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MDPI

Hyaluronic acid-functionalized $CaCO_3$ crystals as novel polyelectrolyte multilayer reservoirs for CPT-RB (Chemotherapy and Photodynamic therapy) targeting multiple myeloma

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INTRODUCTION & AIM

Multiple myeloma (MM) means clonal expansion of a malignant B-cell neoplasm characterized by destructive growth of mutated plasma cells within the bone marrow [1]. Multiple myeloma comprises 1% of all cancers worldwide and approximately 10% of all hematologic malignancies [2]. In 2023, an estimated 35,730 persons (19,860 men and 15,870 women) in the United States were recognized to have multiple myeloma, and more than 12,000 patients died from the disease [3]. In the UK, myeloma is the 19th most common cancer diagnosed, with 2% of all new cancer cases (2016-2018). Since 5700 new cases were diagnosed with myeloma in the UK per year, and around 3000 deaths each year [4]. In Ireland, around 380 patients are diagnosed per year [58]. According to the Canadian Cancer Society, 4000 residents were diagnosed with Multiple myeloma in 2022 [5].In 2016, there were about 130,000 cases of myeloma, translating to an age-standardized incidence rate of 2.1 per 100,000 persons. Multiple myeloma caused 98,437 deaths globally, with an age-standardized incidence ratio of 1.5 per 100,000 persons [6]. Therefore, the incidence cases of myeloma increased globally from 1990 to 2016 by 126%, and the percentage of patients dead from myeloma reached 94% [7]. In Turkey, the incidence is approximately four cases per 100,000 people. An average of around three thousand multiple myeloma diagnoses are made each year [8]. The current clinical treatment options for MM are limited to radio- and chemotherapy (principally bortezomib) regimens after surgical resection; however, recurrence is almost inevitable [9]. Various factors, including soluble factors, physical contact between myeloma and stromal cells, and interactions with the bone marrow extracellular matrix, may influence the survival and growth of multiple myeloma (MM) [10]. For instance, IL-6 secreted by stromal cells has been demonstrated as a survival molecule for multiple myeloma through cell surface mediators such as CD56, fibronectin, and particularly CD44 [11].

Our aim here is to fabricate polyelectrolyte multilayered nanocapsules loaded with chemotherapeutic agents and photosensitizers (**Camptothacin** and **Rose Bengal**) to target multiple myeloma.

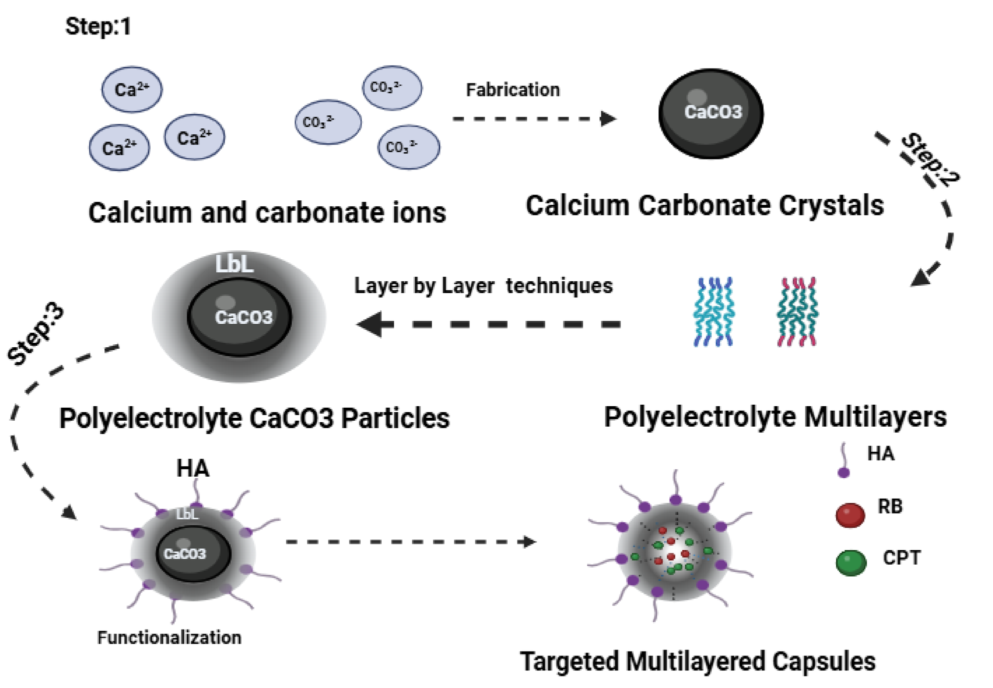
To achieve this purpose:

1. Soyasaponin was isolated and inserted into the moieties of capsules as an intermolecular mediator.

2. Hyaluronic acid is used to target CD44 overexpressed in multiple myeloma cells.

3. Two pairs of (chitosan/polyacrylic acid) and (polydopamine/hyaluronic acid) used as polyelectrolyte multilayers.

METHOD



Scheme 1: Illustrates the Fabrication of CaCO3 particles and Drug loading
2. Fabrication of (CHI/PAA) and (PDA/HA) multilayers 3. Core removal

RESULTS & DISCUSSION

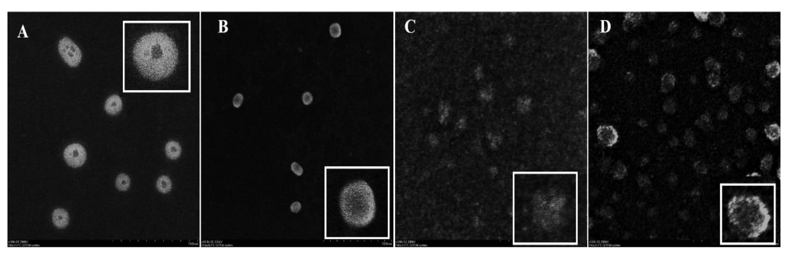


Figure 1: TEM images showed the structure of multilayered capsules. A) Multilayered capsules-SS1. B) Multilayered capsules-SS1-CPT. C) Multilayered capsules-SS1-RB. D) Multilayered capsules-SS1-CPT-RB.

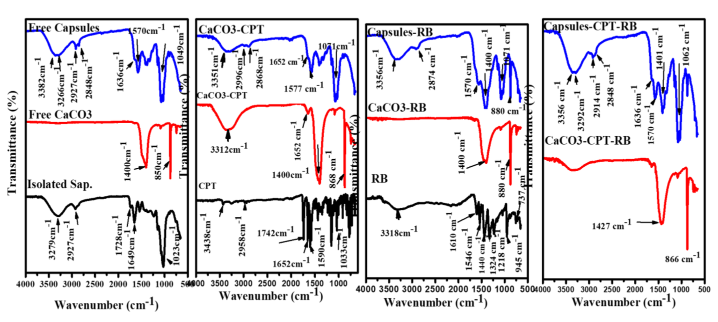


Figure 2: FTIR spectra observed a characteristic band of SS1, CaCO3, CPT, RB, and the combination.

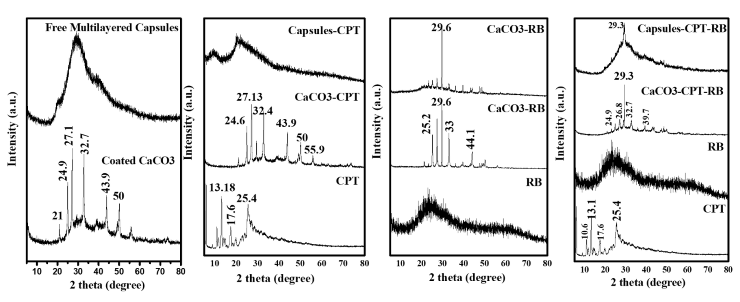


Figure 3: The XRD diffraction showed the crystalline structure of CaCO3, CPT, RB.

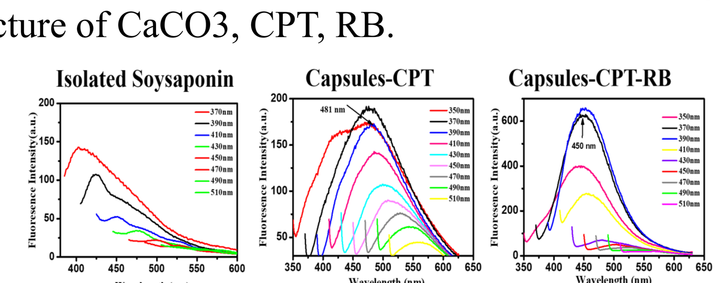


Figure 4: Photoluminescence spectroscopy showed fluorescence emission of isolated SS1 (A), Encapsulated CPT(B) and Encapsulated-CPT-RB (C)

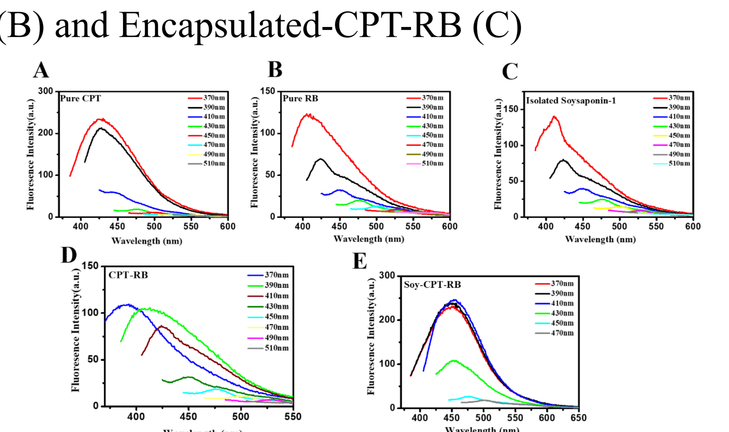


Figure 5: Photoluminescence spectroscopy showed the fluorescence emission of CPT pure (A) and RB pure (B) mixing with isolated SS1.

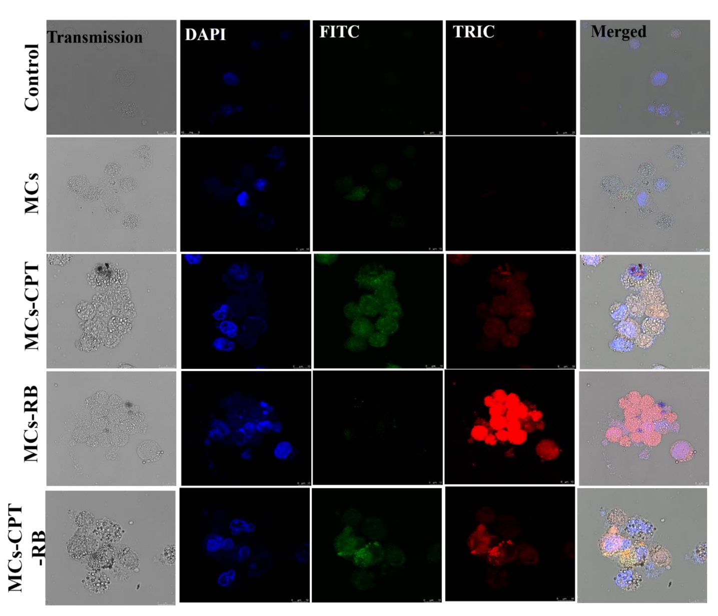


Figure 6: Laser Scanning Confocal Microscopy illustrates the cellular uptake of Multilayered Capsules.

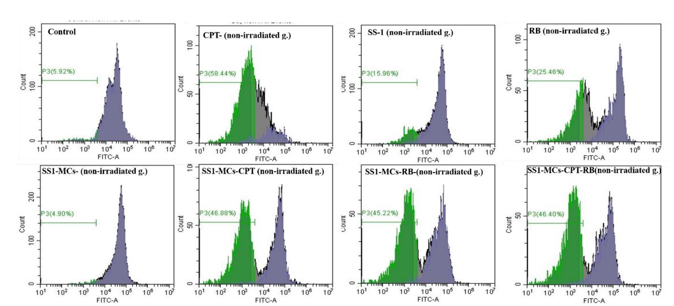


Figure 7: Flow cytometry measurement observed ROS activation in non-irradiated K562 cells after their exposure to CPT, RB, SS1.SS1-MLCs, SS!-MLCs -CPT and SS1-MLCs-CPT-RB.

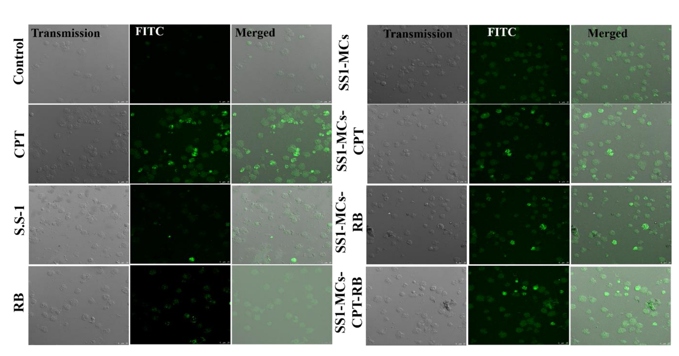


Figure 8: Confocal microscopy images showed fluorescent emission of activated ROS in non-irradiated K562 cells after their exposure to CPT, RB, SS1, SS1-MLCs, SS1-MLCs-CPT, SS1-MLCs-RB, and SS1-MLCs-CPT-RB.

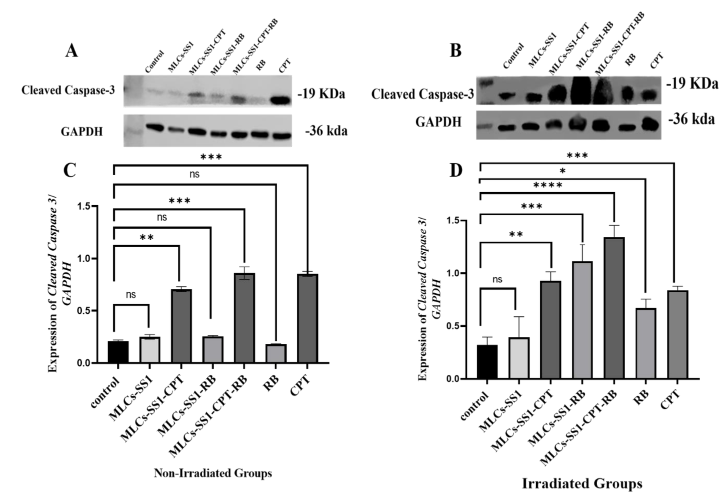


Figure 9: Western blot bands of non-irradiated samples (A). Western blot bands of irradiated samples (B).Expression level of Cleaved Caspase-3 of non-irradiated samples (C) and Expression level of Cleaved Caspase-3 of irradiated samples (D).

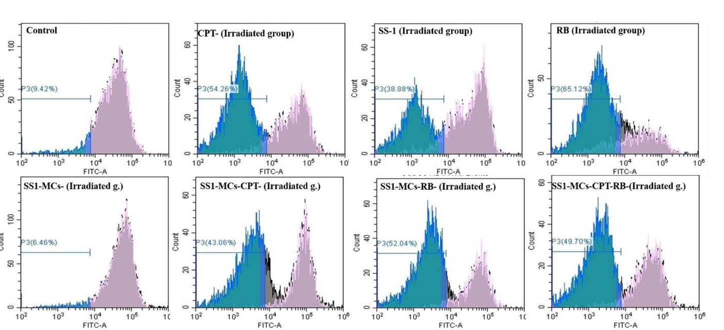


Figure 10: Flow cytometry measurement showed ROS activation in irradiated K562 cells after their exposure to CPT, RB, SS1,.SS1-MLCs, SS1-MLCs –CPT, SS1-MLCs –RB, and SS1-MLCs-CPT-RB.

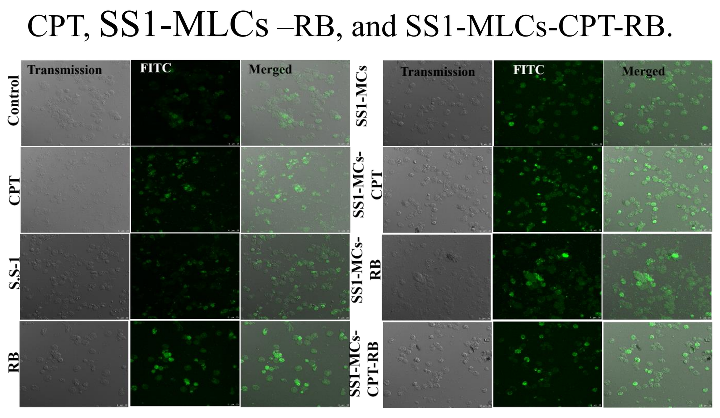


Figure 11: Confocal microscopy images showed fluorescent emission of activated ROS in non-irradiated K562 cells after their exposure to CPT, RB, SS1,.SS1-MLCs, SS!-MLCs –CPT, SS!-MLCs –RB, and SS1-MLCs-CPT-RB.

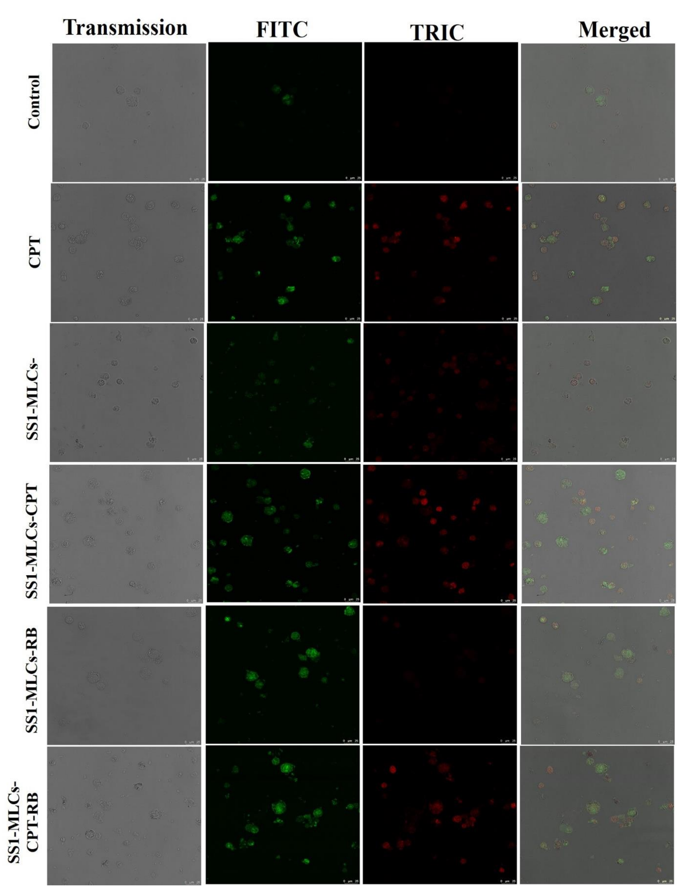


Figure 12: Laser Scanning Confocal Microscopy images illustrated the morphological appearance of non-irradiated multiple myeloma after incubation with nanomaterials using AO and EB stains

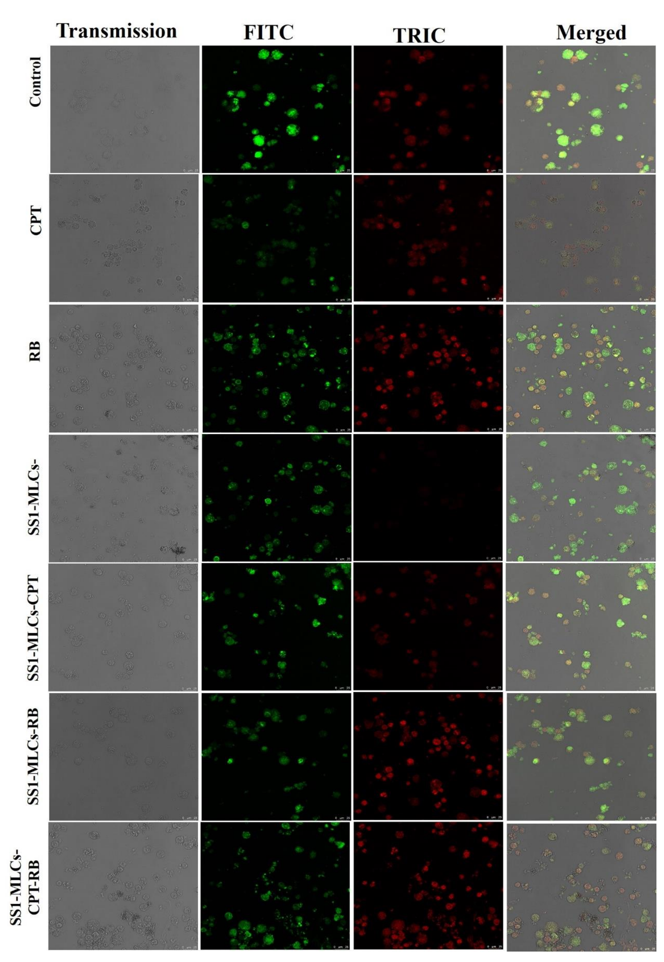


Figure 13: Laser Scanning Confocal Microscopy images observed the morphological appearance of irradiated multiple myeloma after incubation with nanomaterials using AO and EB stains.

Discussion

In the current study, TEM images revealed the crystal structure of CaCO3, incorporating CPT into its tiny crystal. The spherical multilayered capsules were obtained after dissolving the CaCO3 crystals using EDTA solution. The FTIR spectra showed incorporation of CPT and RB inside the moieties of multilayered capsules. The XRD diffraction confirmed the crystalline structure of CaCO3 crystals. An amorphous structure appeared after their core removal. The stretching vibration of carbon-carbon in the aromatic ring at 1400 cm-1 confirmed the incorporated RB structure in the spectrum of multilayered capsules. Besides, the carbonyl structure of CPT was located at 1636 cm-1 in the spectrum of multilayered capsules -CPT-RB. This spectrum confirms the presence of soysaponin-1 in its characteristic peaks at 1062 cm-1for the C-O-C stretching vibration and the C-H mode at 2914cm-1 and 2848 cm-1. The fluorescence intensity of CPT and RB was detected in MM cell lines treated with Multilayered Capsules-CPT and Multilayered Capsules-RB, respectively, and in combination as well. This finding suggests that Multilayered capsules offered a superior cellular uptake efficiency. The result confirms that hyaluronic acid-targeted CD44 enhanced the cellular accumulation of Multilayered Capsules, and it could be a great promise in targeted drug delivery. They were not absorbed in normal cells, confirming the targeting mechanism.

CONCLUSIONS

A comparison between multilayered capsules loaded with RB or with CPT, and multilayered capsules loaded with a mixture of CPT and RB. The result reveals the enhanced cytotoxicity of the multilayered capsules in the treatment of multiple myeloma cell lines. Clarification was reported on the role of soysaponin-1 in improving the fluorescence quenching process of RB-CPT compared to the Intensity of pure CPT, RB, or even CPT-RB alone. The result showed the greatest application of $CaCO_3$ as a reservoir structure in encapsulating CPT and RB simultaneously or separately.

FUTURE WORK

We will study the drug efficacy, drug distribution, and penetration in an animal model, multiple myeloma

FUTURE WORK/ REFERENCES/ACKNOWLEDGMENT

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