DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(11-13), 2259-2279 (1986)

STUDIES OF CYCLODEXTRIN INCLUSION COMPLEXES :

I - Inclusion Complexes between α-and β-Cyclodextrins and Chloramphenicol in Aqeuous Solutions.

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SUMMARY

Chloramphenicl was found to form inclusion complexes with α-and β-cyclodextrins (α-CyD and β-CyD) in aqeuous solution. Phase solubility diagrams were obtained with β-CyD and found to be Bs type curve. An apparent 1:1 complex formation constant (Kc) of $8077 \times 10^{4} M^{-1}$ was obtained for chloramphenicol in β-CyD.

For α-CyD the phase solubility diagrams indicate A_L TYPE CURVE. The complex stochiometric ratios were found to be 1:1 and 1:2 (guest : Host). The apparent formation constant , Kc and Kc´ , for chloramphenicol in α-CyD were found to be $3017 \times 10^{4} M^{-1}$ and $957 \times 10^{4} M^{-1}$, for 1:1 and 1:2 stochiometric ratios respectively. Thus the apparent complex formation constant for chloramphenicol is higher in β-CyD than α-CyD relatively.

It was found that the aqueous solubility of chloramphenicol more enhanced by α- and β-CyD inclusion complexation than the non-ionic surfactant solutions used in a previous study. The higher values obtained for the complex formation constants indicate a particularly good fitness of the chloramphenicol molecule with the β-and α-CyD cavities relatively.

Microcrystalline solid inclusion complex of chloramphenicol and β-CyD, 1:1, was isolated and investigated by I.R., in comparison with a physical mixture 1:1, to characterize the interaction takes place between chloramphenicol and β-CyD within the complex. Thus chloramphenicol complexed in β-CyD in aqueous and solid phases.

The effect of certain water soluble carriers, in 5% w/v concentration, on chloramphenicol complexation in α-and β-CyD cavities was investigated. The aim of adding such additives is to reduce the

0363-9045/86/1211-2259$3.50/0

concentration of the CyDs used in formulating chloramphenicol in solution. It was found that propylene glycol and P.E.G. 400 assist chloramphenicol complexation in β-CyD, forming higher KC values, 46221 x 10^4 M^{-1} and 39883 x $10^4 M^{-1}$ respectively. While glycerol deminish chloramphenicol complexation in β-CyD. In case of α-CyD, P.E.G 4000 and propylene glycol rise KC and KC′ for chloramphenicol respectively, and the reverse is true for glycerol.

Introduction.

Cycloamyloses (also called cyclodextrins) are cyclic oligomers containing six or more D-glucose units linked 1 — 4; they are produced by the action of *Bacillus macerans amylose* on starch. The six unit substance is called cyclohexaamylose (α-CyD), the seven unit substance is called cycloheptamylose (B-CyD) and the eight unit substance is called cyclooctaamylose (γ-CyD). These molecules are torous or doughnut in shape. They possess central cavities of fixed shapes and sizes (5.2, 6.4 and 8.4 Å for the larger interance sides of α-, β-, and γ-CyD respectively[1]. Their hydrophobic cavities and hydrophillic faces (composed of hydroxyl groups) have led to considerable interest in their chemical properties and their pharmaceutical uses in formulations. The production, purification modulation, and chemistry of the cyclohexaamyloses have been reviewed[2-5]. Any molecule smaller than the cavity of a cycloedextrin can enter the cavity and there undergo non-covalent interaction with the atoms lining and rimming the cavity. The resulting association product is called an inclusion complex. The cyclodextrin is thus a host for the smaller (guest) molecule. The dimensions of the α-cyclodextrin cavity permit the inclusion of

many mono- and disubstituted benzene derivatives. A 1:1 stochiometry is commonly observed(and often assumed in experimental studies), but it has now been well established that 1:2 complexes (i.e., 1 substrate : 2 cyclodextrins) or higher ratios may exist in some systems[14,6-10].

Cyclodextrins have received considerable attention because they are able to modify the physical and the chemical properties of drug molecules through inclusion complexation.[11-13]

Such complexation may be utilized in pharmaceutical formulation to improve the aqueous solubility, dissolution rate chemical stability and/or bioavailability of certain drugs.[11,12,14-22]

cyclodextrin-drug complexation also may affect drug volatility, dissolution rate, chemical reactivity, and thus become the object of many application studies in medicinal field.

Chloramphenical, the well known antibiotic, was solubilized previously by series of non-ionic surfactant solutions, alone and in presence of certain organic and inorganic additives.[23] The present work represents the complexation of chloramphenicol in aqueous solutions of α- and β-CyDs, alone and in presence of certain organic additives including glycerol, propylene glycol and P.E.G 4000 just to investigate the role of those additive in such complexation. Finally a comparison is made between the effect of non-ionic surfactant solutions[23] and CyDS in solubilizing chloramphenicol.

Experimental

Materials:

- α-CyD and β-CyD were used without further purification.

- Chloramphenicol[2] was obtained commericially.
- Plyethylene glycol 4000[3], propylene glycol[3] and glycerol[3] of analytical grade were used.

Equipment :

- Top to bottom rotating shaker, thermostatically controlled at 25 ± 0.5°C.
- Self recording double beam, u.v., spectrophotometer. (Pye Unicam SP 1750).
- Single beam u.v., Spectrophotometer (Pye Unicam SP6-400).
- Double beam infra-red spectrophotometer (Pye Unicam SP 1025).

Solubility Studies:

These were carried out according to Higuchi and Lach[24]. Excess amount of guest molecule (chloramphenicol) were added to different concentrations (Moles/Liter) of aqueous α-CyD or β-CyD, alone or containing the organic additives used in 5% w/v concentration. The screw capped tubes containing the last mentioned ingredients were rotated on a mechanical spindle top to bottom at 25 ± 0.5°C. After solubility equilibrium was ascertained (About 5 days), an aliquot was centrifuged and pippetted through a cotton filter. A 0.5 or 0.2 ml aliquot of the sample solution was diluted with distilled water and analyzed spectrophotometerically for its chloramphenicol content at 278 nm against a blank having the same concentration of the additives, glycerol P.E.G 4000 and propylene glycol,

1 - Sigma Chemical Company
2 - El-Nasr Chemical Co. Egypt.
3 - B.D.H., Poole, England.

in the dilution range used). The concentrations of chloramphenicol were found from straight Beer's plot, and calculated in moles/liter. It was found that neither the presence of CyDS nor the presence of additives, in the dilution range used, interfer with the spectrophotometric assay of chloramphenicol, as seen in Fig. (1). The apparent formation constant, KC was calculated from the initial straight line portion of the phase solubility diagram according to the following equation:[1,21,25-30]

$$K_C = \frac{\text{Slope}}{\text{intercept (1-slope)}}$$

indicating that the complex stochiometric ratio is 1:1 (guest. host), as in B-CyD inclusion complexes.[1,21,25-30] In case of α-CyD another KC' is calculated[1,21,25-30] from the second straight line portion of the phase solubility diagram indicating that the stochiometric ratios are 1:1 and 1:2[1,21,25-30] (guest : host).

Preparation of β-CyD-chloramphenicol solid complex :

Solid complex of chloramphenicol with β-CyD was prepared using conditions derived from the descending part of the solubility diagram (an arrow in Fig. (2)). 2.27 gm β-CyD(0.1 M) and 0.645 gm chloramphenicol in 20 ml distilled water were sealed in a flask and shaken top to bottom for one week at 25 ± 0.5°C.

The complex which precipitated as a white micro-crystalline powder was separated, washed twice with chloraform to remove any excess chloramphenicol, filtered and dried. This powder corresponded to 1:1 chloromphenicol-β-CyD complex which has a molecular weight of 1458.1.

Infra Red investigation for the chloramphenicol β-CyD complex:

The I.R. of the last prepared complex was measured as a potassium bromide disc. For comparison the I.R. spectra of a physical

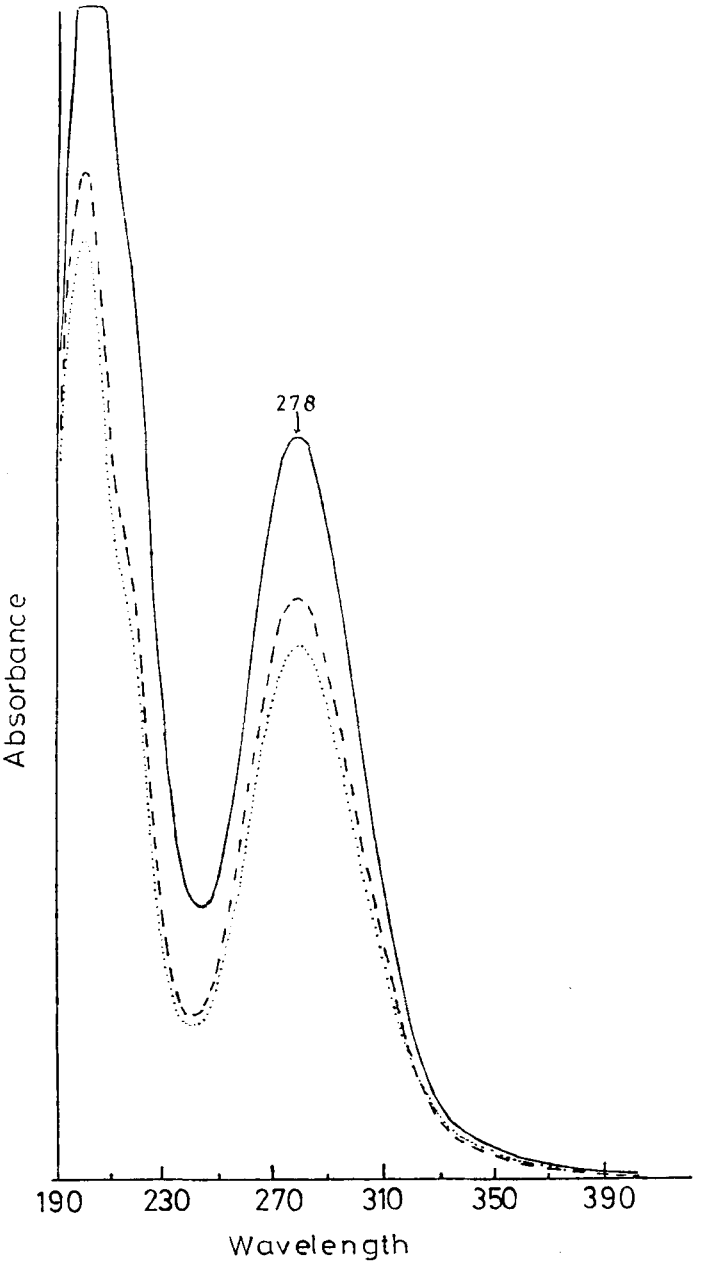

Fig.(1): Ultraviolet spectra of chloramphenicol in absence and in presence of CyDs in different additives at 25°C.
Key: ····· Chloramphenicol in distilled water .
– – – Chloramphenicol in 5% w/v P.E. G 4000 containing 0.09 moles of α-CyD.
—— Chloramphenicol in 5% w/v propylene glycol containing 0.09 moles of β-CyD.

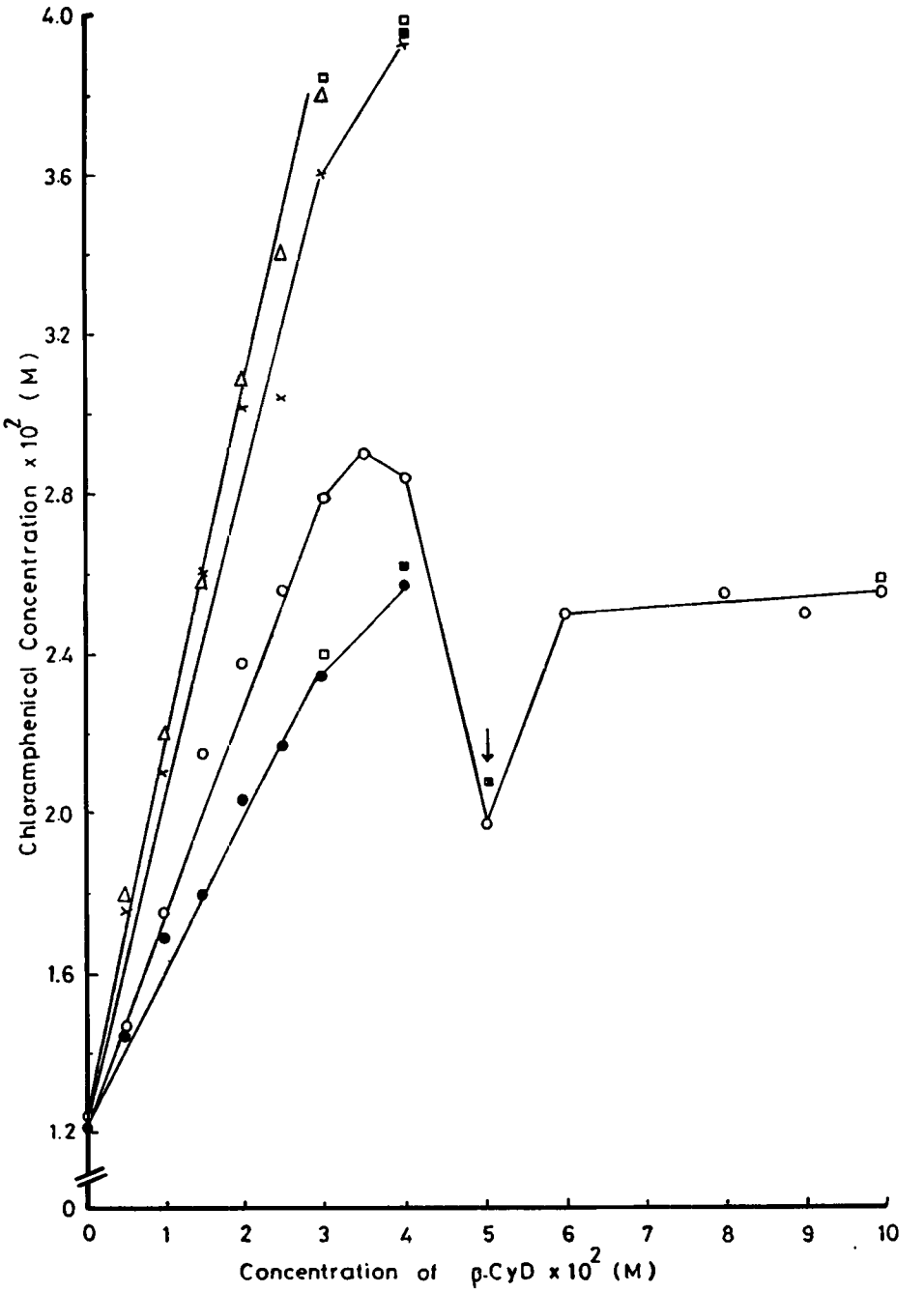

Fig.(2): Phase solubility diagram of chloramphenicol β-cyclodextrin in water, glyceriol P.E.G 4000 and propylene glycol at 25°C.
▣ Formation of chloramphenicol-β-cyclodextrin solid complex.
□ Maximum solubility of β-cyclodextrin
Key: ○ β-Cyclodextrin alone in water
● β-cyclodextrin in 5% w/v glycerol
✕ β-CyD in 5% w/v P.E.G 4000
△ β-CyD in 5% w/v propylene glycol.

mixture of chlaramphenicol-ß-CyD, 1:1, was carried out using the same procedures. The scanning is shown in Fig. (4).

Results and Discussions

Figure 2 shows the equilibrium phase solubility diagram obtained for chloramphenicol with ß-CyD in water and in different additives used including glycerol, P.E.G 4000 and propylene glycol in 5% w/v concentration.

The plots, specially for chloramphenicol in ß-CyD alone, show a typical Bs-type solubility curve,[1,25,27,29,30,31,32] with precipitation of microcrystalline complex at higher B-CyD concentration (0.05 moles in B-cyD alone). Obviously, the formation of the microcrystalline solid complex cause a marked decrease of chloramphenicol in solution (an arrow in Fig. (2)), after which a relative increase of chloramphenicol in solution increases, as B-CyD concentrations increases further. The stochiometry of this complex was analyzed and it was found that it is 1:1 complex, in agreement with the last findings[12,14,17,27-29,33].

The apparent formation constant (Kc) for the complex was determined from the initial straight line protion of the solubility diagram according to the previously mentioned equation[1,21,25-30]. KC was found to be 8077 x 10^4 M^{-1} Table 1). It is of interest to note the high values of the complex formation constants in aqueous media, indicating a particularly good fitness of the chloramphenicol molecule with the B-CyD cavity.[30] . It is noticed from Fig. (2) that the maximum solubility of B-CyD alone in distilled water is 0.01 moles.

The aim of formulating B-CyD in 5% w/v glycerol, P.E.G 4000 and prophylene glycol is to reduce the concentration of B-CyD

Table 1 : Apparent Complex formation constants (K Values*) for chloramphenicol (CH) in α- and β-CyDS in different solvents at 25°C.

Complex	Solvent w/v	Molar Ratio guest Host	KC x $10^4 M^{-1}$	KC′ x$10^4 M^{-1}$	Solubility of CH in CyDS M/M	Coefficient of Determination
CH-β-CyD	D-water	1:1	8077	-	0.5	0.98
CH-β-CyD	5% glycerol	1:1	4860	-	0.37	0.99
CH-β-CyD	5% P.E.G.4000	1:1	39883	-	0.828	0.98
CH-β-CyD	5% Propylene glycol	1:1	46221	-	0.848	0.99
CH-α-CyD	D.water	1:1 1:2	3017	957	0.272 0.106	1.0 0.92
CH-α-CyD	5%glycerol	1:1 1:2	3004	1070	0.266 0.114	0.99 0.99
CH-α-CyD	5% P.E.G4000	1:1	6557	-	0.442	0.97
CH-α-CyD	5% propylene glycol	1:1 1:2	3365	1088	0.289 0.116	0.99 0.94

* Calculated according to Higuchi and Connors method[31].

needed to attain the therapeutic dose of chloramphenicol in eye or ear drops, as the CyDs is expensive economically.

Fig. (2) and Table 2 show the effect of varying the concentrations of B-CyD in 5% w/v of the different additives used . It was found that incorporating B-CyD in 5% w/v glycerol decreases the efficiency of the former toward chloramphenicol complexation. This may be attributed to the competition of glycerol for chloromphenicol in the B-CyD cavity as glycerol contains relatively longer hydrocarbon chain (3CH) thus decrease the quantity of chloramphenicol fitted to B-CyD cavity.

Table 2 : Comparison among the efficiencies of surfactants, CyDs and macromolecules[23] solutions in bringing chloramphericol into solution at 25 ± 0.5°C.

Solubiizer alone	Solubility mg CH/gm solubilizer.
Polysorbate 20	75.4
Polysorbate 40	81.6
Polysorbate 60	76.2
Polysorbate 80	87.5
Eumulgin C1000	97.7
Eumulgin C1500	82.5
Myrj 52	63.4
Myrj 53	54.4
Myrj 59	34.7
Sodium lauryl sulphate	135.0
Cetrimide	338.6
P.E.G4000	13.3
P.E.G 600	8.0
β-CyD	142.3
α-CyD	90.3

Glycerol also favours the formation of chloramphenicol-B-CyD solid complex at lower concentration of B-CyD (0.04 moles), as glycerol compete with chloramphenicol in the B-CyD cavity, it renders the less solubility of the chlorampherical-B-CyD complex hence its formation at lower B-CyD concentration. Glycerol in the used concentration inhibit the solubility of B-CyD alone in water from 0.1 moles in case of B-CyD alone in water to 0.03 moles in case of glycerol. This less solu-

bility of B-CyD may be attributed to the incorporation of the hydrocarbon chain of glycerol in B-CyD cavity rendering the latter more hydrophobic, less water soluble.

The K_c value for chloramphenicol in B-CyD decreases in the presence of glycerol 5%w/v to nearly half its absence, Table 2. Also the solubility of chloramphenicol mole/mole B-CyD decreases relatively in B-CyD containing glycerol than in B-CyD alone. Comparing the effect of 5% w/v of both P.E.G 4000 and propylene glycol on the complexation of chloramphenicol in B-CyD, Fig. 2 and Table 2, it is obvious that both of the two additives cause marked increase in the concentration of chloramphenicol complexed in the aqeuous phase compared to B-CyD alone .The K_c values for chloramphenicol in B-CyD containing 5% w/v propylene glycol and P.E.G 4000 are 46221 x 10^4 M^{-1} and 39883 x $10^4 M^{-1}$ respectively. Thus the K_c values increases 6 and 5 times in B-CyD containing those two additives than B-CyD alone. This may be attributed to the effect of the glycol group (CHOH) in strengthing the physical interaction (Hydrogen bond formation) between chloramphericol and B-CyD rendering the complex formation more easier, leading to more stable complexes and thus higher K_c values. This idea of incorporating such additives is very excellent and can be utilized successfully in attaining higher concentrations of chloramphenicol in lower B-CyD concentration by incorporating such lower concentration of propylene glycol and P.E.G 4000 respectively.

The presence of propylene glycol and P.E.G.4000 in this concentration in B-CyD promote the solid complex formation between chloromphenicol and B-CyD at lower concentration than in B-CyD alone respectively. Also those two additives

render B-CyD alone to be less water soluble respectively. Fig. (3) and Table (2) show the effect of α-CyD, alone and containing the additives, on the aqueous complexation of chloramphenicol. In this case, the solubility of chloramphenicol increases linearly as a function of α-CyD concentration and the solubility curve can be classified as A_L type[27,31]. In this type of solubility curves no solid complexes formed between the guest and the host.[1,25,27,31] So no solid complex formed at all between α-CyD and chloramphenicol in the α-CyD soluble range (0.05 - 0.4 moles, Fig.(3)), indicating that a smaller cavity size of α-CyD apparently allows little penetration of chloramphenicol molecule .

The stochiometry of the complex formed between chloramphenicol and α-CyD is found to be 1:1[1,25,27,31] and 1:2[1,25,27,31] (guest : host) as the solubility curves for chloramphenicol, as seen in Fig. (2), show two slopes in each case. Thus Kc and K_c' for 1:1 and 1:2 complexes are calculated from the slopes respectively. This seems to be logic, as at higher α-CyD concentrations,the molecules become crowdeded, and each chloramphenicol molecule can interact with two smaller cavited α-CyD molecules[27,31]. It was noticed, in all cases, that K_c' for chloramphenicol in α-CyD is always smaller than Kc in each case.

This may be attributed to the strongly bound chloramphenicol molecule to one α-CyD cavity in smaller α-CyD concentration resulting in higher K_c value compared to the loosly bound chloramphenicol molecule between two cavities of α-CyD in higher concentration resulting in smaller K_c' value respectively.

Comparing the complexing efficiency of α-CyD and β-CyD, alone or in presence of the additives, it is clear that

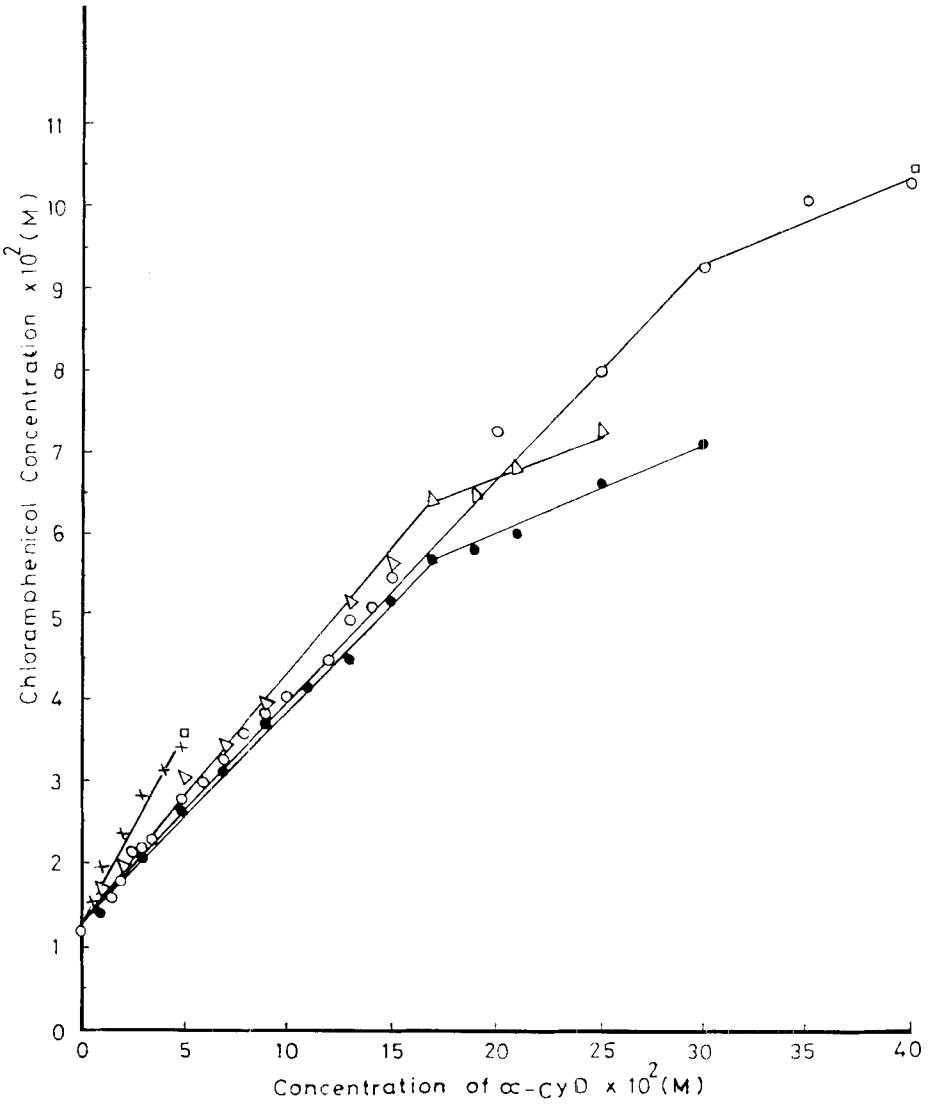

Fig.(3): Solubility diagram of chloramphenicol -α-cyclodextrin at 25°C.

□ Maximum solubility of α-CyD
○ α-CyD alone
● α-CyD in 5% w/v glycerol
X α-CyD in 5% w/v P.E.G 4000
△ α-CyD in 5% propylene glycol

(Fig. (2), Fig. (3) and Table 2), β-CyD is always more effective than α-CyD in bringing chloramphenicol into solution . This is evident since β-CyD has wider cavity (6.4-Å) than α-CyD (5.2 Å). Furthermore, the dimension of chloramphenicol may fit exactly to the β-CyD cavity than α-CyD one. Thus the Apparent formation constant for chloramphenicol in α-CyD alone is nearly 0.37 of that belongs to β-CyD alone. The same is more or less true in the presence of different additives in the two CyDs investigated.

The effect of additives studied including glycerol, P.E.G 4000 and propylene glycol in 5% w/v concentration on the aqueous complexation of chloramphenicol in α-CyD is shown in Fig. (3) and Table 1. Those additives do not change the picture of chloramphenicol complexation in α-CyD i.e., A_L type solubility curve, but they generally inhibit α-CyD solubility in water in their existance. It is noticed that glycerol decreases the efficiency of α-CyD to bring chloramphenicol to solution (the same finding was observed with β-CyD). Thus the K_c for chloramphenicol decreases from 3917×10^4 M^{-1} to 3004×10^4 in the presence of glycerol. On the contrary P.E.G 4000 and propylene glycol increase the Apparent formation constants, Kc of chloramphenicol in α-CyD to 6557×10^4 M^{-1} and 3365×10^4 M^{-1} respectively. Thus, on these basis we can reduce the concentration of α-CyD needed to bring the therapeutic dose of chloramphenicol into solution by incorporating those two additives. The only problem is that P.E.G 4000 in this concentration although it rises the effeciency of α-CyD it render the insolubility of α-CyD itself beyond 0.05 moles, as it forms a white paste, gelly like, after that.

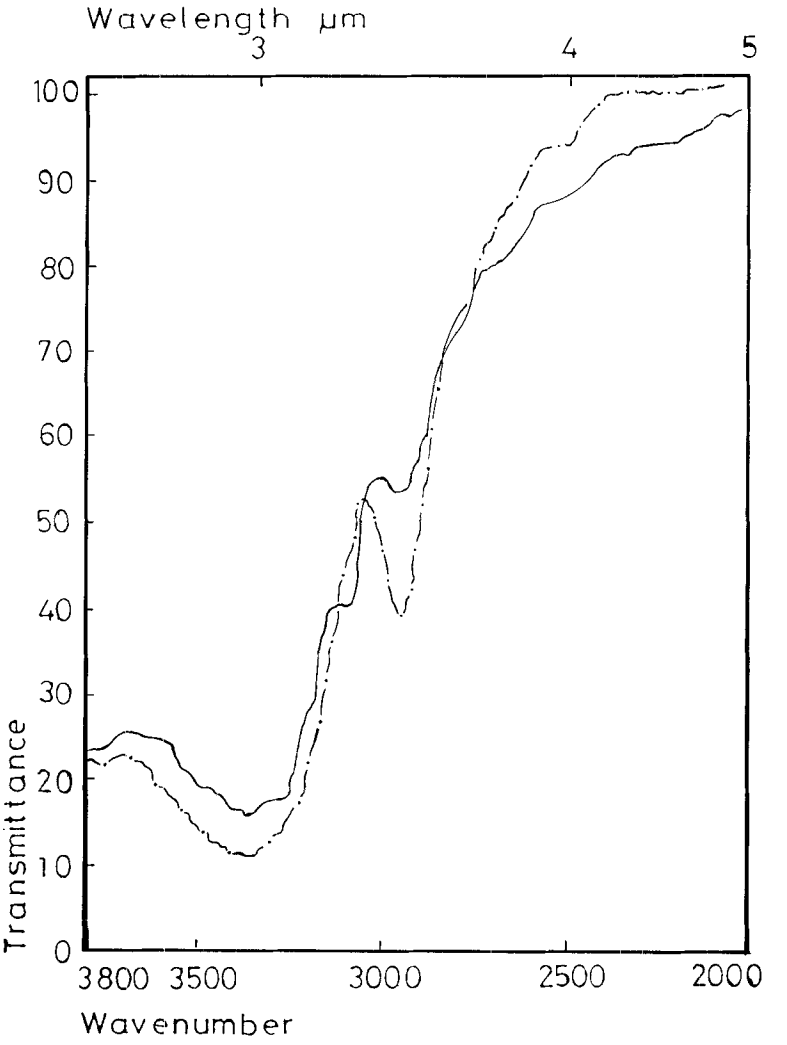

Fig.(4): The I.R. spectra of chloramphenicol-β-CyD solid complex — and physical mixture (1:1) of chloramphenicol and β-CyD.———

The same expaination in case of β-CyD is valid for the effect of those additives on chloramphenicol complexation in case of α-CyD.

The solubility of chloramphenicol in moles per mole of the studied CyD alone, and containing the additives is calculated, Table 2. They are in accordance with the determined Kc and Kc′ values.

Table 3 : Comparison among the efficiencies of surfactants and CyDs Solutions Containing certain additives in bringing chloramphericol into solution at 25 ± 0.5°C.

Solubilizer containing the addiitve	Solubility mg CH/gm solubilizer
Polysorbate 20 in 5% w/v propylene glycol	67.3
Polysorbate 80 in 5% w/v propylene glycol	86.8
Eumulgin C1000 in 5% w/v propylene glycol	108.8
Eumulgin C1500 in 5% w/v propylene glycol	90.4
Myrj 52 in 5% w/v propylene glycol	68.5
Myrj 59 in 5% w/v propylene glycol	40.9
β-CyD in 5% w/v glycerol	105.3
β-CyD in 5% w/v P.E.G 4000	235.7
β-CyD in 5% w/v propylene glycol	241.4
α-CyD in 5% w/v glycerol	88.3
α-CyD in 5% w/v P.E.G 4000	146.8
α-CyD in 5% w/v propylene glycol	96.0

Fig. (4) investigate the I.R. spectrum of the chloramphenicol β-CyD complex , 1:1, and a physical mixture 1:1 of chloramphenicol : β-CyD. Since chloramphenicol and β-CyD exhibit intramolecular hydrogen bonding, no shift takes place for the carbonyl group in the complex formation by the formation of intermolecular hydrogen bond. The only difference which can anticipate intermolecular hydrogen bond formation between β-CyD and chloramphenicol is the increase in the intensity of hydrogen bond absorption in the complex than in the physical mixture in the range of 3400 cm^{-1}. This increase in the intensity of the hydrogen bond formed in the complex than

the physical mixture indicates that the intermolecular hydrogen bond formed between chloramphenicol and β-CyD is stronger than the intramolecular hydrogen bond takes place in each molecule alone.

Table 2 and Table 3 include a comparison between the efficiency of the surfactant solutions, alone or combined with certain additives toward chloramphenicol solubilization[23] and the studied CyD solutions in this respect. Sodium lauryl sulphate and cetrimide are investigated only for comparison, since they are hemolytic and toxic, and cannot be used except externally. From the tables it is evident that among all the solutions investigated to solubilize chloramphenicol β-CyD in 5% w/v propylene glycol is the most efficient in this aspect followed by β-CyD in 5% w/v P.E.G 4000.

In fact the β-CyD also has the advantages of being naturally produced, easily tolerated in the body and less irritant than the non-ionic surfactant solutions. Further study on the stability as well as availability of chloramphenicol from these solubilized systems will be investigated.

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