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Stability of Ibuprofen in its Inclusion Complex with β-Cyclodextrin

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Abstract. The ibuprofen-β-cyclodextrin inclusion complex was prepared by the co-precipitation method. The identity of the obtained product was verified by X-ray and thermogravimetric techniques. The effect of β-cyclodextrin on the stability of ibuprofen was analysed.

Key words: β-Cyclodextrin complex, ibuprofen, co-precipitation, thermogravimetric analysis, stability analysis, X-ray diffraction analysis.

1. Introduction

Ibuprofen (IB) is a non-steroid drug commonly used in therapeutics due to its strong anti-inflammatory, analgesic and antipyretic action [1–3]. Side-effects, particularly ulcerogenic ones, which accompany treatment with this drug, are either the result of an excessive dosage or inappropriate drug form [4].

An improvement in pharmacokinetic parameters and a reduction in side-effects can be achieved by the increase in IB solubility in water and body fluids due to the formation of inclusion compounds between ibuprofen and β-cyclodextrin (β-CD) [5]. The formation of the latter complexes can result in increased solubility of the pharmacologically active component of the drug [6–8]. This study is aimed at preparing the inclusion complex of IB with β-CD and determining the effect of the compounds studied on the stability of the drug.

2. Experimental

Reagents: β-cyclodextrin, Chinoin (Hungary); ibuprofen (IB) racemate, Sigma (U.S.A). Other reagents used in the study were of AR grade.

Apparatus: Thermostated chamber KBC G-65/250, Premed; UV-VIS spectrophotometer model 118 C, Varian; derivatograph (TGA/DTA analyser), Q 1500 D, MOM (Hungary); X-ray diffractometer TUR M 62 (Germany); shaker equipped with temperature controller, model 357, Elpan.

Table I. Loss in mass during heating of the samples analysed

Sample	Mass loss [%] in the temperature range		
	20–120°C	120–320°C	320–550°C
β-CD	14.00	55.00	30.78
IB	1.00	81.10	17.90
IB-β-CD inclusion complex	4.50	66.70	28.80
Physical mixture of IB and β-CD	4.20	61.20	34.50

IB solutions in ethanol (0.03 mol/l) and CD solutions in water (0.03 mol/l) were prepared.

50 mL of β-CD aqueous solution, heated to 60 °C, were added to 50 ml of IB ethanolic solution. The above mixture was shaken for 12 h at room temperature and then allowed to stand in a refrigerator at 4 °C. The precipitate obtained was centrifuged at 2500 rpm, dried at 50 °C under a reduced pressure to constant weight and screened through a 100 μm sieve. The drug content in the co-precipitated sample was determined by UV spectroscopy; the molar ratio in the solid complex obtained was 1 : 1.

The product of the complexing reaction was investigated by means of X-ray diffraction (XRD) and thermogravimetric analysis in order to verify its identity. XRD measurements were performed by using nickel-filtered CuK_α (λ = 1.5418 Å) radiation (X-ray tube voltage: 30 kV, current: 30 mA). The compounds investigated were identified by comparing XRD patterns of the complex with those of pure IB, β-CD and their mechanical mixture. The XRD patterns are shown in Figure 1. Thermogravimetric analysis was carried out by using the same derivatograph parameters as those given in Ref. [9]. The identity of the samples analysed was verified on the ground of mass loss curves. The loss in mass is listed in Table I.

In order to determine the solubility of IB, 10 mg portions of IB were placed in Erlenmeyer flasks of 25 mL in capacity and then 10 mL of water or an aqueous solution of β-CD (0.1 mol/l) were added. The suspensions were shaken for 30 min and allowed to stand for 24 h in a thermostat at 20 °C. Then the samples were filtered through G-4 filtering crucibles and the IB content in the filtrates was determined spectrophotometrically at a wavelength of λ_{max} = 222 nm. Results of the measurements of IB solubility in water and aqueous solution of β-CD are given in Table II.

The kinetics of the decomposition of IB and its inclusion complexes with β-CD were studied using an accelerated ageing test. 10 mg portions of IB or 20 mg portions of its inclusion complex with β-CD were placed in glass ampoules of 10 mL capacity, then the ampoules were sealed and left for 1440 h in a thermostated chamber at 50, 70 and 90 °C. After 360, 720, 1080 and 1440 hours at a given temperature, 3 ampoules were taken from the thermostat and the IB content

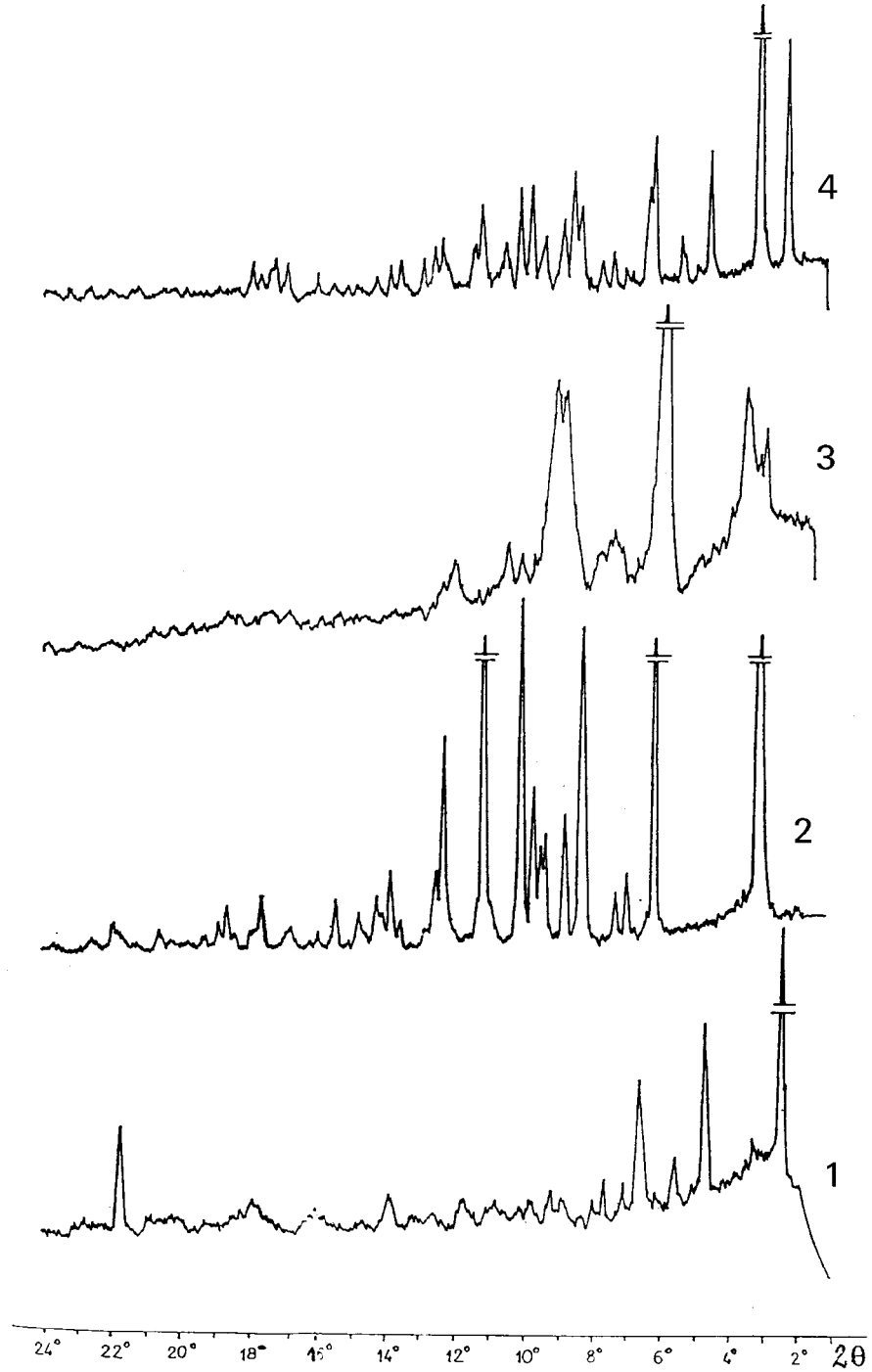

Figure 1. X-ray diffraction patterns: (1) β-CD; (2) IB; (3) IB-β-CD inclusion complex; (4) physical mixture of IB and β-CD.

Table II. Ibuprofen solubility

Solvent	Solubility [μg/mL]
Distilled water	11.8
Aqueous solution of β-CD (0.1mol/l)	66.3

was determined by means of chromatography and spectrophotometry. An ethanolic solution of IB or its inclusion complex with β-CD, equivalent to 100–200 μg of the pharmacologically active compound, was placed on a starting line of a chromatoplate coated with silica gel G according to Stahl, activated for 1 h at 105 °C. Chromatograms were developed along a 16 cm path using ethyl acetate-methanol-ammonia in the ratio of 85 : 10 : 5 as a mobile phase. Then the chromatoplates were dried at room temperature and observed in UV light (254 nm). The spot of the substance analysed (R_f value consistent with a standard) was contoured, then the gel scraped out of the spot was eluted with 2 mL of absolute ethanol and the eluate absorbance was measured at a wavelength of λ_{max} = 222 nm in a 1 cm cell. Ethanol was used as a reference.

The results of the absorbance measurements were used to plot the dependence of the change in ibuprofen concentration with time (Figure 2). The least squares method was employed for the preparation of the plot. The reaction rate constants at different temperatures were calculated, using the slope of the straight line representing the function $A = f(t)$, according to the formula

$$A = A_0 - k_0 t$$

where A is the concentration of undecomposed substance – mol/l, A_0 is the initial concentration of substance – mol/l, k_0 is the zero order reaction constant and t is the reaction time – [s].

Moreover, the half-life time $t_{0.5}$ and the time of the 10% decomposition $t_{0.1}$ were calculated. The rate constants of IB decomposition (a reaction of zero order) at different thermostating temperatures were used to make Arrhenius plots (Figure 3).

The results of the kinetic studies of the decomposition of IB and its inclusion complexes with β-CD are shown in Table III.

3. Discussion

The products of the complexing reaction, obtained by the co-precipitation method, were subjected to XRD and thermogravimetric measurements to verify their identity. The X-ray powder patterns for the individual components, complex and physical mixture (1 : 1), are reported in Figure 1. A comparision of the IB-β-CD diffraction patterns with that of the physical mixture can be interpreted as an approximate

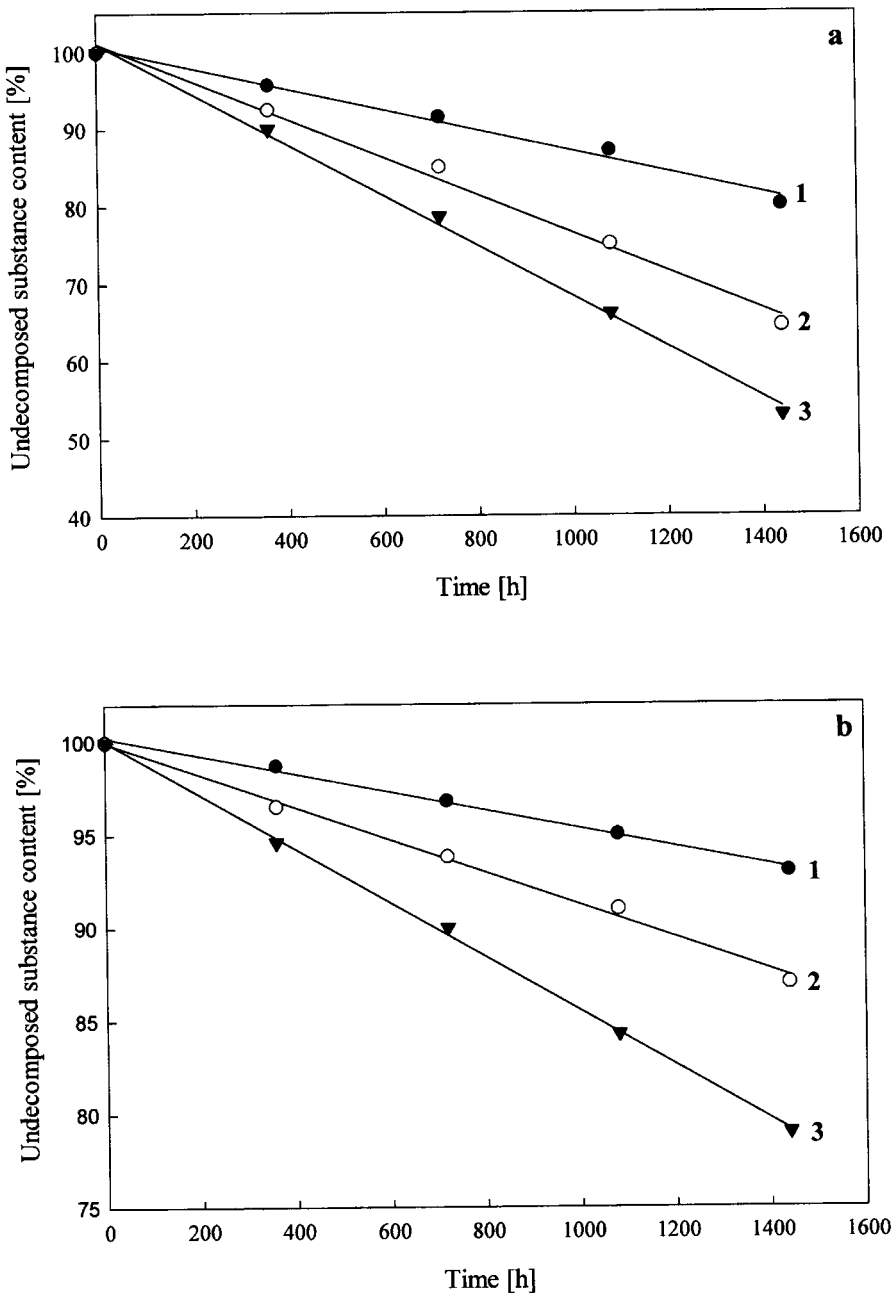

Figure 2. Kinetics of the decomposition of: (a) IB, (b) IB-β-CD inclusion complex: (1) at 50 °C, (2) at 70 °C, (3) at 90 °.

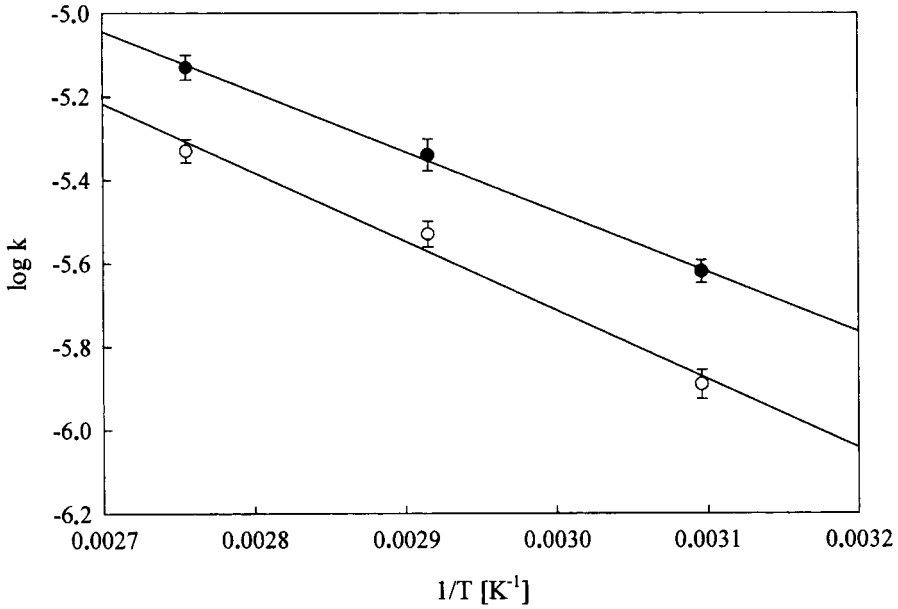

Figure 3. Arrhenius plots for the decomposition of: ● IB; ○ IB-β-CD inclusion complex.

Table III. Parameters of the decomposition of IB and the IB-β-CD inclusion complex

Parameter		IB	
	Temperature [°C]	Unbound	Bound to β-CD in the inclusion complex
k_0 [mol dm^{-3} s^{-1}]	50	2.40×10^{-6}	1.30×10^{-6}
	70	5.01×10^{-6}	2.95×10^{-6}
	90	7.40×10^{-6}	4.70×10^{-6}
$t_{0.5}$ [h]	50	5787	10 684
	70	2771	4 708
	90	1877	2 955
$t_{0.1}$ [h]	50	1157	2 137
	70	554	942
	90	375	591
E_a [kJ mol^{-1}]		27.66	31.54
Arrhenius equation parameters		$a = -1.1580 \pm 0.1970$	$a = -0.7627 \pm 0.6209$
		$b = -1439 \pm 67$	$\beta = -1650 \pm 212$
		$r = 0.9989$	$r = 0.9918$

superposition of the components. The X-ray pattern of the inclusion complex (Figure 1) shows only peaks characteristic of the IB-β-CD complex, namely at 3, 8.5 and 9.5 2Θ degrees, which points to the formation of a new crystal lattice of the inclusion complex.

The mass loss values, calculated from thermogravimetric curves, for the IB-β-CD complexes are considerably different from those for pure IB and β-CD (Table I) which suggests differences in the composition of the above samples.

The results of the determination of the ibuprofen content in the inclusion complex gives the ratio of the guest molecules to the host molecules as 1 : 1.

On the grounds of the studies of the water solubility of free IB and IB bound to β-CD in the inclusion complex, it was established that the presence of β-CD results in an increase of the IB solubility by a factor of 5.

In order to determine the effect of β-CD on the stability of IB, the samples (IB an IB-β-CD complex) were subjected to the accelerated ageing test for a period of 2 months at 50, 70 and 90 °C. It was found that the pharmacologically active compound, both free and bonded in the inclusion complex with β-CD, decomposes. The latter shows, however, a higher stability.

The influence of the temperature of decomposition of IB in the solid phase follows according to the Arrhenius equation. The straight-line of the plot $\log k = f(1/T)$ makes possible the calculation of the activation energy (E_a). The activation energy of the inclusion complex is higher than that of uncomplexed IB.

The kinetic order of the thermal decomposition of IB and its inclusion complex with β-CD was determined from the plot ($[A] = f(t)$) showing the linear dependence of the undecomposed substance concentration on the time at various temperatures. It has been established that the above reaction is of zero order. Parameters of the decomposition of the samples studied, calculated by using kinetic equations ($y = a + bx$), are listed in Table III. Data shown in the table indicate that a temperature increase by 20 °C results in a twofold increase in the decomposition reaction rate constant. A further increase in temperature affects the above parameter only to a smaller extent.

Of particular importance is the fact that IB bound to β-CD in the inclusion complex shows higher thermal stability. The decomposition times, $t_{0.5}$ and $t_{0.1}$, for the above complex are almost twice as long as in the case of unbound substances.

Analysis of the results obtained gives the following conclusions:

- Co-precipitation of IB with β-CD results in the formation of an inclusion complex in the solid phase.
- The mole ratio of the components in the complex is 1 : 1.
- The complexation with β-CD leads to a considerable increase in IB solubility in water.
- The inclusion complex formation has a stabilising effect on the pharmacologically active substance and this fact is confirmed by the kinetic parameters of the thermal degradation.

References

1. F. Barbato, M. La-Rotonda, and F. Quaglia: *J. Pharm. Sci*. **86**, 225 (1997).
2. H. D. Höltje: *Pharm. Ztg*. **140**, 8 (1995).
3. X. Y. Su, R. Al-Kassas and A. Li Wan Po: *Eur. J. Pharm. Biopharm*. **40**, 73 (1994).
4. B. Bole-Vunduk, K. Verhnjak and J. Zmitek: *J. Pharm. Pharmacol*. **48**, 1153 (1996).
5. F. A. Menard, M. G. Dedhiya, and C. T. Rhodes: *Drug Dev. Ind. Pharm*. **14**, 1529 (1988).
6. DN. D. Chow and A. H. Karara: *Int. J. Pharm*. **28**, 95 (1986).
7. J. Szeman and J. Szejtli: *Acta Pharm. Technol*. **33**, 27 (1987).
8. N. Nambu, M. Shimoda, Y. Takahashi, H. Ueda and T. Nagai: *Chem. Pharm. Bull*. **26**, 2952 (1978).
9. T. Hładoń and B. Ćwiertnia: *Acta Polon. Pharm. – Drug Research* **54**, 421 (1997).