Pharmaceutical Chemistry Division[1], University Institute of Pharmaceutical Sciences, and Department of Chemistry[2], Panjab University, Chandigarh, India

# Kinetics of degradation of diclofenac sodium in aqueous solution determined by a calorimetric method

R. Chadha[1], N. Kashid[1], D. V. S. Jain[2]

*Received January 17, 2003, accepted March 9, 2003*

*Dr. Renu Chadha, Reader Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160014, India*
*renukchadha@rediffmail.com*

*Pharmazie 58: 631–635 (2003)*

An isothermal heat conduction microcalorimeter has been used to study the stability of diclofenac sodium both alone and its inclusion complex with β-cyclodextrin in aqueous solution. The rates of heat evolved during degradation of diclofenac sodium have been measured by a highly sensitive microcalorimetric technique as function of concentration, pH and temperature. The calorimetric accessible data have been incorporated in the equations for determination of rate constants, change in enthalpy and order of reaction. The decomposition of diclofenac sodium both alone and its inclusion complex with β-cyclodextrin in solution corresponds to a pseudo-first order reaction. The values of rate constants, k's at 338.15 K, (calculated from the variation of heat evolution with the time) for the degradation of diclofenac sodium at pH 5, 6, 7, 8 and its inclusion complex with β-cyclodextrin at pH 7 are found to be $4.71 \times 10^{-4}$, $5.69 \times 10^{-4}$, $6.12 \times 10^{-4}$, $6.57 \times 10^{-4}$ and $4.26 \times 10^{-4}$ $h^{-1}$ respectively. There is good agreement between calorimetric determined $t_{0.5}$ and literature values. It has been found that β-cyclodextrin retards the degradation of diclofenac sodium. The kinetic parameters have been calculated for the reaction. The negative entropy of activation suggests the formation of an ordered transition state.

## 1. Introduction

Recent developments in isothermal microcalorimetry allow the direct determination of both kinetic and thermodynamic parameters for slow reactions over long durations from studies conducted at appropriate temperature and under designated environmental control. The heat effects produced due to degradation are influenced only by the progress of the reaction and unaffected by static conditions existing in the solution. The technique has a wide scope to study the solid state as well as the solution stability profiles of simple as well as complex reactions following consecutive, first order mechanism of drugs, drug/excipients and dosage forms [1–12] and thermodynamic properties [13]. Thus, the technique of calorimetry has much potential in the prediction of long-term stability and compatibility data for pharmaceutical materials [5–7]. An alternative to the standard HPLC method is to use isothermal microcalorimetry. Microcalorimetry has been shown, in some instances, to give more information as to the mechanism, kinetics and thermodynamics of a degradation reaction than either conventional techniques can provide [1]. It has also been demonstrated to be more sensitive than HPLC analysis, enabling less valuable time to be spent on stability or compatibility testing.

Diclofenac is not freely solubile in water due to its hydrophobicity and is also susceptible to photo-degradation in aqueous solution [14]. The formation of two degradation products of diclofenac sodium in solution, solid state [15] and gel-ointment [16] has been demonstrated recently. The recommended storage conditions for the parenteral dosage form of diclofenac sodium state [17] to protect ampoules for injection from heat and light. The stability of diclofenac sodium and its inclusion complexes with β-cyclodextrin in solid state [18] show that the inclusion complexation makes diclofenac sodium more thermal stable. However, no detailed study has been reported on the effect of pH and temperature on the stability of diclofenac sodium in solution except one report in which the undecomposed drug in absence and presence of cyclodextrins has been determined [12]. A recent study has reported the pH dependent formation of an indolinone derivative as a product under the conditions of autoclaving [19].

The present study is undertaken to explore the potential of isothermal microcalorimetric technique in determining the stability of diclofenac sodium over the pH range 5–8 and its inclusion complex with β-cyclodextrin in solution. The kinetic and thermodynamic parameters of its degradation have been determined.

## 2. Investigations, results and discussion

Heat evolved as a function of time has been studied for solution of diclofenac sodium at different initial concentrations in the temperature range 318.15–338.15 K and in aqueous solution (pH range 5–8) for eight days. In one case the study was carried for 21 days. Similar studies are

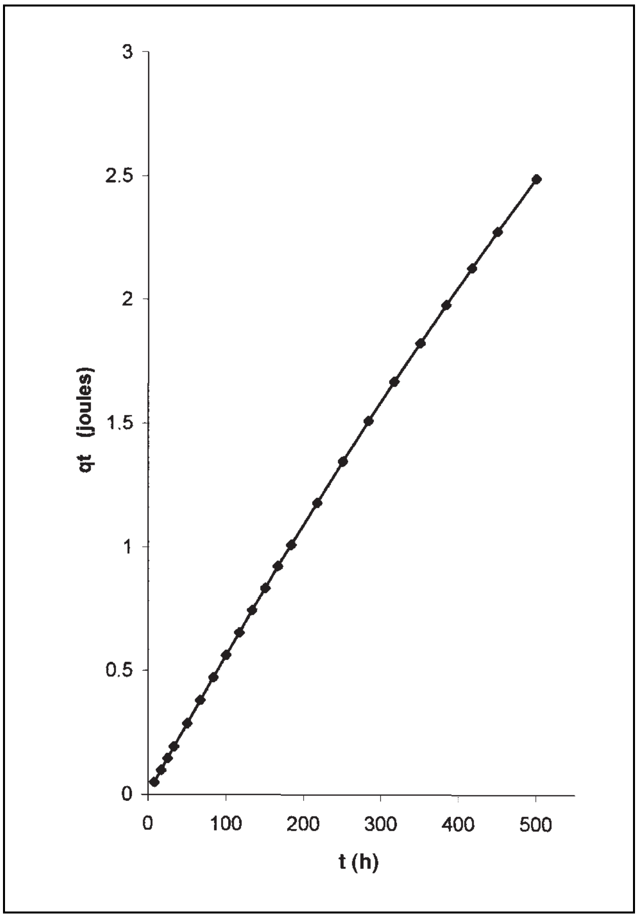


Fig. 1: Heat evolution vs time for degradation of diclofenac sodium ($9.43 \times 10^{-3}$ M and pH 8) at 338.15 K

carried out on its inclusion complex with β-cyclodextrin also. The data of heat evolution vs. time are plotted in Fig. 1.

It is assumed that total heat produced during degradation is proportional to the initial concentration of drug ($q_0 = c_0V\,\Delta_rH^0$) for first order reaction [1]. Here $c_0$ is the initial concentration of the drug, V is the volume (in litre) of the solution taken in the calorimeter and $\Delta_rH^0$ is the enthalpy of degradation reaction. The heat evolved up to time t, $q_t = (c_0 - c)\,V\,\Delta_rH^0 = q_0 - cV\,\Delta_rH^0$ where, c = concentration of the drug at any time.

It can be shown that

$$\frac{dq_t}{dt} = k(q_0 - q_t) \tag{1}$$

$$\ln\frac{q_0}{(q_0 - q_t)} = kt \tag{2}$$

From the calorimetric data we know $q_t$ but due to slowness of reaction, only a small fraction of the drug degrades even in 8 days and therefore for determining of $q_0$ we follow the following procedure. It is known that $dq_t/dt$ is a function of time and if denote $dq_t/dt = \phi$ and determine the value of $\phi$ at two different times $t_1$ and $t_2$, we have at

$$t = t_1 \quad \phi_1 = k(q_0 - q_{t1})$$

$$t = t_2 \quad \phi_2 = k(q_0 - q_{t2})$$

$$\frac{\phi_2}{\phi_1} = \frac{q_0 - q_{t2}}{q_0 - q_{t1}} \tag{3}$$

**Table 1: Heat evolved at various time intervals for concentration $9.43 \times 10^{-3}$ M at pH 5 and 338.15 K.**

| t (min) | $10^2 \times q_t$ (joules) | $\ln(q_0 - q_t)$ |
|---|---|---|
| 500 | 4.0 | 2.337 |
| 1000 | 8.1 | 2.333 |
| 1500 | 12.1 | 2.329 |
| 2000 | 16.2 | 2.325 |
| 3000 | 24.2 | 2.317 |
| 4000 | 32.1 | 2.309 |
| 5000 | 40.0 | 2.302 |
| 6000 | 47.8 | 2.294 |
| 7000 | 55.5 | 2.286 |
| 8000 | 63.2 | 2.278 |
| 9000 | 70.9 | 2.270 |
| 10000 | 78.5 | 2.262 |
| 11000 | 86.0 | 2.254 |

or

$$q_0 = q_{t1} + \frac{q_{t1} - q_{t2}}{\phi_2/\phi_1 - 1} \tag{4}$$

where,

$q_0$ = total heat evolved in degradation reaction starting with V litre of solution with initial concentration ($c_0$)
$q_{t1}$ = heat evolved up to time $t_1$
$q_{t2}$ = heat evolved up to time $t_2$
$\phi_1$ = rate of heat evolution at $t_1$
$\phi_2$ = rate of heat evolution at $t_2$

$$\text{and} \quad \Delta_rH^0 = q_0/c_0V \tag{5}$$

The $q_0$ is estimated using eq. (4). Table 1 gives value of heat evolved up to various interval of time for concentration $9.43 \times 10^{-3}$ M at pH 5 and 338.15 K. The value for $q_0$ has been calculated to be 10.39 joules. It may be noted that $q_0$ is proportional to the initial concentration of the drug where $(q_0 - q_t)$ is proportional to concentration of the drug at time t.

The values of $\Delta_rH^0$ calculated from eq. (5) with two different initial concentrations are given in Table 2. It can be seen that the value differs slightly with pH and temperature but is otherwise in excellent agreement with each other for two different initial concentrations of the drug. $\Delta_rCp^0$ is also calculated from temperature dependence of $\Delta_rH^0$ at different pH and these are also given in Table 3.

For the first order reaction the rate constant is given by the equation

$$k = 1/t \ln\frac{q_0}{q_0 - q_t} \tag{6}$$

The plots between ln $(q_0 - q_t)$ against t are straight lines (Fig. 2) at various concentrations and pH. The values of first order rate constant, k, calculated from the slope of the straight line plot at different concentration, pH and temperature are given in Table 2. The values of k for two concentrations ($6.29 \times 10^{-3}$ and $9.43 \times 10^{-3}$ M) are constant within the experimental limit at a particular pH and temperature indicating that the reaction follows pseudo first order kinetics.

There is a number of research articles indicating the occurence of an indolinone derivative (III) during degradation of diclofenac sodium [15, 16, 19–21]. Its yield is supposed to decrease with increase in pH [19]. However, the presence of two orthochlorine atoms in the benzene ring and the presence of C=O in the indoline makes the N–C bond susceptible to hydrolysis which should be faster at higher pH, the hydrolysis products being the dichloro phe-

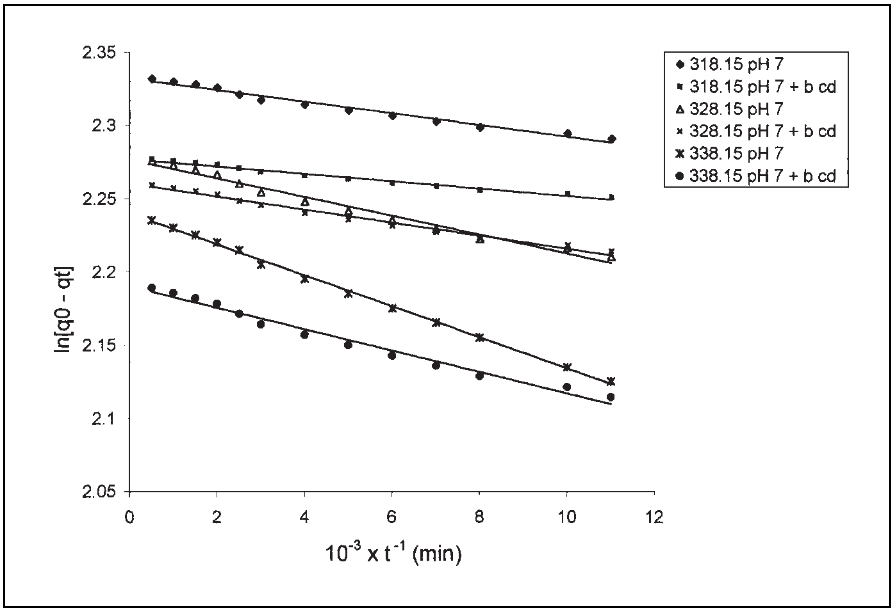


Fig. 2:
First order plots for the degradation of diclofenac sodium ($9.43 \times 10^{-3}$ M) at pH 7 and its inclusion complex with β-cyclodextrin at 318.15–338.15 K

Table 2: **Kinetic parameters of degradation of diclofenac sodium over the pH range 5–7 and of its inclusion complex with β-cyclodextrin at pH 7**

| pH | $10^3 \times$ [DS] (M) | $\Delta_rH^0$ (kJ $mol^{-1}$) | $q_0$ (joules ) | $10^4 \times k$ ($hr^{-1}$) | $t_{0.5}$ (days) |
|---|---|---|---|---|---|
| 318.15 K | | | | | |
| 5 | 6.29 | −239.2 | 7.52 | 1.65 | 175 |
| | 9.43 | −239.2 | 11.28 | 1.62 | 178 |
| 6 | 6.29 | −228.0 | 7.17 | 2.03 | 142 |
| | 9.43 | −228.1 | 10.76 | 1.99 | 145 |
| 7 | 6.29 | −218.5 | 6.87 | 2.31 | 125 |
| | 9.43 | −218.8 | 10.32 | 2.34 | 123 |
| 8 | 6.29 | −204.8 | 6.44 | 2.66 | 109 |
| | 9.43 | −205.9 | 9.71 | 2.71 | 107 |
| 7+ | 6.29 | −209.3 | 6.58 | 1.47 | 196 |
| β-CD | 9.43 | −206.9 | 9.76 | 1.48 | 195 |
| 328.15 K | | | | | |
| 5 | 6.29 | −229.6 | 7.22 | 2.72 | 106 |
| | 9.43 | −229.8 | 10.84 | 2.75 | 105 |
| 6 | 6.29 | −214.7 | 6.75 | 3.30 | 88 |
| | 9.43 | −215.6 | 10.17 | 3.25 | 89 |
| 7 | 6.29 | −208.3 | 6.55 | 3.76 | 77 |
| | 9.43 | −207.1 | 9.77 | 3.76 | 77 |
| 8 | 6.29 | −197.8 | 6.22 | 4.23 | 68 |
| | 9.43 | −197.4 | 9.31 | 4.13 | 70 |
| 7+ | 6.29 | −204.2 | 6.42 | 2.66 | 109 |
| β-CD | 9.43 | −203.5 | 9.60 | 2.59 | 111 |
| 338.15 K | | | | | |
| 5 | 6.29 | −220.1 | 6.92 | 4.71 | 61 |
| | 9.43 | −220.3 | 10.39 | 4.71 | 61 |
| 6 | 6.29 | −208.0 | 6.54 | 5.65 | 51 |
| | 9.43 | −207.4 | 9.78 | 5.72 | 50 |
| 7 | 6.29 | −198.1 | 6.23 | 6.12 | 47 |
| | 9.43 | −198.2 | 9.35 | 6.11 | 47 |
| 8 | 6.29 | −188.6 | 5.93 | 6.65 | 43 |
| | 9.43 | −188.3 | 8.88 | 6.48 | 45 |
| 7+ | 6.29 | −190.8 | 6.00 | 4.25 | 68 |
| β-CD | 9.43 | −190.0 | 8.96 | 4.27 | 68 |
| 344.15 K | | | | | |
| 7.4 | – | – | | 4.81[a] | 60[a] |
| 7.4 | – | – | | 2.88 [b] | 100[b] |

Literature values for diclofenac sodium[a] and its inclusion complex[b] [12]

Table 3: **Arrhenius parameters for the degradation reaction of diclofenac sodium over the pH range 5–7 and of its inclusion complex with β-cyclodextrin at pH 7**

| pH | $E_a$ (kJ $mol^{-1}$) | Log A | $\Delta_rCp$ kJ $mol^{-1}K^{-1}$ |
|---|---|---|---|
| 5 | 47.29 | 3.97 | 0.95 |
| 6 | 46.42 | 3.92 | 1.02 |
| 7 | 43.23 | 3.46 | 1.02 |
| 8 | 39.97 | 2.99 | 0.85 |
| 7+ β-CD | 47.46 | 3.96 | 0.89 |

nol (IV) and oxindole (V). Eyjolfsson has also detected the peaks corresponding to degrade (II) and (III) in the solution of diclofenac sodium in a HPLC mobile phase (phosphate buffer pH 2.5 / methanol, 34/66, v/v) on standing for 7 days in the presence of atmospheric oxygen and white light.

We propose a tentative mechanism for the degradation of diclofenac sodium shown in the Scheme.

It is proposed that a rapid equilibrium exists between I and II which is then converted into the indolinone derivative. This hydrolyzes to give IV and V. It can be seen that at no stage oxidation take place. Therefore, the suggestion that ferric ions or oxygen facilitate oxidation is not correct. However, the present ferric ion may act as a Lewis acid and may facilitate the cyclization process by bonding

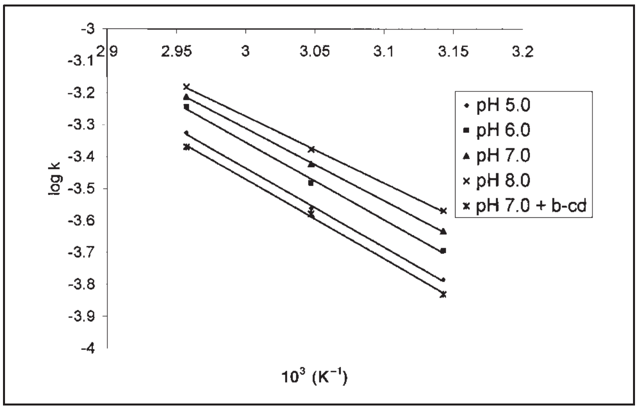
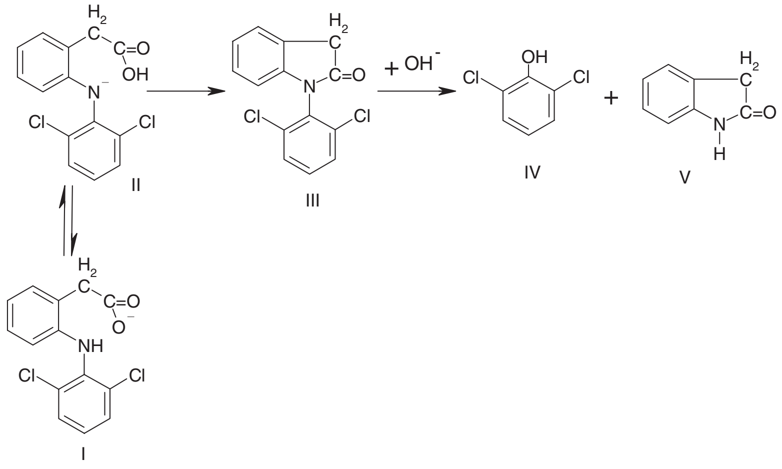


Fig. 3: The Arrhenius plot for degradation of diclofenac sodium

## Scheme



to $-COO^-$. Large negative entropy of activation also suggests the formation of an ordered transition state.

The specific rate constant for decomposition is less at weakly acidic pH 5 and it increases with pH (Table 2). Diclofenac (pKa 4.2), a weak acid, exists in solution in mainly ionized form between pH 6–8. The effect of pH can not be due to ionic strength effects since all the buffers have been prepared with an ionic strength equal to 0.2 M. The rate constant determined is the overall rate constant and the dependence on pH is not easy to decipher. The kinetic studies at lower pH were not performed due to the drugs poor solubility.

A degradation study of diclofenac sodium was also performed in its inclusion complex with β-cyclodextrin at pH 7. The 1 : 1 stoichiometry of diclofenac sodium and β-cyclodextrin inclusion complex formation in aqueous solution has been established by solution microcalorimetry [22] and spectrofluorimetry [23]. Values for the rate constants for the degradation of the inclusion complex of diclofenac sodium with β-cyclodextrin (1 : 1) in solution for ($6.29 \times 10^{-3}$ M and $9.43 \times 10^{-3}$ M) initial concentrations at pH 7 are given in Table 2. Lower values of rate constants in the presence of β-cyclodextrin suggest that cyclodextrin has a stabilizing effect on the drug. The results prove that the degradation of diclofenac sodium both alone and in its inclusion complex with β-cyclodextrin occurs according to the pseudo-first-order reaction. To our knowledge there is no literature data for the rate constants under these experimental conditions for the comparison our results. There is one report regarding the influence of β-cyclodextrin on degradation of diclofenac sodium with and without cyclodextrin [12]. The reported values of $t_{0.5}$ are in agreement with our results.

**Table 4: Activation parameters for the degradation reaction of diclofenac sodium over the pH range 5–7 and of its inclusion complex with β-cyclodextrin at pH 7 at 318.15 K**

| pH | $\Delta G^*$ (kJ mol$^{-1}$) | $\Delta S^*$ (J K$^{-1}$ mol$^{-1}$) | $\Delta H^*$ (kJ mol$^{-1}$) |
|---|---|---|---|
| 5 | 122.28 | −264.12 | 47.28 |
| 6 | 122.29 | −264.96 | 46.41 |
| 7 | 121.90 | −274.70 | 43.22 |
| 8 | 121.52 | −284.40 | 39.96 |
| 7 + β-CD | 123.11 | −263.42 | 47.45 |

## 3. Experimental

### 3.1. Chemicals

Diclofenac sodium (99.9% pure) procured as gift sample from Ind-swift ltd, India and β-cyclodextrin (AR) supplied by E. Merck (Germany) were used without further purification. The drug was sieved and fractions with a particle size of 300–350 μm were used throughout the study. Phosphate buffers were prepared using AR grade chemicals by mixing solutions of monosodium and disodium salts of phosphoric acid [24]. The ionic strength of all phosphate buffers was 0.2 M. The pH values of all phosphate buffers were measured using a pH meter (Elico, India) calibrated with standard solutions of pH 4.0, 7.0 and 9.2. No attempt was made to exclude oxygen from the solution.

In order to determine the stability of the drug in cyclodextrin both constituents were taken in a 1 : 1 molar ratio. The solutions of β-cyclodextrin were prepared in phosphate buffer (pH 7.0). To obtain 1 : 1 stoichiometry with diclofenac sodium in solution 10 mg and 15 mg of drug was mixed to 5 ml $6.29 \times 10^{-3}$ M and $9.43 \times 10^{-3}$ M concentrations of β-cyclodextrin solution, respectively.

### 3.2. Solution calorimetry

A heat flux microcalorimeter model-C-80 (Setaram, France) was used to study the degradation process of diclofenac sodium in phosphate buffers and aqueous solution of β-cyclodextrin. In accordance with the Calvet principle, two experimental vessels (reference and sample) were placed in a calorimetric block. The temperature control by the thermostat of calorimeter was within ± 0.001 K.

Degradation of diclofenac sodium was followed by loading the reference cell of the calorimeter with 5 ml of buffer of desired pH/cyclodextrin solution of desired concentration. The sample cell was filled with 5.00 ml of desired buffer and an accurately weighed amount (10.00 mg and 15.00 mg) of drug, which was separated from the liquid by a displaceable lid. After stabilization the calorimetric block containing the vessels was rotated by 180° several times, which displace the lid between the drug and solution leading to their mixing [13]. The signal was automatically recorded on the strip chart recorder. The reaction was followed for 8 days except for the degradation study of drug at pH 8 and temperature 338.15 K where the reaction was monitored for 21 days. The deviation of the sample signal from the base line is the rate of heat produced by the sample and is proportional to the reaction rate at that particular concentration, pH and temperature.

The performance of the calorimeter was tested by measuring the enthalpy of solution of potassium chloride in triple-distilled water [25]. The precision of any individual measurement was better than 0.02 kJ mol$^{-1}$ for three consecutive experiments and agreed with the standard value within ± 0.03 kJ mol$^{-1}$. The samples were weighed in the lower container of the calorimetric vessel itself using a single pan Mettler balance with an accuracy of ± 0.01 mg. Therefore, the maximum error in concentration due to their experimental uncertainties is ± 0.003 M.

Acknowledgement: The financial assistance provided to one of the author (N. Kashid) by the University Grants Commission, New Delhi (India) is gratefully acknowledged.

## References

1 Willson, R. J.; Beezer, A. E.; Mitchell, J. C.; Loh, W.: J. Phys. Chem. **99**, 7108 (1995)
2 Beezer, A. E.; Gaisford, S.; Hills, A. K.; Willson, R. J.; Mitchell, J. C.: Int. J. Pharm. **179**, 159 (1999)
3 Pikal, M. J.; Dellerman, M.: Int. J. Pharm. **50**, 233 (1989)
4 Buckton, G.; Beezer, A. E: Int. J. Pharm. **72**, 181 (1991)
5 Oliyai, R.; Lindenbaum, S.: J. Pharm. Sci. **73**, 30 (1991)
6 Willson, R. J.; Beezer, A. E.; Mitchell, J. C.: Thermochim. Acta **264**, 27 (1995)
7 Willson, R. J.; Beezer, A. E.; Mitchell, J. C.: Int. J. Pharm. **132**, 45 (1996)
8 Phipps, M. A.; Mackin L. A.: PSTT **3** (1), 9 (2000)
9 Loftsson T. Brewster M. J. Pharm. Sci. **85**, 1017 (1996)
10 Angberg, M.; Nystrom, M.; Castensson, S.: Acta. Pharma. Suec. **25**, 307 (1988)
11 Oliyai, R.; Lindenbaum, S.: Int. J. Pharm. **73**, 33 (1991)
12 Backensfeld, T.; Muller, B. W.; Kolter K.: Int. J. Pharm. **74**, 85 (1991)
13 Jain, D. V. S.; Kashid, N.; Kapoor, S.; Chadha, R.: Int. J. Pharm. **201,** 1 (2000)
14 Bonomi, L.; Perfetti, S.; Bellucci, R.; Massa, F.; De Franco, I.: Ann. Opthalmol. **19**, 142 (1987)
15 Eyjolfsson, R.: Drug. Dev. Ind. Pharm. **26**, 451 (2000)
16 Karamancheva, I.; Dobrev, I.; Brakalov, L.; Andeeva, A.: Anal. Lett. **31**, 117 (1998)
17 Lund, W.; Editor. The pharmaceutical codex, London, p. 836, The Pharmaceutical Press
18 Cwiertnia, B.; Hladon, T.; Stobiecki, M.: J. Pharm. Pharmacol. **51**, 1213 (1999)
19 Roy, J.; Islam, M.; Khan, A. H.; Das, S. C.; Akhteruzzaman, M.; Deb, A. K.; Mahbub Alam, A. H.: J. Pharm. Sci. **90**, 541 (2001)
20 Larsan, C.; Bundgaard, H.: Arch. Pharm. Chem. Sci. Ed., **8**, 100 (1980)
21 Racz, I.: Drug Formulation p. 352., Wiley, Budapest 1990
22 Chadha, R.; Kashid, N.; Kumar, A.; Jain, D. V. S.: J. Pharm. Pharmacol. **54**, 481 (2002)
23 Arancibia, J. A.; Escandar, G. M.: Analyst. **124**, 1833 (1999)
24 G. D. Christian, in Analytical chemistry, 4th edition, pp. 143–145. John Wiley & Sons, Inc., New York 1986
25 Balk, P.; Benson, G. C.: J. Phys. Chem. **63**, 1009 (1959)