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Inclusion complexation of 2-aminopyrimidines with β-cyclodextrin, physico-chemical and nuclear magnetic spectroscopic studies

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Inclusion complexation of 2-aminopyrimidines with β-cyclodextrin was studied in the solid state by infrared spectroscopy (IR), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). The aminopyrimidine-β-CD complexes were also investigated in a solution by nuclear magnetic resonance spectral techniques (^{1}H-NMR and ^{13}C-NMR). Qualitative modifications in the position and number of peaks or bands obtained from spectral methods as well as thermal analysis indicated the inclusion.

Keywords: *inclusion; cyclodextrin; aminopyrimidine*

1. Introduction

Cyclodextrins (CD) have been described as "seductive" molecules, appealing to investigators in both pure research and applied technologies [1]. Judging by the logarithmic growth in publications and patents [2] dealing with these compounds, such characterization seems to be justified. CDs are cyclic molecules composed of glucopyranose ring units forming truncated cone type, doughnut structures [3]. The most common are the α, β, and γ-cyclodextrins, which are composed of six, seven, and eight sugar units, respectively. The exterior of the CDs is hydrophilic while the interior is hydrophobic, and the different CDs possess different cavity sizes according to the number of glucopyranose rings present. In the 1950s, the chemical process for the production of CDs was thoroughly examined by French and co-workers [4], and the existence of even larger CDs was confirmed. Also, at that time Cramer and co-workers first began to uncover CDs potential as complexation agents [5]. They examined the ability of CDs to complex with a variety of drug molecules, and noted stabilization, volatility reduction, and solubility changes that occurred as a result of complexation. They subsequently obtained a patent [5] in 1953 that encompassed the potential drug related applications foreseen as a result of their studies. Since then, the number of patents and papers has increased exponentially. Today, CD is a relatively inexpensive material and an important industrial commodity. Hirai and co-workers [6] found that when the naphthalene was included within cyclodextrin then the yields of the 2,6-naphthalene dicarboxylic acid were greatly increased. The cyclodextrin host sterically shielded the undesirable reaction sites on the naphthalene ring leading to greater selectivity. Another area of research involving the use of cyclodextrin is in the field of rotaxane and polyrotaxane chemistry. There have been a few reviews [7, 8] along with a number of research papers [9–11] that have been published recently, concerning the utility of cyclodextrins on this field of chemistry. The specific cavity size of cyclodextrins has been used to selectively incorporate compounds based on chirality, molecular weight, and steric bulk [12, 13].

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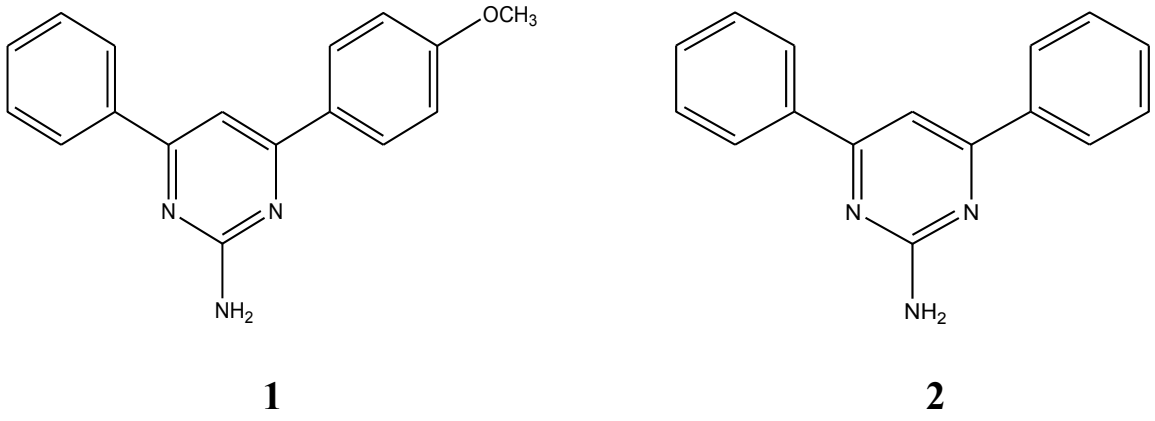


Fig. 1. The structures of the prepared 2-aminopyrimidines: 2-Amino-6-(4-methoxyphenyl)-4-(1-phenyl)pyrimidine (**1**), 2-Amino-4, 6-diphenylpyrimidine (**2**).

This aspect of cyclodextrin complexes has been used in selective complexation and removal of water born contaminants [14, 15]. The scope of this work is to prepare β-CD inclusion complexes of pharmacologically and biologically important pyrimidine molecules [16–19]. The 2-amino-6-(4-methoxyphenyl)-4-(1-phenyl)pyrimidine and 2-amino-4,6-diphenylpyrimidines were synthesized, and their CD-inclusion complexes were prepared. The inclusion complexes were characterized using ^{1}H, ^{13}C NMR, FT-IR, DSC and SEM studies.

2. Experimental

2.1. Preparation of 2-aminopyrimidines

A mixture of styryl phenyl ketone (0.01 mole) guanidine hydrochloride (0.01 mole) and sodium hydroxide pellets (0.5 mole) was finely powdered in a pestle and mortar. The mixture was transferred into a beaker and irradiated in a domestic microwave oven (LG Grill, MG 395 WA). The mixture was irradiated at 250 W for 60 – 70 sec. The excess of alkali and the solid products were filtered and dried. The products were purified by column chromatography using benzene and ethyl acetate mixture as eluting solvent. The structures of the prepared 2-aminopyrimidines are given in Fig. 1.

2.2. Preparation of inclusion complexes

Equimolar solutions of 2-aminopyrimidines and β-cyclodextrin were used for the preparation of inclusion complexes. β-cyclodextrin (0.1 mole) was dissolved in 25 ml of water and 0.1 mole of the 2-aminopyrimidine in 10 ml of ethanol. The two solutions were mixed and shaken well at 25 °C for 24 hours, then filtered to remove the excess of 2-aminopyrimidine. The solvent was removed and the product was dried for 48 hours in a desiccator.

2.3. Analysis techniques

Infrared (FT-IR) spectra were recorded in AVATAR-330 FT-IR instrument. The samples were mixed thoroughly with KBr and pelletised. DSC scans were recorded on a Mettler Tolendo DSC 821^{e} differential calorimeter with a Star^{e} system. Samples were placed in crimped aluminium pans, before being heated at a scanning rate of 10 °C/min from 0 °C to 200 °C. NMR spectra for all samples were recorded on a Brucker AMX-400 spectrometer operating at 400 MHz. The compounds/complexes were prepared by dissolving 10 mg of material in deuterated dimethyl sulphoxide (DMSO-d6) containing 1 % TMS. Scanning electron micrographs were recorded using JEOL JSM 561 OLV scanning electron microscope. The samples were dried and pre-coated with platinum before SEM recording.

Table 1. ^{1}H NMR spectral data of compounds **1** and **2** and the inclusion complexes.

Nature of protons	Chemical shifts (ppm)					
	1	**1**-β-CD complex	$\Delta\delta$	**2**	**2**-β-CD complex	$\Delta\delta$
Methoxy protons	2.74	2.50	0.24	–	–	–
Amino protons	5.15	5.70	−0.55	5.18	5.64	−0.46
H-5	7.47	7.50	−0.03	7.45	7.51	−0.06
Aromatic protons	7.02 – 8.09	7.1 – 8.2	(−0.08) (−0.11)	7.16 – 8.06	7.26 – 8.20	(−0.1) – (−0.14)

Table 2. ^{1}3C NMR spectral data of compounds **1** and **2** and the inclusion complexes.

Nature of protons	Chemical shifts (ppm)					
	δ_1	δ_2	$\Delta\delta_1 - \delta_2$	δ_3	δ_4	$\Delta\delta_3 - \delta_4$
Methoxy carbon	77.02	78.62	−1.60	–	–	–
C-5	103.58	102.41	1.17	104.3	102.69	1.61
C-4	163.47	–	–	163.56	164.02	−0.46
C-6	165.62	–	–	166.24	165.44	0.80
C-2	137.8	–	–	137.70	137.57	0.13
Aromatic carbon	127.07 – 130.36	128.60	1.53	127.11 – 130.48	125.94 – 130.40	1.17 – 0.08

δ_1 = CD; δ_2 = **1**-β-CD complex; δ_3 = **2**; δ_4 = **2**-β-CD complex

3. Results and discussion

The prepared inclusion complexes were characterized using various instrumental techniques.

3.1. ^{1}H NMR study of the β-CD inclusion complexes

The NMR analysis provides information about orientation of a guest molecule and its conformation within a host. ^{1}H NMR evidence for the formation of an inclusion complex between the β-CD and a guest molecule is provided by changes in the chemical shift of the protons, based on the shielding of the protons of the compounds **1** and **2**, while the locations of such changes pin point the regions of the molecule implicated in the association. Table 1 shows the ^{1}H NMR spectral data for the compounds **1** and **2** and their corresponding inclusion complexes.

The amino and aromatic protons are deshielded and methoxy protons are shielded. The changes in the chemical shift values of inclusion complex protons when compared to compounds **1** and **2** suggest the formation of strong inclusion complexes. The NMR data of the inclusion complex of **1** suggests that it might be formed by incorporating the –OCH_3 group and the phenyl ring in the β-CD cavity. The large variation in the chemical shift values of the amino protons of the both inclusion complexes also confirms the complexation.

3.2. ^{13}C NMR study of the β-CD inclusion complexes

^{13}C NMR spectroscopy affords considerable information on the environment of individual carbons and intermolecular interactions. So it is an useful technique to analyse inclusion phenomena. In the ^{13}C NMR spectra of the compound **1** the signal at 77.02 ppm is assigned to methoxy

Table 3. IR spectral data of compounds **1** and **2** and the inclusion complexes.

Assignments	Vibrational frequency (cm^{-1})					
	$\bar{\nu}_1$	$\bar{\nu}_2$	$\Delta\bar{\nu}_1$ - $\bar{\nu}_2$	$\bar{\nu}_3$	$\bar{\nu}_4$	$\Delta\bar{\nu}_3$ - $\bar{\nu}_4$
N–H asymmetric and symmetric vibration	3325.6	3373.6	−48.0	3470.0	3322.4	147.6
C–H stretching	2932.5	2926.1	6.4	2933.8	2925.4	8.4
N–H in plane bending	1644.1	1646.2	−2.1	1679.7	1629.1	50.6
C–N stretching	1238.8	1240.9	−2.1	1228.6	1236.8	−8.2
C–O stretching of methoxy group	1176.4	1156.8	19.6	–	–	–
C=C stretching of aromatic group	1588.7	1567.2	21.5	1592.0	1567.3	24.7
C–C stretching vibration of aromatic phenyl group	822.0	859.3	−37.3	839.2	846.2	−7.0

$\bar{\nu}_1$ = **1**; $\bar{\nu}_2$ = **1**-β-CD complex; $\bar{\nu}_3$ = **2**; $\bar{\nu}_4$ = **2**-β-CD complex

carbon. The signal observed at 103.58 ppm is due to C-5 carbon signal whereas the ones at 163.47 and 165.62 ppm correspond to C-4 and C-6, respectively. Aromatic carbons resonate in the region of 127.07 – 130.36 ppm. For the compound **2**, C-5 carbon resonates at 104.3 ppm. The C-4 and C-6 carbons appear at 163.56 and 166.24 ppm, respectively. The aromatic carbons resonate between 127.11 – 130.48 ppm. The changes in the chemical shift values of **1** and **2** are given in Table 2. In **1**-β-CD and **2**-β-CD inclusion complexes, the chemical shift values are displaced. The changes in ^{13}C chemical shift values of the complexes suggest the inclusion complex formation

3.3. FT-IR spectral studies of the inclusion complexes

FT-IR is a highly sensitive method of analysis of structural changes. More evidences for the inclusion complex formation have been obtained from FT-IR study. Table 3 shows the changes in the vibrational frequency bands for compounds **1** and **2** and their corresponding inclusion complexes. The changes in the position of the peaks for –N–H,–C–H, C–O etc suggest the complexation in both cases.

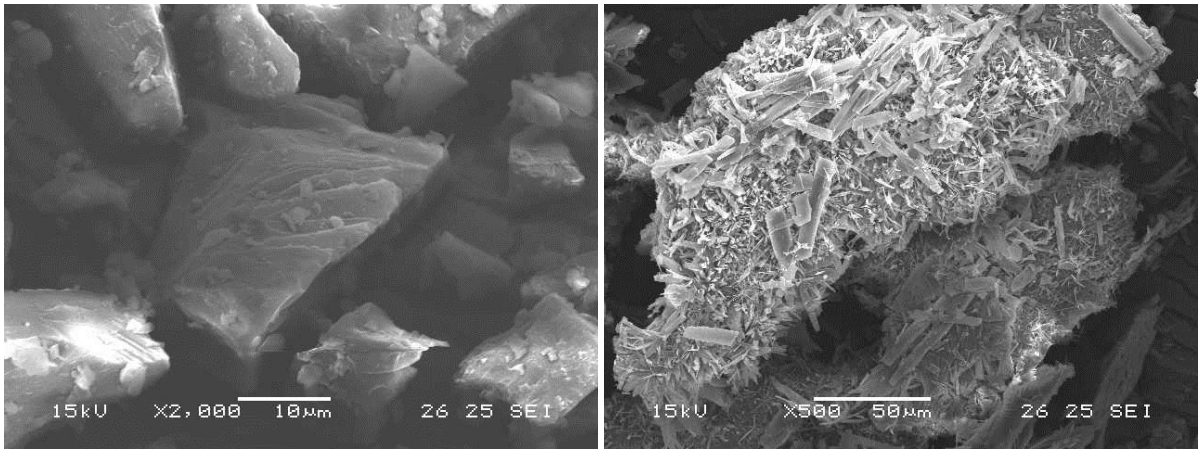
3.4. Differential scanning calorimetric studies of the β-CD inclusion complexes

The evidences for inclusion complexation were obtained from the thermal analysis study. When guest molecules are embedded in the CD cavity, their melting or sublimation point generally shifts to a different temperature. The DSC curve of β-CD shows a broad endotherm in the range of 90 – 170 °C (maximum at 138.13 °C) corresponding to the release of water molecule. The DSC curve of compound **1** shows endothermic peaks at 134.14 °C and 151.45 °C. The DSC thermogram of **2** shows an endothermic peak at 110.10 °C corresponding to the melting point of the pure compound.

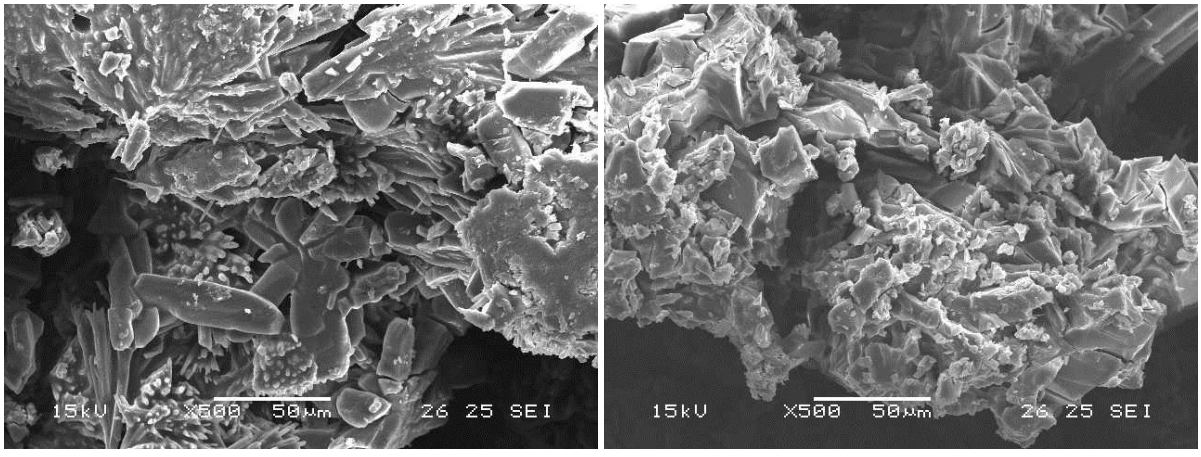
After inclusion of the above compounds with β-CD, the endothermic peaks of the complexes of **1** and **2** are shifted to 157.62 and 151.50 °C, respectively. The shift of the peaks in the complexes shows the formation of an inclusion complex. For all the complexes, the disappearance of melting point is observed with smaller peak of water loss.

3.5. Scanning electron microscopic (SEM) examination

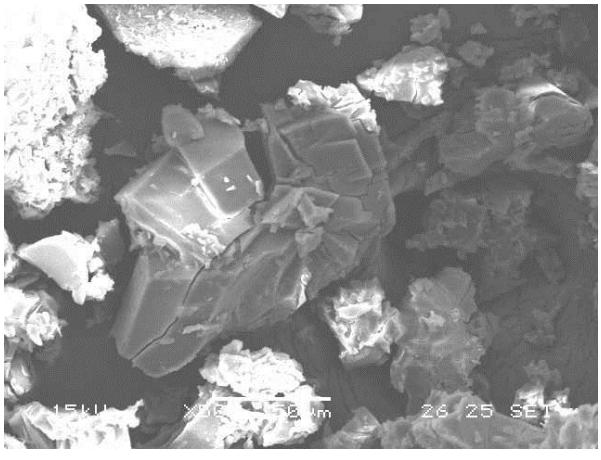
SEM was used to assess the changes in morphology of the compound and the complexes formed. Fig. 2 shows the morphology of β-CD, **1, 2**, **1**-β-CD and **2**-β-CD complexes at low and high magnifications. β-CD appears as long tubular crystals. The compounds **1** and **2** appear like flat-plate crystals. The morphology of **1** and **2** inclusion complexes are totally different from that of the pure compounds and β-CD. These changes



(a) (b)



(c) (d)



(e)

Fig. 2. Scanning electron microscopic photographs of (a) β-CD alone, (b) compound **1**, (c) compound **2**, (d) compound **1**-β-CD complex, (e) compound **2**-β-CD complex.

in the crystal structure also suggest the formation of inclusion complexes.

4. Conclusion

The complexation of 2-amino-6-(4-methoxyphenyl-4-(1-phenyl) pyrimidine and 2-amino-4,6-diphenylpyrimidine with β-CD was successful. With a mixing time of one day and subsequent solvent removal, β-CD complexes were formed. Characterization by ^{1}H NMR, ^{13}C NMR, FT-IR, DSC and SEM were performed and all these methods were utilized to support the complexes formation. All complexes were found to be water-soluble and suitable for subsequent applications.

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