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SOME PRACTICAL FINDINGS FOR TA IN ORGANIC AND PHARMA INDUSTRY

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Abstract

Routine tests by TG and DSC with the common heating rates of 10°C min^{-1} show large batch-to-batch variations for certain hydrate compounds. By additional measurements and changing to a gradient of 1°C min^{-1} most differences are wiped out giving almost uniform characters.

A possible correct interpretation of the solid state measurements can give useful structure information in an early stage of a drug development. In these cases the rather rare tunnel- and zeolite-type structures are responsible for the observed dynamic variations.

Keywords: hydrates, zeolite and tunnel structures

Introduction

In the drug design process most molecules are prepared as salts and very often as hydrates i.e. pseudosolvates. The main reason for this is to obtain substances with good water solubility and with good stability in moist environments, before less soluble ones.

In some previous papers and meetings [1–4] certain ageing phenomena observed by TA-methods have been discussed which give drastic effects to the crystalline hydrate compounds due to metastable conditions.

This report deals with the interpretation of the results from thermal analysis which at first sight indicated materials with complicated phase composition.

Two different monohydrate samples were chosen and crystallize morphologically almost identical as thin flakes with two dimensions sometimes several mm in length. The unit cell dimensions revealed from XRD measurements are shown in Fig. 1.

Experimental

Remoxipride·H_2O

While testing the first production serie of 30 batches these could be grouped together in five main categories according to the TG and DSC characters obtained with a heating rate of 10°C min^{-1}, Fig. 2. However, all diagrams are different from each other.

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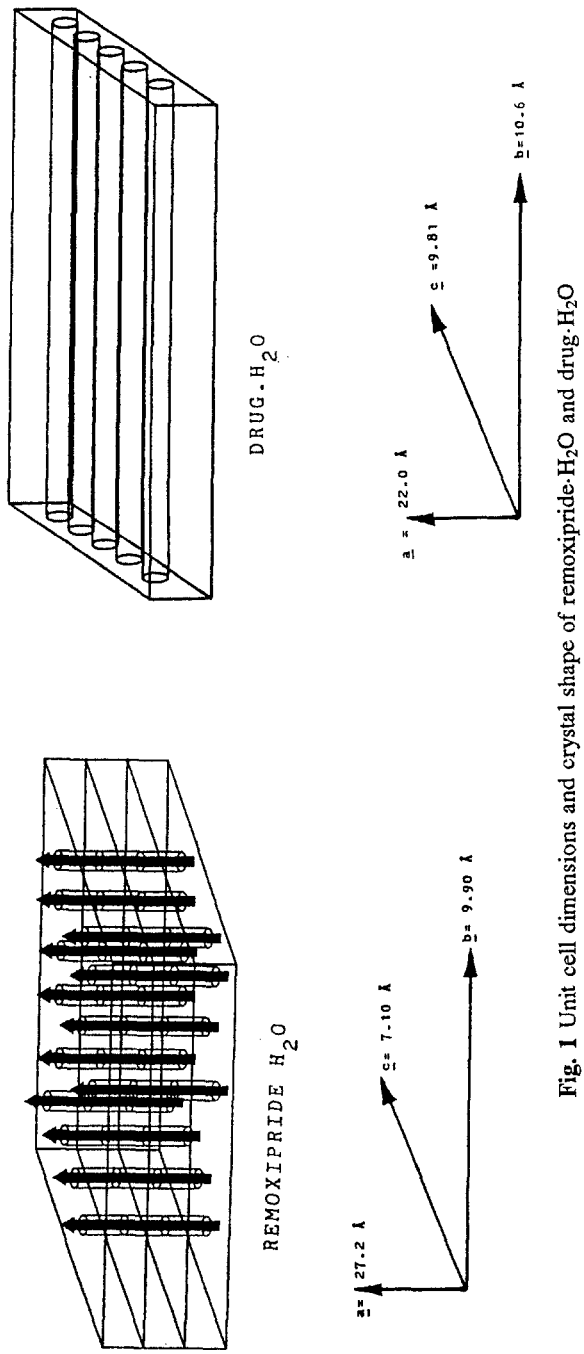


Fig. 1 Unit cell dimensions and crystal shape of remoxipride·H_2O and drug·H_2O

All the samples were also analysed according to Karl Fischer and found to be strictly monohydrates.

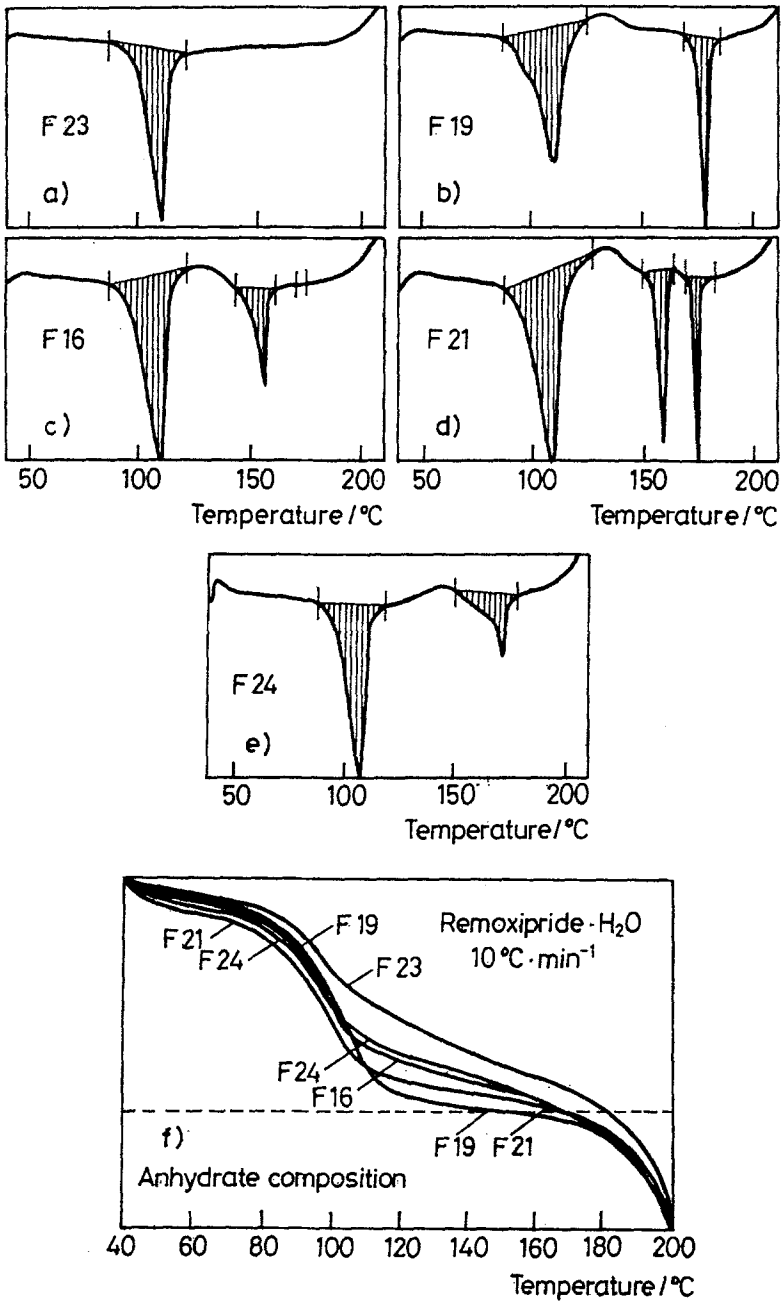


Fig. 2 Remoxipride·H_2O TG and DSC characteristics with a heating rate of 10°C min^{-1}

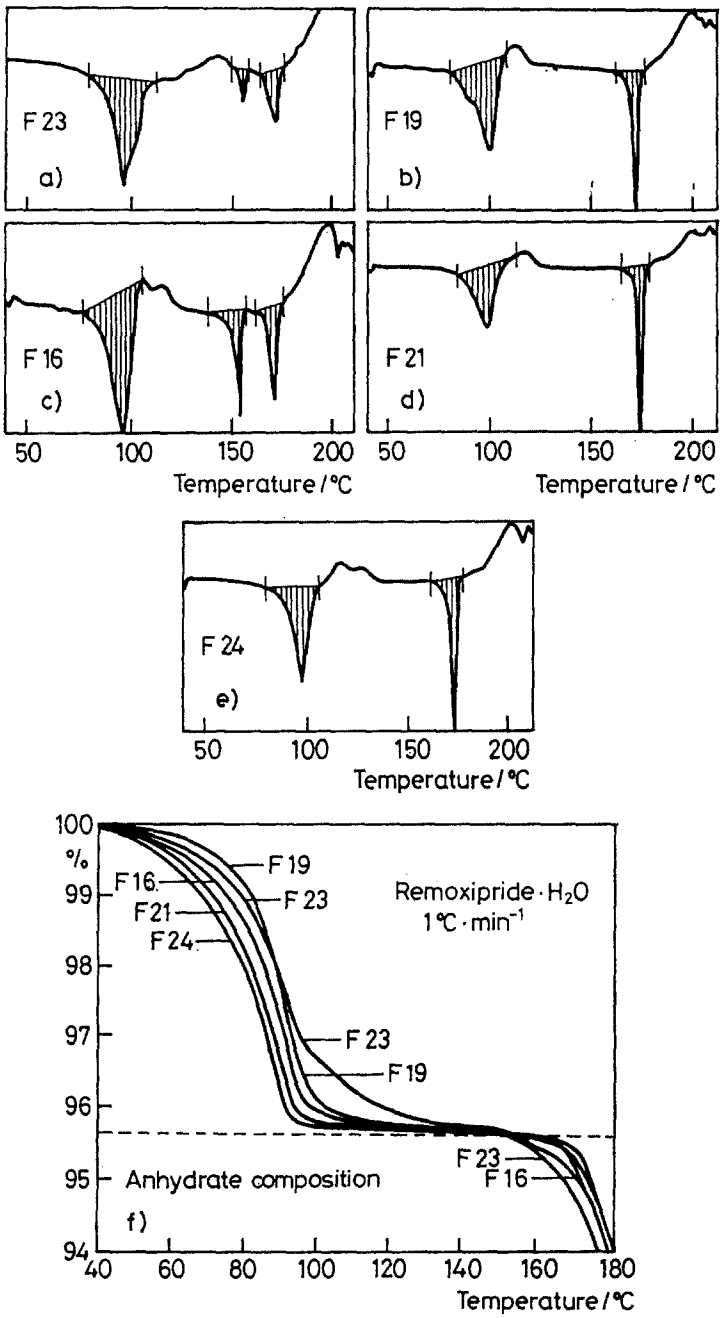


Fig. 3 Remoxipride·H_2O TG and DSC characteristics with a heating rate of 1°C min^{-1}

A phase analysis by XRD powder method reveals one possible indexing only according to the single crystal data [5] for the title compound. No extra signals nor any distortion from the unit cell dimension are registered.

By analysing the same group of materials with a heating rate of 1°C min^{-1} only, we arrive at the results found in Fig. 3. The main discrepancies are wiped out and the thermal characteristics become almost uniform. From the crystal structure Fig. 4 with the projection perpendicular to the flakes we can see parallel tunnels like a honeycomb. The water molecules are placed in shallow cavities on the sides of these tunnels.

If the dehydration/heating round the temperature interval 100–120°C is fast, variable amounts of water molecules are trapped in the lattice. They form new complex high temperature systems which give rise to the DSC signals found in Fig. 2.

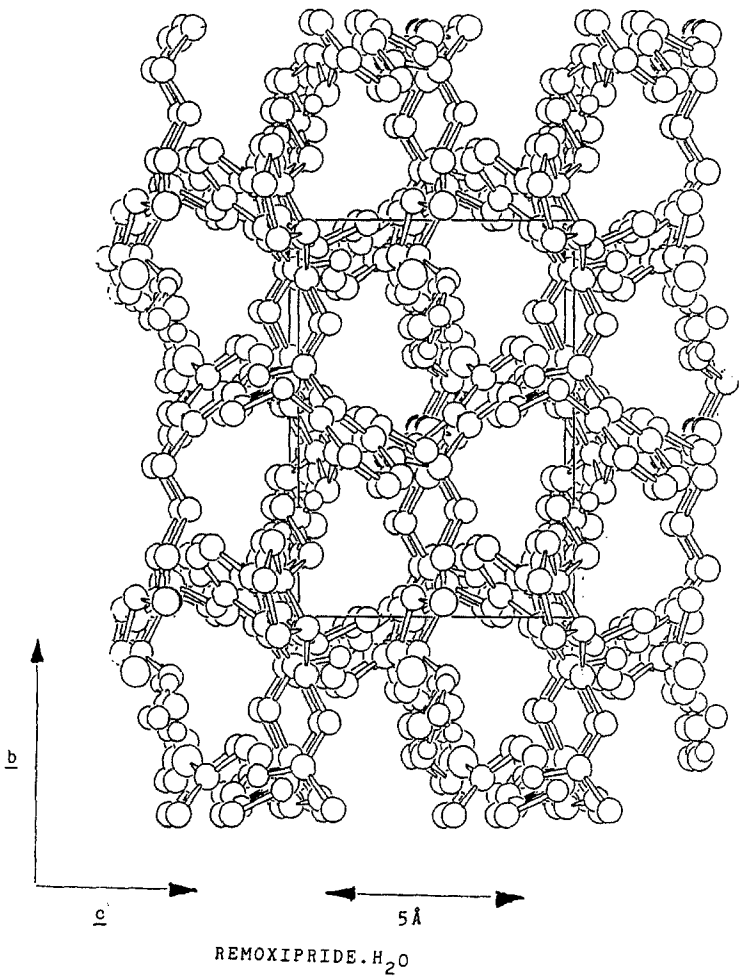
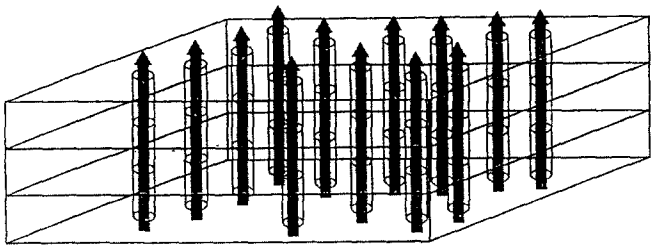
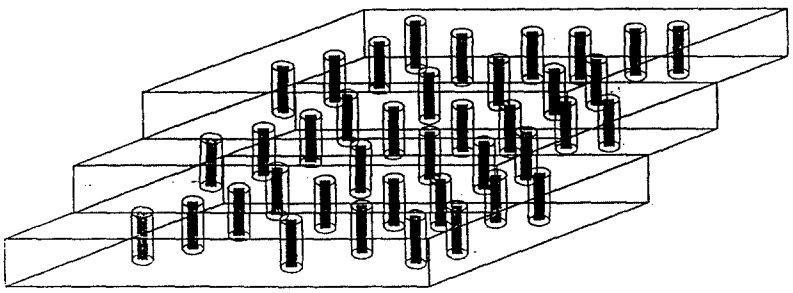


Fig. 4 The crystal structure of remoxipride·H_2O perpendicular to the bc-plane



REMOXIPRIDE.H_2O A "good" crystal.



REMOXIPRIDE.H_2O A "bad" crystal

Fig. 5 Example of a 'good' and a 'bad' crystal of remoxipride·H_2O

Mechanical stress or nonequilibrium conditions are other factors which prohibit water to be expelled stoichiometrically and thus produce non reproducible thermal diagrams.

The bc-plane, where faults easy can be introduced, is thus perpendicular to the holes, Fig. 5.

Drug-monohydrate

In these crystals the infinite tunnels run parallel to the thin flakes i.e. perpendicular to the ones previously discussed.

From the TG and DSC characteristics, Fig. 6, the dehydration process between 80 and 120°C is also variable among different preparations registered with a fast heating rate i.e. 10°C min^{-1}.

A slow temperature increase, 1 or 2°C min^{-1}, give almost the same appearance. The differences are mainly due to crystal dimensions.

A detailed crystal structure analysis is planned to reveal the atomic and molecular arrangement. The results will be published elsewhere including the interpretation of the strange reversible dynamic decomposition and restoration.

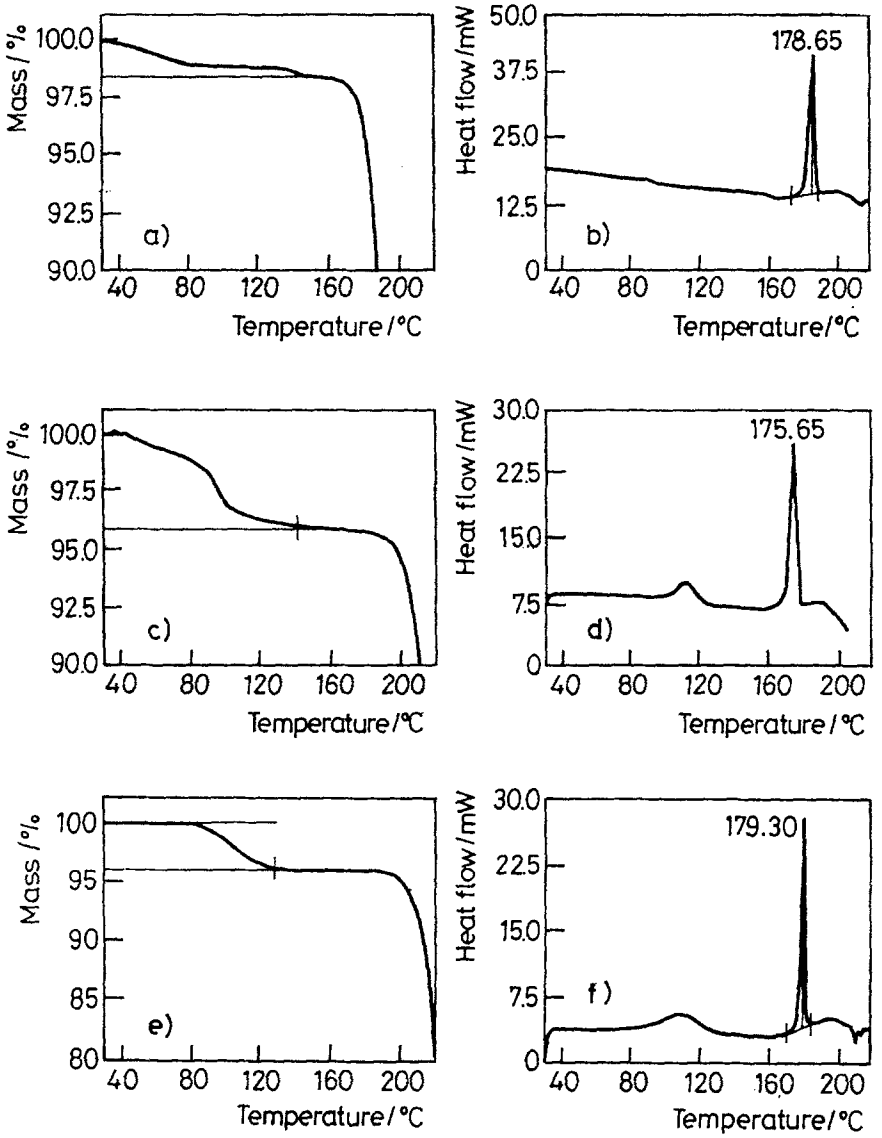


Fig. 6 Drug·H_2O TG and DSC diagrams of three preparations with a heating rate of 10°C min^{-1}

The XRD measurements, Fig. 7, before and after dehydration, show two dimensions, b and c, not to be influenced. The c-axes corresponding to the thickness, decreases about 1%. The crystal structure is thus intact indicating the property of a zeolite or inclusion compound (6) with water as a guest molecule. True density measurements (7) show this statement to be most probable.

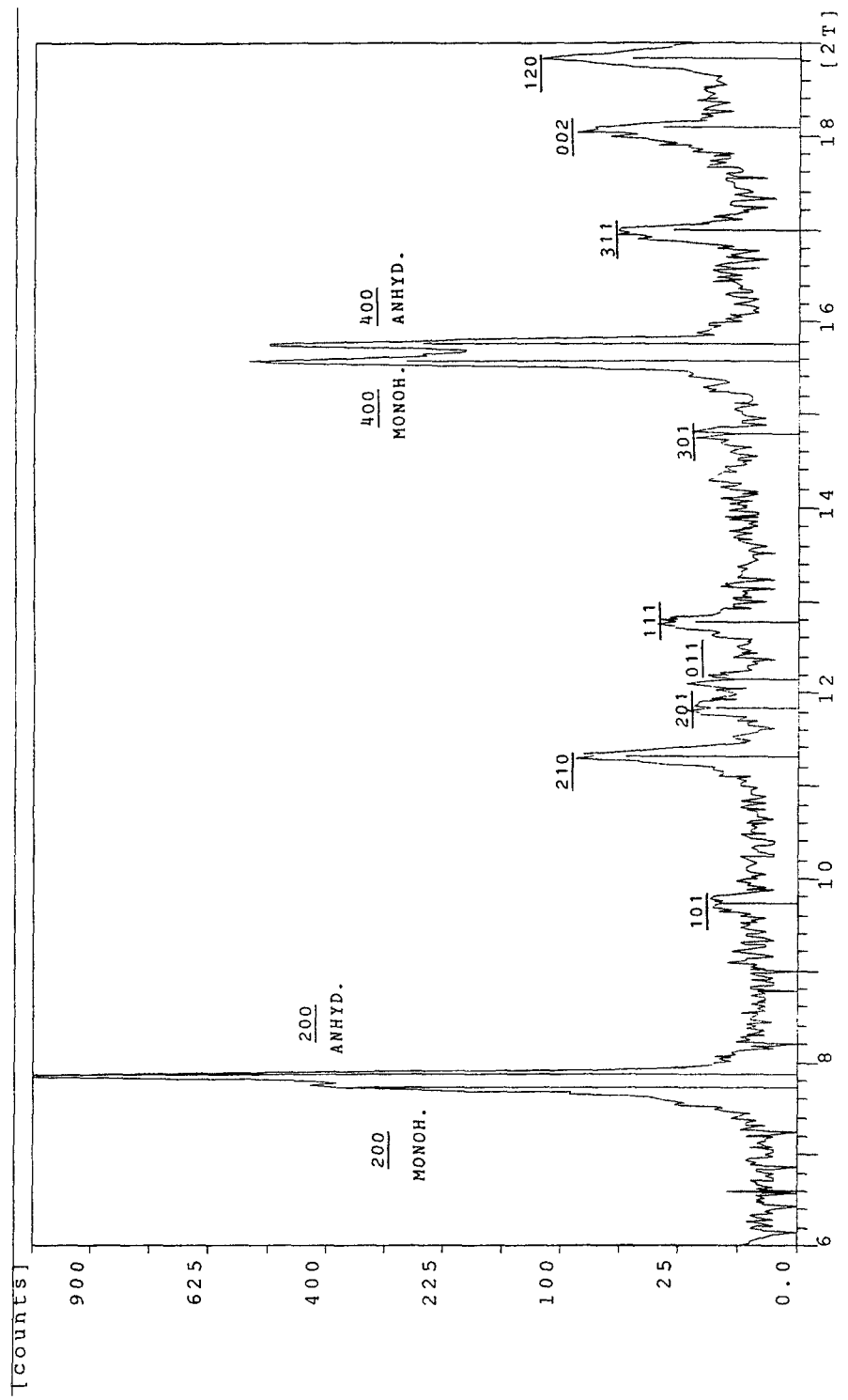


Fig. 7 The first part of the X-ray diffraction diagram obtained with reflecting technique of a partly, about 50%, decomposed drug·H_2O

$$D_{\text{anhydrate}} = 1.38_{\text{obs}} \text{ and } 1.36 \text{ g cm}^{-3}{}_{\text{calc}}$$

$$D_{\text{monohydrate}} = 1.36_{\text{obs}} \text{ and } 1.33 \text{ g cm}^{-3}{}_{\text{calc}}$$

* * *

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