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## Synthesis and Quality Control of Benzyl Alcohol Used in Pharmacy as Solvent for Injectable Preparations

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**Abstract** Benzyl alcohol is an aromatic alcohol, it's used as a solvent for injectable preparations and classified as notorious effect excipient. It is contraindicated in infants and children less than three years of age because it causes a fatal toxic reaction. We synthesized this solvent in Therapeutic Chemistry laboratory of pharmacy department of Sidi Bel-Abbes according the protocol using the Cannizzaro reaction and the yield obtained is 29.29%. The quality control of the synthesized benzyl alcohol is carried out according to the requirements of the European Pharmacopoeia 8<sup>th</sup> edition. It would be very interesting to introduce this work as a practical work of Therapeutic Chemistry module for the third-year pharmacy students and residents of Therapeutic Chemistry in post-graduate.

**Keywords** Benzyl alcohol, Solvent, Cannizzaro reaction, notorious effect excipient

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### 1. Introduction

Benzyl alcohol is an aromatic alcohol that consists of benzene bearing a single hydroxymethyl substituent. It has a role as a solvent, a metabolite, an antioxidant and a fragrance [1]. In pharmacy, it's used as a solvent for injectable preparations and conservative, it's classified as notorious effect excipient whose declaration is mandatory in the leaflets and on the packaging of medicines [2, 3]. It is contraindicated in infants and children less than three years of age because it causes a fatal toxic reaction [1, 4].

Benzyl alcohol is active against Gram positive bacteria and has some weak activity against gram negative bacteria, yeasts and molds. Benzyl alcohol also has some mild local anesthetic and anti-spasmodic properties [5]. Common side effects of Benzyl Alcohol include irritations of the skin, scalp, and eyes, and numbness at the site of application. As with all medications, it is important to use benzyl alcohol, as labeled to maximize benefits and minimize risks [6].

In this article, we synthesize the benzyl alcohol as pharmaceutical raw material and we control its physicochemical quality.

### 2. Materials and Methods

#### 2.1. Synthesis of Benzyl Alcohol by Cannizzaro reaction



A three-necked 500 ml was equipped with a separating bulb and a condenser, 35 g of potassium hydroxide was dissolved in 50 ml of water and we proceeded to heating. 40 ml of benzaldehyde was cast rapidly and reflux heating was carried for one hour. Cooling at room temperature was performed. A volume of water necessary for the complete dissolution of the solid phase was added then the solution was transferred to a separating bulb and rinsed with a little water and then with 25 ml of toluene. We decanted and then carried out two extractions on the aqueous phase with 25 ml of toluene and the three organic phases were united [7].

We washed the organic solution with water up to pH=7. The remaining benzaldehyde was removed by bisulfite combination: washing of the organic phase with a solution of sodium sulfite in methanol until no more precipitate was formed. A third wash of the organic phase with 10% sodium carbonate solution to pH = 7. We removed toluene and traces of water by fractional distillation at atmospheric pressure. We finished with a rectification under reduced pressure to recover the benzyl alcohol at  $T=205^{\circ}\text{C}$  [7].

## 2.2. Quality Control of Synthesized Benzyl Alcohol

The control of the synthesized benzyl alcohol is carried out according to the requirements of the European Pharmacopoeia 8<sup>th</sup> edition [8].

### 2.2.1. Organoleptic characteristics and solubility

We checked the appearance and odor of the synthesized benzyl alcohol, as well as its solubility in water and in ethanol 96% according to the requirements of the European Pharmacopoeia [8].

### 2.2.2. Measure of boiling point

We took a small volume of benzyl alcohol in a beaker and heated it on the hot plate by placing a thermometer inside. When the first bubble appears, we have noted the boiling point [8].

### 2.2.3. Characterization by chemical processes

To 1 ml of benzyl alcohol, we added 1 ml of ethanol, the solution obtained was titrated with 0.1 M sodium hydroxide solution in the presence of 0.1 ml of phenolphthalein. If the turn of the indicator to pink does not require more than 1 ml of sodium hydroxide, it is benzyl alcohol [8].

## 3. Results and discussion

### 3.1. Synthesis of Benzyl Alcohol by Cannizzaro reaction

The different steps of benzyl alcohol synthesis (Settling, extraction, washing, distillation and recovery of benzyl alcohol at  $T = 205^{\circ}\text{C}$ ) are illustrate in Figure 1 and 2.



Figure 1: Cooling, settling and extraction



Figure 2: Washing, distillation and recovery of benzyl alcohol at  $T = 205\text{ }^{\circ}\text{C}$ .

The calculated synthesis yield of benzyl alcohol by Cannizzaro reaction is  $Y: 29.29\%$ .

### 3.2. Quality Control of Synthesized Benzyl Alcohol

#### 3.2.1. Organoleptic characteristics and solubility

Appearance: the synthesized benzyl alcohol is an oily liquid, clear, and colorless, of sweet and aromatic odor (figure 3).

Solubility: the solubility test showed that the synthesized benzyl alcohol is insoluble in water and soluble in ethanol at 96% (figure 3).

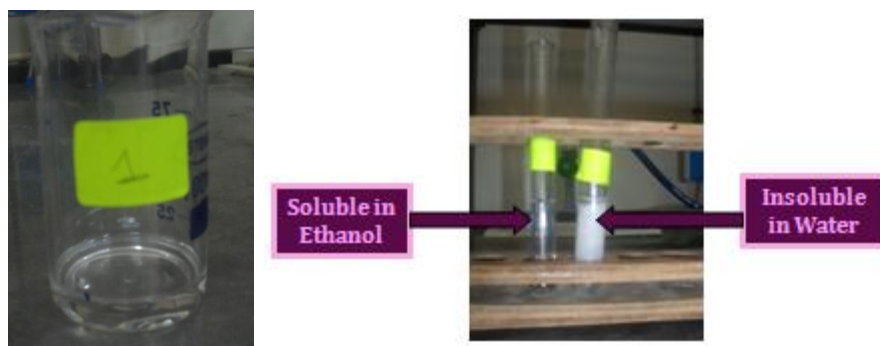


Figure 3: Organoleptic characteristics and solubility test

#### 3.2.2. Measure of boiling point

Measurement of the boiling point of benzyl alcohol revealed a value of  $200\text{ }^{\circ}\text{C}$ , a value close to the required value of  $205.3\text{ }^{\circ}\text{C}$  (figure 4).

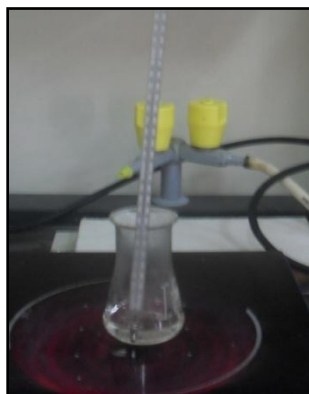


Figure 4: Measure of boiling point



### 3.2.3. Characterization by chemical processes

The addition of one NaOH drop in presence of phenolphthalein to a solution of 1 ml benzyl alcohol and 1 ml ethanol resulted in a turn from the colorless solution to purplish pink according to the requirements of the European Pharmacopoeia 8<sup>th</sup> edition (figure 5).



Figure 5: Turn colorless solution to purplish pink.

### 4. Conclusion

The benzyl alcohol was synthesized according the protocol using the Cannizzaro reaction from two molecules of benzaldehyde, one of which is reduced to benzyl alcohol. The calculated synthesis yield of benzyl alcohol by Cannizzaro reaction is 29.29 %. The quality control of the synthesized benzyl alcohol is carried out according to the requirements of the European Pharmacopoeia 8<sup>th</sup> edition, but by lack of means, the gas chromatographic assay couldn't be used. As prospects, it would be very interesting to introduce this work as a practical work of Therapeutic Chemistry module for the third-year pharmacy students and residents of therapeutic chemistry in post-graduate.

### References

- [1]. National Toxicology Program. Technical Report Series No. 343. Toxicology and Carcinogenesis Studies of Benzyl Alcohol. (CAS No. 100-51-6). Available from, as of Sept 25, 2014: <http://ntp.niehs.nih.gov>
- [2]. National Agency for the Safety of Medicines and Health Products. List of Excipients with Notorious Effect. Update of the list and the wordings according to the European Guideline 2003. Second revision of March 3, 2009; 1-84.
- [3]. Excipients and information for notice. Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. 2017; 1-22.
- [4]. US EPA. Health and Environmental Effects Document for Benzyl Alcohol. EPA/600/8-90-033 (NTISPN91213694). Available from, as of Sept 25, 2014. <http://cfpub.epa.gov/ncea/cfm/recorddisplay.cfm?deid=38729>
- [5]. European Medicines Agency (EMA), The European Agency for the Evaluation of Medicinal Products, Veterinary Medicines Evaluation Unit, Committee for Veterinary Medicinal Products; Benzyl Alcohol, Summary Report (1997). Available from, as of July 8, 2008: <http://www.emea.europa.eu/pdfs/vet/mrls/Benzylalcohol.pdf>
- [6]. FDA; FDA Approves Benzyl Alcohol Lotion for the Treatment of Head Lice, FDA News (April 9, 2009) Available from, as of April 20, 2009: <http://www.fda.gov/bbs/topics/NEWS/2009/NEW01993.html>
- [7]. Jullien A, Beaudoin G J, Flamand E. Experimental organic chemistry. 2<sup>nd</sup> edition, Berlin. 1997; 691-3.
- [8]. European Pharmacopoeia 8<sup>th</sup> edition. Benzyl Alcohol monograph. 2017; 1393-94.

