Characterization of Paracetamol and Meta-Hydroxyacetanilide

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Abstract

Paracetamol is a common analgesic and antipyretic drug that is used for the relief of fever, headaches and other minor aches and pains. Their determination in pharmaceuticals is of paramount importance, since an overdose of paracetamol can cause fulminating hepatic necrosis and other toxic effects. The aim of the present study is to characterize paracetamol, its oxidized product and meta-hydroxyacetanilide so that these data can be utilized for development of procedures for their quantitative estimations and applications to various pharmaceutical preparations. Chemical, Infra Red and Ultra violet analyses of paracetamol, its oxidized product and meta-hydroxyacetanilide were carried out to characterize them. Chemical, I.R. and U.V. analyses suggested that the possible oxidation reaction with acidic potassium dichromate involves oxidation of p-hydroxyacetanilide to 4-hydroxy-N-carboxylaniline. The anodic oxidation product probably is other; in this case oxidation of p-hydroxyacetanilide results in formation of N-acetyl-p-benzoquinoneimine; the suggested structure is a postulation but could not be confirmed.

Keywords: Paracetamol, Oxidized product of Paracetamol, Meta-hydroxyacetanilide, Infra Red and Ultra violet analyses.

Introduction

Overdoses of the analgesic and antipyretic acetaminophen represent one of the most common pharmaceutical product poisonings in the United States today [1]. Although considered safe at therapeutic doses, in overdose, acetaminophen produces a centrilobular hepatic necrosis that can be fatal [2]. Whereas the initial biochemical and metabolic events that occur in the early stages of toxicity have been well described, the precise mechanisms of hepatocyte death are poorly understood. Necrosis is recognized as the mode of cell death and apoptosis has been ruled out [3] [4]. Several recent excellent reviews on acetaminophen toxicity have been recently published [5] [6]. The analgesic acetaminophen causes a potentially fatal, hepatic centrilobular necrosis when taken in overdose. The role of covalent binding in toxicity as well as other factors recently identified that contribute to the toxicity. These factors include oxidative stress, nitrotyrosine formation, inflammatory cytokines, and the possible importance of mitochondrial permeability transition [7]. Form III is the most unstable polymorph of paracetamol discovered and has not been fully characterized. Its instability in air means that it must be formed in situ in whichever instrument is used for analysis and even its melting point is the subject of discussion, because it undergoes a solid-solid conversion to form II when heated. The recent development of rapid-
heat differential scanning calorimetry (RHDSC), which offers heating rates up to 2000 degrees C/min, provides a new opportunity to characterize unstable polymorphs because of the likelihood that form changes can be inhibited at higher heating rates. Hence the specific aim of this work was to use RHDSC to isolate and characterize paracetamol form III [8].

The interactions between paracetamol (PC) and human serum albumin, in non-glycated (HSA) and glycated form (GHSA), were investigated using continuous cyclic voltammetry in acetate buffer pH 7.4. The contentious coulometry was also used to determine the binding parameters [9]. Paracetamol (PCM) is a poor water soluble drug which comes under Biopharmaceutical classification system (BCS) class III, having (log p =0.5) and shows dissolution rate limited absorption. The solid dispersion of this using PEG 4000 as a carrier in different ratio prepared by using trituration method and solidification technique followed by a formation of a solid solution phase. The prepared dispersions characterized for a solubility study, drug content analysis, in-vitro release profile and stability study [10]. Paracetamol is a common analgesic and antipyretic drug that is used for the relief of fever, headaches and other minor aches and pains. Their determination in pharmaceuticals is of paramount importance, since an overdose of paracetamol can cause fulminating hepatic necrosis and other toxic effects. The aim of the present study is to characterize paracetamol, its oxidized product and meta-hydroxyacetanilide so that these data can be utilized for development of procedures for their quantitative estimations and applications to various pharmaceutical preparations.

Methodology

Oxidized product of paracetamol was synthesized by treating 2.5 g paracetamol with 40 ml of 1 N potassium dichromate solution; it was then extracted with ether.

Anodic oxidized solution of paracetamol is made by electrolyzing solution of paracetamol in 0.1 M HClO₄ at a Rotating Platinum micro Electrode (RPE) as anode and Saturated Calomel Electrode (S.C.E.) as cathode for 25 minutes.

Meta-hydroxyacetanilide was synthesized by adding 11 g of m-aminophenol in 30 ml water and 12 ml 0.1 M acetic anhydride. The mixture was stirred vigorously and warmed on a water bath. After dissolution it was cooled, the solid acetyl derivative was crystallized out, filtered and washed with a little cold water. It was further recrystallised from hot water and air dried.
Chemical, Infra Red and Ultra violet analyses of paracetamol, its oxidized product and meta-hydroxyacetanilide were carried out to characterize them.

**Observations**

In oxidation of paracetamol the nature of the oxidation product is unknown which is important in formulating the electrode reaction. The amount of the oxidation product formed is so small that it escapes analytical identification. Amounts that are sufficient for identification may be made by prolonged electrolysis at a Rotating Platinum micro Electrode (RPE) as anode and Saturated Calomel Electrode (S.C.E.) as cathode. Such electrolytic preparations are essential in order to postulate reactions. Electrolytic preparations at controlled potentials are not as yet suitable on a large scale since long periods of time are required in such work. The electrolysis product formed under these conditions may not be identical with that of actual but may be a disproportionation product or a dimer from the intermediate formed. In any case the nature of the compound isolated is valuable in interpreting the electrode reaction. Chemical, infra red and ultra violet analyses has proved to be the best methods for characterizing qualitatively the paracetamol, oxidized product of paracetamol, and meta-hydroxyacetanilide.

IR spectrum of paracetamol and its acid dichromate oxidized product are shown in Fig. 1 and 2. UV spectrum of meta-hydroxyacetanilide, Paracetamol, its acid dichromate oxidized product, anodic oxidized solution are shown from Fig. 3 to 6 respectively.

![Fig. 1. IR Spectrum of Paracetamol](image-url)
Fig. 2. IR Spectrum of acid dichromate oxidized Paracetamol.

Fig. 3. UV Spectrum of meta-hydroxyacetanilide.

Fig. 4. UV Spectrum of Paracetamol.
Results and Discussion

When paracetamol (p-hydroxyacetanilide) is treated with acidic dichromate solution the redox reaction may be represented as:

\[
4\text{Cr}_2\text{O}_7^{2-} + 56\text{H}^+ + 24\text{e}^- \rightarrow 8\text{Cr}^{3+} + 28\text{H}_2\text{O}
\]

\[
\begin{align*}
\text{p-hydroxyacetanilide} & \quad \text{4-hydroxy-N-carboxylaniline} \\
\end{align*}
\]
The overall redox reaction can be expressed by

\[
4\text{Cr}_2\text{O}_7^{2-} + 3 \text{p-hydroxyacetanilide} + 32\text{H}^+ = 8\text{Cr}^{3+} + 3 \text{N-acetyl-p-benzoquinoneimine} + 3\text{CO}_2 + 19\text{H}_2\text{O}
\]

Oxidation of p-hydroxyacetanilide to 4-hydroxy-N-carboxylaniline is further evident from I.R. studies of these compounds. The I.R. spectrum of paracetamol shows a medium sharp band at 3400-3100 cm\(^{-1}\) region which is characteristic of N-H stretch. O-H stretch also superimposes on the same region. The presence of amine group is further supported by the N-H band of medium strength in the 1700-1500 cm\(^{-1}\) region. Several absorption bands in the 1400-700 cm\(^{-1}\) region is due to the skeletal frequencies. The oxidized product of paracetamol (with acidic potassium dichromate) shows marked change in the pattern of absorption bands of I.R. spectrum. Peak in the region 1700-1600 cm\(^{-1}\) which is strong and characteristic of C=O stretch. Strong peak in the region 3700-3000 cm\(^{-1}\) is characteristic of O – H stretch. These observations suggest that the possible oxidation reaction with acidic K\(_2\)Cr\(_2\)O\(_7\) is as shown above. The anodic oxidation probably is other in this case following reaction is possible.

\[
p\text{-hydroxyacetanilide} + 2\text{e} + 2\text{H}^+ \rightarrow \text{N-acetyl-p-benzoquinoneimine}
\]

It is clear from Fig. 4 and 6 that both the spectra are identical as for position of the bands are concerned. This shows that there may be formation of very trace quantity of oxidized product which does not show any significant changes in the spectrum of the solution. Therefore the suggested structure is a postulation but could not be confirmed. UV Spectrum of acid dichromate oxidized product of paracetamol (in 0.1 M HClO\(_4\)) shows a secondary band at 215 nm which seems to be shifted to shorter wave length compared to the secondary band of paracetamol. In case of meta-hydroxyacetanilide (in ethyl alcohol) the primary band shifted to 210 nm and the secondary band was observed at 245 nm. Band for carbonyl chromophore was observed at 280 nm with very low intensity.

**Conclusion**

Chemical, I.R. and U.V. analyses suggested that the possible oxidation reaction with acidic potassium dichromate involves oxidation of p-hydroxyacetanilide to 4-hydroxy-N-carboxylaniline. The anodic
oxidation product probably is other; in this case oxidation of p-hydroxyacetanilide results in formation of N-acetyl-p-benzoquinoneimine; the suggested structure is a postulation but could not be confirmed.

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