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Research Article

PHYSICS

The cytotoxic effects of cetuximab-loaded egg serum albumin nanoparticles on Caco-2 cells in vitro

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KEY WORDS

Cetuximab (CET), Egg Serum Albumin Nanoparticles (ESA-NPs), X-Ray diffraction (XRD), MTT assay.

ABSTRACT

Cetuximab is a name for a monoclonal antibody against the epidermal growth factor receptor. It is known to raise the median survival rate for people with colon cancer. Using of chemotherapeutic carriers such as egg serum albumin nanoparticles (ESA-NPs), could increase the susceptibility of cancer cells to the chemotherapeutic drugs and increase their toxicity on tumor cells. So, this study aimed to study the effect of the chemotherapeutic drug, cetuximab either alone or loaded on ESA-NPs. Using glutaraldehyde as a crosslinking agent, ESA nanoparticles (ESA-NPs) and cetuximab-loaded albumin nanoparticles (CET-ANPs) were created using the straightforward enhanced desolvation approach. Characterization of nanoparticles and the albumin nanoparticles loaded cetuximab (CET-ANPs) has occurred using X-ray diffraction (XRD) transmission electron microscope (TEM). The cytotoxicity of the cetuximab and CET-ANPs were evaluated against Caco-2 cancer cells in vitro using an MTT assay after 48 hr. The obtained results show that the CET-ANPs have a potent effect on cancer cells with a median lethal dose (IC_{50}) of concentrations, where CET-ANPs were more effective than CET alone after 48 hr. Interestingly, the treatment of target cells with different concentrations of CET and ESA-NPs achieved higher efficiency in treatment. In conclusion, the present results indicate that loading CET with ESA-NPs showed more efficiency against colon cancer cells, which might be useful for future human treatment.

Introduction

One of the most prevalent cancer types is colorectal cancer worldwide, which continues to be a leading cause of cancer-related death in both men and women **(Kamangar *et al*., 2006)**. The most significant limitations of traditional remedy, such as radiation treatment and chemotherapy, are their toxicity and lack of tumor specificity **(Kelloff *et al*., 2006)**. Recent studies are looking into new therapeutic options like immunotherapeutic methods, which take advantage of the body's built-in defenses and can trigger immune responses specific to a given type of tumor.

About two-thirds of an egg's weight is made up of egg white. The remaining 10% is made up of protein, trace minerals, fatty substances, vitamins, and glucose with about 90% of it being water **(Sharif *et al*., 2018)**. One raw large U.S. egg contains about 33 grams of egg white, 3.6 grams of protein, 0.24 grams of carbohydrate, and 55 milligrams of sodium. There are roughly 17 k calories in it, and it is free of cholesterol. Interestingly, the egg white is made up of about 149 proteins, for instance; ovalbumin (OVA) (55%), Ovomucin (3.5%), lysozyme (3.4%), ovomacroglobulin (0.5%), Ovotransferrin (12%), ovomucoid (11%), ovoglobulin (4%), ovomucin (3.5%), and other less common proteins are present. **(Karami *et al*., 2020)**.

Improved survival has resulted from the use of novel biological treatments for patients with metastatic disease, such as monoclonal antibodies **(Klapper *et al*., 1999)**. Targeting the A promising method for treating cancer is epidermal growth factor receptor (EGFR), which is overexpressed in a variety of solid tumors and is linked to the onset of the disease **(Arsene *et al*., 2006).** Epidermal growth factor receptors (EGFR) are the target of cetuximab, a chimeric monoclonal antibody, which works by competitively blocking EGFR's native ligands, promoting EGFR internalization, and altering EGFR-dependent signaling. Most of the advanced squamous cell skin cancer, non-small cell lung cancer (NSCLC), EGFR-expressing, and colorectal cancer with KRAS mutations are among the FDA's unapproved uses for cetuximab **(Oliveira-Silva *et al*., 2016; Chidharla *et al*., 2022).**

Additionally, cetuximab has a variety of side effects that are linked to how it affects healthy cells, as well as a papulopustular rash (acne-like) that appears in 80–86% of patients while xerosis, eczema, fissures, telangiectasia,

hyperpigmentation, and changes to the nails and hair happen lower frequency **(Štulhofer *et al.*, 2016)**.

Because it helps to maintain intravascular colloid osmotic pressure, remove toxins, and transport medications, albumin is one of the most crucial proteins in the body and the egg. Thus, the key goal is the preparation of optimal nanoparticles to drive the cetuximab drug having the ability to overcome cancer thereby using natural substances such as albumin.

Material and methods

Chemicals

Egg serum albumin (ESA) powder with analytical grade From ALPHA CHEMIKA (Mumbai, India), 95.2% (CAS no.9006-59-1) was obtained. PBS pills (PREPARING PBS 1X BY VOLUME: Phosphate-buffered saline (PBS) is an isotonic solution that is used in many biological research applications. To make 1L of PBS, add 100 mL of 10X PBS to 900 mL of water. This PBS recipe contains 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, and 1.8 mM KH_2PO_4). From Oxoid Limited in Basingstoke, Hampshire, England, where they were purchased. Each PBS tablet was dissolved in 100 ml deionized H_2O to obtain a solution with pH 7.3. Eli Lilly and Co., USA Indianapolis, Indiana, provided the drug cetuximab (Erbitux). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), was purchased from (Sigma-Aldrich Inc., St. Louis, MO, USA), Ethanol obtained from Sigma Aldrich (USA).

Preparation of Cetuximab-loaded egg serum albumin nanospheres and egg serum albumin nanoparticles (ESA-NPs) (CET-ANPs) using the desolvation method

Desolvation methods have many benefits, including easy preparation, quick reaction times, and no need to add surfactants. It is the currently most popular method for creating albumin nanoparticles and is suitable for encapsulating various hydrophobic drugs **(Salim *et al*., 2022).** After freeze-drying, nanoparticles can be kept for a long time and then resuspended for further processing, such as drug adsorption or covalent modification of specific ligands on the particle surface. Desolvation-produced nanoparticles have received much attention in recent years for their potential as antitumor agents **(Meng *et al*., 2022)**. The desolvation method produced doxorubicin-loaded human serum albumin nanoparticles exhibiting strong antitumor activity **(Kimura *et al*., 2019)**. A type of BSA nanoparticle was created by Ziaaddini *et al*., using the desolvation method, which can improve the effectiveness and lessen the cytotoxicity of anticancer drugs

(Ziaaddini *et al.*, 2020). Breast cancer cells can be targeted by Chitosan-decorated HSA nanoparticles produced by desolvation **(Akbarian *et al.*, 2020)**. 40mg of ESA was dissolved in 10mM NaCl (pH 8.5), and after stirring for 5 min 32 mL of 90% ethanol was added to the mixture till turbidity occurred. As a crosslinking agent, glutaraldehyde (12l/mL) was added with stirring overnight. The nanoparticles were centrifuged three times before being washed in deionized water **(Ye *et al.*, 2021)**.

To prepare cetuximab-loaded ESA-NPs (CET-ANPs), 80 mL of double-distilled water was used to dissolve 50 mg of ESA. After 15 minutes of stirring and 10 minutes of sonication. Following that, 10 ml of 0.9 % saline was used to dilute 4 ml of 20 mg CET before adding it to the ESA solution. 5 ml of ethanol (99%) was added after 30 minutes of stirring, and the CET-loaded ESA-NPs were maintained for freeze-drying and lyophilization **(Karami *et al.*, 2020)**.

Characterization

The characterization of pure ESA and ESA-NPs was investigated by XRD and TEM.

X-ray diffraction (XRD)

An X-ray diffraction instrument was used to examine egg serum albumin (GNR analytical X-ray diffraction, APD 2000 PRO Italy). CuKa1 radiation (= 1.540598 nm) was used for X-ray analysis between 5° and 90° (2). The current and voltage used were 34.97 kV and 34.75 mA, respectively. To eliminate the interference peak, a K -a beta filter was also used. The samples were placed in a sample holder, and the measurement was carried out indefinitely. Before each analysis, standard curves were checked **(Ullah *et al.*, 2020)**.

Transmission Electron Microscope (TEM)

To prepare the prepared NP samples, 1 ml of the dispersion was diluted with the solvent and sonicated for 5 minutes before to TEM examination. Then, some NP in microliters solutions sprayed to a conventional TEM carbon-coated Cu-grid, the solvent was allowed to completely evaporate within 15 minutes, and then the Cu-grids were stained with an aqueous solution of phosphor tungstic acid. A JEOL JEM 2100 TEM microscope operating at 200 kV was used to image the samples after the grid had been thoroughly air-dried **(Abbasi *et al.*, 2011)**. The cancer cell lines Caco-2 (Cancer coli-2) was established from a human colorectal adenocarcinoma by Jorgen Fogh at the Sloan-Kettering Cancer Research Institute.

MTT assay for cell viability in 48 hr

Caco-2 colon cancer cells shown to be viable were assessed at serial concentrations of pure ESA and pure CET (0, 12.5, 25, 50, 100, and 200 µg/mL), as well as the impact of ESA-NPs and CET-ANPs on tumor cell growth, was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl-tetrazolium-bromide (MTT; Assay by Sigma-Aldrich Inc., St. Louis, Missouri, USA). This test is based on the reduction of yellow MTT to purple formazan in the presence of mitochondria **(Hanafy *et al.*, 2020)**.

Briefly, after 48 hr, a 5 mg/mL MTT reagent was applied to each well after drug exposure to cells at earlier doses, and the reaction was then allowed to run for 3–4 hours at 37°C. The precipitated formazan crystals were then dissolved in 200L of DMSO after the culture medium was taken out of the equation. Using a microplate multi-well reader, the absorbance of each well was determined at 570 nm and was directly correlated with the quantity of living cells still present. A percentage of the vehicle-treated data was used to standardise absorbance data control and graphed. Using the probit analysis, the outcomes were utilised to determine each drug's or NP's IC_{50} values (SPSS, Ver 22, SPSS incorp, Chicago, U.S.A).

Results

Characterization of ESA-ESA-NPs

The obtained egg serum albumin was characterized by using XRD, TEM, and cytotoxicity by MTT assay as follows:

X-ray diffraction (XRD)

The crystalline structure of egg serum albumin was investigated using X-ray diffraction. The X-ray diffraction pattern revealed that the egg serum albumin was amorphous and resembled egg serum albumin nanoparticles (Fig. 1). Graph B showed that egg serum albumin had two distinct peaks at 2 (10-21), whereas graph A showed that egg serum albumin nanoparticles had two distinct diffraction peaks at 2 (10-21).

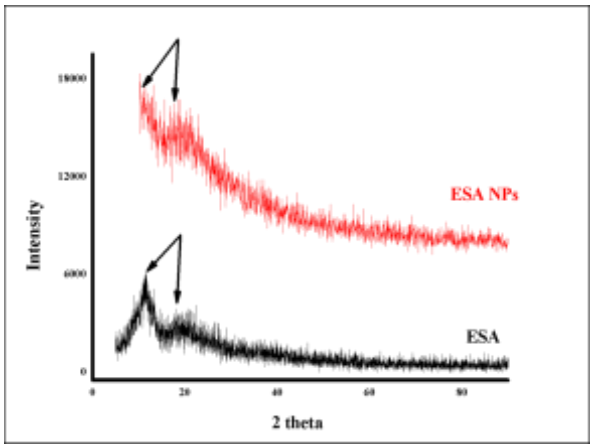

Fig. (1): X-ray diffraction pattern of ESA-NPs (upper curve) and ESA (lower curve).

Morphology of nanoparticles by Transmission Electron Microscopy (TEM)

By using a desolvation method, the current study was prepared in the ESA-NPs. A cross-link network structure was produced as a result of CET incorporated

when ethanol is present, into the moieties structure of ESA. The creation of core-shell spherical nanoparticles with average diameters of about 29 nm and unique properties in mono dispersion and repulsing condition was another outcome. The 3D shape of the CET-ANPs speared in the TEM electron micrographs shows that the NPs were strongly cross-linked and that CET could interact with the chemical makeup of ESA by ionising interaction through amino, carboxyl, and intermolecular hydrogen bonds (Fig.2).

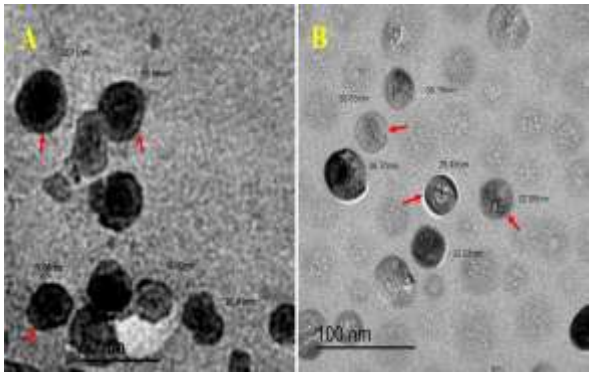

Fig. (2): Transmission electron micrograph showing images demonstrating the ESA-nano-spherical ANPs' shape and size quantification (A), and an electron micrograph confirming the nano-spherical CET-ANPs in a 3D shape with a core-shell cross-link is shown in the magnified portion (arrow) (B).

In vitro studies

The cytotoxic activity of CET, ESA, ESA-NPs, and CET-ANPs against human colon cancer in vitro cells, Caco-2 was evaluated using MTT assay. The results showed that, Caco-2 cells were much less proliferative than other cell types, according to decreased by 450.005%, 600.005%, and 300.01% ($p < 0.05$) after 48 hours of exposure to 200 g/mL respectively of CET, ESA-NPs, and CET-ANPs (Fig. 3). The values of IC_{50} for pure ESA, pure CET, ESA-NPs, and CET-ANPs are (200 g/ml, 190 g/ml, 51.2 g/ml, and 101 g/ml), respectively.

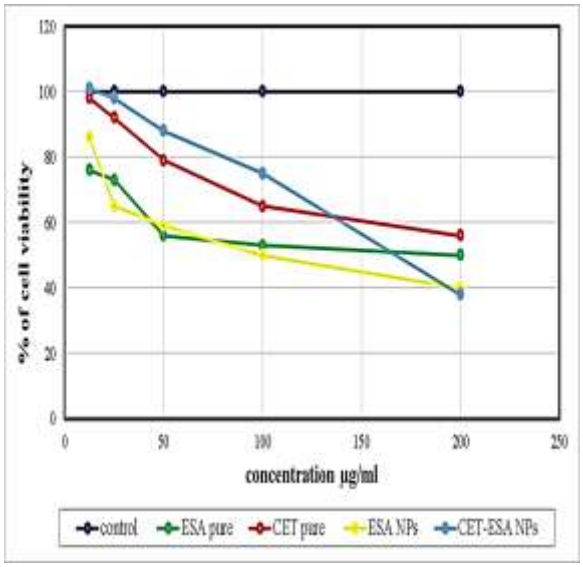

Fig. (3): Caco-2 cells were incubated for 48 hours at various concentrations (12.5 to 200 g/mL) of pure ESA, ESA-NPs, pure CET, and CET-ANPs, and the effect of these concentrations on the rate of cell viability.

Discussion

Targeted drug combinations with cytotoxic drugs are the mainstay of targeted drug therapy for cancer. The timing and dosage of the drug combinations must be optimized, and further study is required to find the biomarkers that can predict a patient's sensitivity to various combination therapies as well as single-agent medications **(Rosenkranz and Slastnikova, 2020)**. Due to its role in cancer proliferation, invasion, metastasis,

and angiogenesis, epidermal growth factor (EGFR) has recently attracted significant interest as a promising biological targeted therapy. In the present study, CET-loaded ESA-NPs displayed well distribution and a spherical shape with a diameter of about 29 nm **(Mahobia *et al*., 2016)**. It was noted that this outcome, which is a result of the aggregation of CET-ANPs in solution, was consistent with the TEM findings. Also, the ESA NPs have the same result.

Additionally In the current study, egg serum albumin was compared to egg serum albumin nanoparticles in our study using x-ray diffraction (XRD), which showed a few typical diffraction peaks and produced ESA that was slightly crystalline. Similar research found that ESA's low crystallinity had a readily bioavailable state, enabling nanoparticles to release drugs quickly **(Zhu *et al*., 2010)**.

Growth factors bind to particular membrane receptors to control cell homeostasis and proliferation. One EGF receptor, known as EGFR, is frequently linked to the biology of human epithelial malignancies as well as it is overexpressed in a number of cancers **(Hubbard *et al*., 2005; Hynes *et al*., 2005)**. Due to the EGFR signalling pathway's involvement in the development of colorectal cancer, here, we analysed the MTT assay and the effect of using different concentrations of (CET -ANPs, pure ESA, pure CET, and ESA NPs) on the response of caco-2 cell lines to treatment **(Hynes *et al*., 2009)**. We noticed the following serial concentrations for 48 hours: 12.5, 25, 50, 100, and 200 µg/ mL. The growth of Caco-2 was significantly inhibited CET-ANPs ($P \leq 0.001$) by 101 ± 0.0, 98 ± 0.01, 88 ± 0.01, 75 ± 0.02, 38 ± 0.01 respectively. While, ESA displayed a considerable inhibition $P \leq 0.001$ to Caco-2's growth by 76±0, 73±0.01, 56±0.01, 53±0.01, 50±0.01 respectively. Because ESA has a high toxicity rate because it contains, Ovotransferrin which is toxic, increased the cytotoxic activity against various cancer cells, this makes its ability to eliminate Caco-2 cells higher, and thus this makes it a good target for cancer cells **(Rathnapala *et al*., 2021)**.

Also, cells were treated with cetuximab and, specific to EGFR, to assess the role of the EGFR receptor on Caco-2 cell viability. After plating the cells or while they were momentarily suspended before plating, antibodies were introduced alone so, CET significant inhibition $P \leq 0.0001$ for Caco-2 by 98 ± 0.01, 92 ± 0.1, 79 ± 0.08, 65 ± 0.05, 56 ± 0.1 respectively. After 48 hours, Caco2 cells' growth was

inhibited and almost similar results were obtained by **(Luca *et al*., 2014)**.

Finally, ESA NPs significant inhibition $P \leq 0.0001$ for Caco-2 by 86±0.0, 65±0.02, 59±0.05, 81±0.5, 45±0.0 respectively.

Conclusion

Based on the identification of biological indicators of possible responsiveness to agents that induce cetuximab, we think that the best patient selection for the use of EGFR-targeted drugs will depend on this. Additionally, cetuximab has an impact on Caco-2 colon cancer cells. Using ESA NPs as a carrier improved particle cell penetration and increased cellular internalization. CET-ANPs were more effective than pure CET in terms of their anti-tumor activity and apoptotic effect. For in vivo studies, these findings represented effective therapeutic strategies.

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التأثيرات السامة للخلايا لجزيئات الألبومين النانوية المحملة بالسيتوكسيماب على خلايا Caco-2 في المختبر

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Cetuximab هو اسم لجسم مضاد أحادي النسيلة ضد مستقبل عامل نمو البشرة. من المعروف أنه يرفع متوسط معدل البقاء على قيد الحياة للأشخاص المصابين بسرطان القولون. يمكن أن يؤدي استخدام ناقلات العلاج الكيميائي مثل الجسيمات النانوية لألبومين مصل البيض (ESA-NPs) إلى زيادة تعرض الخلايا السرطانية لأدوية العلاج الكيميائي وزيادة سميتها على الخلايا السرطانية. لذلك ، هدفت هذه الدراسة إلى دراسة تأثير عقار العلاج الكيميائي سيتوكسيماب إما بمفرده أو محمل على ESA-NPs. باستخدام الجلوتارالدهيد كعامل تشابك ، تم إنشاء الجسيمات النانوية ESA (ESA-NPs) وجسيمات الألبومين النانوية المحملة بـ cetuximab (CET-ANPs) باستخدام نهج الإزالة المحسّن المباشر.

تم توصيف الجسيمات النانوية وجزيئات السيتوكسيماب المحملة بالألبومين (CET-ANPs) باستخدام مجهر انتقال الأشعة السينية (XRD). تم تقييم السمية الخلوية للسيتوكسيماب و CET-ANPs ضد الخلايا السرطانية Caco-2 في المختبر باستخدام اختبار MTT بعد ٤٨ ساعة. تظهر النتائج التي تم الحصول عليها أن CET-ANPs لها تأثير قوي على الخلايا السرطانية بجرعة مميتة متوسطة (IC_{50}) من التركيزات ، حيث كانت CET-ANPs أكثر فعالية من CET وحدها بعد ٤٨ ساعة. ومن المثير للاهتمام أن علاج الخلايا المستهدفة بتركيزات مختلفة من CET و ESA-NPs حقق كفاءة أعلى في العلاج.

في الختام ، تشير النتائج الحالية إلى أن تحميل CET بـ ESA-NPs أظهر كفاءة أكبر ضد خلايا سرطان القولون ، والتي قد تكون مفيدة للعلاج البشري في المستقبل.