ADVANCED OXIDATIVE PRETREATMENT PROCESS FOR ENHANCE BIODEGRADATION OF COMPLEX WASTEWATER GENERATED FROM PHARMACEUTICAL INDUSTRY

A dissertation submitted in partial fulfillment for the requirement to award the Degree of

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ENVIRONMENTAL SCIENCE & TECHNOLOGY

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CERTIFICATE

This is to certify that the report entitled **"Advanced oxidative pretreatment process for enhance biodegradation of complex wastewater generated from pharmaceutical industry"** is a bonafide record of work done by Miss Manisha Verma for the fulfillment of the requirement for the award of degree of **Master of Technology in Environmental Science and Technology** of the Thapar University Patiala, Punjab, during the academic year 2009-2011. She has fulfilled the requirement for the submission of this report, which to the best of my knowledge has reached the requisite standard.

This part of project was carried out under the guidance and co-guidance of Dr. R.A.Pandey and Mr.Anoop Verma respectively and has not been submitted elsewhere for the award of any other degree.

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CHAPTER 1

INTRODUCTION

Pharmaceutical waste is one of the major complex and toxic industrial wastes. Pharmaceutical industry produces a wide variety of products. This industry uses both inorganic and organic as raw materials the latter being either of synthetic or of vegetable and animal origin. Antibiotics and vitamins are produced by fermentation of fairly complex nutrient solutions of organic matter and inorganic salts by fungi or bacteria. If a crude waste from an antibiotic plant is discharged into a stream it not only imparts objectionable odor to the stream but also adversely affects the flora and fauna. The volume and composition of the liquid waste not only vary from plant to plant but also from section to section in a plant, producing different type of drugs from raw materials and using varieties of processes**. (Samuel Suman Raj et al., 2003)**

1.1 CHARACTERSTICS OF PHARMACEUTICAL WASTE

Characteristics of the pharmaceutical industry wastewater are influenced by diversity of their process operations, which gives rise to a wide variation in the liquid wastes. There is little similarity between effluents from different factories and individual effluents may differ continually as a result of process changes. In many cases, these effluents contain little or no biodegradable organic matters and the pollutant loads in terms of biological oxygen demand (BOD) may be negligible hence higher chemical oxygen demand (COD) than BOD**. (Madukasi et al., 2009)**

In general most of the wastes are toxic to biological life and are usually characterized by high BOD, COD and a high BOD: COD ratio. Wastes from these plants are either highly alkaline or acidic. Wastes from the manufacture of drugs also contain toxic components including cyanide. Highly alkaline wastes originate from the manufacture of Sulfa drugs and Vitamin B12. Manufacture of certain organic

intermediates gives rise to highly acidic waste. **(Samuel Suman Raj et al., 2003).**General characteristics of pharmaceutical waste are given in **Table1**:

1.2 PHARMACEUTICAL MANUFACTURING PROCESSES & THEIR EFFLUENTS

The five different pharmaceutical manufacturing processes and their effluents are shown in **Table 2.**

The pharmaceutical waste water used in present study was collected from an industry manufacturing active pharmaceutical ingredients such as carbamazepine, Azithromycin, Citaloporam, Risperidon,Valsartan, Oxcarbazepine and tramadol hydrochloride Individually or in combination.

The chemical oxygen demand (COD) of liquid waste streams varies in the range of 5000-80000 mg/l. Industry generates different type of solids and hazardous waste including waste solvent and solvent residues. Most of the liquid waste are generated from equipment washing, floor- washing and wash basin and process waste water viz. recovery units of products, by-products, concentrator, steam condensate etc The waste solvents include toluene, isopropyl alcohol (IPA), acetone, cyclohexane, methylene dichloride, while solvent residues, include toluene residues, Methanol residue, IPA residue. The complexity and multicomponent nature of the waste warrants effective treatment strategies for meeting the specific discharge guidelines of regulatory agencies and hence there is a need of investigating newer treatment strategies for the same. In this context the current work focuses on AOP's such as Fenton oxidation and comparatively new concept of Cavitation as pretreatment options for complex wastewater such as Pharmaceutical waste.

CHAPTER 2

REVIEW OF LITERATURE

A large variety of pharmaceutical drugs such as analgesics, anti-inflammatories, antimicrobials, estrogens and lipid regulators have been detected as emerging pollutants in surface, ground and drinking waters at low content up to micrograms per litre.This contamination is mainly due to emission from production sites, direct disposal of drugs in households, excretion after drug administration to humans and animals and inadequate treatment of manufacturing waste. Powerful oxidation methods are then needed to be developed for achieving total removal of drugs and their by-products from wastewater, thus avoiding their adverse health effects on human beings and animals**. (Skoumal et al., 2008)**

2.1 SOURCES & CHARACTERSTICS OF WASTEWATER

The manufacture of pharmaceutical compounds using chemical synthesis involves a complex series of mainly batch processes, in which many intermediate stages and chemical reactions are performed sequentially. The processes use numerous raw materials and generate wastes and emissions. The wastewaters, arising mainly from equipment cleaning, contain a variety of organic and inorganic constituents including spent solvents, catalysts, reactants and small amounts of intermediate or product, in addition to the usual manufacturing streams such as pump seal waters, waste scrubbers wastewaters, boiler blow down and floor washing.

The wastewater may therefore be high in biochemical oxygen demand (BOD), COD and total suspended solids (TSS), with a wide range of pH from 1 to 11. The wastewater is not suitable for physical and/or chemical treatment because of their low efficiency for dissolved COD removal and high consumption of chemicals **(Y.A.Okem et al., 2007).** Wastes from these plants are either highly alkaline or acidic. Wastes from the manufacture of drugs also contain toxic components including cyanide. Highly alkaline

wastes originate from the manufacture of Sulfa drugs and Vitamin B12. Manufactures of certain organic intermediates give rise to highly acidic waste. **(D. Samuel Suman Raj et al., 2002)**

2.2 OCCURRENCE & FATE OF PHARMACEUTICALS IN ENVIRONMENT

Until recently pharmaceutical compounds in the environment have drawn very little attention. Although their presence in sewage treatment plant effluents was reported by **Richardson and Bowron, (1985)**, it had been anticipated that these compounds were easily biodegradable in environment as most of them could be metabolized and transformed to some extent in humans**.** However, a large number of recent studies have demonstrated persistence of these pharmaceuticals in the aquatic environment. The occurrence of several pharmaceutical compounds have been reported in sewage treatment plant effluents as well as in surface waters in Germany, the Netherlands, Switzerland, Canada, Brazil, Italy and the United States **(Kolpin et al., 2002).** The detected compounds included antibiotics, anticonvulsants, painkillers, cytostatic drugs, hormones, lipid regulators, beta-blockers, antihistamines, and X-ray contrast media. There are several possible sources and routes for the occurrence of pharmaceutical compounds in the aquatic environment **(Figure 1)**. For human pharmaceuticals, on-prescription drugs and some prescription drugs are consumed in households, and other prescription drugs are consumed in healthcare facilities such as hospitals and clinics. These drugs are partially metabolized and excreted in the urine and faeces and go into a wastewater collection system**.** Some unused, surplus, or expired drugs may be disposed into toilets, although this kind of practice is not recommended nowadays. Wastewater from the hospitals may be treated separately or combined with municipal wastewater and then treated at sewage treatment plants. Some of the pharmaceuticals and (human) metabolites in wastewater are degraded completely or partially, giving rise to a mixture of parent compounds and a variety of microbial metabolites. Some pharmaceuticals such as

ibuprofen and bezafibrate are relatively biodegradable, while others such as carbamazepine and diazepam are practically non-biodegradable **(Larsen et al., 2004).**

1.4 ENVIRONMENTAL IMPACTS OF PHARMACEUTICAL EFFLUENTS

As the Pharmaceutical residues have been detected in environmental samples including groundwater, surface water, and municipal wastewater. Pharmaceutical drugs given to people as well as to domestic animals include antibiotics, hormones, pain relievers, tranquilizers, and chemotherapy drugs for cancer patients. Many drugs are designed to be persistent and lipophilic, so that they can retain their chemical structure long enough to do their therapeutic work. These drugs are excreted and distributed into the environment by flushing toilets as well as by spreading manure and sewage sludge onto soil. These chemicals persist in the environment, enter the food chain, bioaccumulate, biomagnify, and cause harmful effects in wildlife and humans. Because of aquatic contamination by these chemicals, bacteria and other microbes in the aquatic environment can become more resistant to these chemicals. This results in the development of more antibiotic resistant and virulent pathogens in the environment. Therefore, the persistence of pharmaceutical chemicals in the environment has become a global problem. **(Jones O.A et al, 2005b)**

2.2 CONVENTIONAL TECNOLOGIES

Conventional technologies including biological, thermal, and physicochemical treatments have been used to remove the aqueous pollutants. Treatment of pharmaceutical wastewater has always been troublesome to reach the desired effluent standards due to the wide variety of the products produced in a drug manufacturing plant, thus, there is variable wastewater composition and fluctuations in pollutant concentrations. The substances synthesized in a pharmaceutical industry are structurally complex organic chemical that are resistant to biological degradation. Although biological method is

widely applied for the treatment of residual wastewaters, it requires a long residence time for microorganisms to degrade pollutants and is not suitable to treat the toxic contaminants due to biomass poisoning. Incineration is appropriate for the treatment of effluents having more than 100 g/L of chemical oxygen demand (COD). However, it requires an extremely high energy and presents considerable emission of other hazardous compounds such as dioxin and furan. Some other techniques such as flocculation, precipitation, adsorption, air stripping, and reverse osmosis require a post-treatment to dispose of the pollutants from the newly contaminated environment. For this reason, conventional treatment methods are usually inappropriate for the treatment of pharmaceutical wastewaters and hence there is a need for advanced oxidation methods. **(Vlyssides et al., 2008)**

Since pharmaceutical waste is a structurally complex waste, treatment of this waste biologically is not an easy task. As an alternative these waste can be treated Chemo-biologically. Chemo-biological process enhances the biodegradation of complex pharmaceutical waste water. Thus the pharmaceutical waste needs to be given a pretreatment process like chemical process (fenton & cavitation) so as to increase the biodegradability of the waste.

2.3 ADVANCED OXIDATION TECHNOLOGIES

Advanced oxidation processes (AOPs) with the capability of exploiting the high reactivity of hydroxyl radicals in driving oxidation have emerged a promising technology for the treatment of wastewaters containing refractory organic compounds. Several technologies like Fenton, photo-Fenton, cavitation, ozonation, photocatalysis, etc. are included in the AOPs and their main difference is the source of radicals. **(Kim et al., 2010).**

AOPs can be broadly defined as aqueous phase oxidation methods based on the intermediacy of highly reactive species such as (primarily but not exclusively) hydroxyl radicals in the mechanisms leading to the destruction of the target pollutant. The main

mechanism of AOPs function is the generation of highly reactive free radicals. Hydroxyl radicals (HO•) are effective in destroying organic chemicals because they are reactive electrophiles (electron preferring) that react rapidly and non-selectively with nearly all electron-rich organic compounds. (**A.S. Stasinakis, 2008).**

2.4 ASSEMENT OF AOPs PERFORMANCE FOR PHARMACEUTICAL REMOVAL

2.4.3 Fenton oxidation

Fenton's oxidation, an advanced oxidation method, appeared to be the most promising method, in terms of cost-effectiveness and ease of operation. Fenton's oxidation is very effective method in the removal of many hazardous organic pollutants from wastewaters. Fenton's oxidation can also be an effective pretreatment step by transforming constituents to by-products that are more readily biodegradable and reducing overall toxicity to microorganisms in the downstream biological treatment processes the quantification of the influence of Fenton's reagent on the efficiency of both Fenton's oxidation and biological treatment was performed through a factorial experimental design. **(Tekin et al., 2006).**

The oxidation using Fenton's reagents (Fenton's process) causes the dissociation of the oxidant and the formation of reactive hydroxyl radicals that destroy organic pollutants to harmless compounds (CO_2, water and inorganic salts). Fenton's reagents are H_2O_2 and ferrous ions.

They generate hydroxyl radicals following the chain reaction schematized as follow:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^{-} \quad \text{(chain initiation)} \quad (1)$$

$$OH^{\bullet} + Fe^{2+} \rightarrow OH^{-} + Fe^{3+} \quad \text{(chain termination)} \quad (2)$$

As shown in Eqs. (1) and (2), the ferrous iron (Fe^{2+}) starts the reaction and catalyses the decomposition of H_2O_2 in hydroxyl radicals. However, the newly formed ferric ions

(Fe^{3+}) may decompose hydrogen peroxide in water and oxygen (forming ferrous ions and radicals):

$$Fe^{3+} + H_2O_2 \leftrightarrow Fe - OOH^{2+} + H^+ \quad (3)$$

$$Fe - OOH^{2+} \leftarrow HO_2^{\bullet} + Fe^{2+} \quad (4)$$

The above reactions are referred as Fenton-like reaction.

The organics (RH) are oxidised by hydroxyl radicals proton abstraction ending with the production of organics radicals ($R^{\bullet}$) **(Bianco et al., 2010).**

In Fenton oxidation, the pH value has to be in the acidic range to generate the maximum amount of hydroxyl radicals to oxidize organic compounds. However, pH value should not be too low since at very low pH values (<2.0) the reaction is slowed down due to the formation of complex iron species and formation of oxonium ion $[H_3O_2]^+$.

On the other hand, at high pH (pH > 4), the generation of hydroxyl radicals gets slower because of the formation of the ferric-hydroxo complexes. Therefore, the initial pH value has to be between 2 and 4 to generate the maximum amount of hydroxyl radicals to oxidize organic compounds **(Tekin et al., 2006).**

Optimum operating condition

Operating pH

pH of the system significantly affects the degradation of pollutants. The optimum pH observed to be 3 in the majority of the cases and hence is recommended as the operating pH. At lower pH (pH<2.5), the formation of $(Fe (II) (H O))^{2+}$ occurs, which reacts more slowly with hydrogen peroxide and, therefore, produces less amount of reactive hydroxyl radicals thereby reducing the degradation efficiency .In addition, the scavenging effect of hydroxyl radicals by hydrogen ions becomes important at a very low pH and also the reaction of Fe^{3+} with hydrogen peroxide is inhibited. At operating pH of >4, the decomposition rate decreases because of the decrease of the free iron species in the

solution, probably due to the formation of Fe (II) complexes with the buffer inhibiting the formation of free radicals and also due to the precipitation of ferric oxyhydroxides which inhibit the regeneration of ferrous ions. Also, the oxidation potential of $HO^{\bullet}$ radical is known to decrease with an increase in the pH.

Amount of Ferrous ions

Usually the rate of degradation increases with an increase in the concentration of Ferrous ions but an enormous increase in the Ferrous ions will lead to an increase in the unutilized quantity of iron salts, which will contribute to an increase in the TDS content of the effluent stream.

Concentration of hydrogen peroxide

Concentration of hydrogen peroxide plays a more crucial role in deciding the overall efficacy of the degradation process. Usually percentage degradation of the pollutant increases with an increase in the dosage of hydrogen peroxide. The residual hydrogen peroxide contributes to COD and hence excess amount is not recommended. Also, the presence of hydrogen peroxide is harmful to many of the microorganisms and will affect the overall degradation efficiency significantly, where Fenton oxidation is used as a pretreatment to biological oxidation. One more negative effect of hydrogen peroxide, if present in large quantities is that it acts as a scavenger for the generated hydroxyl radicals. Thus, the loading of hydrogen peroxide should be adjusted in such a way that the entire amount is utilized.

Initial concentration of the pollutant

Usually lower initial concentration of the pollutants are favored but the negative effects of treating large quantity of effluent needs to be analyzed before the dilution ratio can be fixed. For real industrial wastes, many times some dilution is essential before any degradation.

The application of fenton oxidation for pharmaceutical wastewaters is shown in **Table 3.**

2.4.4 Cavitation

Cavitation is defined as the phenomena of the formation, growth and subsequent collapse of micro bubbles or cavities occurring in extremely small interval of time (milliseconds), releasing large magnitudes of energy. Some of the important effects of cavitation can be given as the generation of hot spots, release of highly reactive free radicals, continuous cleaning as well as increase in the surface area of the solid catalysts, enhancement in the mass transfer rates due to turbulence generated as a result of acoustic streaming etc.

Cavitation is classified into four types based on the mode of generation viz.Acoustic, Hydrodynamic, Optic and Particle, but only acoustic and hydrodynamic cavitation has been found to be efficient in bringing about the desired chemical changes whereas optic and particle cavitation are typically used for single bubble cavitation, which fails to induce chemical change in the bulk solution. **(Gogate et al., 2004)**

Acoustic cavitation

In the case of acoustic cavitation, the pressure variations in the liquid are effected by using high frequency sound waves, usually ultrasound, with frequencies in the range of 16 kHz-100 MHz. If a sufficiently large pressure is applied to the liquid so that the average distance between the molecules exceeds the critical molecular distance required to hold the liquid intact, cavities or voids will be created. Subsequent compression and rarefaction cycles of the sound waves causes the bubble cavity formed to expand, reach a maximum bubble size depending on the operating conditions and then collapse releasing a large amount of energy which produces spectacular effects. **(Gogate et al., 2004).**

Reactor used for the generation of acoustic cavitation

Ultrasonic Bath Equipped with Longitudinally Vibrating Horn

The novel ultrasonic bath is irradiated using a single longitudinally vibrating transducer kept at the bottom of the reactor (vibrations are in direction away from the base of the reactor). An additional heater equipped with a temperature controller has been also provided so as to facilitate some moderately high temperature reactions as shown in **Figure 2.**

Generation of intense cavitation by the use of multiple frequencies or higher frequencies might not necessarily mean higher cavitational yields for the specific pollutant. It also depends on the relative rates of the reaction between the pollutant and the free radicals and the recombination reaction between the free radicals. If the availability of the pollutant or the reaction between the pollutant and free radicals is the controlling factor, generation of intense cavitation, and thus the generation of higher number of free radicals, will only result in an increase in the rate of recombination reaction such that dissipating more power will not be beneficial. Therefore, a detailed kinetic analysis in terms of establishing the rates of reactions using the free radicals is a necessity before the selection of the operating conditions and the reactor configurations. **(Gogate et al., 2004)**

The application of cavitation for pharmaceutical wastewaters is shown in **Table 4.**

The state of the art (literature review) indicates that although there are several technologies in use for the treatment of pharmaceutical wastewater, the conventional methods used individually as complete treatment schemes fail to render the wastewater fit for disposal. Hence there is an urgent need for investigating pretreatment methods especially AOP's like Fenton and newer areas like Cavitation which have been explored for limited applications.

OBJECTIVES OF PRESENT STUDY

The literature reports on the characteristics of the pharmaceutical wastewater indicate its complex and recalcitrant nature. Thus there is a need for efficient pretreatment options which can effectively reduce/alter/modify the recalcitrance/toxicity profile of the wastewater and hence keeping in view with this the study envisaged of following aims and objectives:

- Evaluation of Fenton oxidation as an individual pretreatment option
- Evaluation of Cavitation (Acoustic) as an individual pretreatment option
- Statistical design and optimization of process variables for individual pretreatment options
- Assessment of hybrid Fenton-Cavitation for pretreatment of Pharmaceutical wastewater
- Assessment of biodegradability index (BOD: COD ratio) pre and post-treatment.

CHAPTER 3

MATERIALS AND METHOD

3.1 Sample Collection

The pharmaceutical waste waters used in present study was collected from an industry manufacturing active pharmaceutical ingredients. The pharmaceutical wastewater was stored at 4^0C before analysis and was allowed to retain the room temperature before pretreatment, any solid residues visible were removed manually and the wastewater was shaken manually to get a uniform suspension before subjecting to any of the pretreatments.

3.2 Fenton oxidation set up

The studies were carried out to optimize the pH, dose of H_2O_2 and Fe^{2+} ions for the pretreatment of pharmaceutical wastewater. The studies were conducted in a 300 ml stoppered flasks. The operational conditions for both the waste waters were given in **Table 5 & 6.**

3.3 Cavitation for pretreatment

Fast Clean make ultrasonic bath (model 3-5L100H) with frequencies 36±3 KHz with water bath capacity of 3.5L was used for cavitation and fenton assisted cavitation experiments as shown in **Figure 3**.

3.4 Chemicals and Glasswares

The chemicals used in the COD analysis viz. potassium dichromate, mercuric sulphate, ferrous ammonium sulphate, silver sulphate, concentrated sulphuric acid and ferroin indicator were procured from Qualigens Chemicals, India Ltd. COD test was conducted using Erlenmeyer flasks .The chemicals used for BOD analysis were Sodium thiosulphate, alkali iodide azide, manganous sulphate, starch, potassium dihydrogen phosphate, dipotassium hydrogen orthophosphate, disodium hydrogen phosphate, ammonium chloride, calcium chloride, magnesium sulfate and ferric chloride. BOD bottles of 300 ml capacity made of borosil were used for conducting the BOD test. BOD incubator set at 27^0C was used for incubating the BOD samples.

Fenton oxidation and Fenton coupled cavitation was carried out by using Ferrous sulphate ($FeSo_4.7H_2O$) and Hydrogen peroxide (30%v/v).The pH of the wastewater during Fenton oxidation was adjusted by using 0.5N H_2SO_4/1N NaOH. Borosilicate glassware of 300ml capacity was used for Fenton oxidation. Whatman filter paper no. 42 was used throughout the study for general sample filtration purposes.

3.5 Analytical methods

Distillation set up as shown in **Figure 4** was used for refluxing the COD samples. The COD analysis was done as per the standard methods (APHA 1999).The BOD analysis was carried out using incubator set at 27^0C for incubating the samples as per standard procedures (APHA 1999). pH meter(Orion 420 A+) was used for pH measurements. Ultrasonic reactor was used for cavitation experiments.

3.6 Design of Experiments for Optimization of Discrete Parameters (DOE)

Two level (2^k) factorial design

The 2^k (k is number of factors) experiments are one of the most important and fundamental families of experiments in Design of Experiments (DOE). In present study

2^3 factorial designs was used to analyze interaction effects of selected factors on response.

Design matrix shows total number of 16 runs. To prevent the effect of study variables from being confounded with lurking variables, the runs performed in random order. Experiments were performed in triplicate by randomizing the order of the runs within each replicate. Here replicates were treated as blocks to protect against lurking variables that changes from block to block. A regression analysis of 2^3 factorial experiments can fit the following model:

$$\mathbf{Y= b_0+b_1x_1+b_2x_2+b_3x_3+b_{12}x_{12}+b_{13}x_{13}+b_{23}x_{23}+b_{123}x_{123}}$$

Where the "b's" are all regression coefficients. The $\mathbf{b_0}$ term is referred as the model's constant; the b_1, b_2, b_3 are called main effects; and b_{12}, $b_{13}$and b_{23} terms are two factor interaction; and b_{123} is three factor interaction. Since all of the design variables in 2^3 experimental have an equal number of runs at their -1 and +1 level, the average level of each design variable is = 0. This means that constant in regression model must be equal to the grand mean of the response. While it is appropriate to compare the magnitude of b_1, b_2 ,….. , b_{123} to each other, b_0 may be several orders of magnitude different than the other regression coefficient. It's best to interpret b_0 as reference value for response and other regression coefficient as perturbation to the response due to different model terms. In presented work following study were carried out for optimization of process factors.

3.7 Biodegradability Index (BOD: COD)

BOD: COD ratio is generally expressed as biodegradability index. A significant proportion of soluble COD is not removed by the physico-chemical treatment. To achieve maximum treatment biological treatment is needed. So biodegradability index (BOD: COD) was taken in order to achieve high quality of treated waste water. Waste water can be considered biodegradable if it has a ratio between 0.4 and 0.8. (**Aboulhassan et al., 2008)**

CHAPTER 4

RESULTS AND DISCUSSIONS

4.0 Wastewater characterization

The pharmaceutical waste water used in present study was collected from an industry manufacturing active pharmaceutical ingredients such as carbamazepine, Azithromycin, Citaloporam, Risperidon,Valsartan, Oxcarbazepine and tramadol hydrochloride Individually or in combination. Physico-chemical characteristics of the two waste water samples are presented in **Table 7 & 8**.

4.1 Experimental design

A 2^k factorial experimental design was used to analyze main and interaction effect of selected process parameters viz. ferrous ions, contact time, pH and hydrogen peroxide on the% COD removal.

4.1.1 Experimental results of Fenton oxidation for % COD removal of sample I and Model fitting

The uncoded values of the test variables and the experimental results for % COD reduction are presented in **Table 9** Factorial fit of the experimental data yielded the following regression equation for the %COD reduction:

$$Y = 48.2785 - 311.681 * X1 - 0.111156 * X2 + 25.0394 * X3 - 191.645 * X4 + 2.04828 * X1 * X2 + 9.5916 * X1 * X3 + 313.402 * X1 * X4 - 0.238098 * X2 * X3 + 2.16030 * X2 * X4 - 22.0592 * X3 * X4$$

Where Y is % COD reduction, X_1 is Fe^{2+} concentration, X_2 is contact time X_3 is pH and X_4 is H_2O_2 concentration.

The value of regression coefficient (R^2 = 93.19%) is closer to one, indicating the suitability of second order polynomial to predict the % COD removed of pharmaceutical wastewater in terms of independent variables, and the predicted values were found in close agreement with that of experimental results as shown in **Fig 5 and Table 9**.

The Estimated effect of model parameter for the % COD reduction is shown in **Table 10.** Model fitting is required to test the significance and adequacy of the model. It is observed from the **Table 10** that the coefficients for the most of the individual and 2 way interaction of model terms are highly significant (P = <0.05). The Predicted R^2 of 86.63%is as close to the Adjusted R^2 of 86.15% as one might normally expect. This indicates a negligible block effect and model and/or data are best fit for optimization.
Higher R^2 value of predicted model with low or no outliers yields the adequate precision of 779.766.The standard deviation is found to be 6.21 indicates model shows great compliance with predicted responses. The *P*-values are used as tool to check the significance of each of the coefficients, which in turn, may indicate the patterns of the interaction among the variables. Larger the magnitude of T and smaller the value of P indicate that the corresponding coefficient is more significant. Values of P<0.05 indicate model terms are highly significant at 95% Confidence Interval (CI). In this case X_3, X_4, X_1X_2, X_2X_3, X_2X_4 are significant model terms.

ANOVA results of model variables shown in **Table 10** imply that the overall main effects of process parameters are predominate over their interactive effects. Among the different process variables selected for the study X_3 and X_4 are found highly significant at their main effect. The positive effect of X_4 predominate over the negative effect of X_3, and had found greatly influences the % COD reduction as (P< 0.05) at 95% CI. . From the full factorial analysis it was confirmed that Contact time (X_2) interact positively with X_1 and X_4 whereas negatively with X_3.

These significant interaction means that effect of X_1on % COD reduction is depend on level of X_2 used. Similarly, the effect of X_2 on the % COD is depending on levels of X_3 and X_4 respectively.

Negative effect of pH, Contact time*pH means that at high level, they tend to decrease the % COD reduction. The significant main and interactive of selected process parameters shows an overall curvilinear effect on the % COD reduction.

Optimization and validation of experimental model

The contour plots are plotted to understand the interaction of the variables and to determine the optimum level of each variable for maximum response. It is evident from the elliptical nature of the contours that the interaction between the individual variables is significant as shown in **Fig.6,7,8,9.**The studies of the contour plot also reveal the best optimal values (to maximize % COD reduction) of the process conditions for all process parameters and are: X_1, 0.15-0.2; X_2, 130-170 min; X_3, 2-3 and X4, 0.1-0.2.

The numerical point prediction tool of MINITAB RELEASE14 was used to find the optimal values of test variables for maximizing % COD reduction (> 40%). The optimum values of the test variables were: X_1-0.173; X_2-150 min; X_3-2 and X_4-0.19. A validation of the model results and regression equation was performed by Fenton oxidation with X_1 (0.173), X_2 (150 min), X_3 (2) and X_4 (0.19). The predicted response for % COD reduction was 40%, while the experimental response was 43%, thus proving the validity of the model. The composite desirability value (D) of predicted yield at optimized level of variables were found to be very close to 1 (D=0.99831) owing to higher precision of validation. This result shows that the regression model developed in this study resulted in good agreement between the actual and predicted responses.

4.1.2 a. Experimental results of Fenton oxidation for % COD removal of sample II and Model fitting

The uncoded values of the test variables and the experimental results for % COD reduction are presented in **Table 11.** Factorial fit of the experimental data yielded the following regression equation for the %COD reduction:

$$Y = 36.2805 - 67.1276 * X1 - O.0996973 * X2 - 3.44988 * X3 + 90.8481 * X4 + 0.576968 * X1 * X2 - 0.23632 * X1 * X3 - 165.840 * X1 * X4 + 0.0200872 * X2 * X3 - 0.035620 * X2 * X4 - 11.6724 * X3 * X4$$

Where Y is % COD reduction, X_1 is Fe concentration, X_2 is contact time X_3 is pH and X_4 is H_2O_2 concentration.

The value of regression coefficient (R^2 = 88.39%) is closer to one, indicating the suitability of second order polynomial to predict the % COD removed of pharmaceutical wastewater in terms of independent variables, and the predicted values were found in close agreement with that of experimental results as shown in **Fig.10 and Table 11**.

The Estimated effect of model parameter for the % COD reduction is shown in **Table 12** Model fitting is required to test the significance and adequacy of the model. It is observed from the **Table 12** that the coefficients for the most of the individual and 2 way interaction of model terms are highly significant (P = <0.05). The Predicted R^2 of 85.78% is as close to the Adjusted R^2 of 85.18% as one might normally expect. This indicates a negligible block effect and model and/or data are best fit for optimization. Higher R^2 value of predicted model with low or no outliers yields the adequate precision of 779.766.The standard deviation is found to be 3.90254 indicates model shows great compliance with predicted responses. In the Fenton cavitation experiments with pharmaceutical waste water (Sample 2) X_2, X_3, X_1X_2, X_2X_3 are found significant model terms.

ANOVA results of model variables shown in **Table 12** imply that the overall main effects of process parameters are predominate over their interactive effects. Among the

different process variables selected for the study X_2 and X_3 are found highly significant at their main effect. The positive effect of X_2 predominates over the negative effect of X_3, and had found greatly influences the % COD reduction as ($P< 0.05$) at 95% CI. . From the full factorial analysis it was confirmed that Contact time (X_2) interact positively with X_4whereas negatively with X_1 and X_3. .

These significant interaction means that effect of X_1on % COD reduction is depend on level of X_2 used. Similarly, the effect of X_2 on the % COD is depending on levels of X_3 and X_4 respectively.

Negative effect of pH, Fe^2+, Contact time*H_2O_2, Fe^{2+}*pH, Fe^{2+}*H_2O_2 & pH*H_2O_2 means that at high level, they tend to decrease the % COD reduction. The significant main and interactive of selected process parameters shows an overall curvilinear effect on the % COD reduction.

Optimization and validation of experimental model

The contour plots are plotted to understand the interaction of the variables and to determine the optimum level of each variable for maximum response. It is evident from the elliptical nature of the contours that the interaction between the individual variables is significant as shown in **Fig.11, 12, 13, 14.** The studies of the contour plot also reveal the best optimal values (to maximize % COD reduction) of the process conditions for all process parameters and are: X_1, 0.15-0.2; X_2, 200-170 min; X_3, 1-3 and X_4 0.2-0.4.

The numerical point prediction tool of MINITAB RELEASE14 was used to find the optimal values of test variables for maximizing % COD reduction (> 40%). The optimum values of the test variables were: X_1-0.35; X_2-240 min; X_3-1 and X_4-0.4. A validation of the model results and regression equation was performed by Fenton oxidation with X_1 (0.35), X_2 (240 min), X_3 (1) and X_4 (0.4). The predicted response for % COD reduction was 40%, while the experimental response was 43%, thus proving the validity of the model. The composite desirability value (D) of predicted yield at optimized level of variables were found to be very close to 1 (D=0.909686) owing to higher precision of

validation. This result shows that the regression model developed in this study resulted in good agreement between the actual and predicted responses.

4.1.2 b. Experimental results of fenton oxidation For BOD/COD, % COD reduction of Sample 2 and model fitting

The uncoded values of the test variables and the experimental results for % COD reduction are presented in **Table 11.** Factorial fit of the experimental data yielded the following regression equation for the %COD reduction:

$$Y = 0.549688 + 0.106250 * X1 - 2.70833 * X2 - 0.0032292 * X3 + 0.665625 * X4 + 0.00208333 * X1 * X2 - 0.0062500 * X1 * X3 - 1.81250 * X1 * X4 - 1.38889 * X2 * X3 + 0.00041667 * X2 * X4 - 0.0562500 * X3 * X4$$

Where Y is % COD reduction, X_1 is Fe^{2+} concentration, X_2 is contact time X_3 is pH and X_4 is H_2O_2 concentration.

The value of regression coefficient (R^2 = 98.50%) is closer to one, indicating the suitability of second order polynomial to predict the % COD removed of pharmaceutical wastewater in terms of independent variables, and the predicted values were found in close agreement with that of experimental results as shown in **Fig. 10 and Table 11.**

The Estimated effect of model parameter for the % COD reduction is shown in **Table 13.** Model fitting is required to test the significance and adequacy of the model. It is observed from the **Table 13** that the coefficients for the most of the individual and 2 way interaction of model terms are highly significant (P = <0.05). The Predicted R^2 of 85.78% is as close to the Adjusted R^2 of 91.63% as one might normally expect. Higher R^2 value of predicted model with low or no outliers yields the adequate precision of 735.36. The standard deviation is found to be 0.0378979 indicates model shows great compliance with predicted responses. In the Fenton oxidation experiments with

pharmaceutical waste water (Sample 2) X_2, X_3, X_1X_2, X_2X_4 are found significant model terms.

ANOVA results of model variables shown in **Table 13** imply that the overall main effects of process parameters are predominate over their interactive effects. Among the different process variables selected for the study X_2 and X_3 are found highly significant at their main effect. The positive effect of X_2 predominates over the negative effect of X_3, and had found greatly influences the % COD reduction as ($P< 0.05$) at 95% CI. From the full factorial analysis it was confirmed that Contact time (X_2) interact positively with X_4 & X1 whereas negatively with X_3.

These significant interaction means that effect of X_1on % COD reduction is depend on level of X_2 used. Similarly, the effect of X_2 on the % COD is depending on levels of X_3 and X_4 respectively.

Negative effect of pH, Fe^{2+}, Contact time*pH, Fe^{2+}*pH, Fe^{2+}*H_2O_2 & pH*H_2O_2 means that at high level, they tend to decrease the % COD reduction. The significant main and interactive of selected process parameters shows an overall curvilinear effect on the % COD reduction.

Optimization and validation of experimental model

It is evident from the elliptical nature of the contours that the interaction between the individual variables is significant as shown in **Fig.15.** The studies of the contour plot also reveal the best optimal values (to maximize % COD reduction) of the process conditions for all process parameters and are: X_1, 0.15-0.2; X_2, 200-250 min; X_3, 1-3 and X_4 0.2-0.4.

The numerical point prediction tool of MINITAB RELEASE14 was used to find the optimal values of test variables for maximizing % COD reduction (> 40%). The optimum values of the test variables were: X_1-0.15; X_2-240 min; X_3-1 and X_4-0.4. A validation of the model results and regression equation was performed by Fenton oxidation with X_1 (0.15), X_2 (240 min), X_3 (1) and X4 (0.4). The predicted response for % COD reduction was 40%, while the experimental response was 43%, thus proving the validity of the model. The composite desirability value (D) of predicted yield at optimized level of

variables were found to be very close to 1 (D=0.620833) owing to higher precision of validation. This result shows that the regression model developed in this study resulted in good agreement between the actual and predicted responses.

4.3 Experimental results of Fenton Cavitation For % COD reduction of Sample I and model fitting

The uncoded values of the test variables and the experimental results for % COD reduction are presented in **Table 14** Factorial fit of the experimental data yielded the following regression equation for the %COD reduction:

$$Y = 38.1667 + 24.0550 * X1 - 0.0973375 * X2 - 0.63062 * X3 + 15.7938 * X4 + 0.309917 * X1 * X2 - 19.1225 * X1 * X3 + 21.7250 * X1 * X4 - 0.0273667 * X2 * X3 + 0.022000 * X2 * X4 - 4.24000 * X3 * X4$$

Where Y is % COD reduction, X_1 is Fe^{2+} concentration, X_2 is contact time X_3 is pH and X_4 is H_2O_2 concentration.

The value of regression coefficient (R^2 = 99.29%) is closer to one, indicating the suitability of second order polynomial to predict the % COD removed of pharmaceutical wastewater in terms of independent variables, and the predicted values were found in close agreement with that of experimental results as shown in **Fig. 16 and Table 15**.

The Estimated effect of model parameter for the % COD reduction is shown in **Table 15.** Model fitting is required to test the significance and adequacy of the model. It is observed from the **Table 15** that the coefficients for the most of the individual and 2 way interaction of model terms are highly significant (P = <0.01 and P =<0.05). The Predicted R^2 of 97.37% is as close to the Adjusted R^2 of 97.52% as one might normally expect. Higher R^2 value of predicted model with low or no outliers yields the adequate precision of 84.7717. The standard deviation is found to be 1.20550 indicates model

shows great compliance with predicted responses. In the Fenton cavitation experiments with pharmaceutical waste water X_1, X_2, X_3,X_4, X_1X_2,X_1X_3, X_2X_3 are found significant model terms.

ANOVA results of model variables shown in **Table 15** imply that the overall main effects of process parameters are predominate over their interactive effects. Among the different process variables selected for the studyX_1, X_2, X_3 and X_4 are found highly significant at their main effect. The positive effect of X_1, X_2, and X_4 predominate over the negative effect of X_3, and had found greatly influences the % COD reduction as ($P<$ 0.01) at 99% CI. From the full factorial analysis it was confirmed that Contact time (X_2) interact positively with X_1 and X_4 whereas negatively with X_3.

These significant interaction means that effect of X_1on % COD reduction is depend on level of X_2 used. Similarly, the effect of X_2 on the % COD is depending on levels of X_3 and X_4 respectively.

Negative effect of pH, Contact time*pH and Fe^{2+}* pH means that at high level, they tend to decrease the % COD reduction. The significant main and interactive of selected process parameters shows an overall curvilinear effect on the % COD reduction.

Optimization and validation of experimental model

It is evident from the elliptical nature of the contours that the interaction between the individual variables is significant as shown in **Fig.17 & 18.**The studies of the contour plot also reveal the best optimal values (to maximize % COD reduction) of the process conditions for all process parameters and are: X_1, 0.15-0.2; X_2, 130-170 min; X_3, 2-4 and X_4 0.2-0.3.

The numerical point prediction tool of MINITAB RELEASE14 was used to find the optimal values of test variables for maximizing % COD reduction (> 60%). The optimum values of the test variables were: X_1-0.34; X_2-108 min; X_3-2 and X_4-0.3. A validation of the model results and regression equation was performed by Fenton oxidation with X_1 (0.34), X_2 (108 min), X_3 (2) and X4 (0.3). The predicted response for % COD reduction was 61%, while the experimental response was 61%, thus proving the

validity of the model. The composite desirability value (D) of predicted yield at optimized level of variables was found to be 1.00 which is highly desirable owing to higher precision of validation. This result shows that the regression model developed in this study resulted in good agreement between the actual and predicted responses.

4.3.1 a. Experimental results of fenton cavitation for % COD reduction of Sample II and model fitting

The uncoded values of the test variables and the experimental results for % COD reduction are presented in **Table 16.** Factorial fit of the experimental data yielded the following regression equation for the %COD reduction:

$$Y = 45.105 - 0.136 * X1 + 3.711 * X2 - 2.638 * X3 + 1.206 * X4 + 3.178 * X1 * X2 + 0.754 * X1 * X3 - 1.688 * X1 * X4 + 0.431 * X2 * X3 - 0.651 * X2 * X4 - 1.014 * X3 * X4$$

Where Y is % COD reduction, X_1 is Fe^{2+} concentration, X_2 is contact time X_3 is pH and X_4 is H_2O_2 concentration.

The value of regression coefficient (R^2 = 97.50%) is closer to one, indicating the suitability of second order polynomial to predict the % COD removed of pharmaceutical wastewater in terms of independent variables, and the predicted values were found in close agreement with that of experimental results as shown in **Fig. 19 and Table 16**.

The Estimated effect of model parameter for the % COD reduction is shown in **Table 17.** Model fitting is required to test the significance and adequacy of the model. It is observed from the **Table 17** that the coefficients for the most of the individual and 2 way interaction of model terms are highly significant (P =<0.01 and P = <0.05). The Predicted R^2 of 87.76% is as close to the Adjusted R^2 of 87.93% as one might normally expect. Higher R^2 value of predicted model with low or no outliers yields the adequate precision of 318.635. The standard deviation is found to be 2.33716 indicates model

shows great compliance with predicted responses. In the Fenton cavitation experiments with pharmaceutical waste water (Sample 2) X_2, X_3, X_4, X_1X_2, X_1X_4 are found significant model terms.

ANOVA results of model variables shown in **Table 17** imply that the overall main effects of process parameters are predominate over their interactive effects. Among the different process variables selected for the study X_2, X_3 and X_4 are found highly significant at their main effect. The positive effect of X_2 and X_4 predominate over the negative effect of X_1, X_3, and had found greatly influences the % COD reduction as ($P<$ 0.01) at 99% CI. From the full factorial analysis it was confirmed that Contact time (X_2) interact positively with X_4 whereas negatively with X_1 and X_3.

These significant interaction means that effect of X_1on % COD reduction is depend on level of X_2 used. Similarly, the effect of X_2 on the % COD is depending on levels of X_3 and X_4 respectively.

Negative effect of Fe^{2+}, pH, Fe^{2+}*H_2O_2, pH*H^2O^2 means that at high level, they tend to decrease the % COD reduction. The significant main and interactive of selected process parameters shows an overall curvilinear effect on the % COD reduction.

Optimization and validation of experimental model

It is evident from the elliptical nature of the contours that the interaction between the individual variables is significant as shown in **Fig. 20,21,22,23.** The studies of the contour plot also reveal the best optimal values (to maximize % COD reduction) of the process conditions for all process parameters and are: X_1, 0.15-0.35; X_2, 45-60 min; X_3, 1-3 and X_4 0.2-0.4.

The numerical point prediction tool of MINITAB RELEASE14 was used to find the optimal values of test variables for maximizing % COD reduction (> 50%). The optimum values of the test variables were: X_1-0.16; X_2-60 min; X_3-1 and X_4-0.4. A validation of the model results and regression equation was performed by Fenton oxidation with X_1 (0.16), X_2 (60 min), X_3 (1) and X4 (0.4). The predicted response for % COD reduction was 50%, while the experimental response was 53%, thus proving the

validity of the model. The composite desirability value (D) of predicted yield at optimized level of variables were found to be very close to 1 (D=0.972233) owing to higher precision of validation. This result shows that the regression model developed in this study resulted in good agreement between the actual and predicted responses.

4.3.1.b. Experimental results of fenton cavitation For BOD/COD, % COD reduction of Sample II and model fitting

The uncoded values of the test variables and the experimental results for BOD/COD, % COD reduction are presented in **Table 16.** Factorial fit of the experimental data yielded the following regression equation for the %COD reduction:

$$Y = 0.67750 - 0.050000 * X1 - 0.0020833 * X2 - 0.567500 * X3 - 843750 * X4 + 0.0116667 * X1 * X2 + 1.65000 * X1 * X3 - 4.12500 * X1 * X4 + 0.0115833 * X2 * X3 - 0.030000 * X2 * X4 + 2.45625 * X3 * X4$$

Where Y is % COD reduction, X_1 is Fe^{2+} concentration, X_2 is contact time X_3 is pH and X_4 is H_2O_2 concentration.

The value of regression coefficient (R^2 = 97.08%) is closer to one, indicating the suitability of second order polynomial to predict the % COD removed of pharmaceutical wastewater in terms of independent variables, and the predicted values were found in close agreement with that of experimental results as shown in **Fig. 19 and Table 16**.

The Estimated effect of model parameter for the % COD reduction is shown in **Table 18** Model fitting is required to test the significance and adequacy of the model. It is observed from the **Table 18** that the coefficients for the most of the individual and 2 way interaction of model terms are highly significant (P = <0.05), (P = <0.01). The Predicted R^2 of 89.44% is as close to the Adjusted R^2 of 89.79% as one might normally expect. Higher R^2 value of predicted model with low or no outliers yields the adequate precision of 3.83125.The standard deviation is found to be 0.0119373 indicates model

shows great compliance with predicted responses. In the Fenton cavitation experiments with pharmaceutical waste water (Sample 2) X_1, X_2, X_1X_2, X_1X_3, X_2X_3, X_2X_4 and X_3X_4 are found significant model terms.

ANOVA results of model variables shown in **Table 18** imply that the overall main effects of process parameters are predominate over their interactive effects. Among the different process variables selected for the study X_2 and X_4 are found highly significant at their main effect. The positive effect of X_2 and X_4 predominate over the negative effect of X_1 and X_3, and had found greatly influences the response viz. % COD reduction as ($P<$ 0.01) at 99% CI. From the full factorial analysis it was confirmed that Contact time (X_2) interact positively with X_4 whereas negatively with X_1 and X_3.

These significant interaction means that effect of X_1on % COD reduction is depend on level of X_2 used. Similarly, the effect of X_2 on the % COD is depending on levels of X_3 and X_4 respectively.

Negative effect of Fe^{2+}, pH, Fe^{2+}*contact time, Fe^{2+}*pH, Fe^{2+}*H_2O_2, contact time*H_2O_2 means that at high level, they tend to decrease the % COD reduction. The significant main and interactive of selected process parameters shows an overall curvilinear effect on the % COD reduction.

Optimization and validation of experimental model

It is evident from the elliptical nature of the contours that the interaction between the individual variables is significant as shown in **Fig. 24,25,26,27,28**. The studies of the contour plot also reveal the best optimal values (to maximize % COD reduction) of the process conditions for all process parameters and are: X_1, 0.15-0.2; X_2, 45-60 min; X_3, 1-3 and X_4 0.2-0.4.

The numerical point prediction tool of MINITAB RELEASE14 was used to find the optimal values of test variables for maximizing % COD reduction (> 50%). The optimum values of the test variables were: X_1-0.16; X_2-60 min; X_3-1 and X_4-0.4. A validation of the model results and regression equation was performed by Fenton oxidation with X_1 (0.16), X_2 (60 min), X_3 (1) and X4 (0.4). The predicted response for %

COD reduction was 50%, while the experimental response was 53%, thus proving the validity of the model. The composite desirability value (D) of predicted yield at optimized level of variables were found to be very close to 1 (D=0.620833) owing to higher precision of validation. This result shows that the regression model developed in this study resulted in good agreement between the actual and predicted responses.

4.3 Cavitation

The pharmaceutical waste water samples were subjected to ultrasonic irradiation using as a pretreatment. For both the samples it was found that there are only 3 to 4.5% reductions in %COD removal as shown in **Table 19& 20.**.

It was observed from the results that higher time of cavitation does not aid in COD removal (Table 19 & 20).Also the waste water sample II where in the initial BI is 0.59, after pretreatment does not even aid in enhancing the BOD of the waste water. Thus Acoustic Cavitation does not seem to favor COD removal and BOD enhancement for present investigation using pharmaceutical waste water.

Guo et al., 2005 studied the effect of Acoustic cavitation and Fenton oxidation followed by acoustic cavitation (Fenton + cavitation) on 2, 4-dinitrophenol.They have reported 4% and 82% of COD removal in acoustic cavitation and fenton + cavitation respectively after 60 min of reaction time, thus indicating that individual Cavitation cannot aid in COD removal, however, higher removal can be achieved in the coupled / hybrid pretreatment process.

Table 1

General Characteristics of pharmaceutical waste water

PARAMETERS	CONCENTRATION
pH	1-11
COD(mg/lt)	5,000-80,000
BOD(mg/lt)	14,000 – 38,000
TSS(mg/lt)	25.268

Table 2

Pharmaceutical manufacturing processes & their effluents

Process Description	Components
Research &Development: includes chemical research, microbiological research, and pharmacological research	Halogenated and non-halogenated solvents, photographic chemicals, radionuclide's, bases, and oxidizers.
Chemical synthesis: one or more batch reactor vessels are used in a series of reaction, separation and purification steps to make the desired end product.	Mother liquor containing unconverted reactants, reaction byproducts, and residual products in the organic solvent base. Acids, bases, cyanides, and metals may also be generated.

Natural product extraction: includes production of pharmaceuticals from natural material sources such as roots, leaves, and animal glands.	Water-soluble solvents, solvent vapors and waste waters.
Fermentation: processes consist of two major steps: inoculum and seed preparation for fermentation, followed by crude product recovery and purification.	Unconsumed raw materials such as corn steep liquor, fish meal, and molasses. Filtration processes generates large quantities of solids in the form of spent filter cake which includes solid remains of the cells, filter aid, and some residual product.
Formulation: Pharmaceutical formulation is the preparation of dosage forms such as tablets, capsules, liquids, parenterals, creams & ointments	Chemical spills, rejected products, inorganic salts, sugars and syrups.

Table 3

References for Fenton oxidation

AUTHOR	YEAR	TITLE	CONCLUSION
Martinez et. al	2003	Pre-oxidation of an extremely polluted industrial wastewater by the Fenton's reagent	Optimal values of hydrogen peroxide and ferrous ion concentrations were 3 and 0.3M respectively; a COD reduction of 56.4% resulted.
Tekin et.al	2006	Use of Fenton oxidation to improve the biodegradability	Average COD removal was highest when the ratio of H_2O_2/Fe^{2+} was around 155, 0.3M H_2O_2 and 0.002M Fe^{2+},

		of a pharmaceutical wastewater	provided 45-60% COD removal.
Vlyssides et.al	2008	Fenton oxidation and biological treatment on pharmaceutical wastewater	Treatment with Fenton's oxidation improved the biodegradability and reduced the toxicity of pharmaceutical wastewater upto 70%.
Badawy et.al	2009	Fenton-biological treatment processes for the removal of some pharmaceuticals from industrial wastewater	Fenton as a pre-treatment process would increase the biodegradability and/or remove the toxicity of the wastewater, which represent physicochemical characteristics of the raw wastewater and their treated effluents by means of Fenton process followed by biological activated sludge.
Yang et.al	2009	Microwave enhanced Fenton-like process for the treatment of high concentration pharmaceutical wastewater	The COD removal, UV254 removal were 57.53% and 55.06%, respectively, and BOD_5/COD was enhanced from 0.165 to 0.470 under this optimal condition.
Hussian et.al	2011	COD reduction of waste water streams of active pharmaceutical ingredient- Atenolol manufacturing unit by advanced oxidation –Fenton process	Rate of degradation of the Atenolol molecule is maximum at 2.0 and maximum COD reduction is upto 54% at this pH.
Bianco et.al	2011	Fenton treatment of complex industrial wastewater: Optimization of process conditions by surface response method	80% of the initial COD (32 g/L), with the following setup: 0.58 [CODi]/[H_2O_2] and 15 [H_2O_2]/[Fe_{2+}]. This shows how Fenton process can be considered as a powerful tool to wastewater treatment in a wide range of conditions, tuning the concentrations of the reagents following the predictions of the surface response function.

Table 4

References for Cavitation

AUTHOR	YEAR	TITLE	CONCLUSION
Bhirud et.al	2004	Ultrasonic bath with longitudinal vibrations: a novel configuration for efficient wastewater treatment	The reactor is suitable for the degradation of formic acid and the extent of degradation increases with a decrease in the initial concentration of formic acid and using optimized concentration of hydrogen peroxide.
Neppolian	2004	Effect of Fenton-like oxidation on enhanced oxidative degradation of para-chlorobenzoic acid by ultrasonic irradiation	The coupled ultrasound/FeOOH–H_2O_2 process appears to have a positive synergistic effect on the degradation of chloro-aromatic compounds
Guo et.al	2005	Effect of various sono-oxidation parameters on the removal of aqueous 2,4-dinitrophenol	High ultrasonic intensity and high acid concentration enhances DNP degradation.
P. R. Gogate	2008	Treatment of wastewater streams containing phenolic compounds using hybrid techniques based on cavitation: A review of the current status and the way forward	Combination of cavitation with other oxidation techniques or use of additives leads to enhanced generation of the hydroxyl radicals which eventually results in higher oxidation rates.
AH Mahvi	2009	Application of Ultrasonic Technology for Water and Wastewater Treatment	Ultrasonic in low-kilohertz frequency range has some efficacy in inactivating some disease agents in water. This would suggest that transient cavitation is the physical mechanism responsible for affecting the microorganisms.
Pradhan et.al	2010	Degradation of p-nitrophenol using acoustic cavitation	Advanced Fenton process (AFP) is more efficient in degradation of pollutants than conventional Fenton process, attributed to

		and Fenton chemistry.	the fact that presence of solid particles enhances the cavitational activity.
Guo et.al	2010	Sonochemical degradation of the antibiotic cephalexin in aqueous solution.	Ultrasound can effectively decompose cephalexin in aqueous solution and the extent of degradation depends strongly on the operating conditions, such as ultrasound power and pH value of the medium.

Table 5

Operational conditions for waste water sample I

Parameters	**Range**
Fe^{2+} (g/100ml)	0.15-0.35
Contact Time (mins)	90-150
pH	2 to 4
H_2O_2 (ml/100ml)	0.1-0.3

Table 6

Operational conditions for waste water sample II

Parameters	**Range**
Fe^{2+} (g/100ml)	0.15-0.35
Contact Time (mins)	150-240
pH	1 to 3
H_2O_2 (ml/100ml)	0.2-0.4

Table 7

Characteristics of the Sample I

Sr.No	Parameter	Value
1.	pH	4.38
2.	COD(mg/lt)	20,000-25,000
4.	TSS(g/lt)	25.268
5.	TDS(g/lt)	122.28
6.	TS(g/lt)	137.096

Table 8

Characteristics of the sample II

Sr.No	Parameter	Value
1.	pH	6.29
2.	COD(mg/lt)	60,000-65,000
3.	BOD(mg/lt)	35,000-38,000
4.	TSS(g/lt)	23.592
5.	TDS(g/lt)	103.904
6.	TS(g/lt)	113.632

Table 9
Factorial design for pharmaceutical waste along with predicted and experimental values

Runs	Fe^{2+} (%)	Contact Time(min)	pH	H_2O_2 (%)	% COD removal	
					Observed	Predicted
1	0.15	150	4	0.1	6.475391	3.11036
2	0.35	90	2	0.3	25.0203	28.1485
3	0.35	150	2	0.3	26.9565	74.80666
4	0.15	90	2	0.3	28.8956	30.9749
5	0.35	150	4	0.3	46.0434	46.93466
6	0.15	150	2	0.3	58.2608	53.0537
7	0.15	90	4	0.3	29.02608	27.83802
8	0.35	150	2	0.1	34.2608	35.2122
9	0.15	90	4	0.1	35.2898	35.52692
10	0.15	150	4	0.3	17.029	21.34506
11	0.15	90	2	0.1	30.968	29.84012
12	0.15	150	2	0.1	21.7391	25.99532
13	0.35	90	2	0.1	18.5565	14.47764
14	0.35	90	4	0.3	32.8672	28.84826
15	0.35	90	4	0.1	19.03069	24.00108
16	0.35	150	4	0.1	18.00586	16.16388

Table 10

Analysis of variance (ANOVA) of effect & coefficient for % COD reduction

Sources	Effects	Coefficient	P value
Constant	--	48.2785	0.000
Main Effect	--	--	0.040
$Fe^{2+}(X_1)$	5.113	-311.681	0.208
Contact time(X_2)	7.121	-0.111156	0.105
pH(X_3)	-11.093	25.0394	0.031
$H_2O_2(X_4)$	15.953	-191.645	0.009
2-Way interaction	--	--	0.046
Fe^{2+}*Contact time (X_1*X_2)	12.290	2.04828	0.023
Fe^{2+}*pH(X_1*X_3)	1.918	9.5916	0.603
Fe^{2+}*H_2O_2 (X_1*X_4)	6.268	313.402	0.139
Contact time*pH (X_2*X_3)	-14.286	-0.238098	0.014
pH*H_2O_2 (X_3*X_4)	-4.412	-22.0592	0.265
S = 6.21725	Press = 2254.83	R^2 = 93.19%	R^2(predicted)=86.63%
R^2(adjusted)=86.15%			

Table 11

Factorial design for pharmaceutical waste along with predicted and experimental values

Runs	Fe^{2+} (%)	Contact Time(min)	pH	H_2O_2 (%)	BOD/COD	%COD Observed	%COD Predicted
1	0.15	240	3	0.2	0.63	34.8102	31.54287
2	0.35	150	1	0.4	0.67	31.61435	33.91803
3	0.35	240	1	0.4	0.68	46.5846	43.64529
4	0.15	150	1	0.4	0.74	43.51692	43.34897
5	0.35	240	3	0.4	0.69	37.5384	36.8840
6	0.15	240	1	0.4	0.76	41.8871	42.69081
7	0.15	150	3	0.4	0.65	36.4923	33.06651
8	0.35	240	1	0.2	0.74	38.6666	41.12871
9	0.15	150	3	0.2	0.63	24.041	27.94418
10	0.15	240	3	0.4	0.67	33.23338	36.02406
11	0.15	150	1	0.2	0.61	33.405	33.55763
12	0.15	240	1	0.2	0.64	33.8266	33.54063
13	0.35	150	1	0.2	0.65	32.58666	30.76029
14	0.35	150	3	0.4	0.6	22.25093	23.54108
15	0.35	150	3	0.2	0.62	26.81964	25.05230
16	0.35	240	3	0.2	0.63	37.90461	39.03642

Table 12

Analysis of variance (ANOVA) of effect & coefficient for % COD reduction

Sources	Effects	Coefficient	P value
Constant	--	36.2805	0.000
Main Effect	--	--	0.033
$Fe^{2+}(X_1)$	-0.969	-67.1276	0.641
Contact time(X_2)	6.663	-0.0996973	0.019
pH(X_3)	-6.187	-3.44988	0.025
$H_2O_2(X_4)$	3.819	90.8481	0.108
2-Way interaction	--	--	0.224
Fe^{2+}*Contact time	5.193	0.576968	0.045
Fe^{2+}*pH	-0.047	-0.23632	0.982
$Fe^{2+}*H_2O_2$	-3.317	-165.840	0.150
Contact time*pH	1.808	0.0200872	0.052
$pH*H_2O_2$	-2.334	-11.6724	0.285
S = 3.90254	Press = 779.766	R_2 = 88.39%	R_2(predicted)=85.78%
R_2(adjusted)=85.18%			

Table 13

Analysis of variance (ANOVA) of effect & coefficient for BOD/COD % COD reduction

Sources	Effects	Coefficient	P value
Constant	--	0.549688	0.000
Main Effect	--	--	0.111
$Fe^{2+}(X_1)$	-0.00875	0.106250	0.664
Contact time(X_2)	0.03125	-2.70833	0.023
pH(X_3)	-0.04875	-0.0032292	0.050
$H_2O_2(X_4)$	0.03625	0.665625	0.114
2-Way interaction	--	--	0.588
Fe^{2+}*Contact time	0.01875	0.00208333	0.041
Fe^{2+}*pH	-0.00125	-0.0062500	0.950
$Fe^{2+}*H_2O_2$	-0.03625	-1.81250	0.114
Contact time*pH	-0.00125	-1.38889	0.050
pH*H_2O_2	-0.01125	-0.0562500	0.579
S = 0.0378979	Press = 735.36	R_2 = 98.50%	R_2(predicted)=89.78%
R_2(adjusted)=91.63%			

Table 14

Factorial design for pharmaceutical waste along with predicted and experimental values

Runs	Fe^{2+} (%)	Contact Time(min)	pH	H_2O_2 (%)	% COD removal	
					Observed	Predicted
1	0.15	45	4	0.1	42.67	41.9089225
2	0.35	30	2	0.3	58.5	58.2154595
3	0.35	45	2	0.3	51.8	67.6759625
4	0.15	30	2	0.3	53.5	54.1714535
5	0.35	45	4	0.3	49.9	49.8854425
6	0.15	45	2	0.3	60.3	59.9129525
7	0.15	30	4	0.3	48	47.3139375
8	0.35	45	2	0.1	61	60.6404525
9	0.15	30	4	0.1	38.67	39.7154275
10	0.15	45	4	0.3	49.37	49.7714325
11	0.15	30	2	0.1	49.3	48.2689435
12	0.15	45	2	0.1	53	53.7464425
13	0.35	30	2	0.1	50.8	51.4439495
14	0.35	30	4	0.3	43.41	43.7089435
15	0.35	30	4	0.1	35.9	35.2414335
16	0.35	45	4	0.1	40.78	41.1539325

Table 15

Analysis of variance (ANOVA) of effect & coefficient for % COD reduction

Sources	Effects	Coefficient	P value
Constant	--	38.1667	0.000
Main Effect	--	--	0.001
$Fe^{2+}(X_1)$	1.645	24.0550	0.067
Contact time(X_2)	5.827	-2.70833	0.001
pH(X_3)	-13.172	-0.0032292	0.002
$H_2O_2(X_4)$	7.317	0.665625	0.004
2-Way interaction	--	--	0.033
Fe^{2+}*Contact time	1.860	0.00208333	0.048
Fe^{2+}*pH	-3.825	-0.0062500	0.004
$Fe^{2+}*H_2O_2$	0.435	-1.81250	0.546
Contact time*pH	-1.642	-1.38889	0.851
pH*H_2O_2	0.848	-0.0562500	0.268
S = 1.20550	Press = 84.7717	R_2 = 99.29%	R_2(predicted)=97.37%
R_2(adjusted)=97.52%			

Table 4.16

Factorial design for pharmaceutical waste along with predicted and experimental values

Runs	Fe (%)	Contact Time(min)	pH	H_2O_2 (%)	BOD/COD	%COD Observed	%COD Predicted
1	0.15	60	3	0.2	0.71	45	44.99
2	0.35	45	1	0.4	0.67	39.02	39.20
3	0.35	60	1	0.4	0.63	54.89	54.58
4	0.15	45	1	0.4	0.74	53.44	52.04
5	0.35	60	3	0.4	0.65	49.44	49.34
6	0.15	60	1	0.4	0.73	52.5	52.49
7	0.15	45	3	0.4	0.73	45.8	45.34
8	0.35	60	1	0.2	0.69	51.9	51.89
9	0.15	45	3	0.2	0.64	35.8	35.79
10	0.15	60	3	0.4	0.59	40.8	40.79
11	0.15	45	1	0.2	0.68	43.79	42.78
12	0.15	60	1	0.2	0.72	44.8	44.79
13	0.35	45	1	0.2	0.7	41.6	41.59
14	0.35	45	3	0.4	0.63	34.6	34.43
15	0.35	45	3	0.2	0.66	37.1	36.28
16	0.35	60	3	0.2	0.67	51.2	50.19

Table 17

Analysis of variance (ANOVA) of effect & coefficient for % COD reduction

Sources	Effects	Coefficient	P value
Constant	--	71.2388	0.000
Main Effect	--	--	0.023
$Fe^{2+}(X_1)$	-1.585	-74.3250	0.283
Contact time(X_2)	8.735	-0.867750	0.002
pH(X_3)	-3.963	-49.5263	0.036
$H_2O_2(X_4)$	3.725	72.9687	0.044
2-Way interaction	--	--	0.124
Fe^{2+}*Contact time	5.043	2.55833	0.017
Fe^{2+}*pH	0.195	97.9750	0.886
$Fe^{2+}*H_2O_2$	-4.687	-588.125	0.022
Contact time*pH	2.175	0.976583	0.165
$pH*H_2O_2$	-0.715	0.439167	0.606
S = 3.90254	Press = 779.766	R_2 = 88.39%	R_2(predicted)=95.18%
R_2(adjusted)=95.78%			

Table 18

Analysis of variance (ANOVA) of effect & coefficient for BOD/COD, % COD reduction

Sources	Effects	Coefficient	P value
Constant	--	42.67750	0.000
Main Effect	--	--	0.043
$Fe^{2+}(X_1)$	-0.05200	-0.050000	0.001
Contact time(X_2)	0.01450	-0.002083	0.091
pH(X_3)	-0.01300	-0.567500	0.118
$H_2O_2(X_4)$	0.00950	-0.843750	0.020
2-Way interaction	--	--	0.124
Fe^{2+}*Contact time	-0.01950	0.0116667	0.041
Fe^{2+}*pH	-0.00700	1.65000	0.345
$Fe^{2+}*H_2O_2$	-0.04450	4.12500	0.002
Contact time*pH	0.01950	0.0115833	0.041
pH*H_2O_2	0.01450	2.4562	0.091
S = 0.0119373	Press = 3.83125	R_2 = 97.08%	R_2(predicted)=98.18%
R_2(adjusted)=98.78%			

Table 19

Effect of cavitation on % COD reduction for sample I

Contact time (min)	**% COD reduction**
30 min	3.46
45 min	3.92

Table 20

Effect of cavitation on Biodegradability index (BI), %COD reduction for sample II

Contact time (min)	**% COD reduction**	**BOD/COD**
45 min	4.33	0.60
60 min	4.46	0.60

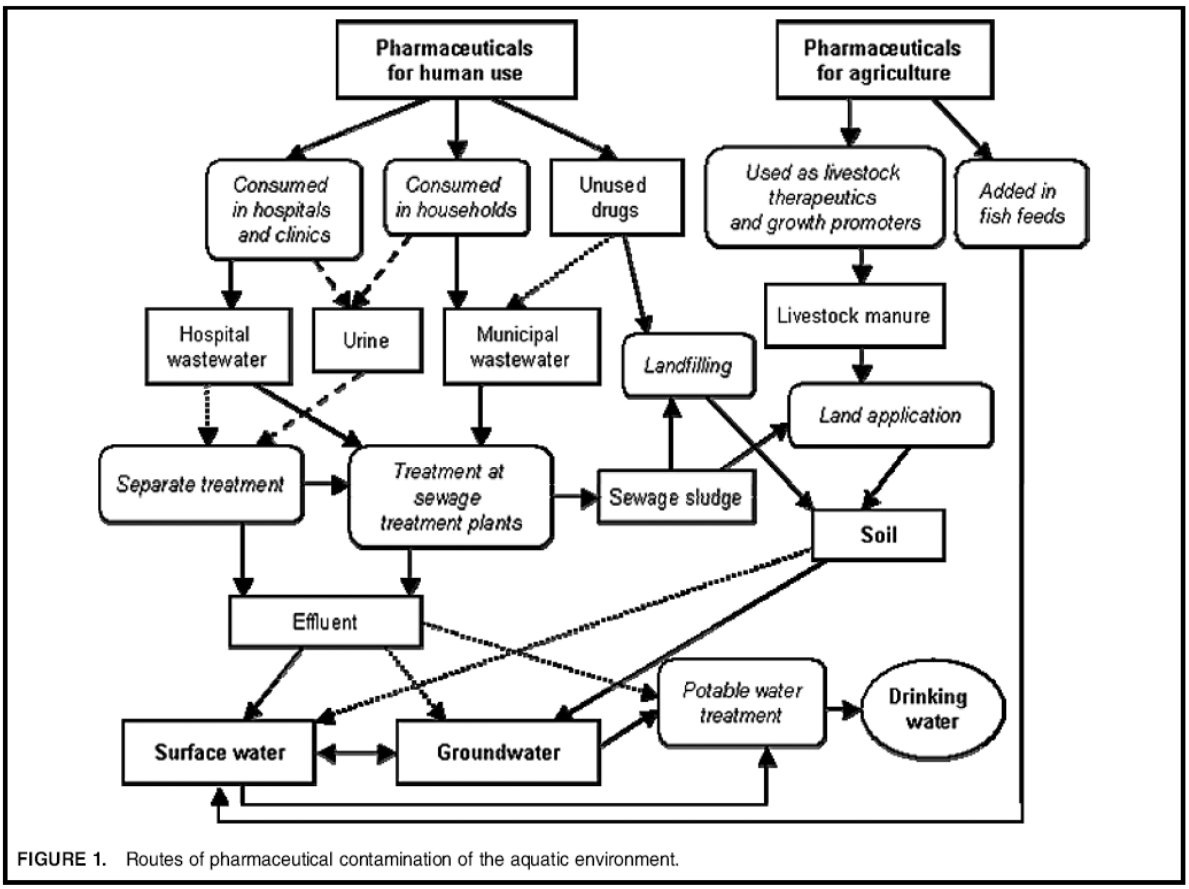
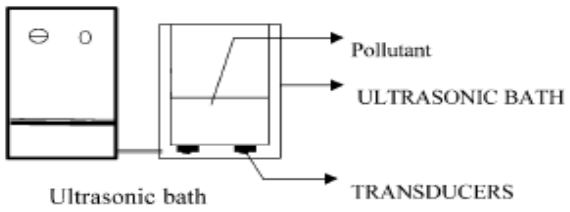


Figure 1: Routes of pharmaceutical contamination of the aquatic environment



Ultrasonic bath

Figure 2: Acoustic cavitation reactor

Figure 3: Acoustic cavitation reactor

Figure 4: Distillation apparatus

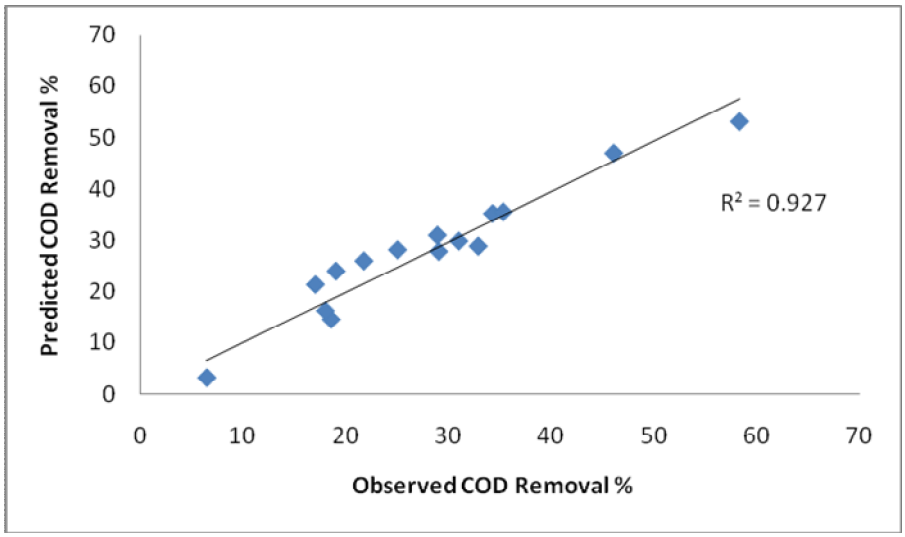


Figure 5: Correlation between experimental and predicted values of the% COD reduction

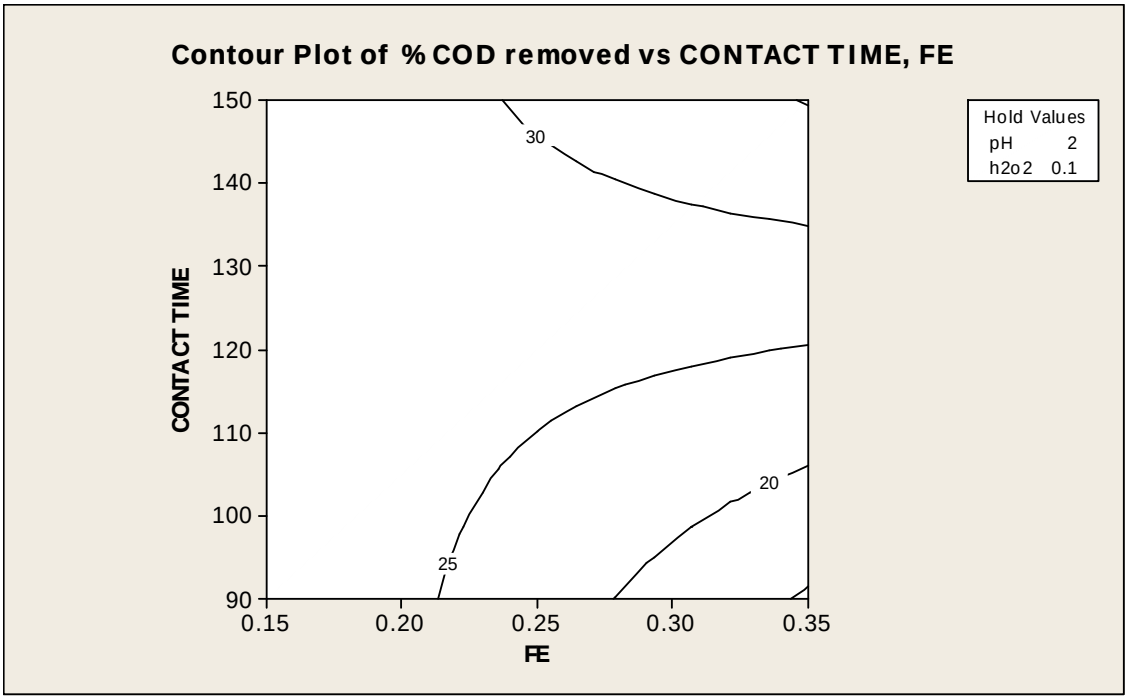


Figure 6: Contour plot for %COD reduction, Fe^{2+} and contact time at pH 2 & H_20_2 0.1

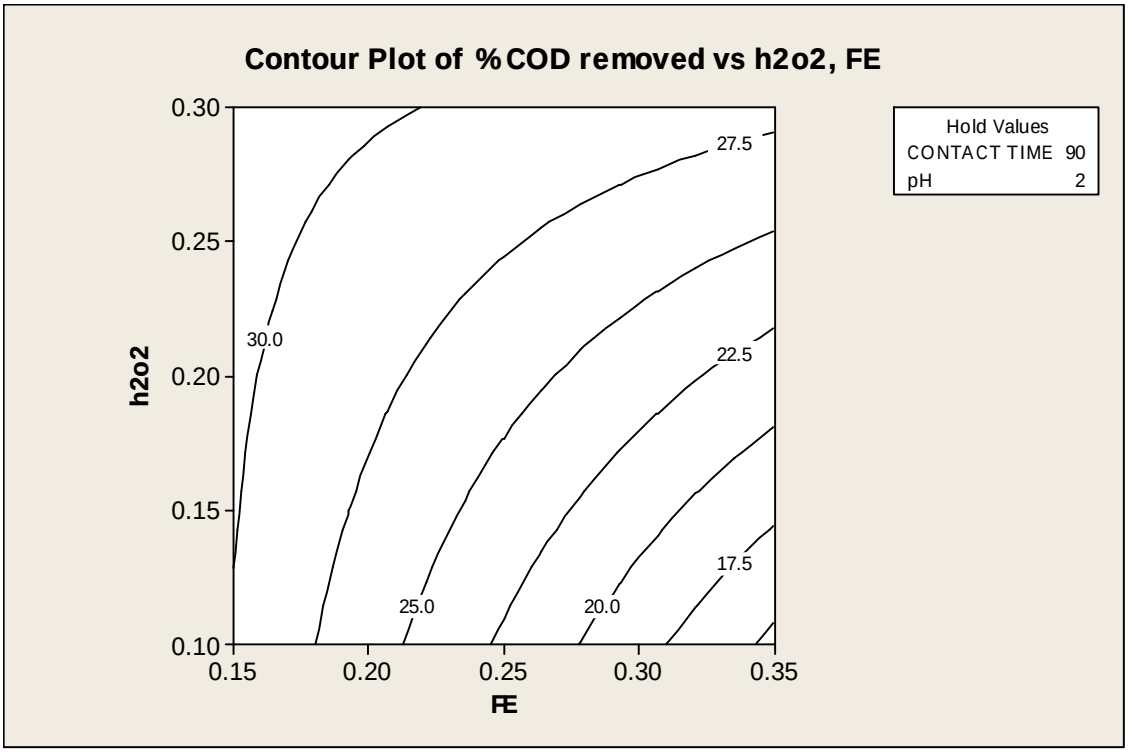


Figure 7: Contour plot for % COD reduction, Fe^{2+} and H_2O_2 at contact time 90 min & pH 2

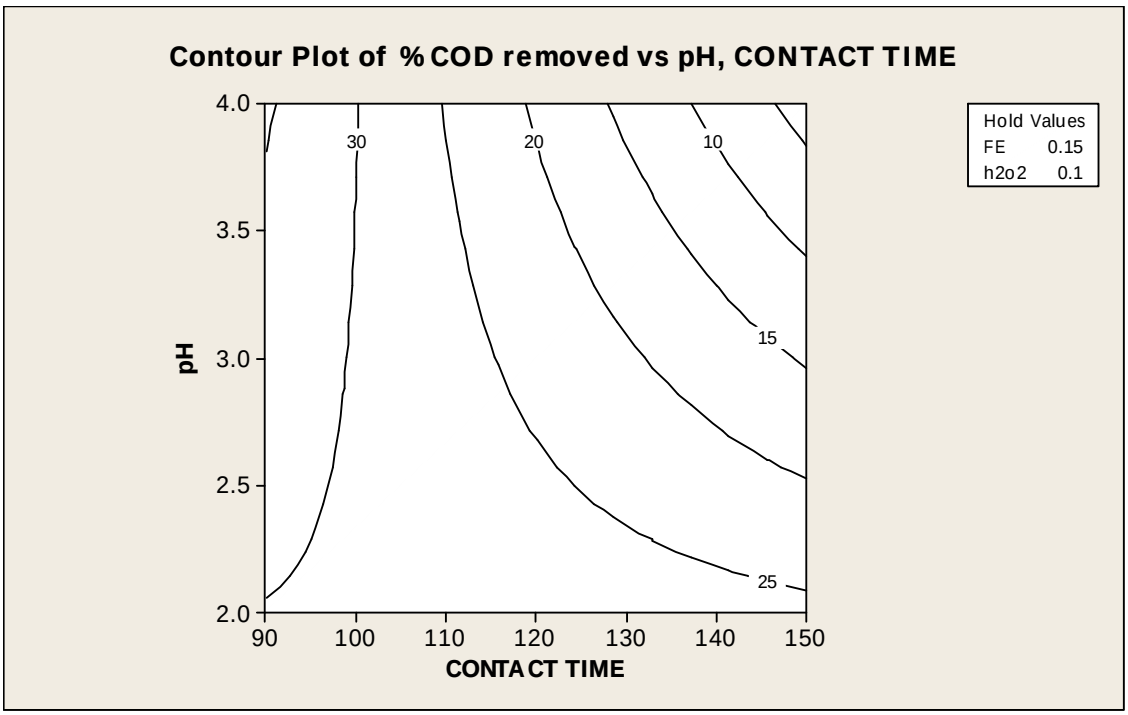


Figure 8: Contour plot for % COD reduction, pH and contact time at Fe^{2+} 0.15 & H_2O_2

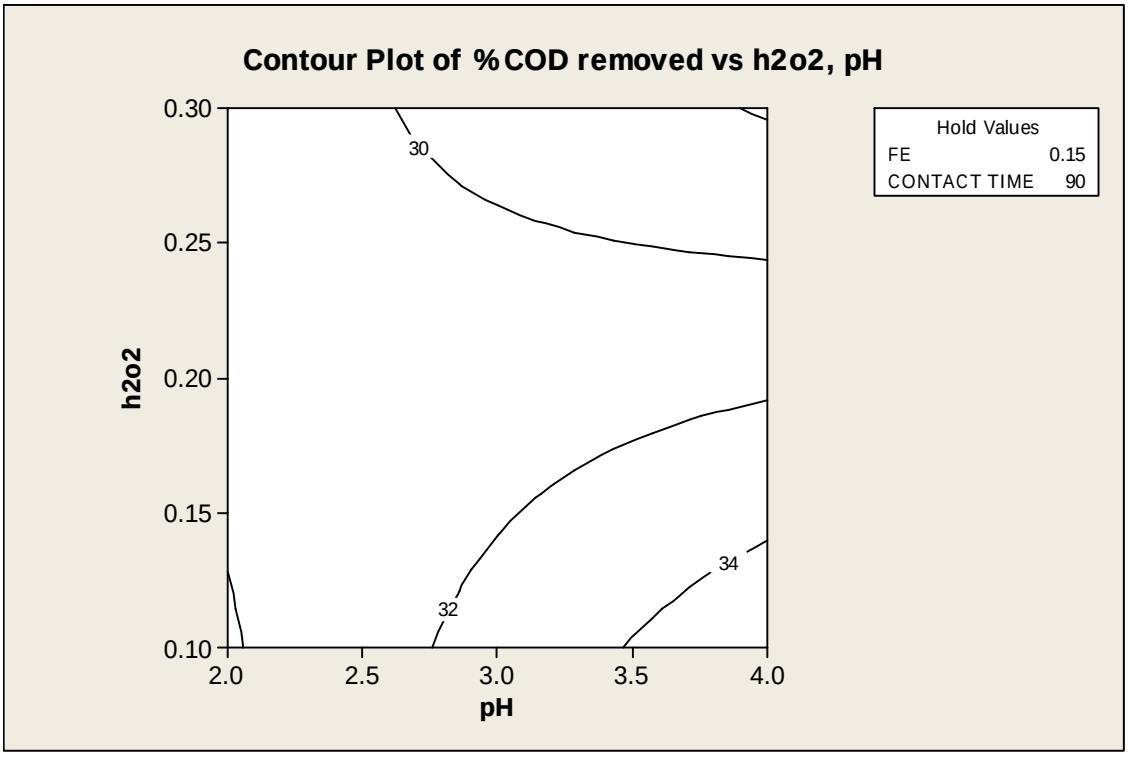


Figure 9: Contour plot for % COD reduction, pH and H_2O_2 at Fe^{2+} 0.15 & contact time 90min

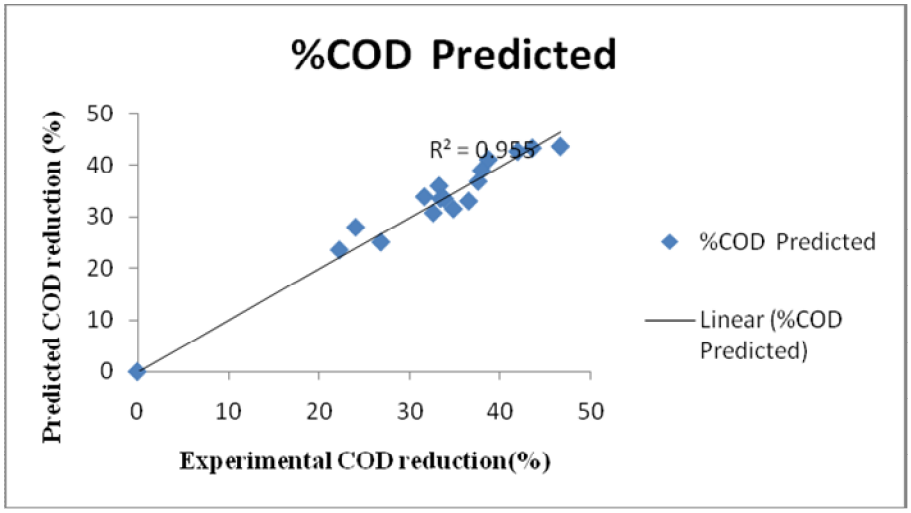


Figure 10: Correlation between experimental and predicted values of the% COD reduction

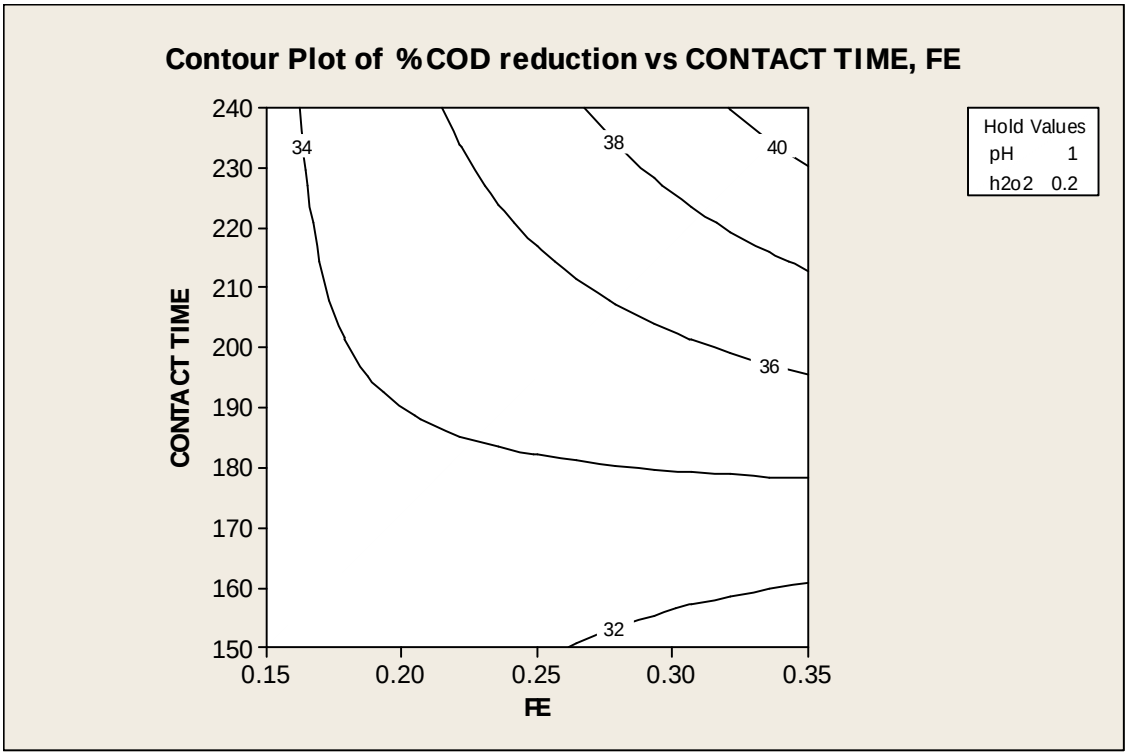


Figure 11: Contour plot for % COD reduction, Fe^{2+} and contact time at & pH 1& H_2O_2 0.2

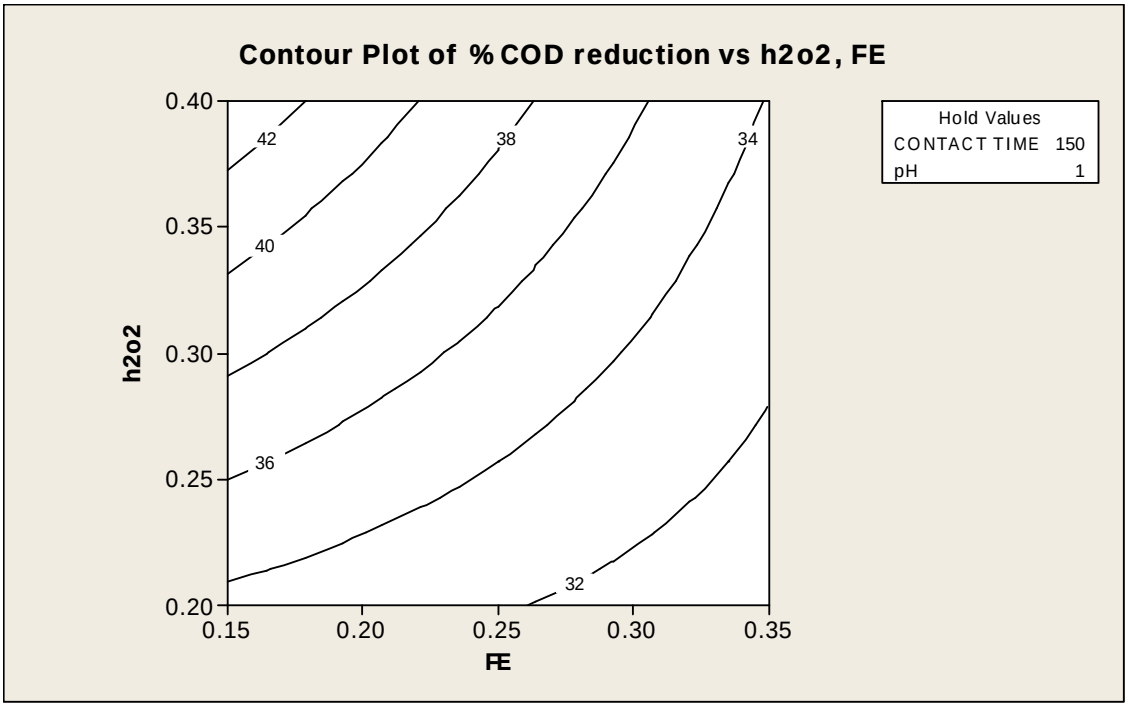


Figure 12: Contour plot for % COD reduction, Fe^{2+} and H_2O_2 at contact time 150min & pH 1

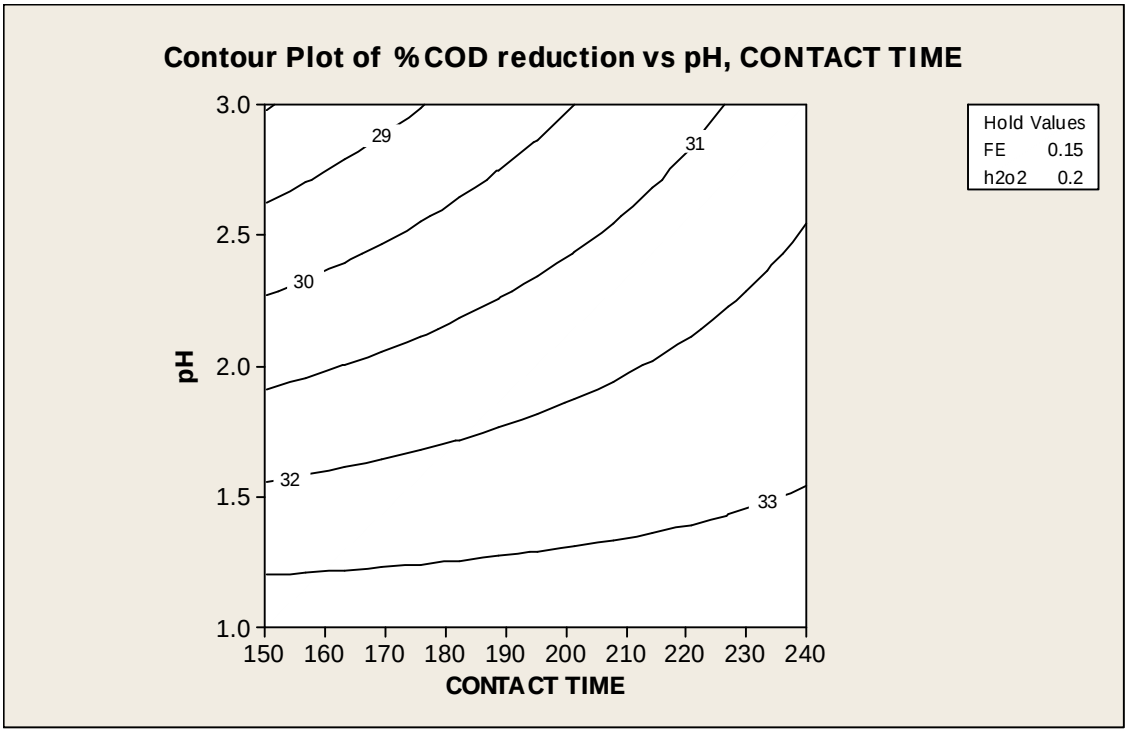


Figure 13: Contour plot for % COD reduction, pH and contact time at Fe^{2+} 0.15 and H_2O_2 0.2

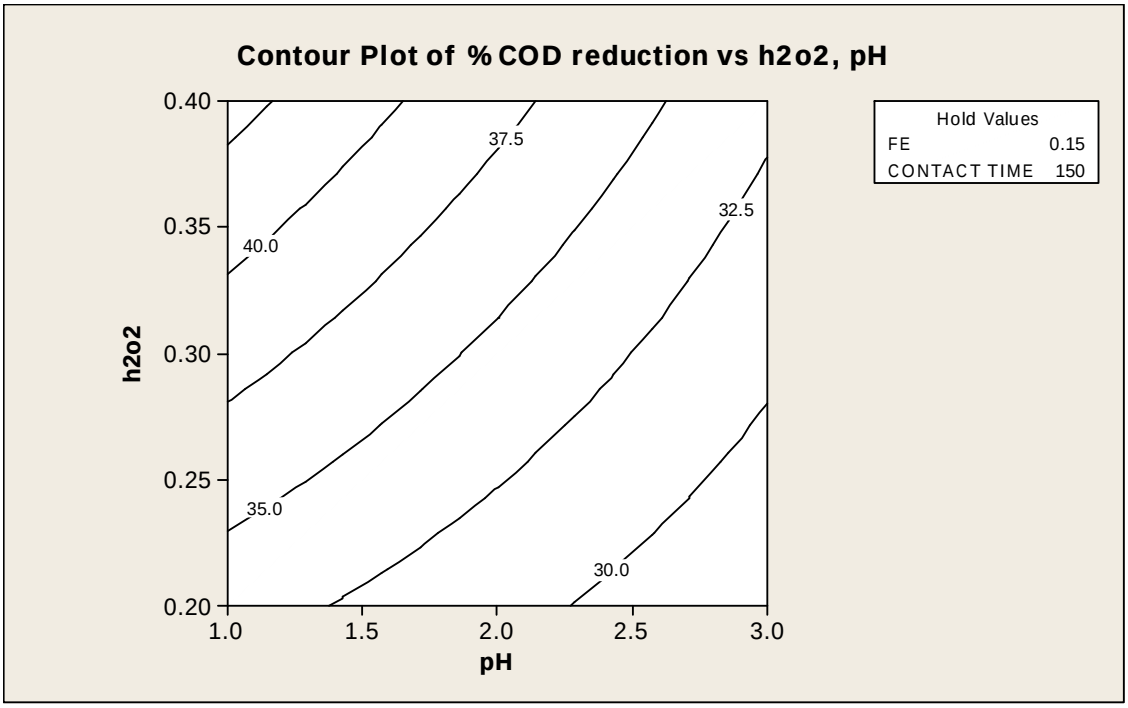


Figure 14: Contour plot for % COD reduction, pH and H_2O_2 at Fe^{2+} 0.15 & contact time 150min

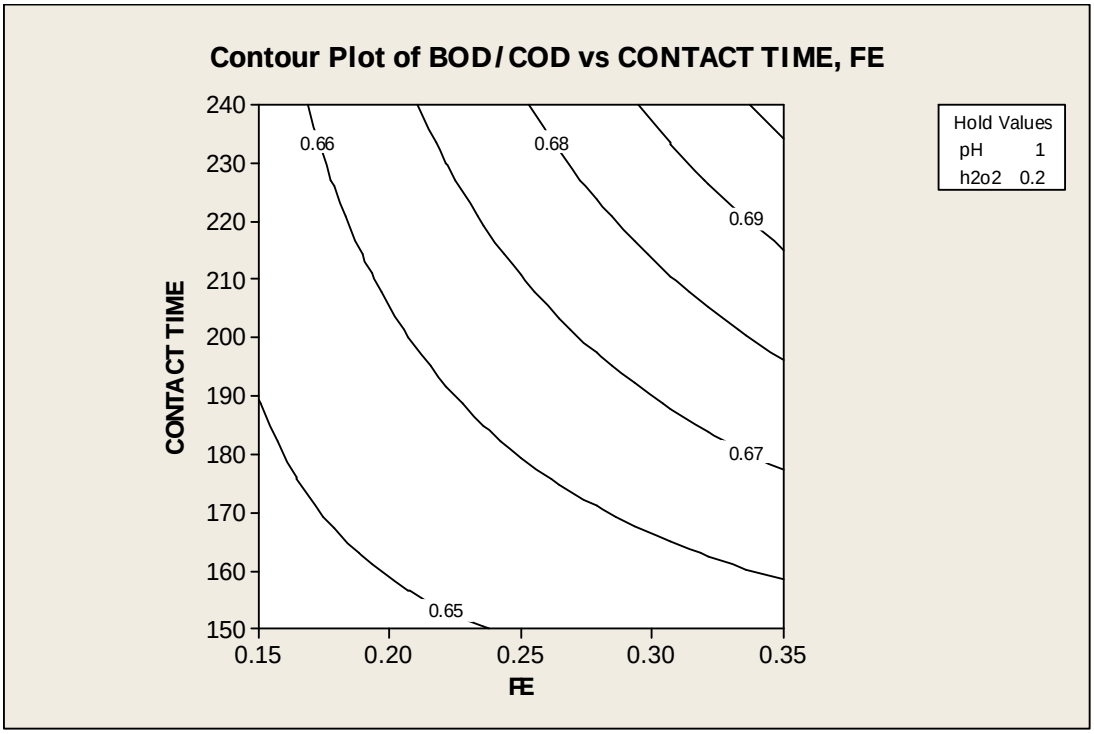


Figure 15: Contour plot for BOD/COD, contact time and Fe^{2+} at pH 1 and H_2O_2 0.2

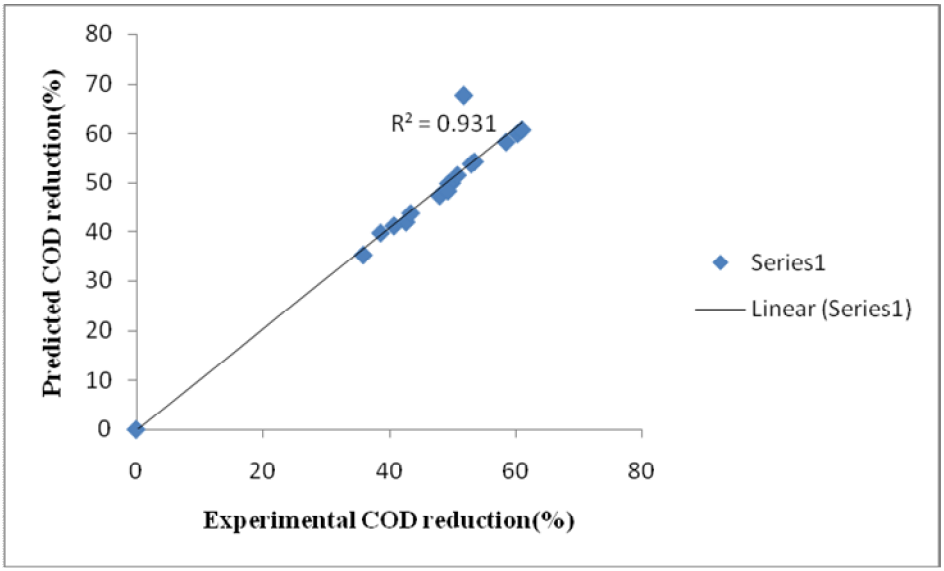


Figure 16: Correlation between experimental and predicted values of the% COD reduction

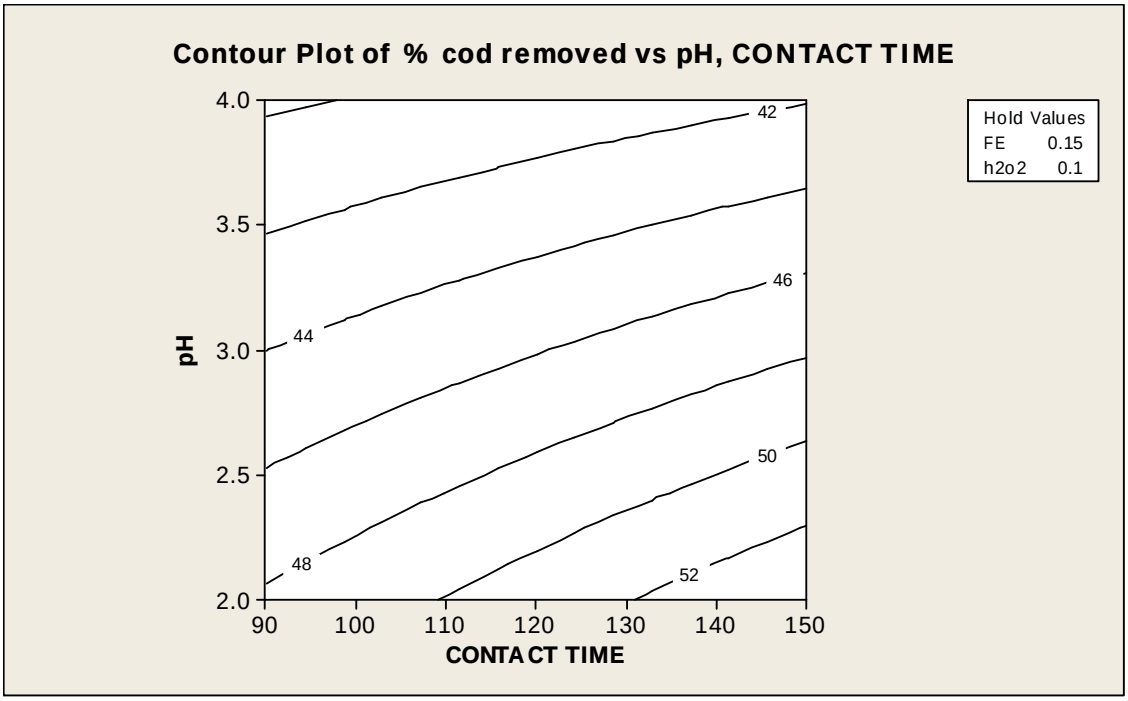


Figure 17: Contour plot for % COD reduction, contact time and pH at Fe^{2+} 0.15 H_2O_2 0.1

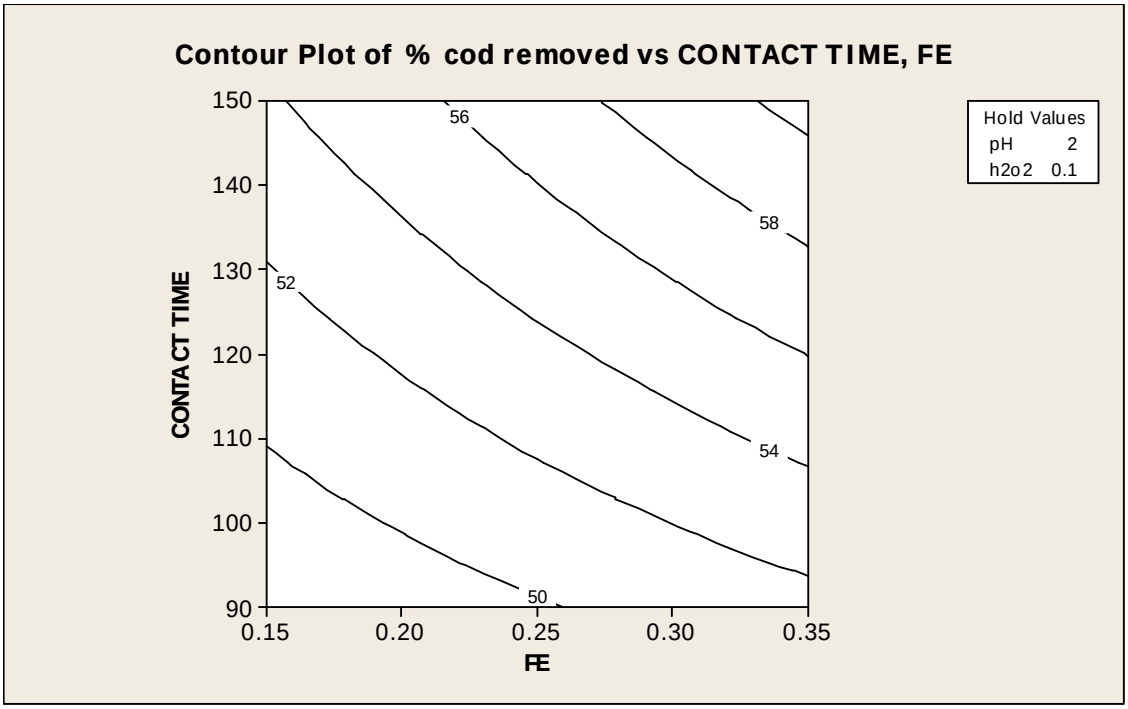


Figure 18: Contour plot for % COD reduction, contact time and Fe^{2+} at pH 2 & H_2O_2 0.1

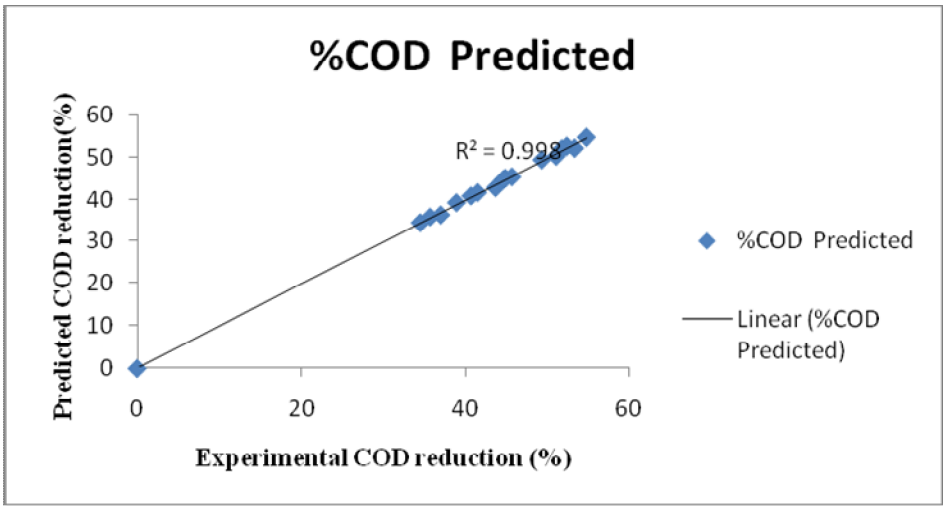


Figure 19: Correlation between experimental and predicted values of the% COD reduction

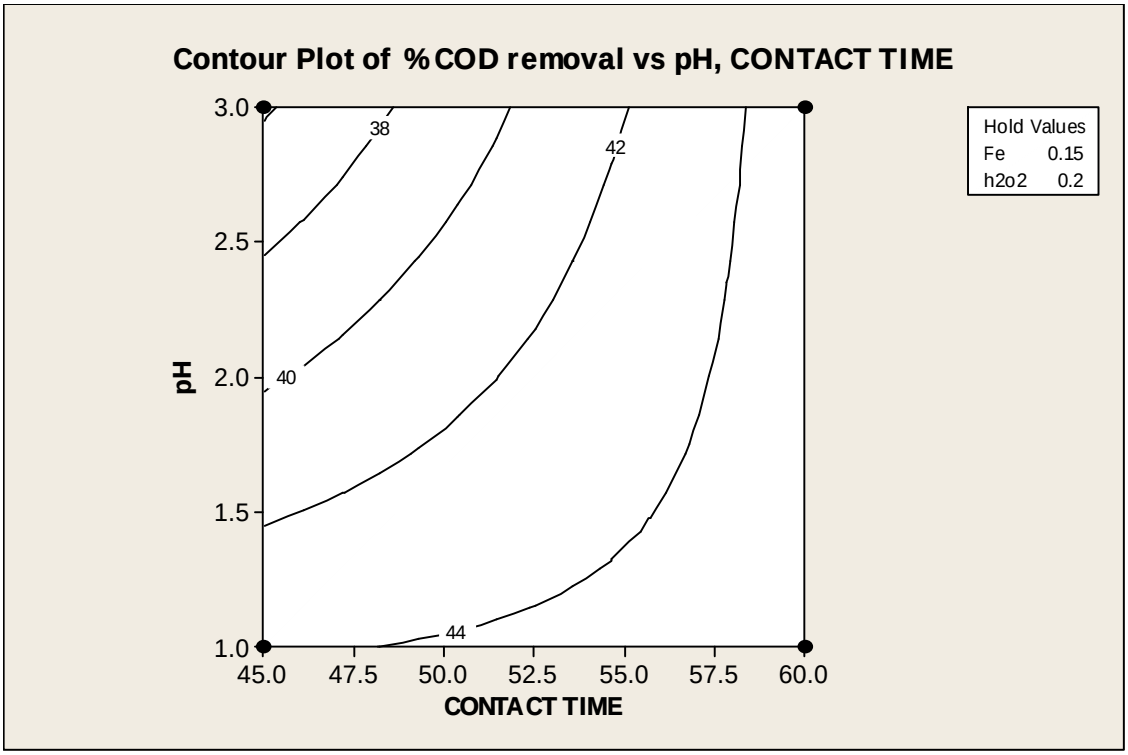


Figure 20: Contour plot for % COD reduction, pH and contact time at H_2O_2 0.2 & Fe^{2+} 0.15

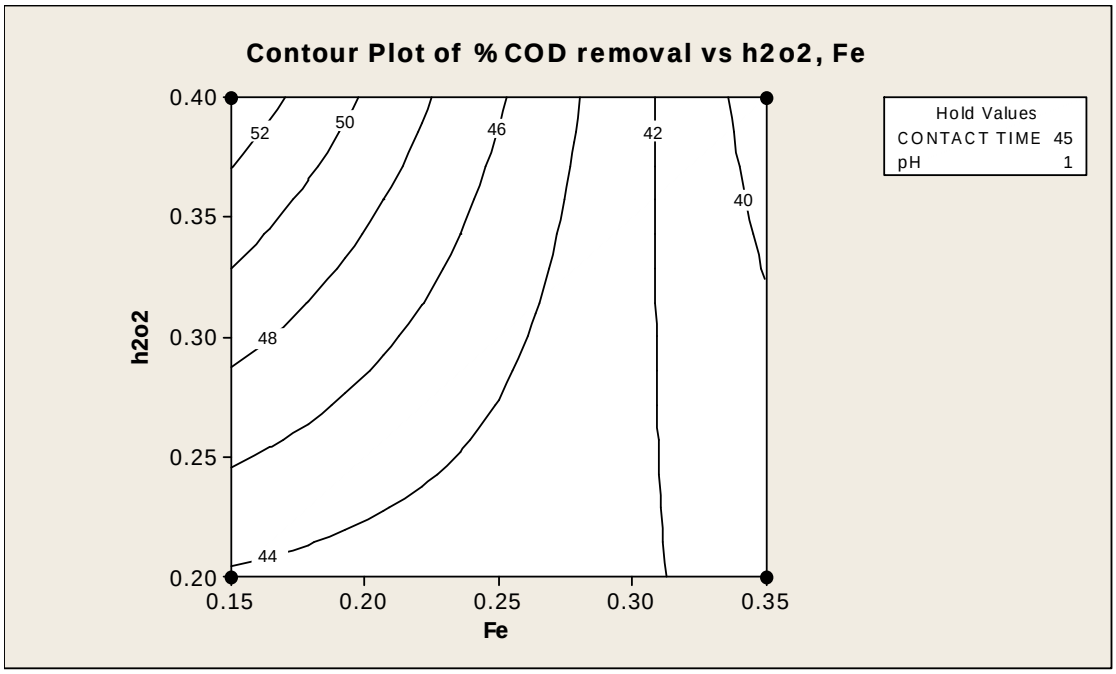


Figure 21: Contour plot for % COD reduction, H_2O_2 and Fe^{2+} at contact time 45min & pH 1

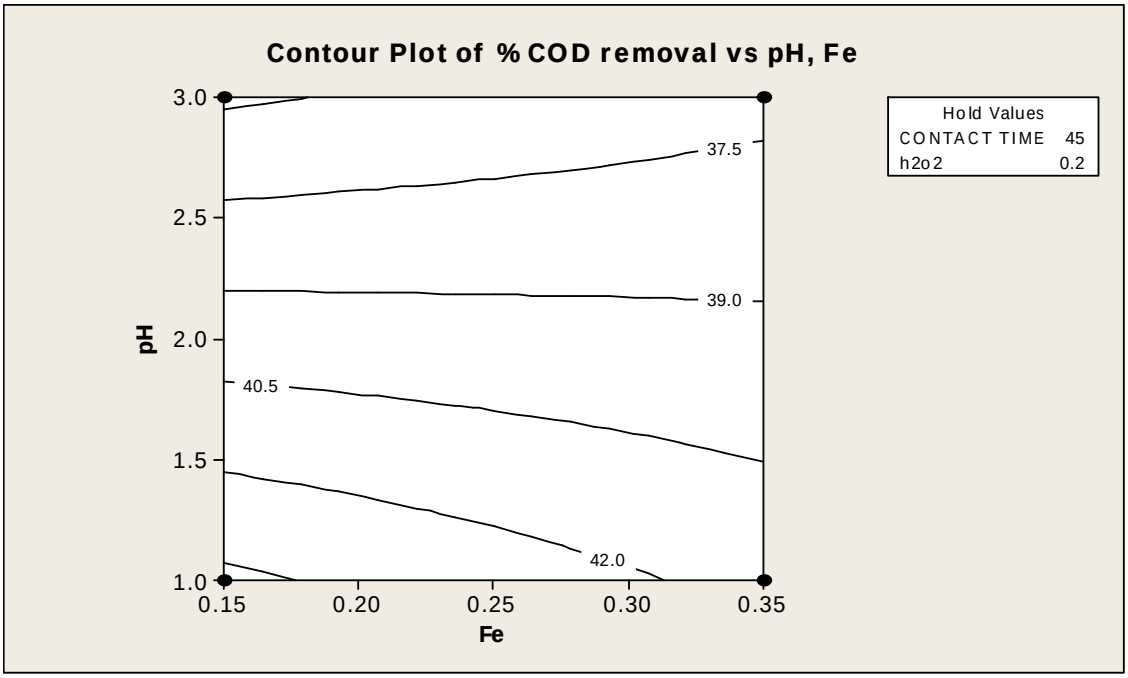


Figure 22: Contour plot for % COD reduction, pH and Fe^{2+} at contact time 45min & H_2O_2 0.2

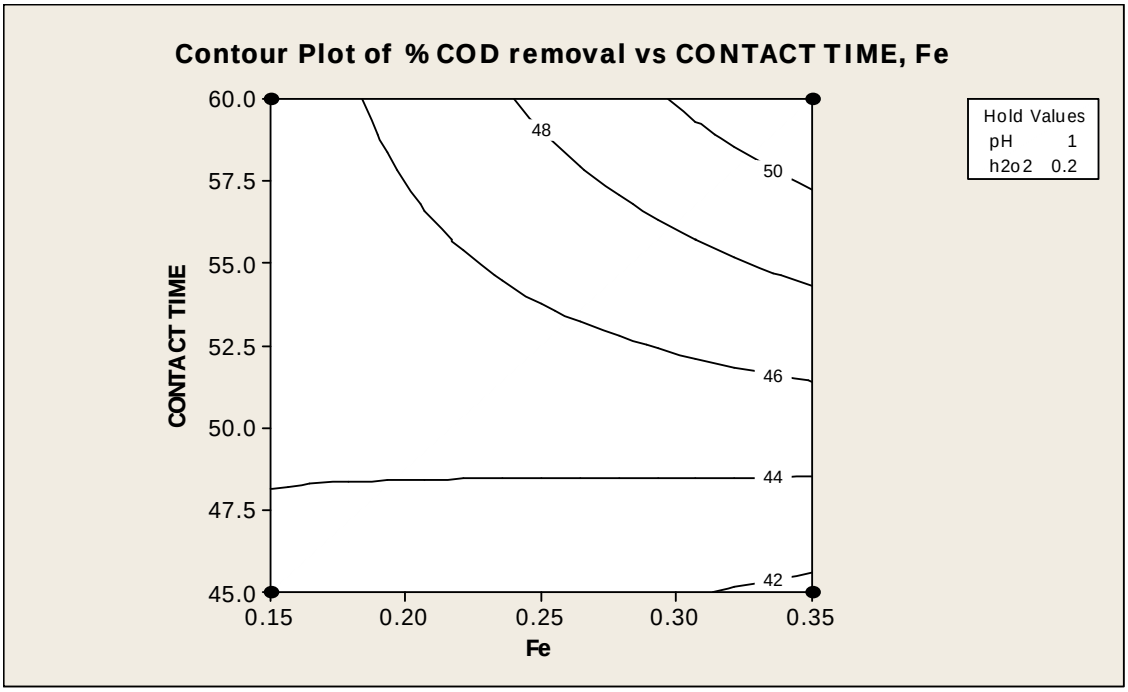


Figure 23: Contour plot for % COD reduction, Fe^{2+} and contact time at pH 1 & H_2O_2 0.2

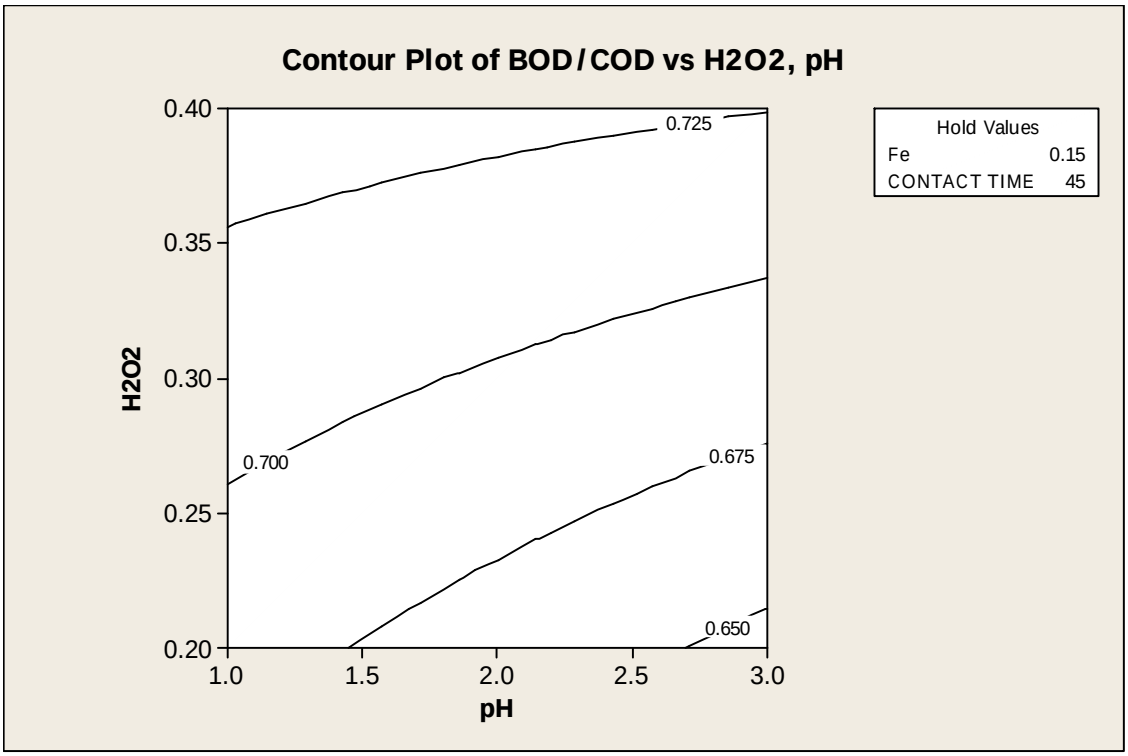


Figure 24: Contour plots for BOD/COD, H_2O_2 and pH at Fe^{2+} 0.15 &contact time 45min

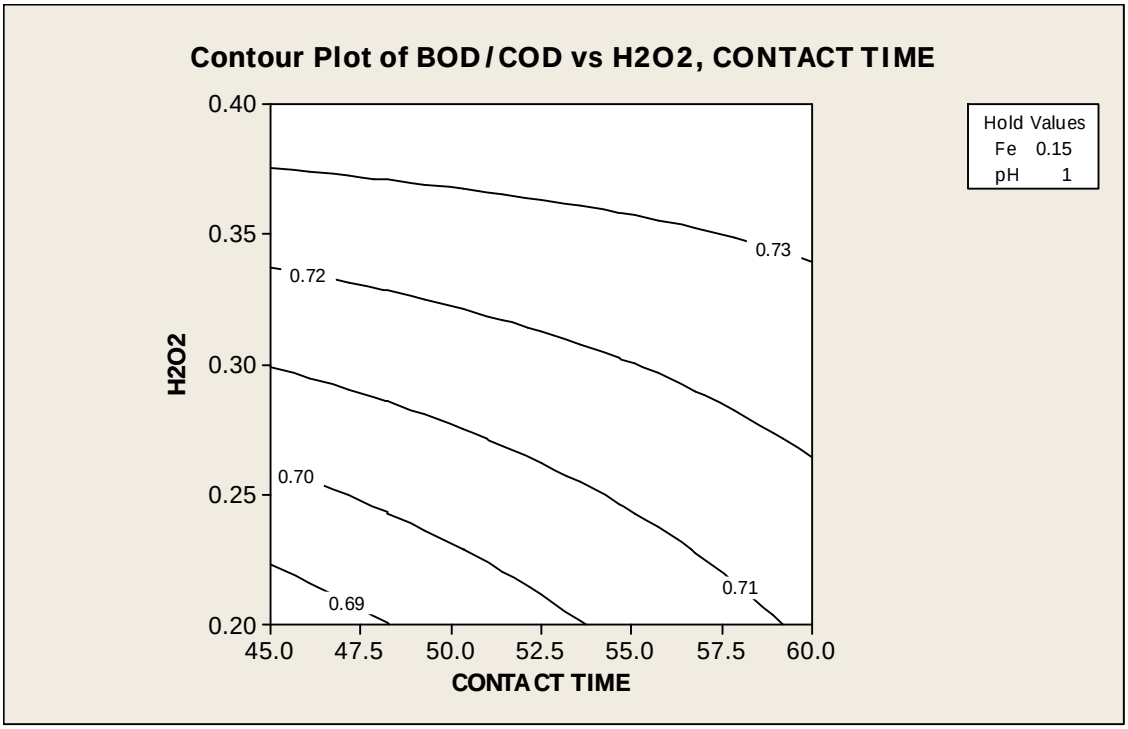


Figure 25: Contour plots for BOD/COD, H_2O_2 and contact time at pH 1& Fe^{2+} 0.15

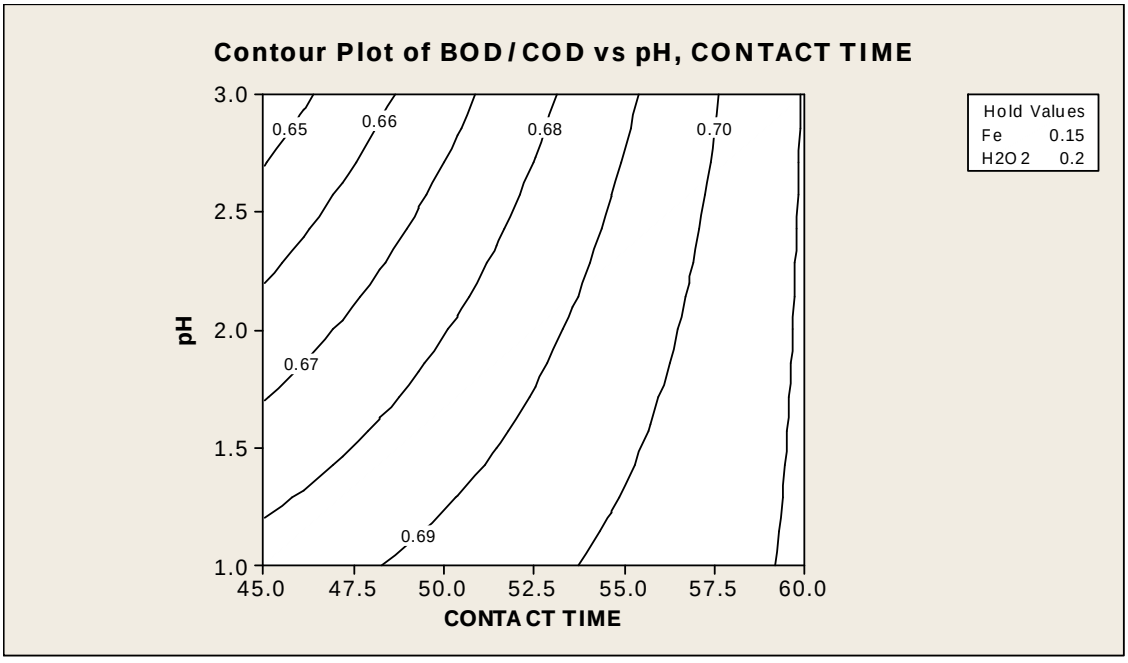


Figure 26: Contour plots for BOD/COD, pH and contact time at H_2O_2 0.2 & Fe^{2+} 0.15

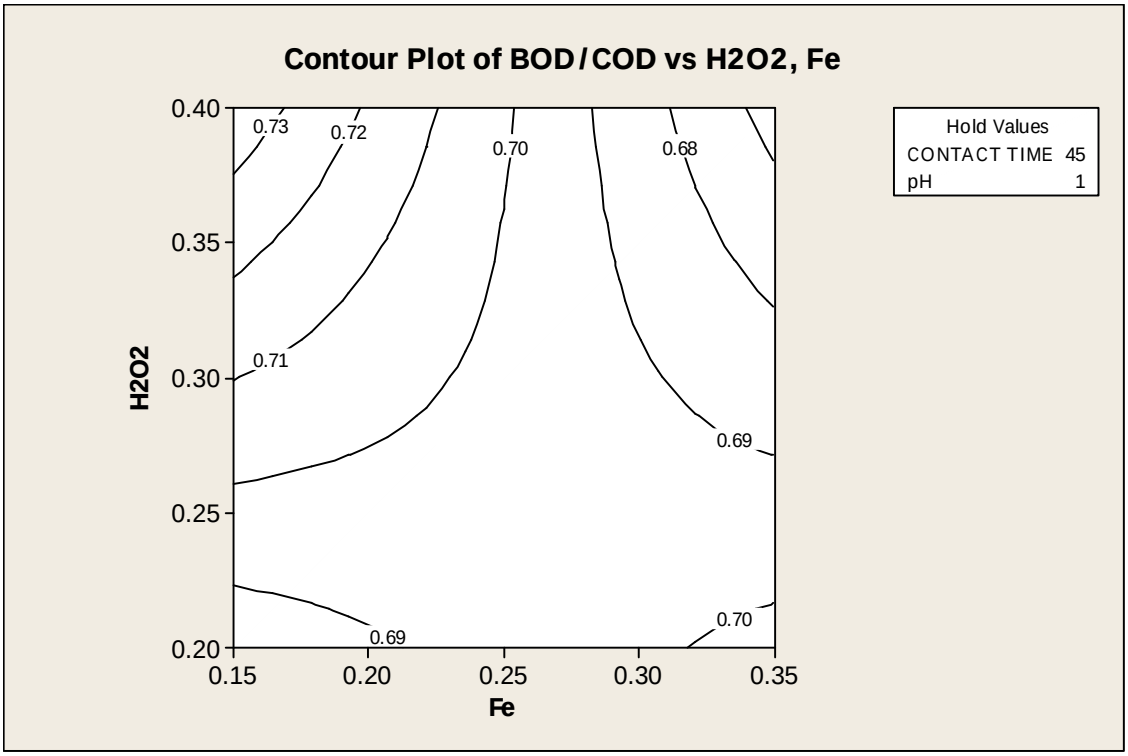


Figure 27: Contour plots for BOD/COD, H_2O_2 and Fe^{2+} at contact time 45min & pH 1

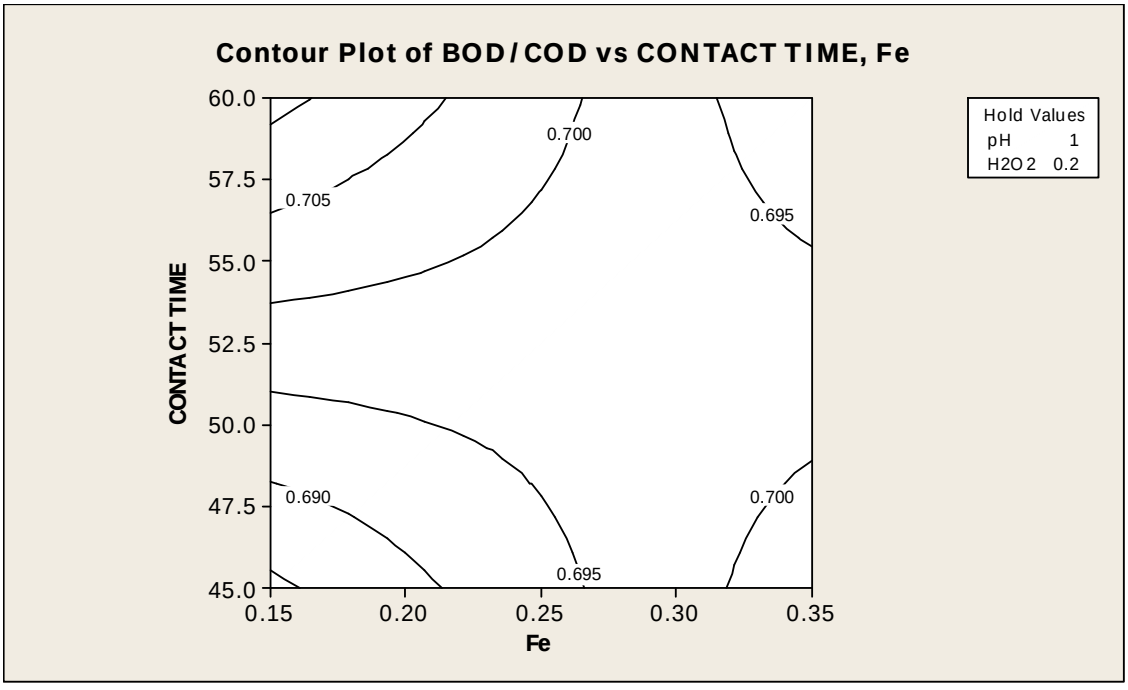


Figure 28: Contour plots for BOD/COD, contact time and Fe^{2+} at H_2O_2 0.2 & pH 1

SUMMARY AND CONCLUSION

- Pharmaceutical waste is one of the major complex and toxic industrial wastes. Conventional treatment methods do not render the wastewater fit for disposal. Advanced oxidation processes (AOP's) are observed to be effective as pretreatment options for such complex wastewaters. Advanced oxidation processes not only reduced the COD of wastewaters but also aided in enhancing the biodegradability, more so when used as hybrid process.

- Fenton oxidation was found to be an effective pretreatment method for the pharmaceutical wastewaters. Fenton oxidation reduced the COD efficiently and improved the biodegradability of the pharmaceutical wastewaters as evident from enhanced biodegradability index.

- Acoustic cavitation as a independent pretreatment option does not yield any significant COD reduction, nor does help in enhancing the biodegradability of pharmaceutical wastewater

- Hybrid process Fenton followed by Acoustic cavitation was observed to be a most promising and effective pretreatment method for highest COD reduction and enhanced biodegradability. Due to common methods of destruction the combined method worked better than individual cavitation and fenton oxidation.

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