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Polymorphism of paracetamol: A comparative study on commercial paracetamol samples.

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Paracetamol (acetaminophen) is an important analgesic and antipyretic drug which is used worldwide. Paracetamol shows polymorphism and exists in three forms. These are monoclinic (Form I, stable), orthorhombic (Form II, metastable) and Form III (unstable and not yet characterized). Most of the paracetamol drug samples belong to monoclinic form which is the most stable polymorph. Paracetamol is prepared by the reaction between 4-aminophenol and ethanoic anhydride and is purified. The product obtained is characterized by melting point and spectral techniques like IR and UV-Visible spectroscopy. Various commercial paracetamol tablets were collected, powdered and their melting points were determined. All the eleven drug samples analyzed are found to be belonging to the stable monoclinic form.

Keyword: Paracetamol, Acetaminophen, Polymorphism, Monoclinic, Orthorhombic.

1. Introduction

Paracetamol or acetaminophen is widely used over the counter analgesic (pain reliever) and antipyretic (fever reducer) and is chemically named as n-acetyl-p-aminophenol [1-3]. Paracetamol is the International nonproprietary name and British approved name, while acetaminophen is the United States adopted name

and Japanese adopted name [4-6]. It is a major ingredient in numerous cold and flu remedies and is commonly used for the relief of headaches and other minor aches and pains. In combination with opioid analgesics, paracetamol can also be used in the control of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients [7].

Polymorphism is defined as the ability of a substance to exist in two or more crystalline forms and is an important property of crystalline substances. Chemical species that can exist in different lattice structures often lead to significant variations in the physical properties like thermodynamic, spectroscopic, interface and mechanical properties. Polymorphs differ in solubility, shape, compression and filtration properties and in the case of pharmaceutical compound dissolution rate and bioavailability may be altered with polymorphic form. A slight modification in the crystallization process, such as a variation of the cooling rate or the agitation can produce a different polymorph. Therefore proficient control of such processes is necessary to ensure the quality and conformity of the final product. An unpredicted and unwanted change in properties can lead to safety issues as well as large loss of time and money [8]. Some of the properties like tableting which are related directly to the utility of the drug are influenced by crystal morphology, size and shape. It is very important and significant to detect a polymorphic transformation in situ in drug samples and have great value in drug synthesis [9, 10].

A suitable pharmaceutical model system to study the effects of confinement on the crystallization behavior is paracetamol and is found to exist in three different crystalline forms [11-14]. The commercially used monoclinic form I is the most stable one and has a melting temperature of about 167–169 °C. The orthorhombic form II is metastable and melts at around 156 °C [15, 16]. There are several procedures reported to achieve these two crystalline forms either from solution or from the melt by thermal treatments [11-14]. A third polymorph of paracetamol called form III is reported which is unstable and usually inaccessible in case of bulk samples. This form has been found only in special situations where paracetamol was confined between glass plates or in thin glass capillaries [17, 18]. Thus, there is limited information about this third polymorph. The third polymorph of paracetamol was reported by Raman spectra and wide angle X-ray scattering data recently [17, 18]. However, the

investigated form III samples are produced by chance, melting of this crystalline form has never been reported and thermodynamic parameters are basically unknown.

2. Materials and Methods

2.1. Materials

4-aminophenol (NICE Chemicals, India) and acetic anhydride (Merck, India) were used after purification in the synthesis of paracetamol. Various commercial paracetamol samples were collected and have been used for assessing their polymorphic form and are given below.

Fepanil (Veritaz Healthcare Limited, Hyderabad), Starmol (Cadila Pharmaceuticals Limited, Samba), Dolo-650 (Micro Labs Limited, Nalagarh Dist), Febrex (Indoco Remedies Limited, Mumbai), Vamol (Variety PharmaceuticalS Limited, Shornur), P-250 (Apex Laboratory Private Limited, Tamil Nadu), Medomol (Medopharm, Malur, Karnataka), Paracetamol (Modern Pharmaceuticals Pvt. Ltd., Tirur), Calpol (Glaxosmithkline Pharmaceuticals Limited, Mumbai), Pyremol (Alembic, Baddi, Himachal Pradesh) and Paracip (Cipla Limited, Baddi, Himachal Pradesh).

2.2. Methods

2.0 g of 4-aminophenol and 10 ml of distilled water were taken in a 50 ml beaker and stirred briskly at room temperature in order to suspend the solid in the water. 2 ml of ethanoic anhydride was added to the stirred suspension and gently shaken to mix. The solid got dissolved after about 30 seconds. Shaking was continued until a precipitate was formed. After 10 minutes the solid was filtered off under suction, washed with a little cold water and dried. The product was purified by crystallisation from distilled water, by dissolving the crude product in the minimum of distilled water at about 80 °C. The clear solution was allowed to cool slowly to room temperature and the recrystallised product was collected by suction filtration. The recrystallised product was dried between filter papers, and the yield was determined. The melting point of the dry,

recrystallised product was also noted. IR and UV-Visible spectral studies are carried out for the characterization of the formed product.

3. Results and discussion

The obtained product after recrystallisation is dried and yield is determined. The yield is found to be around 60%. The melting point of the product is determined and is found to be 167 ± 2 °C. The melting point of pure paracetamol reported is 169 °C. This gives an idea that the obtained product will be paracetamol. This was further confirmed by IR and UV-Visible spectral analysis of obtained product. IR and UV-Visible spectra of obtained product were compared with

that of pure paracetamol and shows excellent similarities.

The reaction sequence can be given as figure 4.1.

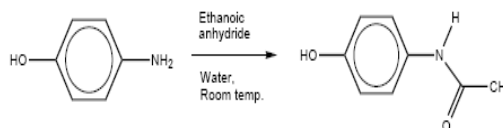


Fig 4.1: Reaction sequence for the synthesis of paracetamol

3.1. IR spectral studies

The IR spectrum of the obtained product was recorded from KBr pellets using Jasco FT-IR 4100 spectrophotometer (Japan) and is shown in Figure 4.2.

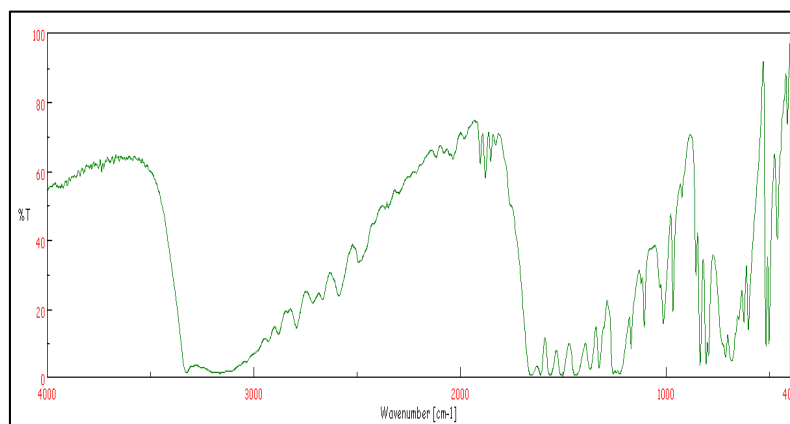


Fig 4.2: IR spectrum of synthesized paracetamol

The IR spectrum showed sharp peaks at 3360 cm^{-1} (N–H stretching), a broad peak at 3300 cm^{-1} (O–H stretching), 3090 cm^{-1} (Aromatic C–H stretching), 1800 cm^{-1} (=C–H bending), 1650 cm^{-1} (C=O stretching), 1600 cm^{-1} (aromatic C=C stretching), 1570 cm^{-1} (N–H bending), and 1136 cm^{-1} (C–NH stretching). The presence of all these peaks leads to the conclusion that the product formed may be paracetamol. Further this spectrum was compared with that of pure paracetamol and found to have excellent similarities.

3.2. UV-Visible spectral studies: UV-Visible absorption of the products was recorded by Hitachi U-3000 UV-Visible spectrophotometer

using 1cm quartz cell and spectrograde methanol (Merck, India) as solvent. UV-Visible spectrum of the product showed wavelength of maximum absorbance at 247 nm. The UV-Visible spectrum of the product obtained was compared with that of pure paracetamol and gave excellent similarities.

All the above analyses, viz., melting point determination, IR and UV-Visible spectral studies confirmed that the obtained product is paracetamol.

The polymorphic study of commercial paracetamol is carried out by determining its melting point and is given in Table 1. The melting point determination is done in triplicate and all results are tabulated in Table 1.

Table 1: Melting point of various commercial paracetamol samples.

S. No	Trade name	Manufactured by	Melting point (°C)
1.	Fepanil	Veritaz Healthcare Limited, Hyderabad	167 _± 2
2.	Starmol	Cadila Pharmaceuticals Limited, Samba	166 _± 2
3.	Dolo-650	Micro Labs Limited, Nalagarh Dist	166 _± 2
4.	Febrex	Indoco Remedies Limited, Mumbai	165 _± 2
5.	Vamol	Variety PharmaceuticalS Limited, Shornur	166 _± 2
6.	P-250	Apex Laboratory Private Limited, Tamil Nadu	170 _± 2
7.	Medomol	Medopharm, Malur, Karnataka	165 _± 2
8.	Paracetamol	Modern pharmaceuticals Pvt. Ltd Tirur, kerala	170 _± 2
9.	Calpol	Glaxosmithkline Pharmaceuticals Ltd., Mumbai.	166 _± 2
10.	Pyramol	Alembic pharmaceuticals Baddi, Himachal Pradesh	165 _± 2
11.	Paracip	Cipla Limited, Baddi, Himachal Pradesh	167 _± 2

All the commercial paracetamol samples are having melting point in the range 165–170 °C. This shows that all the commercial drug samples under study belong to monoclinic form (form I) which is more stable than form II and is the thermodynamically stable form.

The prepared paracetamol sample also found to be in the most stable monoclinic form and this can be used for drug formulation only after proper purification.

4. Conclusion

Paracetamol is prepared by using the reported method and analysed by melting point, IR and UV-Visible spectrophotometric techniques. The obtained paracetamol belongs to the most stable monoclinic polymorphic form. Various commercial paracetamol samples were collected and their polymorphism is studied by melting point determination. All the samples are found to be belonging to the thermodynamically stable monoclinic form.

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