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Hydrate modifications of the non-steroidal anti-inflammatory drug diclofenac sodium: Solid-state characterisation of a trihydrate form

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Abstract

Diclofenac sodium is a non-steroidal anti-inflammatory drug widely used in painful and inflammatory diseases. It can exist in different hydrate phases. By exposure to different conditions of temperature and relative humidity can be isolated a trihydrate form never described in literature.

The methods of preparation of the trihydrate form (named DSH3) were described and its physico-chemical properties were investigated. Data from FTIR spectroscopy, X-ray powder diffraction and thermal analysis were used for identification and characterisation of DSH3 in comparison with the anhydrous form (DS, the commercial form) and the hydrate form DSH (obtained by exposure of DS to relative humidity even below 60% and already described and characterised in a previous article of the same authors). Intrinsic dissolution studies were performed to compare the pharmaceutical properties of DS and DSH with DSH3, since this form was accidentally found on the Italian market as active pharmaceutical ingredient (API).

This work stresses the importance of assessing the correct crystalline form also in API of well-established use to guarantee quality, safety and efficacy of the final dosage form.

Furthermore, this study suggests that isomorphic hydrate forms with a different dislocation of water within the crystal structures can exist.

Keywords: Diclofenac sodium; Solid-state; Hydrate forms; Infrared spectroscopy; Thermal analysis; X-ray powder diffractometry; Isomorphic forms

1. Introduction

Pharmaceuticals can exist in various solid forms, which can feature different physical and chemical properties.

A thorough understanding of solid-state characteristics of active substance includes all solid forms of the same molecule that have the same vapour, liquid or solution phase. These solid forms include "true polymorphs", solvates, hydrates, desolvated and amorphous solids [1,2].

This extended definition reflects both the current regulatory expectations for the characterisation of new drug products [3] and the practical need to characterise all solid forms of drug substance that can be produced by standard pharmaceutical processes.

Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules.

It has been estimated that approximately one-third of the pharmaceutical active substances are capable of forming crystalline hydrates. The water molecule, because of its multidirectional hydrogen bonding capability, is also ideal for linking a majority of drug molecules into stable crystal structures [4].

Manufacturing processes may involve the presence of water in the synthesis and/or crystallisation of the drug substance or in the formulation of the drug product through excipients. Dehydration steps may occur in drying, milling, mixing and tabletting processes. Furthermore during storage, drug substances and drug products are submitted to different temperatures and relative

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Table 1
Different modifications of diclofenac sodium cited through the paper with a brief description and the relative abbreviations attributed for practical purposes

Modification	Description	Abbreviation
Anhydrous diclofenac sodium	Supplied by Sigma–Aldrich and used as such	DS
Almost tetrahydrate diclofenac sodium (20.9% water content).	By storing DS in water saturated chamber and described in [17]	DSH
Tetrahydrate diclofenac sodium	Described by other authors [11–15]. Cited by the authors but not studied in this paper: the denomination is assigned only for practical purposes	DSH1
Trihydrate diclofenac sodium (15.9% water content)	By heating DSH in an oven at 40 °C for 3 min or by storing DS in an incubator at 40 (±2)°C and 75 (±5)% RH for 20 min	DSH3
Pentahydrate diclofenac sodium	Described by other authors [16]. Not studied in this paper	–

humidities, due to various climatic conditions, giving rise to unexpected hydration or dehydration aging phenomena [5].

Water can be adsorbed onto the solid surface and/or may be absorbed into the bulk solid structure. The formation of a hydrate form can strongly affect physico-chemical properties such as stability, solubility, dissolution rate and hence bioavailability. Moreover the anhydrous form of a substance is more soluble in water than the corresponding hydrate [5].

Therefore the manufacture and the characterisation of hydrates should be part of the study of the physical properties of drug substances.

Diclofenac sodium, sodium salt of [2-(2,6-dichlorophenyl amino)phenyl] acetic acid is a well-known non-steroidal anti-inflammatory drug available in various pharmaceutical dosage forms and marketed since 1970. It is a potent non-steroidal anti-inflammatory drug with pronounced analgesic and antipyretic properties. It is widely used in the long-term treatment of degenerative joint diseases [6]. It has weak acidic properties (p*K*a about 4) and its solubility depends on the pH of the medium. It is slightly soluble in water, very slightly soluble in phosphate buffer at pH 6.8 and practically insoluble in hydrochloric acid at pH 1.1 [7].

Extensive literature is available for diclofenac sodium anhydrous form (DS) on chemical and spectroscopic characteristics and its crystal structure and thermal behaviour have been also described in Refs. [7–10].

A tetrahydrate form of diclofenac sodium re-crystallised from water or obtained by suspension in boiling water has been previously described in Refs. [11–15] (and indicated as DSH1 by the authors for practical purposes) together with a pentahydrate form crystallised with chitosans and characterised by single crystal X-ray diffractometry [16].

In a recent work the capability of DS to uptake water from the environment-giving rise to a new hydrate form DSH was investigated. This approximately tetrahydrate form was obtained by exposure to water vapour even below 60% relative humidity. It was showed that DSH has physico-chemical properties different from DS that can affect the shelf life, the process behaviour and in the end, the performance of the finished product [17].

The present work resumes the issue of hydration of diclofenac sodium and reports the preparation and the characterisation of a new hydrate form, named DSH3.

The physico-chemical and pharmaceutical properties of the new form were compared with the anhydrous form DS (the commercial form and the only one complying with the Ph. Eur. CRS requirements) and with the hydrate form DSH.

Furthermore this study suggests that isomorphic hydrate forms of DSH3 with differing crystallinity and different dislocation of water within the crystal structures can exist.

Table 1 summarises the different modifications of diclofenac sodium cited through the paper with a brief description and the relative abbreviations attributed for practical purposes.

2. Materials

Diclofenac sodium reference substance was supplied by Sigma–Aldrich (minimum 99.5% purity by the Ph. Eur. HPLC assay procedure) and was used without further purification.

Analytical grade organic solvents were purchased from Sigma–Aldrich (Milan, Italy).

Analytical grade potassium dihydrogen phosphate, sodium hydroxide, and methanol were purchased from Sigma–Aldrich (Milan, Italy). Deionised water obtained from an Ultra Pure Water System Type Integra (SG, Barsbüttel, Germany) was used for the preparation of dissolution medium.

3. Methods

3.1. Preparation of the different modifications

Diclofenac sodium supplied by Sigma–Aldrich was re-crystallised from various organic solvents of different polarity in order to check its capability to give rise to different crystalline modifications, both polymorphs and solvates.

In each experiments about 50 mg were dissolved in an appropriate amount of water, acetone, isopropanol, ethyl acetate, absolute ethanol, 95% aqueous ethanol, methanol and absolute ethanol/95% ethanol/ethyl acetate (1:1:5) mixture. Re-crystallisation was first obtained by evaporation of solvent at room temperature, then it was forced either by evaporating the solvent on a boiling water bath or by crystal precipitation on an ice bath.

Efforts were made to obtain different modifications also by varying environmental conditions such as temperature and relative humidity using a saturated chamber without a drainage system or an incubator (M80-RH Incubator, MPM Instruments, Italy).

The resulting samples were tested by DSC, FTIR and XRDP to assess the crystalline form and by TGA for water content.

Identification of water as solvent of crystallisation was performed at first by TG coupled with FTIR and then by ^{1}H NMR spectroscopy.

The RH was checked by a digital thermo-hygrometer (Escort Junior Data Logger, Escort Data Logging Systems Ltd., Auckland, New Zealand).

HPLC analysis by the Ph. Eur. assay procedure performed on the forms obtained by forced hydration or heating indicated that no degradation had taken place.

3.1.1. DS

Diclofenac sodium supplied by Sigma–Aldrich is the anhydrous form named DS by the authors for practical purpose and it was used as such.

3.1.2. DSH

DSH, the hydrate form with a 20.9% water content, was routinely prepared by storing DS in a water saturated chamber without a drainage system (at relative humidity of 100%) at room temperature for 24 h as previously reported [17].

3.1.3. DSH3

DSH3 (water content about 16%) was obtained either by heating DSH in an oven at 40 °C for 3 min or by storing DS in an incubator at 40 (±2)°C and 75 (±5)% RH (ICH accelerated storage conditions [18]) for 20 min. The second method was selected for the routinely preparation of DSH3 because the hydration taking place in more controlled and reproducible conditions.

3.2. Characterisation of DSH3 in respect to DSH and DS

FTIR spectra of DS, DSH and DSH3 were obtained using a mull in liquid paraffin (nujol), a dispersion (0.5%) in alkali halide (KBr) disk and directly on untreated powder by means of a Perkin-Elmer FTIR spectrometer equipped with an ATR (attenuated total reflection) sampling system (Golden Gate, Specac, UK). Spectra were recorded at room temperature from 4000 to 370 cm^{-1} on a Perkin-Elmer System 2000 spectrometer. For each sample 16 scans were collected at a resolution of 4 cm^{-1}.

Variable temperature FTIR experiments were performed in ATR with the Heated Golden Gate Controller (Specac, UK).

X-ray powder diffraction (XRPD) patterns were obtained with a Philips P.W. 1729 diffractometer equipped with a personal computer for data acquisition and analysis (software Philips APD) in the 2θ range between 5° and 35° using Cu Kα radiation-Ni filtered (40 kV; 30 mA). The step scan mode was performed with a step width of 0.01° at a rate of 1 step s^{-1}. Samples were mildly pre-ground with a pestle in an agate mortar to make them homogeneous, to control crystal size and to minimise preferred orientation effects.

DSC curves were recorded using a Perkin-Elmer DSC7 instrument and a Pyris 1 DSC. Approximately 1 mg of sample were weighed into a DSC pan. The DSC profiles were recorded at 10 °C min^{-1}, under nitrogen flux, from 25 °C (DSC7) or 5 °C (Pyris 1 DSC) to about 150 °C. The experiments were conducted using closed pans with a cover hole made by the Perkin-Elmer's Accupik system. The DSC temperature scale was calibrated using extrapolated onset temperatures of the fusion endotherms of indium and lead pure standards, heated at the same rates used for the samples. Each DSC experiment was repeated at least three times. Programmed heat–cool cyclic DSC studies were also performed at 10 °C min^{-1}.

Thermogravimetric curves were recorded with a Perkin-Elmer Pyris 1 TGA at the heating rate of 1 °C and 10 °C min^{-1}. Approximately 5 mg of substance were weighed. The cooling accessory C6 chiller (Perkin-Elmer) allowed starting from 15 °C. A temperature calibration of the thermogravimetric apparatus was performed measuring the magnetic transition temperature of two standards, alumel and nickel. Each TGA experiment was repeated at least three times.

3.3. Intrinsic dissolution on DS, DSH and DSH3

For all dissolution tests the Distek Intrinsic Dissolution Apparatus was used (USP II, paddle method) employing 900 ml of simulated intestinal fluid without pancreatin (SIF [19]) at 37 ± 0.5 °C and at 50 rpm. Preliminary studies showed these conditions were the most discriminating ones. The Distek holder was immersed, pellet side up, into the flat bottom dissolution vessel. Pellets were prepared compressing 100 mg of powder (as anhydrous base) in a Perkin-Elmer hydraulic press using an 8 mm punch and die set.

Compression effect on solid-state properties was evaluated by IR, DSC, TGA and X-ray diffractometry. Analysis of the compressed discs by FTIR confirmed that the crystal form of the original powder was retained following the compression procedure.

All dissolution runs were carried out in triplicate, under sink conditions. The linear portion of each dissolution profile, i.e., before depletion of the disc and alteration of its surface area, was used to derive the intrinsic dissolution rate (IDR).

The dissolution system was fitted with a DISTEK PREMIERE 5100 dissolutor (Distek Inc., NJ, USA), a HP 89092A seven-channel peristaltic pump (Agilent Technologies Italia S.p.A., Roma, Italy), PC directed control through the Idis EE software (Icalis Data System Ltd., UK). Released percentages of the active ingredient were automatically measured every 5 min up to 150 min at 276 nm using a HP 8452A diode array detector (Agilent Technologies Italia S.p.A.) equipped with a linear seven-cell transporter. The flowcell pathlength was 1 mm. Filtration of aqueous samples was performed on-line on Whatman GF/C (1.2 μm) filters (Whatman, Kent, England). Check for adsorption to the filters revealed no significant loss of drug.

4. Results and discussion

4.1. Preparation of the different modifications

Efforts were made to obtain different modifications of the anhydrous phase by crystallisation from numerous organic solvents.

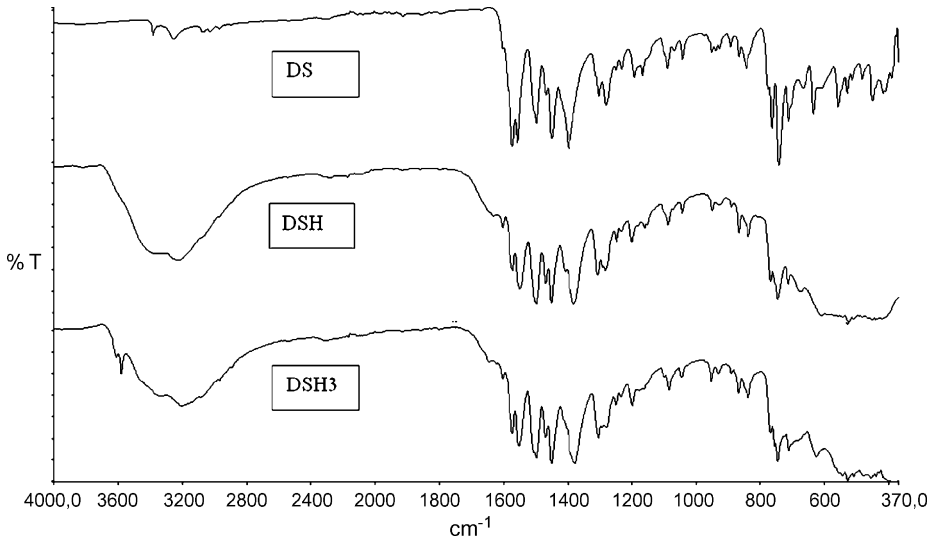

Fig. 1. FTIR spectra by ATR of DS, DSH and DSH3.

Polymorphs of DS could not be isolated either by crystallisation or by dehydration of DSH.

Crystallisation experiments showed that the solvent-mediated hydration could give rise to hydrate forms different from DSH (obtained by water vapour exposure and previously described in Ref. [17]). The crystallisation from boiling water at room temperature gave rise to the tetrahydrate form DSH1 (already described by other authors [11–14]).

The crystallisation of DS solutions in isopropanol or ethyl acetate by evaporation of solvent at room temperature gave rise to the trihydrate form DSH3. It could be also produced by lyophilisation of a DS water solution but with a very low recovery.

The other crystallisation conditions gave rise to mixtures of hydrate forms and DS as checked by FTIR spectra, TG profiles and X-ray diffraction patterns.

The environmental conditions, namely temperature and relative humidity, at which DS and DSH were stored in the solid-state affected the form of the resulting solid: in fact the trihydrate form DSH3 was generated either by heating DSH at 40 °C for a few minutes or by storing DS in an incubator at 40 ± 2 °C 75 ± 5% RH (ICH accelerated storage conditions [18]) for 20 min. However the temperature of heating seems to be the key parameter to obtain DSH3 instead of DSH.

DSH3 shows crystals of smaller size and more reproducible thermal behaviour/XRPD pattern when prepared via solid state transformation (routine method of preparation; see 3.1.3) than when its crystals are grown from solution by crystallization.

In fact the DSH3 obtained by crystallisation showed the same FTIR spectrum, but slightly diverse thermal behaviour and an X-ray diffraction powder pattern different in peak intensities and peak intensity ratios from that one obtained by the chosen method of preparation.

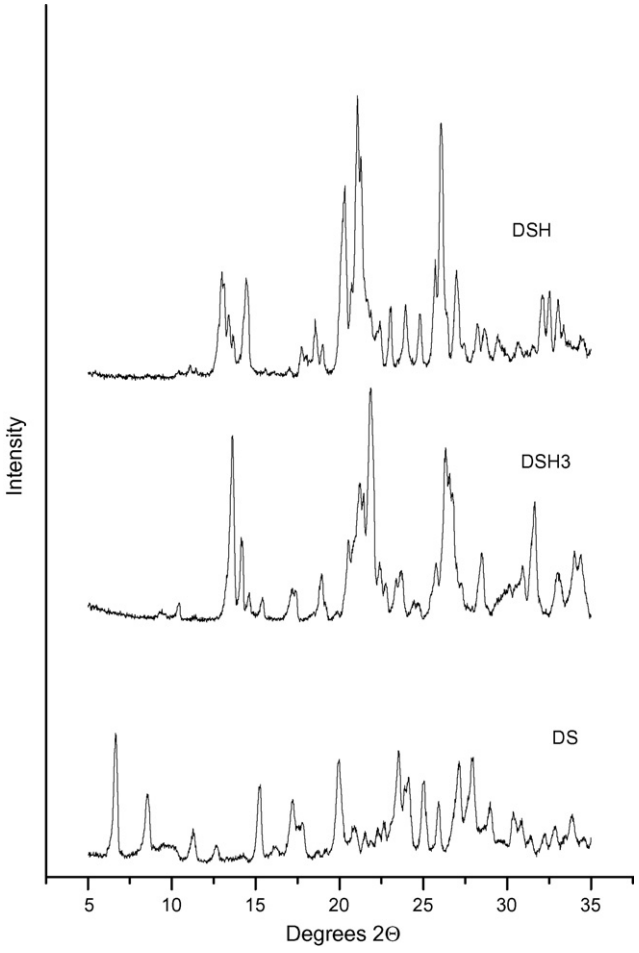

Fig. 2. XRDP patterns of DS, DSH and DSH3.

4.2. FTIR experiments

The trihydrate form DSH3, was characterised in comparison with DS and DSH.

DSH3 crystalline structure seemed to be neither altered nor destroyed by pelletting. The FTIR spectra were obtained directly on the powder by ATR, nujol mull and as dispersion in KBr pellet.

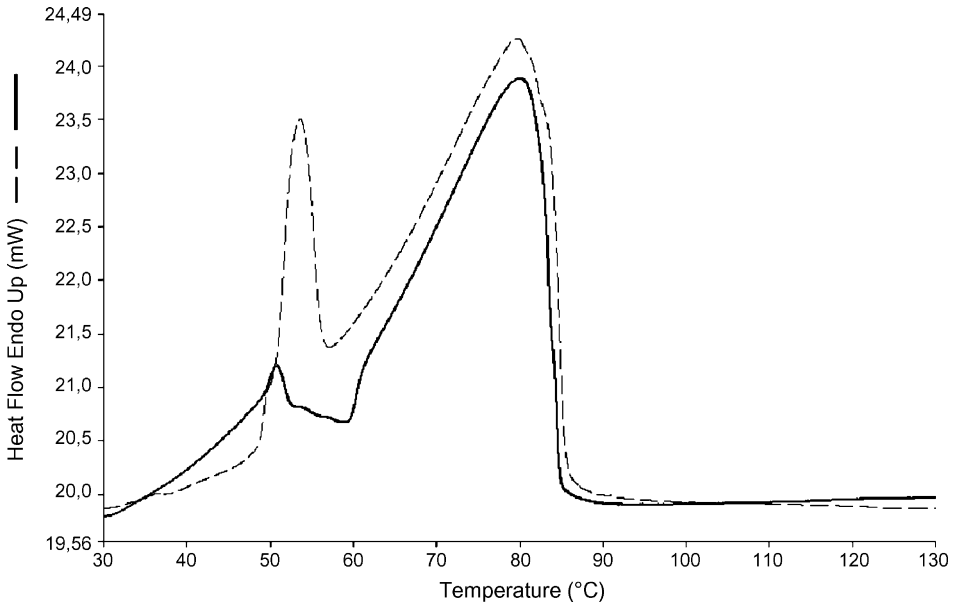

Fig. 3. DSC profiles of DSH (solid line) and DSH3 (dashed line), 10 °C min^{-1}, scan rate; heat flow, endothermic scale.

FTIR spectroscopy was a useful tool to distinguish the new form from DS and DSH:DSH3 exhibited significant differences in the observed vibrational transitions in the 3600–2000 cm^{-1} range of frequencies (Fig. 1).

By variable temperature IR spectroscopy DSH3 retains its own spectrum up to 60 °C, then in the 60–70 °C range gives rise to an unstable intermediate form, that after cooling come back to the DSH3 structure (data not shown).

4.3. XRDP experiments

DSH3 could be easily distinguished from DS and DSH by XRDP (Fig. 2).

It showed differences both in positions of the peaks and intensity ratios that could not be attributed to a preferred orientation of crystal growth. Samples were mildly pre-ground with a pestle in an agate mortar to make them homogeneous and to minimise preferred orientation effects.

Differences in X-ray diffraction patterns indicated different arrangements of diclofenac sodium molecules in the crystal lattice of the hydrate forms. DSH3 exhibited numerous different peak positions distinguishing itself from the anhydrous form and from the hydrate forms previously reported [11–17].

4.4. DSC and TG experiments

The thermal behaviour of DS and DSH has already been extensively reported [9,10,17].

DSC curves of DSH3 in comparison with DSH are showed in Fig. 3.

Hydrate form DSH3 displayed a DSC profile with two endotherms very close to each other in the 40–110 °C range (Fig. 3), before the fusion with decomposition that is superimposed to the one of anhydrous form DS. The first sharp endotherm showed an onset temperature of 50.4 ± 0.3 °C (peak temperature: 55 ± 2 °C) and the second bigger and broader one showed a peak temperature of 82 ± 2 °C. The total enthalpy was of 465 ± 3 J g^{-1}.

The DSH3 TG curve exhibits a weight loss of about 15.9 ± 0.2% from 30 to 115 °C, at a scanning rate of 10 °C min^{-1} The phenomenon started slowly from 30 °C reaching a maximum between 90 and 100 °C (data not shown). The water content of DSH3 is in agreement with an approximately trihydrate stoichiometry.

A TG scanning rate of 1 °C min^{-1} allowed distinguishing an earlier leakage of water from the crystals at lower temperature (Fig. 4).

Thermal behaviour suggested that DSH3 could be classified as a channel type hydrate. In fact the first weight loss is probably originated by the escape of water molecules from

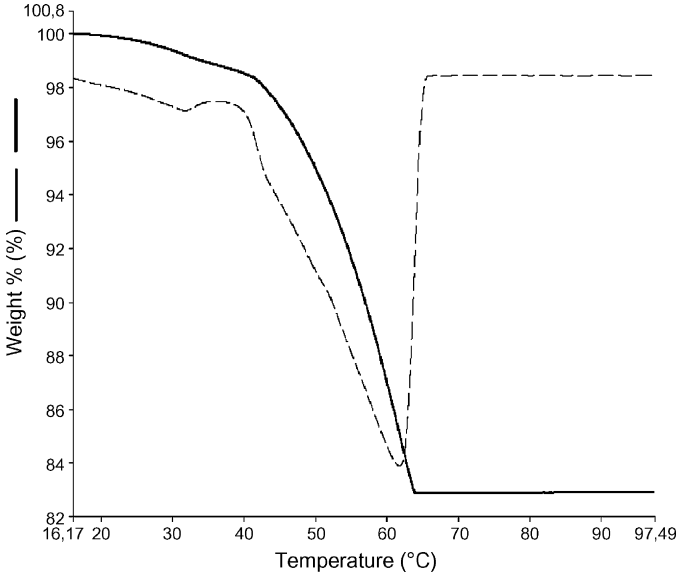

Fig. 4. TG profile (1 °C min^{-1}) with derivative (dashed lines) of DSH3.

the outer channels near the surface, while the second one, at higher temperature, represents the overlapped phenomena of the fusion of the solvate crystals and evaporation of main portion of bound water from the inner channels. The channel structure seems to be very common to all the alkaline diclofenac salts [14].

4.5. IDR experiments

DSH3 has the same thermal behaviour, water content, IR spectrum and X-ray diffraction pattern of a commercial lot of diclofenac sodium found on the Italian market. This lot had been marketed and used as API, although its characteristics such as IR spectrum and water content did not comply with Ph. Eur. CRS specifications. This lot was probably originated from an improper GMP control during manufacturing process (crystallisation step or drying process) or during shelf life storage with an unsuitable packaging.

Consequently intrinsic dissolution studies were performed to further characterise DSH3 in respect to DS and DSH.

Fig. 5 shows the mean release profiles for DS, DSH and DSH3 in the selected dissolution medium. Remarkable differences in slope and extent can clearly be noticed: as expected [5,20] the relative intrinsic dissolution rate order is: DS > DSH3 > DSH.

From this IDR study the solubility ratio between the three forms was estimated [21].

Assuming the diffusion layer in aqueous solution for DS, DSH and DSH3 are equal and that sink conditions apply, the difference in intrinsic dissolution rate is explained by differences in saturation solubility of the drug. Thus the IDR values were related to the saturated solubility values as follows:

$$\frac{\mathrm{IDR}^{\mathrm{DS}}}{\mathrm{IDR}^{\mathrm{DSH}}} = \frac{C_{\mathrm{S}}^{\mathrm{DS}}}{C_{\mathrm{S}}^{\mathrm{DSH}}}$$

$$\frac{\mathrm{IDR}^{\mathrm{DS}}}{\mathrm{IDR}^{\mathrm{DSH3}}} = \frac{C_{\mathrm{S}}^{\mathrm{DS}}}{C_{\mathrm{S}}^{\mathrm{DSH3}}}$$

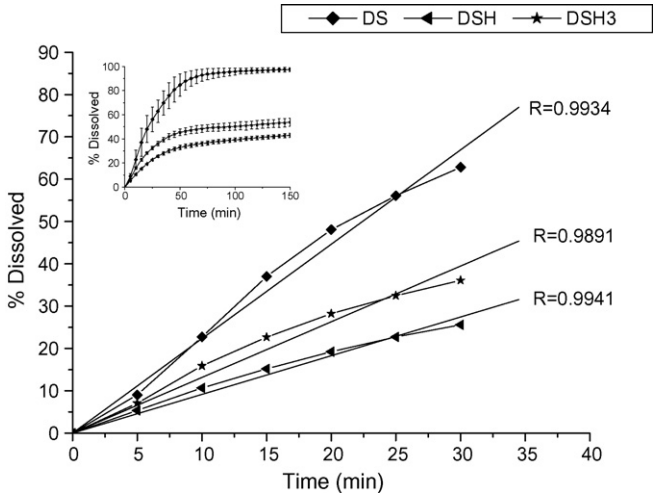

Fig. 5. Mean intrinsic dissolution profiles of compressed discs of DS, DSH and DSH3 in SIF, at 37 °C, 50 rpm.

where C_s denotes the saturation solubility. The IDR values were calculated from the initial linear portion of the dissolution plot as 1.1 mg min^{-1} cm^{-2} (DS), 0.46 mg min^{-1} cm^{-2} (DSH) and 0.65 mg min^{-1} cm^{-2} (DSH3), which suggest that DSH and DSH3 solubility is, respectively, about 2.5 and 1.7 times lower than that of DS.

4.6. Preliminary stability studies

Although systematic studies have not yet been performed, DSH3 seemed unaffected by mild grinding or pelletting. Preliminary grinding experiments showed that DSH3 could decrease its water content to about 14.5% without altering its crystal structure.

Experimental findings suggest the existence of isostructural hydrates of DSH3 with the same or similar X-ray diffraction patterns but a different amount and dislocation of water molecules in the crystal lattice. Some of these are located in discrete crystal sites, more tightly bound and relatively immobile, while others are trapped in cavities (clathrate type inclusion) and could be highly mobile. This hypothesis is confirmed by the results of the aforementioned grinding experiments and by the evidence that samples with the same X-ray diffraction pattern often showed slightly different DSC and TG profiles.

While highly sensitive to differences in crystal structures, X-ray powder diffraction may be unaffected by the position of non-structural water. Thermal analysis, instead, is more informative about difference in location of included water [22].

Although systematic stability studies have not yet been completed, preliminary results are useful to assess the physical stability of the different forms and to assume a possible relationship between them.

DS samples were stored in controlled conditions of temperature and humidity to check its tendency to uptake water from the environment and its physical stability.

As previously reported the storage of DS at RH of 59% or 98% at room temperature and at RH of 100% without drainage system at 20 and 30 °C gave rise always to the same hydrate form DSH [17].

DS stored for few minutes in an incubator at 40 °C and 75% relative humidity (ICH accelerated storage conditions) gave rise to DSH3.

DS stored in open air for various months gave rise to DSH.

Furthermore samples of DS stored at −20 °C for more than 1 year gave rise to DSH.

The hydrate form DSH is stable at room temperature for at least 2 years. On heating for 3 min at 40 °C DSH is completely transformed in DSH3 and at 50 °C it gives rise to DS as checked by FTIR, DSC and TG analysis.

Only one lot of DSH after storing for 30 months on open air was completely transformed in DSH3. As the method of preparation and storage conditions of this lot was the same of those others that retained the original characteristics, this transformation has been attributed to an accidental contamination of the lot with some crystals of DSH3 form.

However, as this lot belongs to the early production of DSH, it could not be excluded that a solid–solid transition DSH-DSH3 by aging could occur.

DSH3 was stable for at least 1 year. However the API found on the market with the same crystalline form of DSH3 was stable for at least 2 years.

However the complete transformation of the aforementioned lot of DSH into DSH3 after 30 months (probably after accidental seeding or by aging) suggested that DSH3 is the most stable of the known hydrate forms.

5. Conclusions

This study elucidates the hydrate form diversity of diclofenac sodium. In particular it explores the solid-state properties and physico-chemical characteristics of a new hydrate form DSH3. DSH3 can be produced by varying environmental conditions on storage of DS (40 °C and 75% RH) or by heating DSH (at 40 °C for few minutes).

The almost trihydrate form was characterised by thermal analysis (DSC and TGA), FTIR spectroscopy and X-ray powder diffractometry.

Preliminary grinding experiments and the accidental finding of forms with the same or very similar X-ray powder diffraction patterns, but different water content suggested that DSH3 can exist in different isomorphic hydrate forms with a different dislocation of water as assessed by DSC profiles.

As a commercial lot of diclofenac sodium discovered on the Italian market was found to have the same crystal form of DSH3, intrinsic dissolution studies were performed to further characterise DSH3 in respect to DS and DSH. This lot was probably originated from an improper GMP control during manufacturing of API. Intrinsic dissolution study demonstrates significant differences among the forms (IDR rate order is: DS > DSH3 > DSH) and the IDR values suggest that DSH and DSH3 solubility is, respectively, about 2.5 and 1.7 times lower that of DS.

Preliminary stability results are useful to assess the physical stability of the different forms and to postulate a reasonable relationship among them. Experimental studies suggest that DSH3 was the most stable. Although DSH was demonstrated to be stable at room temperature for at least 2 years, it could not be excluded a tendency to solid–solid transition into DSH3 by aging.

The anhydrous form DS, that is the only one complying with the Ph. Eur. CRS requirements, as previously reported tends to uptake water from the environmental in standard conditions (25 °C and RH even below 60%) giving raise to DSH, an almost tetrahydrate form. Furthermore the trihydrate form DSH3 could arise from DS or from DSH when unsuitable environmental conditions are set during drying process or shelf-life storage.

The presence of different hydrate modifications or mixtures of them alters the water content and then the assay and also affects the solubility, the technological properties and the stability of API powder.

Therefore manufacturers of generic products should not underestimate the importance of assessing of crystal form and solid-state properties of diclofenac sodium, because only the knowledge of the physical characteristics of the API can assure the robustness of manufacturing process, batch-to batch reproducibility and bioavailability of the finished product.

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