Toxicity evaluation of methacryloyloxyethyl phosphorylcholine/selenium nanocomposite on oral squamous cell carcinoma

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Abstract: The Taguchi method was used to determine the optimal conditions for obtaining methacryloyloxyethylphosphorylcholine/selenium (MPC/selenium) nanocomposites and to investigate their anticancer activity on oral squamous cell carcinoma (OSCC) cells. The MTT test was used to assess the cytotoxicity and viability of OSCC cells at different concentrations of MPC/selenium. Due to their high anticancer activity (94.9%), the developed nanocomposites can be used as new therapeutic agents in the treatment of oral squamous cell carcinoma.

Keywords: methacryloyloxyethyl phosphorylcholine, selenium nanoparticles, human health, oral cancer, Taguchi method.

Ocena cytotoksyczności nanokompozytu metakryloyloksyetylofosforylocholina/selen w stosunku do raka płaskonabłonkowego jamy ustnej

Streszczenie: Metodą Taguchi określono optymalne warunki otrzymywania nanokompozytów metakryloyloksyetylofosforylocholina/selen (MPC/selen) i zbadano ich aktywność przeciwnowotworową na komórki płaskonabłonkowego raka jamy ustnej (OSCC). Do oceny cytotoksyczności i żywotności komórek OSCC, przy różnych stężeniach MPC/selen, stosowano test MTT. Ze względu na wysoką aktywność przeciwnowotworową (94,9%) opracowane nanokompozyty mogą znaleźć zastosowanie jako nowe środki terapeutyczne w leczeniu płaskonabłonkowego raka jamy ustnej.

Słowa kluczowe: metakryloyloksyetylofosforylocholina, nanocząstki selenu, ochrona zdrowia, nowotwór jamy ustnej, metoda Taguchi.

Some diseases, such AIDS, autoimmune diseases, antibiotic resistance, and cancer remain difficult to treat globally even with advancements in recent years [1–4]. Head and neck tumors are the sixth most common cancer in the world, and oral tumors make up one-third of them. Oral cancer ranks as the eighth most common cancer in males and the fifteenth in women, typically affecting individuals over the age of 50. The most common malignancy is OSCC, accounting for 90% of epithelial lesions. The primary sites of manifestation include the tongue, vermilion lip, floor of the mouth, and buccal mucosa [5, 6]. Every year, 22,000 Americans get oral cancer, and 90% of them have squamous cell carcinoma. In Taiwan, oral cancer has been one of the top 10 causes of cancer deaths since 1991. There are 350,000 to 400,000 new cases each year across the world. Unlike some other cancers where rates have gone down, oral cancer is becoming more common among young people and women [7, 8]. Most oral and throat cancers are squamous cell carcinomas based on their tissue type. People under 45 are now becoming more affected by oropharyngeal squamous cell carcinoma, which used to mostly affect people over 45. Over 60% of patients have neck lymph node involvement, and 10-15% have distant metastases [9]. Common treatments for oral squamous cell carcinoma include surgery, radiation, and chemotherapy. Only 40-60% of patients survive five years, even with fast improvements in treatment tech and lots of research. In addition, these tough treatments cause significant side effects and lower the patient's quality of life [10].

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The rate of survival for OSCC patients is only 50-59%, despite recent advances and complex combined treatments [11, 12]. As this disease is common, preventing it is important, but it takes time and effort. Smoking should be stopped, lifestyle changes should be made, and chemo-prevention methods should be used to prevent cancer. People get exposed to radiation, chemicals, and lifestyles that bring cancer-causing stuff early in life, which cannot be avoided. Things like diet, tobacco, alcohol, and personal habits all mix to increase exposure to these risks [13]. Therefore, basic prevention methods like quitting smoking and alcohol, plus early detection, and new treatment methods, should be used to keep up with this growing disease and help patients do better [14].

A nanocomposite is defined as a composite material with at least one dimension in the nanoscale, where all solid phases range between 1–100 nanometers [15]. Nanocomposites have been extensively developed and are widely utilized globally [16]. Currently, nanocomposites are employed to prevent disease, improve treatment prognosis, reduce side effects, and enhance patients' quality of life [17, 18]. For instance, studies have shown that selenium may inhibit carcinogenesis, as evidenced by tumor model studies, epidemiological data, and in vitro experiments demonstrating reduced mutagen-induced carcinogenesis. Selenium affects the metabolism of certain carcinogens, exhibits low toxicity, and has weak protein binding, allowing it to compete for binding sites in target organs [19]. Metal nanoparticles, such as gold, silver, selenium, and platinum, have applications in various fields, including cancer therapy. Nanoscale compounds made from these nanoparticles have unique features that allow us to create new, effective treatments for oral cancers. In recent years, these nanoscale compounds have garnered attention as promising cancer treatment strategies [20, 21].

A novel nanocomposite based on a polymer and utilizing 2-methacryloyloxyethyl phosphorylcholine and selenium nanoparticles with anticancer properties was designed for oral squamous cell carcinoma using the Taguchi method. To this end, selenium nanoparticles were produced via a biological method, and 2-methacryloyloxyethyl phosphorylcholine was commercially sourced. The MPC/Selenium nanocomposite was synthesized through direct mixing synthesis. The aim of this research was to investigate the potential of MPC/Selenium nanocomposite as an innovative and effective approach in combating oral cancer.

EXPERIMENTAL PART

Materials

The materials used in this study were as follows: sodium chloride (Neutron, Iran), Dulbecco's Modified Eagle Medium/F-12 (DMEM-F12 media, Gibco, USA), fetal bovine serum (FBS, Gibco, USA), 2-methacryloyloxyethyl phosphorylcholine polymer (MPC, 97%), sodium selenite and ferrous sulfate (Sigma Aldrich, USA), D-glucose monohydrate, di-potassium hydrogen phosphate, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT), dimethyl sulfoxide (DMSO), phosphate-buffered saline (PBS) (Merck, Germany).

Synthesis of selenium nanoparticles

To produce selenium nanoparticles through bacterial means, the *Halomonas elongata* bacteria (IBRC-M 10433) was used. The growing media for the bacteria was prepared by mixing 0.2 g of glucose, 3 g of NaCl, 0.028 g of K_2HPO_4, and 0.0001 g of $FeSO_4$ with 100 mL of distilled water in a container. It was stirred until clear using a magnetic stirrer. Following the sterilization of the medium in an autoclave, one bacterial colony was transferred to Erlenmeyer flasks. The bacteria and media were maintained in the flasks at 37°C for 48 hours. To separate the bacteria and collect the upper liquid for nanoparticle production, the mixture was centrifuged at 5000 rpm for 5 minutes. The nanoparticles were preserved for 48 hours using 0.8 mg/mL sodium selenite and 7.5 mg/mL glucose. The glucose-based medium and the upper liquid were prepared according to the design, with the former being combined in equal parts with solutions containing 0.8 mg/mL sodium selenite. The combinations were shaken at 140 rpm in a shaking incubator set at 30°C for 48 h. After that, the nanoparticles were spun at 5000 rpm for 15 min to separate them. The solutions were prepared for structure testing by being autoclaved at 80°C for 24 h [22].

Synthesis of MPC/selenium nanocomposite

To determine the optimal approach for producing a nanocomposite with strong anti-cancer properties, nine trials were designed using the Taguchi method and Qualitek-4 software. Variations in MPC polymer concentration, selenium nanoparticle concentration, and mixing duration were investigated. Experimental conditions for determining the anti-cancer impact included direct mixing with solutions of MPC polymer (1.5, 3, and 4.5 mg/mL), selenium nanoparticles (2, 4, and 6 mg/mL), and durations of mixing ranging from 40 to 120 min. Nine different nanocomposite samples were created, with composition presented in Table 1. The solutions of all the components were combined using a magnetic stirrer and mixed for one hour. After that, the three solutions were mixed for 15 min at room temperature using an ultrasonic homogenizer. The next step was to slowly add the selenium nanoparticle solution to the MPC polymer solution. After the first hour of mixing, the ingredients were re-mixed for a further fifteen minutes. The final nanocomposite was formed by heating the mixture to 60°C for 24 h in an oven. Powdered nanocomposite materials were created by scraping the solids with a spatula and then grinding them in a mortar [23, 24].

T a b l e 1. Taguchi's experiment plan

Sample	MPC mg/mL	Stirring time min	Selenium NPs mg/mL
S1	1.5	45	2
S2	1.5	60	4
S3	1.5	75	6
S4	3	45	4
S5	3	60	6
S6	3	75	2
S7	4.5	45	6
S8	4.5	60	2
S9	4.5	75	4

Cell culture

Oral cancer cells (KB cells) were procured from the Pasteur Institute in Tehran, Iran. The cells were cultured in DMEM-F12 media supplemented with 10% FBS (v/v) and 1% penicillin-streptomycin at 37°C, with 5% CO_2 and 95% humidity, until they reached sufficient density.

Cytotoxic study

The MTT assay was employed to evaluate the toxicity of MPC/selenium nanocomposites on KB cells. On the tests, cells were cultivated on 96-well plates, with each well containing 20,000 cells and a total volume of 200 mL. The plates were maintained in an incubator at 37°C. Each treatment consisted of three wells. Following a 24-hour incubation period, the treatment was administered to the cells. Subsequently, the cells were rinsed with approximately 200 microliters of phosphate-buffered saline (PBS). Subsequently, 150 microliters of yellow MTT solution, combined with complete medium at a 1:10 ratio, was introduced to each well, and the plate was incubated in the dark for 4 h. Subsequently, 100 microliters of DMSO were introduced to each well, and the plate was agitated for 10 minutes to ensure full dissolution of the crystals. The absorption of light at 570 nm was quantified. The mean absorption of the three wells of each treatment was contrasted with the control (DMSO treatment) [25].

Methods

Chemical structure was conducted by Fourier transform infrared spectroscopy (FT-IR) using ThermoFisher Scientific spectrometer (Waltham, USA). The spectra were recorded using at least 32 scans with 2 cm^{-1} resolution, in the spectral range of 4000-400 cm^{-1}, using KBr pellets technique. Crystal structure was determined by X-ray diffraction spectroscopy (XRD) using Philips X' Pert (Amsterdam, the Netherlands) diffractometer with monochromatic CuK α radiation (γ = 0.154056 nm) at 40 kV and 30 mA, and 2θ angles of 20-80°. A high-resolution field emission scanning electron microscope (FESEM), model MIRA3 (Tescan, Brno, Czech Republic), at a voltage of 30 kV was used for structure analysis. Elements distribution maps were determined by employing X-ray energy diffraction spectroscopy (EDS) with Bruker (Billerica, MA, USA) type equipment. A high-resolution scanning electron microscope equipped with a SAMX X-ray energy detector was used to conduct this study. A transmission electron microscope (TEM), model EM208S from Philips (Amsterdam, The Netherlands), was used to study the morphology of the nanocomposites at a voltage of 100 kV and in the range of 200–800 nm. The light absorption properties were evaluated by UV-Vi's NIR spectroscopy using a Shimadzu UV-160 spectrophotometer (Kyoto, Japan) in the range of 200–800 nm.

RESULTS AND DISCUSSION

Anticancer activity

The optimal formula of MPC/selenium nanocomposite to fight cancer cells was selected based on nine tests using the Taguchi method (Table 1). Nanocomposites obtained in different conditions were evaluated for their ability to inhibit the growth of oral cancer cells (Figure 1).

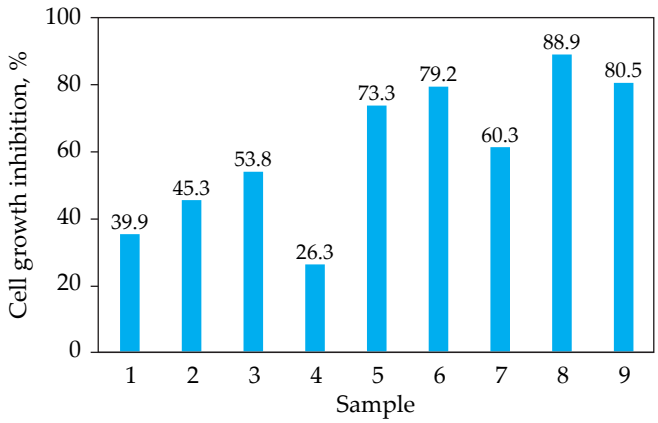

Fig. 1. Inhibition of cancer cell growth by the nanocomposites

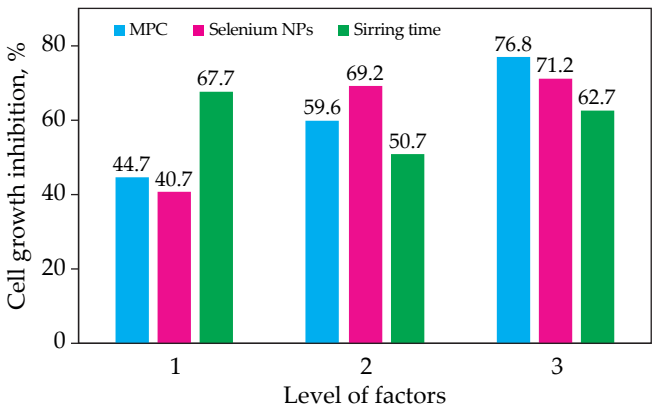

Fig. 2. The influence of factor levels on the anticancer properties of the nanocomposites

T a b l e 2. Variability of factors influencing the anticancer properties of the nanocomposites

Factors	DOF*	Sum of squares	Variance	F-ratio (F)	Pure sum	Percent (%)
MPC, mg/mL	2	1543.96	771.98	21.12	1470.86	38.52
Selenium NPs, mg/mL	2	1744.85	872.42	23.87	1671.74	43.78
Stirring time, min	2	456.23	228.12	6.24	383.13	10.03

*DOF - degree of freedom

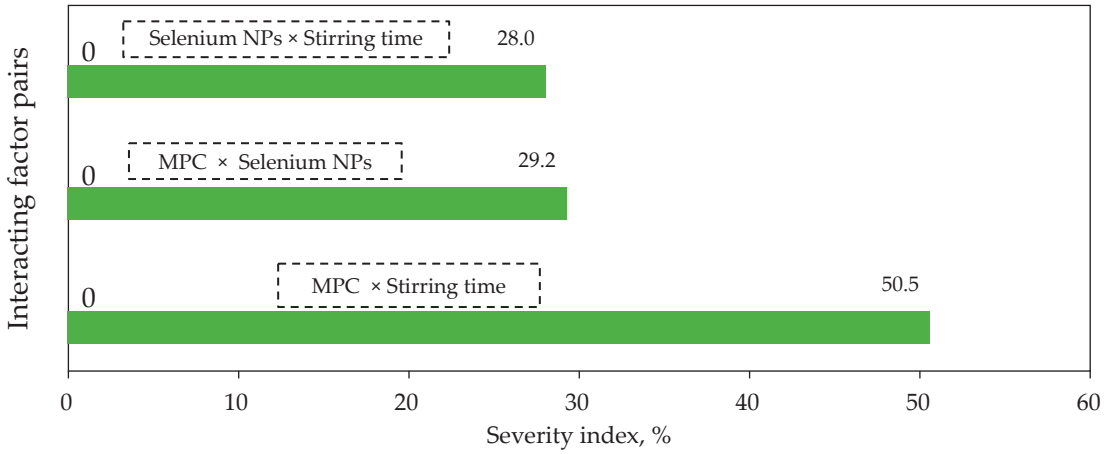

Fig. 3. Relationships between the agents evaluated on the anticancer properties of the nanocomposites

Sample S8 (4.5 mg/mL MPC, 4 mg/mL selenium nanoparticles, mixed for 40 min) stopped the most cancer cell growth. Figure 2 shows how different amounts of each factor (MPC, selenium nanoparticles, and mixing time) affected cancer cell growth. MPC worked best at level 3 with 76.75% and worst at level 1 with 44.69%. Selenium nanoparticles were best at level 3 with 71.17% and worst at level 1 with 40.69%. Mixing time was best at level 1 with 67.68% and worst at level 2 with 50.70%. Figure 3 exhibits how the factors worked to stop oral cancer cell growth. The strongest influence was between MPC at level 3 and mixing time at level 1, with 50.50%. The weakest was between selenium nanoparticles at level 2 and mixing time at level 1, with 27.97%. The collaboration between MPC at level 3 and selenium nanoparticles at level 2 was 29.20%.

Table 2 displays the analysis of variance (ANOVA) regarding the parameters influencing oral cancer cell proliferation. Selenium nanoparticles had the most significant effect, stopping growth by 43.78%. Mixing time had the most negligible impact (10.03%), and MPC helped stop oral cancer cells (KB cell line) by 38.52%. After checking the factors and how they worked together using the Taguchi method and Qualitek-4 software, the best conditions were suggested for making the MPC/selenium nanocomposite with the most potent anti-cancer activity in Table 3. MPC and selenium nanoparticles at level 3 and mixing time at level 1 were the best. MPC had the most significant role in stopping cell growth at 16.40% while mixing time had the smallest at 7.34%. Selenium nanoparticles helped stop oral cancer cell growth by 10.82%. On average, all composite materials stopped the growth of 60.34% of oral cancer cells. However, the nanocomposite obtained in the suggested best conditions is expected to stop 94.90% of oral cancer cell growth using the Taguchi method (KB cell line).

T a b l e 3. Estimation of ideal conditions for obtaining the nanocomposites with the highest anticancer potential

Factors	Level	Contribution, %
MPC, mg/mL	3	**16.40**
Selenium NPs, mg/mL	3	10.82
Stirring time, min	1	7.34
Total contribution from all factors		34.56
Current grand average of performance		60.34
Cell growth inhibition at optimum condition		**94.90**

FT-IR analysis

MPC polymer, selenium nanoparticles, and the nanocomposite were evaluated with FT-IR in the 400-4000 cm^1 range, shown in Figure 4. For MPC biopolymer, peaks were observed at 1627 cm^{-1}, which shows the stretching of C=O groups in MPC. A peak at 1226 cm^{-1} was linked to C-O stretching, typical for MPC. Other peaks at 1118 cm^{-1} and 478 cm^{-1} showed the bending of C=C and the vibration of C=CR1R2 structure [26-28]. In the FT-IR spectrum of selenium, two distinct peaks were observed at 3423 cm^{-1} and 1653 cm^{-1}, corresponding to the stretching vibrations of the hydroxyl group. The peak at 1290 cm^{-1} was associated with C=O, –NH and $-NH_2$ groups. These groups stabilize the selenium nanoparticles and help to transform sodium selenite into elemental selenium [22]. The FT-IR spectrum of the nanocomposite showed peaks originating from the polymer and selenium nanoparticles with different strengths, which shows that the com-

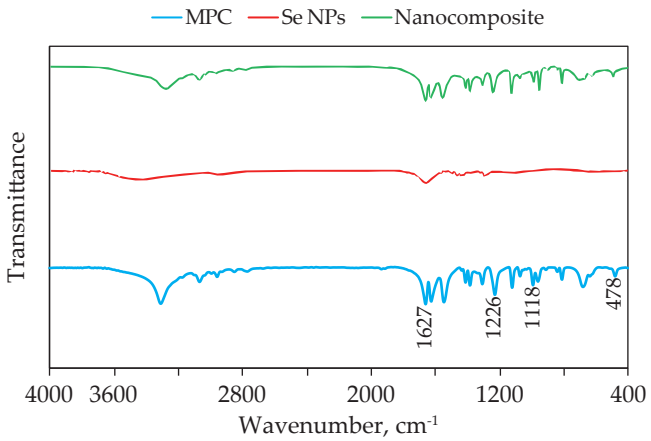

Fig. 4. FT-IR spectra of MPC, selenium NPs and the nanocomposite

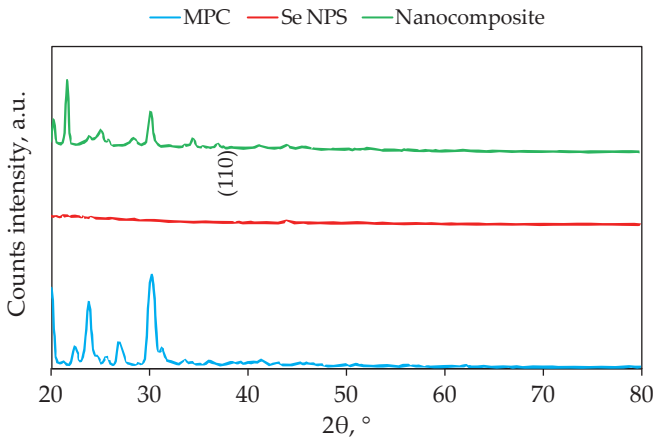

Fig. 5. XRD patterns of MPC, selenium NPs and the nanocomposite

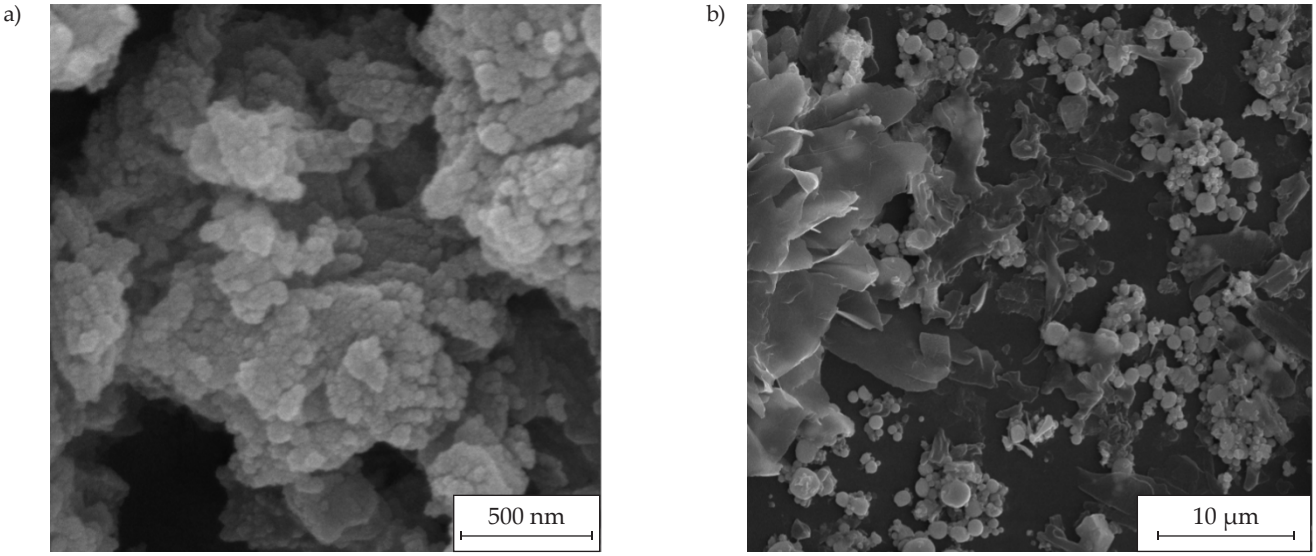

Fig. 6. FESEM images: a) MPC, b) MPC/selenium nanocomposite

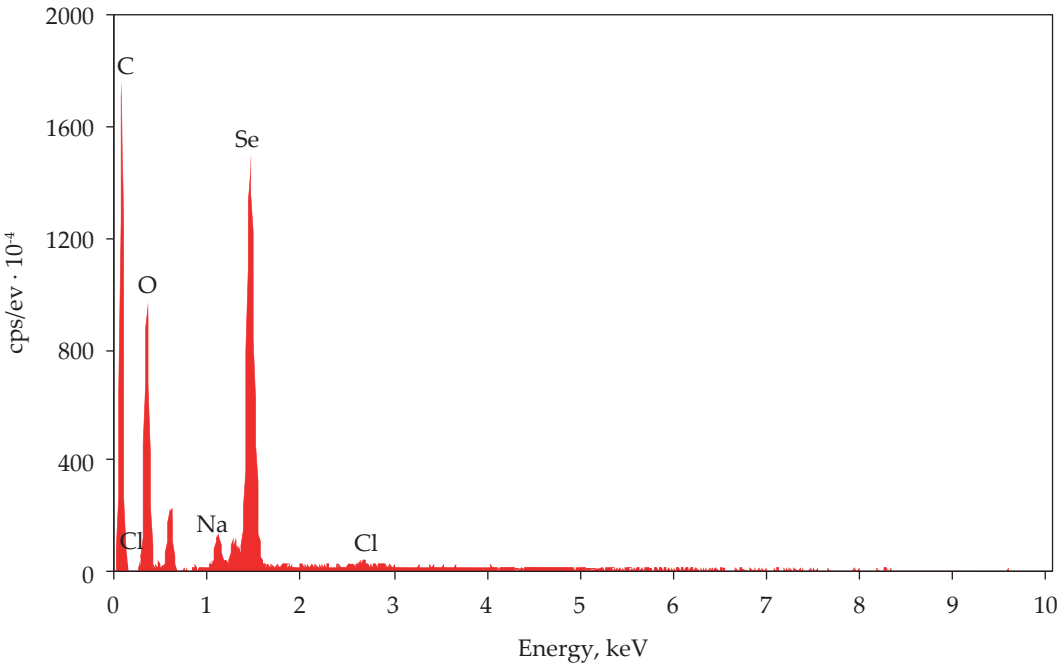

Fig. 7. EDX pattern of the nanocomposite

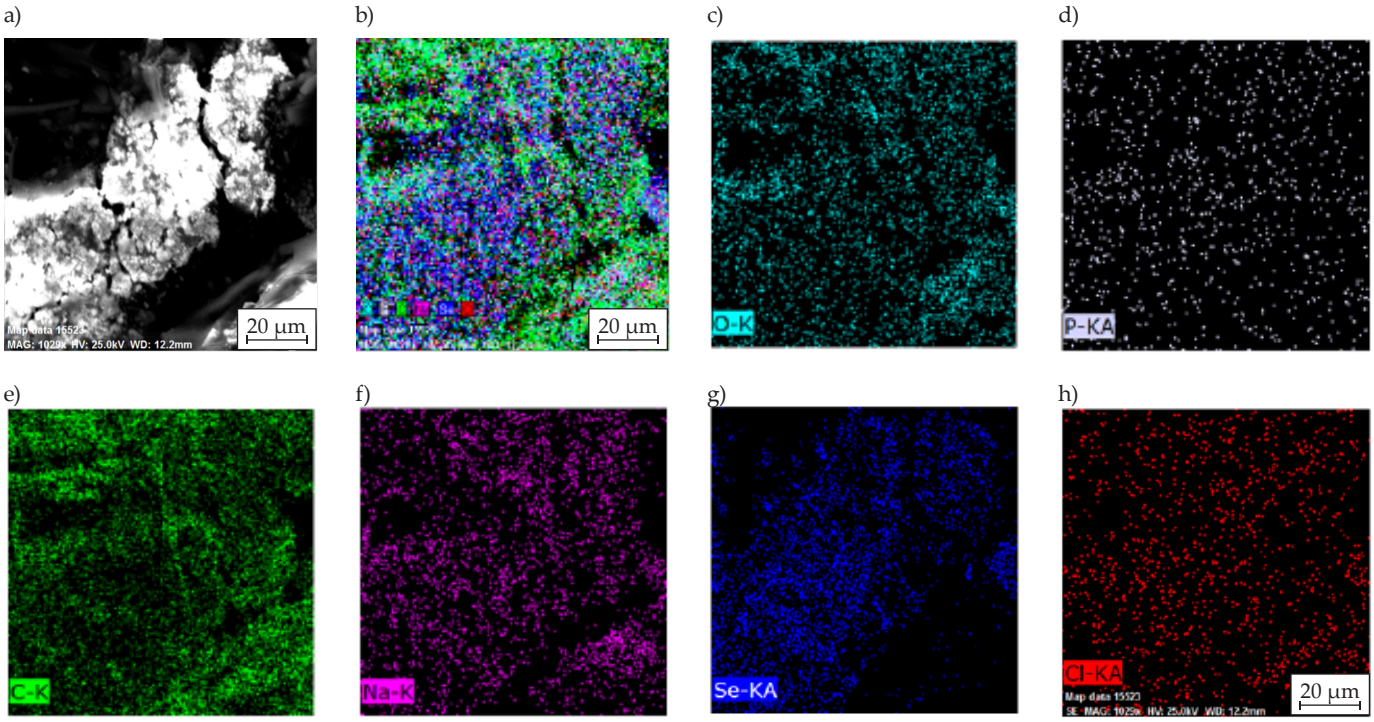

Fig. 8. Dispersion map of the nanocomposite: a) surface image, b) all elements, c) oxygen, d) phosphorus, e) carbon, f) sodium, g) selenium, h) chlorine

ponents interacted with each other and confirms that a nanocomposite was obtained.

XRD analysis

X-ray diffraction was employed to examine the crystal structure of MPC polymer, selenium nanoparticles, and the nanocomposite (Figure 5). MPC's XRD pattern was analyzed using Xpert HighScore software and showed the material has two ICDD cards, numbers 00-041-1604 ($C_{10}H_{14}N_2O_7$) and 00-017-1041 ($C_8H_{17}N_3O$), which are polymeric and hydrocarbon-like. The peaks might be due to the small particle size. XRD pattern for selenium nanoparticles had sharp, narrow peaks, showing a good crystal structure. Peaks at 2θ values of 23.5, 29.2, 41.4, 43.3, 45.4, 52.5, 55.7, and 62.7 matched crystal planes (100), (101), (110), (102), (111), (201), (112), and (202) from the standard (JCPDS card No. 06–362). The nanocomposite's XRD pattern differed from its parts and had lower intensity, wider peaks, some missing peaks, and shifted positions, showing that the nanocomposite had formed.

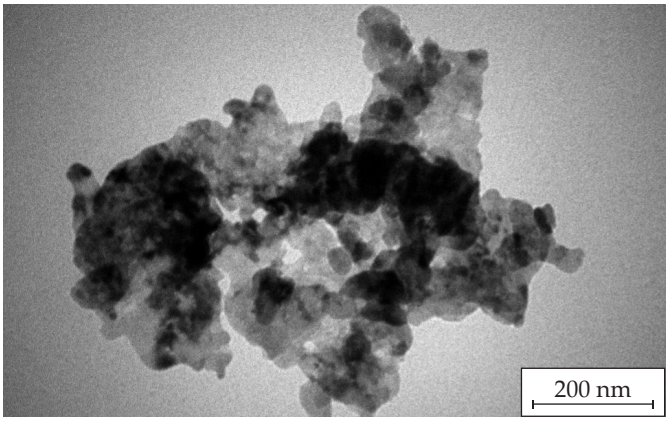

Fig. 9. TEM image of the nanocomposite

FESEM analysis

The surface and shape of MPC polymer and the nanocomposite were checked using a field emission scanning electron microscope (Figure 6). FESEM images showed that the MPC polymer forms a connected network. The nanocomposite showed small particles or cells of various shapes and sizes distributed on the fracture surface. These particles had complex and irregular shapes, some resembling clusters of beads and others irregular shapes.

SEM and EDS analysis

The components of the MPC/selenium nanocomposite were identified by energy dispersive X-ray spectroscopy (EDS), as shown in Figure 7. The composite consists of carbon (63.22 wt%), oxygen (19.85 wt%), selenium (14.91 wt%), sodium (1.79 wt%), and chlorine (0.23 wt%), confirming the nanocomposite was made. Figure 8 shows how these elements are spread on the nanocomposite's outer layer as a map. The regular spread of magnesium, oxygen, nitrogen, and carbon in the nanocomposite's structure also confirmed its formation. In other words, carbon, oxygen, selenium, sodium, chlorine, and phosphorus were evenly spread in the nanocomposite.

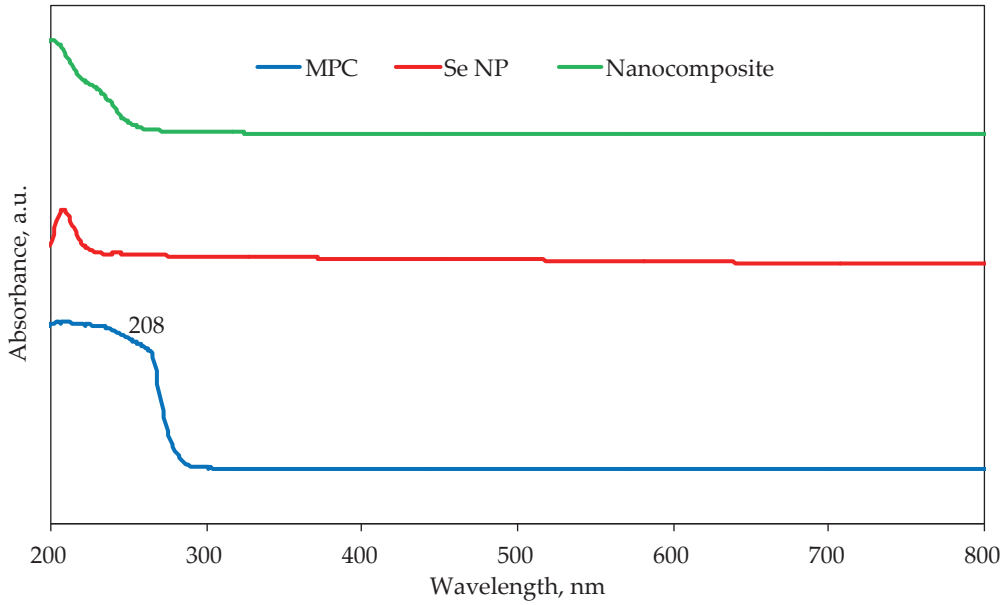

Fig. 10. UV-Vi's spectra of MPC, selenium NPs and the nanocomposite

TEM analysis

A transmission electron microscopy (TEM) image of the nanocomposite was obtained at 200 nm magnification (Fig. 9). The nanocomposite looked like an uneven, dense cluster with shades of gray, showing different densities or makeup. The darker areas were selenium nanoparticles spread randomly in the polymer matrix, forming the nanocomposite. The texture was rough, with some parts darker and others lighter, which might show differences in density or thickness.

UV-Vis analysis

Fig. 10 shows the UV-Vis absorption spectra of MPC, selenium nanoparticles and nanocomposite in the wavenumber range of 200–800 nm. The absorption of light by nanoparticles and MPC depends on their structure and size. The maximum absorption wavelength in the MPC spectrum was observed at 208 nm. There is a sharp band at around 212 nm in the UV-Vis absorption spectrum of selenium nanoparticles, which shows their unique shape and smaller size compared to MPC. A broad, stretched band at 207 nm was observed for the nanocomposite.

CONCLUSIONS

The Taguchi method was used to optimize the composition of MPC/selenium nanocomposites obtained by the direct mixing method, with a strong anticancer effect on oral cancer cells (KB cell line). Under optimal conditions (high MPC effect, moderate selenium nanoparticle effect, and low stirring time effect), the nanocomposite inhibited 94.90% of oral cancer cell growth. The developed nanocomposites may find application in medicine as an anticancer agent for the oral cavity.

Authors contribution

M.S. – research concept, methodology, writing-review and editing, investigation; F.K. –investigation, writing-original draft; M.P. – investigation, data analysis, research concept; L.S.W. – conceptualization, writing-review and editing, validation.

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Conflict of interest

The authors declare no conflict of interest.

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