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THERMOANALYTICAL, FTIR AND X-RAY STUDIES OF GEMFIBROZIL–CYCLODEXTRIN COMPLEXES

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Inclusion complexation between dimethyl-β-cyclodextrin and a very poorly water-soluble serum lipid-regulating agent, gemfibrozil, was studied. Products were prepared by several methods (physical mixing, kneading, spray-drying and ultrasonic treatment) in four different molecular ratios (2:1, 1:1, 1:2 and 1:3). The possibility of complex formation between the drug and the host molecule was studied by thermal analysis. Supplementary techniques, such as Fourier transformation-infrared spectroscopy and X-ray diffractometry, were also applied to interpret the results of thermal study of the products.

Keywords: *dimethyl-β-cyclodextrin, DSC, FTIR spectroscopy, gemfibrozil, X-ray diffractometry*

Introduction

The cyclodextrins (CDs) are cyclic oligosaccharides containing 6–8 glucose units (α, β and γ forms) with a hydrophilic outer surface and a central lipophilic cavity. The CDs have the unique property of the ability to form inclusion complexes with a variety of organic/inorganic guest molecules of suitable size and polarity, leading to changes in the physicochemical properties of the guest [1]. The CDs have mainly been applied as complexing agents to increase the aqueous solubility of poorly water-soluble drugs, and to increase their bioavailability and stability [2–5]. The thermal analysis of various CDs and their inclusion complexes has been used to differentiate inclusion complexes from adsorbates, and to characterize the special thermal effects due to molecular entrapment during a well-defined, standard heating process [6–11]. Thermoanalytical methods can also be used to determine the host-guest ratio, or the water or volatile component content (in mass/mass%) in the investigated product, and to identify products with a spherical appearance [1, 12–15].

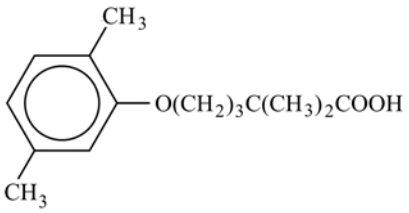

Fig. 1 Chemical structure of gemfibrozil

The aim of the present study was to examine the possibility of formation of complexes between gemfibrozil (GEM) and dimethyl-β-CD (DIMEB) by thermal analysis, FTIR spectroscopy and X-ray diffractometry [1, 16, 17]. The authors would like to point to the relationship between the different analytical techniques.

Experimental

Materials

Gemfibrozil (USP 25 quality) (Fig. 1) [3, 18]: 2,2-dimethyl-5-(2,5-xylyloxy)valeric acid (Plantex Chemicals, Israel, API Division Teva Group); heptakis-2,6-di-O-methyl-β-CD (DIMEB) (degree of substitution (DS): 14.00; molar mass: 1331.0 g mol^{-1}) (Cyclolab R&D Laboratory Ltd., Budapest, Hungary); other chemicals (Reanal Co., Budapest, Hungary).

Methods and apparatuses

Products were prepared in four different molar ratios (GEM:CD molecular ratio=2:1, 1:1, 1:2 and 1:3). Physical mixtures (PMs): the pure drug and CD were mixed and co-ground in a mortar and sieved through a 100 μm sieve. Kneaded products (KPs): PMs of the drug and DIMEB were mixed (Erweka LK5 mixer) with the same quantity of a solvent mixture of ethanol+water (1:1). They were kneaded continuously until the bulk of the solvent mixture had evaporated. After this, they were dried at room temperature (25°C, normal atmospheric pressure) and were then pulverized and sieved through a 100 μm sieve. Spray-dried prod-

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ucts (SDs): the PMs of GEM and DIMEB were dissolved in 50% ethanol. The SDs were obtained by using a Büchi Mini Dryer B-191, at 75°C inlet temperature, with a compressed air flow of 800 L min^{-1} and a nozzle diameter of 0.5 mm. The aspirator rate was 75–80%, and the pump rate was 3–7%. Products prepared by ultrasonic treatment (USs): PMs with different molecular ratios of GEM and DIMEB were dissolved in 50% ethanol, mixed to obtain clear solutions, then placed in the ultrasonic apparatus for 1 h, dried, pulverized and sieved through a 100 μm sieve. Products were stored under normal conditions at room temperature in well-closed glass containers [19].

TG, DTG and DTA curves were performed with a Derivatograph-C apparatus (MOM, Hungary). 50 mg of the sample was investigated under normal air flow, at a heating rate of 5 K min^{-1}. The temperature interval was 25–300°C.

The DSC analysis was carried out with a Mettler Toledo STAR^e thermal analysis system, version 6.0, DSC 821^e (Switzerland), at a heating rate of 5 K min^{-1}, with argon as carrier gas (10 L h^{-1}). The sample size was in the range 2–5 mg and examinations were made in the temperature interval 25–300°C, in open pans.

Standard KBr pellets were prepared from the samples, taking into account the GEM content of the samples to provide approximately the same intensities of the GEM bands, resulting in the same signal-to-noise ratio for them. Thus, all the pellets contained 1.0 mg of active agent in 157 mg of potassium bromide for IR spectroscopy (Merck KGaA, Darmstadt, Germany). All spectra were recorded on an Avatar 330 Fourier Transform Infrared (FTIR) spectrometer (Thermo Nicolet, USA), equipped with a DTGS (deuterated triglycyl sulfate) detector, in the range 4000–400 cm^{-1}. The spectral resolution was 4 cm^{-1}, and 64 scans were collected to provide a good signal-to-noise ratio. All spectral manipulations were performed with GRAMS/AI Ver. 7 (Thermo Galactic, USA) software.

XRD spectra were recorded with a DRON UM-1 diffractometer (Russia) system with $CuK_{\alpha 1}$ radiation (λ=1.54051 Å) over the interval 2–44°/2θ. The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 35 kV; current, 20 mA; time constant, 1 s; angular range 2°<2θ<44°; angular step 0.030°.

Results and discussion

Thermoanalytical investigations

The sharp, narrow endothermic peak in the DSC spectrum of GEM at 59.25°C shows the melting point of the material (the melting enthalpy was 150.23 J g^{-1}, SD±2.04). The stability of the active agent was not affected (no degradation observed) up to 160°C; the broad endothermic peak relates to the evaporation and degradation of the substance. The baseline can be seen in the DSC curve after 230°C, as the total amount of the material tested was evaporated from the container. The substance has no moisture content, as concluded from the TG curve. The mass decrease starts at the same temperature range as seen in the DSC curve (Figs 2 and 3).

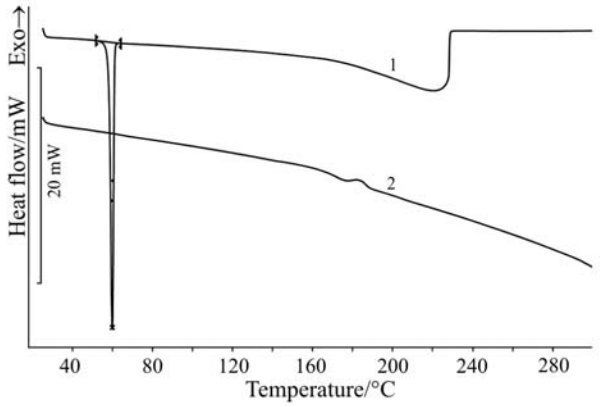

Fig. 2 DSC curves of 1 – GEM and 2 – DIMEB

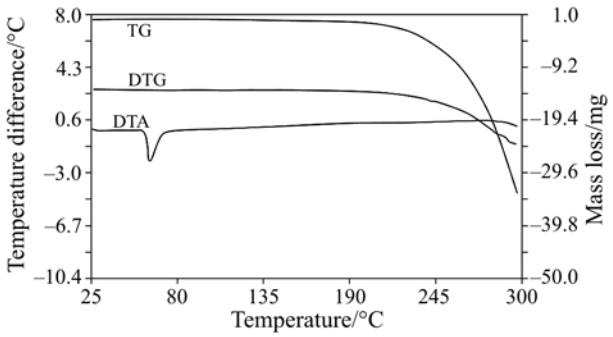

Fig. 3 TG, DTG, DTA curves of GEM

The moisture content of DIMEB is less than 0.5%, as determined from the TG curve and traditional gravimetry after drying in a drying chamber. The moisture contents of the products were also very low, which favoured the evaluation of the measurements; as there was no broad endothermic peak before 100°C (representing the water content), this did not disturb the examination of the active agent with its low melting point. A linear part was observed within the melting range of the active agent in the DSC curve of DIMEB. The small endothermic and exothermic peaks at 180°C were due to the impurities in the CD derivative. DIMEB underwent chemical degradation at higher temperatures: a slow decrease in mass was observed, with a broad endothermic peak in the DSC curve (Figs 2 and 4).

The endothermic peak reflecting the melting point of the active agent was present at all compositions of the GEM PMs (Fig. 5). The area under the peak decreased with increasing CD ratio, as the active

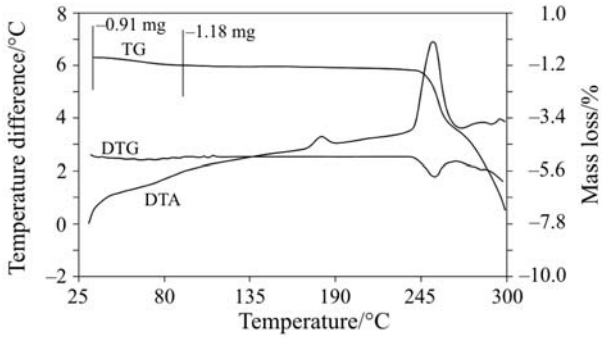

Fig. 4 TG, DTG, DTA curves of DIMEB

agent content decreased in parallel. Partial complex formation can be presumed on the basis of the normalized integral. Complex formation due to heating has been described in the CD literature by some authors [12], and interactions could also occur between the active agent and the auxiliary materials. This latter does not mean complexation, but the amount of crystalline active agent could decrease. X-ray measurements were performed in order to clarify this phenomenon.

The presumed uncomplexed guest (active material) percentages were estimated semiquantitatively from the DSC curves by using the following equation:

$$c_{un} = \frac{\Delta H_i}{\Delta H_0 c} 10^4$$

where c_{un} is the uncomplexed guest %; ΔH_i is the normalized integral value for the product; ΔH_0 is the normalized integral value for the active ingredient; and c is the percentage of active ingredient in the product. Table 1 presents the results for the different compositions.

Partial complex formation was detected for the 2:1 active agent: CD KP and US (80–90%) (Fig. 6); no endothermic peak (indicating the melting of the active agent) was detected at other ratios. On this basis, complete complex formation was assumed for the 1:1, 1:2 and 1:3 ratios. This was confirmed by the good dissolution and in vitro membrane diffusion ability of these products [19].

Table 1 Percentage assumed uncomplexed guest in the products

Product	Uncomplexed guest%
GEM-DIMEB PM 2:1	69
GEM-DIMEB PM 1:1	71
GEM-DIMEB PM 1:2	78
GEM-DIMEB PM 1:3	78
GEM-DIMEB KP 2:1	13
GEM-DIMEB US 2:1	15

No melting process was observed for the SDs, so crystalline phase might have not been assumed in all cases (Fig. 7).

FTIR results

Comparison of the vibrational spectra of GEM, DIMEB and the samples prepared by different physical methods at various GEM to DIMEB ratios revealed well-defined differences, although the preparation of the pellet was expected to promote complex

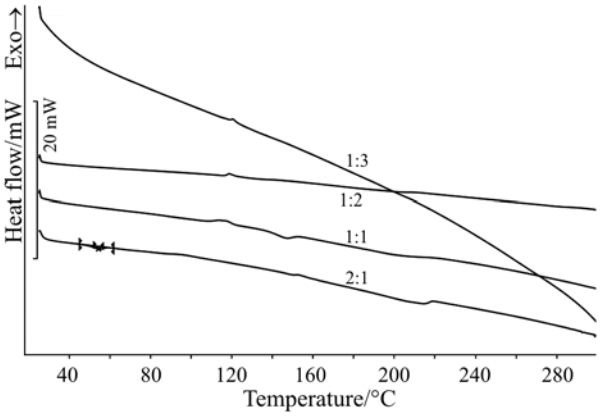

Fig. 6 DSC curves of GEM+DIMEB kneaded products

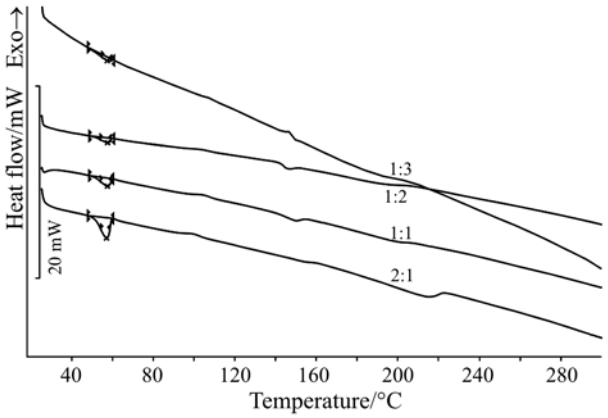

Fig. 5 DSC curves of GEM+DIMEB physical mixtures

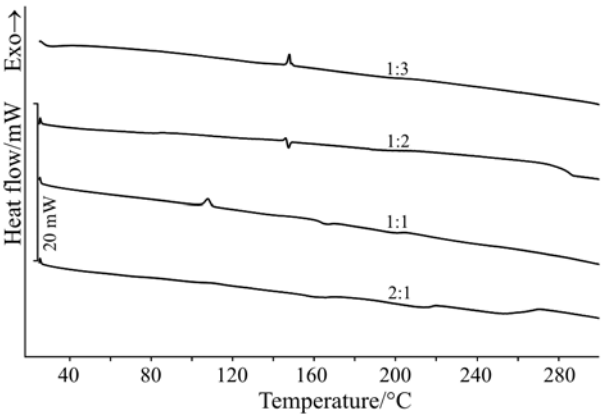

Fig. 7 DSC curves of GEM+DIMEB spray dried products

formation. The most significant changes were found in the ranges of the characteristic frequencies of the carboxyl group (–COOH), indicating that the complex formation altered the hydrogen-bonded cyclic dimer structure of the carboxyl-group. The most intense C=O stretching band shifted from 1709 to 1730 cm^{-1}, suggesting a less strong or no H-bonding interaction. The other two characteristic, combination bands (C–C–O–{H} stretching and C–O–H in-plane bending modes) also shifted, to lower wavenumbers (from 1403 to 1396 cm^{-1} and from 1271 to 1265 cm^{-1}), confirming that the strength of the hydrogen-bonds decreased and complexation occurred through the carboxyl group. Evaluation of the O–H stretching (around 3000 cm^{-1}) and the O–H out-of-plane bending (around 940 cm^{-1}) regions was prevented by the strong absorption of DIMEB. On the other hand, DIMEB has a band with appropriate intensity at 1375 cm^{-1}, away from the bands of GEM, which allows normalization of the sample spectra. All spectra were transformed by performing a spectral offset, which resulted in zero intensity at 1900 cm^{-1}, and division by the doubled intensity of the above-mentioned reference band. The spectral intensities for the samples prepared by the same method followed the expected sequence in the C=O stretching region, based on the GEM to DIMEB ratio (Fig. 8). The C=O stretching region is dominated by the strong peak at 1730 cm^{-1}, but new bands appear at higher GEM to DIMEB ratios. The intensities and the positions of the new bands depended on the method of preparation, but they always appeared on the lower wavenumber side of the band characteristic of complexed GEM (Fig. 9). The intensities of the new bands increased in the sequence SD, KP, US and PM. Three new components were revealed by Fourier self-deconvolution [20–23] in these overlapping bands, at 1709, 1699 and 1690 cm^{-1}. The first and the last of these were found to be characteristic of pure GEM. Samples prepared by the US, KP and PM methods featured all three new bands with various relative intensities, while the spectrum of the SD sample showed only the band at 1699 cm^{-1}. Since spray drying usually resulted in an amorphous product, and this band was the only additional one in the SDs, it can be assumed that it was characteristic of GEM in an amorphous state (Fig. 10). The other possibility is to assign it to the complexed form.

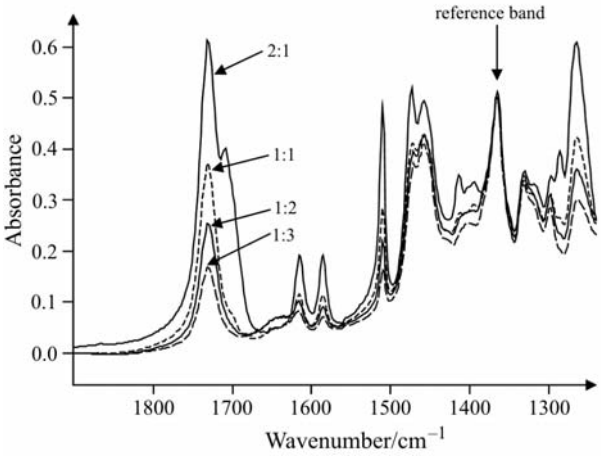

Fig. 8 FTIR spectra of kneaded products

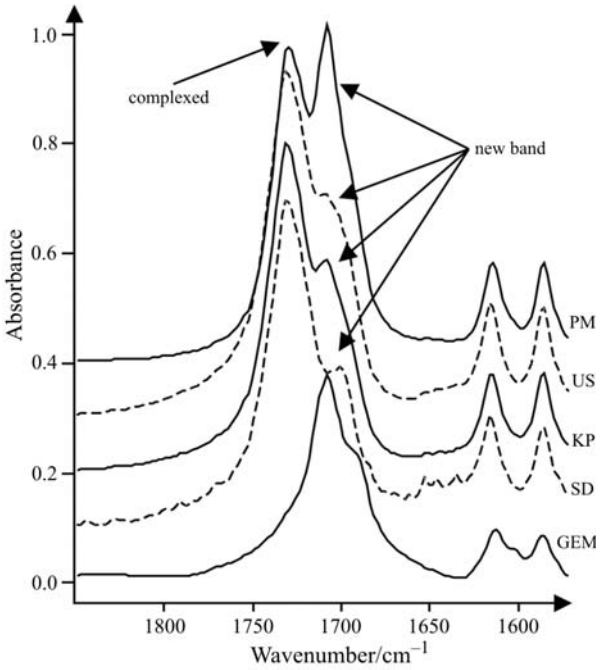

Fig. 9 FTIR spectra of 2:1 products and GEM

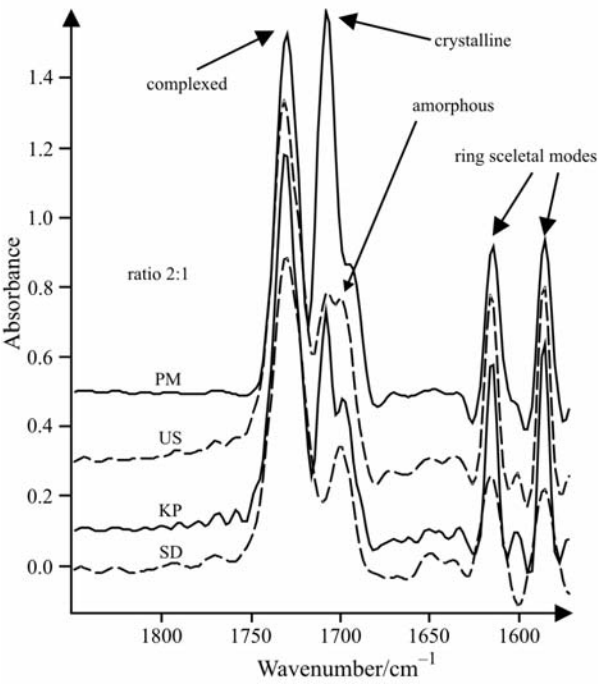

Fig. 10 Fourier-self-deconvolusion results

Since the pellet preparation somewhat altered the state of the samples, it was not expected that the same quantitatively evaluable intensities would be obtained as concerns the ratio of complexed and crystalline GEM. A semiquantitative picture was derived from the spectra of samples prepared at a ratio of 2:1, by fitting eight mixed Gaussian–Lorentzian-functions between 1850 and 1570 cm^{-1}. The fitted bands included two bands assigned to the skeletal modes of the aromatic ring in GEM. The sum of the area of these bands served as a reference to calculate the ratio of the fitted bands. First of all, the intensity ratio of the bands at 1730 and 1699 cm^{-1} changed essentially, so they can not be interconnected. The latter should therefore be assigned to amorphous GEM. The relative intensity of the band attributed to the complexed GEM was nearly the same for the samples prepared by the SD, KP and US methods. The SD sample did not show the presence of crystalline GEM, but the highest ratio of the amorphous GEM. The contributions of the bands of the crystalline and the amorphous GEM were low, and were also nearly the same in intensity for the KP and US samples. The relative intensities of the bands fitted to the spectrum of the PM showed the highest ratio of the crystalline and the lowest ratio of the amorphous phase. Hence, all the results agreed with those of the DSC measurements.

X-ray powder diffraction results

X-ray powder diffraction can elucidate the nature of the host-guest interactions in crystalline CD inclusion compounds. The changes in the powder crystallinity of the samples were studied by comparing their diffraction patterns.

The X-ray spectra of the active agent, the CD derivative, the SD 1:2 and the PM 1:2 products were recorded during the experiments (Fig. 11). The spectrum of GEM is that of a crystalline material, as expected. The degree of crystallinity of DIMEB is negligible, and this was also found for the SD. The amorphous structure of the SD is due to the high drying rate used during the preparation. It was interesting that the PM 1:2 product (PM 1:2 1 ver.) also displayed only slight crystallinity, similarly to the previously mentioned SD preparation. On the basis of these results and also taking into consideration the DSC and FT-IR measurements, we assume that the inclusion complex is formed in the solid phase and this also occurred in the case of the PM. To prove this, we prepared the 1:2 PM without any milling and sieving step during the preparation. The components were pulverized separately and then homogenized with care (PM 1:2 2 ver.). The peaks relating to the crystalline active agent are to be found in the X-ray diffractogram, with lower intensities as compared with those of the active agent itself, in accordance with the active agent content of the product (9.88%).

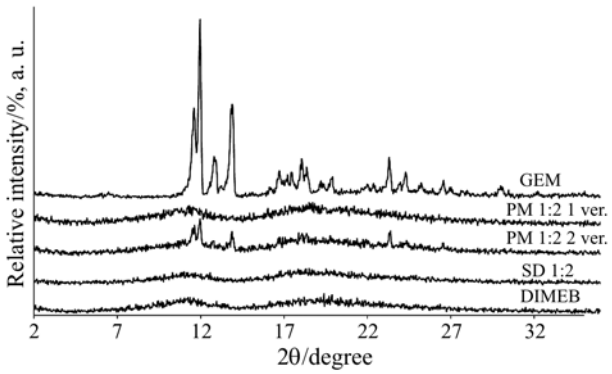

Fig. 11 X-ray powder diffraction diagrams

Conclusions

DIMEB is able to form an inclusion complex with GEM. The amount of material complexed depends on the host:guest molecular ratio of the products, and on the preparation methodology. The possibility of interaction (inclusion complex formation) between the components was studied by using thermonalytical methods, FTIR spectrometry and X-ray diffractometry.

DSC measurements pointed to partial complex formation in the 2:1 PMs, KPs and USs; the other compositions and products showed total complex formation. These results were confirmed by FTIR and X-ray measurements.

The most significant changes occurred in the vibrational bands characteristic of the carbonyl group, suggesting that the interaction between GEM and DIMEB takes place through this group as a result of complex formation. The relative intensity changes followed the expected trend as the GEM to DIMEB ratio increased. Four C=O stretching bands were identified by Fourier self-deconvolution. The band at 1730 cm^{-1} was assigned to complexed GEM, while the bands at 1709 and 1690 cm^{-1} indicated the presence of non-complexed, crystalline GEM. The band at 1699 cm^{-1} was attributed to the presence of amorphous GEM. Gaussian–Lorentzian functions were fitted to the normalized spectra and the peak areas were compared with the intensities of the skeletal bands of the aromatic ring of GEM. The differences in relative intensity between the samples prepared by the various studied methods, at a ratio of 2:1, supported the conclusions drawn from the DSC measurements.

The XRD spectra indicated that the SDs were amorphous, and partial inclusion complexation was observed for the PMs in the solid phase. This was verified by the examination of PMs prepared without any physical power input.

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