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Qualitative and quantitative analysis of clopidogrel bisulphate polymorphs

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This study deals with characterization and quantification of form I and form II of clopidogrel bisulphate (CLP), a selective and irreversible inhibitor of ADP-induced platelet aggregation. Thermal (DSC, TGA, HSM), crystallographic (XRD) and spectroscopic (FTIR) methods were used for characterization. After characterization of active pharmaceutical ingredient (API), these techniques were further used for identification of the polymorphic form present in three marketed formulations (tablets). FTIR method was successfully developed and validated for the quantification of form I in polymorph mixtures.

Keywords: clopidogrel bisulphate, polymorphs, characterization, FTIR, quantification

Polymorphism specifying the diversity of nature is widely observed in pharmaceutical compounds (1). Differences in their physico-chemical and mechanical properties led to the emergence of characterization based stringent quality control measures of these altered solid-state forms, in active pharmaceutical ingredients (APIs) and drug products, both during filing of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) (2). The lower energy form, though the most stable and preferred form for the final dosage form, exhibits lower solubility and dissolution profiles, an issue especially important for the biopharmaceutics classification system (BCS) class II and IV drugs. Additional complexities can arise due to the differences in flow properties, compactability, water uptake behavior, crystal morphology and hence processability of different forms (3, 4). The sudden appearance or disappearance of a crystalline form can threaten process development, and can lead to serious pharmaceutical consequences if the transformation occurs during the manufacturing or storage of the dosage form (5–8). Therefore, qualitative and quantitative analyses of polymorphs must be incorporated early on in the drug development stage, both in the API manufacturing and the formulation stage (9, 10).

Pharmaceutical companies engaged in generic products aim at developing a formulation that is qualitatively and quantitatively closest to the innovator product in terms of excipients and the API polymorphic form. However, USFDA allows the use of alternate

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polymorphic forms as long as the criteria of pharmaceutical equivalence and bioequivalence are met (2). The safest and fastest strategy is to use a polymorphic form similar to the innovator product. Solid-state characterization including the polymorphic form of API used by the innovator should be an integral part of a reverse engineering exercise aimed at unveiling the qualitative and quantitative formula of the innovator product.

For this study, clopidogrel bisulphate (CLP), (+)-methyl-α-5-[4,5,6,7-tetrahydro-[3,2--c]thienopyridyl]-(2-chlorophenyl)acetate hydrogensulphate (Fig. 1), a selective and irreversible inhibitor of ADP-induced platelet aggregation, was selected (11, 12). Six different polymorphic forms and an amorphous form of the drug have been identified but only forms I and II are used in pharmaceutical formulations (13). For both polymorphs,

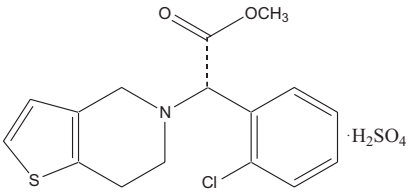

Fig. 1. Chemical structure of clopidogrel hydrogensulphate.

only the dextrorotatory isomer exhibits activity on platelet aggregation whereas the levorotatory isomer is less active and poorly tolerated. Form II is still under patent though the patent of form I has already expired. Hence, polymorphism may play a critical role for an early generic product entry and it is worthwhile to characterize the polymorphic forms and identify the form present in the dosage forms.

EXPERIMENTAL

Materials

CLP form I and form II were a gift by Ind-Swift Laboratories Ltd. (India). Methanol AR grade (Loba Chemie, India) and potassium bromide FTIR grade (Aldrich, USA) were used as received from the suppliers. The following dosage forms (tablets) were purchased from the local market: Caruvin 75 mg (Dr. Reddy's Laboratories Ltd., India), Deplatt 75 mg (Torrent Pharmaceuticals Ltd., India), Noklot 75 mg (Zydus Medica, India).

Solid-state characterization of CLP polymorphs

Optical and polarized light microscopy. – Microscopy was carried out using a Leica DMLP polarized microscope (Leica, Germany) attached to LM50 v1.2 digital imaging software. The mounted samples were observed under normal and polarized light at various magnifications.

Thermal analysis

Hot stage microscopy (HSM). – Thermal transitions in the samples were studied using Leica LMW Hot Stage and Leica DMLP polarized microscopes. The samples were heated on the hot stage and observed under normal and polarized light as described previously.

Differential scanning calorimetry (DSC). – DSC analysis was performed using a Mettler Toledo 821^e DSC (Mettler Toledo, Switzerland) operating with version 5.1 of Star^e software. The samples (4–6 mg) were encapsulated in aluminium pans having pierced lids to allow escape of volatiles. The heating rate of 10 °C min^{-1} and nitrogen purge at 80 mL min^{-1} were employed. The temperature axis and the cell constant were calibrated using indium.

Thermogravimetric analysis (TGA). – The mass loss of the sample as a function of temperature was determined using a Mettler Toledo 851^e TGA/SDTA (Mettler Toledo, Switzerland). The samples were placed in open aluminium crucibles and heated at a rate of 10 °C min^{-1} under a nitrogen purge (20 mL min^{-1}).

Fourier transform infrared spectroscopy (FTIR)

Qualitative analysis. – The FTIR spectra were recorded on a FTIR multiscope spectrophotometer (Perkin Elmer, UK) equipped with spectrum v3.02 software. KBr pellets were prepared so as to contain approximately 3% of polymorph powder. The spectrum for each sample (an average of 16 co-added scans) was recorded over the 450 to 4000 cm^{-1} spectral region with a resolution of 4 cm^{-1}.

Quantitative analysis. – For quantitative analysis, both CLP forms I and II were passed through a sieve (BSS sieve number 80, opening ~ 180 mm) to obtain uniform particles. Grinding was avoided because it could cause polymorphic transformation. Spectra of pure forms I and II and 10, 20, 30, 50, 60, 70 and 90% mixtures of form I in form II were recorded in triplicate. The components were weighed to a total amount of 200 mg and mixed thoroughly. Mixtures were stored in glass vials stored in a vacuum dessicator with phosphorus pentoxide as dessicant. KBr pellets having a 3% (*m/m*) polymorph mixture were prepared at a pressure of 20.7 MPa and a dwell time of 30 s. The spectrum for each sample (an average of 16 co-added scans) was recorded over the 450 to 4000 cm^{-1} spectral region with 4 cm^{-1} resolution. The method was validated for accuracy and precision by performing recovery studies and calculating the difference between actual and theoretical values. Instrument reproducibility was checked by recording the spectra of form I six times without removing the sample. Repeatability was investigated at three concentrations (40, 60, 80% form I in form II) in triplicates.

FTIR spectra were also recorded using a Combipress® sampling assembly (Perkin Elmer, UK) wherein powder spectra are recorded without formation of pellets. Polymorph powder was sandwiched between the two diamond windows of the assembly and spectra were obtained using the above-described parameters. Also, the effect of increasing pressure on the polymorphic behavior was studied by preparing pellets at different pressure. KBr pellets were prepared using a 3% polymorph mixture at pressures of 20.7, 34.5, 51.7, 69.0 and 82.8 MPa with a dwell time of 30 s.

X-ray powder diffraction (XRPD)

Powder X-ray diffraction patterns were collected on a Philips PW 1729 powder diffractometer (Philips, The Netherlands), using monochromatic CuK_α (λ for $K_{\alpha1}$ = 1.54060 Å; λ for $K_{\alpha2}$ = 1.54439 Å) radiation obtained at 20 mA and 35 kV. The diffractometer was equipped with a 2θ-compensating slit and calibrated with a silicon pellet. The scans were run from 5° to 40° 2θ, increasing at a step size of 0.02° with a counting time of 1 s for each step. Samples were passed through a sieve (BSS sieve number 60, opening of 2.5 mm) to avoid the effect of preferred orientation. Data were processed using the PAD v4 software.

Identification of polymorph(s) in dosage forms

The tablet coat was removed using a surgical blade and the tablet core was scraped to obtain the powder. The powder was passed through a sieve (BSS sieve number 60, opening 2.5 mm) and stored in glass vials in a vacuum dessicator. The powders were characterized for solid-state forms by microscopy, XRD, FTIR and DSC analysis.

RESULTS AND DISCUSSION

Solid-state characterization of pure polymorphs

Microscopy. – Form I occured as irregular plates whereas agglomerates were seen in the powdered form II. The agglomeration in form II could be due to the high interfacial free energy of the particles and the particles aggregate in order to reduce this surface free energy and to attain thermodynamic stability.

The two forms exhibited differences when viewed under polarized light. Form I appeared to be alternately dark and bright as the stage was rotated by 45°. On the other hand, crystals of form II showed parallel extinction behavior. The crystals appeared alternately fully bright and dark at a complete rotation of 90°. At intermediate positions of 30° and 60°, form II exhibited half extinction. Both forms contain crystals of anisotropic type (14).

Thermal analysis. – DSC and TGA curves of CLP polymorphs are shown in Fig. 2. No mass loss was observed during TGA analysis, indicating that the forms were anhydrous and nonsolvated.

DSC analysis showed three endothermic peaks for both forms. Form I showed a melting endotherm at 181-186-190 ± 1 °C (onset-peak-endset) with enthalpy of 33 ± 2 kJ mol^{-1}, while form II melted at 177-179-182 ± 0.5 °C with enthalpy of 35 ± 1 kJ mol^{-1}. The endothermic peaks after melting are attributed to the thermally induced decomposition in both forms as no transition was observed after melting under the hot stage microscope. Also the TGA curve showed initiation of mass loss corresponding to the first endotherm in DSC, which continued even at higher temperatures. These results point to a complex decomposition pattern associated with the forms.

One of the properties of practical interest for a polymorphic substance is the relative thermodynamic stability of the forms. The lower heat of fusion in the case of the higher

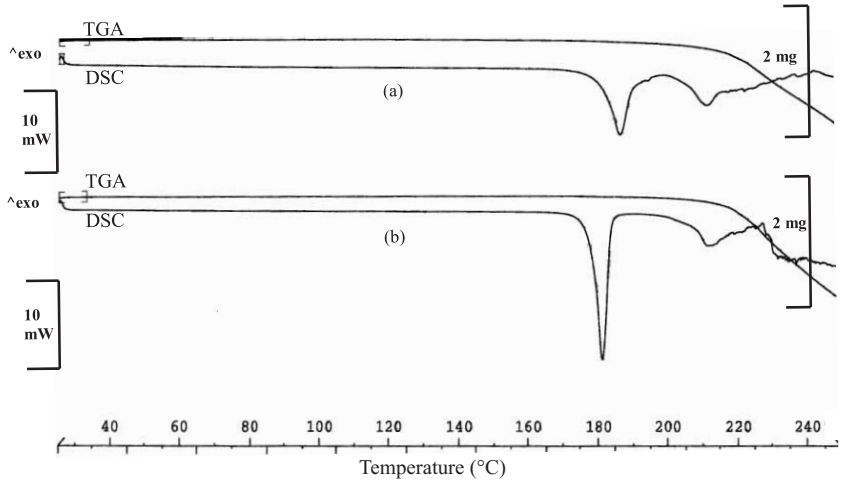

Fig. 2. DSC and TGA curves (heating rate: 10 °C min^{-1}, pin holed crimped pans and N_2 at 80 mL min^{-1} for DSC and 20 mL min^{-1} for TGA) of CLP polymorphs: (a) form I, (b) form II.

melting form, form I, indicates the enantiotropic relationship between the two polymorphs, as described by the heat of fusion rule, which states that if the higher melting form has a lower heat of fusion, the two forms are usually enantiotropic, otherwise they are monotropic (15).

This fact is also confirmed by the density rule, which suggests that if one form of a molecular crystal has a lower density than the other, it may be assumed to be less stable at zero Kelvin (15) as the energetically most favorable packing of molecules in a crystal has the strongest interactions between the molecules and hence the highest density. It can be inferred from the density rule that form II is less stable (1.462 g cm^{-3} is the reported density from X-ray diffraction analysis) compared to form I (1.505 g cm^{-3}) at zero Kelvin (13).

FTIR

FTIR is one of the most widely reported spectroscopic techniques for solid-state characterization and can be used for both qualitative and quantitative analyses of drugs (16–20). A number of pharmaceutical compounds have been studied using this method (21).

Qualitative analysis. – It is reported that clopidogrel moiety, which acts as a cation in CLP, has different conformations in CLP polymorphs, leading to different chemical environments in both forms, hence generating dissimilar FTIR spectra. Fig. 3 shows FTIR spectra of CLP polymorphs. The band due to aromatic C–H stretching vibrations was present at 3121 cm^{-1} in form II, while it was shifted to 3103 cm^{-1} in form I. This indicates that the C–H bond in the chlorophenyl ring is stronger in form II compared to form I. Both forms showed a broad absorbance band at about 2500–2550 cm^{-1} associated with stretching vibrations of bonded N^+–H occurring due to salt formation between the qua-

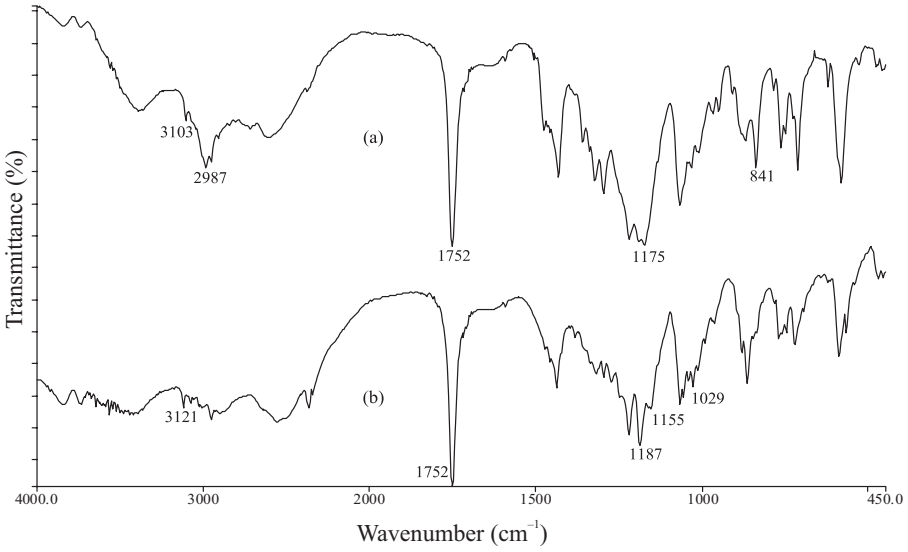

Fig. 3. FTIR spectra of CLP polymorphs: (a) form I, (b) form II.

ternary nitrogen of clopidogrel and –OH of hydrogen sulphate. Also, both forms showed a strong absorbance band due to C=O stretching vibrations at 1752 cm^{-1} and due to O–H stretching of the hydrogen sulphate moiety around 3300 cm^{-1}. The band associated with C–O stretching appeared at 1175 cm^{-1} in form I with a small shoulder, and at 1187 cm^{-1} and 1155 cm^{-1} in form II. It was found from the structure of form II that Cl and O (of $-OCH_3$ group) are in close proximity, creating electron repulsion between the lone pair electron of Cl and O and thus making the C–O bond stronger in form II. Also, forms I and II exhibited unique absorption bands at 841 and 1029 cm^{-1}, respectively. These two bands are very useful for qualitative and quantitative determination of CLP polymorphs.

Quantitative analysis. – If a mixture of two or more polymorphs is present in an API sample, then it is necessary to quantify the polymorphs. In the cases of sufficiently large spectroscopic differences between polymorphs, quantification of the polymorph mixture can be done using this method. Characteristic absorption bands of CLP at 2987, 1175 and 841 cm^{-1} and 1497, 1187 and 1029 cm^{-1} for form I and form II, respectively, were explored for quantification.

Calibration. – Among the bands mentioned above, band at 841 cm^{-1} was used for quantification of form I in a binary polymorph mixture. The absorbance band at 841 cm^{-1} was selected because of its sensitivity and the region where the difference in spectra was readily interpretable. The regression line equation for the quantification of form I in the binary polymorph mixture was found to be $y = 0.0023\ \gamma + 0.016$. A band unique to the CLP form I at 841 cm^{-1} was integrated from 850 to 823.5 cm^{-1}, and this area was divided by the area of the reference band at 1752 cm^{-1}, which was integrated from 1794 to 720 cm^{-1}. While the band at the analytical frequency (841 cm^{-1}) monitors the level of

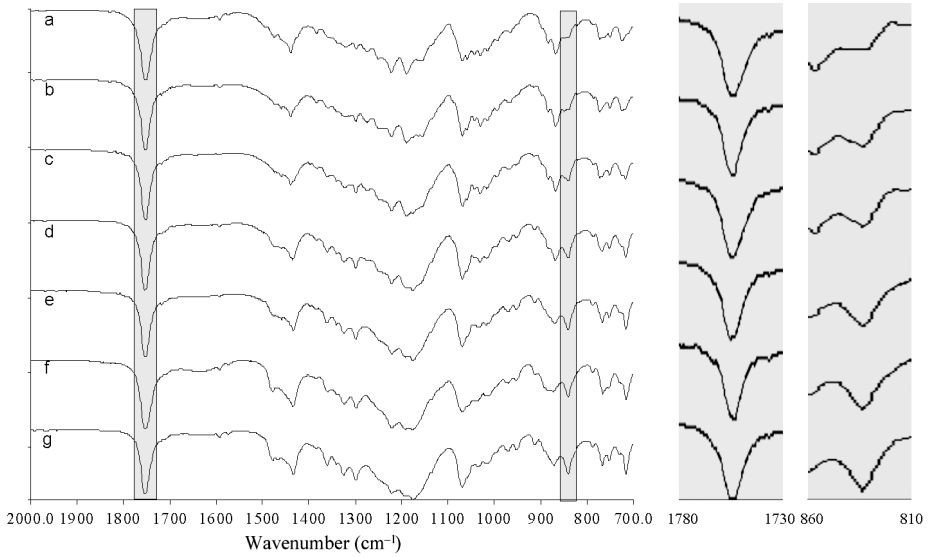

Fig. 4. FTIR spectra of binary mixtures of form I in form II: (a) 0%, (b) 10%, (c) 30%, (d) 50%, (e) 70%, (f) 90% and (g) 100% form I. Pattern II is the enlarged version of the 1752 cm^{-1} and 841 cm^{-1} peaks.

form I in the sample, the reference band (1752 cm^{-1}), which is common to both polymorphs, acts as an internal standard (Fig. 4). The 841 cm^{-1} absorbance band was selected, because it is not affected by pressure and, therefore, form I can be unambiguously quantified in binary mixtures. The reference band remains essentially constant irrespective of the crystal form, thus serving to minimize matrix effects caused by the sample preparation and crystal form composition. The calibration plot showed good linearity over the entire concentration range with a high correlation coefficient (R^2 = 0.9906) with an extremely small intercept. The method was validated and found to be accurate (Table I) and precise with R^2 of 0.9969 (Table Ib). The instrument variability was negligible with RSD of 0.8% (Table I).

The characteristic band of form II appearing at 1049 cm^{-1} could not be used in a similar manner because of its weak intensity. The band is not perceptible below a 30% concentration of form II in the mixture, thus making it worthless for quantification purposes.

A key factor to be considered while using FTIR, both for qualitative and quantitative estimation, is to ensure that the polymorphs are stable during the sample preparation procedure (16). The sensitivity of the forms to the stresses dominating during grinding, compression and decompression operations required for pellet formation must be investigated. Transformations due to compressional pressures have been reported in literature (17, 18) and for these drugs emphasis is on the use of other techniques, like the diffuse reflectance infrared Fourier transform spectroscopy and attenuated total reflectance, which do not subject the sample to thermal or mechanical stresses sufficient to cause polymorph transformation (16).

Table I. Accuracy and repeatability of FTIR quantification of CLP powder mixtures (form I in form II)[a]

Actual (%)	Predicted (%)	Recovery (%)	RSD (%)
20	20.15	100.8	–
40	–	–	4.5
60	60.00	100.0	5.0
80	80.78	101.0	3.8

[a] $n = 3$

The powder (obtained using Combipress®) as well as the pellet FTIR spectra of both forms coincide with each other; hence, KBr pellet formation induces no polymorphic changes or defects in the crystal lattice (data not shown). Moreover, spectra of form I and form II showed no shifts or appearance of any new peaks with the increase in pressure, pointing to the conclusion that pressure experienced by the forms during pellet preparation does not lead to any phase transformation. Therefore, FTIR is a safe method for both qualitative and quantitative analysis of CLP polymorphs.

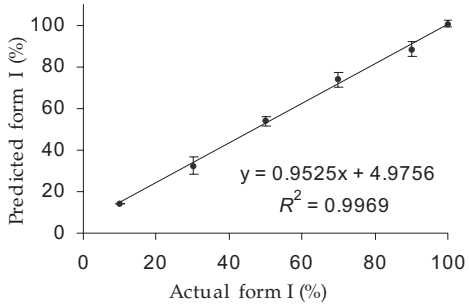

Fig. 5. Plot of observed *vs.* theoretical percentage of form I in form II, obtained using the ratio of peak areas in FTIR (mean ± SD, $n = 3$).

XRPD. – Fig. 6 shows XRPD patterns of both CLP polymorphs. Form II showed a larger number of peaks in the region of 30° to 50° 2θ. Two high intensity peaks at 21.69° and 23.0° 2θ were observed in form II while form I showed the highest intensity peak at 23.15° 2θ. At the lower 2θ angle, form I showed specific peaks at 9.26° and 14.39° 2θ while unique peaks were present at 8.91° and 12.44° 2θ in the case of form II. The lowest interplanar distance (d-spacing) was found to be 9.53 Å and 9.91 Å, respectively, in form I and form II. This suggests that form I is more densely packed compared to form II. This correlated well with the published data that the crystalline structure of form II is less dense (1.462 g cm^{-3}) than the crystalline structure of form I (1.505 g cm^{-3}) (13).

Identification of polymorph(s) in dosage forms

Three tablet formulations of CLP were analyzed for the polymorphic form present in them. DSC scans of each tablet powder showed peaks due to excipients, which overlapped with the melting peak of the drug (data not shown). In addition, the matrix effect

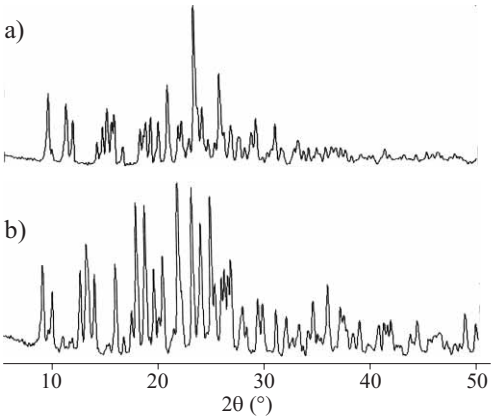

Fig. 6. XRPD patterns of CLP polymorphs: (a) form I, (b) form II.

caused by excipients led to a shift in the melting peak towards lower temperature. Hence, DSC was not a useful method for polymorph identification in CLP tablets. Therefore, XRPD and FTIR were used for identification of the solid-state form in tablets.

XRPD. – Powder obtained from the tablets was first analyzed using XRPD. Excipient peaks complicated the XRD patterns of all three tablets, but identification of CLP peaks was possible in all cases (Fig. 7). All three dosage forms were found to contain form II. The unique peaks related to form II were unambiguously identified and no peak due to form I was observed. The position of crystalline reflections (2θ) remained the same within experimental error, regardless of the shift from the baseline. This shift from the baseline was due to the presence of excipients in tablets. In all cases comparison revealed that peak positions were in accord with the USP limit. The USP general chapter on X-ray diffraction states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree within ± 0.20 degrees with that of reference material (19). In all formulations, relative intensities of the peaks decreased. Intensity of the diffraction peaks can be affected by dilution due to excipients in the dosage form and/or preferred orientation. Grinding the tablets could have minimized the preferred orientation, which, however, was avoided to prevent phase transitions.

The shift from the baseline and the change in intensity of peaks due the presence of excipients precludes the use of XRPD for quantification. Accurate quantification using XRPD relies profoundly on the absence of orientation effects and the particle size uniformity. The difference in the particle size distribution of API and excipients is a matter of great concern. Moreover, differences in mass absorption coefficients between the drug and excipients may result in severe deviations from linearity during quantification (20). Sophisticated methods of pattern subtraction, pattern-fitting by the Rietveld method and quantitative phase analysis may help in quantification of API in dosage forms using XRPD (21).

FTIR. – CLP tablets contain a large mass fraction of excipients; hence, the FTIR spectra exhibited a number of bands associated with excipients. However, it was possible to identify the bands of CLP. For identification of polymorphs, the bands chosen were 841

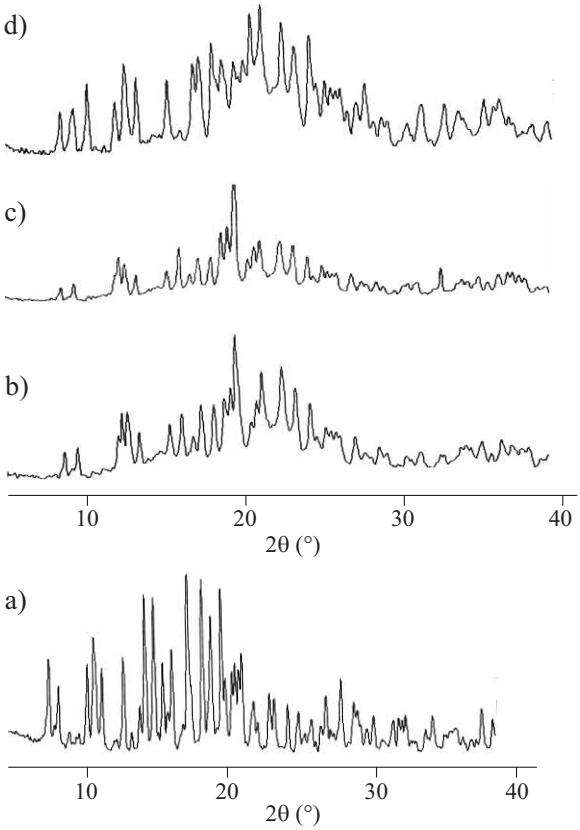

Fig. 7. Comparative XRPD patterns of CLP form II commercial formulations: (a) pure form II powder (b) Caruvin, (c) Noklot, (d) Deplatt.

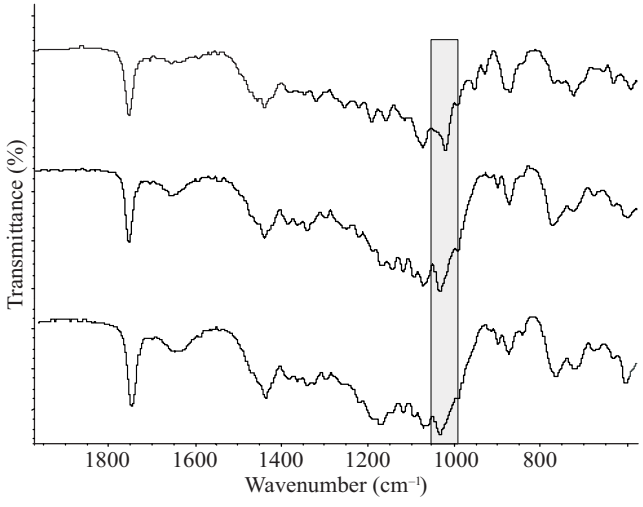

Fig. 8. FTIR spectra of CLP tablets: (a) Caruvin, (b) Noklot, (c) Deplatt. The shaded box shows the peak at 1029 cm^{-1}, characteristic of form II.

and 1029 cm^{-1} for form I and form II, respectively. These characteristic bands have little interference from other bands. All three tablets showed the presence of a band at 1029 cm^{-1}, as shown in Fig. 8. The band at 841 cm^{-1} was not observed. It was concluded from these observations that only form II was present in tablets. The results obtained from FTIR studies were found to support the findings of the XRPD analysis.

CONCLUSIONS

Forms I and II of CLP can be distinguished easily by thermal, crystallographic and spectroscopic methods due to the differences in their melting points, 2θ values and unique vibrational peaks, respectively. Both forms are pure polymorphs and showed no loss during the TGA analysis. The forms are enantiotropically related, as predicted by the heat of fusion and density rules. Differences in their spectral patterns were successfully utilized for the quantification of forms I and II in powder mixtures. The forms undergo no transformations and exhibit no crystal defect generation when exposed to pressure during the KBr pellet formation. Therefore, FTIR is a safe approach for quantification of CLP polymorphs. All the three commercial formulations tested contained form II, as seen by the XRPD pattern and FTIR spectra of the powder obtained from the tablets.

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S A Ž E T A K

Kvalitativna i kvantitativna analiza polimorfa klopidogrel bisulfata

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U radu je opisana karakterizacija i kvantifikacija forme I i forme II klopidogrel bisulfata (CLP), selektivnog i ireverzibilnog inhibitora ADP-inducirane agregacije krvnih pločica. Za karakterizaciju su uporabljene termičke (DSC, TGA, HSM), kristalografske (XRD) i spektroskopske (FTIR) metode. Nakon karakterizacije aktivne supstancije, te metode su dalje uporabljene za identifikaciju polimorfnih formi u ljekovitim oblicima (tri vrste registriranih tableta). Razvijena je i validirana FTIR metoda za određivanje forme I u smjesi polimorfa.

Ključne riječi: klopidogrel bisufat, polimorfi, karakterizacija, FTIR, određivanje

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