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RESEARCH

Preparation of β-Cyclodextrin Conjugated, Gelatin Stabilized SBA 15-$CuInS_2$/ZnS Quantum Dot Nanocomposites for Camptothecin Release

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Abstract
Camptothecin (CPT) is a potential anticancer drug. However, it faces challenges due to its poor water solubility and the need for an efficient drug release system. Herein, we developed a novel system composed of gelatin stabilized, mesoporous silica SBA15 encapsulated $CuInS_2$/ZnS (CIS/ZnS) quantum dots (QDs) conjugated with β-cyclodextrin (β-CDs) for its potential use in the release of CPT. In this multifunctional system, β-CDs served as the drug carrier, SBA15 encapsulated QDs is capable of imaging and the gelatin was used to enhance the carrier-drug interaction. Fourier transform infrared (FTIR) analysis confirmed the successful conjugation of β-CDs to the Gel-SBA15 CIS/ZnS QDs, while optical analyses revealed excellent emission properties and high photostability. The β-CD-conjugated Gel-SBA15-CIS/ZnS QD nanocomposite was used to obtain the soluble derivate of CPT which further demonstrated a drug release profile following the triphasic model. Overall, the improved photostability and acceptable drug release profile of the β-CD conjugated Gel-SBA15-CIS/ZnS QD nanocomposite hold great promise for both imaging and therapeutic applications.

Keywords Quantum dots · Mesoporous silica · Photostability · Drug delivery

1 Introduction

Ternary chalcopyrite quantum dots (QDs) have emerged as a promising platform for biomedical applications, including bioimaging, photodynamic therapy, and cell and tissue targeting, due to their favourable intrinsic optical properties and biocompatibility [1]. However, their practical use is limited by their instability in ambient conditions and low photoluminescence quantum yields (PLQYs) [2, 3]. To address these issues and enhance their fluorescence, inorganic shells with wider bandgaps, such as ZnS, are frequently used to coat the QDs [4–8]. Despite the presence of surface stabilizing agents, QDs are still vulnerable to environmental factors, which can compromise their stability. Therefore, there is a critical need for an encapsulating or passivating agent, such as mesoporous silica, that can protect the fluorescent properties of QDs. The use of mesoporous silica (Santa Barbara Amorphous 15, SBA15) has been demonstrated to improve the stability and biocompatibility of the QDs [9–12].

Creating a multifunctional system that can perform imaging and drug delivery concurrently is desirable to increase its versatility [13–15]. For instance, by conjugating a chemotherapeutic drug to the silica composite, it can be directed to the tumour site for simultaneous imaging and drug delivery [16, 17]. Camptothecin (CPT) has been used as an anticancer drug and has been reported to have significant activity on ovarian and colorectal tumours [18]. CPT is an alkaloid

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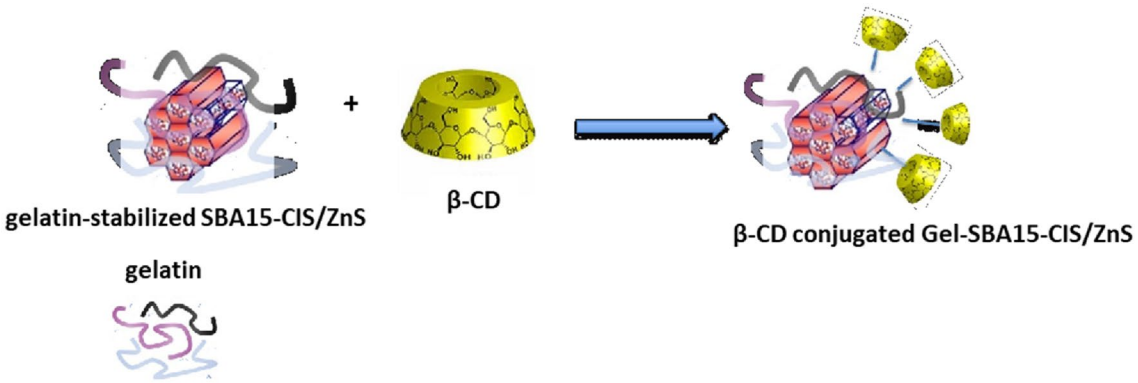

Scheme 1 Schematic representation of conjugation of β-CD with gelatin-stabilized SBA15-CIS/ZnS QD composites

that is isolated from Camptotheca acuminata and is known to inhibit topoisomerase I, thereby suppressing the proliferation of cancer cells. However, CPT faces several challenges, including instability at physiological pH and hence various drug carriers are being investigated to address this issue [19, 20]. Cyclodextrin (CD) has gained much interest among various drug carriers due to its good interaction with hydrophobic guest molecules. CDs are a family of cyclic oligosaccharides composed of glucose units and are characterized by their unique cone-like molecular structure, which consists of a hydrophobic cavity and a hydrophilic exterior. Among the different cyclodextrins, β-CD which contains seven glucose units is widely investigated as drug carriers because its cavity diameter is similar to the size of many biomolecules including CPT [21, 22]. Nevertheless, β-CD suffers from poor solubility in water, highlighting the need for modifications to enhance its solubility and optimize its potential as a drug carrier. Conjugation of β-CD with biopolymers such as gelatin has been demonstrated as an effective approach to improve its water solubility. This conjugation strategy not only addresses the solubility issue but also enhances the complexation capabilities of β-CD, making it a promising option for various drug delivery applications [23, 24].

Building upon the aforementioned considerations, our present study focuses on the development of a novel theranostic agent with substantial capabilities in both imaging and drug delivery. Previously, we reported on the synthesis of gelatin-stabilized SBA15-CIS/ZnS QDs composites, where the gelatin stabilization resulted in significant improvements in the photoluminescence (PL), durability, and photostability of the composites [12]. In this work, we present a protocol for conjugating the gelatin-stabilized silica-QDs composites with a drug carrier β-CD. Through the utilization of FTIR spectroscopy and PL spectroscopy, we investigated the conjugation process and evaluate the resulting optical properties. We then achieved a soluble CPT derivative by loading it into the β-CD-conjugated Gel-SBA15- CIS/ZnS QDs composite. To assess the potential of the conjugates as a drug delivery system, we conducted drug release studies. The results of this study demonstrated the promising potential of the β-CD-conjugated Gel-SBA15-CIS/ZnS QDs composite for simultaneous dual imaging and drug delivery applications.

2 Materials and Methods

2.1 Materials

Gelatin, β-Cyclodextrin, camptothecin (CPT), PBS buffer, and ethanol used in this study were purchased from Sigma Aldrich, South Africa. All chemicals were of analytical-grade and utilised without additional purification. All of the experiments utilised double-distilled water.

2.2 Conjugation of β-Cyclodextrin with Gelatin-Capped SBA15-CIS/ZnS QDs Composites

In brief, amine-functionalized SBA15 and CIS/ZnS QDs were used to synthesize SBA15-CIS/ZnS QDs composites following a previously described procedure [12, 25]. The composites were then purified by washing out excess QDs and centrifugation. The composite was mixed with an aqueous gelatin solution at a 1:1 ratio (50 °C) for 6 h to stabilize it with gelatin. After centrifugation, the resulting SBA15-CIS/ZnS QDs composites were dispersed in water.

The conjugation of β-CD with the Gel-SBA15-CIS/ZnS QD composites was performed according to Scheme 1. First, 100 mg of β-CD was dissolved in 10 mL of double-distilled water. Then 100 mg of the Gel-SBA15-CIS/ZnS QD composites were dissolved in 1.5 mL of PBS (pH 7) solution. This solution was added to the β-CD solution under continuous stirring at 1000 rpm for 3 h. The resulting suspension

was then purified by centrifugation at 4000 rpm for 15 min. Finally, the obtained composite was dried at 37 °C for 24 h.

2.3 Characterization

The photoluminescence spectra were recorded using Shimadzu, Japan (RF-6000) spectrophotometer. Fourier transform infrared spectroscopy (FTIR) analysis was carried out in the spectral region of 4000 cm^{-1} to 400 cm^{-1} using Spectrum two UATR spectrometer, Perkin Elmer, UK. The morphologies of the synthesized samples were determined using a field emission scanning electron microscope (FESEM, Carl Zeiss). For the absorption measurement, a Perkin Elmer Lambda 25 Ultraviolet-visible (UV–Vis) spectrophotometer was employed.

2.4 Preparation of Drug-Loaded Composites

40 mg of β-CD-conjugated Gel-SBA15-CIS/ZnS QD and 2.0 mg of CPT were dissolved in a mixture of PBS and ethanol. The mixture was stirred constantly for 24 h at 50 °C (in the dark). After 24 h, the supernatant was analysed using UV–Visible spectroscopy to check the presence of a CPT trace. Following complete evaporation of the ethanol in a vacuum, the suspension was filtered. Finally, the product was lyophilized and made into powder. The drug-loaded composite powder was highly dispersible in water.

2.5 In Vitro Drug Release Studies

To determine the in-vitro release pattern of CPT from the composite, a release study was conducted in PBS solution at pH 7.4. The CPT-loaded composite (5 mg) was placed into a dialysis membrane with a molecular weight cut-off of 12,000 Da containing 5 mL of release medium. The dialysis membrane was then placed in a beaker containing 50 mL of double-distilled water, which was then heated to 37 °C with gentle stirring. At specific time intervals, 2 mL of supernatant was withdrawn from the outer media and replaced with the same volume of fresh double-distilled water. The amount of released CPT was then determined using a UV spectrophotometer.

3 Results and Discussion

Figure 1 shows the FTIR spectra of β-CD, gelatin-stabilized SBA15-CIS/ZnS QDs composite, and β-CD-conjugated gelatin-stabilized SBA15-CIS/ZnS QDs. The spectra of β-CD confirm the characteristic peaks of –CH (2922 cm^{-1}), –C–O–C (1155 cm^{-1}), –C–C (1080 cm^{-1}), and C–O bonds (1030 cm^{-1}). After the conjugation of β-CD with gelatin-stabilized SBA15-CIS/ZnS QDs, the Si–O–Si stretching of

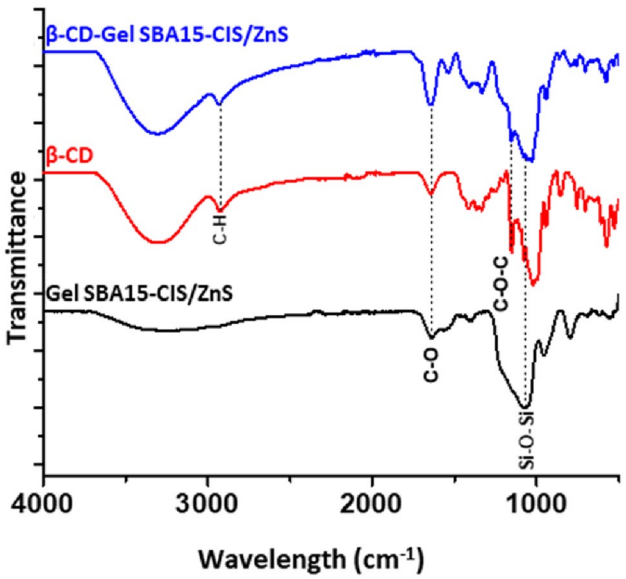

Fig. 1 FTIR spectra of β-CD, Gel-SBA-CIS/ZnS QD composites, and β-CD conjugated Gel-SBA-CIS/ZnS QD composites

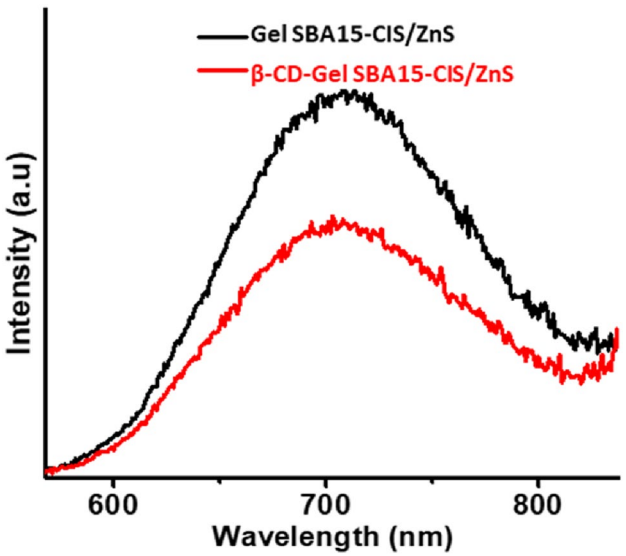

Fig. 2 PL spectra of Gel-SBA-CIS/ZnS QD composites before and after β-CD conjugation

SBA in the composite merged with C–O–C stretching of β-CD with the shift to lower wavenumber, and the transmittance of –C–O stretching increased [19]. In addition, the presence of –CH stretching peak of β-CD was also seen in the conjugate. These results strongly suggested the successful conjugation of β-CD with the gelatin-stabilized SBA15-CIS/ZnS QDs composite.

Figure 2 shows the PL spectra of the Gel-SBA15-CIS/ZnS QDs composites before and after conjugation with β-CD. The maximum emission position of the composites

remained around 710 nm even after conjugation, indicating that the conjugation did not significantly affect the emission wavelength. However, a significant reduction in PL intensity was observed after the conjugation process, which may be attributed to the conjugation between the β-CD and the Gel-SBA15-CIS/ZnS QDs and the reduction of surface functional groups on the composites.

As demonstrated in our previous publications [11, 12], photostability is important for imaging probe like QDs for any long-term biological application. Figure 3 represents the photostability of β-CD conjugated Gel-SBA15-CIS/ZnS QDs composite under continuous excitation at 365 nm. The photostability was measured at regular time intervals. The PL intensity of the composite initially increased by 160% after 1 h of irradiation and gradually dropped to 140% after 4 h. This result shows the applicability of the composites for long-time bioimaging applications along with drug delivery.

In Fig. 4, the FTIR spectra confirm the successful encapsulation of the CPT drug in the β-CD-conjugated Gel-SBA15-CIS/ZnS QDs composites. The reduction in hydroxyl stretching vibration at 3,336 cm^{-1} is indicative of hydrogen bonding between the drug and β-CD, which suggests successful loading of CPT. The PL emission spectra of the drug-loaded composites were also analysed and shown in Fig. 5. After the loading of CPT in the β-CD capped Gel-SBA15-CIS/ZnS QDs composites, there was a blue shift in emission position from 706 nm to 686 nm without significant change in emission intensity.

The morphology of the CPT drug-loaded samples was analyzed using FESEM (Fig. 6). The micrograph shows rod-shaped morphology attributed to the SBA15 in the composite. These rods seem to aggregate together as a sphere possibly by the presence of gelatin.

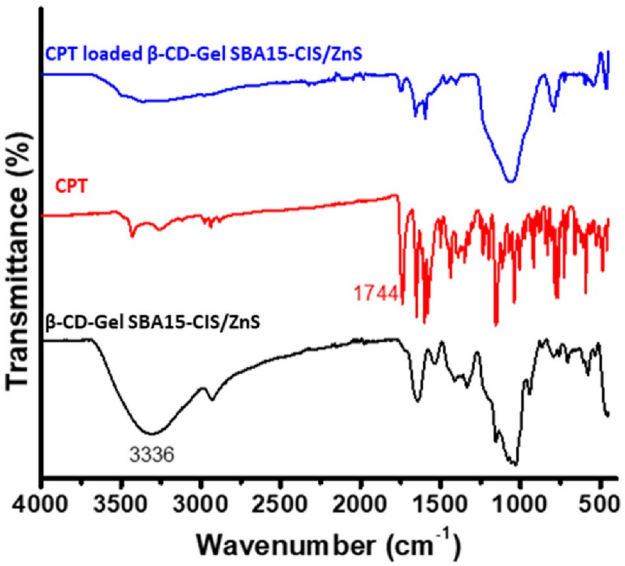

Fig. 4 FTIR spectra of CPT, β-CD conjugated Gel-SBA15-CIS/ZnS QD composites and corresponding CPT loaded composite

3.1 In-Vitro Drug Release

Administering drugs through gradual release is crucial for maintaining therapeutic levels in the body or specific target tissues over a specific period. Figure 7 shows the release

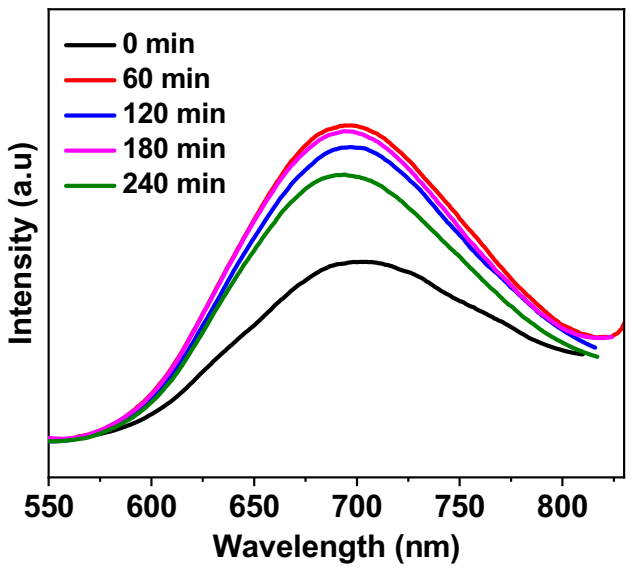

Fig. 3 PL spectra of β-CD conjugated Gel-SBA15-CIS/ZnS QD composites under UV light

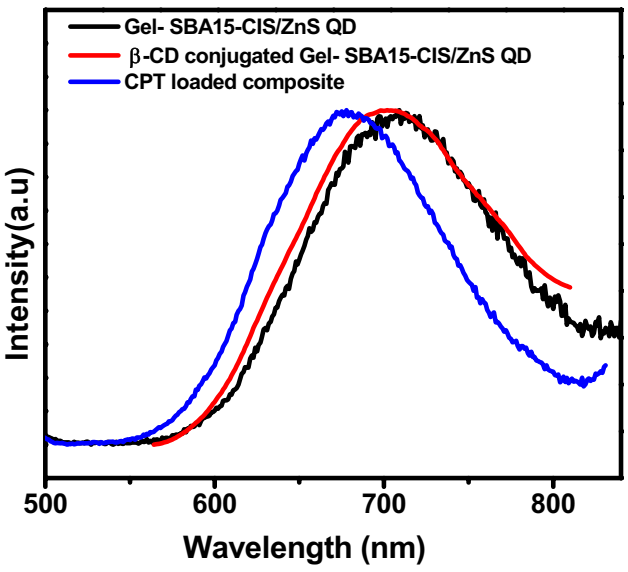

Fig. 5 PL spectra of Gel-SBA15-CIS/ZnS QD composites, β-CD conjugated Gel-SBA15-CIS/ZnS QD composites and the corresponding CPT loaded composites

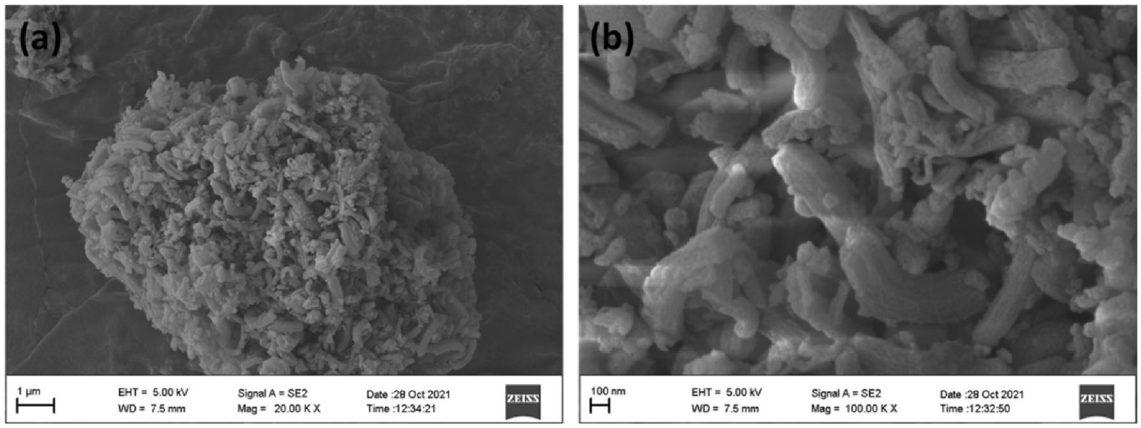

Fig. 6 FESEM images of CPT loaded β-CD conjugated Gel-SBA15-CIS/ZnS QDs composites at **a** low (20 K) and **b** high (100 K) magnification

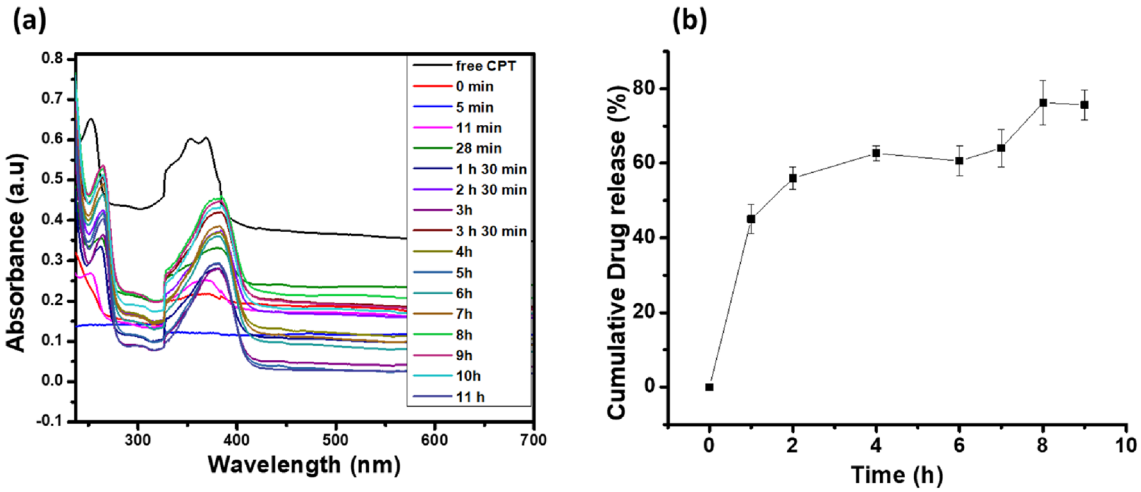

Fig. 7 **a** In vitro CPT drug release analysis by UV–Vis absorption spectra and **b** its cumulative drug release graph

profile of the CPT drug from the conjugate at pH 7.4 and demonstrated an initial burst release of approximately 45% within the first hour. Subsequently, a controlled release of an additional 15% of the drug was observed over the next five hours. From 6 to 8 h, a sudden release of 20% was observed which was eventually slowed down. This could be attributed to the erosion of the drug carrier β-CD/gelatin at random events thereby indicating that the drug release follows a triphasic model [26–28]. The change in the spectral shape of the released CPT drug from the nanocarrier was also observed, with the free CPT in ethanol solution displaying shoulders corresponding to electronic transitions occurring in the organic lactone function. However, when released into PBS buffer at pH 7.4, the lactone function may undergo hydrolysis, resulting in the generation of carboxylate moieties and a reduction in the shoulders observed. This, in turn, leads to broadband at 365 nm[29].

4 Conclusions

In summary, we have successfully prepared a novel onjugate of β-cyclodextrin (β-CD) with gelatin-stabilized SBA15 encapsulated ternary chalcopyrite $CuInS_2$/ZnS quantum dots (QDs). This conjugate was employed as a drug carrier for the anticancer drug camptothecin (CPT). The conjugation process and drug loading were confirmed using FTIR spectroscopy. The optical analysis indicated that the resulting conjugate maintains its red emission of QDs and exhibited excellent photostability under irradiation. In vitro drug release studies indicated that the release profile follows a

triphasic model with 80% of the drug released over a period of 9 h. These findings indicate that the reported β-CD conjugated SBA15-QD composites hold promise for simaltaneous imaging and drug delivery applications.

Author Contributions Conceptualization, OSO; Data curation, JR; Formal analysis, JR, VPRR, TL, RM and OA; Funding acquisition, OSO; Investigation, JR; Methodology, JR; Project administration, OSO; Resources, OSO and ST; Software, JR; Supervision, ST and OSO; Validation, SP; Visualization, OSO; Writing—original draft, JR; Writing—review & editing, SP and OSO.

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Data Availability Data are available on request.

Declarations

Conflict of interest No conflict of interest to declare.

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