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Application of vibrational spectroscopy, thermal analyses and X-ray diffraction in the rapid evaluation of the stability in solid-state of ranitidine, famotidine and cimetidine

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ABSTRACT

This paper reports the study on applicability of Fourier transform infrared (FTIR), near-infrared (NIR) and Raman spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) for the estimation of the chemical stability and photostability of histamine H_2-receptor antagonist substances. Ranitidine hydrochloride (RAN), famotidine (FAM) and cimetidine (CIM) were tested and differences in sensitivity were measured via soft independence modeling of class analogies (Simca) model. The low values of variations for FAM and CIM and high variations obtained for RAN using FTIR and NIR techniques indicated that these methods were suitable and applicable to classify the degradation of RAN. Examined methods are recommendable in the first technological stage of drug production, and the preclinical and clinical development of pharmaceuticals or their quality control.

1. Introduction

Stability and photostability studies of medicinal compounds and its final dosage form are essential to ensure their quality and safety. A combination of several analytical methods is commonly applied to fully characterize the physical form changes of active pharmaceutical ingredient (API) with excipient mixtures following preparation and accelerated stress testing. Standard solid-state methods used to study the physical forms of API in solid dosage formulation matrices include Raman spectroscopy, FTIR and NIR spectroscopy, diffraction and thermal analysis as DSC, solid-state NMR and chemical imaging [1–4]. Multi-instrumental studies of stability are essential for physical characterization of pharmaceutical solids and polymers [4–9], polymorphic description characterization of pharmaceuticals as piracetam [10], indomethacin [11], sulfamerazine [12], nitroguanidine [13], carbamazepine [14]. Moreover, those methods allow estimating the chemical composition of tested samples exposed to such factors as high moisture, light and higher temperature. DSC is often used in parallel to estimate chemical or physical changes of samples properties during stability testing, as phase transitions, solid–liquid reactions or interactions [4,15–19]. XRD diffraction techniques allow characterizing any instability process of pharmaceutical solids on the stage of single crystal lattice [18–21].

The aim of this study was to evaluate chemical stability in the solid state of a labile active pharmaceutical compound and its formulated tablets with ranitidine hydrochloride (RAN – N-[2-[[[5-[(dimethylamino)methyl]furan-2-yl]methyl]thio]ethyl]-N′-methyl-2-nitroethene-1,1-diamine hydrochloride) and to compare the results with its structurally analogue famotidine (FAM – 3-[({2-[(diaminomethylidene)amino]1,3-thiazol-4-yl}methyl)sulphanyl] N′-sulfamoylpropanimi-damide) and cimetidine (CIM–1-cyano-2-methyl-3-(2-{[4-methyl-*1H*-imidazol-5-yl)methyl] sulfanyl}ethyl)guanidine) powders. Therefore, the usefulness of NIR and Raman spectroscopy as well as X-ray diffraction and DSC for the monitoring of the earliest degradation and chemical instability was determined. Structures of tested compounds are presented in Fig. 1.

Drug compounds chosen for the study are antagonistic to the histamine H2 receptor, commonly used to treat esophageal reflux diseases and peptic ulcers. The results of analysis conducted over

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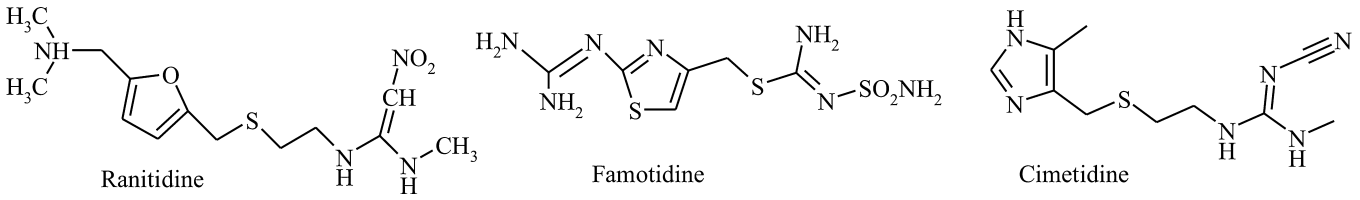

Fig. 1. Chemical structure of A) RAN, B) FAM and C) CIM.

Table 1
Tablets formulation.

Substance	Formulation		
	A	B	C
Ranitidine hydrochloride	168 mg	168 mg	Ranigast, Polpharma, Poland, 150 mg
Avicel PH 101	120.6 mg	–	
Avicel PH 102	–	120.6 mg	
Crosspovidone	9.0 mg	9.0 mg	
Colloidal anhydrous silica	0.9 mg	0.9 mg	
Magnesium stearate	1.5 mg	1.5 mg	

the years 1980–2013 indicate a number of issues with both the low chemical stability of ranitidine *in sub*. and pharmaceutical products containing this active substance. Many factors were identified as influencing structural changes of RAN, among which the most frequently mentioned are high humidity, light, and impurity of the compound. However, RAN stability associated with the presence of di-hydrochloride with mono-hydrochloride in technological powders of RAN [22–24]. This is produced in parallel and is very difficult to remove from a mixture of acid addition salts. Di-hydrochloride as a powder contamination is a source of rapid water absorption. Besides, there are published results from the detection and identification of volatile degradation compounds using GC–MS technique in the case of ranitidine hydrochloride photodegradation in solid-state [25], however serious problems are also observed with surface changes and degradation, for which the application of modern analytical tools might be useful (Table 1).

Famotidine stability is main concern of researches, but still unrecognized thoroughly. Studies regarding chemical stability of FAM have confirmed its degradation under wide range of pH values, increased temperature and the presence of light with degradation products identification. It was found that FAM in an acidic medium at pH ≅ 2 and in light conditions is chemically unstable even in the presence of excipients in pharmaceutical formulations [26,27]. In contrary, cimetidine stability was confirmed during electrochemical oxidation [28] and in solid-state under high humidity [29].

In this study, NIR and Raman spectroscopy were used to relate RAN, FAM and CIM solid-state examined powders and formulations to physical changes or chemical degradation during photo and stability testing in a climate chamber. Both DSC and XRD methods were used to investigate phase transformation and degradation related to thermal or hydro and photo reactions.

2. Materials and methods

2.1. Materials

Ranitidine hydrochloride and famotidine bulk powders were supplied as white crystalline powders (Polpharma Pharmaceutical Works, Starogard Gdański, Poland). Cimetidine was purchased from Sigma–Aldrich (Poznań, Poland). The following agents were purchased from different manufactures: Avicel PH 101 Ø 50 μm (FMC Europe – Brussels, Belgium), Avicel PH 102 Ø 100 μm (FMC Europe – Brussels, Belgium), Kollidon CL (BASF – Ludwigshafen, Germany), Aerosil 200 Pharma (Degussa, Germany). Commercial product containing ranitidine hydrochloride – Ranigast 150 mg batch 140,407 were obtained from Polpharma, Starogard Gdański, Poland, water purified RO by Elix3 (Millipore, Bedford, USA). All other reagents used were of analytical grade.

2.2. Preparation of samples for stability testing

Three main stress conditions are evaluated during stress testing in the solid state: temperature, humidity, and UV–vis irradiation for powdered RAN, FAM and CIM as well as for commercial tablets Ranigast.

Samples of RAN, FAM and CIM of 0.2 g were placed in a 20 mL glass vial and sealed with Parafilm. In parallel for the photostability testing, a second vessel with RAN was placed in an exposure chamber but was kept in the dark (covered tightly with aluminum foil), this sample was used as a dark (blank). Not tested samples used as reference were assigned as zero. Both samples (RAN zero and tested) were irradiated in a Suntest CPS+ Atlas chamber (Accelerated Tabletop Exposure Systems) equipped with a xenon lamp (1.1–1.5 kW). Exposure behind window glass is accurate for photostability testing (Indoor Indirect Daylight) of pharmaceutical products according to the ICH guideline [30]. The illuminance was set at an exposure power value of 500 [W m^{-2}]). The irradiation tests were conducted for 12, 24, 48 and 120 h.

Independently, tablets were prepared from RAN by compression using a single stroke tablet press (type Korsch EKO, Berlin, Germany) with spherical punches of 10 mm diameter. Weighed compounds for tablet formulation (Tab.1) were sieved through a 0.8 mm sieve (temp. 28.9 °C, RH = 36%). The force of compression was 5–6 kN. The individual tablet weight was 300.0 mg.

Samples of RAN, FAM and CIM for stability testing under a higher temperature and humidity weighing 0.2 g were placed in glass vials. Half the samples were sealed with Parafilm and the other half was open. For each sample of RAN, FAM and CIM, three identical samples were prepared. A climate chamber (Binder, Tuttlingen, Germany) was used for the stability testing of RAN, CIM and FAM and tablets with RAN, where samples were stored for 1, 2, 4 and 6 months (temperature 40 ± 0.5 °C, relative humidity 75%).

2.3. FTIR and NIR spectra recording

The infrared spectrum of each sample was determined by Fourier transform infrared (FTIR) spectroscopy (Jasco-410; Jasco