EVALUATION OF HYDRATION PHENOMENA IN COMMERCIAL TABLETS AND IN-LAB FORMULATIONS CONTAINING DICLOFENAC SODIUM

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INTRODUCTION

Diclofenac sodium is a non-steroidal anti-inflammatory drug widely used in painful and inflammatory diseases. It was previously demonstrated that by exposure to relative humidity even below 60% at 25 °C, the anhydrous form of diclofenac sodium (DS) gives rise to an hydrate form (DSH) [1].
The aim of this work was to verify if DS contained in medicinal products may uptake water from the environment thus transforming into DSH.
Various medicinal products were stored into an incubator under different temperature and humidity conditions and DS hydration was monitored.
Subsequently dissolution studies were performed to verify if DS hydration is capable of influencing the dissolution profile of the medicinal products.

EXPERIMENTAL METHODS

Materials

Diclofenac sodium reference substance was supplied by Sigma-Aldrich (Milano, Italy - minimum 99.5% purity by the Ph. Eur. HPLC assay procedure) and used without further purification.
Analytical grade potassium dihydrogen phosphate, sodium chloride, sodium hydroxide, hydrochloric acid and methanol were purchased from Sigma-Aldrich.
Deionised water obtained from an Ultra Pure Water System Type Integra (SG, Barsbüttel, Germany) was used for the preparation of dissolution media.
Diclofenac sodium prolonged-release tablet formulations were obtained from pharmacies in the national market. They all contained 100 mg of diclofenac sodium but greatly differed as concerns the excipients composition.

Methods

To verify the DS hydration in the medicinal products the following techniques were employed:

- Differential Scanning Calorimetry (DSC): DSC curves were recorded using a Perkin Elmer DSC7 instrument. Sample weight ranged from 1.5 to 5 mg . The DSC profiles were recorded at 10 °C min^{-1}, under nitrogen flux, from 25 °C to about 150 °C. The experiments were conducted using closed pans with a hole made by the Perkin Elmer's Accupik system.
- Thermo-Gravimetry (TG): thermogravimetric curves were recorded by a Perkin Elmer Pyris1 TGA at the heating rate of 1 °C min^{-1}. Approximately 10 mg of substance were weighed. The experiments were conducted using closed pans with a cover hole made by the Perkin Elmer's Accupik system.
- Infrared Spectroscopy (FTIR): FTIR spectra were obtained directly on untreated powder by means of an ATR sampling system (Golden Gate-Specac, England) coupled with a Perkin Elmer FTIR System 2000 spectrometer (Perkin Elmer, USA) and by dispersing the powder in mineral oil. Spectra were recorded at room temperature from 4000 to 370 cm^{-1}. For each sample 16 scans were collected at a resolution of 4 cm^{-1}.

To verify if the DS hydration in the medicinal products can influence the dissolution profiles, the selection of the dissolution testing conditions was based on EMEA guidelines [2,3].
For all dissolution tests the European Pharmacopoeia apparatus 2 was used (paddle method), employing 900 ml of dissolution medium at a temperature of 37 ± 0.5 °C and a rotational speed of 100 rpm in simulated intestinal fluid (SIF) without pancreatin (pH 6.8) according to USP 28 [4]. This medium was chosen for its capability to discriminate among the previously studied formulations [5].

The dissolution system was fitted with a DISTEK PREMIERE 5100 dissolutor (Distek Inc., NJ, USA), an HP 89092A 7-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 at 276 nm using an HP 8452A diode array detector (Agilent Technologies Italia S.p.A.) equipped with a linear 7-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.

Calibration curves for diclofenac sodium reference substance were obtained by measuring the absorbance at 276 nm. Standards were prepared in the concentration range 0.001-0.17 mg/ml. Absorptivity values were calculated and employed in the analysis software. The linearity of the calibration curves was

confirmed over the concentration range 5 to 150 % dissolution of the drug.

RESULTS AND DISCUSSION

The various medicinal products investigated showed the tendency to undergo hydration when stored at 25°C and 60% relative humidity. DS seemed to transform into DSH after 7-10 days on average. The process came to an end after several weeks with the DS-DSH transition almost complete. In fig.1 the DSC curves of one of the investigated products are depicted: the thermal profile shows the hydration of DS after 10 days and after 50 days. Preliminary TG and FTIR data confirmed this hypothesis.

To verify if this hydration process may influence the dissolution profile, dissolution tests were performed for each medicinal product:

1. before hydration
2. after the hydration process was complete.

All the products showed marked differences in release profiles between 1 and 2 as for the sample reported in figure 2.

In fact after hydration in-lab formulations and commercial tablets showed a lower release rate during both the initial and the final tract of the dissolution curve. The observed differences in dissolution profiles can be ascribed to a combination of factors: the decrease of diclofenac sodium solubility due to the hydration, the change of hardness and friability of the tablets, the variation of excipient characteristics.

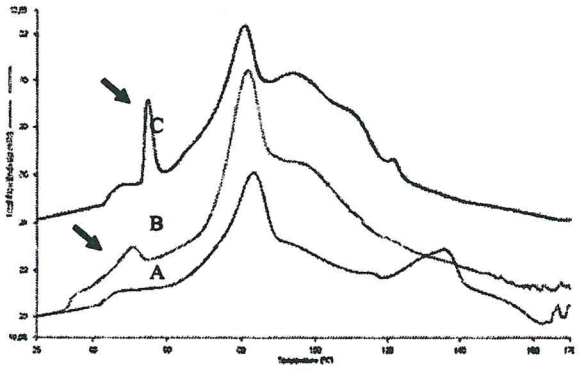

Figure 1. *DSC curves of a medicinal product chosen as an example. The curve A refers to the anhydrous product before storage in the incubator; the curve B refers to the product stored for 10 days in the incubator; the curve C refers to the same product stored for 50 days in the incubator. The arrows show the growing DSH endotherm.*

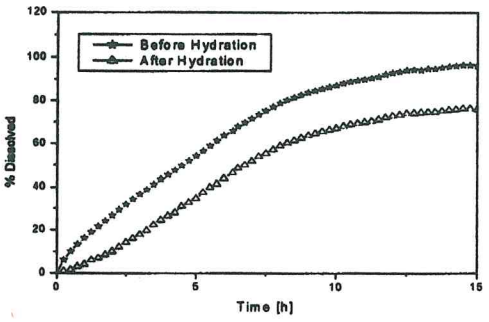

Figure 2. *Dissolution profiles of diclofenac sodium commercial tablets.*

CONCLUSIONS

The obtained data show a tendency of the commercial tablets and the in-lab formulations containing diclofenac sodium to uptake water from the environment and thus change their release characteristics considerably.

The differences in release characteristics before and after hydration suggest likely implications for the bioavailability of the active ingredient thus involving the opportunity to keep their storage conditions under control. Nevertheless further advice would be needed to determine whether the observed *in vitro* differences are of any clinical significance.

ACKNOWLEDGMENTS

The Authors are grateful to Mr. Stefano Alimonti and Mrs. Laura Romanini for their technical assistance.

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