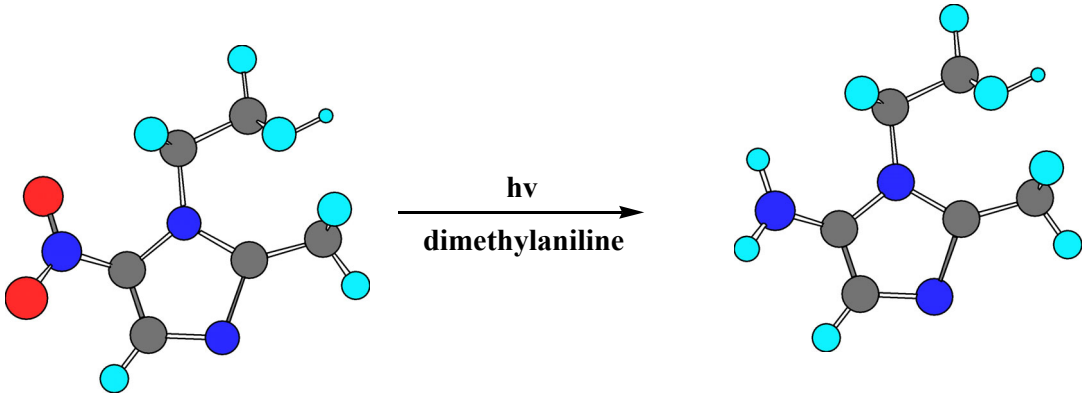

Fig. 2. 3D Representation of reactant and product.

The product formation involves various steps. First, when the metronidazole was irradiated with a light of 254 nm it absorb the radiation and reaches in the excited state; in the excited state the metronidazole interact with N,N dimethyl aniline and generate different reaction intermediates like nitro radical anion, nitroso and a hydroxyl amine derivative. The hydroxyl amine derivative is the last reaction intermediate which are finally converted into the photoproduct. The formations of these reaction intermediates are basically responsible for the phototoxicity or the adverse photobiological effect associated with the metronidazole (**Fig. 3**).

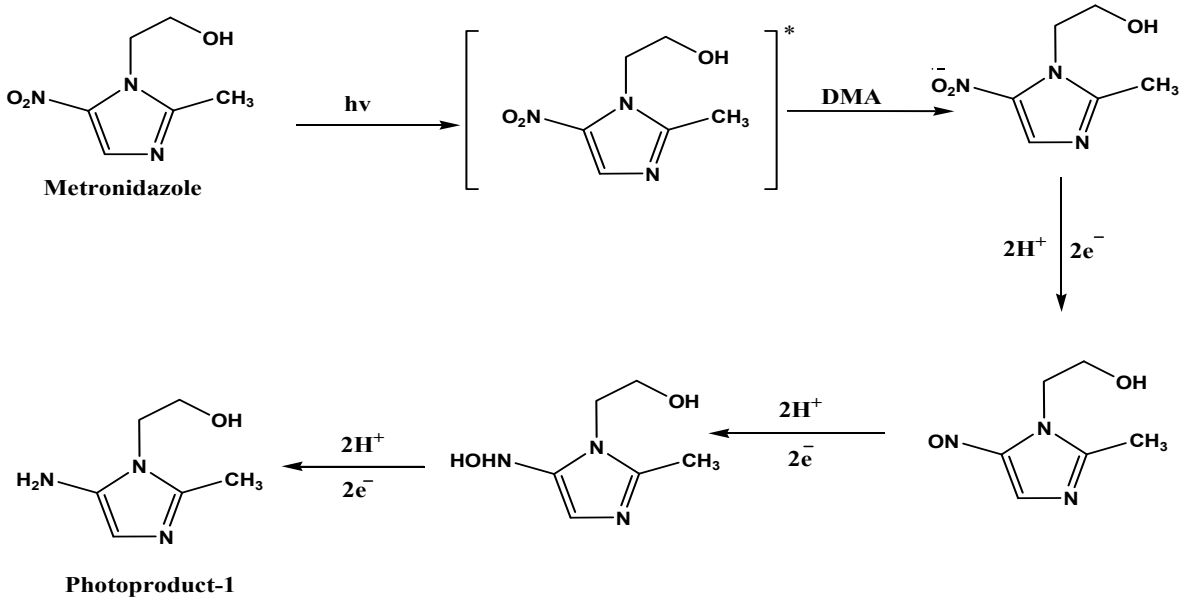

Fig. 3. Mechanistic pathway of the photochemical transformation of metronidazole

2.2 Irradiation of metronidazole in presence of ZnO NPs

The Photocatalytic efficiency of the ZnO nanoaparticles was investigated in the photodegradation of the metronidazole under different sources of light (Solar light UV light-254 nm and 310 nm light). The different source of light affects the photodegradation drastically. The rate of the degradation of the metronidazole directly depends on the intensity of the light and irradiation time. Numerous reports reported that photodegradation efficiency of the ZnO nanoparticles increases with the increase of the irradiation time. Further different researchers also reported that ZnO nanoparticles have high UV light response. The result of the photocatalytic study of the metronidazole is shown in figure. The result of the photocatalytic study clearly established that at 310 nm UV light irradiation the rate of the photocatlytic degradation is the highest (**Fig. 4**).

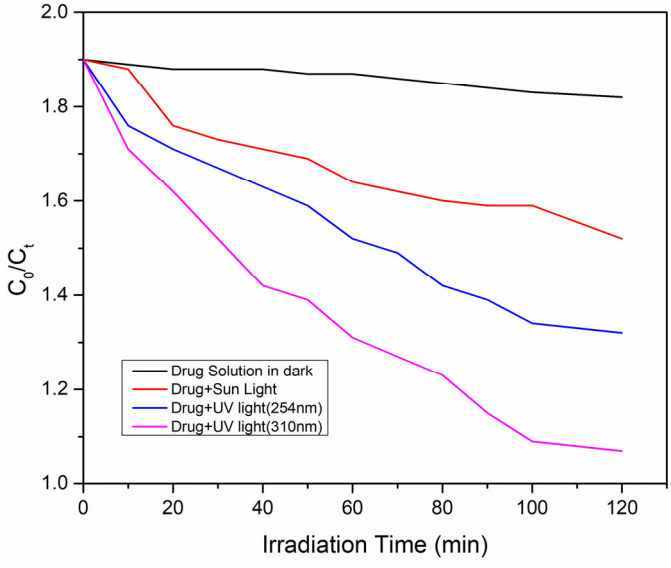

Fig. 4. Degradation behavior of metronidazole in presence of ZnO NPs

The ZnO nanoparticles are a very good example of heterogeneous photocatalysis. When the ZnO NPs is irradiated by a light irradiation having energy equal or greater than the band gap of ZnO NPs then the transmission of electrons takes place and the positive charged holes and free electrons are generated in the valence band and conduction band respectively. These two species electron-holes generated on the surface of nanoparticles play a prominent role in the redox reactions. The positive holes (h^+) generated in the valence band interact with the adsorbed water and hydroxyl group and generated a powerful reactive oxygen species hydroxyl free radical which converted the toxic metronidazole residue into the nontoxic product **(Eqs. 1-8).** The electrons produced in the conduction band interact with the dissolved oxygen and produce a reactive oxygen species superoxide free radical which converts into the hydrogen peroxide (**Fig. 5**).

$$ZnO+hv \rightarrow \frac{e^-}{(CB)}+\frac{h^+}{(VB)} \quad (1)$$

$$\frac{h^+}{(VB)}+H_2O \rightarrow H^+ + OH^{\bullet} \quad (2)$$

$$\frac{h^+}{(VB)}+O^- \rightarrow OH^{\bullet} \quad (3)$$

$$\frac{e^-}{(CB)}+O_2 \rightarrow O^{\bullet -} \quad (4)$$

$$O^{\bullet -}+H^+ \rightarrow HO_2^{\bullet} \quad (5)$$

$$HO_2^{\bullet}+H\dot{O}_2 \rightarrow H_2O_2+O_2 \quad (6)$$

$$\frac{e^-}{(CB)}+H_2O_2 \rightarrow OH^{\bullet}+OH^- \quad (7)$$

$$H_2O_2+O_2^{\bullet -} \rightarrow OH^{\bullet}+OH^- +O_2 \quad (8)$$

Fig. 5. Reactions involved in the ZnO NPs mediated photodegradation of metronidazole

The generated hydrogen peroxide reacts with the superoxide radical anion and generated hydroxyl free radical. The hydroxyl free radical interacts with metronidazole adsorbed on the surface of the nanoparticles; produces an intermediate compound which ultimately converted in to the nontoxic product **(Fig. 6).**

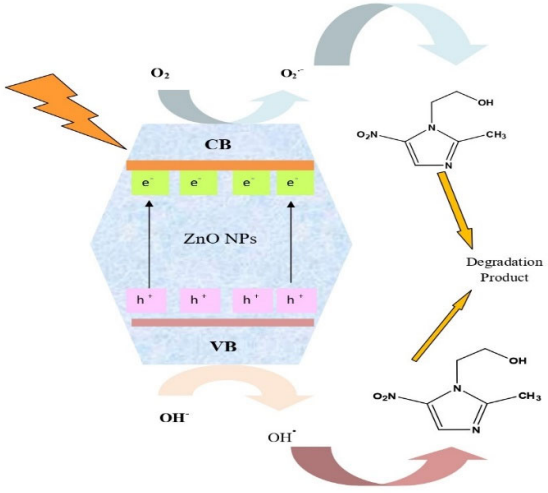

Fig. 6. Diagrammatic representation of the ZnO mediated metronidazole degradation.

3. Conclusion

The present study evaluates the effect of an electron donor on the photochemical behavior of a nitroimidazole derivative antibiotic metronidazole. The results of this study indicate that in presence of an electron donor the metronidazole undergo photochemical transformation and give a photoproduct. The photoproduct was isolated by using column chromatography and the structure of the photoproduct was established by using standard analytical procedures. The findings of the present study clearly established that the metronidazole undergoes photochemical transformation via an electron transfer mechanism. The result of the photocatlytic degration of the metronidazole by utilizing ZnO NPs is very promising and provides a low cost effective simple method for the treatment of waste water contaminated with pharmaceutical and organic pollutants.

4. Experimental

4.1 Materials and method:

N,N dimethyl aniline, Ethanol, Chloroform, methanol, dichloromethane, ZnO NPs and all other chemicals which were used in this research were procured from Sigma Aldrich. The Photolysis of the selected drug was performed in a photochemical reactor equipped with 254 nm fluorescence lamps. The IR (Infrared spectroscopy) analysis of the isolated photoproduct was carried out by using Thermo scientific FT-IR spectrometer. UV absorbance spectra were recorded by using Systonic UV visible spectrophotometer. Proton Nuclear Magnetic Resonance spectra and ^{13}C NMR (Nuclear Magnetic Resonance) spectra of the isolated photoproducts were examined by using the Standard NMR spectrophotometer. In the NMR & ^{13}C NMR study $CDCl_3$ (Deuterated chloroform) was used as a solvent. TMS (Tetramethylsilane) were used as an internal standard in the spectroscopic study. The mass spectra were recorded by using thermo scientific mass spectrometers.

4.2 Photo irradiation procedure:

Metronidazole (1) was irradiated in a photochemical reactor equipped with 254 nm fluorescence lamps. The thin layer chromatography was used to monitor the course of photolysis experiments. For the thin layer chromatography chloroform and methanol in the ratio of 98:2 were used as a mobile phase solvent. When the reaction was completed as indicated by TLC (Thin layer chromatography), the photoproduct was isolated by using column chromatography.

4.2.1 Irradiation of metronidazole in presence of N, N dimethyl aniline:

The methanolic solution of metronidazole along with an electron donor N,N-dimethylaniline was illuminated for about 6 h in a photochemical reactor equipped with 254 nm fluorescence lamps. After 6 h of continuous irradiation 2-(5-amino-2-methyl-imidazol-1-yl)-ethanol was obtained as a major photoproduct (1).

2-(5-amino-2-methyl-imidazol-1-yl)-ethanol:

Yield: 86 mg, HRMS analysis (M^+) $C_6H_{11}N_3O$ 141.09 found 141.02 IR(KBr) 1234, 1310, 1376, 1394, 1452, 1531, 1592, 1652, 3102 and 3802, 3442-3462 ^{1}H-NMR ($CDCl_3$δ, ppm) 6.7(s, 1H, H-4), 4.5(s,2H, NH_2),3.98(t,2H,H-1') 3.79 (t,2H,H-2'), 2.40 (s, 3H, H-2),2.0(s,1H,OH) ^{13}C-NMR ($CDCl_3$, δ, ppm) 152.01(C-2), 126 (C-5),123 (C-4), 62.8(C-1'),37.2 (C-2'),8.9(CH_3), MS: m/z: 141(M^+),126 (M^+-15), 96 (M^+- 45).

4.2.2 Irradiation of metronidazole in presence of ZnO NPs

The photocatalytic behavior of the ZnO NPs was investigated against the nitroimedazole derivative drug metronidazole in photochemical reactor equipped with 254 and 310 nm lamp. For this study approximately 10 mg ZnO NPs were dispersed in the 50 mL (25 mg/mL) of drug solution. The suspension of drug and nanoparticles were continuously stirred and placed in dark for about the 30 min to established the adsorption and desorption equilibrium between nanoparticles and metronidazole. The resultant test solution was now placed in the photochemical reactor and illuminated with the UV light irradiation under 254 nm and 310 nm for about 120 min with continuous stirring. The temperature of the test solution was maintained by 25 to 30 ^{0}C. Approximately 5 mL aliquots of the test solution irradiated by 254 nm and 310 nm withdraw from the reactor at regular interval of 10 min and centrifuged to remove the Photocatalyst and measure the absorbance of the test solution at 340 nm to evaluate the extent of metronidazole degradation.

The Photodegradation efficiency of the ZnO NPs in degradation of the metronidazole was examined by the following equations **(Eq. (9)).**

$$\text{Removal Efficiency} = \frac{C_0 - C}{C_0} \times 100 \tag{10}$$

where C_0 = Initial Concentration of metronidazole at t_0 without treatment

C = Final Concentration of metronidazole at final time after treatment

Data availability

The author confirms that the data of the present study's findings are available in the article and the raw data of the present study are available from the corresponding author on reasonable request.

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