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Hyaluronic-acid-based β-cyclodextrin grafted copolymers as biocompatible supramolecular hosts to enhance the water solubility of tocopherol

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ABSTRACT

Hyaluronic acid (HA), a common biopolymer found in the extracellular fluid, was grafted with β-cyclodextrin (β-CD) to form a composite polymer that could form inclusion complexes with tocopherol (VE), enhancing its water-solubility and serving as a model drug delivery system. Herein, different copolymers were prepared with varying HA:β-CD ratios and characterized. VE loading capacity was directly correlated with increased β-CD composition in the polymers and morphological changes were observed upon VE binding. The host materials and their VE inclusion complexes are not cytotoxic, and are thus useful for VE and drug delivery.

1. Introduction

In food chemistry, vitamin E (VE) is associated with lipids and absorbed through the small and large intestines (Hernandez et al., 1980). VE has many postulated biological functions, especially as a lipid-soluble antioxidant scavenger of free radicals, e.g., for skin protection from UV radiation-induced damage (Kuang Chow, 2004; Machlin, 1985). VE is commonly used as a functional component to form polymeric nanocarriers in drug delivery systems (Chen et al., 2017; Gao et al., 2017) or in wound dressing materials (Hobson, 2016) because of its excellent antioxidant properties. (Sheng et al., 2013; Taepaiboon et al., 2007). Despite its utility, it can be difficult to use because it is insoluble in water and unstable upon exposure to oxygen, light, transition metal ions, and alkaline conditions, which has limited its pharmacological application (Ball, 1998; Bramley et al., 2000). Food processing can also damage VE and reduce its concentration during cooking, canning, and freezing processes. However, VE deficiencies are uncommon and usually caused by poor lipid absorption in the gastrointestinal tract. In healthy individuals, > 64% of ingested VE is eliminated in the feces (Mehlert and Diplock, 1985; Tudehope et al., 1985). In some cases, e.g., pharmacological applications, stabilized water-soluble versions of VE are desirable to improve its bioavailability. Biotechnological and chemical approaches to enhance the solubility of lipophilic molecules in water include using a co-solvent (Shamshina et al., 2015), solid dispersion (Han et al., 2011), chemical modification (Dubbs and Gupta, 1998), or through a supramolecular complex. Inclusion complexes (ICs) of pharmaceuticals in a macrocyclic host, such as cyclodextrins (CDs), cucurbiturils, calixarenes, and their derivatives have the added benefit of improving drug stability (Cheng et al., 2016; Dong et al., 2015; Webber et al., 2015).

CDs are widely investigated supramolecules obtained from the enzymatic degradation of starch (Zhang et al., 2019). These are oligosaccharides with hydrophilic exteriors and a hydrophobic cavity (Crini, 2014; Davis and Brewster, 2004a; Harada et al., 2009). However, supramolecular carriers must be biocompatible and with high loading capacity (Mann et al., 2018). CDs in combination with biomolecules have been demonstrated to enhance drug solubility and improve their therapeutic efficacy (Davis and Brewster, 2004b; Namgung et al., 2014). For instance, CDs and polyethylenimine-based supramolecular complexes have been successfully used for gene delivery (Lv et al., 2017), whereas various CDs have been reported for solubility enhancement of VE (Aytac et al., 2017; Aytac and Uyar, 2016; Celebioglu and Uyar, 2017; Huang et al., 2002; Sueishi et al., 2012) (Table S1). In this attempt, we chemically grafted β-CD onto hyaluronic acid (HA), a

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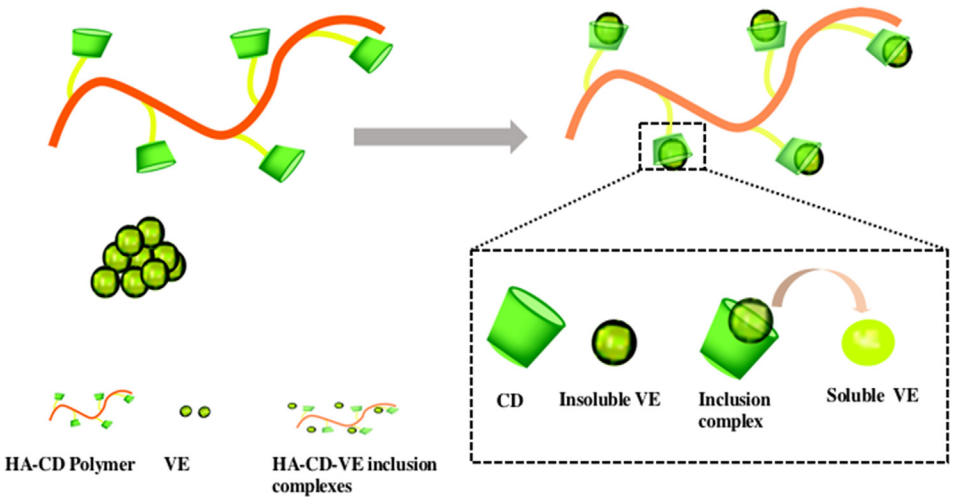

Scheme 1. Tocopherol (VE) solubility enhancement by hyaluronic acid-β-cyclodextrin (HA-β-CD) grafted copolymer.

Table 1
Polymers synthesis conditions.

Sample	Composition (CD:DPC:HA)	Reaction time (h)	Temperature (°C)
S-1	1:2:1	12	80
S-2	1:4:1	12	80
S-3	2:4:1	12	80
S-4	4:4:1	12	80
S-5	1:4:2	12	80
S-6	1:2:1	12	25
S-7	1:2:1	24	80

major constituent of the extracellular matrix (Laurent, 1989), which is essential for tissue organization, proper cell growth, regulation of cell adhesion, cell proliferation, migration, differentiation, and organ structure stability (Entwistle et al., 1996; Hua et al., 1993; Knudson and Knudson, 1993).

CDs as a supramolecular polymer along with HA can enhance the cosmetic and therapeutic efficacy of VE. Biomolecular backbones containing CD-VE ICs have great potential for biomedical applications. These compounds require chemical grafting of CDs onto a biomolecular backbone and thus the synthetic conditions, e.g., reaction time, temperature, and crosslinker concentration, can greatly affect the reaction product and subsequently the drug loading capacity and therapeutic efficiency.

Previously, the synthesis of CD-grafted HA polymers required time consuming multi-step procedures (Ji et al., 2017). Herein, the synthesis was accomplished by a one-step chemical crosslinking reaction, producing an HA-β-CD polymer suitable for tocopherol delivery (Scheme 1). VE was selected as a model drug molecule because, in combination with HA, it could be widely used for skin and other disease treatment. The enhanced solubility of VE was confirmed with various analytical techniques and the effect of supramolecular-biomolecular complexation on the VE solubility was investigated.

2. Experimental section

2.1. Materials

Hyaluronic acid sodium salt was purchased from Shandong Topscience Biotech Co., Ltd. (Rizhao, Shandong, China). β-cyclodextrin (β-CD) was purchased from Anhui Sunhere Pharmaceutical Excipients Co., Ltd. (Huainan, Anhui, China). Diphenyl carbonate (DPC) was purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China). α-Tocopherol (VE) was purchased from Shanghai Zhongyi Sunve Pharmaceutical Co. Ltd. (Shanghai, China). Triethylamine (TEA), dimethylformamide (DMF), ethanol (EtOH), and all other chemicals and reagents were purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China), were of analytical grade, and used without further purification. HeLa cells were obtained from the Chinese Academy of Sciences (Shanghai, China). Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum (FBS) were purchased from Gibco (Thermo Fisher Scientific, Waltham, MA, USA).

2.2. Hyaluronic acid-β-cyclodextrin grafted copolymer synthesis

For synthesis of the HA-β-CD polymer (S-1), we used DPC as the crosslinking agent (Singh et al., 2020). Briefly, 10 mL of β-CD and HA (each 60 mM) in DMF was heated to 80 °C in a round bottom flask. DPC was then added with 300 μL of TEA as a catalyst and stirred for 10 min at different concentrations and temperatures (Table 1) to link CD and HA through transesterification of DPC. The crude mass was cooled to ambient temperature and poured into 6 volumes of EtOH to precipitate the polymer, which was mechanically disaggregated and centrifuged at 4000 rpm for 10 min. The residue was washed by resuspending it to remove phenol and other impurities under vortex for 5 min followed by centrifugation. The product was thoroughly washed with acetone before Soxhlet extraction with EtOH for 8 h. The product was then dried in vacuo overnight at 45 °C. After drying, samples were characterized by microscopic and spectroscopic methods.

2.3. Sample characterization

Synchrotron radiation Fourier-transformed infrared spectroscopy (SR-FTIR) was performed at the BL01B beamline at the Shanghai Synchrotron Radiation Facility (Shanghai, China) and was used for primary characterization of the grafted copolymer to confirm the presence of the expected pendent functionalities. All spectra were recorded using a Thermo Scientific Nicolet TMiSTM5 FT-IR spectrophotometer in the region of 4000–650 cm^{-1} and the data were processed using OMNIC software. Proton nuclear resonance spectroscopy (^1H NMR) analysis of all samples was performed using a Bruker Avance 400 MHz. Samples were dissolved in D_2O. All samples were processed using MestRe-C software. The sample powder morphology was investigated using a scanning electron microscope (SEM, S-3400N, Hitachi), wherein the specimens were immobilized on a metal stub with a double-sided adhesive tape and coated with a thin gold film. Powder X-ray diffraction (PXRD) was performed on a D8 Advance diffractometer (Bruker, Germany) using CuKα radiation at ambient temperature (40 kV, 40 mA, 2θ 3–40°, 8° min^{-1}) and was used to determine the internal structure of the copolymers. Thermogravimetric analysis (TGA) was performed

Table 2
Tocopherol loading conditions.

Sample	Composition (CD:DPC:HA)	Reaction time (h)	Reaction temperature (°C)	Appearance After 8 h	Appearance After filtration
IC-1	HA	8	60	Hazy	Hazy
IC-2	β-CD	8	60	Hazy	Hazy
IC-3	1:2:1	8	60	Transparent	Transparent
IC-4	1:4:1	8	60	Hazy	Transparent
IC-5	2:4:1	8	60	Hazy	Transparent
IC-6	4:4:1	8	60	Hazy	Hazy
IC-7	1:4:2	8	60	Transparent	Transparent
IC-8	1:2:1	12	45	Transparent	Transparent
IC-9	1:4:1	12	45	Hazy	Transparent
IC-10	2:4:1	12	45	Hazy	Transparent
IC-11	4:4:1	12	45	Hazy	Hazy
IC-12	1:4:2	12	45	Transparent	Transparent

using a Perkin-Elmer Pyris-1 TGA using a nitrogen gas flow of 20 mL min^{-1} over the range 40–600 °C at 20 °C min^{-1} and processed using Pyris software.

2.4. Tocopherol inclusion complexes

Drug encapsulation was optimized by incubating the graft copolymers with varying concentrations of VE for different time intervals. Briefly, 200 mg of each sample was sonicated in 20 mL water for 5 min. VE (211.8 mg) was sonicated in 14 mL of EtOH and 2 mL of VE solution was then added dropwise to the polymer solutions, causing the solutions to become hazy. The reaction conditions are listed in Table 2. After incubation, the remaining EtOH was removed by rotatory evaporation and the samples were passed through a 0.22 μm filter paper before lyophilization (SIM International Group Co. Ltd., Beijing, China) for 12 h. Furthermore, 5 mg of lyophilized sample was dissolved in 5 mL of water and VE encapsulation was analysed by HPLC. These samples were further characterized by various analytical techniques detailed as below.

2.5. Quantification of tocopherol inclusion complexes

High-performance liquid chromatography (HPLC Agilent Technology, 1290 infinity) with a UV detector was used to quantify the VE loading capacity of the ICs. Briefly, ~5 mg of each sample was sonicated in 1 mL of Milli-Q water for 2 min yielding a transparent solution. The samples were centrifuged at 12000 rpm for 5 min, filtered through a 0.22 μm membrane filter, and injected into the HPLC (see the SI).

2.6. In vitro evaluation of biocompatibility of ICs

The *in vitro* cytotoxicity of the ICs was tested using an Enhanced Cell Counting Kit-8 (CCK-8, Beyotime) by seeding HeLa cells into 96-well plates and incubating for 24 h (2000 cells $well^{-1}$). Experimental details on the cell culture are given in the Supporting Information. Randomly selected IC samples (20 μL of 10, 20, 40, 80, and 100 μg/mL) and controls without ICs were then added and incubated for 12 h before CCK-8 solution (20 μL) was added and further incubated for 3 h. The absorbance was measured at 450 nm using microplate reader (Thermo Scientific, Multiscan Go) and each treatment was tested in eight replicates. The cell viability was calculated as follows (Eq. (1)):

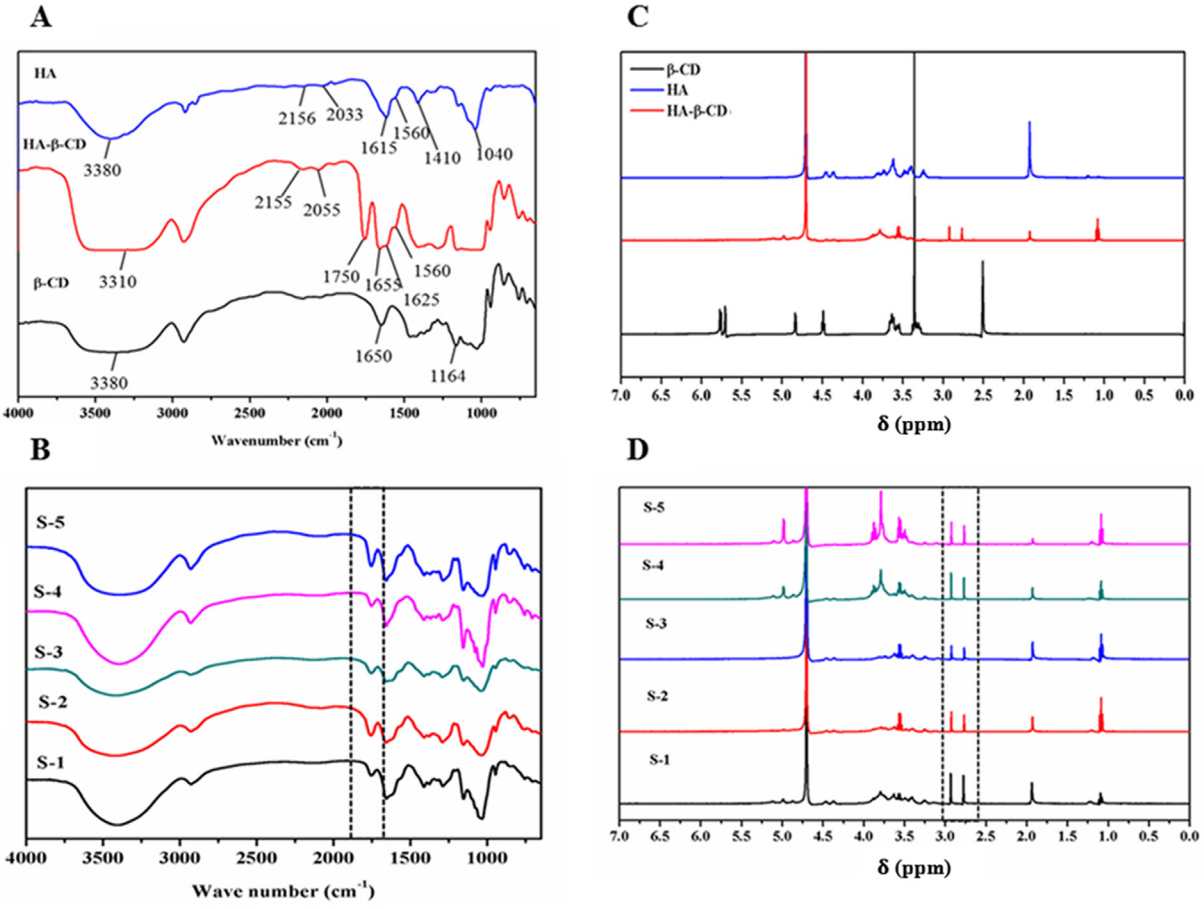

Fig. 1. Infrared spectra of (A) HA-β-CD polymer and (B) derivative samples. NMR spectra of (C) the polymer and starting materials and (D) derivative samples.

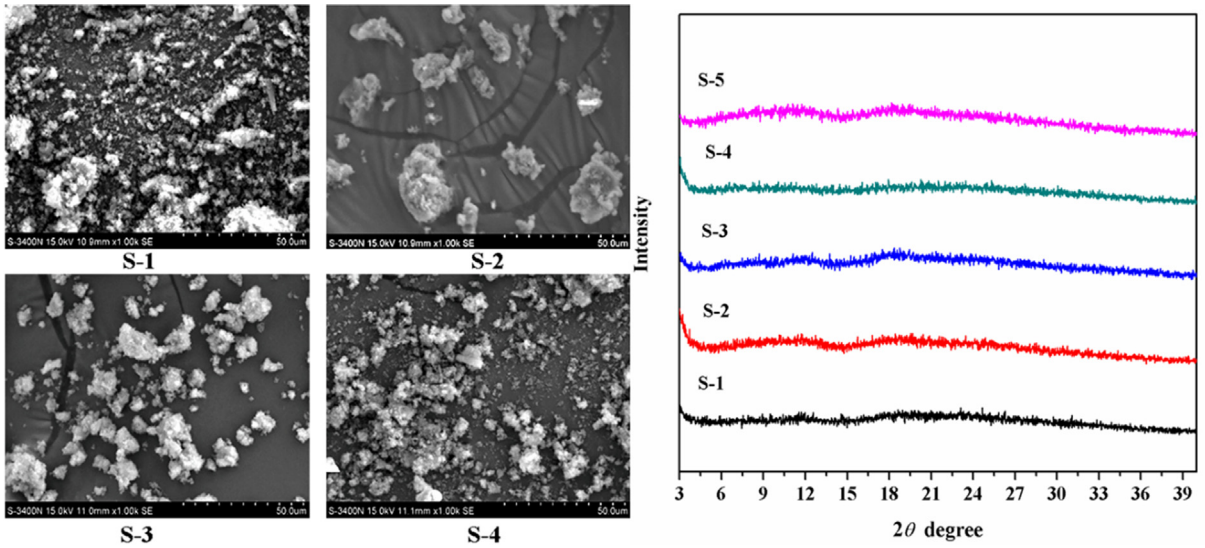

Fig. 2. Sample morphology (left) and powder X-ray diffraction spectra (right).

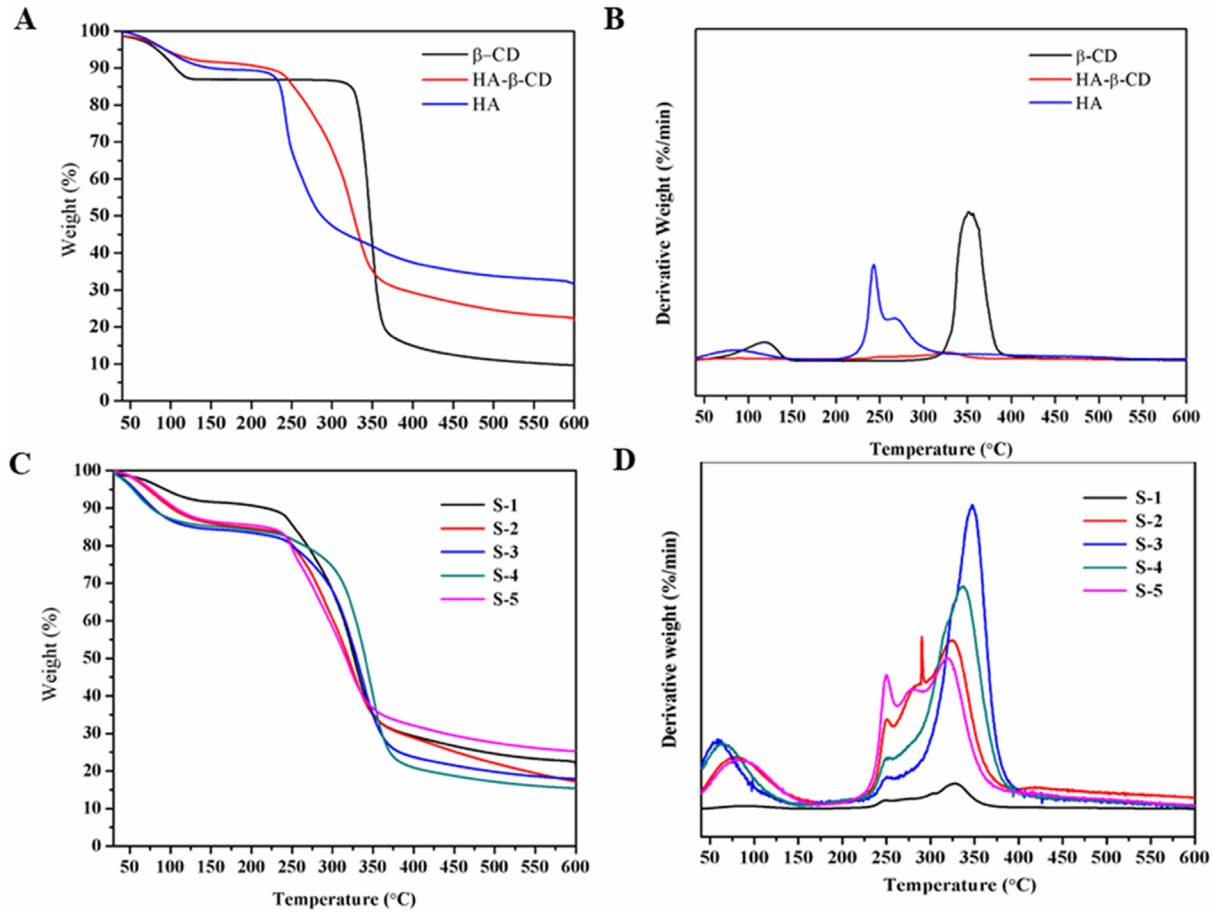

Fig. 3. The (A) thermogravimetric analysis and (B) differential thermogravimetry curves of the precursors and parent HA-β-CD polymer in comparison with (C and D) the derivative compounds.

$$Cell\ Viability(\%) = \frac{OD_{exp} - OD_{blank}}{OD_{control} - OD_{blank}} \times 100 \quad (1)$$

where OD_{exp}, OD_{blank}, and $OD_{control}$ are the absorbances of the sample, blank, and control experiments, respectively.

3. Results and discussion

The graft copolymer was prepared using a method previously reported by our lab (Singh et al., 2020) whose by-products were removed with EtOH and acetone washing (Fig. S1). All synthetic reactions were successful except S-6 because the ambient temperature was insufficient for the transesterification. SR-FTIR spectroscopy confirmed the

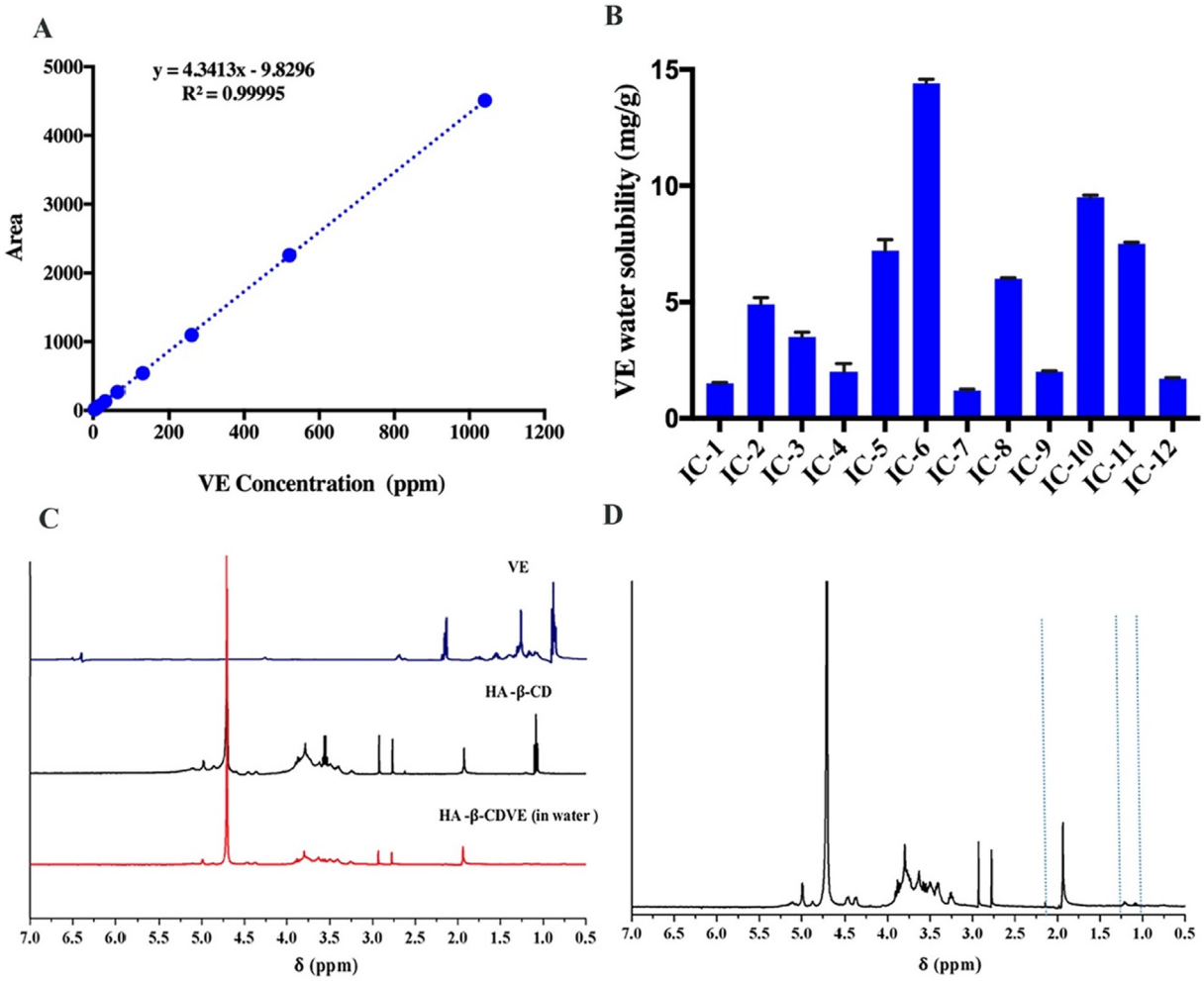

Fig. 4. (A) VE calibration curve for HPLC quantification. (B) VE water solubility of the polymer samples of different compositions. NMR spectra of (C) HA-β-CD polymer, VE, and HA-β-CD-VE ICs and (D) a representative spectrum of VE-loaded HA-β-CD polymer showing a successful IC with VE marked by dotted lines.

formation of the carbonate linkage through the sharp band at 1750 cm^{-1} unique from the reactants. Other relevant bands include a broad 3310 cm^{-1} band corresponding to O–H and N–H stretching and 2156 cm^{-1} and 2050 cm^{-1} bands corresponding to C-N stretching. The characteristic bands of HA were observed at 1560 cm^{-1} and 1040 cm^{-1}. In Fig. 1B, the spectra of derivatives were similar to the parent compound in Fig. 1A (the characteristic peaks are marked with a dotted box).

In the HA-β-CD polymer ^{1}H NMR spectra, δ 4.25 and 4.55 ppm peaks corresponding to H-1 from the glucuronic acid and H-1 from the N-acetyl glucosamine unit of HA, respectively, were observed (Fig. 1C). Peaks from 3.1 to 3.9 (H-2–H-6) corresponded to HA and β-CD. New peaks between 2.7 and 2.9 ppm correspond to protons adjacent to the newly formed carbonate linkages and are not comparable to the parent compounds. All synthesized compounds were similar (linking can be seen in Fig. 1D in a dotted line box).

Different ratios of starting materials and the DPC concentration significantly changed the morphological structures of the polymers (SEM micrographs in Fig. 2). Sample 1 (S-1) features small round particles that agglomerate. Sample S-2, with a higher concentration of DPC, features larger micrometer size particles. S-3 and S-4 are small porous particles, whereas S-5 (data not shown) has large round particles. PXRD showed that all samples were amorphous (Fig. 2, β-CD forms crystals but HA does not).

TGA (Fig. 3) was employed to characterize the thermal stability of the polymer and obtain semi-quantitative (or quantitative) information regarding its composition (Bai et al., 2012; Riela et al., 2011). The TGA graph showed that the compounds were reasonably thermally stable and with a high residual content after heating to 600 °C. The residue likely consisted of some sodium-containing ash (the sodium salt of HA was used in our experiments), which is consistent with higher residual masses present in samples with higher HA:β-CD ratios (Fig. 3C). Differential thermogravimetric curves were used to compare the onset of decomposition of the HA backbone and grafted β-CD. β-CD degrades at 329 °C whereas HA has degradation peaks at 250 and 270 °C (Fig. 3B), the peak areas roughly corresponded to the HA:β-CD ratio (Fig. 3D).

A molecular stimulation study showed high affinity of β–CD toward VE (Fig. S2). ICs of HA-β-CD and VE were prepared under different conditions (Table 2). Ethanolic solutions of IC-4, IC-7, IC-9, and IC-12 were turbid because they were insoluble in the solutions (Fig. S3).

For VE quantification at various stages, we used a reported HPLC method as per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for its linearity, the limit of quantification (LOQ), and limit of detection (LOD) (Fig. S4) (Drotleff et al., 2015). The VE water solubility enhancement by the grafted HA-β-CD polymers of various composition were compared with their parent compounds (IC-1 and IC-2, Fig. S5). VE encapsulation was quantitatively evaluated at various stages, such as after 8 h of stirring (Fig. S6A), after evaporation of EtOH (Fig. S6B), and after filtration (Fig. S6C). VE release from the lyophilized samples shows that IC-6 exhibits the highest water solubility enhancement (compared to IC-4 and IC-5), because it contains the highest amount of

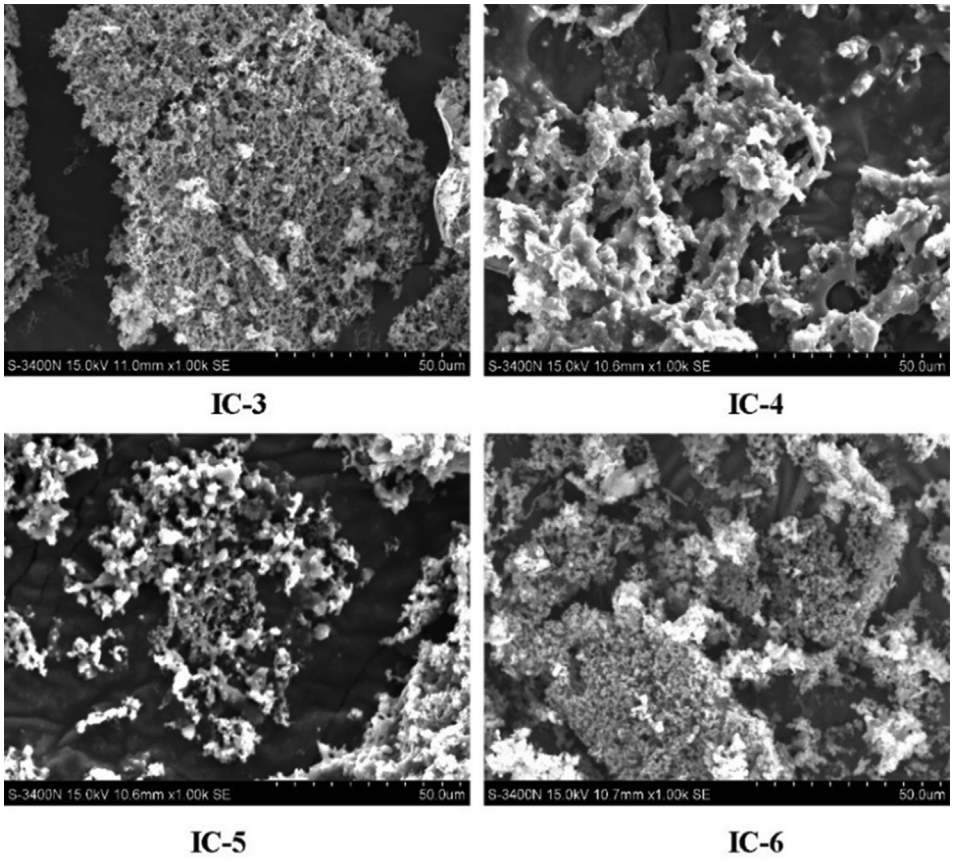

Fig. 5. Morphological variation of different inclusion complexes (IC-3 to IC-6).

β-CD (Fig. 4B and S6D and Table S-2). Although β-CD alone (IC-2) enhanced the VE water solubility, by complexing with the water-soluble polymer HA, the VE water solubility was further increased by ~ 3 times (Fig. 4B).

All ICs were characterized by spectroscopic and microscopic techniques, including FT-IR (Fig. S7) and NMR (Fig. S8). NMR analysis showed significant peaks of VE in ICs at 1.3 and 2.2 ppm (Fig. 4C and D). TGA analysis supported inclusion complexation with VE (Figs. S9–S11). Moreover, the amorphous nature remains constant after encapsulation with VE (Fig. S12). It was consistent with liquid chromatography, i.e., showing higher and lower amounts of VE in IC-6 and IC-7, respectively, based on their residual mass.

Lyophilized ICs were visualized under SEM (Fig. 5). Sample porosity was likely caused by the freeze-drying step (IC-3 and IC-6), which can preserve the three-dimensional structure of the materials as they are frozen. IC-4 showed gel like structures whereas the IC-3 and IC-6 had a similar sponge-like structure. Finally, we performed cell viability assays using HeLa cells to test the biocompatibility of the ICs, which is necessary for drug delivery applications. The results showed that the ICs were nontoxic, as HeLa cells remained viable after 12 h of co-incubation with the grafted polymers, even when their concentrations were 100 μg/mL in the cell medium, which we believe was due to using the nontoxic HA biomolecular backbone and CD molecules (Fig. S13).

4. Conclusion

HA-β-CD is an advanced drug delivery agent using a biomolecular backbone with grafted supramolecular hosts. Reactions parameters, e.g., reaction time and HA:DPC:β-CD ratios were varied to obtain different polymer derivatives to optimize VE complexation. Increasing the β-CD ratios enhances the VE loading capacity and water solubility. The cell viability assay showed the biocompatibility of the inclusion complexes. Other therapeutic properties, such as VE release kinetics and stability in the GI tract are very important and will be studied in ongoing work. Nevertheless, even with the demonstrated excellent solubility enhancement, drug loading capacity, and biocompatibility, the HA-β-CD polymer is promising for various therapeutic and cosmetic applications.

CRediT authorship contribution statement

Parbeen Singh: Conceptualization, Methodology. **Li Wu:** Software. **Xiaohong Ren:** Validation. **Wei Zhang:** Software. **Yan Tang:** Software. **Yongli Chen:** Writing - Review & Editing. **Andrew Carrier:** Writing - Review & Editing. **Xu Zhang:** Supervision. **Jiwen Zhang:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2020.119542.

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