

## Taste Masking Techniques: Dicyclomine Hydrochloride by Inclusion Complexes with $\beta$ -Cyclodextrin Using Various Oral Formulations

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### ABSTRACT

Dicyclomine hydrochloride is anticholinergic drug used as an antispasmodic. It is very bitter in taste. The purpose of this research was to reduce the bitterness of Dicyclomine hydrochloride. Taste masking was done by complexing Dicyclomine hydrochloride with  $\beta$  Cyclodextrin. Drug  $\beta$ - Cyclodextrin complexes were prepared in the ratio 1:1, 1:2 and 1:3 by kneading method. The complexes were characterized by Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffraction (XRD) patterns. These studies indicated the inclusion of Dicyclomine in the cavity of  $\beta$ -cyclodextrin. The 1:3 complexation ratio resulted in mask of taste of dicyclomine was selected as it showed acceptable taste and for further use in mouth dissolving oral formulations.

**Keywords:** Dicyclomine hydrochloride,  $\beta$ -cyclodextrin, Oral disintegrating tablets, Taste masking.

### INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the oral

disintegrating tablet (ODT) and fast dissolving film (FDF) is the most widely preferred commercial products.<sup>1</sup>

Taste is the capability to identify the flavor of substances like food, drugs etc. Taste is now became a significant factor governing the patient compliance and

product quality. It gained importance as the most of the drugs are administered through oral route. Administration of unpalatable drugs is hampered by their unpleasant taste particularly in case of pediatric and geriatrics.<sup>1,2</sup>

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist. The ideal solution to reduce or inhibit bitterness is the discovery of a universal inhibitor of all bitter tasting substances that does not affect the other taste modalities such as sweetness or saltiness.<sup>3,4</sup>

#### Various techniques taste masking

1. Polymer coating and conventional granulation
2. As flavors, sweeteners and amino acids
3. Ion exchange resins
4. Spray congealing with lipids
5. Inclusion complexes with Cyclodextrin
6. Freeze drying process
7. Preparing multiple emulsions
8. Prodrug approach
9. Miscellaneous using gelatin, liposomes

Several parts like extent of bitter taste, dose, dosage form and type of the patient influence the method to be used for masking the taste of the bitter drugs. Evaluation of taste masking by electronic tongue is a recent innovation. Advatab, Microcaps, Liquitard, Kleptose, Formulplex and Formulcoat are the new taste masking technologies which are found to be better than existing ODT technologies like Zydis, Orasolv and Quicksolv etc. In addition to oral drug delivery, the taste masked drug delivery research is gaining importance for get better the quality of the treatment for paediatrics and geriatrics.<sup>2,3</sup>

Factors that are taken into consideration during the taste masking formulation include.<sup>2</sup>

- Extent of the bitter taste of the API
- Required dose load

- Drug particulate shape and size distribution
- Drug solubility and ionic characteristics
- Required disintegration and dissolution rate of the finished product
- Desired bioavailability
- Desired release profile

#### Types and mechanism of taste<sup>1,2,4</sup>

Taste is one of the usual five senses and is the capability to detect the flavor of substances such as food, certain minerals, and poisons, etc. It decides the selection of food, its palatability and stimulation of reflexes for secretion of saliva, gastric juices and pancreatic juices. The sensation of taste can be categorized into,

- Sweet (sugars, glycerol)
- Saltish (sodium)
- Sour (acidic substances)
- Bitter (quinine, nicotine)
- Umami

Humans receive tastes through sensory organs, taste buds, (also known as gustatory calyculi) concentrated on the upper surface of the tongue.

## MATERIAL AND METHOD

### Material

Dicyclomine hydrochloride was a gift and  $\beta$ -Cyclodextrin was obtained from the (Himedia, India) by the Institute other analytical reagents were used without further purification. Deionized double-distilled water was used throughout the study.

### Method

#### Formation of inclusion complexes of Dicyclomine HCl with $\beta$ -Cyclodextrin<sup>4-6</sup>

Dicyclomine HCl was complexed with  $\beta$ -cyclodextrins in ratio 1:1, 1:2, 1:3 by kneading method.

In this method, accurately weighed quantity of  $\beta$ -Cyclodextrin (1gm for 1:1 ratio), (2 gm for 1:2) and (3 gm for 1:3) was mixed with sufficient quantity of water to obtain a smooth and homogeneous paste. Weighed quantity of Dicyclomine HCl (1 gm.) and citric acid (solubilizing agent) was slowly added. The mixture was stirred for 1 hour along with heat. During this process, appropriate quantity of water was added to maintain suitable consistency. Finally the paste was dried in oven at 40°C for 48 hours. The complex was finally scrapped off from mortar and passed through sieve no. 100. Direct Complexation was done by stirring Dicyclomine HCl and  $\beta$ -Cyclodextrin. (See figure 1.)

#### Equipment and instrumental condition

UV-Spectrophotometric study was carried out in order to determine the  $\lambda_{\max}$  of Dicyclomine hydrochloride in pH 6.8. The test medium was scanned for absorption maxima from 200-400 nm. The scanned  $\lambda_{\max}$  was found to be similar as that of reported  $\lambda_{\max}$  (214 nm).<sup>7</sup>

#### Standard curve of dicyclomine hydrochloride in pH6.8 phosphate buffer at $\lambda_{\max}$ - 214nm

##### Selection of media

For the preparation of standard calibration curve Phosphate buffer pH 6.8 was selected.

##### Procedure

Dilutions of 0, 2, 4, 6, 8, 10 $\mu$ g/ml were prepared. After that the absorbance was taken at 214 nm and standard curve between concentrations vs. absorbance was plotted. The result obtained is shown in graphically depicted in Fig. 2.<sup>8</sup>

#### Characterization of complex

##### FTIR of dicyclomine hydrochloride

Infra red (IR) studies: The batches 1:1, 1:2, 1:3 of inclusion complexation were analyzed by IR spectroscopy. The FTIR of pure drug and complex (dicyclomine with  $\beta$ -cyclodextrin) was measured using Fourier Transform Infra Red Spectrophotometer (Spectrum GX FT-IR, Perkin Elmer, USA). Pure drug and complex were separately mixed with IR grade KBr and converted into KBr pellet by hydraulic press and scanned over a range of 4000 to 400  $\text{cm}^{-1}$ . FTIR tracings of Dicyclomine hydrochloride molecule are presented in Fig. 3 and the interpretation is shown in Table 1. The FTIR tracings for  $\beta$ -cyclodextrin used are given in Fig. 4, Complex ratio 1:1, 1:2 and 1:3 are shown in Fig. 5, Fig 6, and Fig 7.

##### Differential scanning calorimetry (DSC) analysis

The DSC thermograms of pure drug (Dicyclomine) and complex (dicyclomine with  $\beta$ -cyclodextrin) were carried out using DSC-PYRIS-1 (Perkin-Elmer, USA). The samples were heated from 50 to 450 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.<sup>10</sup>

The optimized batch (1:3) of inclusion complexation were subjected to differential scanning calorimetry (DSC) analysis. The change in endothermic peaks of dicyclomine hydrochloride were observed, which confirms the interaction between dicyclomine hydrochloride and  $\beta$ -Cyclodextrin and are shown in Fig. 8 and Fig. 9.<sup>11</sup>

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complexation indicates the formation of complex.<sup>12</sup>

#### XRD of dicyclomine<sup>7,13</sup>

The X-ray powder diffraction patterns (XRPD) were obtained at High temperature (RT- 16000 C) using The Bruker D8 X-ray diffractometers with cobalt as anode material, Scintillation counter detector, Lynx eye detector controller and Operated at a voltage of 40 KV. The samples were analyzed in the 2 $\theta$  angle range of 2 °C – 60°C and process parameters were set as: scan step size of 0.025° (2  $\theta$ ), scan step time of 1.53s and the time of acquisition of 1hr, Electron probe current range up to 40mA.

## RESULT AND DISCUSSION

#### FTIR studies

The FTIR spectra of the pure drug showed significant bands at 1134.07, 1193.85, 1718.45 and 2929.67 cm<sup>-1</sup> which indicates the presence of C-N stretching, C-O stretching, C-H stretching, and C-O stretching respectively. The FTIR spectra of the drug were compared with spectra provided for the reference drug in Indian Pharmacopeia (IP 2007). The characteristic peaks of drug matched with the reference. However, the FT-IR spectrum of Dicyclomine hydrochloride complex with  $\beta$ -cyclodextrin was found to exhibit some significant difference in the characteristic peaks of Dicyclomine hydrochloride, revealing modification of drug environment. Characteristic peaks of pure drug at 1134.07 and 1718.45 cm<sup>-1</sup> were sifted to 1124.42 and 1720.39 cm<sup>-1</sup> respectively, rest of the peaks were did not appear which clearly suggest the formation of complexation of drug with  $\beta$ -cyclodextrin as shown in [Fig. 7].<sup>6,14</sup>

#### DSC studies

DSC thermogram showed an endothermic peak of Dicyclomine hydrochloride at 174.23 °C, which corresponded to its melting point. The thermo-gram of Dicyclomine hydrochloride with  $\beta$ -cyclodextrin complex did not show any peak at 175.44°C which indicates that there is formation of complex as shown in [Fig. 9].<sup>1,5,15</sup> (See table 1.)

#### XRD studies

XRD study was performed to confirm the results of DSC studies. X ray diffraction (XRD) is a useful method for determination of complexation in powder or microcrystalline state. XRD of Dicyclomine with  $\beta$ -cyclodextrin (Fig.11) showed sharp peaks at 5.318°, 6.373°, 12.310°, 15.560°, 16.672°, 17.438° 22.542°, 55.998° and 60.188°2 $\theta$  positions with height 93.8, 66.4, 58.5, 60.8, 77.9, 100.0, 49.6 and 12.4 cps indicating crystalline nature of the drug. XRD scan complex of Dicyclomine with  $\beta$ -cyclodextrin did not show crystalline nature with peak at 17.438° 2 $\theta$  positions with height 100.0 cps.<sup>3,16</sup>

#### *In-vitro* taste evaluation

*In vitro* taste was evaluated by determining drug release in simulated salivary fluid (P<sup>H</sup> 6.8) to predict release in the human saliva. If equivalent to 20 mg of dicyclomine hydrochloride was taken, than drug content should equal in all complex ratios.<sup>3,11,17</sup> (See table 2.)

## CONCLUSION

Taste masking of Dicyclomine hydrochloride was done using  $\beta$ -Cyclodextrin as a taste masking agent. It was found out that at optimized ratio 1:3 of Dicyclomine hydrochloride to  $\beta$ -Cyclodextrin desired taste masking could be obtained. Excellent taste masking was achieved using cyclodextrins as complexing agent. *In vitro* taste was

evaluated by determining drug release in simulated salivary fluid ( $P^H$  6.8) to predict release in the human saliva was used as a technique for taste masking in further study.

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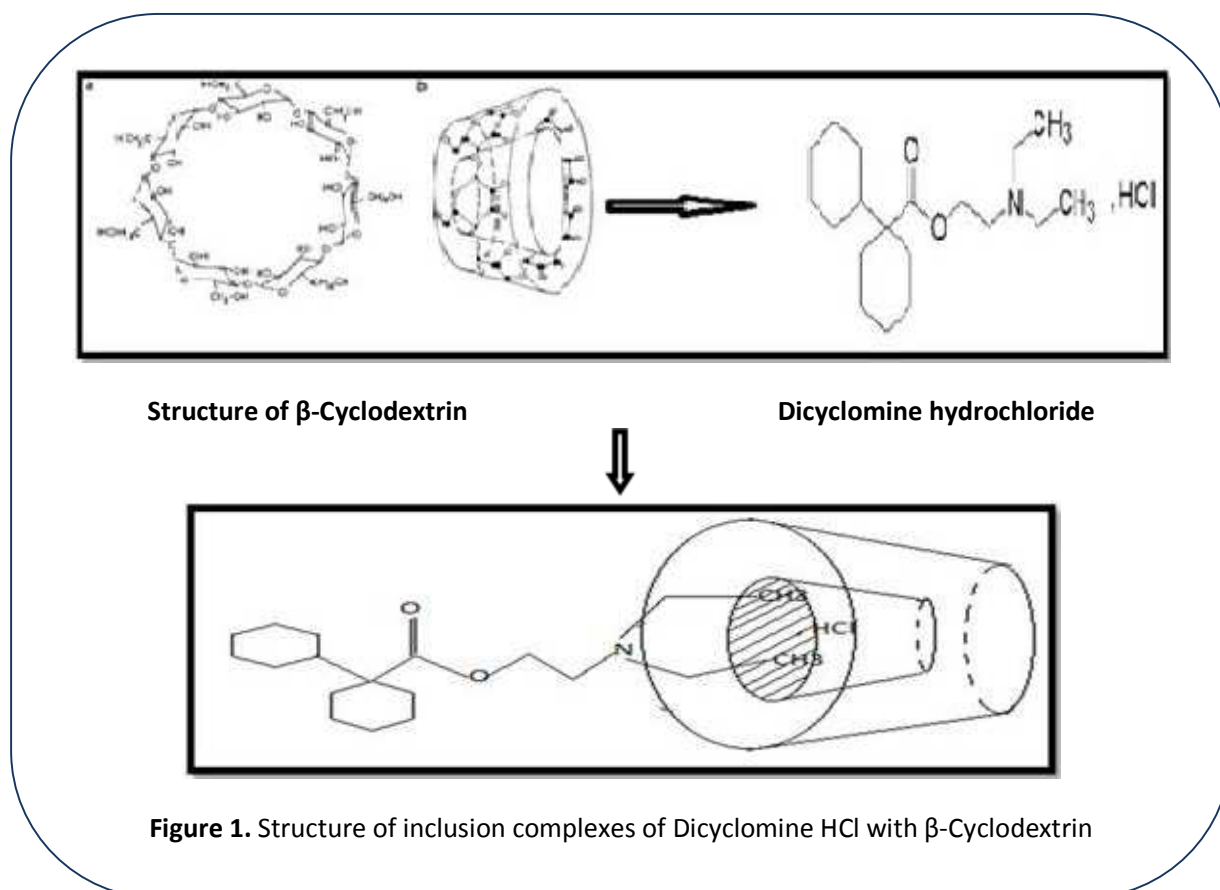
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**Table 1.** Peak value of pure drug

Dicyclomine pure drug	Complex peak value
174.23°C	175.44°C

**Table 2.** Drug content

S. No.	Drug and $\beta$ -cyclodextrin ratio	% of drug content of drug complex
1	1:1	77.04 $\pm$ 0.93
2	1:2	36.66 $\pm$ 0.57
3	1:3	18.23 $\pm$ 0.29





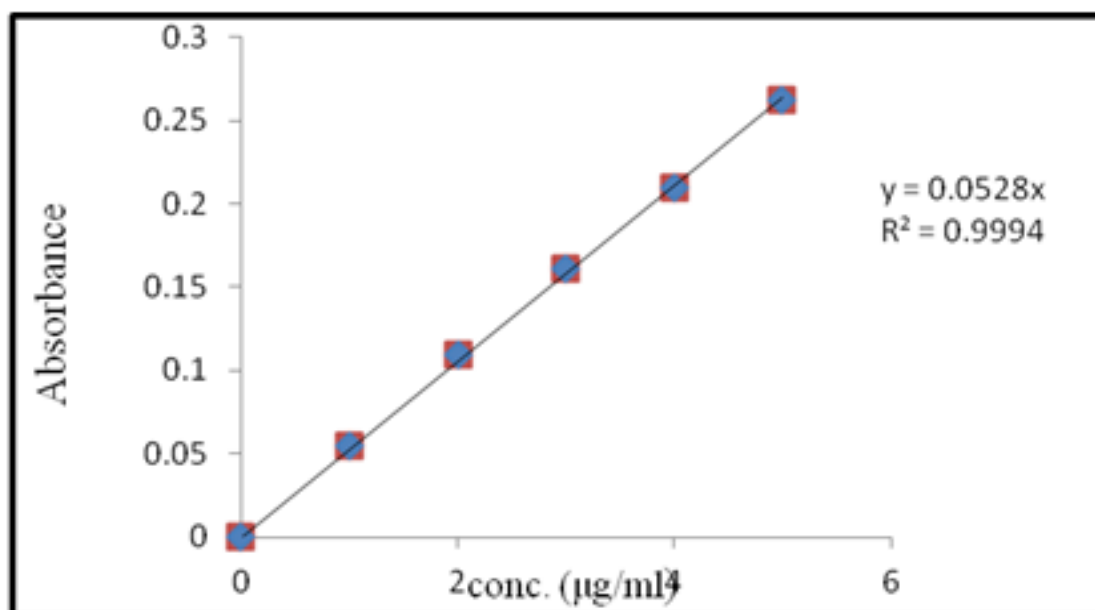


Figure 2. Calibration curve data of Dicyclomine hydrochloride

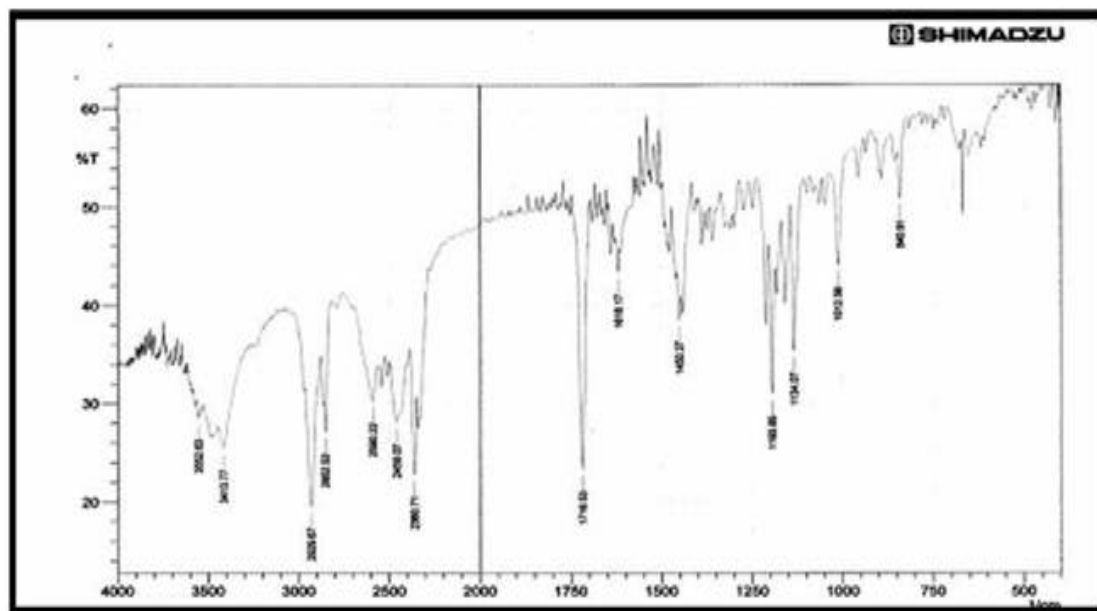


Figure 3. FTIR of pure drug (dicyclomine hydrochloride)

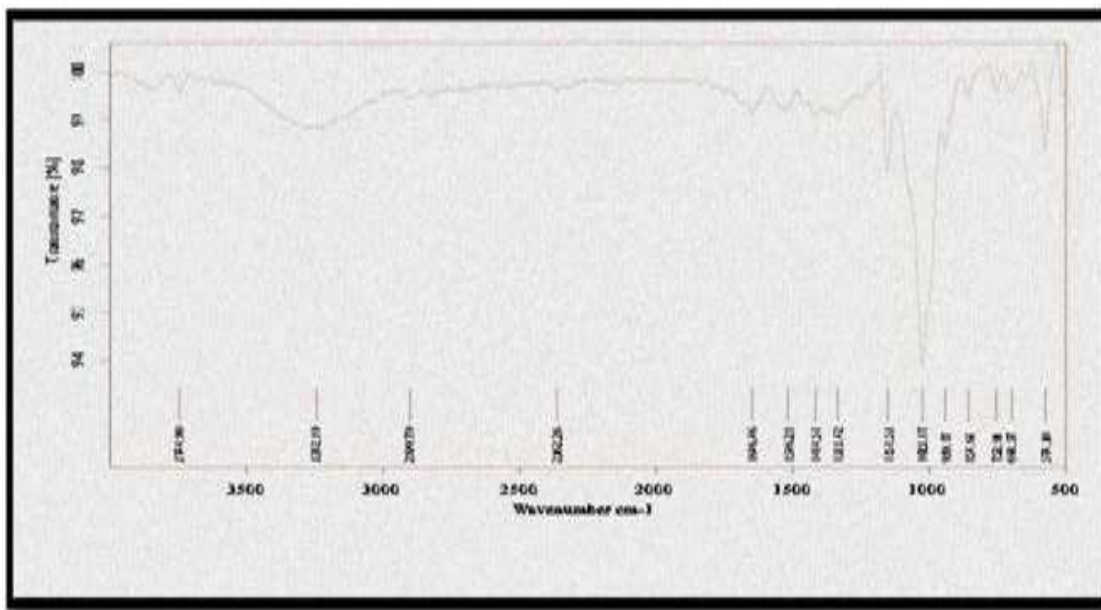


Figure 4. FTIR spectra  $\beta$ -cyclodextrin

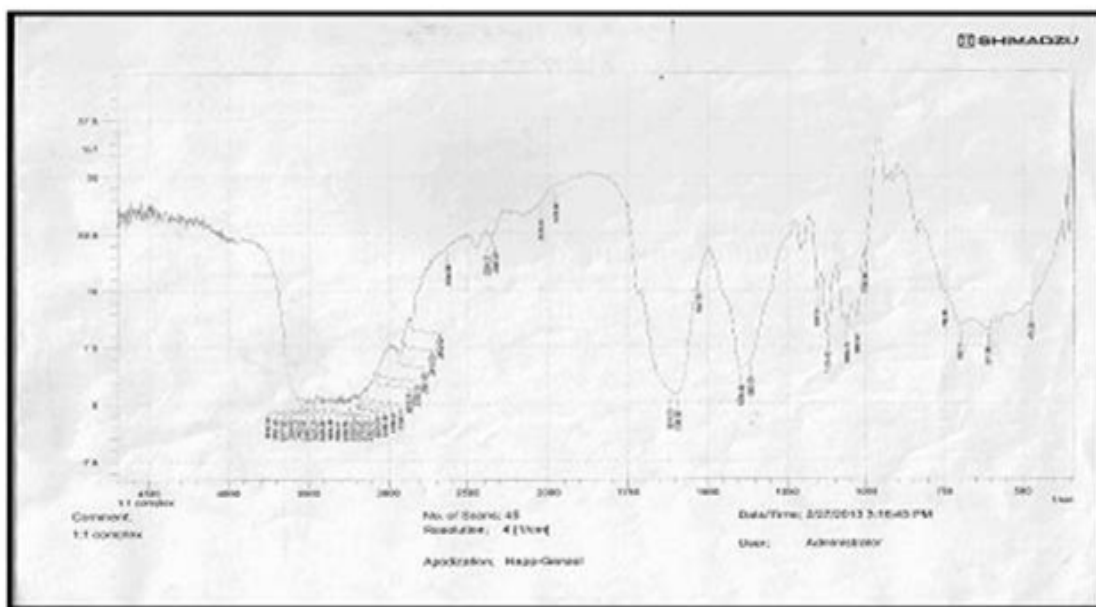


Figure 5. Drug with complexation with  $\beta$ -cyclodextrin ratio (1:1)



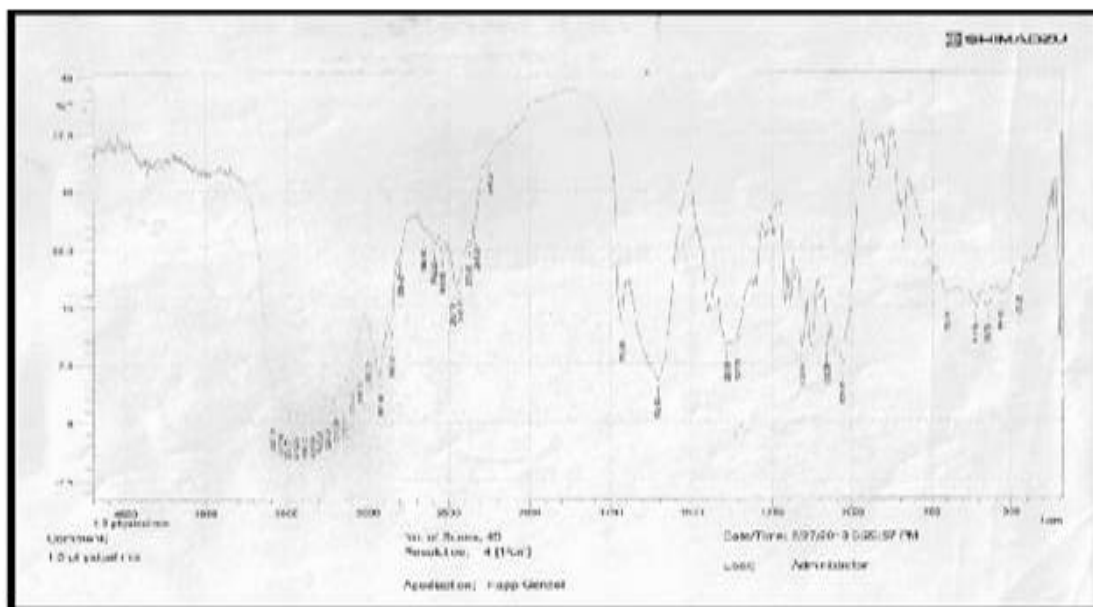


Figure 6. Drug with complexation with  $\beta$ -cyclodextrin ratio (1:2)

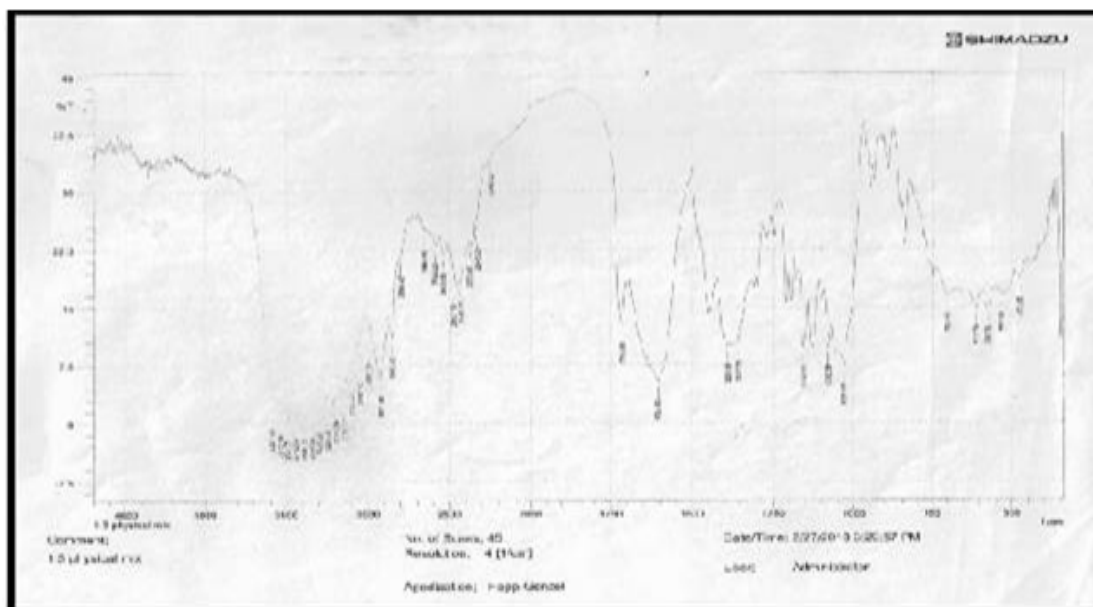


Figure 7. Drug with complexation with  $\beta$ -cyclodextrin ratio (1:3)

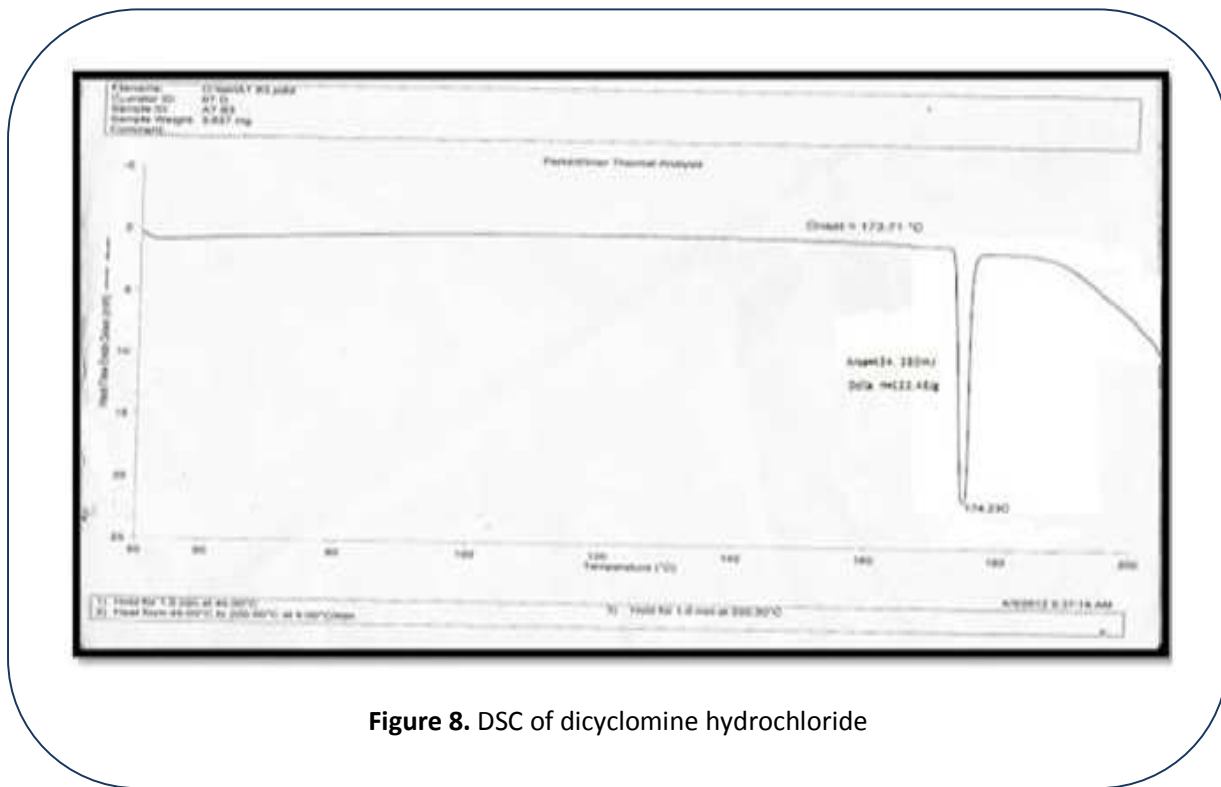


Figure 8. DSC of dicyclomine hydrochloride

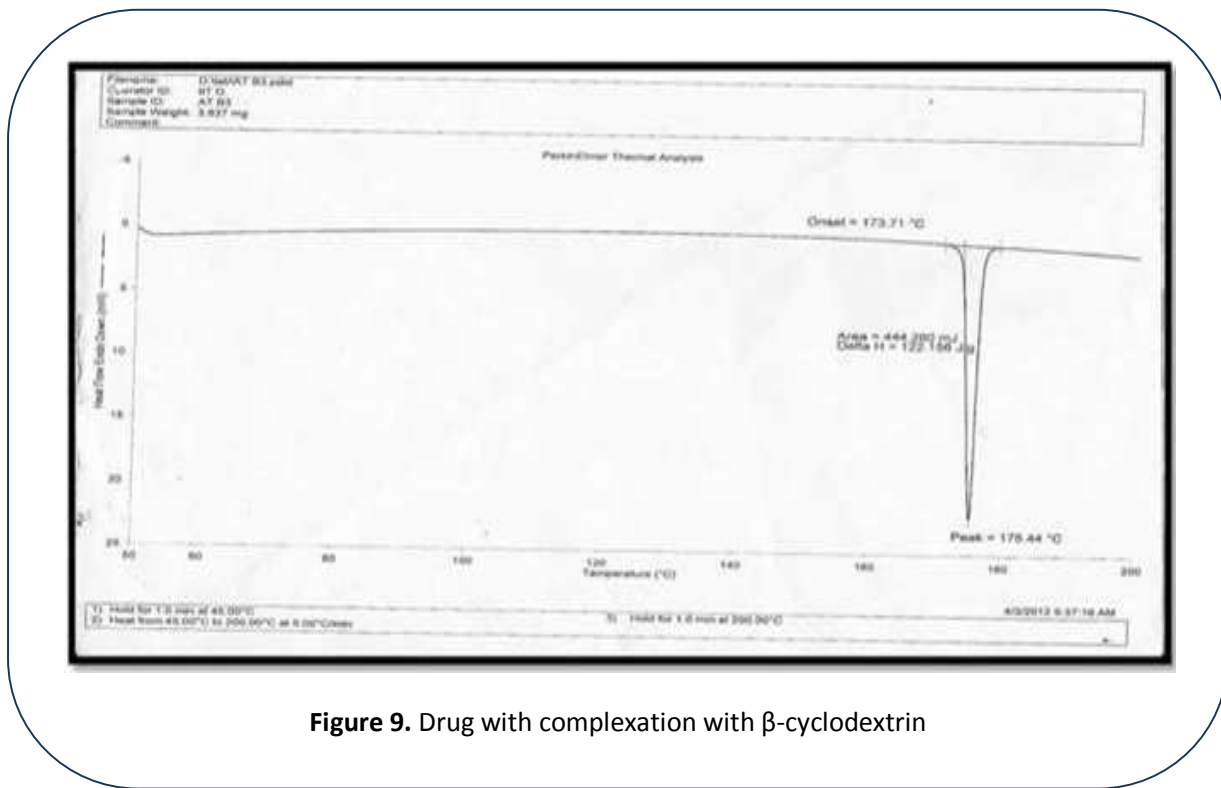


Figure 9. Drug with complexation with  $\beta$ -cyclodextrin

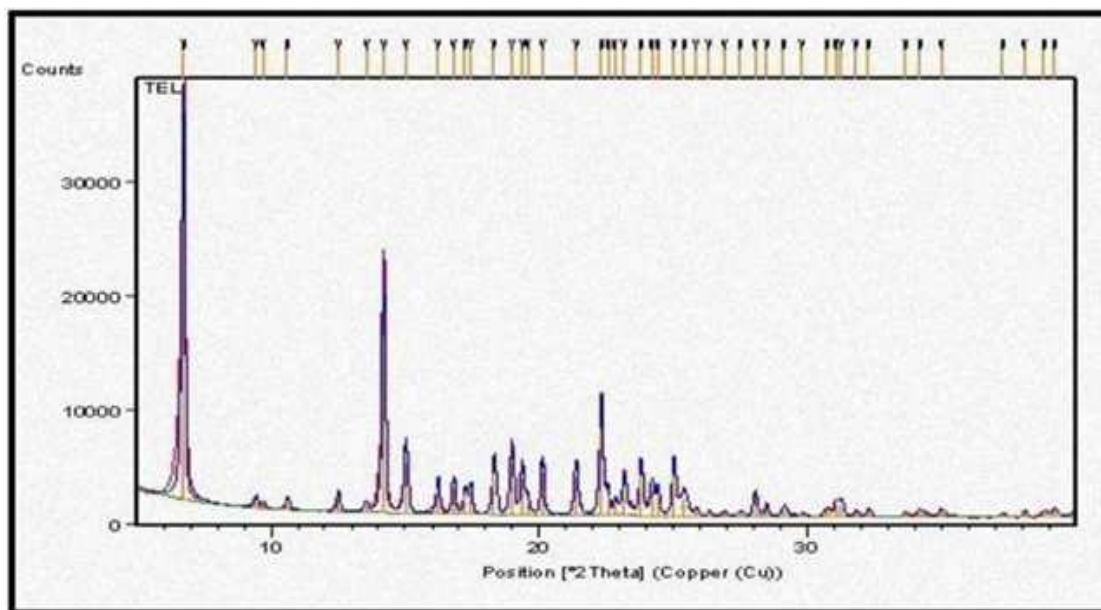


Figure 10. XRD of dicyclomine Hydrochloride

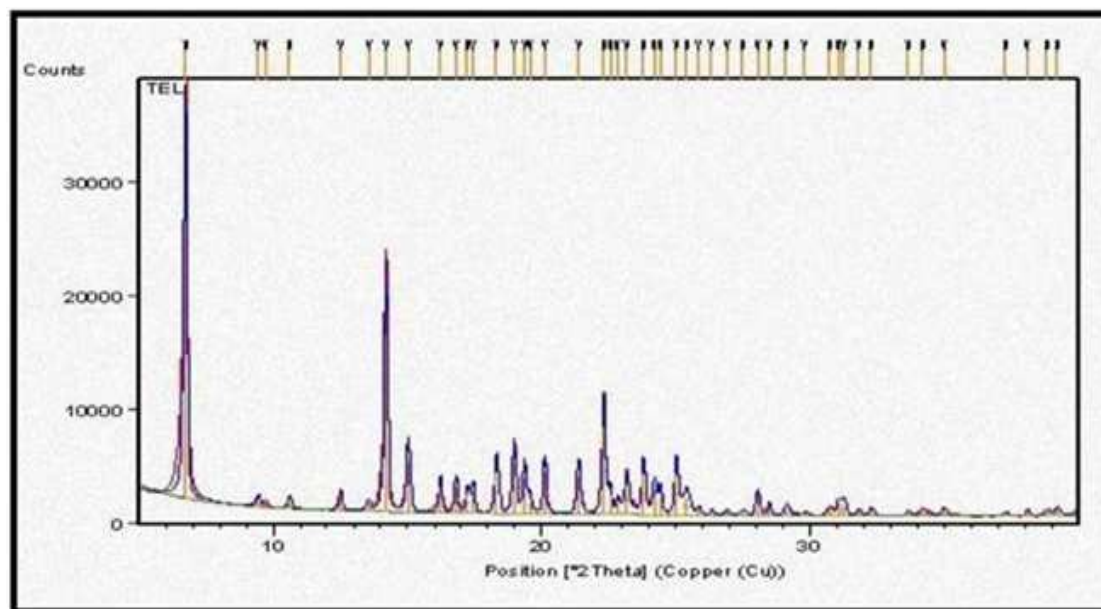


Figure 11. Comparative XRD of dicyclomine hydrochloride (Bottom), complex of pure drug and  $\beta$ -CD (Top)