Inclusion Complex of Theophylline with β–Cyclodextrin: Influence of Method of Preparation

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CERTIFICATE

This is to certify that the project entitled **"Inclusion Complex of Theophylline with β–Cyclodextrin: Influence of Method of Preparation"** being submitted by Mr. Anam Behera (Roll No.: 413CY2004) to the Department of Chemistry, National Institute of Technology, Rourkela, Odisha, for the award of the degree of Master of Science is a record of bonafide research carried out under my supervision and guidance. To the best of my knowledge, the matter embodied in the report has not been submitted to any other University / Institute for the award of any Degree or Diploma.

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Anam Behera

ABSTRACT

Inclusion complexes of Theophylline (THP) with β-cyclodextrin (β–CD) were prepared in order to improve the solubility and bioavailability of the poorly water soluble drug. Solution phase interaction was studied by UV-Vis and Fluorescence techniques. The linear Benesi–Hildebrand plot indicated the formation of only one type of complex with a host-guest composition of 1:1 in the solution. The effect of method of preparation of the THP-β–CD inclusion complexes (ICs) was investigated. The ICs were prepared by the conventional methods of physical mixing (PM), kneading (KN), co-precipitation (CP) and freeze drying (FD) and also by the novel approach of microwave irradiation method (MW). The solid inclusion complexes were characterized by various spectroscopic techniques such as FTIR, XRD, DSC, SEM and ^{1}H NMR. The characterization techniques indicated the formation of true inclusion complexes in case of CP, FD and MW. The *in vitro* dissolution rate of THP was considerably enhanced when the inclusion complexes were employed. Therefore, the bioavailability of THP can be improved significantly by forming inclusion complexes with cyclodextrin.

CHAPTER 1

INTRODUCTION

1.1 Cyclodextrins

Cyclodextrins (CD) are cyclic oligosaccharides derived from starch containing six (α-CD), seven (β-CD), eight (γ-CD), nine (δ-CD) or ten (ε-CD) or more (α-1, 4)-linked α-D-glucopyranose units (Figure 1). Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form non-covalent inclusion complexes. Chemically they are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α glucosidic bonds [1].

Table 1. Characteristics of natural cyclodextrins; α-CD, β-CD and γ-CD

Cyclodextrin	Molecular weight	Number of glucose units	Dimensions (nm)			Solubility (g/ 100mL)
			H	OD	ID	
α-Cyclodextrin (α-CD)	972	6	0.78	1.37	0.57	14.5
β-Cyclodextrin (β-CD)	1135	7	0.78	1.53	0.78	1.85
γ-Cyclodextrin (γ-CD)	1297	8	0.78	1.69	0.95	23.2

H: Height, OD: Outer diameter, ID: Inner diameter

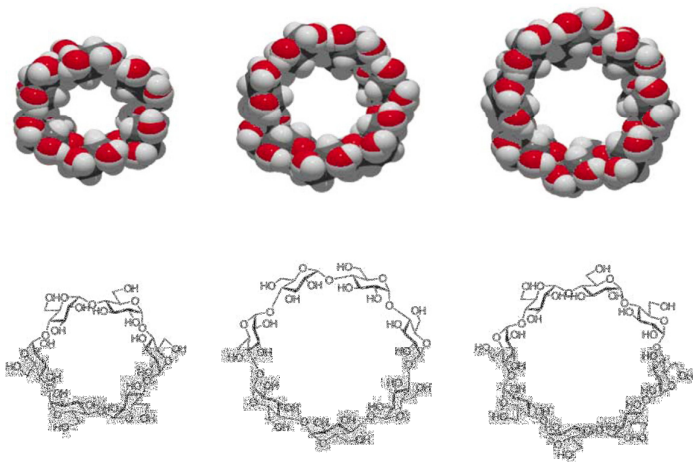

Figure 1. Geometrical representation of α–CD, β–CD and γ–CD molecules.

CDs adapt to the shape of a truncated cone rather than a perfect cylinder because of the chair conformation of the glucopyranose units; the primary and secondary hydroxyl groups oriented outwards (Fig. 2).

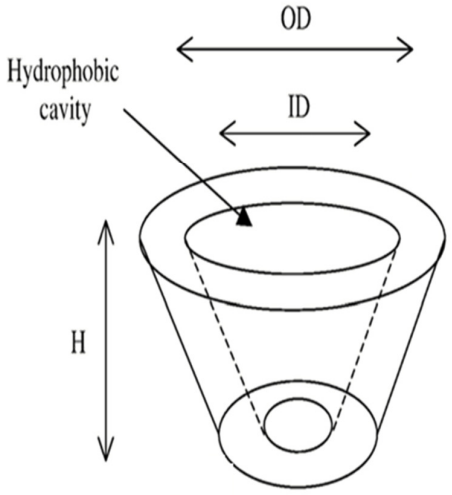

Figure 2. Truncated cone/ torus shape of cyclodextrins.

As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers and can entrap guest molecules in their internal cavity. No covalent bonds are formed or broken during drug–CD complex formation, and upon dilution, the complexes readily dissociate and free drug molecules remain in equilibrium with the molecules bound within the CD cavity.

CDs with lower than 6 glucose units cannot be formed due to steric hindrances while the higher homologues with more than 9 units are difficult to purify. The cavity size of α-CD is insufficient for many drugs while γ-CD is very expensive. In general, δ-CD has weaker complex formation ability than the conventional CDs. β-CD has been widely employed in pharmaceutical applications for the entrapment for a variety of molecules including drugs due to its suitable cavity size and ready availability [2].

Chemically modified CD derivatives have been prepared with a view to extend the physico-chemical properties and the inclusion efficiency of the parent CDs. Several amorphous, non crystallisable CD derivatives with enhanced aqueous solubility, physical and microbiological stability and reduced parenteral toxicity have been developed by chemical modification of CD [3, 4]. Some of the commonly used CD derivatives have been listed below in the Table 2.

Table 2. Commonly used abbreviations for CD derivatives

Cyclodextrin (CD)	**Abbreviation**
Hydroxyethyl-β-CD	HE-β-CD
Hydroxypropyl-β-CD	HP-β-CD
Sulfobutylether-β-CD	SE-β-CD
Methyl-β-CD	M-β-CD
Dimethyl-β-CD	DM-β-CD (DIMEB)
Carboxymethyl-β-CD	CM-β-CD
Carboxymethyl ethyl-β-CD	CME-β-CD
Glucosyl-β-CD	G_1-β-CD
Maltosyl-β-CD	G_2-β-CD
Tri-O-methyl-β-CD	TRIMEB
Tri-O-ethyl-β-CD	TE-β-CD
Tri-O-butyryl-β-CD	TB-β-CD
Tri-O-valeryl-β-CD	TV-β-CD

Factors Affecting Inclusion Complexation

The type of CD employed can influence the formation of inclusion complex as well its performance [5]. For the inclusion phenomenon, the cavity size of CD should be appropriate to accommodate the guest molecule [6]. Compared with neutral CDs, the complexation will

be efficient when the CD and the drug carry opposite charges. In case of ionisable drugs, the presence of charge plays a significant role in the drug/ CD complexation and a change in the solution pH can vary the overall association constant..

Higher temperature has been reported to decrease the magnitude of the apparent binding constant of the drug–CD complex and the effect has been attributed to reduction in drug–CD interaction forces. The list of factors affecting CD complexation has been compiled in Table 3. [7, 8]

Table 3. List of factors affecting inclusion complexation

Factor	Drug	CDs used	Observation
Type of CD	Ketoprofen Albendazole	β-CD, M-β-CD	Solubility enhancement
Cavity size	Digitoxin	β-CD, HP-β-CD	Enhanced solubility
pH	Piroxicam	β-CD	Effective complexation at low pH
Temperature	Sulindac	β-CD	Lower temperature increases binding constant

Effects of CD on Drug Properties in Formulations

- *Improved Drug Solubility and Dissolution*

CDs play a vital role in improving the apparent drug solubility or the dissolution rate through inclusion complexation by acting as hydrophilic carriers for drugs. Some common examples of CD applications as drug solubilising agents are summarized in Table 4.

Table 4. List of CD-enhanced solubility and dissolution of drugs

CD	**Drugs**
α-CD	Praziquantel
β-CD	Naproxen, Ibuprofen, Lorazepam, Ketoprofen, Piroxicam *etc*
γ–CD	Digoxin, Omeprazole
HP-β-CD	Albendazole, Rutin, Itraconazole, Ketoprofen

- *Enhanced Drug Bioavailability*

In case of hydrophobic drugs, CDs increase the permeability by increasing drug solubility, dissolution and thus making the drug available at the surface of the biological barrier, from where it partitions into the membrane without disrupting the lipid layers of the barrier [9].

- *Control of Drug Release*

The combined use of CD inclusion complexes and CDs conjugate can be helpful for designing various kinds of time-controlled type oral drug delivery formulations. The release of drug from the drug/CDs conjugate after oral administration shows typical delayed-release behaviour. Therefore, when the CD conjugates are combined with other different release preparations, more advanced and optimized drug release system, securing balanced oral bioavailability, and prominent therapeutic efficacy can be achieved [10].

- *Site-specific Drug Delivery*

CDs have the inherent property to be fermented to small saccharides by colonic microflora and thus absorbed as maltose or glucose in the large intestine. This biological property of CDs can be exploited for site-specific delivery of drugs to colon [11].

- *Improved Drug Stability*

Cyclodextrin complexation provides molecular shielding by encapsulating labile drug molecules at molecular level. Thus insulate them against various degradation processes due to heat and light and increase the shelf life of drugs [12].

- *Improved Drug Efficacy*

CDs have been used to reduce the irritation caused by drugs [13]. The increased drug efficacy and potency (i.e., reduction of the dose required for optimum therapeutic activity), caused by CD-increased drug solubility, may reduce drug toxicity by making the drug effective at lower doses.

1.2 Theophylline

Theophylline (1, 3-dimethylxantine), TPH (Figure 3), is a poorly water soluble purine alkaloid. It is widely used in medicinal and pharmaceutical fields in the treatment of diseases related to respiratory problems like asthma, emphysema and chronic obstructive pulmonary diseases.

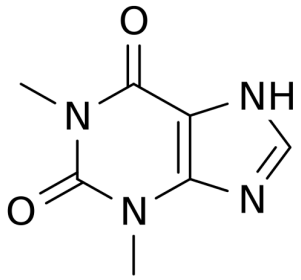

Figure 3. Chemical structure of Theophylline (THP).

As a member of the xanthine family, THP bears structural and pharmacological resemblance to theobromine and caffeine.

The main actions of THP involve [14]:

- relaxing bronchial smooth muscle
- increasing heart muscle contractility and efficiency; as a positive inotropic
- increasing heart rate: (positive chronotropic)
- increasing blood pressure
- increasing renal blood flow
- anti-inflammatory effects
- central nervous system stimulatory effect mainly on the medullary respiratory centre.

However the use of THP is limited by its very rapid absorption [15] and conversion to inactive metabolites [16]. The metabolic product of THP is methyluric acids such as 1,3-dimethyl uric acid and 1-methyl uric acid in urine. Inactive metabolites may cause

undesirable side effects that can harm human health [17]. Moreover, the aqueous solubility of THP is very low because of which the formulation of this drug is challenging [18].

1.3 Objectives

The specific objectives of the present study are:

- To study of solution phase inclusion process of THP with β–CD by UV-Vis and Fluorescence spectroscopic methods.
- Preparation of solid inclusion complexes (IC) of THP with β–CD by the conventional methods such as physical mixing, kneading, co-precipitation and freeze drying and also by the microwave irradiation method.
- Characterisation of ICs by various spectroscopic techniques such as FTIR, XRD, DSC, SEM and ^{1}H NMR techniques.
- To study the dissolution characteristics of THP and the ICs.
- Compare the efficacy of the methods of preparation of ICs for better and improved characteristics.

CONCLUSIONS

- The solid inclusion complexes of THP with β–CD have been prepared by the conventional methods of physical mixing, kneading, co-precipitation and freeze drying and also by the novel approach of microwave irradiation method.
- Solution phase interaction was studied by UV-Vis and Fluorescence techniques.
- The linear Benesi–Hildebrand plot indicated the formation of only one type of complex with a host-guest composition of 1:1 in the solution.
- The solid inclusion complexes were characterized by various spectroscopic techniques such as FTIR, XRD, DSC, SEM and ^{1}H NMR.
- The characterization techniques indicated the formation of true inclusion complexes in case of CP, FD and MW.
- The *in vitro* dissolution rate of THP was significantly enhanced when the inclusion complexes were employed.
- Therefore, the bioavailability of THP can be improved significantly by forming inclusion complexes with cyclodextrin.

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