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Full Length Research Paper

Energetics of the interaction between piroxicam and beta-cyclodextrin (β-CD) in inclusion complexes

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The thermodynamic parameters of the inclusion complexation interaction of piroxicam and beta-cyclodextrin have been evaluated. Inclusion complexes of piroxicam and beta-cyclodextrin were produced by different methods such as physical mixture, kneading, coprecipitation, evaporation and heating under reflux. X-ray powder diffraction (XRPD) studies confirmed formation of inclusion complexes between piroxicam and beta-cyclodextrin. Positive Gibb's free energy (ΔG) values were obtained for all the inclusion complexes of piroxicam and beta-cyclodextrin suggesting that the interaction is favoured in non-spontaneous process (-that is, the process led to a decrease in the free energy of the system). The higher value of ΔG obtained at higher temperatures may be related to the surface vibration, as the temperature increases. The enthalpy (ΔH) values calculated for the beta-cyclodextrin - piroxicam inclusion complexation interaction were all negative as well as the ΔS values. All these indicate that the interaction were exothermic and spontaneous and is highly favoured and beta-cyclodextrin could be utilized in the complexation of piroxicam for increased solubility and stability.

Key words: beta cyclodextrin, piroxicam, XRPD, inclusion complex, energetics, interaction, stability.

INTRODUCTION

Cyclodextrins have been known for nearly a century and have been isolated by Villiers in 1891 from enzymatic (cyclodextrin glycosyl transferase from different *Bacilli spp* especially *B. macerans*) degradation of starch. They are cyclic oligosaccharides of α-D glucopyranose units, and are toroidal or cone-shaped compounds due to lack of free rotation around the bonds connecting the glucopyranose units with primary and secondary hydroxyl groups crowning the narrower rim and wider rim respecttively, (Loftsson et al., 1996). In aqueous solution, the "–CH" bonds on the ring of the structure points inward, producing a hydrophobic inner cavity and a hydrophilic outer surface, while the "OH" group extends from the top and bottom of the cylinder, producing sites for strong hydrogen bonding (Loftsson et al., 1996; Stella et al., 1997). The toxicity and biocompatibility of cyclodextrins has been studied extensively (Albers et al., 1995; Agu et al., 2005). Beta cyclodextrin (β-CD) improves the solubility (Guyot et al., 1995; Esclusa-Diaz et al., 1996), dissolution rate (Hassan et al., 1990; Moyano et al., 1995, as Loftsson and Brewster, 1996.), stability (Krenn et al., 1992; Zerrouk et al., 1998) and bioavailability of poorly water soluble drugs (Torres-Labandeira et al., 1994).

Piroxicam is a derivative of the oxicam group of non-steroidal anti-inflammatory drugs (NSAID). It is a 4-Hydroxy-2-methyl-N-(pyridin-2-yl)-2H-1, 2-benzothiazine-3-carboxamide-1,1-dioxide, a white slightly yellow and crystalline power, and is practically insoluble in water, with a molecular weight of 331.55 g (Ph. Eur., 2005).

Molecular encapsulation by means of macromolecular inclusion complex formation offers a new form of dosage. It involves the spatial entrapment of a simple "guest" molecule in the cavity of the "host" molecule without formation of any covalent bonds (Valero et al., 1996; and Stella et al., 1997). The bonding strength does not affect

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the dissolution and delivery of the drug from the CD complex (Stella et al., 1999).

The specific aim of the study was to evaluate the various energy changes related to the interaction of "guest" piroxicam with the "host" beta-cyclodextrin.

MATERIALS AND METHODS

Materials

Piroxicam was kindly provided by Drug Field pharmaceutical Ltd (Nigeria). β-CD was kindly supplied by S. A. Chemicals (India) and used without further treatment. All other chemicals and materials were of analytical grade and were used as such.

Methods

Preparation of complexes

β-CD-piroxicam inclusion complexes were formulated by different methods including physical mixing, co-precipitation, kneading and heating under reflux. The formation of inclusion complex was confirmed by X-ray powder diffraction (XRPD) analysis.

Physical mixtures

Appropriate amounts of piroxicam and β-CD to give 1:1 and 1:2 molar ratios were mixed thoroughly in a mortar by geometric dilution technique (Rosel et al., 2000). The physical mixture was sieved and stored in airtight container.

Kneading

Amounts of the piroxicam and β-CD to give 1:1 and 1:2 molar ratios were thoroughly mixed, wetted with a few drops of purified water and triturated with a mortar and pestle. The slurries were kneaded for 30 min, and dried at 25°C under vacuum for 24 h.

Co-precipitation

Amounts of the piroxicam and β-CD to give 1:1 and 1:2 molar ratios were accurately weighed. Piroxicam was dissolved in 20 ml of ether and β-CD was dissolved in 100 ml of water. The two solutions were mixed, agitated for 24 h at 28°C and then cooled to 2°C in a refrigerator. The mixture was filtered, washed with ether and dried at 25°C under vacuum for 24 h. The preparations were passed through a 250 µm mesh sieve.

Evaporation

Appropriate amounts of piroxicam and β-CD were dissolved in methanol and stirred for 24 h at 28°C to prepare 1:1 and 1:2 molar ratios. Then, the mixture was concentrated under vacuum, filtered, and dried under vacuum at 25°C for 24 h.

Heating-under-reflux

Appropriate amounts of piroxicam and β-CD were weighed and added to 25 ml of distilled water to prepare 1:1:and 1:2 molar ratios. ratios. The mixture was heated under reflux for 1 h and then stirred with a magnetic stirrer at room temperature intermittently for 5 days. The solution was concentrated to 10 ml under vacuum and then cooled in a refrigerator for 1 h, filtered and dried under vacuum at 50°C. The product was stored in a desiccator over silica gel until used (Hassan et al., 1990). To exclude the possibility of piroxicam degradation by heat during the preparation of the complex, thin layer chromotagraphy (TLC) was performed. Exactly mg of the prepared inclusion complex was dissolved in 10 ml of methylene chloride as a test solution. The reference solution consists of 10 mg of piroxicam dissolved in 10 ml of methylene chloride. A spot of each solution was applied onto a TLC plate and developed in a solution consisting of acetonitrile : potassium dihydrogen phosphate (2:3). The TLC plate was dried under a current of warm air and examined under UV light at 254 nm.

Thermal stability

Various quantities of the complex batch containing theoretical 1.2 mg of piroxicam were weighed using analytical balance (KERM 770, Germany). Each was poured inside separate test tube. Each test tube and the content was heated in a water bath maintain at 40 ± 1°C for 3 h. These were repeated at 60 and 80°C. The concentration of piroxicam after the predetermined time intervals was analyzed spectrophotometrically at wavelength of 320 nm using dichloromethane as blank.

RESULTS AND DISCUSSION

X-ray studies confirmed the formation of inclusion complexes between β-CD and piroxicam. (Figures 1-7) show XRPD of the different 1:1 complexes where there was increase in the halo of the diffractograms seen between the arbitrary units of 0 and 0.25 (y-axis) formed on mixing the two compounds and the reduction in intensity of the prominent piroxicam peak at 2θ = 8.7°. This resulted in increase in the volume of the beta-cyclodextrin due to inclusion of piroxicam.

In a system in which inclusion complexation is taking place, the stability is a function of the concentration terms of the "guest", "host", and the complex, and generally obeys the following equation:

$$K_S = \frac{[\beta - CD - Drug]}{[Drug][\beta - CD]} \qquad \text{Eq. 1)}$$

Where K_S is the binding constant, which encompasses the stability, and the non-covalent bonding or entrapment of "guest" in the "host". The values of K_S will, of course, change at various temperatures as is evident when the binding constant, K_S is plotted against the reciprocal of temperature. These plots were used to establish the values of ΔH using the equation below (Florence et al., 1981).

$$Log\ K_S = \frac{\Delta H}{2.303R}\frac{1}{T} + C \qquad \text{Eq. 2)}$$

Where R is the gas constant and T is the thermodynamic or Kelvin temperature, and C is a constant.

The negative values of ΔH shown in (Table I) indicate

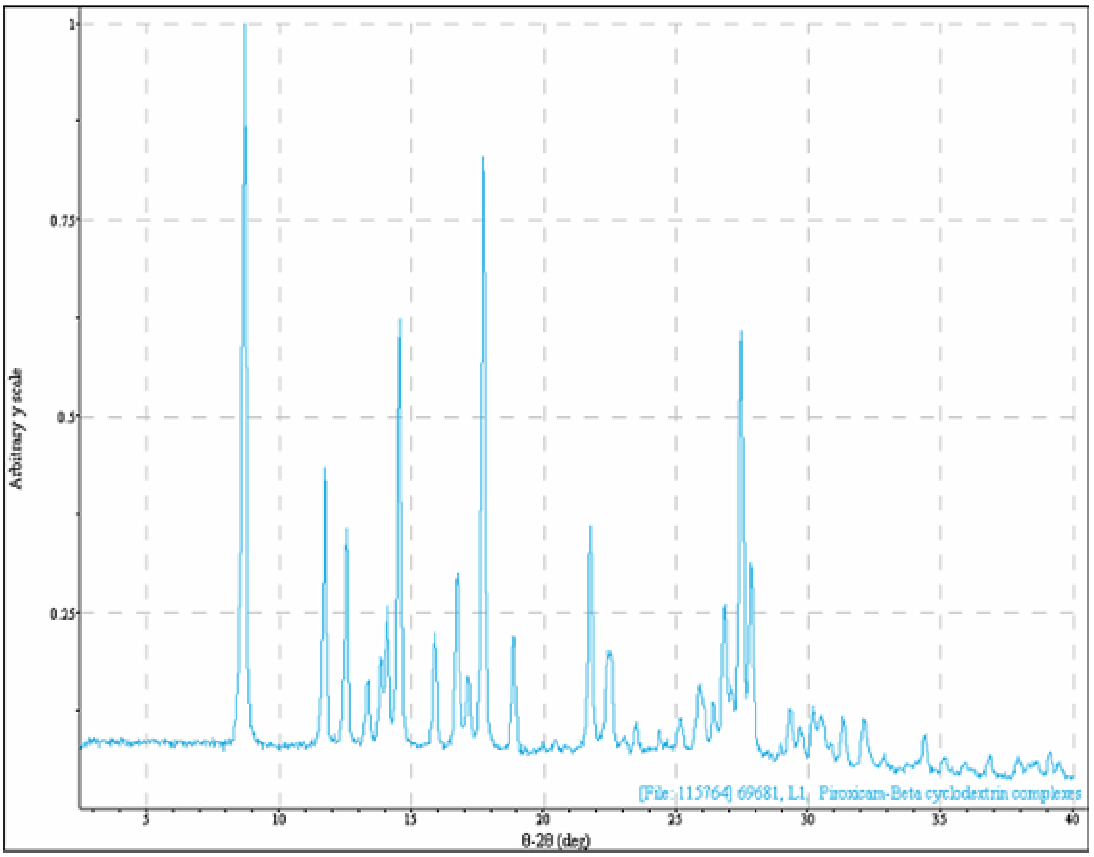

Figure 1. X-ray diffraction pattern of pure piroxicam.

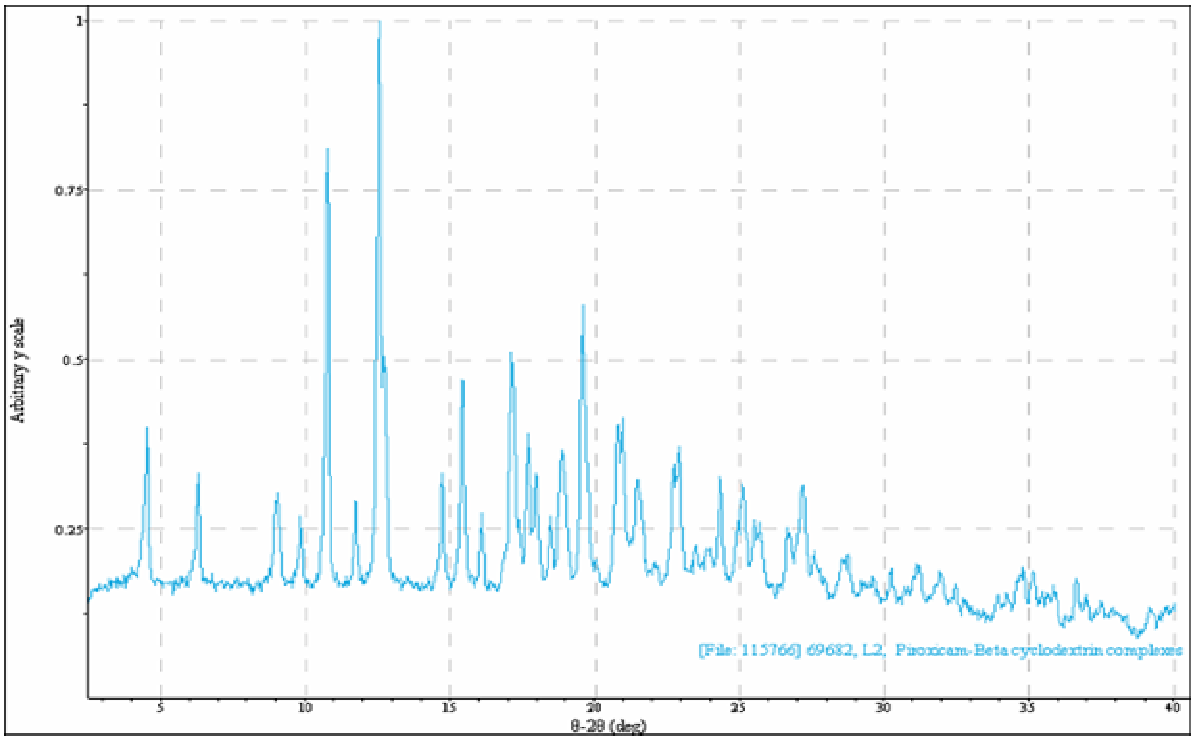

Figure 2. X-ray diffraction pattern of beta-cyclodextrin.

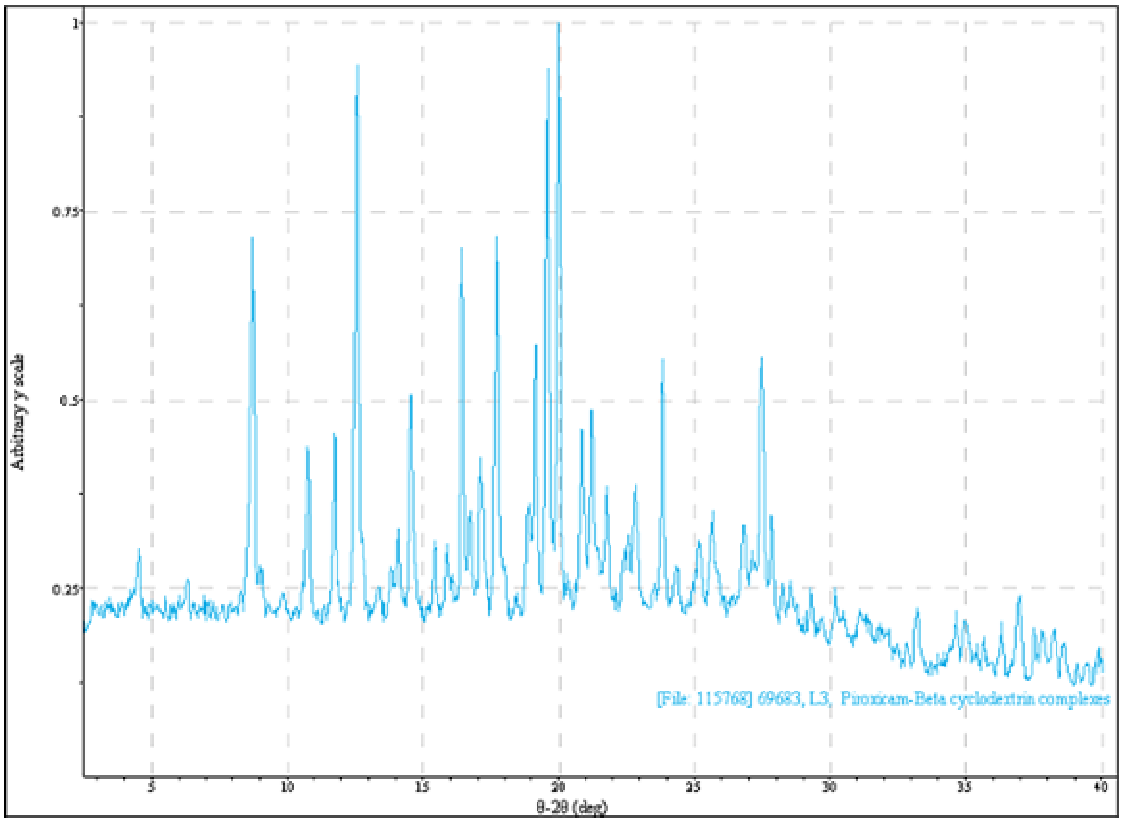

Figure 3. XRPD pattern for piroxicam-beta-cyclodextrin complex prepared by physical mixing (1:1).

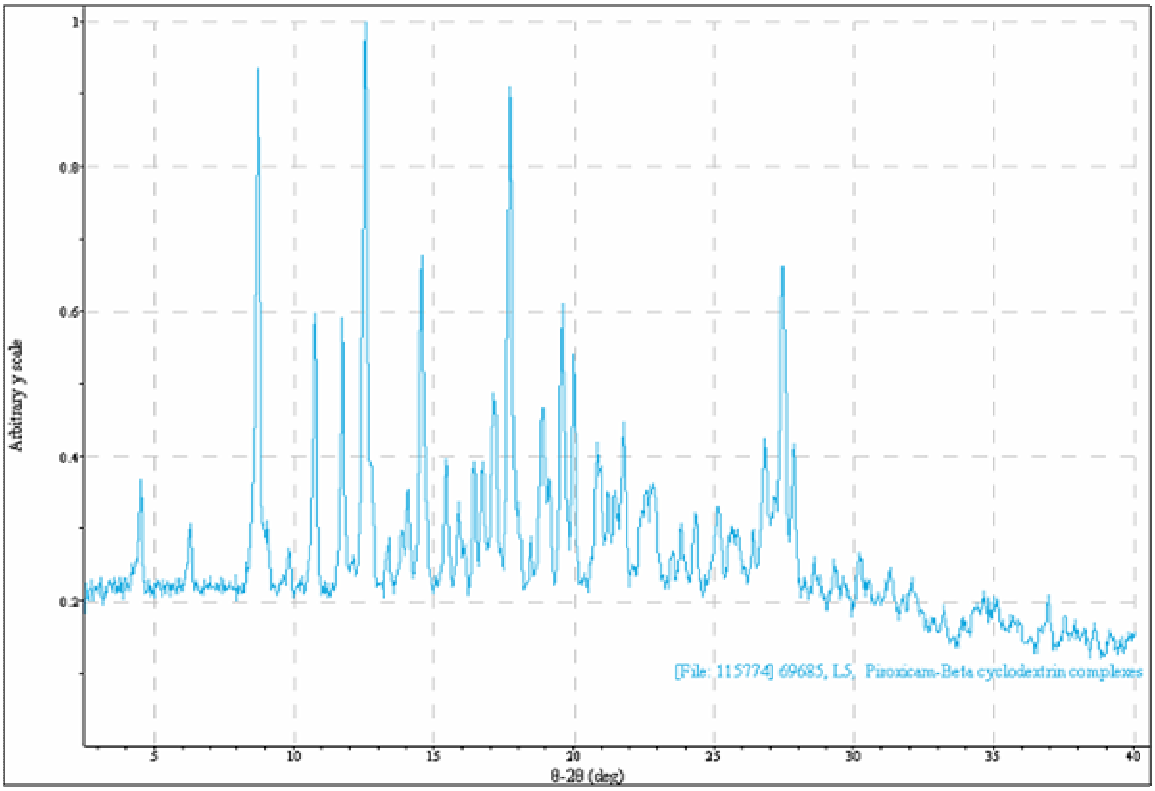

Figure 4. XRPD pattern for piroxicam-beta-cyclodextrin complex prepared by kneading (1:1).

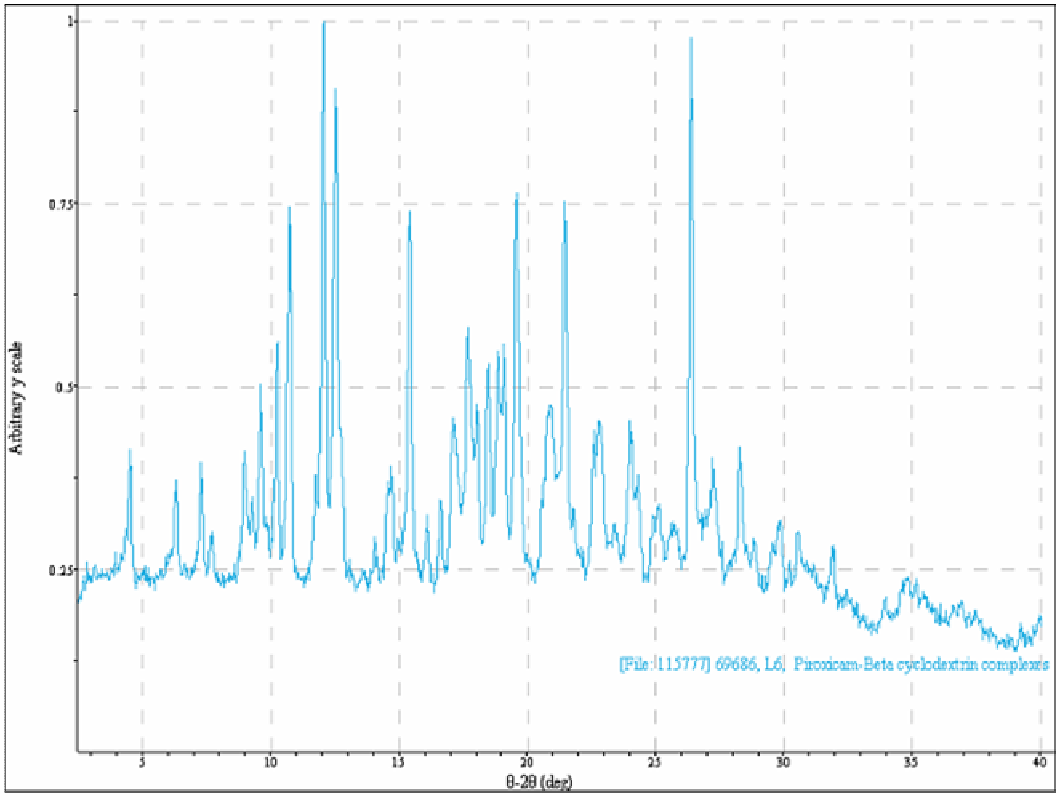

Figure 5. XRPD pattern for piroxicam-beta-cyclodextrin complex prepared by co-precipitation (1:1).

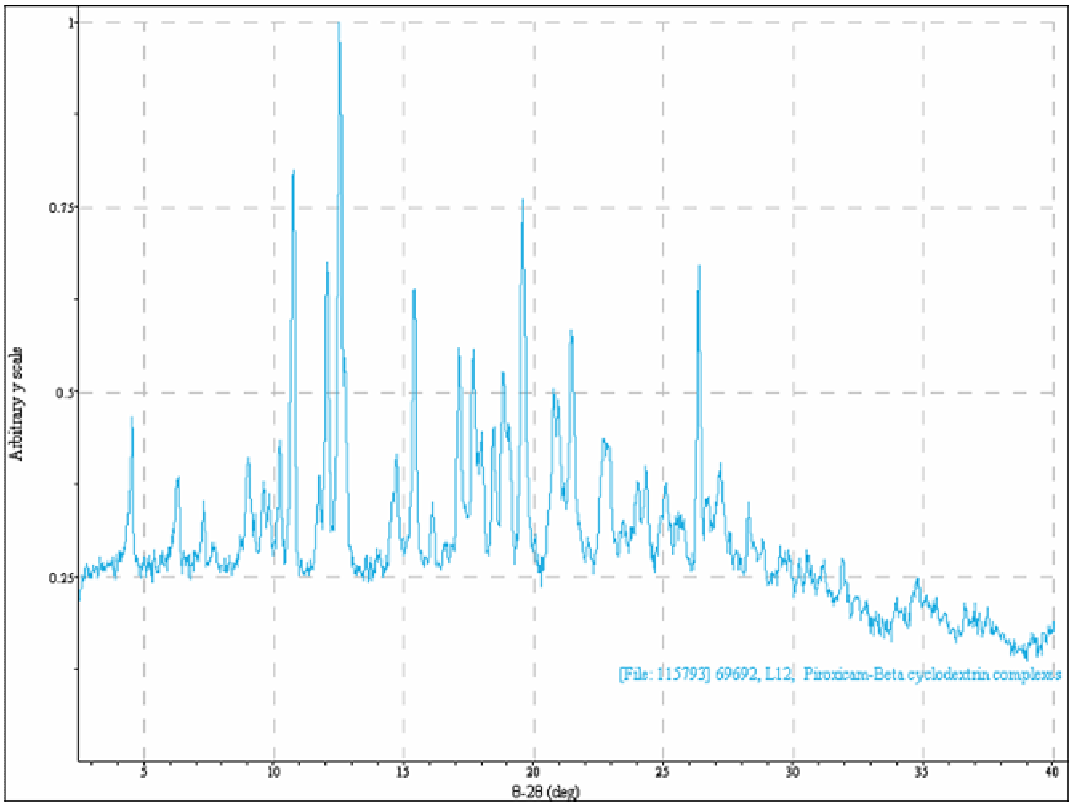

Figure 6. XRPD pattern for piroxicam-beta-cyclodextrin complex prepared by evaporation (1:1).

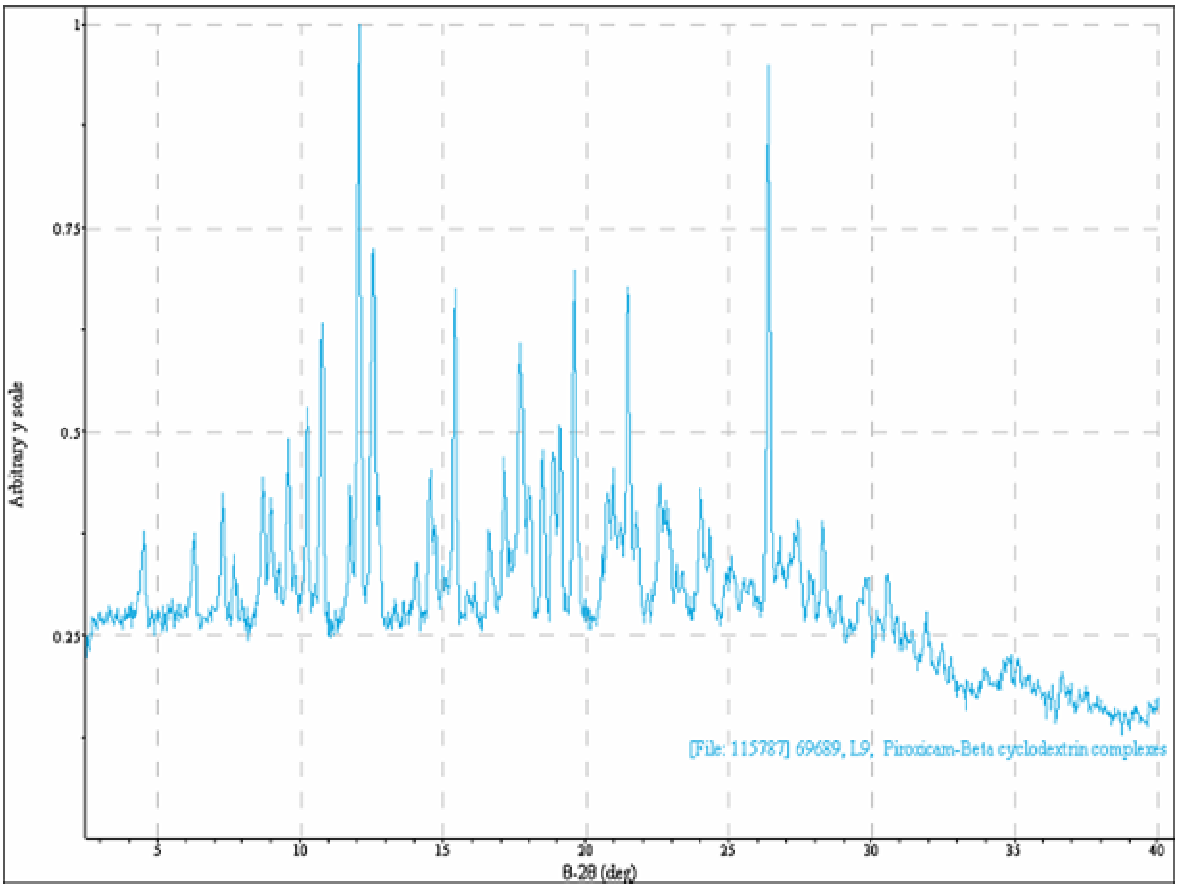

Figure 7. XRPD pattern for piroxicam-beta-cyclodextrin complex prepared by heating under reflux (1:1).

that the interaction is exothermic (Richard, 1972). The physical mixture (1:2) batches had small values of ΔH when compared to other batches and their corresponding molar ratios. Thus smaller energy is liberated in the heating-under-reflux inclusion method.

The value of standard free energy change of the inte-- raction ΔG is shown in (Table I). The values were determined from the expression (Martin et al., 1993).

$\Delta G = -2.303RT\log K_S$ ……Eq. 3)

All the parameters in Eq. 3 retain the same definition as in Eq. 2.

The higher values of ΔG obtained at higher temperature may be related to surface vibrations, which increase as the temperature is increased (Adikwu and Ofokansi, 1998).

At low temperature, it is assumed that there exists a fixed number of interaction sites, all having the same free energy and hence the same interaction potential, and that the occupation of a given site does not affect the occupation of existing sites or a saturation state which corresponds to the occupation of all available sites. It excludes the possibility that an increase in temperature or even entrapped molecule may create a new interaction site.

Thus, we can talk of a bulk site, which exists within the face of the molecule. The difference between the potential energies of a bulk site and a surface site is termed the heat of segregation. The energy or heat of segregation, β may be calculated from equation:

$$\beta = exp.\frac{\Delta G}{RT} \quad \text{……..Eq. 4)}$$

In most solids such as alloys, this free energy of segregation (sometimes called surface enrichment) is mostly affected by the dissolved material; that is, the lower component of the alloy (Bernard, 1983).

In powder systems, the enrichment factor is majorly determined by the extent of communication. Generally, inclusion or entrapment of “guest” in the inner surface of a “host” will lead to changes in the electrochemical properties of the complex. In this study since one must consider the interaction of the “host” inner surface with water molecules for substances suspended in water, the ease of wetting may affect the degree of interaction.

Thus, the total surface exposed will affect the extent of interaction. Each surface has a surface free energy,

Table 1. Thermodynamic parameters of inclusion complexes of piroxicam in the beta cyclodextrin.

Batch	ΔS^{40} (J. mol^{1})	ΔS^{60} (J. mol^{-1})	ΔS^{80} (J. mol^{1}	ΔH (J.K^{1}mol^{-1})
Physical mixture 1.1	1790.8	2657.8	3596.8	-11.17
Physical mixture 1.2	3079.8	3931.5	4592.9	-7.93
Kneading 1.1	1662.5	2235.4	3262.0	-9.75
Kneading 1.2	2859.9	3868.1	4602.7	-9.76
Evaporation 1.1	1332.8	1470.7	2735.8	-8.73
Evaporation 1.2	2727.5	3622.9	4496.2	-10.07
Co-precipitation 1.1	1210.2	1340.5	2614.6	-8.85
Co-precipitation 1.2	2663.7	3254.1	4326.1	-9.36
Heat under Reflux 1.1	855.6	1098.4	2102.0	-8.05
Heat under Reflux 1.2	3016.0	3673.6	4626.7	-9.76

Table 2. Entropy values of the inclusion complexes of piroxicam in the beta-cyclodextrin.

Batch	ΔG^{40} (J. mol^{-1})	ΔG^{60} (J. mol^{-1})	ΔG^{80} (J. mol^{-1})
Physical mixture 1.1	-5.8	-8.0	-10.8
Physical mixture 1.2	-9.9	-11.8	-13.8
Kneading 1.1	-5.3	-6.7	-9.8
Kneading 1.2	-9.2	-11.6	-13.9
Evaporation 1.1	-4.3	-4.4	-8.2
Evaporation 1.2	-8.7	-10.9	-13.5
Co-precipitation 1.1	-3.9	-4.1	-7.9
Co-precipitation 1.2	-8.5	-9.8	-13.0
Heat under Reflux 1.1	-2.8	-3.3	-6.3
Heat under Reflux 1.2	-9.7	-11.0	-13.9

which unlike surface tension may be difficult to measure. The quantity of energy needed from external sources to cause the interaction is dependent on this free surface energy. The extra energy may be provided by a minimal increase in temperature, which could be provided by agitation of the system. Excess addition of energy into the system may lead to decrease in interaction. This decrease could be as a result of thermal roughing of the "host" surface (Bernard, 1983). Thermal roughing may lead to distortion of the interaction site. In any experiment the means of detecting and controlling surface defects at ambient temperatures is usually uncertain. The problem is even more acute when it comes to attempting to measure the increasing number of surface defects that are inevitably produced on heating a specimen. At high temperatures, the defects present in a surface will be predominantly those determined by equilibrium thermodynamics. It would be of both theoretical and practical importance to know equilibrium defect concentrations but there is, in fact, little information on what these concentrations are or on how they vary with temperature. There are however strong indications that surfaces may be very rough on an atomic scale and that it is important to understand the dynamic behaviour of defects.

The degree of atomic-scale roughening depends on the crystallographic orientation (Bernard, 1983). The standard entropy change, ΔS, associated with the interaction of "guest" in the "host" was calculated from the Gibb-Helmotz equation (Heys, 1970).

$$\Delta S = \frac{\Delta H - \ddot{A}G}{T} \qquad \text{Eq. 5)}$$

The negative values of ΔS show a decrease in disorderly orientation of the "guest" molecules in the interaction, that is their freedom was decreased (Table 2). Higher values of ΔS at higher temperatures denote possible dissociation of the complexes at elevated temperatures. It has been shown in this study that the interaction of the 'guest" piroxicam with the "host" depends on the thermodynamic parameters which magnify the effects of chemical, physical or even biological reaction. Generally ΔH and

ΔG becomes more negative as the stability constant for molecular complexation increases. Although, the negative ΔS value is unfavourable to complexation, the large ΔH overcomes the unfavourable entropy contribution leading to favourable ΔG value.

The negative ΔS value indicates that electrostatic forces are not important, but the large negative values of ΔH and ΔS suggest hydrogen bonding between piroxicam and the cyclodextrin (Martin, 1993).

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REFERENCES

Adikwu MU, Ofokansi KC (1998). Energetics of the adsorption of some drug onto the sclerotium of *Pleurotus tuber-regium*. Boll. Chim. Farm. 137(5): 165 –169.

Agu RU, Jorissen M, Willems T, Van den Mooter G, Kinget R, Verbeke N, Augustijns P. (2005). Safety assessment of selected cyclodextrins - effect on ciliary activity using a human cell suspension culture model exhibiting in vitro ciliogenesis. Int J Pharm. 193(2):219 -226.

Albers E, and Muller BW (1995). Cyclodextrin derivatives in pharmaceutics. Crit Rev. The.r Drug Carrier Syst. 12(4):311-337.

Bernard J (1970). Equilibrium adsorption and surface segregation in: studies in surface sciences and catalysis13, Adsorption on metal surfaces: An integrated approach, Elsevier publishing company Amsterdam, pp. 44– 99.

Esclusa-Diaz MT, Gayo-Otero M, Perez-Marcos MB, Villa-Jato JL (1996) Preparation and evaluation of ketokenazole β-cyclodextrin multicomponent complexes. Int. J. Pharm. (142) :183 -187.

*European pharmacopoeia (2005). 5th Ed, Vol 1 Council of Europe Strasbourg. pp. 1282 - 1285.

Florence AT, Attwood D (1981). Surface chemistry In: Physiochemical Principles of Pharmacy 1st Ed. The Macmillan press ltd, London, pp. 177 – 222.

Guyot M, Fawaz F, Bildet J, Bonini F, Lagueny AM (1995) Physicochemical characterization of norfloxacin-cyclodextrin inclusion compounds and PEG solid dispersions. Int. J. Pharm. *(123):* 53 - 63.

Hassan MA, Suleiman MS, Najib NM (1990). Improvement of the in vitro dissolution characteristics of famotidine by inclusion in β-cyclodextrin; Int. J. Pharm. 58: 19-24.

Heys HL (1970). The colloidal state of absorption. In: Physical Chemistry, 4th Ed. George G. Harrap and Co. Ltd., London. pp. 304 – 326.

Krenn M, Gamesik MP, Vogelsang GB, Colvin OM, Leong KW (1992). Improvement in solubility and stability of thalidomide upon complexation with hydroxyl propyl-β-cyclodextrin. J. Pharm. Sci. (81): 685 - 689.

Loffsson T, Brewster M (1996). Pharmaceutical application of cyclodextrin 1. Drug Solubilization and Stabilization, J. Pharm. Sci. 85, 1017-1025.

Martin A, Swabrick J, Cammarata A (1993). Interfacial phenomenon In: Physical Pharmacy, 3rd edition, Lea and Febiger, Philadelphia. pp. 362 – 392.

Moyano JR, Gines JM, Arias MJ, Rabasco AM (1995). Study of the dissolution characteristics of oxazepam via complexation with β-cyclodextrin. Int. J. Pharm. (114): 95 - 102.

Richard JH (1972). Surface and interfacial phenomenon. In: Tutorial Pharmacy, 6th edition, Carter SJ (ed), Sir Isaac Pitmans and Sons Ltd. London. pp 33 – 53.

Rosel CP, Carreno jS, Rodriguez – Baeza M, Alderetr JB (2000). Inclusion of the antiviral drug acyclovir with cyclodextrin in aqueous solution and in solid state. Quimica Nova. 23(6):749 – 752.

Stella VJ, Rajewski RA (1997). Cyclodextrins: their feature in drug formulation, Pharm. Res. (14): 556 - 566.

Stella VJ, Rao VM, Zannou EA, Zia V (1999). Mechanisms of drug release from cyclodextrin complexes. Adv Drug Delivery Rev. 36(1):3 -16.

Torres-Labandeira JJ, Blanco-Mendez, Villa-Jato JL (1994). Biopharmaceutical stability of glibornuride-β-cyclodextrin inclusion complex after one year of storage, STP Pharm. Sci (4):235 - 239.

Valero M, Rodriguez LJ, Valazguez M (1996). Inclusion of non-steroidal anti-inflammatory agents into aqueous cyclodextrin, A UV-aborption spectroscopic study. IL Farmaco. 51(7) 525 – 533.

Zerrouk N, Gines-Dorado JM, Arnaud P, Chemtob C (1998). Physical characteristics of inclusion compounds of 5-ASA in α- and β-cyclodextrin, Int. J. Pharm. (171): 19 - 29.