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Research Article

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Optimization of Synthesis Method and Quality Control of an Active Pharmaceutical Ingredient Denominate Chlorobutanol

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Abstract Chlorobutanol is an active pharmaceutical ingredient used in therapeutic for many years as an antiseptic, analgesic and local anesthetic. It has other properties: hypnotic, anti-inflammatory and anti-emetic. It's used as conservative in some pharmaceutical preparations because it has antibacterial and antifungal properties. We synthesized this active pharmaceutical ingredient in Therapeutic laboratory of pharmacy department of Sidi Bel-Abbes by Referenced method based on the addition of chloroform with acetone under the influence of chemical catalyst (potassium hydroxide) using the distillation assembly. The second synthesis using the optimized method improves the yield of 20 %. The synthesized product was controlled according to the requirements of the European Pharmacopoeia 8th edition: the organoleptic characteristics, solubility, colorimetric reactions and the degree of coloring were positive; its melting point is 78 °C; its water content is estimated to 4.66% and its purity is equal to 98.27%.

Keywords optimization, synthesis, Chlorobutanol, yield, control

1. Introduction

Chlorobutanol is used in pharmaceutical compositions at variable concentrations; it may be combined with other antiseptics such as Chlorhexidine to enhance its antiseptic action which allows a potentiation of the antimicrobial activity of these two active ingredients. This potentiation is exercised on gram-negative bacteria as well as gram-positive bacteria. Due to its bacteriostatic properties, Chlorobutanol is also used as a preservative for pharmaceutical preparations [1]. Chemically, Chlorobutanol is a chlorinated antiseptic that belongs to the alcohol family. At the laboratory scale, it's prepared by a simple nucleophilic addition of chloroform to acetone in the presence of potassium hydroxide; it's more specifically the nucleophilic addition of the trichloromethyl anion to the carbonyl bond of acetone using the distillation assembly [1,2].

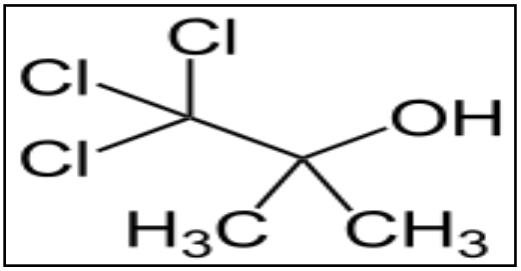

Figure 1: Chemical structure of Chlorobutanol [7]

According to the bibliographic references consulted, the different techniques mentioned for the chemical synthesis of Chlorobutanol give a very low yield varies between 14% and 40% [3]. In this study, we optimize the Synthesis method of Chlorobutanol for provides a better yield and we control its physicochemical quality.

2. Materials and Methods

2.1. Synthesis of Chlorobutanol by referenced method

45 ml of acetone, 5 ml of chloroform and 1 g of potassium hydroxide were mixed in a 250 ml Erlenmeyer flask. The reaction mixture was stirred at -5 °C for two hours, the resulting slurry was filtered and the filtrate was freed of excess acetone by distillation. The yellowish oily residue was mixed with 50 ml of ice water, resulting in a precipitate in the form of white crystals (Chlorobutanol Hemihydrate) which were filtered and dried. Recrystallization was carried out in a small volume of ethanol. Finally, the amount of Chlobutanol obtained was weighed to calculate the synthesis yield [3].

2.2. Chlorobutanol Synthesis by optimized method

We optimized the synthesis conditions with using of reflux heating and we left the container open for spontaneous evaporation of the unreacted acetone.

2.3. Control Quality of the synthesized Chlorobutanol

2.3.1. Organoleptic propreties, solubility and Melting point measurement

We checked the aspect, color and tested the solubility of synthesized Chlorobutanol by the optimized method in water and glycerol 85%. The melting point was measured using BÜCHI Melting Point B-545 [4].

2.3.2. Chemical characterization processes

Reaction A: in a 100 ml beaker, 1 ml of pyridine, 2 ml of concentrated sodium hydroxide solution and 20 mg of synthesized Chlorobutanol were mixed, heated in a water bath and finally let stand [5].

Reaction B: in a 100 ml beaker, 5 ml of ammoniacal solution of silver nitrate and 20 mg of synthesized Chlorobutanol were mixed and heated slightly [5].

Acidity test: in a 100 ml beaker, 20 mg of synthesized Chlorobutanol, 15 ml of ethanol and 0.1 ml of bromothymol blue and 1 ml d'hydroxyde de sodium 0.01M were mixed [5].

2.3.3. Dosage test

In a 200 ml beaker, 0.1 g of synthesized Chlorobutanol was dissolved in 20 ml of ethanol 96%, 10 ml of dilute sodium hydroxide solution was added. The mixture was heated in a water bath for 5 minutes and then cooled. Add 20 ml of diluted nitric acid, 25 ml of 0,1M silver nitrate and 2 ml of dibutyl phthalate. After stirring, 2 ml of ferric sulfate and ammonium solution was added. Finally, a titration with ammonium thiocyanate [6].

2.3.4. Loss on drying: 0.3 g of synthesized Chlorobutanol was dried in the oven at 105 °C for 1 hour. A second weighing was performed after desiccation **[7]**.

3. Results and Discussion

3.1. Synthesis of Chlorobutanol by referenced method

Figure 2: Hydrated Chlorobutanol

Figure 3: Dried Chlorobutanol

The synthesis yield of the referenced method is Y: 40.91%.

3.2. Chlorobutanol Synthesis by optimized method

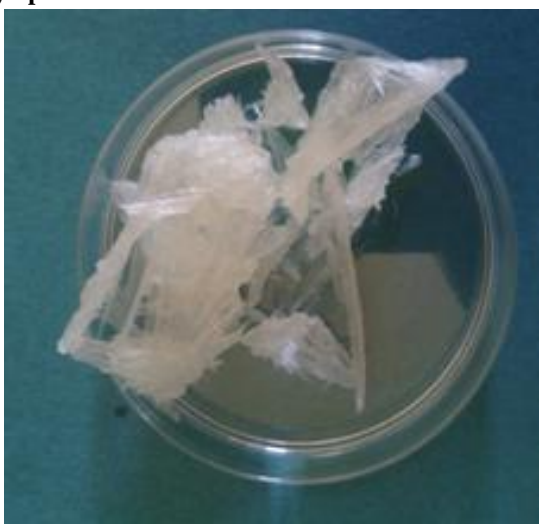

Figure 4: Crystallized Chlorobutanol

The synthesis yield of optimized method is Y: 59.41%.

Figure 5: Synthesis Repeatability (n: 10)

The yield of the optimized method increased by 20% compared to the referenced method. So, the optimized method allowed to improve the yield by 20%.

3.3. Control Quality of the synthesized Chlorobutanol

3.3.1. Organoleptic properties, solubility and melting point

Chlorobutanol synthesized as colorless crystals, its melting point is 78°C, it's soluble in water and glycerol 85%. The Organoleptic characteristics, solubility and melting point meet to the requirements of the European Pharmacopeia 8th edition.

3.3.2. Chemical characterization processes

Figure 6: Pink solution

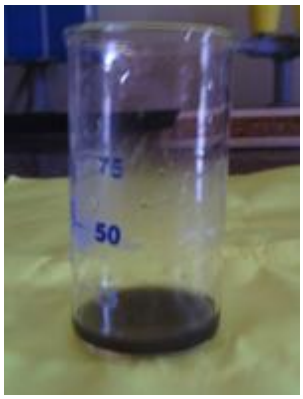

Figure 7: Black precipitate

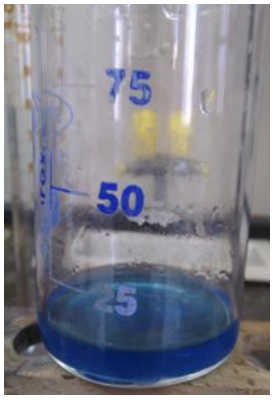

Figure 8: Blue Coloration

The colorimetric reactions A and B were positive according to the standards and the Acidity test answers positive, the solution color changed to blue, after addition of 1ml NaOH.

3.3.3. Dosage test and Loss on drying

Titer determination of Chlorobutanol by titration gave a value of 98.27%, it conform to the standards of the European Pharmacopeia 8th edition [98.0 -101] % and the estimated water content was 4.66%, it conform to the standards required [4.5–5.5] %.

4. Conclusion

Chlorobutanol synthesis using the optimized method in Therapeutic Chemistry Laboratory of Pharmacy Department of Sidi Bel-Abbes gave a best yield of 60%, whereas the referenced method gave an estimated yield of 40%. The synthesized active pharmaceutical ingredient meets to the standards of the European Pharmacopoeia 8th edition.

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