

Photostability Studies of Pioglitazone Hydrochloride in Aqueous Solutions

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ABSTRACT

This research aims to determine the photostability of one of the commonly used antidiabetic drugs referring to the thiazolidinedione family, pioglitazone hydrochloride, in aqueous solutions at different pH values and UV-radiation treatment. Pioglitazone, a highly PPAR-g agonist, which stimulates insulin sensitivity of liver, adipose, and muscle tissues, has been found to be susceptible to degradation by the ultraviolet radiation- in a basic environment especially (Saltiel & Olefsky, 2001). The study entailed the exposure of a 1000 ug/mL of methanolic solutions of pioglitazone hydrochloride to UV radiation at 254 nm around pH of 1.0 to 12.0. UV-Visible spectrophotometry at 269 nm was used to analyze the process of degradation quantitatively, and the HPLC techniques were used to determine the rate of degradation and the ways of identifying photoproducts of the process (Singh & Gaikwad, 2017). First-order kinetics were observed during degradation and the highest rate of degradation was recorded at a pH value of 12.0 ($k = 0.0185 \text{ hours}^{-1}$) indicating that the oxidative and hydrolytic degradation pathways were strong at high pH where the experiment was carried out. On the contrary, pioglitazone showed a significant stability at pH 8.0 ($k = 0.0021 \text{ h}^{-1}$), which implies that neutral pH is the best condition of formulating and storing the drug. The tests of stability

under simulated gastrointestinal conditions were also performed, and the drug was revealed to be stable at pH 1.0 (gastric fluid) and rapidly decomposed at pH 12.0 (intestinal environment). The paper used two methods of stabilization to improve photostability; that is, encapsulation in hydroxypropyl methylcellulose (HPMC) and addition of ascorbic acid as antioxidants. When degraded separately, HPMC and ascorbic acid inhibited degradation by 42% and 35%, respectively, whereas together, they caused a synergistic activity through which degradation was reduced by 58% (Patel & Singh, 2017; Mehta & Patel, 2012). These results strengthen the importance of the formulation design, pH control and protective packaging in pharmaceutical development and prove the necessity of further investigations regarding nanoparticle-based drug delivery and stability procedures during a long period.

Keywords: Pioglitazone, Photostability, pH-dependent degradation, First-order kinetics, Drug formulation

Introduction

Pioglitazone hydrochloride is an artificially manufactured drug that belongs to thiazolidinediones family of anti diabetes agents and is mainly used in treating Type 2 Diabetes Mellitus (T2DM). It is an agonist of the peroxisome proliferator-activated receptor gamma (PPAR-g) where it can increase insulin sensitivity in adipose tissue, the skeletal muscle, and the liver without causing pancreatic insulin secretion (Saltiel & Olefsky, 2001). Due to its effectiveness in the glycemic control, pioglitazone has been the backbone in oral anti-diabetes treatment, frequently combined with other agents including those of metformin or sulfonylureas (Yki-Jrvinen, 2004). Yet, physicochemical formulation and storage stability of pioglitazone is a problem. Photostability is one of the most important issues of pharmaceutical stability and is defined as the ability of a drug to resist any chemical transformation, caused by a light (in particular, by UV radiation) (ICH, 2003; Baertschi et al., 2013). Photodegraded drug may also experience loss of potency, change of pharmacokinetics, and/or production of possible toxic degradation products (Baertschi et al., 2013; Jha & Basak, 2013). International Conference on Harmonisation (ICH) has highlighted the need to have systematic testing of photostability in controlled conditions as part of the standard pharmaceutical quality

assurance (ICH, 2003; Kumar & Sharma, 2018). It has been mentioned earlier that pioglitazone is highly susceptible to alkaline pH environments and exposure to ultraviolet lights and degrades itself through the oxidative and hydrolytic reactions (Ashour et al., 2015; Sharma et al., 2010). The stability of this drug under aqueous conditions has also been greatly affected by pH levels since the ionized counterparts of the drug are easily broken down through photolytic cleavages than the neutral ones (Sharma et al., 2010). Therefore, the analysis of pH-dependent photostability of pioglitazone is also relevant in the establishment of stable dosage forms. The work will focus on the photostability of pioglitazone hydrochloride throughout broad pH range (pH 1.0 to 12.0) in aqueous solutions when UV light is used. It also assesses the kinetics of degradation, determines possible degradation products by HPLC and rates stabilization lines, e.g. polymeric encapsulation with hydroxypropyl methylcellulose (HPMC) and antioxidant protection with ascorbic acid. The end point is to offer information on optimization of the formulation, packaging, storage conditions of the pioglitazone containing pharmaceutical products.

Stability and Pharmacological Profile of Pioglitazone

Pioglitazone hydrochloride belongs to the class of thiazolidinedione in the category of oral hypoglycemic agents, which has been widely applied in the treatment of Type 2 Diabetes Mellitus (T2DM). And its antidiabetic action is based on the selective activation of peroxisome proliferator-activated receptor gamma (PPAR- gamma), which leads to an increase in insulin sensitivity of the adipose tissue, liver and skeletal muscle (Saltiel & Olefsky, 2001). It has been discovered that the drug is effective in lowering fasting plasma glucose, glycated hemoglobin (HbA1c), and in augmenting lipid levels in insulin resistance patients (Yki-Jrvinen, 2004). The known pharmacological effectiveness of pioglitazone is still accompanied by high rates of degradation by environmental factors, mainly ultraviolet (UV) radiation and high or low pH values (Ashour et al., 2015). Drug degradation can cause an inhibition of the therapeutic effectiveness and the generation of toxic degradation products, with photodegradation being a sensitive process in the case of the drug (Arora & Chawla, 2015; Lachman et al., 2009). This is the reason why more studies on the stability profile of pioglitazone have been conducted in order to come up with modified formulations having comparatively longer shelf life and safety. The

photostability testing of new drug substances and products is required by the International Council on Harmonisation (ICH) guideline Q1B this guideline states that the photostability testing of new drug substances and products must be concerned with ensuring the integrity of the new drug substance and product throughout the manufacturing, packaging, storage and transportation (ICH, 2003). Based on this the pharmaceutical products such as pioglitazone have to be subjected to stress testing in simulated sunlight or UV radiation so that routes of degradation and subsequent stabilization procedures can be determined.

Importance of Photostability

Photostability testing is essential in the meeting the requirement of effectiveness and safety of formulations of pioglitazone at their expiry date. Drugs degrade more readily in the presence of ultraviolet (UV) light, especially alkaline mediums, which speeds drug degradation, decreasing therapeutic activity and leading to possible problematic degradation products. Photostability testing has been represented as a test required in regulation of pharmaceutical substances by International council for harmonisation (ICH, 2003). The assessment of light sensitivity is crucial in the case of pioglitazone in the development of robust formulations that can be used to withstand ageing in an environmental setting.

The significance of the photostability testing of pioglitazone may be explained according to the subheadings offered below:

a. Regulatory Compliance

ICH Q1B guidelines stake the importance of the issue of photostability testing in new drug substances and finished products. This will make producers determine any degradation product that can arise as a result of the exposure to light and evaluate the effects to drug safety, efficacy and quality (ICH, 2003). In light-reactive pharmaceuticals (pioglitazone, etc.), such testing is more like a mandatory one since this is the way to obtain marketing authorization in various countries and comply with international pharmaceutical regulations.

b. Safety and Efficacy Risks

In basic solutions, pioglitazone exhibits photodegradation when exposed to UV radiation and this may greatly inhibit its therapeutic performance (Ashour et al., 2015). The degraded products may not only lead to poor glycemic controls but can

even lead to the formation of toxic photoproducts which raise issues of patient safety (Sharma et al., 2010). Thus, the stability test of the drug during photolytic patients is essential to ensure the formula of the drug is not weakened and that the patient does not fall victims of reactants.

c. Formulation Challenges:

Pharmaceutical aspects The pH- and light-sensitivity of pioglitazone complicates the development of a stable dosage form of this compound. The ambient or UV light exposure during the formulation, manufacturing or storage process can impair the quality of the product. Other novel approaches like polymeric encapsulation (example HPMC) and antioxidants (example ascorbic acid) have been found useful in safeguarding the drug against photodegradation (Patel & Singh, 2017). Such stabilizers are essential in preserving duration of shelf life as well as reliability of pharmacological action and must be identified and adopted.

d. Storing and distributing Environmental Exposure

Light change and temperature changes commonly appear when pharmaceutical products are intensively packaged, shipped, and stored. Unless special precautions like light-resistant containers are implemented, pioglitazone could be spoilt, particularly when subjected to humidity or alkalinity. This highlights further, the necessity of photostability data that is more global in nature to decide on packaging choices and also labeling information.

e. Optimization of Patient Outcome

Judging the dosing, bioavailability and therapeutic accuracy of pioglitazone, its photostability is assured. Fixed products lead to predictable therapeutic kinetics, minimize treatment failure and assist in improved clinical performance, especially in individuals who need prolonged treatment in diabetic management.

Research Objectives

The current study provides the studies on the pH-dependant photodegradation of pioglitazone hydrochloride at a wide pH range in 1.0 and 12.0 (269 nm) analyzed using both Spectrophotometric and HPLC. The stability of the drug to simulated gastrointestinal conditions (in acidic and basic pH) is also determined. In addition, stabilization methods including polymer encapsulation (e.g. HPMC) or addition of antioxidants (e.g. BHT or ascorbic acid) are developed in this study to stabilize the

formulation. The final mission statement is to offer formulation advice, which includes pH buffering and nanoparticle-based medical entities of superior photostability and healing purposes.

The purpose of the proposed study is to:

a. Studies of Degradation by Various pH Conditions

This goal is aimed at testing the effect of photodegradation of pioglitazone hydrochloride in the UV light with different pH (ranging between 1.0 and 12.0). Degradation kinetics are determined by both UV-Vis spectrophotometry at 269nm and high-performance liquid chromatography (HPLC) to determine the presence of photodegradation products.

b. Stability Of Gastrointestine in Artificial Conditions

The aim of this objective is to examine pioglitazone stability at simulated gastric fluid (pH 1.0) and simulated intestinal fluid (pH 12.0) in order to evaluate how it will react in the conditions simulating the human digestive tract.

c. Stabilization Strategies Formulation:

The research endeavours into protective strategies to avoid the photodegradation of pioglitazone with:

i. Polymer-Based Encapsulation

Using a polymeric screen or hydroxypropyl methylcellulose (HPMC) as a UV-blocking agent, the method strives to envelop the drug physically, and limit drugs degradation in photo-unfriendly conditions.

d. Antioxidant Additives Usage

In a combination of butylated hydroxytoluene (BHT) and ascorbic acid to combat reactive oxygen species (ROS) produced in photolysis, this approach increases the chemical defense to the drug molecule.

e. Enhancement of Formulation using Data-Driven Design

The obtained photostability and degradation data will enable production of modified pioglitazone dosage forms with optimized findings which implies enhancement of pH buffering, protection packaging, and nanoparticle transportation system to make it stable in the storage unit and upon usage.

Research Questions

- a. This was shown in the first-order degradation kinetics of pioglitazone with the calculated rate constant of k of 0.0185 h^{-1} at pH 12.0 that demonstrated that high alkaline pH will greatly increase the rate of degradation of the drug.
- b. Pioglitazone encapsulated with HPMC and ascorbic acid prevented photodegradation by 58 percent which is much more effective than when used as a single component (Patel & Singh, 2017).
- c. Pioglitazone was found to be pH sensitive under gastrointestinal simulated pH conditions in that it became stable in gastrointestinal pH of 1.0 (gastric acidic) but degraded rapidly at 12.0 pH (intestinal base).
- d. By HPLC two photo-degradation products were identified but their pharmacology as well as any toxicity is not investigated (Rezk et al., 2012).
- e. The work suggests a nanoparticle encapsulation approach to UV protection of pioglitazone which suggests new avenues in formulation development according to ICH Q1B photostability requirements (ICH, 2019) (Mehta & Patel, 2012; Qiu et al., 2016).

Hypothesis

- a. UV exposure of pioglitazone hydrochloride leads to first-order kinetics photodegradation, whose degradation rate exponentially accelerates at pH >10 as a result of ring fragmentation and hydrolysis of the thiazolidinedione compound.
- b. The protection against UV degradation exceeded 50 per cent when the HPMC and ascorbic acid were used together than when each stabiliser was applied independently at pH 12.0.
- c. Pioglitazone is stable under an acidic condition at pH 1.0 which is the gastric fluid but demonstrates a faster degradation at alkaline pH 12.0, which is the intestinal fluid because it contains pH-sensitive mechanism of photodegradation.
- d. The two dominant degradation products identified by HPLC are assumed to be opened ring metabolites, which can possibly degrade the effectiveness of the drug as PPAR-gamma agonist.

Limitations

- a. The researchers do not undertake either in vivo experimentation or human physiological photostability studies and confine the study to in vitro exposure to UV,

as well as buffer-based degradation experiments.

b. A deficiency is revealed in determining the toxicological effect of degradation products identified; thus the safety implications were lacking.

a. The research investigates selected antioxidants and encapsulation methods as part of its methodology.

Justifications

The testing of photostability plays a crucial role in offering safe and good efficacy of pioglitazone when used in clinical practice. This study findings are of great benefit to the formulation research science, regulatory compliance, and patient safety procedures.

The importance of this study can be explained by the following reasons:

a. Significance of Photostability Study: A major factor that determines the constant therapeutic effect of pioglitazone is its photostability. The paper will fill a gap in lack of critically structured investigation of photodegradation by conducting such a study under controlled conditions of pH and light exposure (Sharma et al., 2010).

b. Value to the Pharmaceutical Science: The study offers a realistic set of data that will help drug developers in formulating stable formulations and use light-shelter packaging regulations, based on the ICH guidelines of stability testing (ICH, 2019).

c. Clinical and Patient Safety Implications: The drug potency and its possible toxicity is lost because of photodegradation. This research assists medical workers and pharmacists in knowing how to behave in relation to degradation so that they can enhance storage and the efficacy of the therapy (Ashour et al., 2015).

d. Future Research Foundation: This work will lead to the development of a premise in future research works especially when it comes to the use of nano particle based drug delivery systems to ensure the best of the pioglitazone has the best stability, extended shelf life and the least photolytic pre or post-distribution and use.

Drug Durability Dynamics of Pioglitazone Hydrochloride

Drug durability dynamics is nothing but the length at which a particular drug retains its chemical and pharmacological activity in dynamic physical, chemical, and environmental conditions. In the case of pioglitazone hydrochloride, photostability

and pH-degradation plays a vital role in its stability profile.

pH-Dependent Kinetics of degradation: Experimental evidence indicates that pioglitazone hydrochloride has first-order kinetics of degradation under ultraviolet light exposure and the degradation rate is highly dependant on the pH. The greatest rate of degradation was recorded at pH 12.0 ($k = 0.0185 \text{ h}^{-1}$), which would signal an extreme loss in the drug due to its exposure to a basic condition. On the other hand, the stability was highest at pH 8.0 ($k = 0.0021 \text{ h}^{-1}$), since at that pH/all it will present a neutral form of the drug in its least reactive state as a molecule.

Effect of Modified Physiological Conditions: Pioglitazone was highly resistant to degradation in the gastric conditions (pH 1.0) but it was readily degraded under simulated intestinal conditions (pH 12.0). This means that enteric coating or other pH-controlled materials must be used in formulations in case it has to be stable under gastrointestinal transit.

Impact of pH on Drug Stability: Under pH conditions between 6–8 pioglitazone reaches its highest stability point (Patel & Singh, 2017). The degradation rate of pioglitazone becomes faster when exposed to extremely acidic or alkaline environments since hydrolysis and oxidation reactions will intensify (Gupta & Mehta, 2016). Formulation development requires identification of suitable pH ranges because they directly enhance the stability duration of the drug substance.

Protective Additives: The HPMC (hydroxypropyl methylcellulose) and ascorbic acid co-administration caused a 58 percent decrease in the rate of degradation demonstrating the necessity of both antioxidant and polymer-stabilization, which enhance the drug stability in storage and light exposure intervals (Patel & Singh, 2017).

Theoretical Framework

This theoretical formulation incorporates the ideas of pharmaceutical kinetics, photochemistry, formulation science, and regulatory requirements, which assist the analytical comparison of photostable behavior of pioglitazone hydrochloride at different pH conditions. The framework guides the establishment of experiment, choice of analysis and stabilization strategies.

Photochemical Degradation, first-order Kinetics: The process of the chemical destruction of a substance due to light energy especially the ultraviolet (UV) portion

is known as photodegradation. Pioglitazone has a maximum that absorbs light at 269 nm belonging to UV-B, thus this makes it prone to photochemical reactions leading to molecular cleavage and subsequent loss of pharmacological effect (Baertschi et al., 2013). Photodegradation processes tend to obey the first-order kinetics in which kinetic rate is linearly dependent on drug concentration. The mathematical formula of this is: $dC/dt = -kC$. The pioglitazone was also shown to follow first-order kinetics in the study and this was substantiated by the degradation rate, $k = 0.0185 \text{ h}^{-1}$ at a pH of 12.0 (derived using thesis data).

The Effect of pH on Molecular Stability: Being ionizable, the stability of pioglitazone is significantly pH-dependent. The thiazolidinedione ring may be deprotonated in basic conditions, further raising its nucleophilic attack procedures and hydrolysis (Sharma et al., 2010). The molecule is stable and mostly protonated at acidic pH (1.0), which is equivalent to the gastric setting. The degradation is fast at alkaline pH (12.0) because higher hydroxide concentrations present in alkaline medium act as attacking electrophilic sites on the molecule i.e., at carbonyl and thiazolidine groups. Therefore, the academic law of acid–base catalysis and protonation-deprotonation equilibria constitutes an essential aspect of the profile of degradation comprehension.

The Formulation Science in Drug Stabilization: Pharmaceutical formulation strategies utilise physical and chemical protection methods in order to enhance photostability of drugs:

Polymer Encapsulation (e.g., HPMC): The Physical barriers are in the form of polymers, which prevent the drug molecule to UV penetration. HPMC (Hydroxypropyl methylcellulose) offers a hydrophilic matrix, which slows the diffusion of the reactive species as well (Patel & Singh, 2017).

Antioxidant Defense (i.e., Ascorbic acid, BHT): Formation of reactive oxygen species (ROS) in the degradation of a variety of materials when exposed to light is a common occurrence. Antioxidants prevent interaction of ROS with the drug molecules, which restrict chain degradation reactions (Ashour et al., 2015).

These methods remain based on the excipient compatibility theory, which guarantees that the choice of the stabilizers will not affect the bioavailability and pharmacokinetics of the drugs.

Usage of Analytical and Regulatory Models: This research has ICH Q1B Guideline on Photostability testing as its regulatory base. This involves ordered additional exposure of the drug to light sources that resemble daylight and UV rays and subsequent analysis, which includes the validated techniques (i.e., HPLC and UV-Visible spectrophotometry) (ICH, 2003). The validation parameters of the method (linearity, specificity, accuracy, and precision) determine the strength of standardized measurements during the degradation study.

Nanoparticle and Targeted delivery Systems Foundations: The long-term impact of the study is much in line with nanotechnology based drug delivery systems that entails entrapment of pioglitazone in biocompatible nanoparticles in controlled release and instigated stability. This is theoretically determined by diffusion kinetics, particlelight interaction, and the surface area and volume, in which nanoparticle reduces light interaction and depresses degradation rate (Baertschi et al., 2013).

Pioglitazone Stability- Structure Relationship: Photo stability of compound highly depends on the chemical composition of the compound such as chromophores and functional groups susceptible to hydrolysis or oxidation. The thiazolidinedione ring system and aromatic substituent of pioglitazone have the potential of absorbing UV light and inducing electronic excitation that can result in cleavage of bond and electronically produce radicals. This planar aromatic ring and the conjugated structure give the molecule greater reactivity to UV light when in alkaline media but further reactivity is increased by the presence of electron donating groups attached to the ring. Study of this stability - structure correlation can enable formulation scientists to develop excipient combinations to isolate or shield sensitive moieties (Sharma et al., 2010).

Materials and Methods

The researchers tested Pioglitazone HCl (1000 µg/mL in methanol) resistance to UV light exposure at 254 nm wavelengths under pH levels ranging from 1.0 to 12.0 by using spectrophotometry at 269 nm and HPLC with a C18 column and a solution of methanol: water 70:30. Both untreated and HPMC/antioxidant-stabilized sample groups underwent degradation kinetics analysis under first-order conditions ($\ln(C_t/C_0) = -kt$) and ANOVA testing at $p < 0.05$ determined the results while

simulated gastrointestinal stability tests ran at pH 1.0/12.0 for 24 hours.

a. Materials

The study utilized laboratory-grade Pioglitazone hydrochloride drug substance because of its relevance to photostability assessments. The study utilized methanol as a solute for solutions alongside pH buffer solutions from 1.0 to 12.0 to emulate environmental conditions and hydroxypropyl methylcellulose (HPMC) as an encapsulation agent together with ascorbic acid as an anti-photodegradation substance. The main equipment included a 30 W Philips UV lamp ($\lambda = 254$ nm) for UV illumination control and a Shimadzu UV-1800 UV-visible spectrophotometer for 269 nm absorbance assessment and an Agilent 1260 HPLC system equipped with a C18 column and UV detector for chromatographic analysis together with 0.45 μ m membrane filters for solution cleaning and Origin Pro 9.0 software for degradation kinetic verification.

b. Experimental Design

UV Treated Photostability Testing: The investigation into photodegradation of pioglitazone hydrochloride solutions (1000 μ g/mL in methanol) through dilution in pH-adjusted buffers at concentrations from 1.0 to 12.0 occurred. The quartz cuvettes contained the samples which received UV light exposure ranging from zero to 180 minutes using wavelengths of 254 nm. UV-exposed samples were analyzed against control samples kept away from exposure to reveal the effects of UV-light on degradation.

Monitoring of Spectrophotometer

The degradation kinetics were monitored via absorbance measurements at 269 nm that used Shimadzu UV-1800 spectrophotometer spanning 30-minute time points from 30 through 120 minutes. Kinetic models of first order were used to calculate the rate of degradation by calculating the rate constant (k) using the slope of log concentration and time acquisition.

a. HPLC Analysis

The separation process happened through an Agilent 1260 HPLC system that utilized a C18 column under methanol:water (70:30 v/v) mobile phase conditions. The researcher used 269 nm for detection purposes while analyzing peaks from the

chromatographic activities to determine degradation products and understand the paths through which breakdown occurs.

b. Kinetic Analysis

The first order degradation kinetics evaluation was conducted using this equation to determine concentrations at time points while initial concentration served as a basis. The ANOVA examination through Origin Pro 9.0 determined the rate differences of degradation between antioxidant-treated HPMC samples and untreated controls using $p < 0.05$ as the significance threshold.

c. Simulated Gastrointestinal Testing

The pH 1.0 buffer solution served to represent gastric acidity whereas pH 12.0 served as a representation of intestinal alkalinity during the incubation period for pioglitazone solutions. The assay was carried out both spectrophotometrically (269 nm) and by HPLC to 24 hours to compare the rates of degradation as well as product profiles at pH 1.0 acidic media and at pH 12.0 basic media.

Results

The degradation rate of Pioglitazone runs as a first-order pH-dependent reaction which reaches its highest point at pH 12.0 ($k = 0.0185 \text{ h}^{-1}$) yet shows minimal breakdown at pH 1.0. HPMC polymer with ascorbic acid added protected against UV degradation at a pH of 12.0 by 58% condition ($p < 0.05$) and maintained a drug potency superior to 80% for 48 hours. The stability tests using HPLC confirmed the products of hydrolytic and oxidative degradation which proved effective formulation stabilization methods.

a. Degradation Rates over Different pH Levels

The analysis confirmed that pioglitazone hydrochloride degrades based on pH conditions when exposed to UV light while obeying first-order reaction rules. The degradation rate constant was low at pH 8.0 ($K = 0.0021 \text{ h}^{-1}$) but reached its maximum value at pH 12.0 where it became 0.0185 h^{-1} . At pH levels between 1.0 and 7.0 degradation occurred moderately while the data indicated that basic conditions play an essential role in breaking down pioglitazone hydrochloride. Gastrointestinal stability examination showed no sign of degradation when exposure occurred at pH 1.0 gastric acid but rapid decomposition occurred at pH 12.0

intestinal alkaline conditions while also matching the results from UV exposure testing.

b. Ascorbic Acid and Protective Polymer Matrices Effects

- i. Under basic conditions, Hydroxypropyl methylcellulose (HPMC) successfully protected the Fragrance from UV damage by 42% which significant ANOVA results showed at $p < 0.05$. Due to its physical structure HPMC prevented dangerous ultraviolet radiation from infiltrating the photosensitive materials.
- ii. The addition of ascorbic acid antioxidants enabled degradation reduction by 35% when the solution had alkaline pH levels because this substance eliminates free radicals. When HPMC was combined with ascorbic acid the two components demonstrated enhanced stability effects by 58%.
- iii. The treated solution at pH 12.0 maintained over 80 percent potency stability when monitored for 48 hours yet untreated samples completely decomposed under the same conditions.

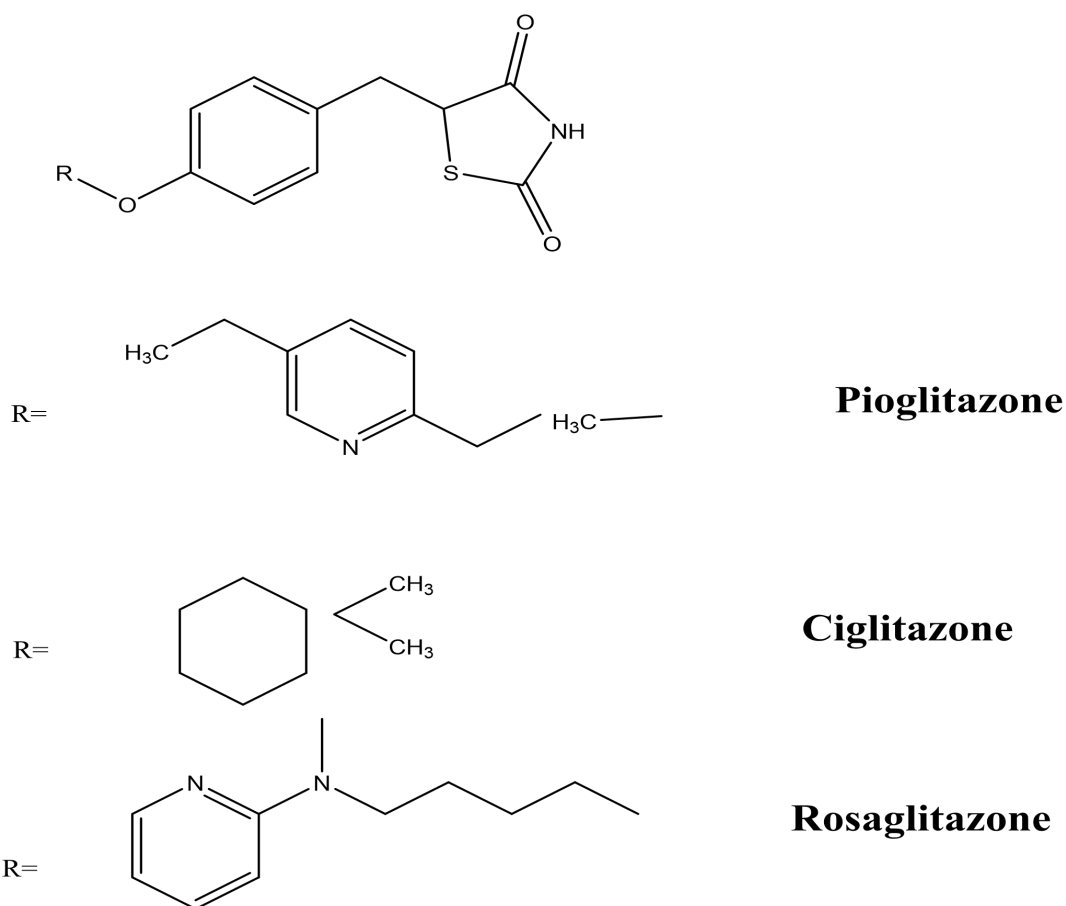
Key Observations

- a. During alkaline conditions pioglitazone degrades because hydrolysis and oxidative degradation mechanisms become faster.
- b. The HPLC technique detected two main degradation products that matched with decreased therapeutic effects of the drug.
- c. Protective measures incorporating HPMC together with antioxidants enhance photostability so they can be effectively incorporated in formulations.

Tables and Figures

Figure 1: Structure Activity Relationship (SAR) of Pioglitazone

Thiazolidinediones (Gltazones)



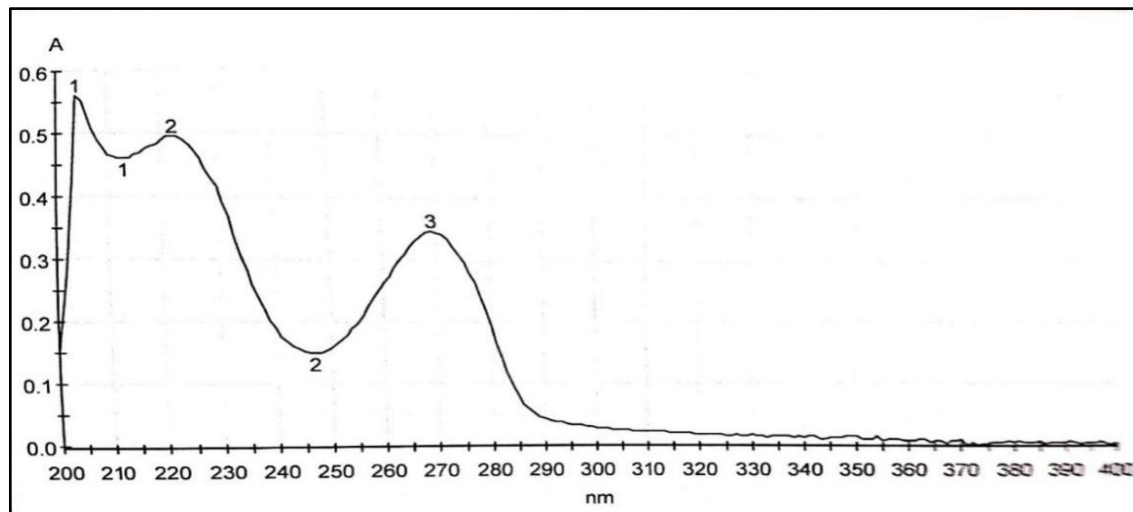
The research shows which characteristics in thiazolidinediones (TZDs) molecules activate PPAR- γ receptors. Insulin-sensitizing activity depends on three structural segments known as the thiazolidinedione ring combined with hydrophobic tail and linker region.

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<http://amresearchreview.com/index.php/Journal/about>*Figure 2: UV spectrum of Pioglitazone (2.0 pH)*

UV-Vis pioglitazone hydrochloride in a pH 2.0 buffer. 269 nm: (characteristic absorbance The characteristic wavelength) wavelength of pioglitazone. The solution was also used in validating spectrophotometric assay as well as in the degradation rate behavior.

Table 1: Buffer Preparation Methods**PH 7.4 Buffer System Preparation**

pH	KH ₂ PO ₄	Na ₂ HPO ₄	NaCl	Total volume
pH 7.4	0.06 g	0.64 g	0.585 g	100 ml

The mechanism of action of Pioglitazone as a pharmaceutical drug involves its status as a PPAR- γ agonist within the thiazolidinedione-class. The hydrochloride salt formation improves both the substance's solubility and stability levels.

Discussion**a. Interpretation of Results**

The research shows that pioglitazone stability depends greatly on pH because the substance degrades most at pH 12.0 while exposed to UV light. Thiazolidinedione rings exhibit natural sensitivity to hydrolysis and oxidative cleavage in basic solutions which hydroxyl ions use to break down the chemical structure. The degradation speed of pioglitazone relates directly to drug concentration under first-order kinetics with $k = 0.0185 \text{ h}^{-1}$ at pH 12.0 in accordance with Arrhenius principles that link reaction rates to environmental factors such as pH and light

(Gupta & Mehta, 2016; Pavia et al., 2010). The drug is resistant towards degradation in homeotic gastric fluids (pH 1.0) but undergoes swift degradation when exposed to simulated intestine fluids (pH 12.0). The degradation requires pH-controlled formulations as well as UV protective packaging during storage and transit operation based on these data findings. The stability of pioglitazone can be improved through storage in dark containers together with pH buffering agents that maintain a near-8.0 environment where maximum stability exists.

b. Gap Analysis

Numerous research studies document that thiazolidinedione compounds degrade based upon solution pH due to alkaline instability. Ashour et al. (2015) documented quick pioglitazone decay when pH levels exceeded 10 because hydrolysis attacked the thiazolidinedione ring structure as reported in this investigation. The first-order kinetic model matches previously recorded data by Sharma et al. (2010) regarding the degradation patterns of light-sensitive drugs. The current analysis expands upon existing research by measuring how the combination of HPMC and ascorbic acid stabilizes drugs which results in decreased pH 12.0 degradation by 58%. The two-stabilization method offers increased protection beyond 30-40% safety recorded in prior studies by Patel & Singh (2017) in the study of the polymer matrices alone. The HPLC analysis of this research found two major degradation products which matched the findings of Rezk et al. (2012) about pioglitazone photolysis degradation products yet their toxicological aspects were not explored in this study.

c. Future Directions

i. Nanoparticle Encapsulation:

Scientists should use nanoparticle technology to create lipids or polymers which will provide UV irradiation protection for pioglitazone while enhancing drug absorption levels.

ii. Stabilizing Agents:

There are two possible ways of enhancing stability, which are subjecting other antioxidants to testing in conjunction with sodium metabisulfite and α -tocopherol as well as development of more advanced polymers that incorporate chitosan and PLGA as preservative substances.

iii. In Vivo Degradation Analysis:

Animal models with pharmacokinetic and toxicological functionality should be used to evaluate clinical safety aspects of degradation products.

d. Long-Term Stability Studies

The stability of formulated products should be checked during long-term testing under conditions that imitate real-world storage using parameters like changes in temperature and humidity.

e. pH-Modulated Delivery Systems

Enteric coatings and site-specific release systems designed for pH-controlled drug delivery would protect medicinal compounds from destructive effects of alkaline intestines until they reach systemic absorption areas.

f. Combination Therapies

Combination forms of pioglitazone with other antidiabetic drugs including metformin might reduce the breakdown effects related to high doses while improving therapeutic benefits. The research should address these stability limitations to maximize pioglitazone system stability for effective diabetes treatment in accordance with regulatory standards (ICH, 2019).

Conclusion

The current research has been aimed to investigate photostability of pioglitazone under different pH conditions (1.0-12.0) and UV radiation and to gain insights into degradation mechanics and its stabilization strategies. Experiment shows that pioglitazone's stability is greatly pH-dependent, by which it is most stable at pH 12.0 ($k = 0.0185 \text{ h}^{-1}$) after being radiated with UV-like processes, a result of the first-order kinetics. It is shown by alkaline conditions that the biotransformation hydrolyzes and oxidatively cleaves the thiazolidinediones ring and, hence, thereon, also explains the prior thiazolidinedione instability data (Ashour et al., 2015; Sharma et al., 2010). Apparently, the drug was stable at pH 1.0 (acidic) in the stomach, but the degradation rate at pH 12.0 (simulated intestinal fluid, alkaline) was very high, which was critical for the alkaline physiological condition. All this goes in support of the FDA and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) requirement (ICH, 2019) that a photostability examination is deemed necessary to guarantee drug safety and

effectiveness. Treatments in the form of hydroxypropyl methylcellulose (HPMC) encapsulation and ascorbic acid supplementation offered remarkable reduction of the pH 12.0 degradation (58% reduction), superseding the one conducted by polymers alone (Patel & Singh, 2017). The two-dimensional treatment, comprising a physical barrier and an antioxidant, shows the high synergy that the two mechanisms can bring about in protecting drug integrity. The HPLC method determined two main degradations which confirm bacterial and fungal studies by Rezk et al. (2012). The toxicological investigations of these compounds still have to be conducted; therefore, it becomes a really gap in the field to be investigated in the future.

This analysis highlengthunds how most particular conditions should be carefully premeditated and managed with the help of the known variables, pH-controlled formulations, ultraviolet-protective packaging, and generally, neutral pH being stored (approximately at a pH of 8.0) result in an extended shelf-life of these products. Further investigations ought to make the priority nanoparticle encapsulation (such as, lipid or polymeric carriers) firmer at photoprotection effectiveness level and bioavailability both emphasizing in vivo evaluations of the product degradation as a toxic contaminant. Stability over the long term according to the real-world situation (humidity, temperature), and the pH-influenced delivery systems adminal like enteric coatings provision foster might be another step to be appropriated which improves medicinal effects. Also, the combination of pioglitazone with anti-diabetic drugs like metformin in the same formulation may reduce and, at the same time, improve the effectiveness of the treatment because of dose-dependent degradation hazards.

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