Chapter II

Background

1. Pharmacology

Dicyclomine hydrochloride was synthesized by Tilford and his co-worker in 1947[10] and introduced in the market in 1950[11]. Dicyclomine hydrochloride is an anticholinergic agent with peripheral effects similar to but much weaker than those of atropine; it also has a direct antispasmodic action and a locol anesthetic action[12,13]. It is used in biliary, gastro - intestinal, or urinary - tract spasm, and is given with antacids in the treatment of gastric and duodenal ulcar. It has been given by mouth to diminish gastric secretion and to reduce gastric and intestinal motility in the treatment of peptic ulceration and pylorospasm[14].

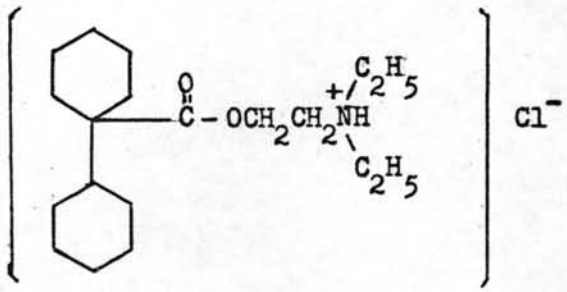
Side effects of dicyclomine[15] include dizziness, feeling of abdominal fullness, and dry mouth. Constipation, blurred vision, fatique, sedation, nausea, vomiting, headache, impotence, urinary retention, and rash occur rarely. Dicyclomine should be used cautiously in patients with prostatic hypertrophy, bladder neck obstruction, pyloric obstruction, and cardiospasm. Even though it does not appear to raise intraocular pressure in narrow - angle glaucoma, it is advisable to monitor the pressure of such patients.

The usual dosage of dicyclomine[14] is 30 to 60 milligrams daily in divided doses. Children up to 1 year may be given 5 milligrams before

feed and children aged 1 to 5 years 5 to 10 milligrams 3 times daily. It has also been given intramuscularly in a dose of 20 mg. It was given in the form of tablet, capsule, syrup and injection.

2. Chemistry

2.1. Chemical Name : The chemical name of dicyclomine hydrochloride is (bicyclohexyl) - 1 - carboxylic acid, 2 - (diethylamino) ethyl ester, hydrochloride.



2.2. Preparation

2.2.1. Dicyclomine hydrochloride was rapidly obtained in 83.3 % yield by treating ethylphenylacetate with 1,5 - dibromopentane in dimethylformamide - benzene mixed with sodium hydride then treating the extracted product with 2 - diethylaminoethanol and sodium in xylene and hydrogenating the product[16].

2.2.2. Cyclohexanol was reacted with hydrogen chloride to form cyclohexyl chloride which was then grignardized with ethyl formate to yield dicyclohexyl carbinol (α - cyclohexylcyclohexanemethanol). Oxidation of the carbinol with sodium dichromate yielded the corresponding ketone which was then chlorinated with sulfuryl chloride to give 1 - chlorocyclohexyl cyclohexyl ketone. Reaction of the ketone with sodium derivative of 2 - (diethylamino)-ethanol furnished an intermediate which rearranged to

dicyclomine (base). The purified base was dissolved in an appropriate solvent and treated with hydrogen chloride to form the hydrochloride[15].

2.3. Description[15] Dicyclomine hydrochloride occurs as a fine, white, crystalline powder that is practically odorless and has a very bitter taste; stable in air and to moderate heat; melts between 169 and 174°C. When it is dried at 105° C for 4 hours, it loses not more than 1.0 % of its wight.

2.4. Solubility[15] Dicyclomine hydrochloride 1 gm dissolve in 13 ml of water, 5 ml of alcohol, 2.5 ml of chloroform, and 770 ml of ether; it is insoluble in an alkaline aqueous medium.

2.5. Method of Analysis

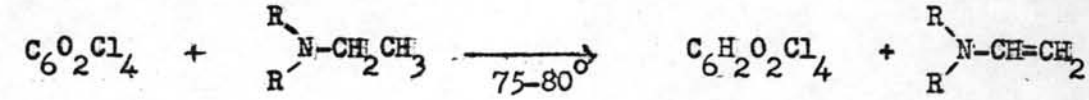
2.5.1. Titration

The titrimetric procedure in the official method[1 - 4] for determination of content uniformity of dicyclomine hydrochloride in pharmaceutical preparations used methyl yellow as an indicator in a two phase system of chloroform and dilute sulfuric acid containing the sample. The solution was then shaked until a bright yellow color was produced in the chloroform layer. Whereas dicyclomine was partitioned into the organic phase, the titrant, 0.004 M sodium lauryl sulfate, was added until the first permanent orange - pink color was produced in the chloroform layer at the end point. The reaction involved in this method[17,18] was based on the assumption that tertiary amines reacted with alkyl sulfate such as sodium lauryl sulfate to form stable water - soluble addition compound. When the equivalent point was passed, the

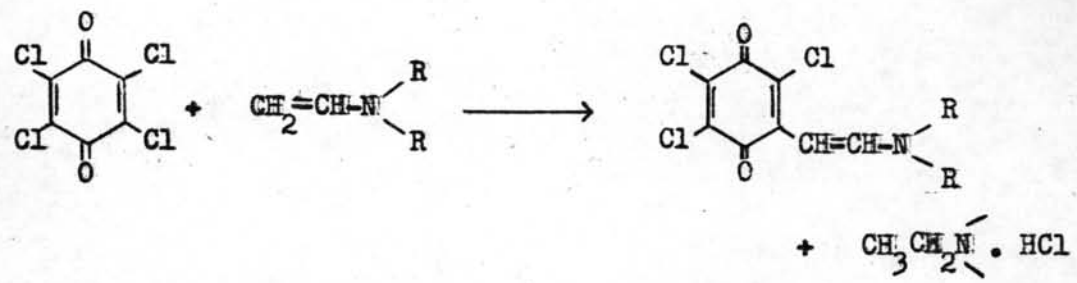
excess titrant partitioned into the chloroform layer to react with methyl yellow which produced the color characteristic of the end point. Some pharmaceutical preparations contained colors which making the observation of the end point difficulty. The titrant, sodium lauryl sulfate, precipitated upon standing, therefore, restandardization before use was necessary. Moreover, methyl yellow has been reported of having carcinogenic effect[5]. These were the disadvantages of using official titrimetric methods.

2.5.2. Spectrophotometry

Abdelkader and Taha[6] described the spectrophotometric procedure for the analysis of dicyclomine hydrochloride via reaction with chloranil in benzene. The amine salt solution in distilled water was treated with phosphate buffer pH 9.5 and the free base was extracted with benzene. A mixture of a solution of the amine free base with chloranil in benzene was heated on a water bath at 75 - 80° C for one hour. A blue-colored product with a maximum absorption wavelength at 680 nm was produced.



chloranil



Under the described assay condition, N - methyl as well as quaternized

N - ethyl compounds did not interfere. This method was specific for N - ethyl drugs, however, the method lacked of sensitivity to micro - amounts and was relative time consuming; and the prepared chloranil reagent was not stable.

2.5.3. Chromatography

Fricke[8] developed the standardized and automated procedure for dicyclomine analysis, using solvent extraction and gas - liquid chromatography. The liquid phased used in this study was Dexsil 300, a polycarboranesiloxane, as it was the most thermally stable liquid phase available. A mixture of water and methanol (1 : 1) was used to extract the dicyclomine from the sample and injected the extract into gas chromatograph.

Meffin et al.[19] described a satisfied method to determine plasma concentration of dicyclomine following its administration at normal therapeutic dose levels in human subject to carry out bioavaibility studies on different dose forms of dicyclomine. A gas chromatographic procedure was described which used a nitrogen sensitive flame detector and a novel method of concentrating the extracted sample of dicyclomine prior to injecting into gas chromatograph. Concentration of 1-2 x 10^{-9} g /ml of plasma could be determined by this method.

Kaplan and Spark[20] determined the dicyclomine hydrochloride in mixed pharmaceutical formulations by using gas - liquid chromatography. A compound tablet containing dicyclomine hydrochloride and trifluoperazine was each separated and analyzed by gas - liquid chromatography on

a 3.5 % OV-17 silanized glass column on 100-20 mesh gas chrom Q using internal standard. The method afforded satisfactory sensitive and reproducibility and allowed direct simultaneous determination of several constituents in a multicomponent system.

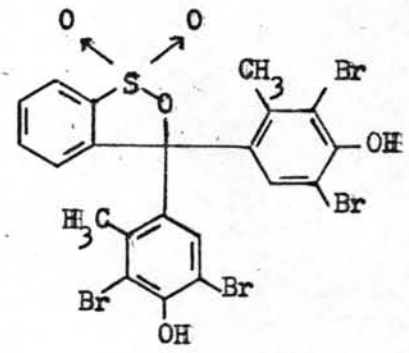
Brownell and Alber[9] described an automated, computerized method to determine the content uniformity of dicyclomine hydrochloride in capsules and tablets, using up to 4 automatic sampler - equipped gas chromatographs interfaced with a minicomputer. A 3 % OV-17 column was used with anthracene as an internal standard.

These chromatographic methods provided an accurate and good results for determination of dicyclomine in formulations, however, the methods were time consuming, required a special technique and availability of certain equipments.

2.5.4. The Proposed Method

From the structural viewpoint, dicyclomine is a tertiary amine so it can be applied the acid dye technique for quantitative determination. Bromcresol green has been reported as a reagent used for the determination of small amounts of tertiary amines, long - chain tertiary alkylamines and quaternary ammonium salts[21 - 23]. Moreover, bromcresol green was used as a spraying agent for identification of dicyclomine[24]. In this study bromcresol green was therefore chosen as an acid dye to form complex with dicyclomine. Bromcresol green was a sulfonphthalein dye which has been widely used in quantitative analysis of a variety of pharmaceutical amines[21-23, 25-27]. Its chemical structure was

shown below.



The determination of amines involved the formation of colored complex with an acid dye could be carried out in two ways.

1. The amine free base was extracted from the aqueous alkali solution of its salt with chloroform. The free base was then reacted with acid dye to form a colored complex which was determined spectrophotometrically.

2. The amine salt was reacted with an acid dye in aqueous buffered at optimum pH and the resulted ion - pair was then extracted with chloroform and determined spectrophotometrically. This ion - pair extraction was based on the requirement[17,28] :-

a) a stoichiometric ion - pair was formed from the positively charged nitrogen compound and the negatively charged dye molecule.

b) this ion - pair was quantitatively extracted into the organic phase.

c) the uncombined dye molecule (which was added in excess) was not extracted into the organic phase.

These two methods were based on the selective complex formation of amine and an acid dye, and the reaction was an acid - base reaction. Most amines exhibited a high sensitivity while acid, neutral, and weakly basic compound as well as the commonly used excipient did not interfere[25]. In this study dicyclomine was determined by two methods as previously mentioned above. These two methods were compared by studying the effect of various factors such as stability of the complex, concentration of dye used, mole ratio of complex formed and linear absorbance - concentration relationship. The suitable one was then selected and used to determine dicyclomine hydrochloride in formulations. The results obtained by the proposed method were compared with official USP method[1]. Since the titrimetric procedure in the USP method was the same as in other official methods such as NF[2], BP[3] and BPC[4], therefore the USP method was selected as a comparative method.

The outline of this thesis was based on the following statements:-

1. Dicyclomine hydrochloride was determined by two methods. Method 1, dicyclomine free base was extracted from aqueous alkaline solution of dicyclomine hydrochloride with chloroform and then reacted with bromcresol green in chloroform. A yellow-colored complex was formed and determined spectrophotometrically. Method 2, dicyclomine hydrochloride was reacted with bromcresol green in aqueous buffered at optimum pH. The yellow-colored complex formed was extracted with chloroform and determined spectrophotometrically. The optimum

conditions for both methods were studied such as stability of complex formed on time and temperature, sensitivity and precision of the reaction and also the optimum dye concentration used. All factors in both methods were then compared, and the suitable method was selected and used to determine dicyclomine hydrochloride in formulations.

2. The accuracy and precision of the proposed method were measured by determining the percent recoveries compared to those obtained by the USP method.

3. The proposed method was applied to determine the content uniformity of dicyclomine hydrochloride in commercial pharmaceutical preparations. The results obtained were compared to those obtained by the USP method.