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Effect of cyclodextrin complexation on the photostability of promazine in aqueous solution

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Phenothiazines are known to be relatively instable and easy to be oxidized [1–4]. Inclusion complexation of instable drugs with cyclodextrins may result in an increase of stability, bioavailability and aqueous solubility of the drug [5–11]. The present study was undertaken to obtain the inclusion complexes of promazine with different cyclodextrins in solution and to examine the influence of molecular encapsulation on promazine photostability.

Inclusion complexes of promazine (PR) with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD), heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CD), heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD) or γ-cyclodextrin (γ-CD) were obtained in phosphate buffer of pH 6.47 and the solutions prepared were protected from light. The formation of inclusion compounds resulted in an insignificant shift of the UV absorption maximum of PR towards longer wavelength (about 2 nm); a small lowering of the maximum accompanied the shift.

The stability constants K_c for the PR-CD complexes were determined spectrophotometrically at $\lambda = 252$ nm and estimated according to the Scott's equation [12]:

$$\frac{S_t L_t}{\Delta A} = \frac{1}{K_c}\,\frac{1}{\varepsilon_c} + \frac{1}{\varepsilon_c}\,L_t$$

where S_t is the total concentration of RP, L_t is the total concentration of CD, ε_c is the difference between the molar absorptivities for PR in the presence and in the absence of CD, and ΔA is the change in absorbance of PR caused by addition of CD.

The greatest value of stability constant K_c, determined from the straight line plots of $S_t L_t/\Delta A$ against L_t, characterized the PR-β-CD complex and the difference, relative to K_c values obtained for configurations with other CDs, was of one order of magnitude (Table).

The changes in chemical shifts, following the interaction between CDs and PR were examined by ^{13}C NMR. The carbon signals of PR as well phenyl (127.64 to 122.68 ppm), as methyl (21.36 ppm) and propyl (54.11 to 41.85 ppm) groups were shifted downfield as a result of CDs addition. This indicates that besides the phenothiazine ring, the dimethyl-propylamino N-substituent of PR takes part in the association with CD. The latter is in agreement with results reported by Otagiri [12].

Table: Stability constants (K_c) and kinetic parameters for photochemical decomposition of promazine (PR)-cyclodextrins (CD) complexes in solution

Compound	K_c [a] (M^{-1})	$k_{obs} \cdot 10^4$ [b] (s^{-1})	$t_{0.5}$ [c] (min)
PR	–	6.19	19
PE-β-CD complex	37385	1.47	79
PR-DM-β-CD complex	5119	2.16	54
PR-TM-β-CD complex	4285	4.34	27
PR-HP-β-CD complex	1505	1.73	67
PR-γ-CD complex	1121	2.67	43

[a] K_c – stability constant of PR-CD complex
[b] K_{obs} – I-order reaction rate constant
[c] $K_{0.5}$ – half-degeneration time of PR

The solutions (in phosphate buffer) of PR and its complexes with CDs were exposed to UV radiation ($\lambda_{max} = 254$ nm). The changes of PR concentration during photodegradation were measured spectrophotometrically at 252 nm (spectra scanned from 200 to 400 nm). It was established that photodegradation of PR in the presence and in the absence of CDs followed first order kinetics. As the graphic representation of $\log c = f(t)$ (where c is the concentration of PR after t min. irradiation) is linear (r from 0.9988 to 0.9877 Fig.) the slope of the line gives photodegradation rate constant (k_{obs}). The values of these constants and the half lifes ($t_{0.5}$) of PR presented in the Table clearly indicate a stabilizing effect of CDs on PR. This effect depends on the stability constant (K_c) of the particular PR-CD-complex and was the greatest for β-CD, which forms the most stable inclusion compound with PR. The photostability of PR complexed with β-CD increased four times relative to that of free PR, but in the case of TM-β-CD this increase was only by one and a half times. The influence of the cyclodextrins on the photochemical stability of promazine increases in the following order:

$$\text{TM-β-CD} < \text{γ-CD} < \text{DM-β-CD} < \text{HP-β-CD} < \text{β-CD}\,.$$

This relation can be explained taking into consideration the structure of the PR-CD inclusion compounds. In PR-β-CD complex the aromatic portion of the phenothiazine moiety is included within the cavity, while the aminoalkyl side chain of the drug interacts with the outside of the cavity of β-CD through hydrogen bonding [12]. The alkylation of hydroxyl groups of β-CD hinders the entrance of the drug into the cavity of β-CD derivative as well as the formation of an external hydrogen bond. This negative effect enhances with the increasing substitution ratio of β-CD (DM-β-CD, TM-β-CD). However, in the case of the hydroxypropylated derivative of β-CD the possibility of hydrogen bonding formation remains unchanged. Different dimensions of γ-CD and β-CD can be the reason for a

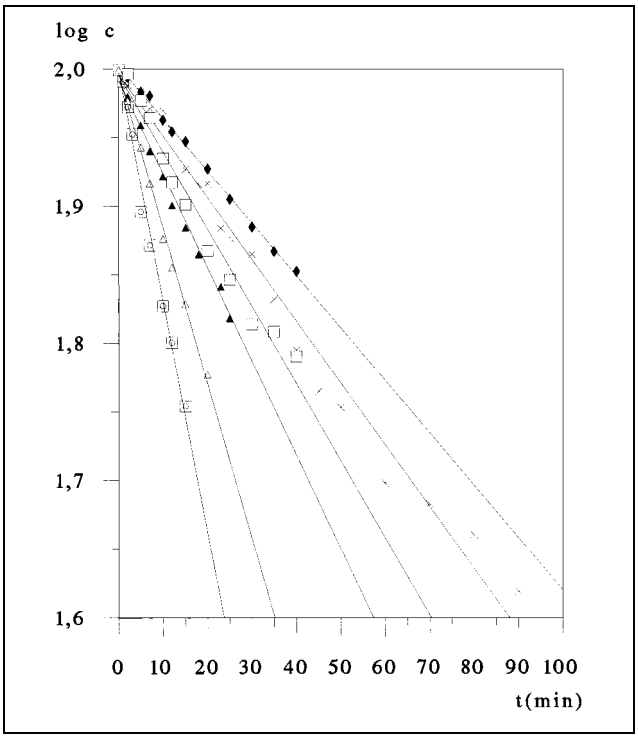

Fig.: First-order-plots for photodegradation of promazine in phosphate buffer solution in the absence of CDs (▣) and complexed with β-CD (◆), DM-β-CD (□), TM-β-CD (△), HP-β-CD (×) and γ-CD (▲)

lower photostability of the PR-γ-CD complex relative to that of PR-β-CD clathrate, however, ^{13}C NMR spectra indicated a similar structure of both inclusion compounds.

Experimental

1. Materials

Analytical grade of promazine hydrochloride and β-cyclodextrin, hydroxypropyl-β-cyclodextrin, heptakis (2,6-di-O-methyl)-β-cyclodextrin, heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin, γ-cyclodextrin from Sigma-Aldrich Chemical Co.

2. Spectroscopic determination of stability constants (K_c)

To seven glass vials, protected from light, containing 10 ml of promazine solution (1.5×10^{-5} mol/l) in phosphate buffer (pH = 6.47), different quantities (0–80 mg) of the selected cyclodextrin were solubilized. The UV absorption changes of promazine, resulting from the addition of cyclodextrin, were measured at $\lambda = 252$ nm (spectrophotometer UV-160 A, Shimadzu). The stability constants K_c of complexes obtained were calculated according to Scott's equation [12].

3. Kinetic studies

The solutions of promazine and promazine-cyclodextrin complexes (in phosphate buffer) were exposed to UV radiation ($\lambda_{max} = 254$ nm, distance 20 cm) in quarz cuvette cells (1 cm). The changes of promazine concentration were followed spectrophotometrically at $\lambda = 252$ nm. To determine the kinetic parameters of photodegradation of promazine a kinetic model of the first-order reaction was used.

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Determination of fluoxetine hydrochloride in capsules and moclobemide in tablets by first, second and third derivative spectrophotometry

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Both fluoxetine and moclobemide belong to a new generation of antidepressant drugs. The literature relating to the determination of this drugs in pharmaceuticals is rather scare.

Fluoxetine hydrochloride in pharmaceuticals was determined by GC [1, 2] and HPLC [3–5]. Moclobemide was determined by an electrochemical method with ionselective electrode [6]. Although the use of derivative spectra is not new, it has only become practical in recent years, with the development of computer technology, wich allows the almost instant generation of derivative spectra. In the derivative ultraviolet (UV) – visible spectroscopy, the information contained in the spectrum is presented in a potentially more useful form, with respect to the versatility of the technique [7–9] and offers a convenient solution to a number of well definied analytical problems: removal of sample turbidity, matrix background and enhancement of spectral details [10].

Two graphical techniques – "peak-zero" and "peak-peak" – have been used. In the case of the "peak-zero"-technique the measurement was made from the maximum value of the peak to the baseline. In the "peak-peak"-technique the amplitude of the neighbouring peaks was measured.

The Lambda 15 spectrophotometer enables to store the spectra's derivatives in its own computer memory and to read the value of a given derivative in any point marked on the received spectra. This makes both the "peak-zero"- and "peak-peak"-technique easy to use.

The influence of $0.1 \text{ mol} \cdot l^{-1}$ sodium hydroxide and $0.1 \text{ mol} \cdot l^{-1}$ hydrochloric acid and methanol on the absorption spectra of fluoxetine hydrochloride and moclobemide and the first, second and third derivative was studied. The best results for analytical purposes were obtained at $0.1 \text{ mol} \cdot l^{-1}$ hydrochloric acid for moclobemide and methanol for fluoxetine hydrochloride.

First, second and third derivative spectra of fluoxetine were determined in methanol in the 190–250 nm wavelength region in concentrations of 15, 20, 25, and

Table 1: Determination of fluoxetine hydrochloride in capsules

Derivative	λ (nm)	Technique	Content of fluoxetine hydrochloride in capsule (mg)	Standard deviation	Confidence interval (95%)
D1	228	P–O[x]	20.96	0.203544	20.71–21.21
D1	228–214	P–P[y]	20.87	0.323466	20.47–21.27
D2	234	P–O	20.84	0.185876	20.60–21.07
D2	222	P–O	20.80	0.206446	20.54–21.05
D2	234–222	P–P	20.85	0.220386	20.57–21.12
D3	236.7	P–O	21.49	0.507149	20.23–22.74
D3	227	P–O	20.84	0.246414	20.54–21.15
D3	236.7–227	P–P	21.21	0.409919	20.19–22.23
D3	215.5	P–O	21.03	0.243783	20.73–21.33
D3	227–215.5	P–P	20.91	0.240375	20.61–21.21

x: "peak-zero", n: number of determinations 6
y: "peak-peak"