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Studies on Inclusion Complex of 2-[4'-Benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole

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The compound 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole has been synthesized in its pure form. Since the drug is insoluble in polar solvent, its bioacessibility is low. To increase the solubility of the compound, its inclusion complex has been prepared with β-cyclodextrin. The formation of inclusion complex has been ascertained by study of spectral characteristic before and after inclusion complex formation. The stability of inclusion complex and nature of interaction between the host and guest are known from the study of thermodynamic parameters like change in free energy, change in enthalpy and change in entropy. The study of antimicrobial properties (antibacterial and antifungal) of the compound increases significantly after inclusion complex formation.

Key Words: 2-Aminobenzothiozole, Inclusion complex, β-Cyclodextrin, Phase solubility, Thermodynamic stability, Antimicrobial activity.

INTRODUCTION

Benzothiazole and its derivatives are well known pharmacophores exhibiting a wide spectrum of pharmacological activities such as antitubercular[1], antimicrobial[2], antifugicidal[3-5] and antiallergic[6]. The amino (-NH_2) group of 2-aminobenzothiazole can be used as a very good target for condensing with 2-oxo-azetidine and their 4-benzylidene moieties generating a series of 2-[4'-arylidene-2'-substituted phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole which have significant antimicrobial activities[7-16].

Since bioacessibility of a drug depends upon its solubility, one of the factors limiting the pharmacological activities of 2-aminobenzothiazole derivatives is their insolubility in aqueous solution[17]. The solubility of this compound can be enhanced by forming inclusion complex with cyclodextrin (CD) which in turn increase their drug efficiency[18]. Among the natural cyclodextrins only the more available β form has certain prospects in application than the other forms (α and γ) because it is cheaper, easily available and has higher stability with respect to heating and oxidation.

In the present work an attempt has been made to synthesize 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1, 3-benzothiazole in its pure form and to prepare its inclusion complex with β-cyclodextrin. The formation of compound and its inclusion complex has been ascertained by the study of spectral characteristics. Thermodynamic properties of the inclusion complex have been studied to have an idea about the stability of the compound in β-cyclodextrin cavity. Finally antibacterial and antifungal activities of the compound and its inclusion complex have been studied to examine whether inclusion complex formation is enhancing the bioacessibility of the drug or not.

EXPERIMENTAL

All chemicals are procured from the local market and are of suitable analR grade. Double distilled water is used as solvent for dilution. Other solvents employed are redistilled before use. The elemental analysis has been performed in a CHN analyzer. Electronic spectra are recorded on Shimadzu UV-1700 spectrophotometer while IR spectra are recorded in KBr pallets in the range of 4000-400 cm^{-1} region in a Shimadzu 8400 S FTIR spectrophotometer. Melting points are recorded by open capillary method.

Phase solubility measurements: The aqueous phase solubility of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole at various concentration of β-cyclodextrin has been studied by Higuchi Connors method[19]. Accurately weighed sample of these compounds in quantities exceeding their aqueous solubility are shaken in a rotary flash shaker at room temperature with aqueous solution of β-cyclodextrin in increasing concentration (0-7 mM) in a series of stoppered conical flasks for a period of 48 h till equilibrium is established. The solutions are filtered through Whatman No. 1 paper and are analyzed in a UV-VIS spectrophotometer at 200-400 nm

range. The various values of optical density at λ_{max} have been plotted against different concentration of β-cyclodextrin.

Synthesis of compound 2-(benzylidene)imino-1,3-benzothiazole (I): The pure compound has been synthesized as follows. Equimolar solution of 2-aminobenzothiazole (5 g, 0.03 mol) and benzaldehyde (3.38 mL, 0.03 mol) with few drops of glacial acetic acid in MeOH (50 mL) is refluxed on a water with bath for about 1 h. The solvent was removed *in vacuo* and the residue was purified over the column of silica gel using $CHCl_3$. The product is crystallized from ethanol to give 2-(benzylidene)imino-1,3-benzothiazole (**I**).

Synthesis of compound 2-[2'-(phenyl)-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole (II): A mixture of the compound **I** (3 g, 0.01 mL) and thioglycolic acid (0.91 mL, 0.01 mol) in presence of $ZnCl_2$ in benzene (50 mL) is refluxed in a water bath for about 15 h. The solvent was removed *in vacuo* and the residue was purified over the column of silica gel using $CHCl_3$ as an eluent. The product is crystallized from ethanol to afford compound 2-[2'-(phenyl)-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole (**II**).

Synthesis of compound 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole (III): Equimolar solution of the compound **II** (2 g, 0.006 mol) and benzaldehyde (0.65 mL, 0.006 mol) in dioxane (20 mL) in the presence of C_2H_5OK is refluxed on a water bath for *ca.* 6 h. The solvent is removed *in vacuo* and the residue was purified over the column of silica gel using $CHCl_3$ as an eluent. The product was crystallized from ethanol to yield compound 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole (**III**). The synthesis of derivatives of 2-aminobenzothiozole is shown in **Scheme-I**.

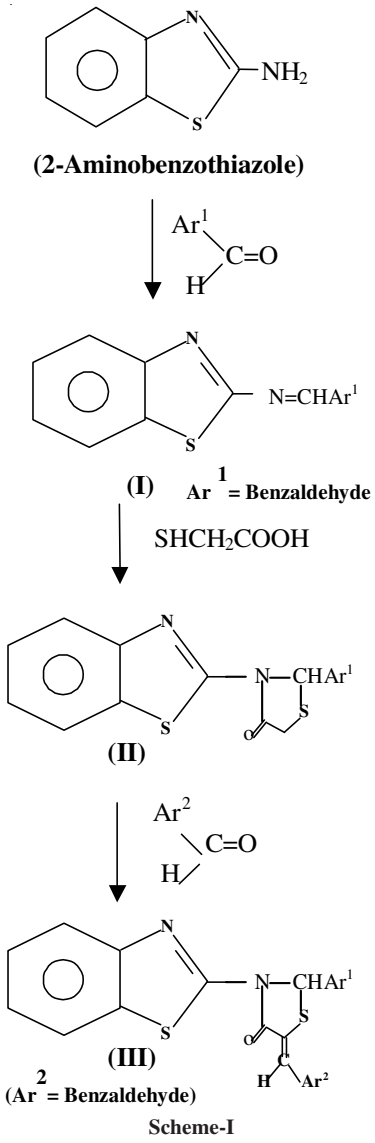
Synthesis of inclusion complex: The inclusion complex of the compound (2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole (**III**) has been prepared by Nayak *et al.*[15]. The solutions of the synthesized compound is prepared in required concentration (0.05 mM) and is added drop wise to previously stirred β-cyclodextrin solution. The mixture is stirred at room temperature for 48 h and filtered. Then the content is cooled for another 48 h in refrigerator. Finally the precipitate obtained is filtered through G-4 crucible, washed with double distilled water and dried in air for 24 h.

Study of thermodynamic properties: The thermodynamic stability constant (K_T) at room temperature of the complex is calculated using Benesi-Hilderbrand relation[20]. The stability constant K (during de-encapsulation) of the complex has been calculated with increasing temperature. The slope of the linear plot of ln K against 1/T gives rise to the calculation of ΔH (change in enthalpy) and then ΔS (change in entropy) is calculated using the integrated form of the Van't-Hoff equation:

$$\ln K = \left(-\frac{\Delta H}{RT}\right) + \frac{\Delta S}{R}$$

The value of ΔG was calculated from the value of K_T at 298 K using the equation

$$\Delta G = -RT \ln K_T$$



Scheme-I

Study of pharmacological properties: The antibacterial and antifungal properties of the drug 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole (**III**) and its inclusion complex with β-cyclodextrin has been studied as per Cappuccino[21] and Morley and Cooper[22,23], respectively.

RESULTS AND DISCUSSION

Synthesis of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole: The synthesis of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole is confirmed from elemental analysis and IR- data as shown in the Table-1. The elemental composition nearly matches with theoretical data. Infrared data of $C{=}O_{str}$ at 1689, $C{=}CHAr_{str}$ at 1639, $N\text{-}HC\text{-}S_{str}$ at 3049, *etc.*, suggest formation of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole. In addition both 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole and its inclusion complex with β-cyclodextrin differ significantly in their melting points (Table-1).

Synthesis of inclusion complex: The synthesis of inclusion complexes of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole have been confirmed

TABLE-1
ANALYTICAL DATA OF 2-[4'-BENZYLIDENE-2'-PHENYL-5'-OXO-1',3'-THIAZOLIDINE]-1,3-BENZOTHIAZOLE AND ITS INCLUSION COMPLEX WITH β-CYCLODEXTRIN

S. No.	Compound	m.p. (ºC)	Elemental analysis (%) found (calcd.)				λ_{max} (nm)	IR (KBr, ν_{max}, cm^{-1})
			C	H	N	S		
1	2-[4'-Benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole	203	71.48 (71.2)	4.12 (4.3)	3.6 (3.4)	20.8 (21.1)	261.0	1689 (C=O), cyclic 1639 (C=CHAr) 1294 (C-N) 3049 ((N-CH-S)
2	Inclusion complex with β-cyclodextrin	212	–	–	–	–	259.8	1676 (C=O), cyclic 1629 (C=CHAr) 3047 (N-CH-S)

from melting point data and spectral characteristics. (UV-VIS and IR) (Table-1). The melting point of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole is 203 ºC while that of the inclusion complex with β-cyclodextrin is 212 ºC. A higher melting point of inclusion complex than 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole itself is due to the fact that extra amount of thermal energy is required for the later to bring it out of β-cyclodextrin cavity.

Study of spectral characteristics: The drug recipient interactions are better identified by employing UV and IR spectrophotometry[24]. The absorption maxima are shown to undergo a distinct blue shift after their inclusion complex formation with β-cyclodextrin (Table-1 and Fig. 1). This observation clearly demonstrates transference of the compound from a more protic environment to a less protic environment (cavity of β-cyclodextrin). The compound and β-cyclodextrin interaction leading to inclusion complex formation is further supported by IR data (Table-1). It is seen that the IR-stretching frequencies due to different bonds C=O, N-HC-S, C=CHAr *etc.*, in case 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole undergo a downward shift towards lower energy and the peaks become broader, weaker and smoother. Such changes in IR spectral characteristics due to the inclusion complex formation may be attributed to development of weak interactions like H bonding vander-Waal forces and hydrophobic interactions between host and guest molecules[25].

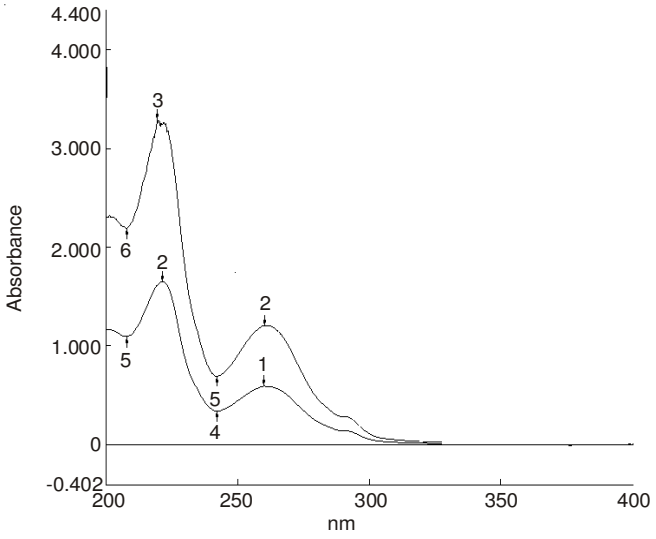


Fig. 1. Comparison of UV spectra of sample and its inclusion complex. Bold line (—) for sample and faded line (—) for inclusion complex

Phase solubility studies: The phase solubility plots of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole in a solution of β-cyclodextrin is shown in the Fig. 2. In such a case, it is seen that there is a linear increase in solubility of the compounds with increasing concentration of β-cyclodextrin. At a higher concentration of β-cyclodextrin, a small negative deviation is observed. Since the slope of plot is less than unity, the stoichiometry of the inclusion complexes is 1:1[26].

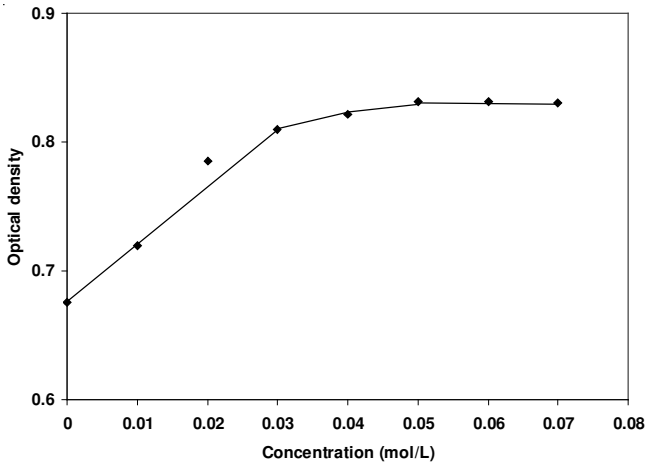


Fig. 2. Phase solubility plot of (optical density *versus* β-cyclodextrin with 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole)

The thermodynamic stability constants (K_T) of inclusion complexes are determined by following Benesi-Hilderbrand reaction:

$$\frac{1}{\Delta A} = \frac{1}{\Delta \epsilon} + \frac{1}{K[guest]_0 \Delta \epsilon} \frac{1}{[\beta - CD]_0}$$

Good linear correlation (Fig. 3) is obtained for a plot of $1/\Delta A$ *verses* $(1/\beta\text{-CD})_0$ for 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole. The value of K_T for the complex is calculated using the relation:

$$K_T = \frac{\text{Intercept}}{\text{Slope}}$$

The K_T value for this inclusion complex *i.e.*, 2-[5'-benzylidene-2'-phenyl-4'-oxo-1',3'-thiazolidine]-1,3-benzothiazole with β-cyclodextrin is found to be 522.42 M^{-1} at 298 K. The data obtained is with in 100-1000 M^{-1} (ideal values) indicating appreciable stability for the inclusion complexes[27].

Thermodynamic properties: The thermodynamic parameters associated with encapsulation of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole with in

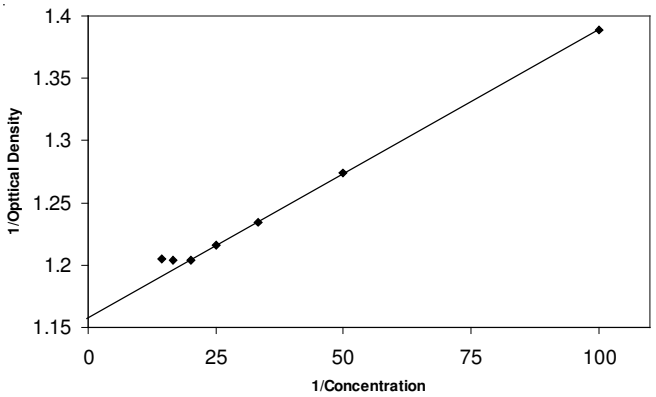


Fig. 3. Plot of (1/optical density *versus* 1/β-cyclodextrine with 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole)

β-cyclodextrin for 1:1 stoichiometry has been calculated by determining the K values at different temperatures. The K value is found to decrease with increasing temperature (deencapsulation) as expected for an exothermic process[28, 29]. The plot of ln K as a function of inverse absolute temperature produced a linear plot (Fig. 4). In such a case, the slope corresponds to (-ΔH/R). From this value and value of K_T at 298 K, ΔG, ΔS and ΔH have been calculated (Table-2).

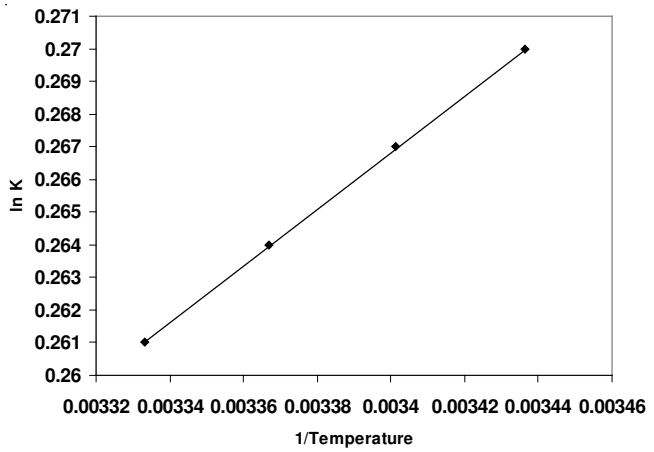


Fig. 4. Plot of ln K *versus* 1/temperature

As can be seen from the table, ΔG value is negative for the complex. The data clearly demonstrates the spontaneous formation of the inclusion complexes. Secondly a negative value of ΔH and a positive value of ΔS at 298 K suggest that the complex formation is an exothermic and enthalpy controlled process. The negative value of change in enthalpy and positive value of change in entropy are due to stabilization of compound with in the cavity of β-cyclodextrin by weak intermolecular forces as suggested earlier[30,31].

Pharmacological study: The data obtained from antibacterial study and antifungal studies suggest that both the antibacterial (*E. coli*) and antifungal activities (*P. notatum*) increases significantly after the formation of inclusion complexes (Table-3). This may be attributed to enhanced solubility of the drug. As the solubility increases, the drug becomes more bioacccessibile to specific tissue leading to increased drug activity.

Conclusion

From the above results and discussions, it is clear that the solubility of 2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole can be improved by inclusion complex formation with β-cyclodextrin which is a very good analytical tool for enhancing the bioavailability of drugs. Further the study furnishes information about the participation of non-covalent intermolecular forces in between the guest (drug) and host β-cyclodextrin.

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REFERENCES

1. S.S. Bhatt, B.R. Shah, P.B. Trivedi, N.K. Undavia and N.C. Desai, *Indian J. Chem.*, **33B**, 189 (1994).
2. B.D. Nask and K.R. Desai, *Asian J. Chem.*, **16**, 1749 (2004).
3. R. Yadav, S. Srivastava, S.K. Srivastava and S.D. Srivastava, *Chem. An Indian J.*, **1**, 95 (2003).
4. V. Kumar and R. Dhakarey, *J. Indian Coun. Chem.*, **46**, 20 (2003).
5. D.U. Warad, C.D. Satish, V.H. Kulkarni and C.S. Bajgur, *Indian J. Chem.*, **39B**, 415 (2000).
6. R.S. Lodhi and S.D. Srivastava, *Indian J. Chem.*, **37B**, 899 (1998).
7. S.K. Srivastava, S. Srivastava and S.D. Srivastava, *Indian J. Chem.*, **38B**, 183 (1999).

TABLE-2
THERMODYNAMICAL DATA OF INCLUSION COMPLEX OF 2-[4'-BENZYLIDENE-2'-PHENYL-5'-OXO-1',3'-THIAZOLIDINE]-1,3-BENZOTHIAZOLE AT 298 K

S. No.	Compound	K (M^{-1})	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (kJ/mol)
1	Inclusion complex with β-cyclodextrin of derivatives of 2-aminobenzothiazole with benzaldehyde	522	-15.5	-0.725	0.052

TABLE-3
PHARMACOLOGICAL DATA OF 2-[4'-BENZYLIDENE-2'-PHENYL-5'-OXO-1',3'-THIAZOLIDINE]-1,3-BENZOTHIAZOLE AND ITS INCLUSION COMPLEX WITH β-CYCLODEXTRIN

S. No	Compound	Concentration (μg/mL)	Antibacterial activity	Antifungal activity
			Zone of inhibition of *E. coli* (diameter) (mm)	Zone of inhibition of *Pencilinium notatum* (diameter) (mm)
1	2-[4'-benzylidene-2'-phenyl-5'-oxo-1',3'-thiazolidine]-1,3-benzothiazole	0.05	9	7
2	Inclusion complex with β-cyclodextrin	0.05	12	14

8. V.K. Panday, V.D. Gupta, M. Upadhyay and V.K. Singh, *Indian J. Chem*., **44B**, 158 (2005).
9. S.K. Srivastava, S.R. Yadav and S.D. Srivastava, *Indian J. Chem.*, **43B**, 399 (2004).
10. S. Giri and M. Khan, *J. Indian Chem. Soc*., **71**, 201 (1994).
11. S. Guru, R. Yadav, S. Srivastava, S.K. Srivastava and S.D. Srivastava, *J. Indian Chem. Soc*., **83**, 1236 (2006).
12. M.A.J.A. Khan and S.S. Shafi, *Asian J. Chem*., **15**, 1443 (2003).
13. K. Mistry and K.R. Desai, *E-J. Chem*., **1**, 189 (2004).
14. M. Purohit and S.K. Srivastava, *Indian J. Pharm. Sci*., **54**, 25 (1992).
15. S.S. Nayak, S. Panda, P.M. Panda and S. Padhy, *Bull. Chem. Commun*., **42**, 147 (2010).
16. K. Mistry and K.R. Desai, *Indian J. Chem.*, **45B**, 1762 (2006).
17. B. Pose-Vilarnovo, I. Perdomo-Lopez and M. Echezarreta-Lopez, *J. Pharm. Sci*., **13**, 325 (2001).
18. V.G. Belikov and E.V. Kompantseva, *Z. Khim-Farm*, **24**, 19 (1990).
19. T. Higuchi and K.A. Connors, *Adv. Anal. Chem. Instrum*., **4**, 117 (1965).
20. H.A. Benesi and J.H. Hildebrand, *J. Am. Chem. Soc*., **71**, 2703 (1999).
21. J.G. Cappuccino, Sherman Microbiology: A Laboratory Manual, Addison Wesley Longman, Inc., Tokyo, edn. 4, p. 329 (1999).
22. D.C. Morley, *J. Phathol. Bacteriol*., **157**, 379 (1945).
23. K.E. Cooper, *Nature*, **176**, 510 (1955).
24. K.G. Mohamed and C.A. Moji, *Pharm. Dev. Technol.*, **6**, 315 (2001).
25. Q. Chen and D. Guowang, *Chem. J.I*. **6**, 37 (2004).
26. A.P. Mukna and M.S. Nagarsenkar, *AAPS Pharm. Sci. Technol*., **5**, 19 (2004).
27. Z. Szetli, Molecular Entrapment and Release Properties of Drugs by Cyclodextrin, Controlled Drug Bioavailability, Wiley Interscience Publications, **3**, 365/420 (1985).
28. S. Tommasini, D. Raneri, R. Ficarra, M.L. Calabro and R. Stancanelli, *J. Pharm. Biomed. Anal*., **35**, 379 (2004).
29. R.A. Rajweski and V.J. Stella, *J. Pharm. Sci.*, **85**, 1142 (1996).
30. Y.L. Loukas, V. Vraka and G. Gregoridias, *J. Pharm. Biomed. Anal*., **16**, 263 (1997).
31. S.S. Nayak and S. Panda, *Res. J. Chem. Environ*., **13**, 57 (2009).