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A comparative Study on Polymorphism of Commercial Ranitidine Hydrochloride Drug Samples in India

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ABSTRACT

Ranitidine hydrochloride is a drug used to treat stomach acid production. It is commonly advised in the treatment of peptic ulcer and gastrophaegal reflux. Ranitidine hydrochloride exists in two different polymorphic forms, namely form I and form II. Various brands of ranitidine hydrochloride tablets manufactured by different pharmaceutical companies in India were collected, finely powdered and recrystallized from ethanol water mixture. The melting points of pure drug samples were determined to assess the polymorphic form present in each sample. All the pure drug samples showed a melting point in the range 135 to 138 °C and prove the existence of polymorph form I. The pure recrystallized drug samples were kept at room temperature for about 60 days in order to study the changes in polymorphic form if any and found fairly stable on prolonged storage. Infrared and UV-visible spectral studies have been carried out by taking Zinetac 150 mg (GlaxoSmithKline Pharmaceuticals Ltd., Mumbai) as the standard in order to prove the chemical constitution of the drug.

KEYWORDS

Polymorphism, Ranitidine hydrochloride.

INTRODUCTION

The term polymorphism is used when one and the same substance can crystallize in more than one form. Polymorphism is defined as the ability of a substance to exist as two or more crystalline phases with different arrangements. Polymorphism can be commonly found in any crystalline material including polymers and is relevant in the fields of pharmaceuticals, agrochemicals, pigments, dyestuffs, food and explosives. Polymorphs have different properties such as packaging, thermodynamic, free energy, melting point, spectroscopic, kinetic, dissolution rate, stability and mechanical properties like hardness, compatibility, stability, tensile strength, *etc*. The unique advantage of polymorphism is that the chemical identity of the material remains unchanged from one polymorph to another, a direct correlation between activity and solid state structure may be made. Polymorphism is an important property shown by most of the drug molecules used today [1-5]. Ritonavir is a novel protease inhibitor for HIV marketed by Abbott Laboratories in 1996 with a trade name norvir. Only one crystal form of ritonavir was identified during development of the compound and 240 lots of norvir capsules were produced with

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no issues on stability and solubility. In mid-1998, several lots of capsules failed the dissolution requirement and when capsule contents were examined using microscopy and X-ray powder diffraction, a new polymorph was identified that had greatly reduced solubility compared to the original crystal form. This new form, referred to as form II, is an example of conformational polymorphism, which occurs when different conformational isomers of a compound crystallize as distinct polymorphs. Company's attempt to formulate form I was found to be very difficult due to the absence of exact conditions and was in market crisis. This is a classic example to show how much polymorphism is important in pharma industry. Today around 30-50 % of pharmaceutical compounds exhibit polymorphism globally. This indicates the significance on the studies of polymorphism in various pharmaceutical samples and to find out methods to control it in industry [6-9].

Ranitidine hydrochloride (Ranitidine-HCl) is one of the most common drugs used globally for the treatment of excessive acidity in stomach. It can be taken by mouth, by injection into a muscle or into a vein. It is sometimes used to prevent stress ulcers, aspiration of stomach acid during anaesthesia and stomach damage caused by non-steroidal anti-inflammatory drug (NSAID). Ranitidine-HCl was first prepared as AH19065 by John Bradshaw in 1977 in the Ware research laboratories of Allen and Hanburys, part of the Glaxo organization [10]. Ranitidine was the result of a rational drug-design process using what was by the histamine H2 receptor and quantitative structure-activity relationships. Glaxo refined the model further by replacing the imidazole ring of cimetidine with a furan ring with a nitrogen containing substituent and in doing so developed ranitidine. Ranitidine was introduced in 1981 and was the world's biggest prescription drug by 1987.

Most of the drugs are formulated and marketed in crystalline form. Many of the drug molecules are highly functionalized and can self-organize in several ways in the solid state with nearly same lattice energy. These features and the conformational flexibility of molecules are primary driving forces for the existence of crystal polymorphism in pharmaceutical ingredients (APIs). Nowadays research on polymorphism and material properties of active drug compounds and excipients is an integral part of drug development. Drugs that were previously known to exist only in single form are now shown to have various polymorphic forms. Ranitidine-HCl can exists in two different polymorphic forms, namely form I (m.p. 134-140 °C) and form II (m.p. 140-144 °C). There are reports on the polymorphism of paracetamol [11-13], aspirin [14-16] and albendazole [17,18]. The extensive use of ranitidine-HCl as a drug, the polymorphism shown by it, commercial preparation by various pharmaceutical companies and very few reports on studies of polymorphism of ranitidine-HCl prompted us to carry out this work [19-21].

In the present study, commercial ranitidine-HCl tablets manufactured by 10 leading pharmaceutical companies in India were collected. The polymorphic form of each drug was assessed by melting point determination and spectral techniques like infrared and UV-Visible spectrometry was used for the structural elucidation by taking Zinetac-150 drug sample.

EXPERIMENTAL

The collected drug samples were finely powdered, dissolved in ethanol water mixture and recrystallized. The melting points of recrystallized samples were determined by using a digital melting point apparatus in triplicate. These drug samples were kept at room temperature for about 60 days and melting points were determined periodically. The obtained results were compared with the authentic values reported in literature [19,20].

The infrared spectrum of Zinetac-150 tablet was recorded by using Jasco FT-IR double beam spectrophotometer. The obtained infrared spectrum was analyzed and peaks due to various functional groups were identified. Moreover, the obtained spectrum was compared with the reported one in the literature. UV-visible absorption of Zinetac-150 tablet was recorded by Hitachi U-3000 UV-Visible spectrophotometer with1 cm quartz cell and spectrograde ethanol (Merck, India) as solvent.

RESULTS AND DISCUSSION

The polymorphic study of Ranitidine-HCl was carried out by determining its melting point. The melting point determination is done in triplicate and all results are tabulated in Table-1. The procedure was repeated after 30 and 60 days.

All the ranitidine-HCl tablets under investigation have melting point in the range 135 to 138 °C. This shows that all the drug molecules under investigation belong to polymorphic form I. Further it is proved that all the drug samples are highly stable at room temperature for about 60 days since there is no appreciable change in melting point. This also confirms the stability of polymorph 1 of ranitidine-HCl and rules out the possibility of any polymorphic transition.

TABLE-1
MELTING POINT OF VARIOUS RANITIDINE SAMPLES

Trade name	Manufactured by	m.p. (°C)	m.p. (°C) after 30 days	m.p. (°C) after 60 days
Rantac-150 mg	JB Chemicals and Pharmaceuticals Ltd., Mumbai	135 ± 2	134 ± 2	136 ± 2
Aciloc-150 mg	Cadila Pharmaceuticals Ltd., Ahmedabad	137 ± 2	136 ± 2	136 ± 2
Histac-300 mg	Sun Pharmaceuticals Industries Ltd., Mumbai	136 ± 2	135 ± 2	136 ± 2
Zinetac-150 mg	GlaxoSmithKline Pharmaceuticals Ltd., Mumbai	137 ± 2	137 ± 2	137 ± 2
Ranitine- 150 mg	Torrent Pharmaceuticals Ltd., Mumbai	135 ± 2	136 ± 2	135 ± 2
R-Loc- 150 mg	Zydus Health Care Ltd., Ahmedabad	138 ± 2	137 ± 2	137 ± 2
Helcoss -150 mg	Lupin Ltd., Mumbai	135 ± 2	135 ± 2	134 ± 2
Monorin-150 mg	Alembic Pharmaceuticals Ltd., Vadodara	136 ± 2	136 ± 2	135 ± 2
Monoloc-150 mg	Intas Pharmaceuticals Ltd., Ahmedabad	135 ± 2	136 ± 2	135 ± 2
Zoran - 150 mg	Dr.Reddy's Laboratories Ltd., Hyderabad	137 ± 2	137 ± 2	137 ± 2

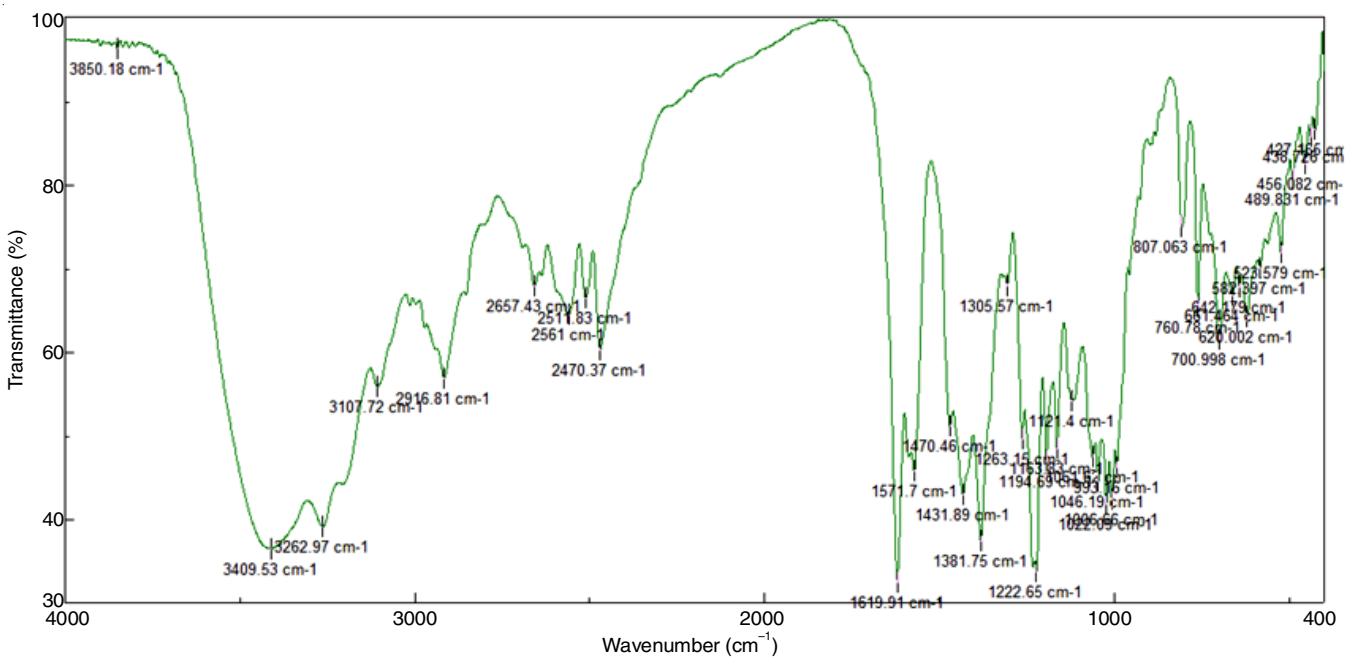

Fig. 1. Infrared spectrum of Zinetac-150

The infrared spectrum of ranitidine-HCl was recorded from KBr pellets using Jasco FT-IR 4100 spectrophotometer (Japan) by taking Zinetac-150 as the sample and is shown in Fig. 1.

The bands appear at 3410 cm^{-1} (N-H *str.*), 3262 cm^{-1} (C-H *str.*), 3107 cm^{-1} (CH/CH_2 asym. *str.*), 2916 cm^{-1} (C-H *str.*), 2657 cm^{-1} (C-H *str.*), 1619 cm^{-1} (C=C *str.*), 1571 cm^{-1} (C-C *str.*), 1470 cm^{-1} (H-C-H sym. *str.*), 1431 cm^{-1} (C-N sym. *str.*), 1381 cm^{-1} (NO_2 sym. *str.*), 1222 cm^{-1} (C-H out-of-plane bending). All these bands clearly suggest that the analyte is ranitidine hydrochloride which was further proved on comparison the infrared spectrum available in literature.

UV-visible absorption of Zinetac-150 was recorded by Hitachi U-3000 UV-visible spectrophotometer using 1 cm quartz cell and spectrograde ethanol (Merck, India) as solvent and is given in Fig. 2. The UV-visible spectrum of Zinetac-150 shows absorption maxima at 345 nm which is the characteristic peak of ranitidine-HCl.

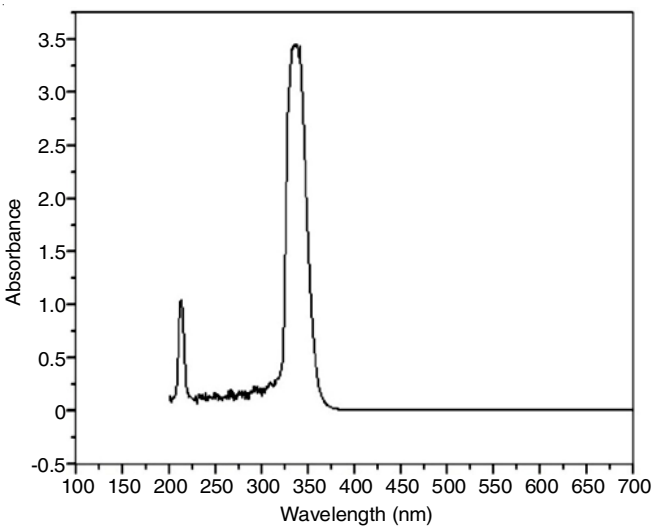

Fig. 2. UV-visible spectrum of Zinetac-150

Conclusion

Ranitidine-HCl is commonly used to treat and prevent ulcers in the stomach and intestines. Commercial ranitidine-HCl drug samples manufactured by leading 10 pharmaceutical companies in India were collected and their polymorphism is studied by melting point determination. The results clearly confirmed that all the drug samples under study belong to form I polymorph. It is further proved that all drug samples show high stability at room temperature for about 60 days. There is no polymorphic transition noticed for any drug samples. Zinetac-150 drug sample was further analyzed by infrared and UV-visible spectral analyses for its chemical characterization.

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