α-Cyclodextrin Complexation - A Viable Route to Taste Masking of Bitterness of Chlorpheniramine Maleate

S. Lizy Roselet*, M. Shirly Treasa, M. AntilinPrincela, B. T. Delma and K. Francy
Department of Chemistry, Holy Cross College (Autonomous), Nagercoil - 629004
Affiliated to Manonmaniam Sundaranar University, Tirunelveli - 627012
***** Corresponding Author - Email**:** lizyroselet@holycrossngl.edu.in

ABSTRACT

Improving patient compliance with significant therapeutic value is highly important to be in concern while developing an oral dosage form. Undesirable taste of the drug can influence patient compliance and product quality. Health care providers are dealing with bitter drug issues while orally administering to each paediatric patients and elderly patients. Masking the unpleasant taste of bitter drugs is a potential tool for the enhancement of patient compliance and success of the product. Various approaches and methodologies of development for masking the undesirable taste of drugs with consideration of applications, evaluation, and technologies for taste masking. This investigation evaluates inclusion complexation by α-cyclodextrin as a masking agent for Chlorpheniramine Maleate.

Keywords: *Taste masking, Inclusion complex, Chlorpheniramine Maleate, α-Cyclodextrin*

Introduction

Paediatrics and elderly patients specifically are difficult to control while administering the unpleasant taste of specific drug, leading to administer fewer doses, which cause less efficiency. Taste masking is the proper way to improve the quality of the treatment [1]. The taste masking defined as a perceived decrease of an unpleasant taste of active pharmaceutical ingredients [2]. There are various taste-masking techniques which may be used to inhibit bitter taste [3]. For solid oral dosage forms, polymer coating of capsules and tablets or monolithic systems such as polymer or lipid extrudates may be used; these approaches may be of less use for paediatric patients for whom swallowing solid dosage forms can be challenging. Among the various taste masking strategies inclusion complex formationis an efficient approach in dealing with patient's compliance. These inclusion complexes can enhance drug solubility, mask bitter taste of the active pharmaceutical ingredient (API) and prevent degradation of drug molecules. Usually, the formation of inclusion complex method is used when low dose drug is required. This technique works by the host and guest link, where the host is the complexing agent; and the guest is the active moiety. The purpose of the complexing agent is to mask the unpleasant taste of specific drug either by reducing its oral solubility or reducing the amount of the drug particles to taste buds. The most commonly

used complexing agent is cyclodextrin, due to its sweet in taste, non-toxic, and cyclic oligosaccharide acquired from starch. In inclusion complexes, the Vander Waals forces are predominantly involved [4-6].

Chlorpheniramine Maleate is an antiallergic medication. It appears as Odor less white crystalline solid or white powder with a bitter taste and has poor patient compliance. Chlorpheniramine maleate (CPM) is a first-generation alkyl amine widely used as antihistamine drug patients to inhibit various histaminic actions [7]. Apart from the most common side effects possess by all the antihistamines, CPM has a major problem related to its oral bioavailability [8]. However, it is well absorbed from the gastrointestinal tract, its oral bioavailability is only 25-40% of the orally administered dose which is due to its high first pass metabolism [9]. Chlorpheniramine Maleate works by blocking the action of histamine, thereby relieving these symptoms. In this study, α-Cyclodextrin is used to mask the bitter taste of Chlorpheniramine Maleate and it is illustrated in Fig. 1.

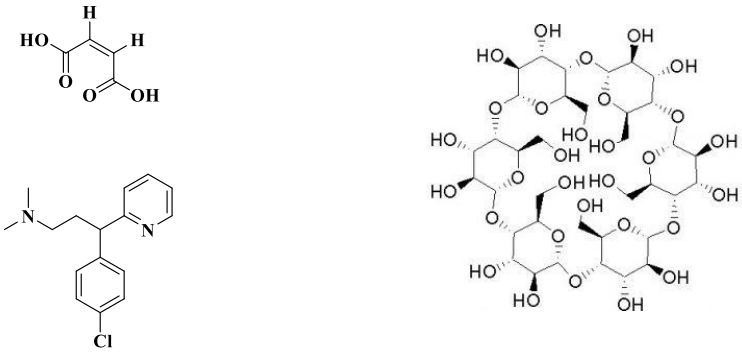

Fig.1 Structure of Chlorpheniramine Maleate and α-Cyclodextrin

Materials and Methods

ChlorpheniramineMaleate and α-Cyclodextrin purchased from Sigma Aldrich were used for the studies. The solvents used were of analytical grade. Triply distilled water was used for the preparation of stock solutions.

Instruments

1. Systronics Smart Double Beam Spectrophotometer-2203
2. JASCO Spectrofluorometer FP-8200.

Preparation of liquid inclusion complex of Chlorpheniramine maleate:α-CD

About 0.0054g of Chlorpheniramine maleate was accurately weighed and dissolved in 10mLethanol. About 0.2918g of α-CD was dissolved in 30mL distilled water in a 250mL beaker. Inclusion complexes of Chlorpheniramine maleate:α-CD were prepared by varying the concentration of α-CD from $2x10^{-3}$M to $1x10^{-2}$M with Chlorpheniramine maleate.

Preparation of solid inclusion complex of Chlorpheniramine maleate: α-CD

About 0.02g of Chlorpheniraminemaleate was accurately weighed and dissolved in 30mLof methanol and about 0.2918g of α-CD was dissolved in 30mL distilled water in a 250mL beaker. Both the solutions were mixed together in a beaker and put over electromagnetic stirrer to stir continuously for 48h at room temperature. The precipitate formed after evaporation was dried and used for characterization.

Results and Discussion

UV-VIS Spectral Analysis of Chlorpheniramine maleate:α-CD

Absorption spectra were used to confirm the formation of inclusion complex. The complexation causes a change in the absorption spectrum of a guest molecule. During the spectral changes, the chromophore of the guest is transferred from an aqueous medium to the non-polar cyclodextrin. These changes must be due to a perturbation of the electronic energy levels of the guest caused either by direct interaction with the cyclodextrin, by the exclusion of solvating water molecules or by a combination of these two effects [10,11]. Small shifts are observed on the UV spectra of the included guests, the method is often used to detect inclusion complexation. In this study, absorption spectra of α-CD, chlorpheniramine maleate and inclusion complexes were taken into consideration. The absorption spectra of the inclusion complexes formed between chlorpheniramine maleate and α-CD are shown in Fig.2.The spectral data are tabulated in Tab.1An absorption peak is obtained at λ_{abs} 252 nm. After the addition of α-CD, the absorption spectra are bathochromically shifted with increase in intensity. With the increase in concentration of α-CD, the intensity of absorbance also increased. It is inferred that the solubility of chlorpheniramine maleate increases with increase in the concentration of α-CD. Spectral shifts are indicative of the inclusion complexes formed between chlorpheniramine maleateandα-CD.

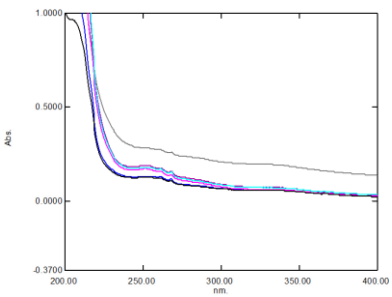

Fig.2. Absorption spectra of chlorpheniramine maleate with varying Concentrationsof α-CD

Table.1 Absorption spectral data of chlorpheniramine maleate with varying concentrations of α-CD

S. No	Concentration of α-CD	λabs	Absorbance	$A-A_0$	$\frac{1}{A-A_0}$	Log E	1/ [α-CD]
1	0	247	0.175			3.65	
2	0.002	247.4	0.200	0.025	40	3.71	500
3	0.004	248	0.215	0.040	25	3.74	250
4	0.006	248.7	0.240	0.065	15.3	3.79	166.6
5	0.008	249	0.255	0.080	12.5	3.82	125
6	0.010	250	0.300	0.125	8	3.89	100

Determination of binding constant

The binding of Chlorpheniramineα-CD inclusion complexes has been studied by absorption spectral technique using Benesi-Hildebrand equation [12].

$$\frac{1}{A-A_0} = \frac{1}{A'-A_0} + \frac{1}{K_B(A'-A_0)\,[\alpha-CD]}$$

Where,

A_0- initial absorbance; A, A'-observed absorbances; K_B- binding constant $[\alpha - CD]$- Concentration of α-CD. The binding constant calculated was found to be 96 M^{-1}.

Determination of the stoichiometry of the inclusion complex

The stoichiometry of the inclusion complex, A plot of $\frac{1}{A-A_0}$versus $\frac{1}{[\alpha\text{-CD}]}$ for absorption gives good linear correlation indicating the stoichiometry for the formation of 1:1 guest host inclusion complex. The stoichiometry can be obtained by using the Benesi-Hildebrand equation which was shown in Fig. 3.

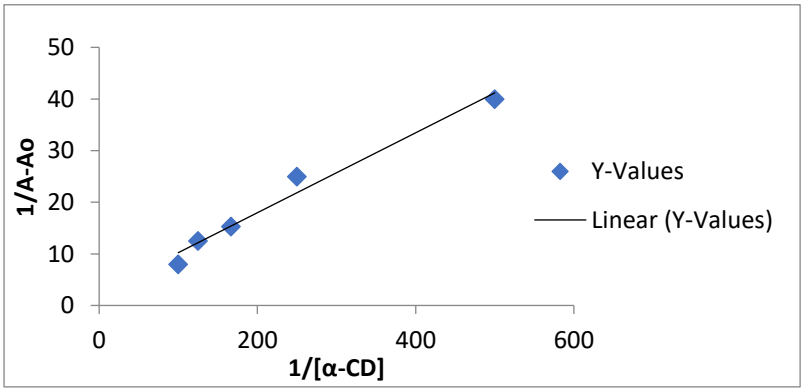

Fig.3. Benesi-Hildebrand plot of Chlorpheniramine maleate: α-CD inclusion complexes

FTIR Spectral Analysis of inclusion complexes of chlorpheniramine maleate: α-CD.

FTIR is a very useful tool to prove the existence of both guest and host molecules in their inclusion complexes Fig 4,5,6 shows the FTIR spectra for the α-CD, chlorpheniramine maleate, inclusion complex of chlorpheniramine maleate:α-CD. The pure drug chlorpheniramine maleate exhibited the peaks at 2924.27 cm^{-1} for C-H aromatic stretching, 650.34 cm-1, 944.87 cm^{-1} for C=C characteristic peaks, 3340.71 cm^{-1} for O-H stretching of Maleate salt, 1703.38 cm^{-1} for C=O and 769.6 cm^{-1} for C-Cl bending. The same peaks of the chlorpheniramine maleate were observed in the inclusion complex with slight shifts in wavelength. The inclusion complex shows a broadened O-H band with change in values from 3400 cm^{-1} to 3394.72 cm^{-1} which indicates that there is intermolecular hydrogen bonding betweenchlorpheniramine maleate and α-CD.

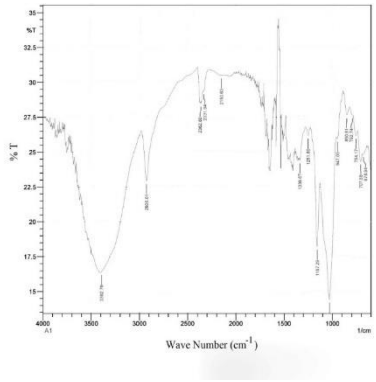

Fig.4 FTIR Spectra of α-CD

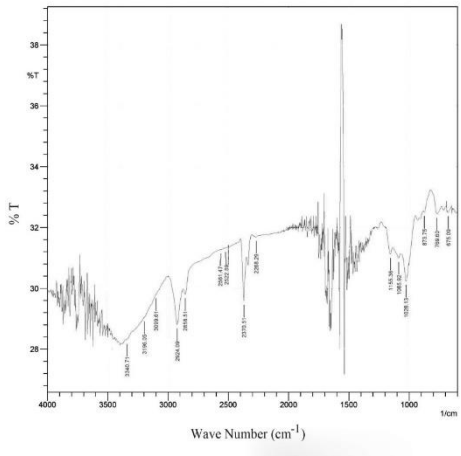

Fig.5 FTIR Spectra of chlorpheniramine maleate

Significant changes are observed in the area between 1600 and 1400 cm^{-1}assigned to C=C aromatic stretching in free due to the interaction between this region of the drug and cyclodextrin cavity and an enlargement of the bands at 1030 cm^{-1} of the is observed due to the

establish of interaction during complexes formation [13]. No new peaks appeared which indicates that no bonds are formed or broken during inclusion complex formation.

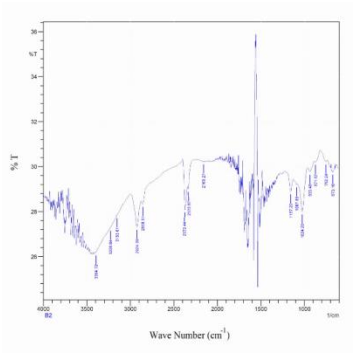

Fig.6 FTIR Spectra of inclusion complex of chlorpheniramine maleate: α-CD

Thin Layer Chromatographic Studies

Thin layer Chromatography also serves as a tool for the inclusion complex formation. The R_f values are calculated for pure drug and the inclusion complexes. The thin layer chromatogram for pure drug and inclusion complex in the ratio of 1:1 diethyl ether: water, chloroform: water, ethyl acetate: water are shown in Fig.7,8 and 9. In all the cases, the R_f values of inclusion complexes are found to be less than that of pure Chlorpheniramine maleate [14]. This is a strong indication that inclusion complexes are formed between Chlorpheniramine maleate and α-CD. Further, the R_f values obtained for chlorpheniramine maleate and chlorpheniramine maleate: α-CD was tabulated in Table 2.

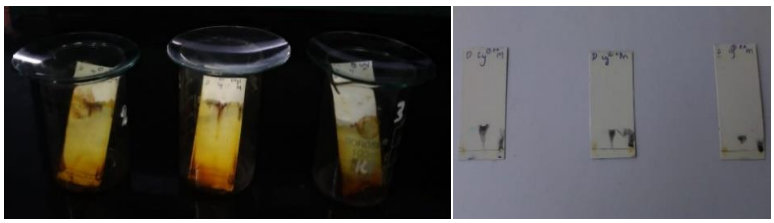

Fig.7 Thin Layer Chromatography images of chlorpheniramine maleate and chlorpheniramine maleate: α-CD in the ratio of 1:1 diethyl ether: water

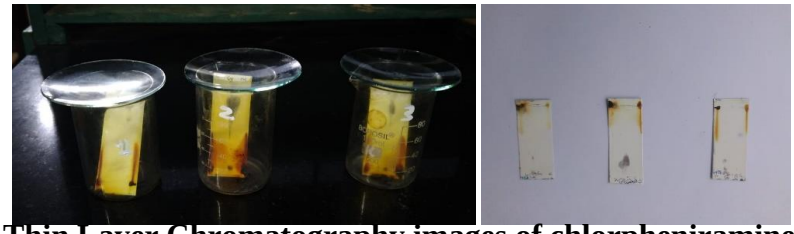

Fig.8 Thin Layer Chromatography images of chlorpheniramine maleate and chlorpheniramine maleate: α-CD in the ratio of 1:1 chloroform: water, ethyl acetate: water

Fig.9 Thin Layer Chromatography images of chlorpheniramine maleate and chlorpheniramine maleate: α-CD in the ratio of 1: 1, ethyl acetate: water

Table.2 Thin layer chromatographic data

solvent	α-CD R_f	CPM R_f	CPM: α-CD R_f
Diethyl ether Phosphate water50:50v/v	0.2345	0.2673	0.2009
CD Chloroform Phosphate water50:50v/v	0.2876	0.2939	0.1978
Ethyl acetate Phosphate water50:50v/v	0.3045	0.3155	0.2987

CPM-chlorpheniramine maleate

The complexing agentα-Cyclodextrins a sweet, non-toxic, starch-derived cyclic oligosaccharide. Bitterness elimination is depended upon the extent of complexation of guest molecule with host, value of complex association constant temperature and the host/guest ratio. chlorpheniraminemaleate forms a 1:1 complex with cyclodextrins, more than 99 % of the bitter drug is complexed with cyclodextrins and as complexed moleculechlorpheniramine maleate cannot react with the taste bud in the buccal cavity, no bitter taste perceived [15,16] and therebysuppression of bitter taste by alpha-cyclodextrin [17]. The complexing agent α-Cyclodextrin is capable of masking the bitter taste of the drug by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Vander Waals forces are mainly involved in inclusion complexes [18-20].

Conclusion

The absorption spectra provide ample information regarding the formation of inclusion complexes of chlorpheniraminemaleate with α-CD. The binding constants were

calculated using the Benesi Hildebrand equation and it was found to be 96.5 M^{-1}.The linear correlation of the Benesi-Hildebrand plot indicates that the inclusion complexes formed were in the stoichiometric ratio 1:1.Considerably higher binding constant values showed the formed inclusion complexes were quite stable.The stability of the inclusion complexes formed shows that the solubility of chlorpheniramine maleate is also further increased upon complexation with α-CD.The formation of inclusion complexes between chlorpheniramine Maleate and α-CD was further confirmed by FTIR studies and thin layer chromatographic studies.Thus it paves the way to remove undesirable bitter effects the drug chlorpheniramine Maleate and enable us to have sustained controlled release of the drug and hence oral bioavailability of the drug. Bitterness elimination is depended upon the extent of complexation of guest molecule with host, value of complex association constant temperature and the host/guest ratio. chlorpheniramine maleate forms a 1:1 complex with α-cyclodextrin, more than 99 % of the bitter drug is complexed with α-cyclodextrin and asthe complexed molecule. chlorpheniramine maleate cannot react with the taste bud in the buccal cavity, no bitter taste is perceived and suppression of bitter taste was done by alpha-cyclodextrin.

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