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Physical characterization of pantoprazole sodium hydrates

V. Zupančič[a], N. Ograjšek[a], B. Kotar-Jordan[b], F. Vrečer[b,*]

[a] *Krka d.d., Novo mesto, Product Supply, Šmarješka cesta 6, 8501 Novo mesto, Slovenia*
[b] *Krka d.d., Novo mesto, R&D Division, Šmarješka cesta 6, 8501 Novo mesto, Slovenia*

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Abstract

Only two crystal forms of pantoprazole sodium, i.e. mono and sesquihydrate, were described in the literature. The objective of the present work was to study the polymorphisms and pseudopolymorphism of pantoprazole sodium and to characterize already known and new crystal forms.

Two additional hydrate forms; i.e. form A, form B and amorphous form were obtained and further characterized by means of thermal analyses, X-ray powder diffraction (XRPD), mid-infrared spectroscopy (IR), near infrared spectroscopy (NIR), Raman spectroscopy, dynamic vapour sorption (DVS), true density, contact angle and solubility. From the results it can be concluded, that the most physically stable form of pantoprazole sodium is form B, whereas form A is the least stable form. Monohydrate and form A are not physically stable and convert into form B from saturated solution/suspension or at high relative humidity. Amorphous form can be obtained by conventional spray drying method or by distillation of solvent under reduced pressure.

Keywords: Pseudopolymorphism; Thermal analysis; Infrared spectroscopy; X-ray powder diffraction; Dynamic vapour sorption; Physical characterization

1. Introduction

Many pharmaceutical substances exhibit polymorphism and pseudopolymorphism. The former is frequently defined as the ability of substance to exist in two or more crystalline phases that have different arrangement of the molecules in the crystal lattice. As a result, the polymorphic solids have different unit cells and hence display different physical properties (such as melting point, solubility, dissolution rate, physical and chemical stability, hygroscopicity, density) including those due to packing, and various thermodynamic, spectroscopic, interfacial and mechanical properties (Grant, 1999; Kristl et al., 1996).

The term pseudopolymorphism relates to the phenomenon of incorporation of solvent molecules into crystal lattice or crystal interstitial voids. When water is incorporated in the crystal lattice the term

* Corresponding author. Tel.: +386 7 33 13 790; fax: +386 7 33 13 751.
E-mail address: franc.vrecer@krka.biz (F. Vrečer).

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hydrate is used. The differences between polymorphs and hydrates are significant. The basis for all these differences is that polymorphs are different crystal structures of the same molecule while hydrates are crystals of drug molecule with incorporated different numbers of water molecules (Halebian, 1975). Members of both polymorphic and hydrate systems have different crystal structures and exhibit different X-ray powder diffraction patterns, thermograms (DSC, TGA), infrared spectra, dissolution rates, hygroscopicity, etc. (Morris, 1999; Brittain, 1999).

It is known that in general water solubility of hydrates is lower than that of anhydrous forms and decrease while increasing the degree of hydration (Brittain and Grant, 1999; Kristl et al., 1996). Monohydrates are the most frequent among the hydrates (Threlfall, 1995).

Hydrates can be according to mechanism of bonding of water molecules divided into three types (Morris, 1999):

1. Isolated lattice site water: water molecules are separated by drug and are not in contact with each other.
2. Lattice channel water: water molecules are in channels formed in the interior of the crystal.
3. Metal ion coordinated water: these types of hydrates are connected/linked to the metal salts of weak organic acids where metal ions are coordinated with water molecules.

On the other hand Bryn (Bryn, 1982) has divided hydrates into polymorphic and pseudopolymorphic types. In polymorphic hydrates, dehydration is associated with a change in the X-ray diffractogram (change of the crystal structure), which is not the case in the pseudopolymorphic hydrates. Another difference between the polymorphic and pseudopolymorphic hydrates is rehydration. In pseudopolymorphic hydrates, rehydration takes place immediately after contact with water, while in the polymorphic hydrates, only after a phase change (Vrbinc and Vrečer, 2002; Kristl et al., 1996; Bryn, 1982).

The behavior of hydrates has become the subject of increasing attention over the last decade, primarily due to the potential impact of hydrates in the development process and dosage form performance (Carstensen, 2001). Hydrates may hydrate/dehydrate in response to changes in environmental conditions, processing or over time if they are in a metastable thermodynamic state. In order to prevent problems associated with changes in the crystal form of drugs or excipients during the production and storage of raw materials and finished products polymorphism and pseudopolymorphism should be investigated during the predformulation phase of development (Morris, 1999).

Pantoprazole sodium, a substituted benzimidazole derivative, is an irreversible proton pump inhibitor, and was developed for the treatment of acid-related gastrointestinal disorders (Reiter et al., 1991).

Examination of the literature confirmed that only two hydrate forms (monohydrate, sesquihydrate) are known and commercially available on the market (Badwan et al., 2002).

The aim of the present study was to obtain new crystal forms of pantoprazole sodium and to perform detailed characterization of pantoprazole sodium crystal forms, i.e. already known mono- and sesquihydrate and new ones.

2. Materials and methods

2.1. Materials

Pantoprazole sodium (5-(difluoromethoxy)-2-(((3,4-dimethoxy-2-pyridinyl) methyl)sulphinyl)-1H-benzimidazole sodium) monohydrate and sesquihydrate were obtained from Aurobindo (India).

Form A was prepared by crystallization from saturated solution in water free organic solvents such as ethyl acetate.

Form B was obtained by precipitation from saturated solution of monohydrate or form A in borate buffer solution (pH 9).

Amorphous form was obtained either by lyophillization of pantoprazole sodium solution in water or by spray drying of pantoprazole sodium sesquihydrate solution in absolute ethyl alcohol on Büchi 190 Mini Spray Dryer using following parameters: air flow rate, 800 ml/min; inlet air temperature 80 °C and outlet temperature 45 °C. Amorphous form was also obtained by distillation of solvent under reduced pressure from pantoprazole sodium solution in water free organic solvents such as: acetone, ethylacetate, isopropanol, chlorophorm or ethyl alcohol.

2.2. Methods

2.2.1. Thermal analysis

DSC was performed on Perkin-Elmer DSC 7 (dynamic N_2 atmosphere, heating rate 10 °C/min). Thermal effects were evaluated using Pyris software.

mtDSC analysis were performed using Perkin-Elmer DSC Pyris 1 in the temperature range 40–180 °C at underlining scan rate 1 °C/min and modulation temperature period 60 s.

Thermogravimetric analysis (TG) were obtained using Perkin-Elmer TGA-7 instrument (dynamic N_2 atmosphere, heating rate 10 °C/min).

FT-IR spectroscopy: the infrared spectra in KBr pellets were recorded within the wave number range of 4000–400 cm^{-1} with a Perkin-Elmer FT-IR spectrometer 1720× at resolution 4 cm^{-1}. Near infrared analysis was performed using Perkin-Elmer GX Custom System. Raman spectra were recorded on FT Raman spectrometer Perkin-Elmer GX Custom System.

X-ray powder diffraction (XRPD): diffractograms were obtained by Phillips PW 1710 diffractometer (Cu K(radiation, $3 \leq 2(\leq 31°$). True densities were determined by AccuPyc 1330 helium pycnometer.

Thermal microscopy: system Microscope Olympus BX50 and Thermosystem Mettler FP900 with hot stage cell FP82HT was used for collecting microphotography.

Contact angle was determined using Wilhelm disc method on Tensiometer Krüss K12 at 20 ± 0.2 °C.

Solubility was determined in borate buffer solution (pH 9) at room temperature (22 ± 1 °C). Excess of pantoprazole sodium was added to 5 ml of buffer solution. The concentration of pantoprazole in the filtrate (0. 22 μm pore size filter) was determined spectrophotometrically.

Dissolution profiles were obtained using VanKel intrinsic dissolution apparatus. Sample (200 mg) was put into die cavity and compressed into a disc. The die with the disc was fixed into the holder, which was mounted through the shaft on the dissolution tester. Holder was sunk into the 500 ml of dissolution medium (phosphate buffer (pH 6.8 ± 0.1) at 37 ± 0.5 °C and rotated at 100 rpm; pantoprazole concentrations in dissolution medium were determined at in advance selected time intervals "on line" using UV–vis diode array spectrophotometer Hewlet-Packard HP 89550A and automatic sampling system (Multicell transport system). Dynamic vapour sorption (DVS) isotherms were obtained using DVS-1, Surface Measurement Systems Ltd.

3. Results and discussion

The study of pantoprazole sodium crystallization from different solvents at different temperatures shows that different hydrate forms can be obtained varying the type of solvents and crystallization rate. Monohydrate was obtained from supersaturated solution in acetone; however sesquihydrate was obtained from supersaturated solution in purified water. Surprisingly, crystallization of pantoprazole sodium from ethyl-acetate and from alkaline borate buffer at pH 9 resulted in two unknown hydrate forms which were resolved as form A and form B.

DSC analyses (Fig. 1) show obvious differences among hydrates and amorphous form. From the results it can be concluded that melting and dehydration are parallel processes in case of mono- and sequihydrate. This finding was confirmed also by the results of mtDSC analyses of both hydrates, i.e. mono- and sesquihydrate, where besides irreversible thermal effects (evaporation of water), also reversible effects (melting) can be observed. Monohydrate has higher transition temperature than sesquihydrate; however sesquihydrate has higher transition enthalpy than monohydrate (Table 1). Higher enthalpy change in case of sesquihydrate is attributed to higher energy required for additional 0.5 mole of water (total 1.5 mole of water is bounded per mole of pantoprazole sodium) in comparison to monohydrate. Combined results of DSC, TG analysis and hot stage microscopy showed that dehydration of hydrates takes place together with melting. It was found out that sesquihydrate is physically more stable than monohydrate. This is attributed to stronger bonding of water molecules in crystal lattice.

The DSC curve of the form B exhibits two partially overlapping not totally divided endothermic effects from about 70–90 °C. Similar situation is shown by TG analysis indicating that at this temperature range the loss of water occurs. Dehydratation takes place at lower temperature than for monohydrate and sesquihydrate. This finding can be attributed either to weaker bonding of water molecules in the crys-

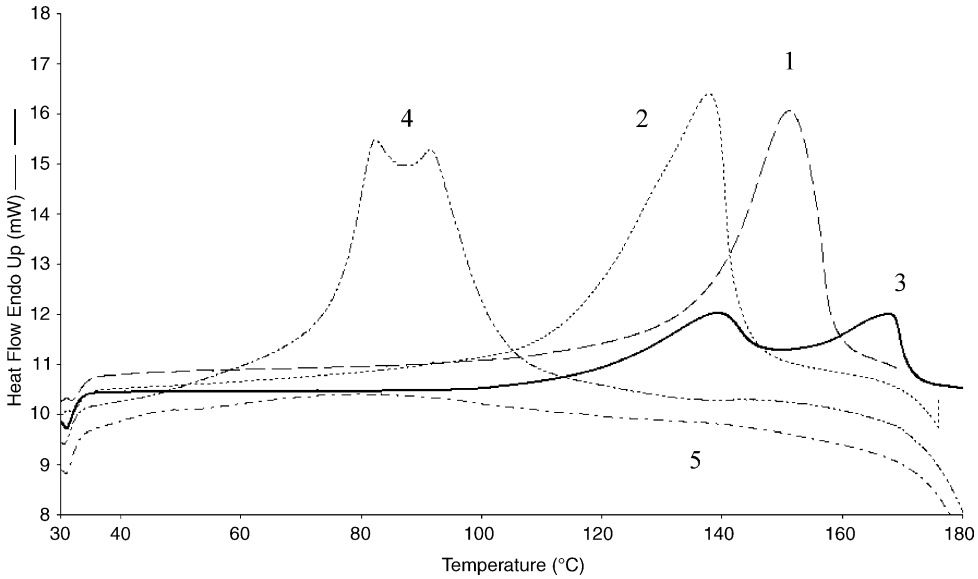

Fig. 1. DSC curves of pantoprazole sodium form A (3), monohydrate (1), sesquihydrate (2), form B (4), amorphous form (5).

tal lattice or to different mechanism of incorporation of water molecules into crystals of mono and sesquihydrate in comparison to form B. As it may be observed during heating under thermo microscope water is released from mono and sesquihydrate during the melting of crystals. In case of form B water is released before melting. After dehydration, crystal structure of form B was destroyed and amorphous form was obtained.

The results of water content determination by Karl-Fisher method are comparable with the data of the mass loss (attributed to the evaporation of bonded water) determined by TGA analysis.

Two-step dehydration was observed in the TG diagram in a sample designated as form A (Figs. 1 and 2). The first dehydration step exhibits a weight loss of approximately 1.6% in the range from 90 to 140 °C, second 1.4% from 140 to 165 °C (Fig. 2). Two endothermic effects can be observed in DSC curve for form A Endothermic degradation is in case of form A moved to higher temperatures in comparison to other hydrates. Results of mtDSC analysis of form A confirm that first endotherm observed in DSC curve represents evaporation of bound water and the second is attributed to the relaxation process, which is typical for amorphous forms. One can conclude from these results,

Table 1
Characteristic results of physical analysis of pantoprazole sodium hydrates

Parameter	Form A	Monohydrate	Sesquihydrate	Form B
Transition T (T_{t1}) (°C)	125.76	138	114	74
Transition T (T_{t2}) (°C)	157.97	–	–	–
Transition enthalpy (ΔH_1) (J/g)	17.24	170	217	299
Transition enthalpy (ΔH_2) (J/g)	16.92	–	–	–
Water content (%); KF analysis	2.99	5.06	6.14	11.38
Δm (%); TG analysis	2.97	4.3	6.4	10.9
Contact angle (glycerol) (°)	77.5	75.6	81.6	77.4
True density (g/cm^3)	1.4405 ± 0.0002	1.4648 ± 0.0009	1.4790 ± 0.0002	1.4752 ± 0.0004
Solubility basic borate buffer pH 9, 22 °C (g/l)	–	286.14[a]	284.34	0.74

[a] Data do not show absolute solubility but maximum concentration obtained during solubility study, because of monohydrate conversion into form B.

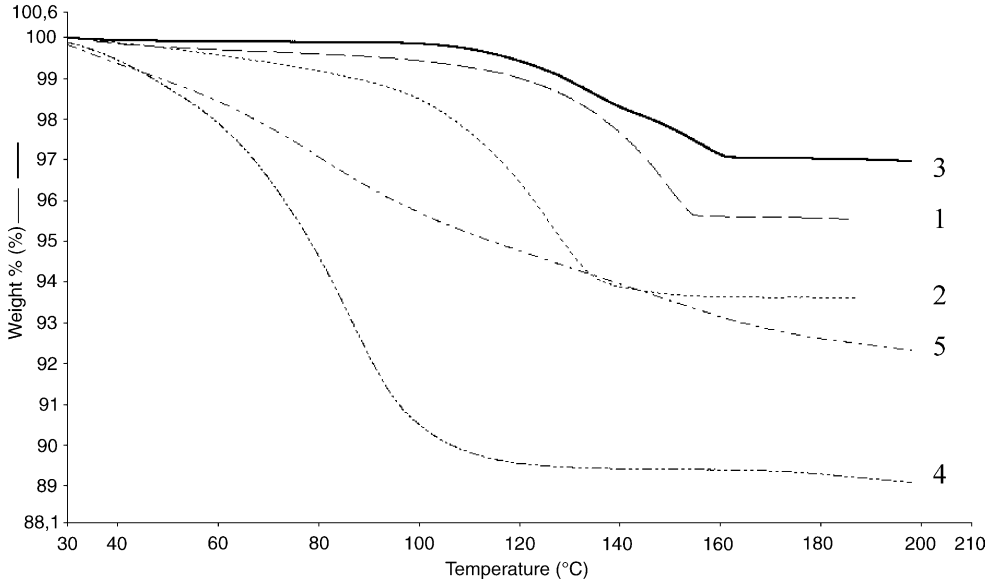

Fig. 2. TG curves of pantoprazole sodium form A (3), monohydrate (1), sesquihydrate (2), form B (4) and amorphous form (5).

that amorphous form is formed after dehydratation of form A.

IR spectra of pantoprazole sodium show significant O–H and C–H absorption bands from 3000 to 3500 cm^{-1}; C=C, C=N absorption bands from 1800 to 1500 cm^{-1} (Badwan et al., 2002).

The major differences between IR spectra of monohydrate and sesquihydrate (Fig. 3) are observed in the range of O–H stretching vibrations (3100–3600 cm^{-1}), minor differences can be observed also in the fingerprint region where monohydrate has absorption band at 823 cm^{-1}, however sesquihydrate has absorption band at 815 cm^{-1}. Very broad absorption band can be observed in IR spectra for form A and form B in the range 3100–3600 cm^{-1} which is not so marked in spectrum of sesquihydrate. Differences were observed also in the finger print regions. Characteristic IR absorption bands for form A: 1029, 991, 974, 935, 873, 808 and 550 cm^{-1} and for form B 3670, 1431, 1410, 1182, 1100, 1024, 932, 876, 831 and 720 cm^{-1}.

Differences can be observed also in Raman spectra of pantoprazole sodium hydrates (Fig. 4). Characteristic bands for monohydrate: 3102, 3019, 2988, 735, 659, 598 and 500 cm^{-1}, for sesquihydrate: 3097, 1277, 1232, 978 and 554 cm^{-1}, for form A: 2981, 2923, 1311, 1285 and 633 cm^{-1} and for form B: 3050, 3011, 2948, 2842, 1567, 1440, 1101, 985 and 831 cm^{-1}.

Pronounced differences can be observed also in NIR spectra of hydrates (Fig. 5). Spectra of mono and sesquihydrate show bigger similarity than those of other hydrates. It can be thus concluded that both hydrate have similar structure. Characteristic NIR bands for monohydrate: 5616, 5186, 4620, 4443, 4396 and 4104 cm^{-1}, for sesquihydrate: 6968, 6007, 5731, 5237, 5121 and 4207 cm^{-1}, for form A: 5829, 5721, 4368 and 4120 cm^{-1} and for form B: 5772, 5586, 5272, 5215, 5085, 4313, 4245 and 4128 cm^{-1}.

X-ray powder diffractograms (Fig. 6) of monohydrate, sesquihydrate, form A, form B and amorphous form exhibit marked differences. Characteristic diffraction lines for hydrate forms are at following angles (2Θ): 6.0083, 9.9546, 11.9728, 17.7480, 19.2815 and 29.7457 for monohydrate; 7.2665, 16.5331, 16.7040, 20.4342 and 27.7315 for sesquihydrate; 8.6100, 13.9736, 15.0724, 16.1078, 19.5648 and 28.1628 for form A and 11.5199, 14.6708, 21.5616 and 26.7702.

Solubility studies were performed in basic borate buffer solution (pH 9). Basic borate buffer was chosen because of instability of pantoprazole sodium in acidic environment. Very fast dissolution together with high

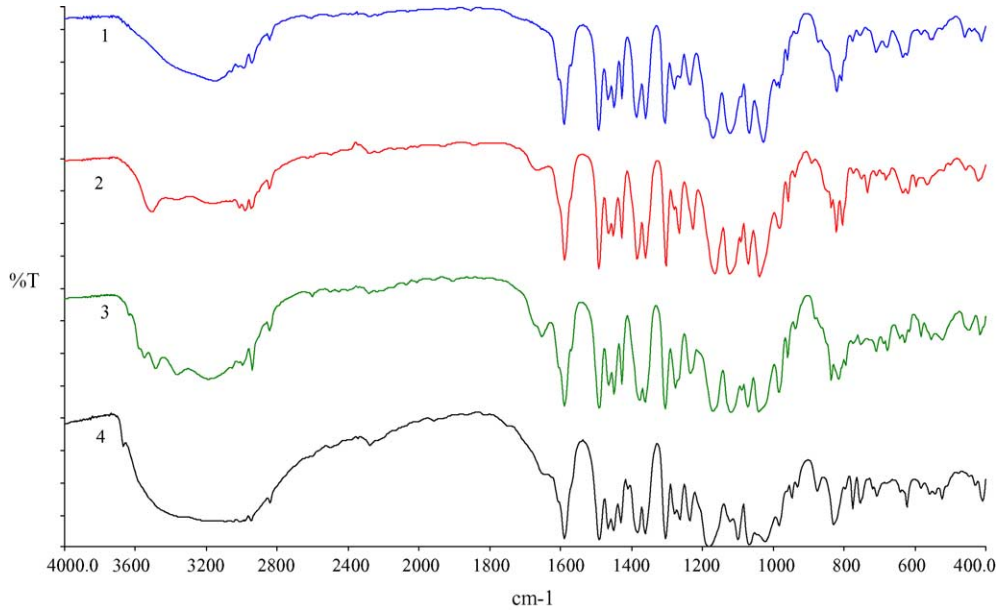

Fig. 3. IR spectrums for pantoprazole sodium form A (1), monohydrate (2), sesquihydrate (3), form B (4).

solubility was observed for all pantoprazole sodium hydrates.

Absolute solubility of monohydrate, form A and amorphous form could not be determined because of their fast conversion to new hydrate form during the test. Sesquihydrate was found to be physically stable in contact with dissolution medium—no conversion into new hydrate form was observed. Its solubility is about

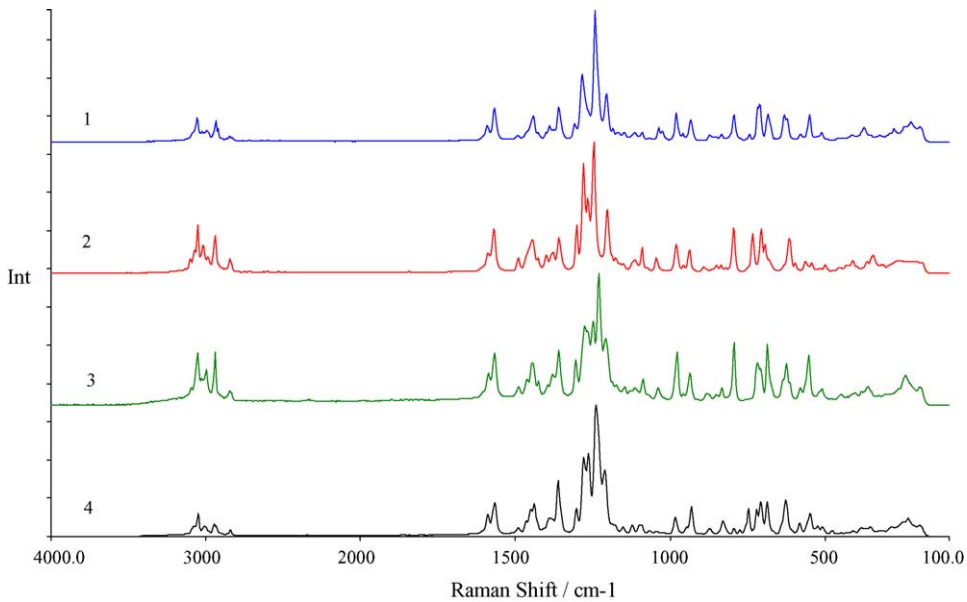

Fig. 4. Raman spectra of pantoprazole form A (1), monohydrate (2), sesquihydrate (3), form B (4).

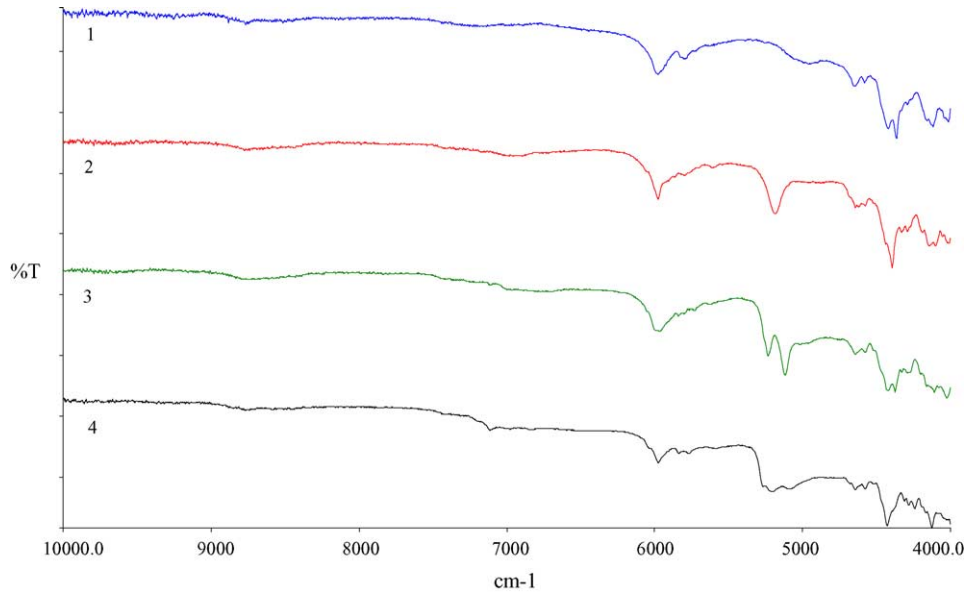

Fig. 5. NIR spectra of form A (1), monohydrate (2), sesquihydrate (3), form B (4).

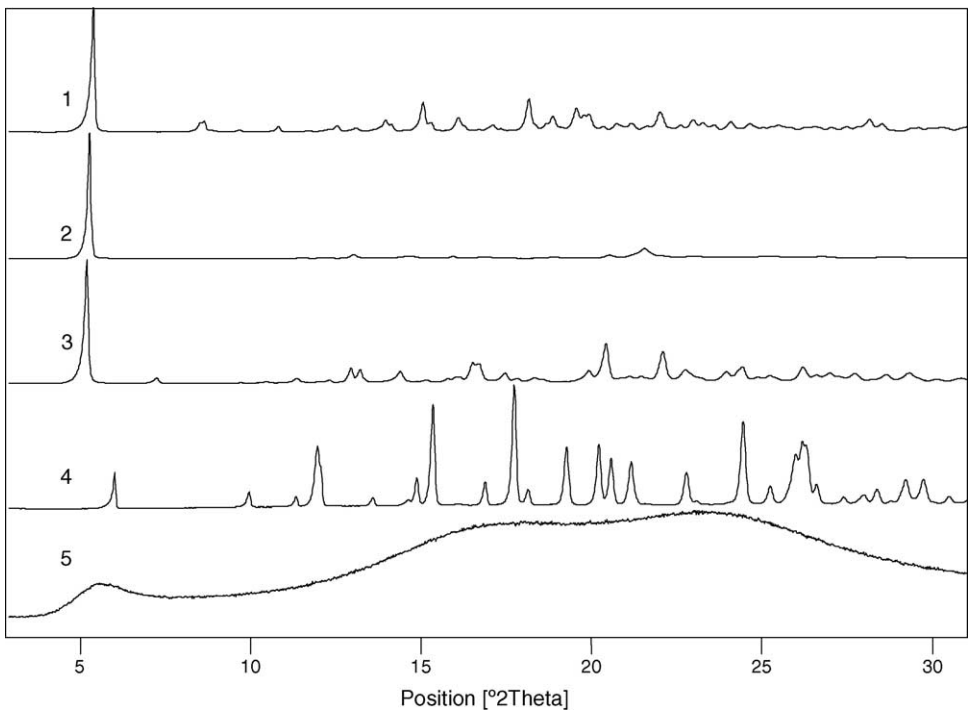

Fig. 6. X-ray diffractograms of pantoprazole sodium form A (1), monohydrate (2), sesquihydrate (3), form B (4), amorphous form (5).

400 times higher than the solubility of form B (Table 1). Solubility of the form B is comparable to the solubility of free acid (pantoprazole).

Wettability of crystal forms of pantoprazole sodium with glycerol was evaluated (Table 1) using contact angle measurement. Water or water based buffer solutions could not be used due to high solubility of pantoprazole sodium hydrates in water. The differences among the results are not large what can be attributed to the similar polarity of the particles surface of the tested hydrates. Among the pantoprazole hydrates monohydrate has the lowest contact angle. On the other hand sesquihydrate has highest contact angle and lowest wettability. Higher wettability of monohydrate in comparison to sesquihydrate should result in higher dissolution rate of the former. Form A and form B have similar wettability as monohydrate.

Due to the very high solubility of pantoprazole sodium hydrates in buffer solutions powder dissolution profiles were not obtained and the dissolution kinetics was analyzed only from compressed discs (intrinsic dissolution rate). Comparison of the intrinsic dissolution profiles in time interval 0–30 min of pantoprazole sodium hydrates in phosphate buffer pH 6.8 at 37 °C showed the highest value (Fig. 7) for monohydrate followed by sesquihydrate and form B. Plateau observed in intrinsic dissolution curves of mono and sesquihydrate is attributed to the observed formation of bubbles in the disc cavity upon dissolution of majority of the compressed disc.

Our results are not in accordance with the results of Reiter et al. (1991), who observed 5–10 times higher dissolution rate of monohydrate in comparison to sesquihydrate.

From the DVS study it can be observed (Fig. 8) that monohydrate at relative humidity lower than 70% shows no water sorption, however at relative humidity higher than 80% monohydrate starts to sorbs water and is converted to new hydrate which is more stable than monohydrate. Desorption curve shows strong bonded water which is removed at humidity lower than 10%. Mass of the sample at the end of sorption/desorption cycle is 1.65% lower than in the starting sample. From this result it can be concluded that new hydrate was formed. New hydrate formation, at relative humidity higher than 80%, was observed also during DVS sorption/desorption of form A and amorphous form. However, sesquihydrate and form B remain unchanged even under conditions of high% of relative humidity.

If we take in consider obtained results of physical-chemical characterization of pantoprazole sodium hydrates (partially shown above), we can conclude that sesquihydrate and form B are the most stable hydrates and from this point the most appropriate for use in the pharmaceutical production.

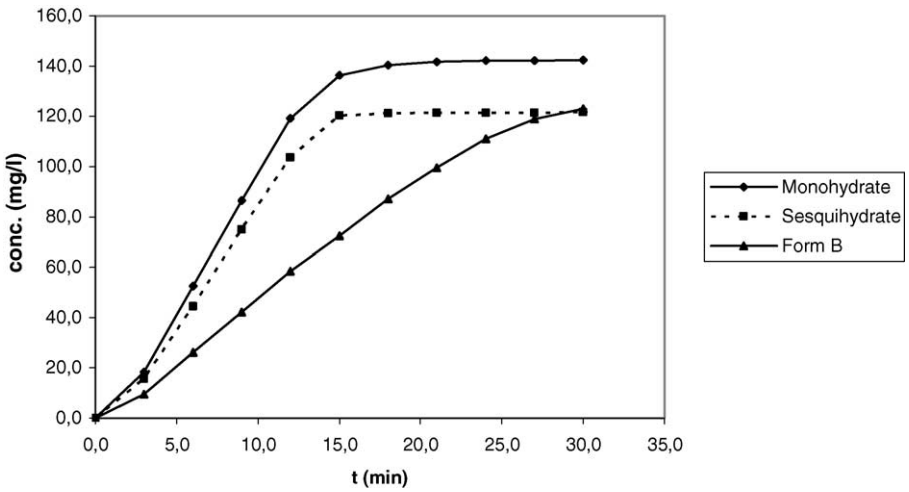

Fig. 7. Dissolution profiles of pantoprazole crystal forms in phosphate buffer pH 6.8.

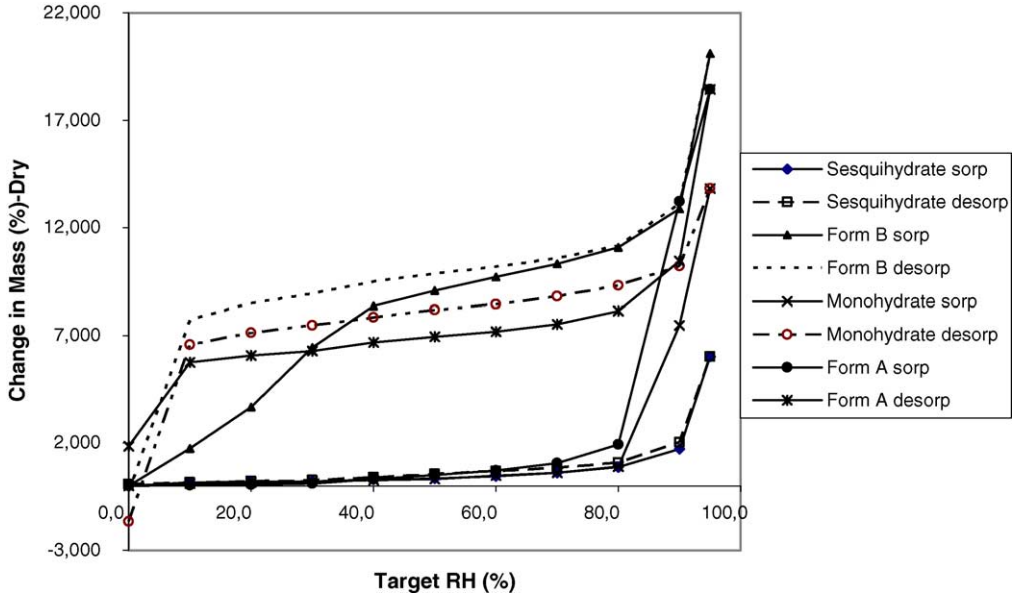

Fig. 8. Sorption/desorption isotherms of pantoprazole sodium hydrates.

4. Conclusions

In conclusion one can say:

- Besides already known and commercially available pantoprazole sodium crystal forms (mono- and sesquihydrate) not yet described hydrate forms were obtained, i.e. unstable form A and very stable form B.
- Lattice channel water crystal structure was proposed for monohydrate and sesquihydrate and isolated lattice water crystal structure for form A and B. From our results we assume that form A represent hemihydrate and form B dihydrate. Exact crystal structure of all crystal forms will be investigated in our future work.
- Water molecules are crucial for crystal lattice stabilization. Anhydrous form of pantoprazole sodium is unstable and is converted to hydrates upon contact with low air humidity or small concentrations of water in solvents. Thermal dehydration of form B results in amorphous form.
- Very fast dissolution together with high solubility was observed for all pantoprazole sodium hydrates, although form B is approximately 400 times less soluble than sesquihydrate. Analytical results showed that form A is physically the least stable form followed by monohydrate, sesquihydrate and form B as the most stable form.
- Because of physical instability and its fast conversion into stable form B it was impossible to determine solubility data for form A and monohydrate. Form B solubility is comparable to that of free acid solubility.
- Amorphous form of pantoprazole sodium can be obtained by either spray drying of solution in appropriate solvents or by distillation of solvent from solution under reduced pressure.

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