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Continuous tank reactor synthesis of highly substituted sulphobutylether β-cyclodextrins

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ABSTRACT

Batch synthesis of sulphobutyl ether β-cyclodextrin (also known as SBE-β-CD or SBECD) is a process effectively divided into three main stages, i.e. initial reagent dissolution, a sulphoalkylation reaction and final reaction quenching. This reaction is followed by downstream processing and purification, and ultimate isolation of the solid SBECD material. However, a feature associated with using this synthetic method is that a high proportion of lower substituted SBECD is observed. There is therefore a need to provide an improved synthetic method for producing higher substituted cyclodextrins.

The authors here present a Continuous Tank Reactor (CTR) method for preparing sulphobutyl ether-cyclodextrins. The method comprises first contacting cyclodextrin with a base to form activated cyclodextrin. The method then involves separately contacting the activated cyclodextrin with an 1,4-butane sultone to form sulphoalkyl ether-cyclodextrin.

The activation reaction is carried out in batch synthesis mode and the sulphoalkylation reaction is carried out under continuous flow conditions resulting in a novel method for the synthesis of highly derivatised cyclodextrins.

The work is particularly concerned with producing controlled substitution in sulphobutyl ether β-cyclodextrins and novel compositions of highly substituted sulphoalkyl ether β-cyclodextrins are described.

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1. Introduction

Sulphobutyl ether β-cyclodextrin (SBECD) is one of a class of polyanionic, hydrophilic water soluble cyclodextrin derivatives. The parent β-cyclodextrin can form an inclusion complex with certain active pharmaceutical ingredients (API) with two benefits, the apparent aqueous solubility of the API increases and, if labile functional groups are included, chemical stability is improved. However, the parent β-cyclodextrin suffers from two problems, including lower aqueous solubility and nephrotoxicity when given via injection, e.g. the intravenous route. Derivatisation of β-cyclodextrin (and its variants α and γ-cyclodextrin) has been shown to be beneficial with respect to both of these two defects. The first derivatised cyclodextrin was the hydroxypropyl derivative, which was later followed by sulphobutyl ether (see Fig. 1). These two derivatised cyclodextrins are the most commercially significant.

SBECD is currently used as an effective pharmaceutical excipient, and has been given the registered trade name Captisol. To date, there are five US FDA-approved, Sulphobutyl ether β-cyclodextrin enabled drug products on the market: Nexterone (Baxter International); Geodon and Cerenia (Pfizer); Kyprolis (Onyx); Abilify (Bristol Myers Squibb).

Shah and Sklavounos (2000) has previously described a batch synthesis of SBECD, the process being effectively divided into three main stages, i.e. initial reagent dissolution, a sulphoalkylation reaction and final reaction quenching. The reaction is then followed by downstream processing and purification, and ultimate isolation of the solid SBECD material. However, a feature associated with using this synthetic method is that a high proportion of lower substituted SBECD is observed. Antle (2009) has also described a continuous manufacturing process. However, there are significant

Abbreviations: ADS, average degree of substitution; β-CD, β-cyclodextrin; BS, 1,4-butane sultone; CD, cyclodextrin; CD-Screen-DAP, HPLC stationary phase for analysis of cyclodextrin-derivatives; CTR, continuous tank reactor; ELSD, evaporative light scattering detection; HPLC, high performance liquid chromatography; IDS, individual degree of substitution; MPA, mobile phase A; MPB, mobile phase B; PTFE, polytetrafluoroethylene; SBE-β-CD, sulphobutyl ether β-cyclodextrin; SBECD, sulphobutyl ether β-cyclodextrin; USP35/NF30, United States Pharmacopeia 35 and National Formulary 30; US FDA, US Food and Drug Administration.

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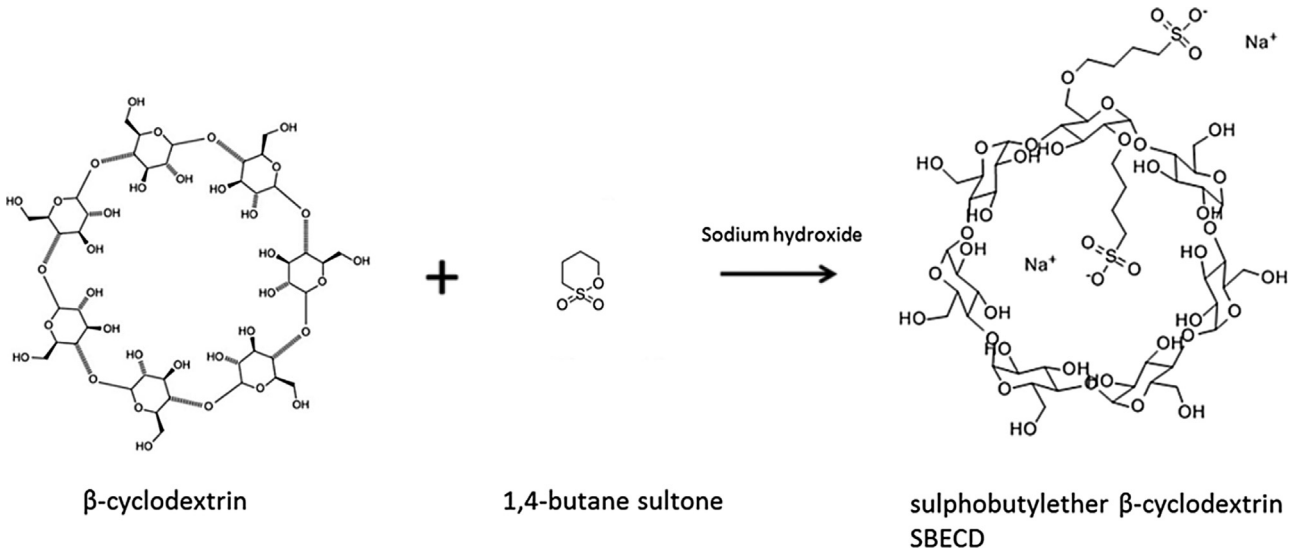

Fig. 1. A general scheme for the synthesis of SBECD from the reagents β-cyclodextrin (β-CD) and 1, 4-butane sultone (BS).

conceptual differences between our approach and that of Antle in that our approach requires lower temperatures and operates at ambient pressure, and also allows for controlled substitution in sulphobutyl ether β-cyclodextrins and the production of novel compositions of highly substituted sulphoalkyl ether β-cyclodextrins.

It has been reported that the method of preparation of a cyclodextrin derivative can have an impact upon the final structure (Tongiani et al., 2005). Previous studies have demonstrated that, of the three types of hydroxyl groups present in CDs, those at the six position (C6, primary hydroxyl) are the most nucleophilic, those at the two position (C2) are the most acidic, and those at the three position (C3) are the most inaccessible (Rong and D'Souza, 1990; Brewster et al., 1993). It has also been reported that at high alkali concentration the primary hydroxyls have higher reactivity than the secondary hydroxyls on C2 (Jindrich et al., 1995). Additionally, bulky substituents prefer to react with the primary hydroxyl on C6 (Jindrich et al., 1995).

2. Methods

2.1. The Continuous Tank Reactor (CTR) based manufacturing process

The continuous flow experiments consisted of two Masterflex pumps connected to a glass double 10 ml jacketed Continuous Tank Reactor (CTR). The two pumps were connected to the CTR holding chamber via a three-way connector and PTFE tubing. Non-return valves were fitted in line in the vicinity of the three-way connector to prevent the reagent stream reverse flow as a result of the differential flow pressure in either of the feed lines. The PTFE

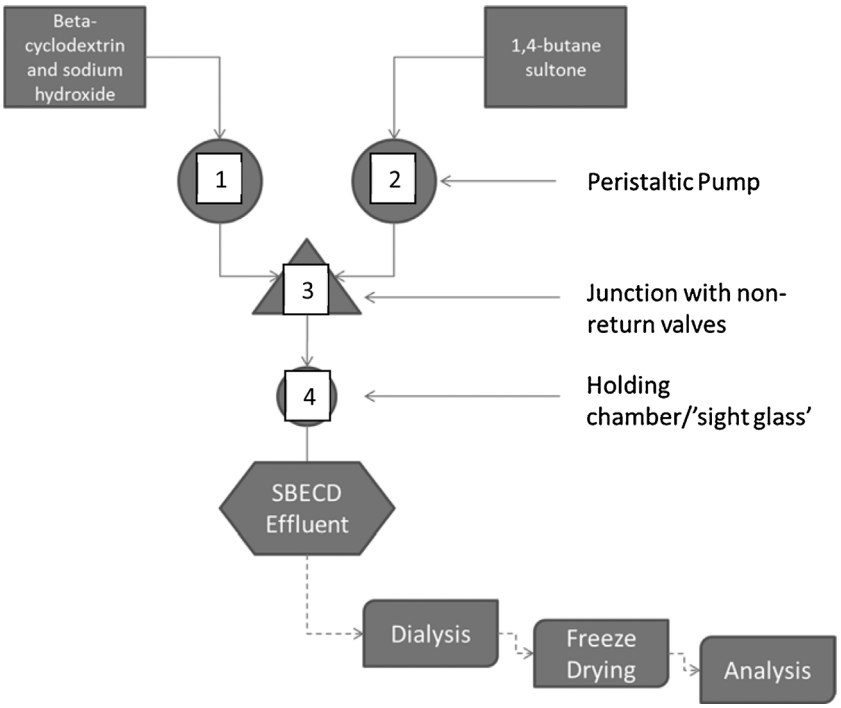

Fig. 2. Continuous Tank Reactor synthesis (CTR) method for producing SBECD.

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