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COMPREHENSIVE STUDIES OF TOLPERISONE·HCl–CYCLODEXTRIN COMPLEXES

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Abstract

Solid inclusion complexes of Tolperisone·HCl with five various cyclodextrins were prepared by kneading and spray drying. The complex formation between the drug and the cyclodextrins were proven using thermoanalytical methods, X-ray diffraction, IR spectroscopy. The results of the solid state investigations were supported by the liquid phase investigations, such solubility and parition constant measurements and stability constant determination. Among all cyclodextrins used the β- and γ-CD-s were found to be the best complexing agents.

Keywords: cyclodextrins, IR spectroscopy, thermal analysis, Tolperisone·HCl, X-ray diffraction

Introduction

One of the most interesting properties of cyclodextrins is their capability to improve the aqueous solubility, physico-chemical stability and bioavailability of a great number of drug molecules through inclusion complex formation in both solution and solid phase. Especially molecular encapsulation of a large number of hardly soluble pharmaceutically active molecules have been targeted by several authors [1–2].

We have aimed encapsulation of Tolperisone·HCl salt (T·HCl) ($C_{16}H_{23}NO \cdot HCl$, Mydeton^R). The T·HCl is a β-aminoketone with antinicotine activity. This is an original Hungarian drug molecule, synthesized by Pórszász and Nádor in 1959 [3], and now several products are marketed world-wide.

The membrane diffusion properties of Tolperisone·hydrochloride were found by Antal *et al.* remarkably affected by the complexation with cyclodextrin derivatives [4–5].

Enantiomers of as racemic Tolperisone·HCl, Fig. 1, were successfully separated using a naphtylethyl-carbamate–β–cyclodextrin and other modified cyclodextrin linked column as stationary phase [6–7].

The relevant literature deals also with the properties of Tolperisone the base itself, which has an alkaline character. It is a pale yellow oil with a characteristic odour. It is stable only in acidic media, most stable at room temperature at about *pH* 2. While in alkaline and neutral solutions it decomposes [8]. Mydeton tablets

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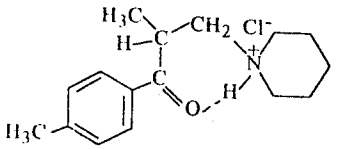

Fig. 1 Chemical structure of Tolperisone·HCl

containing this form decompose also during storage at room temperature. The stabilisation via cyclodextrin complexation was realised by Vikmon *et al.*, where the molecular encapsulation was successfully carried out with suspension and kneading preparation techniques using β-cyclodextrin [9–10].

In the present paper the effects of complexation of T·HCl with various cyclodextrins using different preparation methods (kneading and spray drying) is studied. Our aim was to give a general characterisation about the substances formed, in order to select the best host cyclodextrin for complexation purposes. The inclusion formation was followed using thermal analysis, IR spectroscopy, X-ray powder diffraction and hot stage microscopy.

Experimental

Samples

The following starting materials were used to prepare inclusion compounds:

– Tolperisone·HCl (1-piperidino-2-methyl-3-(*p*-tolyl)-propanon) pharmaceutical grade was provided by Gedeon Richter Pharmaceutical Works, Budapest, Hungary.

– The α-, β-, γ-cyclodextrins (CD), DIMEB (dimethyl-β-cyclodextrin) and RAMEB (radomly methylated β-cyclodextrin) were supplied by CYCLOLAB Cyclodextrin Res. & Dev. Ltd. Budapest, Hungary.

Preparation of inclusions

In all formulas 1:1 and 2:1 initial host:guest molar ratio was kept. Three methods were used to produce the inclusions: The mechanical mixture of the components were produced by a simple mixing in an agate mortar.

Preparation of kneaded products: 1.00 g of T·HCl was mixed with calculated quantities of cyclodextrin derivatives and the calculated amount of 1:1 water:ethanol mixture was added. The systems were continuously kneaded until the solvent had evaporated. After kneading the wet mixture were dried at room temperature and then in a drying oven at 105°C, finally they were pulverised (0.16 mm).

Preparation of spray dried complexes (NIRO Minor Atomizer, Copenhagen, Denmark): 1.00 g of T·HCl was mixed with adequate amounts of CDs, and each powder mixture was dissolved a given quantity of distilled water and ethanol solution. The solutions were spray-dried under the following conditions: 105±5°C drying air inlet, 65–75°C outlet. The feeding rate was about 900–1100 g h^{-1} and the atomizer disk was rotated with 25 000 rpm.

Methods and apparatuses

The following instruments and methods have been applied for the characterization of the active ingredient and the obtained formulations:

DuPont 990 thermal analyser system (TG, DSC, EGD) was used for the thermoanalytical characterization of the solid formulas obtained. The initial sample masses were 5–6 mg for each thermoanalytical runs. 5°C min^{-1} heating rate, flowing argon atmosphere (10 l h^{-1}), as well as opened crucible were applied for the TG and DSC measurements, while 8°C min^{-1} heating rate and nitrogen atmosphere (1.8 l h^{-1}) was used for the EGD measurements.

FTIR spectra were recorded by a Perkin-Elmer Paragon FT-IR spectrometer using KBr pellets in the 500–4000 cm^{-1} range.

In order to achieve a more sophisticated solid state characterization of the samples, X-ray diffraction measurements (Dron UM-1 diffractometer, CuK_α radiation, LiF monochromator) and hot stage microscopy, HSM (Boetius PHMK) observation were carried out.

In liquid phase diffusion constants were measured by using a Sartorius Resorption Modell Type SM 16750 apparatus at $pH=1.1\pm0.1$.

Parition coefficient measurements have been carried out in octanol saturated with water (22 g of water+500 g of octanol) and in water saturated with octanol (1 g

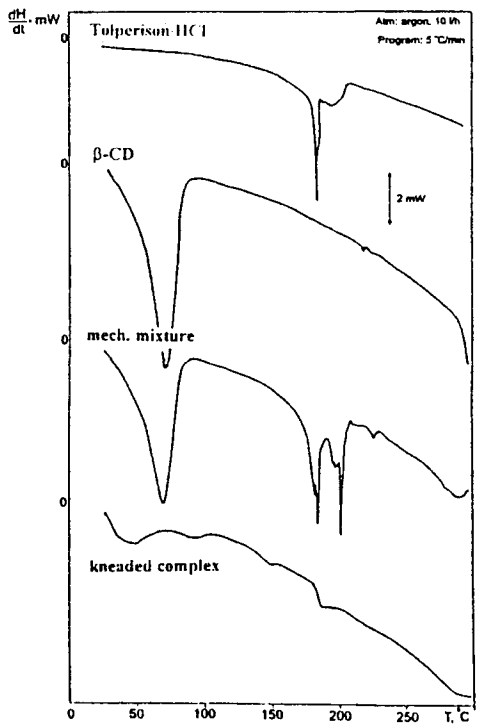

Fig. 2 DSC curves of Tolperisone·HCl–β-cyclodextrin samples

of octanol+500 g of water). The absorbances of the given samples against the pure solvent were measured with a Spektromom 195 UV spectrophotometer at $\lambda =$ 264 nm.

Results and discussion

Thermoanalytical investigation

The pure T·HCl melts at about 180°C, (Fig. 2, upper curve), but after the phase transition it decomposes. (On the base of TG measurements up to 250°C the 92% of the total sample mass decomposed.)

The thermoanalytical behaviour of the β-cyclodextrin (β-CD) has been investigated in detail by different authors [11–12]. At the beginning of the heating period loss of adsorbed water occurs. In case of α-CD and RAMEB between 120–170°C 1–2% mass losses, due to the evaporation of technological contamination is observed. The thermal degradation accompanied with the melting of CD-s began over 250°C except in case of RAMEB. In the latter case – according to the hot stage mi-

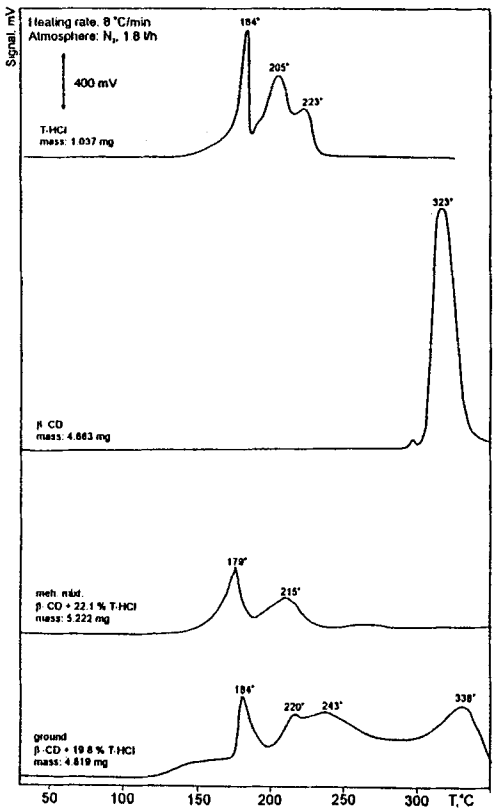

Fig. 3 EGD curves of Tolperisone·HCl–β-cyclodextrin samples

croscopy observations – a softening of the amorphous particles took place between 175–185°C and decomposes over 230°C.

The DSC curve of the mechanical mixtures of T·HCl and β-CD seem to be partially the superposition of the pure components. After melting of T·HCl a broad endotherm can be observed, which is due to a chemical interaction between the two components (Fig. 2). On the DSC curve of the kneaded product no definite melting peak was found. The broad endotherm in the 180–230°C temperature range may attribute to the decomposition of the inclusion complex formed, but with regard to the behaviour of the mechanical mixture, the occurrence of a chemical reaction between host and the uncomplexed amount of guest cannot be excluded.

The EGD analysis of T·HCl–β-CD (curves are drawn in Fig. 3) gave further evidence about the chemical reaction. On the curve of the mechanical mixture the decomposition peak of β-CD shifted towards the lower temperatures. The EGD profile obtained on the kneaded sample is differ from the curve of the physical mixture indicating that the inclusion complex formation between the components was completed by kneading.

Practically the same results were obtained by the evaluation of the DSC curves of the other T·HCl–cylcodextrin systems, except the T·HCl–RAMEB samples. The DSC (Fig. 4) and EGD curves (Fig. 5) of the mechanical mixture, the spray dried

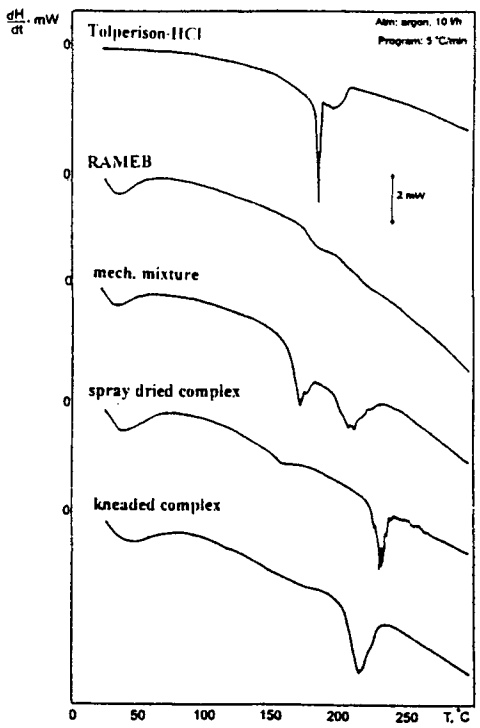

Fig. 4 DSC curves of Tolperisone·HCl–RAMEB samples

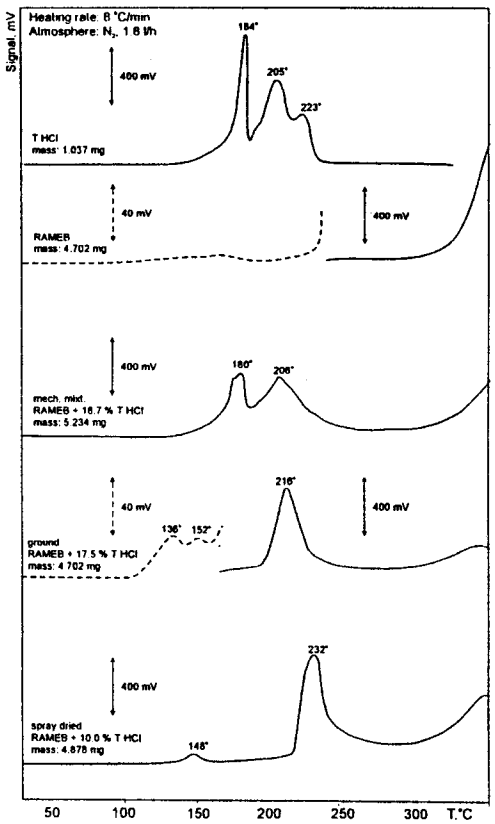

Fig. 5 EGD curves of Tolperisone·HCl–RAMEB samples

and kneaded products of the latter system seem to be very similar, indicating no inclusion complex formation in this system by these methods. Further investigations would be necessary to elucidate the rather complex binary systems.

X-ray diffraction measurements

The differences observed on the powder diffractograms of the mixture and the kneaded products of T·HCl–α-, β- and γ-CD formulas also support the fact of complexation. In Fig. 6 the diffraction peaks of T·HCl and β-CD samples are shown. Whilst both X-ray patterns of T·HCl – DIMEB samples are seem practically identical (Fig. 7), suggesting no inclusion complex formed upon its preparation by kneading.

The diffraction curves of RAMEB showed an amorphous structure in case of the mechanical mixture, the spray dried and kneaded product, when the X-ray diffraction technique could not provide information about complexation in this system.

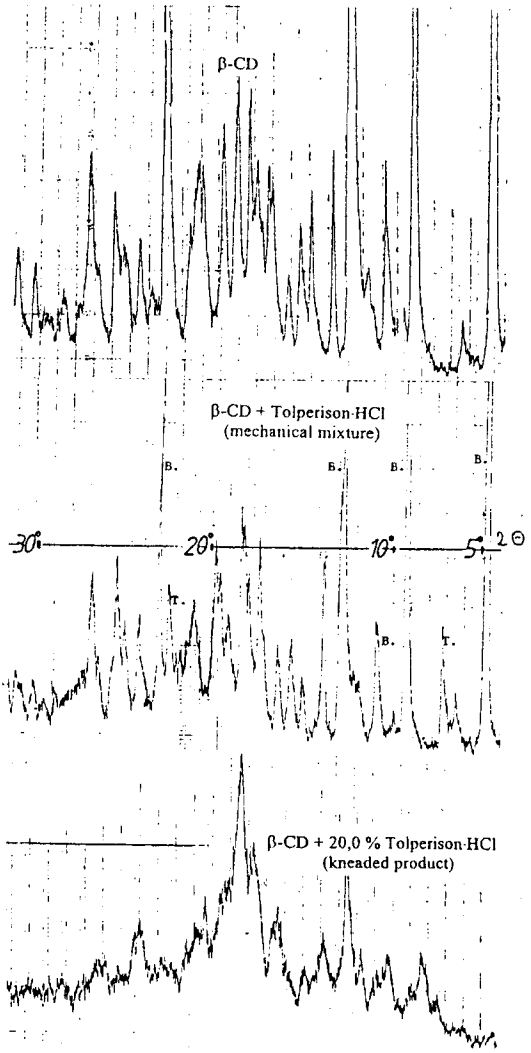

Fig. 6 X-ray diffraction patterns of Tolperisone·HCl–β-cyclodextrin samples

IR spectroscopic measurements

The 1572 and 1607 cm^{-1} bands are representing for the $\nu_{C=C}$ aromatic stretching vibration, and the 1677 cm^{-1} band is due to the vibration of the aromatic carbonyl group. The 2533, 2580 and 2635 cm^{-1} bands are assigned to N–H group, taking part in strong intramolecular hydrogen bonds.

In the IR spectra of all samples only the strongest bands of T·HCl assigned to the aromatic stretching, aromatic carbonyl and N–H group vibrations could be identi-

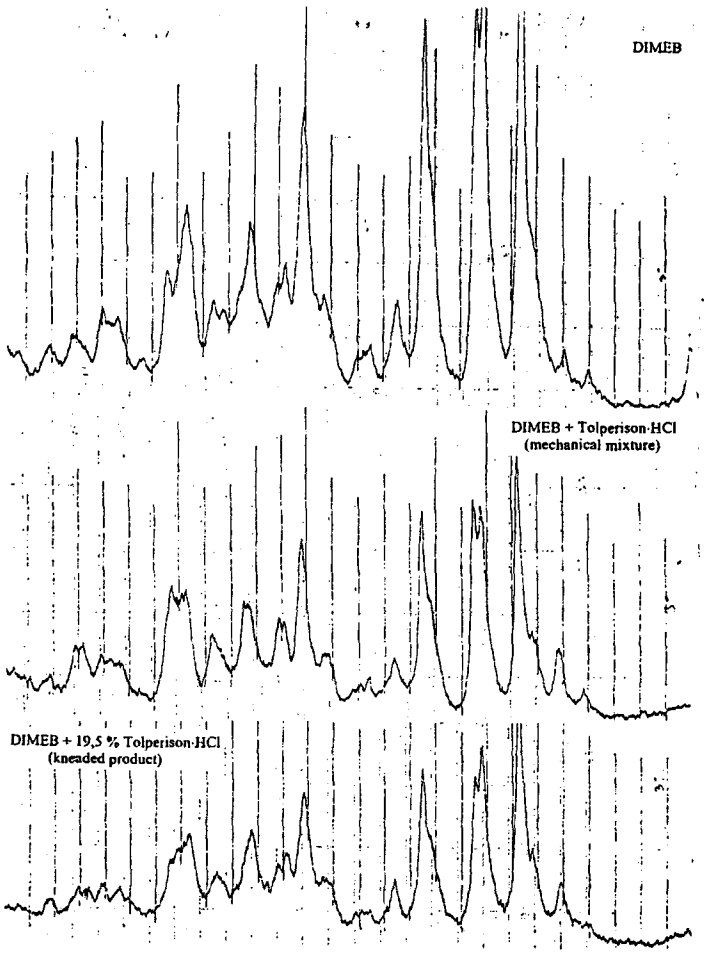

Fig. 7 X-ray diffraction patterns of Tolperisone·HCl–DIMEB samples

fied (Figs 8 and 9). The significant decrease of ν_{N-H} vibrations between 2500 –2700 cm^{-1} shows, that the number of intramolecular hydrogen bonds decreased during the kneading, probably because of complex formation with cyclodextrin.

Diffusion coefficient measurements

Transportation of T·HCl through an artificial gastrointestinal membrane was determined using Sartorius Resorption Modell Apparatus, Type SM 16750 [13]. In this experiments 100 ml of solution containing 100 mg of solubilized T·HCl in artificial gastric juice or artificial intestinal juice was allowed to transfer through two stomach barriers, stomach wall barrier (M1) or intestinal wall barrier (D1) to 100 mg of artificial plasma. 5 ml of samples were taken in every 30 min from each

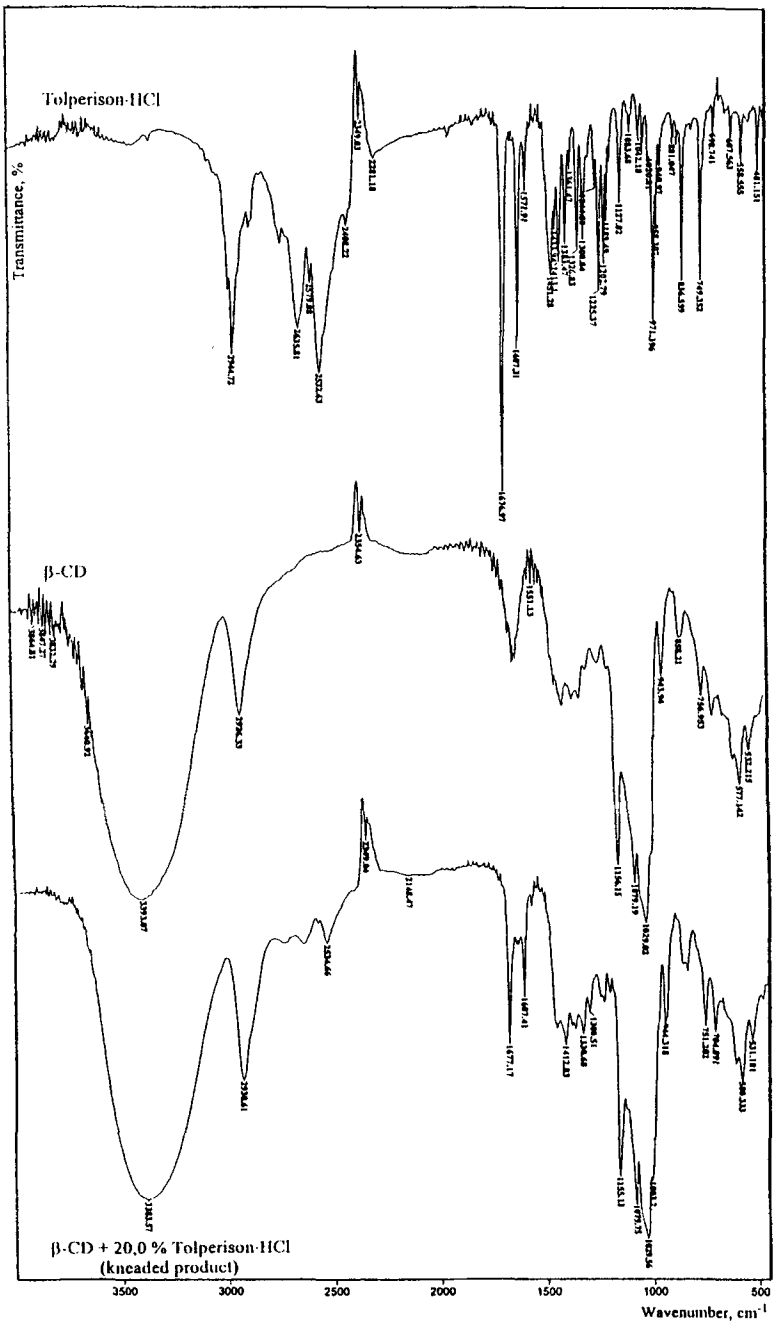

Fig. 8 IR spectra of Tolperisone·HCl–β-cyclodextrin samples

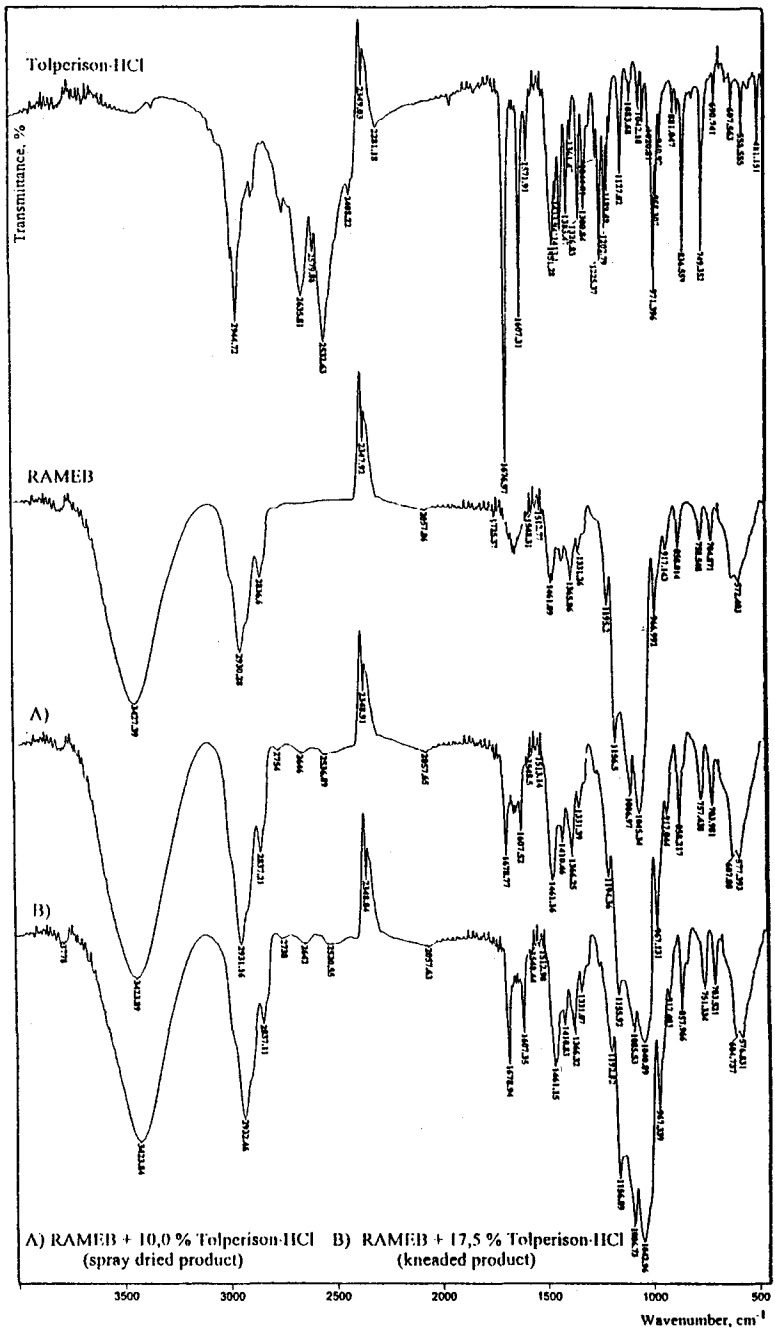

Fig. 9 IR spectra of Tolperisone·HCl–RAMEB samples

of the stomach or intestinal solutions as well as plasma that maintained at 39°C for 150 min. The concentration of the drug remained in the stomach or intestinal juice and that transferred if any of the plasma solution was determined spectrophotometrically al $\lambda = 264$ nm.

Lipid barriers (stomach wall barrier, M1 and intestinal wall barrier, D1) were prepared from the components of the packaged kits of Sartorius membrane filter, the pores of which are filled with a liquid lipid phase. Both phases, representing M1 and D1 are mixtures of two different liquid lipid components (N, S1 or N, S2) respectively.

The T·HCl oneself has a relatively low diffusion coefficient, which is further decreasing after formulation with β- and γ-CD. In case of Tolperisone·HCl – α-CD formula, the value of the diffusion coefficient remained the same, while increased in the preparations produced with DIMEB and RAMEB. These observations can be explained with the different diameters, consequently with the different interactions formed with the CD ring. The results suggest, that the interactions relatively strong between the T·HCl and the β- and γ-CD, and weaker when α-CD, DIMEB and RAMEB were used.

Parition coefficient measurements

The results obtained show, that the T·HCl–DIMEB and T·HCl–RAMEB dissolve better in water than the pure T·HCl oneself, while the solubility of the three other formulas were higher in octanol compared to the pure drug molecule.

Conclusions

The aim of the present work was to give a general characterisation of the substances formed between T·HCl and the various cyclodextrins.

Our general observation was, that the evaluation of the thermoanalytical curves of the compounds obtained were rather difficult. Some of them supported the inclusion complex formation (T·HCl–α-CD, T·HCl–β-CD and T·HCl–γ-CD). In these cases the solid phase investigation using other techniques (X-ray powder diffraction, IR spectroscopy measurements) gave further evidence about the existence of the complexes. When DIMEB and RAMEB were used as host molecules, the host-guest interaction was not so pronounced, some of the measurements indicated no complex formation.

The results of the solid phase experiments were supported by the data of the liquid phase investigation. The diffusion constant determinations were evidenced that strongest interactions occurred between T·HCl–β-CD and T·HCl–γ-CD. It can be explained with their optimal cavity diameter, required by a successful complexation. The values of the stability constants obtained proved the formation of a stable inclusion complex in case of T·HCl–β-CD and weak interaction was found between T·HCl–RAMEB.

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