CHAPTER I

INTRODUCTION

1.1 Research Background

In drug formulations, there are various drugs, including newly discovered drugs, with greater therapeutic efficiency but low solubility in water, causing incomplete absorption and low bioavailability (Nasikkar & Khutle, 2020). Ku & Dulin (2012) stated that about 70% of new drug candidates exhibit low water solubility. Water solubility and dissolution rate of drugs are two critical factors that influence drug formulation and development and may limit their therapeutic application (Amidon et al., 1995). These poorly soluble drugs are classified in class II and IV of the biopharmaceutical classification system and be a challenge in drug formulation and administration (Yasir et al., 2010). Various methods have been carried out to overcome this problem, such as cosolvent and solid dispersion that increase drug solubility, bioavailability, and dissolution properties. However, these methods have several disadvantages, such as low drug loading and large doses (Gidwani & Vyas, 2015). As an alternative to this problem, cyclodextrin is used as a drug carrier.

Cyclodextrins are cyclic oligosaccharides obtained by enzymatic degradation of starch. There are three types of natural cyclodextrins divided by the number of glucose units, namely α-, β-, and γ-cyclodextrins composed of six, seven, and eight glucose units, respectively. The structure of cyclodextrin in the toroid causes a cavity on the inside of the structure. On the outside of the cyclodextrin, free hydroxyl groups give hydrophilic properties. At the same time, the presence of oxygen atoms in glycosidic bonds and C-H bonds causes hydrophobic properties on the inside. These unique properties can form an inclusion complex of guest molecules into the cavity of cyclodextrin (host) (Crini, 2014).

The ability of cyclodextrins to form an inclusion complex with other molecules, one of which is drug molecules, shows the potential application as drug carriers. The application of cyclodextrins in drug formulation, especially in class 2 (with low solubility and high permeability) or class 4 (with low solubility and low permeability) based on the Biopharmaceutics Classification System (BCS), will

increase their solubility and permeability (Loftsson, 2002). One type of cyclodextrin, β-cyclodextrin, is ideal for complexation because of its perfect cavity size, efficient complexation and drug loading, and relatively low cost (Karande & Mitragotri, 2009). However, this type of cyclodextrin has low solubility in water, about 18.5 mg/mL, due to forming of a complete ring of intramolecular hydrogen bonds in β-cyclodextrin. Therefore, it is necessary to modify the cyclodextrin to improve the physicochemical and biopharmaceutical properties of the drug and the inclusion capacity of natural cyclodextrins (Gidwani & Vyas, 2015).

The cyclodextrin can be modified by substituting the hydroxyl group on the cyclodextrin molecule. The derivative cyclodextrin can be classified into uncharged (neutral), positively or negatively charged, amphoteric, and polymerized derivatives (Tsioupi et al., 2013). In addition, the positively charged cyclodextrin modification was still slightly synthesized compared to others (Havlikova et al., 2016). Recently, only a few cyclodextrin derivatives have been marketed as drug carriers, such as 2-hydroxypropyl-β-cyclodextrin, methylated β-cyclodextrin, and sulfobutylether-β-cyclodextrin (Loftsson & Duchene, 2007). These derivates are commercially available as randomly substituted derivates as mixture of isomers (mono-, di-, and more substituted derivatives). These products are characterized by the degree of substitution (DS) which refers to the number of substituents on cyclodextrin. Therefore, the products could not be accurately defined, so the drug formulations using these derivatives are difficult to determine the exact drug formulation because these derivatives have many isomers (Havlikova et al., 2016). Based on that, this study aims to modify cyclodextrin as single cationic cyclodextrin salts using ammonium as a substituent.

Ammonium is one of many substituents that can modify cyclodextrin as positively charged. Ammonium as a substituent contributes to the enhancement of inclusion complex formation by the electrostatic interaction of this positively charged cyclodextrin derivative, which can improve the formation of inclusion complex of guest-host molecules (Béjaoui et al., 2017). In addition, it is also helpful as a chiral selector in the chiral separation of derivated amino acids, neutral analytes, and anionic pharmaceutics (Muderawan et al., 2005a; Tang & Ng, 2008b). These derivatives can also penetrate through biological barriers and be incorporated

into biological membranes so that they have a possibility for pharmacological studies as drug carriers and gene delivery (Bienvenu et al., 2012; Cryan et al., 2004; Shipilov et al., 2017). Therefore, modified cyclodextrin as monosubstituted positively charged increases the solubility of native β-CD in water and has many advantages, such as improving chiral selectivity toward guest molecules usually found in pharmaceutical molecules and enhancing the interaction in biologic membranes. Accordingly, these derivatives have a prospect in drug formulations because the resulting product only has one isomer, thus giving a better understanding of drug formulations. Drug formulations with monosubstituted cyclodextrin are expected to produce appropriate drug formulations in the presence of only one derivative isomer and understand the drug's properties and effects better. Some studies had synthesized single cationic charged CD derivatives but still used non-user-friendly solvents, for example research by Tang & Ng (2008a) that using pyridine as a solvent which is a toxic solvent. Accordingly, the result of this research is supposed to increase the solubility of native β-CD through a more convenient as well as greener synthesis method.

1.2 Research Problems

Based on the background that has been described previously, the problem statements in this study are:

1. How are the method of synthesizing mono-6-deoxy-6-ammonium-β-cyclodextrin chloride salts?
2. How are the structural characteristics and physical-chemical properties of mono-6-deoxy-6-ammonium-β-cyclodextrin chloride salts?

1.3 Research Objectives

The objectives of this research are:

1. To determine the synthesis methods of mono-6-deoxy-6-ammonium-β-cyclodextrin chloride salts.
2. To determine the structural characteristics and physical-chemical properties of mono-6-deoxy-6-ammonium-β-cyclodextrin chloride salts.

1.4 Research Benefits

This research will contribute information to the development of science related to the synthesis method and characterization of cyclodextrin derivatives, especially mono-6-deoxy-6-ammonium-β-cyclodextrin chloride salts. In addition, this research is also expected to be used as a reference for further research on the synthesis, characterization, and application of mono-6-deoxy-6-ammonium-β-cyclodextrin chloride salts as a drug-carrier molecule.