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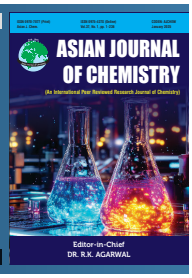

Synthesis and Structural Characterization of Hydroxy Butyl-β-cyclodextrin

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Hydroxy butyl-β-cyclodextrin was successfully synthesized in 1.5% NaOH solution to possess the highest yield of 75.350 ± 0.030% and degree of substitution of 5.230 ± 0.012 prior to structurally characterized. The study employed infrared radiation for main functional groups, ^{1}H, ^{13}C, distortionless enhancement by polarization transfer, correlation spectroscopy, heteronuclear single quantum coherence, heteronuclear multiple bond correlation nuclear magnetic resonance spectra in deuterium oxide solution and mass spectroscopy data to confirm the required structure of the hydroxy butyl-β-cyclodextrin derivatives with varying degrees of substitution.

Keywords: Hydroxy butyl-β-cyclodextrin, Characterization, Substitution, Synthesis.

INTRODUCTION

The pharmaceutical industry faces a significant hurdle in the development of new drugs due to the frequent occurrence of poor aqueous solubility. This solubility limitation results in a substantial number of drug candidates failing to progress to clinical development due to the sub-optimal pharmacokinetic properties [1]. Within the cyclodextrin family, β-cyclodextrin (β-CD) has been extensively studied for complexation to enhance drug solubility [2]. β-CD is a cyclic oligosaccharide consisting of seven glucose molecules connected through α-(1,4) glycosidic linkages (Fig. 1), which is enzymatically produced from carbohydrates by cyclodextrin-glucanotransferase, an enzyme derived from *Bacillus macerans* [3]. Structurally, β-CD shares numerous physico-chemical and biological properties with linear dextrin. However, the low solubility and potential nephrotoxicity of β-CD limit its application [4,5]. Hydroxyalkyl derivatives of β-CD offer a favourable profile with high water solubility and reduced nephrotoxicity compared to native β-CD [6]. These derivatives retain the ability to form inclusion complexes with drug molecules, enhancing drug solubility and dissolution rate to a greater extent [7].

Recent research has also explored the potential of hydroxy butyl-β-cyclodextrin (HB-β-CD) for drug solubilization [8,9]. Research incorporating the synthesis of HB-β-CD for chiral resolution has been conducted but remains incompletely reported in the literature. The application of this product is limited to drug analysis and testing and it is not suitable for the production of HB-β-CD intended for pharmaceutical formulation. The HB-β-CD is presented under the combined molecular formula of β-CD as $C_{42}H_{70}O_{35}$ and the substituents 1,2-butylene oxide $(C_4H_8O)_n$ with $n = 7 \times ms$. The number of studies on the synthesis procedure and characterization of HB-β-CD is limited; thus, this study would provide specific insight into the compound for further investigation and the advantages in pharmaceuticals.

The study aimed to synthesize the HB-β-CD by investigating the effect of NaOH concentration on the reaction yield (1%, 1.5%, 1.75% and 2%) to possess the highest product yield and determine the degree of substitution [10]. The product was structurally characterized by thin layer chromatography (TLC) and infrared spectrophotometer (IR), while the ^{1}H, ^{13}C, distortionless enhancement by polarization transfer (DEPT), correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC) nuclear magnetic resonance (NMR) analysis in deuterium oxide solution (D_2O) and then mass spectrophotometry (MS).

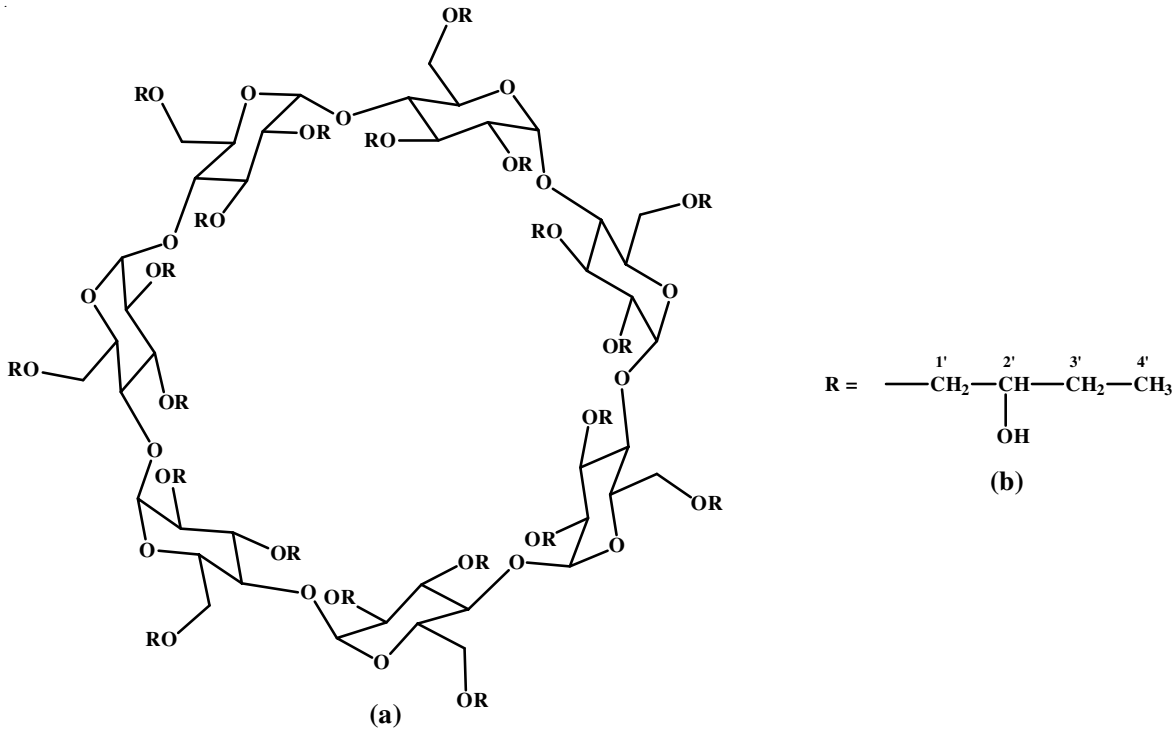

Fig. 1. (a) Hydroxy butyl-β-cyclodextrin structure; (b): 1,2-butylene oxide as the substituent unit

EXPERIMENTAL

The study was conducted using β-CD (Roquette, France) and 1,2-butylene oxide (Merck, Germany). TLC with silica gel GF_{254} was employed for analytical purposes.

Synthesis of hydroxybutyl-β-cyclodextrin: A 250 mL round-bottom flask was charged 1.5 g (0.0375 mol) of NaOH dissolved in 100 mL of distilled water. Subsequently, 5.79 g (5 mmol, 98%) of β-cyclodextrin (β-CD) was added and the mixture was refluxed for 1.5 h. Then, 3.51 mL (2.91 g, 99%, 40 mmol) of 1,2-butylene oxide was added dropwise over 1 h. The reaction mixture was refluxed at room temperature until its completion [11].

TLC analysis: TLC was performed on silica gel plates [12] by an eluent system prepared with isopropanol-NH_4OH (25%)-distilled water (3:1:1, v/v/v). A standard solution of 0.5% (w/v) β-CD in distilled water was spotted on the TLC plate as a reference. The reaction mixture was spotted on a separate lane. Visualization was achieved by iodine vapour staining. The reaction was considered complete when the β-CD spot was no longer detected on the TLC plate.

Purification of hydroxybutyl-β-cyclodextrin: The reaction mixture was neutralized to pH 7.0 by using the 1 M HCl. The solvent was removed under reduced pressure at 80 ºC to collect the crude extract. The residue was then collected and dissolved in 99.5% ethanol with vigorously stirring for 30 min. The insoluble sodium chloride was removed by filtration. Acetone was added to the filtrate and the mixture was stirred at 0-5 ºC for 30 min to induce precipitation. The precipitate was collected by filtration, redissolved in a minimal amount of 99.5% ethanol and reprecipitated with acetone multiple times until a fine, powdery precipitate was obtained. The final product was dried under reduced pressure at 80 ºC to a constant weight [13].

Characterization: The infrared spectrum of the sample was measured by a Shimadzu FTIR-8201PC infrared spectrometer using KBr pallet method. The ^{1}H NMR, DEPT and ^{13}C NMR spectra were recorded in D_2O solvent using a Bruker AC 500 MHz NMR spectrometer. In addition to NMR experiments, the specific NMR including COSY, HSQC and HMBC, were conducted to establish H-H and H-C bonds, which aimed to illustrate the overall 2D structure of HB-β-CD [14]. The structural elucid ation and isomer distribution analysis of synthesized HB-β-CD with varying degrees of substitution (DS) was determined by measuring the absorbance using the Micromass Quattro micro-API-Mass Spectrometer acquired in the range of 0-2000 *m/z* [15].

All calculations throughout this analysis mostly focused on the following equations [16,17]:

$$\text{Product yield (\%)} = \frac{m}{n\times(M_{\beta\text{-CD}} + DS\times M_{1,2\text{-butylene oxide}})}\times 100 \quad (1)$$

where m: mass (g) of purified synthesized product; n: number of moles of β-CD involved in the reaction; $M_{\beta\text{-CD}}$: molecular weight of β-CD; DS: degree of substitution of the synthesized HB-β-CD product calculated from ^{1}H NMR spectrum measured in D_2O, $M_{1,2\text{-butylen oxide}}$: molecular weight of 1,2-butylene oxide.

Molar substitution (ms):

$$ms = \frac{A_1}{3\times A_2} \quad (2)$$

where, A_1: The signal intensity in the region of 0.9-1.2 ppm corresponds to the signal of 3 protons from the methyl group in hydroxy butyl substituent. A_2: The signal intensity in the region of 5.0-5.4 ppm corresponds to the chemical shift of the glycosidic proton.

Degree of substitution (DS) in cyclodextrin derivatives:

$$DS = 7 \times ms \quad (3)$$

where each cyclodextrin has 7 substitution units.

RESULTS AND DISCUSSION

Effect of NaOH concentration on the yields and degrees of substitution: The reaction involved the attachment of hydroxybutyl groups to β-CD (Fig. 2). The site of attachment was influenced by the NaOH concentration at the OH-C-2 or OH-C-3 positions. At low concentrations, the reaction primarily occurred at the OH-C-2 position due to its higher acidity, whereas NaOH concentration increasing, sodium ions interacted with the oxygen at the OH-C-2 position, reducing its reactivity. While the reaction at OH-C-3 continued, resulting in a decrease of overall yield and DS. According to the findings in Table-1, at 1.5% NaOH solution, the reaction possessed the highest yield (75.350 ± 0.030 %) and DS (5.230 ± 0.012) ($p \geq 0.05$).

TABLE-1
DATA BASED ON NaOH CONCENTRATION EFFECTS ON THE YIELDS AND DEGREES OF SUBSTITUTION IN HYDROXY BUTYL-β-CYCLODEXTRIN SYNTHESIS (n = 3)

NaOH concentration	Yield (%)	Degree of substitution (DS)
1.5%	75.350 ± 0.030[a]	5.230 ± 0.012[a]
2.0%	65.720 ± 0.010[b]	4.850 ± 0.015[b]
3.0%	60.420 ± 0.050[c]	4.510 ± 0.009[b]

[a,b,c]Different letters within the column indicate significant differences among the values ($p \geq 0.05$)

Thin layer chromatography: The TLC of β-CD showed a single spot with a retention factor (R_f) value of 0.27. The synthesized HB-β-CD exhibited a spot with an R_f value of 0.77; no residual β-CD was detected.

Infrared spectroscopic studies: The synthesized HB-β-CD was recorded with maximum absorbance at specific wavelengths for each functional group: O-H group in the referent range of (3700-3000 cm^{-1}); C-H group (3000-2850 cm^{-1}); and C-O group (1200-1000 cm^{-1}) [18]. The product HB-β-CD revealed signals in range with the O-H group (λ_{O-H} = 3386.8 cm^{-1}), C-H group (λ_{C-H} = 2933.5 cm^{-1}) and C-O group λ_{C-O} = 1029.9 cm^{-1} (Fig. 3).

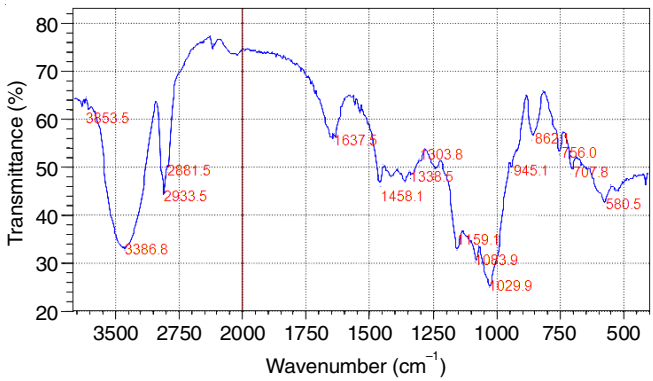

Fig. 3. IR spectrum of synthesized hydroxy butyl-β-cyclodextrin

Nuclear magnetic resonance spectroscopic studies: The ^1H NMR spectrum (Fig. 4) presented only distinct peaks corresponding to H-1 (β-CD peak), H-3′ and H-4′ (of 2-hydroxybutyl) were resolved. The better resolution analysis between the ^1H and ^{13}C NMR spectra was used to assign the ^1H positions *via* HSQC correlation. The spectral data obtained were sufficient to confirm that the synthesized HB-β-CD compound possessed the correct required structure and confirmed the purity of synthesized HB-β-CD (no impurity peaks, except for D_2O solvent peak). Specifically, the presence of 2-hydroxybutyl substituent was evident from the chemical shift of the -CH_2-(1′) peak and the appearance of an additional -CH_2-(3′) peak. The splitting of the H-1 and C-1 peaks of β-CD into three signals further confirmed the disubstitution of β-CD by 2-hydroxybutyl. The splitting of the H-1 and C-1 peaks of β-CD into three signals provides clear evidence of disubstitution by 2-hydroxybutyl groups.

The substitution pattern in HB-β-CD was inferred by the ^{13}C NMR spectrum (Fig. 5). The C_1 atom of 1,2-butylene oxide

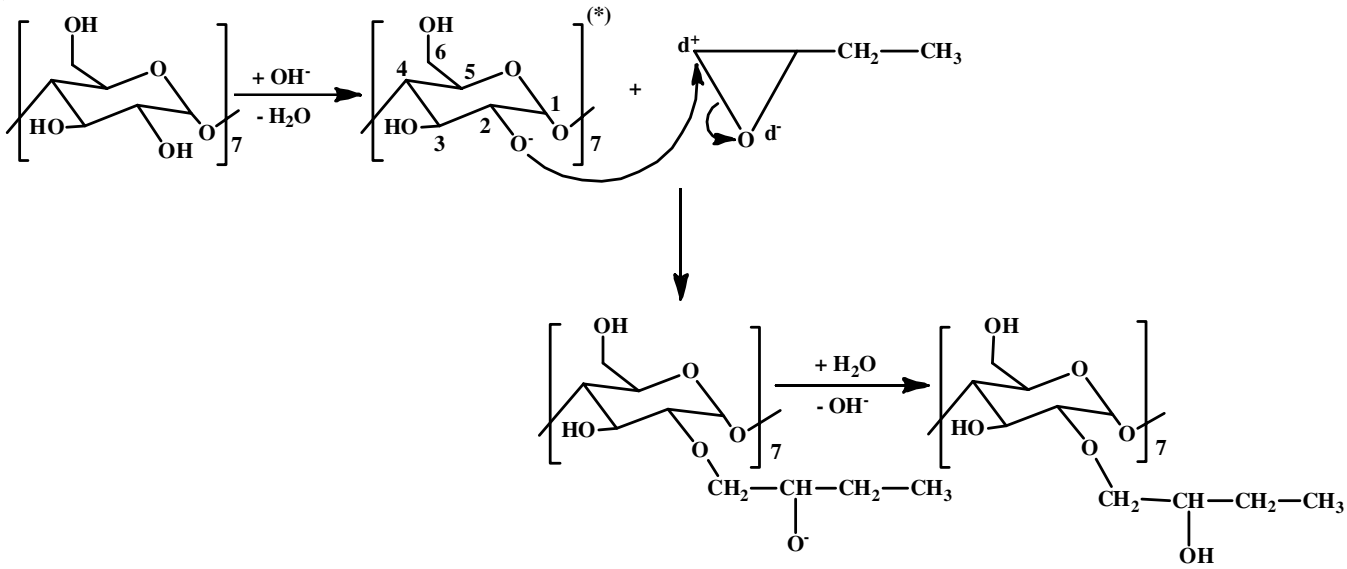

Fig. 2. Mechanism of the synthesis reaction of hydroxy butyl-β-cyclodextrin

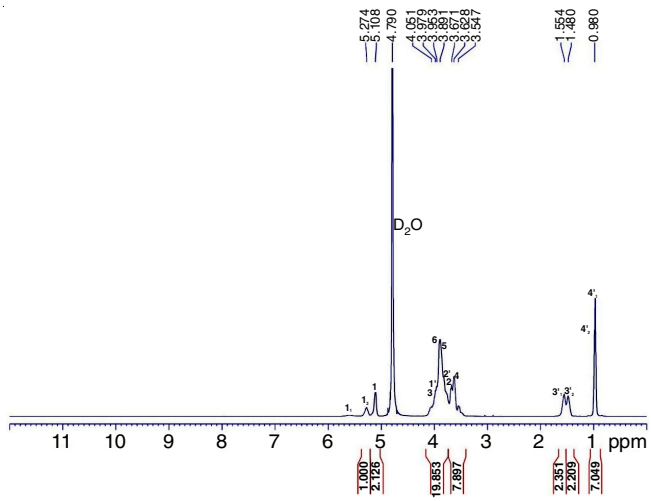

Fig. 4. ^{1}H NMR spectra in hydroxy butyl-β-cyclodextrin in D_2O (500 MHz; temperature: 299 K): 5.108 (H_1); 3,628 (H_2); 4.051 (H_3); 3.547 (H_4); 3.891 (H_5); 3.953 (H_6); 3.879 ($H_{1'1,2}$); 3.671 ($H_{2'1,2}$); 1.554 ($H_{3'1}$); 1.480 ($H_{3'2}$); and 0.980 ($H_{4'1,2}$)

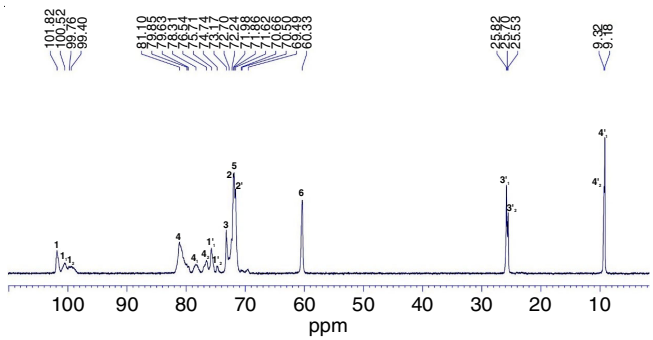

Fig. 5. ^{13}C NMR spectra in hydroxy butyl-β-cyclodextrin in D_2O (125 MHz, temperature: 299 K): 101.82 (C_1); 73.17 (C_2); 74.74 (C_3); 81.10 (C_4); 72.70 (C_5); 60.33 (C_6); 76.54 ($C_{1'1,2a}$); 75.71 ($C_{1'1,2b}$); 72.24 ($C_{2'}$); 25.82 ($C_{3'1}$); 25.53 ($C_{3'2}$); 9.18 ($C_{4'1}$); and 9.32 ($C_{4'2}$)

generally interacted with the OH-^{2} and OH-^{3} groups of β-CD at low alkaline concentrations to form -$C_{(2)}$-O-R (R = -CH_2-CHOH-CH_2-CH_3) and -$C_{(3)}$-O-R linkages, respectively. At higher alkaline concentrations, the OH-^{6} group might also participate in the substitution to form a -$C_{(6)}$-O-R linkage. Since substitution could occur at any glucose unit of β-CD, a mixture of mono-, di- and unsubstituted units was typically observed, unless all seven units were completely disubstituted (100% substitution).

Thereafter, the ^{1}H and ^{13}C NMR signals of HB-β-CD, such as $^{13}C_{(1)}$ or $^{1}H_{(1)}$, split into three peaks: one represented for unsubstituted units (labeled 1), one for the first substituted units (labeled 1_1) and one to next substituted units (labeled 1_2). In principle, the splitting would occur for all ^{1}H and ^{13}C signals; however, any spectral broadening could happen to overlap peaks, especially in the ^{1}H NMR spectrum. Thus, the signals of H-5 and H-6 in β-CD were overlapped even when they had not been substituted. Based on the $\delta^{13}C$ ppm values, the corresponding $\delta^{1}H$ ppm values were further determined using HSQC spectroscopy. COSY (Fig. 6), 2D-HSQC and HMBC (Fig. 7) spectra provided additional structural characterization.

The ^{1}H NMR spectrum presented significant challenges due to various broadening and overlap peaks, except for the signals of H-1 in β-CD and CH_3(3′) in HB-β-CD. The diastereotopic protons of the -CH_2-(1′) group had been proven by clear evidence in the HSQC spectrum, which exacerbated this overlap signal. The $CH_{1'(a)}$ and $CH_{1'(b)}$ signals further complicated the

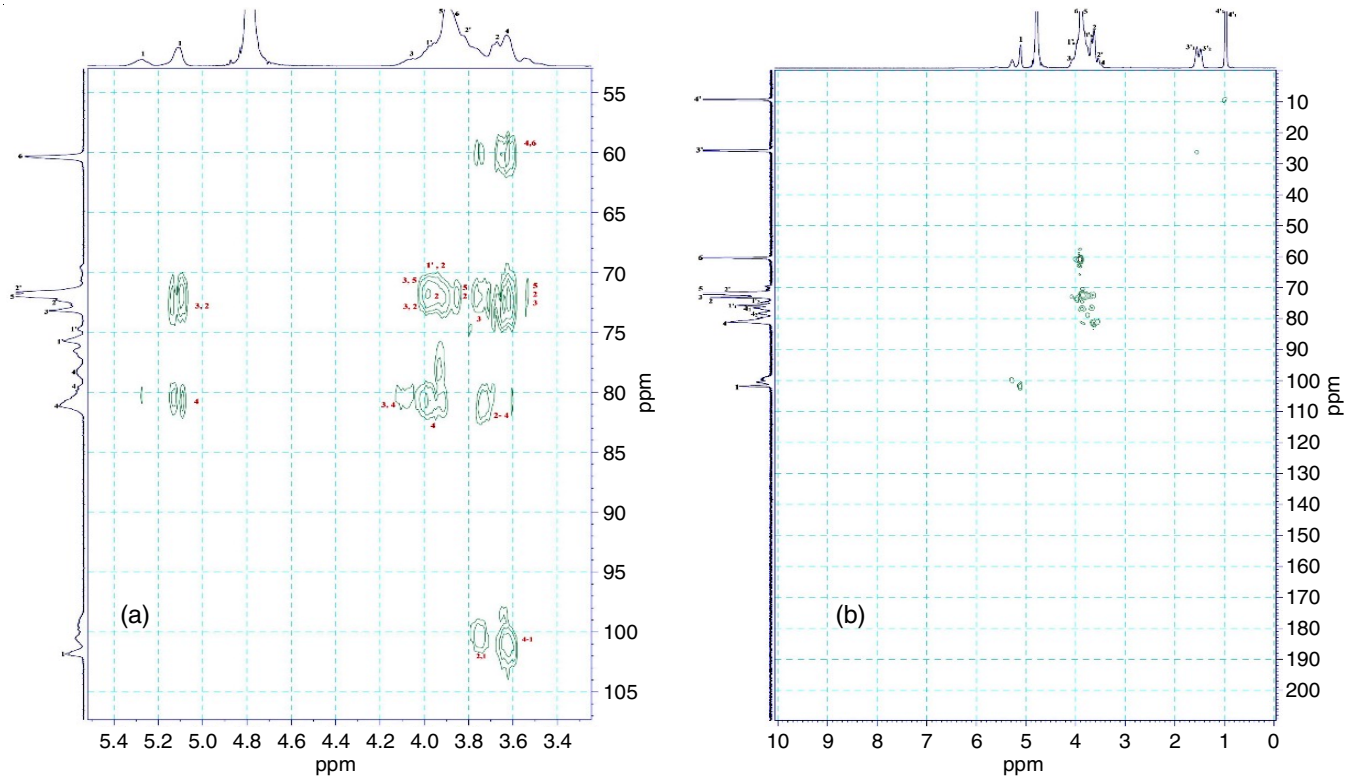

Fig. 6. HMBC and HSQC NMR spectrum of hydroxy butyl-β-cyclodextrin measured in D_2O

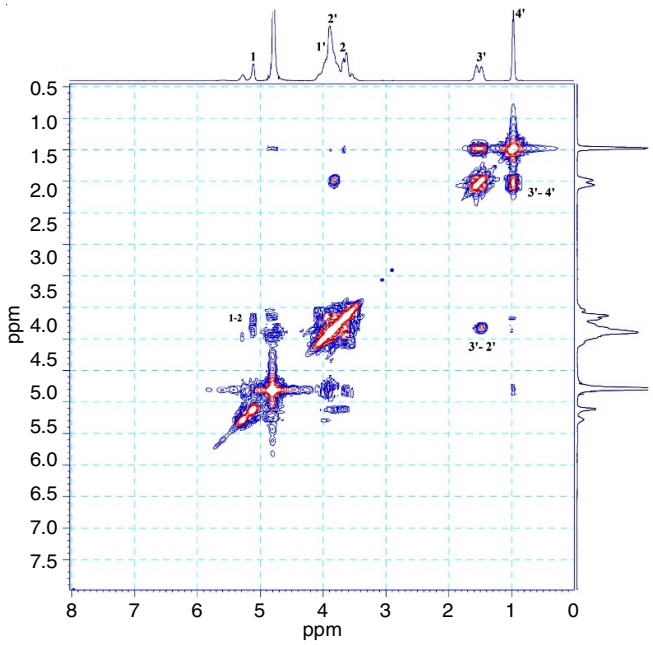

Fig. 7. ^{13}C COSY NMR spectrum of hydroxy butyl-β-cyclodextrin measured in D_2O

spectrum by inserting themselves between existing signal clusters. However, analysis of the ^{13}C NMR (including DEPT 90 and DEPT 135, Fig. 8) and 2D-HSQC spectra provided sufficient data to confidently assign the precise structure of HB-β-CD. A comprehensive analysis of the NMR data (Table-2) confirms that the synthesized HB-β-CD possesses the correct structure and is highly pure. The clean baseline and absence of impurities, except for the D_2O solvent chemical shift at δ_D = 4.705 ppm, support these findings.

Based on the NMR data, the β-CD derivative of HB-β-CD had been successfully synthesized. The obtained compound exhibited the expected chemical structure and high purity, with impurities below the detection limit of NMR.

The signal in Fig. 9 indicates the signal intensity in the region of 0.9-1.2 ppm (A_1) was 7.049 and 5.0- 5.4 ppm (A_2) was (1.000 + 2.126), thus the molar substitution was calculated by eqn. 2:

$$ms = \frac{7.049}{3\times(1.000+2.126} = 0.752$$

The degree of substitution (DS) was then calculated according to eqn. 3:

TABLE-2
MS SPECTRA DATA OF SYNTHESIZED HYDROXY BUTYL-β-CYCLODEXTRIN ACQUIRED IN D_2O. THE ^{13}C NMR, DEPT (90, 135) EXPERIMENTS CONDUCTED AT 125 MHz. THE ^{1}H NMR, COSY, HSQC AND HMBC EXPERIMENTS PERFORMED AT 500 MHz. THE TEMPERATURE OF THE EXPERIMENT WAS MAINTAINED AT 299 K

Position	Functional group	δ^{13}C (ppm)	δ^1H (ppm)	COSY H→H	HMBC H→C
1	—O—CH—O—	101.82	5.108		
1_1	—O—CH—O—	100.52	5.274	2	2,3,4
1_2	—O—CH—O—	99.76			
2, 2_1, 2_2	—CH—O—	73.17	3.628	1	1,3,4
3, 3_1, 3_2	—CH—O—	74.74	4.051		2,4,5
4	—O—CH—	81.10			
4_1	—O—CH—	79.85	3.547		1,2,3,5,6
4_2	—O—CH—	78.31		Overlapping peaks	
5, 5_1, 5_2	—CH—O—	72.70	3.891		2,3,4
6, 6_1, 6_2	—CH_2—O—	60.33	3.953		5
$1'_{1,2}$(a)	—O—CH_2—	76.54			2,2'
$1'_{1,2}$ (b)	—O—CH_2—	75.71	3.879		
$2'_1$,$2'_2$	—CH—O—	72.24	3.671	3'	2
$3'_1$	—CH_2—	25.82	1.554	2',4'	4',2'
$3'_2$	—CH_2—	25.53	1.480		
$4'_1$	—CH_3	9.18	0.980	Overlapped	3',2'
$4'_2$	—CH_3	9.32			

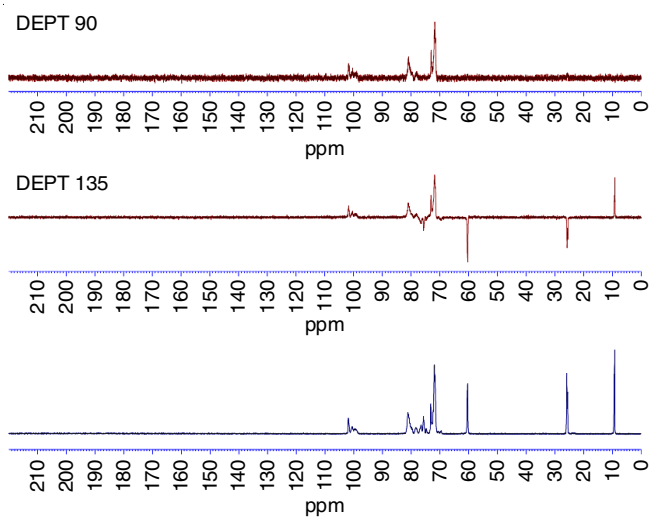

Fig. 8. ^{13}C, DEPT 90 and DEPT 135 NMR spectra of hydroxy butyl-β-cyclodextrin measured in D_2O

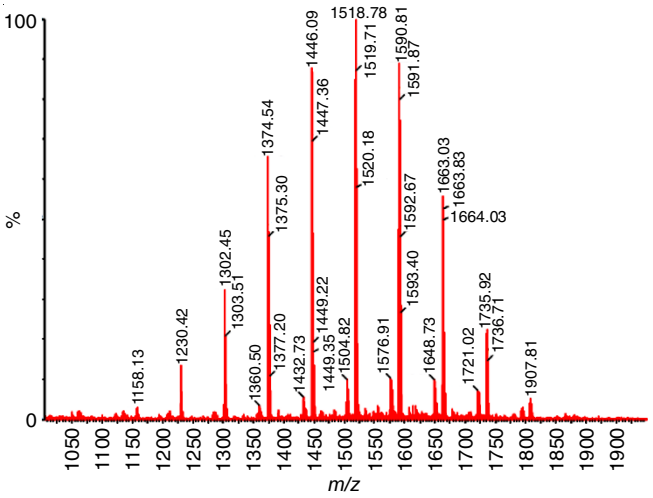

Fig. 9. Mass spectrum of the synthesized hydroxy butyl-β-cyclodextrin

$$DS = 7 \times ms = 7 \times 0.752 = 5.264$$

Mass spectrophotometic studies: The consistency of the subsequent peaks with the substitution of 1,2-butylene oxide into β-CD was possibly demonstrated by $M_{+β\text{-}CD}$. When the substituting into β-CD happened, 1,2-butylene oxide gained one hydrogen atom, whereas β-CD lost a hydrogen atom. Thus, for each substitution, the molecular mass of $^{+}$β-CD would increase by 1 unit (Δm) of 72.110 carbon units.

The mass of the HB-β-CD ion fragments containing the 2-hydroxybutyl substituent were simply calculated from $M_{+β\text{-}CD}$ based on the number of substitutions (n) in carbon units (Da) as the following equation:

$$M_{+HB\text{-}β\text{-}CD\ m/z} = M_{+β\text{-}CD} + (n - 1) \times 72.110$$

The initial substitution reaction involved a nucleophilic attacked by the hydroxyl group at C-2 of β-CD on the C-1 of 1,2-butylene oxide, forming a new ether linkage and resulting in a net gain of one hydrogen atom in the product. Thus, the β-CD component contributing to the formation of the mono-substituted HB-β-CD had a mass of 1133.994 Da (minuting one H atom) and the 1,2-butylene oxide component contributes 73.110 Da (adding one H atom). Consequently, the molecular mass of the resulting to be:

$$M_{HB\text{-}β\text{-}CD}(1) = 1133.994 + 73.110 = 1207.104$$

Then, in the second substitution reaction, the HB-β-CD framework (1) lost an additional hydrogen atom from a hydroxyl group at each substitution site and the doubly substituted HB-β-CD became:

$$M_{HB\text{-}β\text{-}CD}(2) = M_{HB\text{-}β\text{-}CD}(1) - 1 + 73.110 = M_{HB\text{-}β\text{-}CD}(1) + 72.110$$

Therefore, for a molecule of HB-β-CD that had undergone n substitution reactions (n ≥ 1), its molecular mass would be calculated in carbon units by the following equation:

$$M_{HB\text{-}β\text{-}CD}(n) = M_{HB\text{-}β\text{-}CD}(1) + (n\text{-}1) \times 72.110$$

Mass spectra exclusively displayed ionized species (Table-3), especially for electrospray ionization (ES+), the H^+, Na^+ or K^+ were commonly employed as adducts. The choice of adductive locations could vary based on the specific carrier gas and experimental conditions. In ES+ analysis, sodium adduction was particularly prevalent. Fragmentation in mass spectrometry occurred when the ionizing agent-induced bond cleavage within the analyte molecule [19,20]. In the analysis of HB-β-CD, the highest mass peak represented the most substituted species, which upon ionization, can undergo fragmentation-occurring when the ionizing agent induces bond cleavage resulting in two charged fragments. Thus, fragmentation to form an ion from a neutral molecule with a molecular mass of M was then determined to be:

$$M'^{+}_{m/z} = M + m_{Na} = M + 23\ (M'^{+} = M \text{ at } z = 1)$$

$$M'^{+}_{m/z} = M + m_H + m_{Na} = M + 1 + 23$$

TABLE-3
MASS SPECTRUM OF HYDROXY BUTYL-β-CYCLODEXTRIN SYNTHESIZED IN THE RANGE OF 1000 TO 2000 *m/z* ACCORDING TO EQN. 2

M_n	Prediction	Mass spectrum	
	$[m_{Na}]^+$	$[m_{Na}]^+$	$[m_H + M_{Na}]^+$ and isotopes
M_1	1230.10	1230.42	–
M_2	1302.21	1302.45	1303.51
M_3	1374.32	1374.54	1375.33
M_4	1446.43	1446,69	1447.36
M_5	1518.54	1518.78	1519.71
M_6	1590.65	1590.81	1591.87
M_7	1662.76	–	1663.03
M_8	1734.87	–	1735.92
M_9	1806.98	–	1807.81

Given this single fragmentation assumption, any fragment ion could be analyzed to determine the degree of substitution. The mass difference between fragments is primarily due to the varying number of HB-β-CD units (each contributing 72.110 Da). Since the most highly substituted peak might be weak or undetected, the singly substituted ion M^+ (1) would be used for calculations.

$$M'^{+}_{m/z}(1) = M + m_{Na} = M_{HBβCD}(1) + 23 = 1207.10 + 23 = 1230.10$$

There were also corresponding peaks of $[m_H + m_{Na}]^+$ or those arising from the isotopes of carbon or hydrogen formed during

the ionization process that present onto the mass spectrum. The mass spectrum has definitively confirmed that the product is HB-β-CD with the expected molecular formula. The mass spectrum also clearly demonstrates that a disubstitution event has occurred on one unit of the β-CD, consistent with the ^{13}C NMR data [21]. In this regard, the mass spectrum provided unequivocal evidence of disubstitution products. Given that a 7-unit β-CD molecule had undergone 9 substitution reactions, thus, at least two of the β-CD units would experience disubstitution.

Conclusion

In conclusion, the successful synthesis of HB-β-CD was achieved with the highest yield to be 75.350 ± 0.030% and DS 5.230 ± 0.012 at 1.5% NaOH solution. The structure of the synthesized HB-β-CD was then confirmed through various techniques, including IR, NMR and MS. The IR spectrum revealed characteristic peaks with maximum absorbance at specific wavelengths for main functional groups (C=O; C-H; and O-H). The NMR spectra provided detailed signals for the ^{1}H and ^{13}C atoms, supporting the calculation of the molar substitution to be 0.752 while the degree of substitution was 5.264. The MS analysis confirmed the molecular weight and fragmentation pattern, supporting the required structure. This study provides the groundwork for standardizing the synthesis procedure of HB-β-CD and the development of further forming complex with commercially available drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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