DOI: http://dx.doi.org/10.32571/ijct.1060235 E-ISSN: 2602-277X

International Journal of Chemistry and Technology

http://dergipark.org.tr/ijct

Research Article

Developing new polymeric nanoparticles for controlled release of quercetin as an alternative material protecting from COVID-19

Ceren TÜRKCAN*

Istanbul Arel University, Faculty of Engineering and Architecture, Biomedical Engineering, Tepekent, Istanbul, Türkiye

Received: 19 January 2022; Revised: 5 July 2022; Accepted: 5 July 2022

*Corresponding author e-mail: cerenturkcane@arel.edu.tr

Citation: Türkcan, C. *Int. J. Chem. Technol.* **2022**, 6 (1), 76-80.

ABSTRACT

Research of drugs for COVID-19, the most striking studies include the ACE-2 receptors used by COVID-19 by binding to the lung cells for entry. In the researchers conducted, it was determined by the results of the docking studies performed on the agents that block the receptor by binding to the receptor, such as COVID-19, several molecules have the interest to bind to this receptor. One of these numbered molecules is herbal flavonoid called "Quercetin". In this study, quercetin imprinted polymeric materials were designed, synthesized and characterized. For synthesis, emulsion polymerization technique was used for obtaining quercetin imprinted polymeric materials. SEM and Zeta-Size analysis were used as preliminary characterization. After a week release experiment, quercetin imprinted polymeric nanoparticles were released by 14%. In the light of these results, it is predicted that quercetin printed polymeric material can be used for protection from COVID-19 and treatment of COVID-19 on the inhaler route.

Keywords: COVID-19, quercetin, flavonoids, nanoparticles.

COVID-19'dan korunmada alternatif materyal olarak kersetin kontrollü salımı için yeni polimerik nanopartikül geliştirilmesi

ÖZ

COVID-19 için ilaç araştırmalarında en dikkat çekici çalışmalar COVID-19'un akciğer hücrelerine giriş için bağlanarak kullandığı ACE-2 reseptörlerini içeriyor. Yapılan araştırmalarda, COVID-19 gibi reseptöre bağlanarak reseptörü bloke eden ajanlar üzerinde yapılan docking çalışmalarının sonuçlarıyla, birçok molekülün bu reseptöre bağlanma ilgisi olduğu belirlendi. Bu numaralandırılmış moleküllerden biri de "Quercetin" adı verilen bitkisel flavanoiddir. Bu çalışmada, kuersetin baskılı polimerik malzemeler tasarlanmış, sentezlenmiş ve karakterize edilmiştir. Sentez için, kersetin baskılı polimerik malzemelerin elde edilmesinde emülsiyon polimerizasyon tekniği kullanılmıştır. Ön karakterizasyon olarak SEM ve Zeta-Size analizi kullanıldı. Bir haftalık salım deneyinden sonra, kuersetin baskılı polimerik nanopartiküller %14 oranında salındı. Bu sonuçlar ışığında, kuersetin baskılı polimerik materyalin inhaler yolunda COVID-19'dan korunma ve COVID-19 tedavisinde kullanılabileceği tahmin ediliyor.

Anahtar Kelimeler: COVID-19, kersetin, flavonoidler, nanopartiküller.

1. INTRODUCTION

Being confined to the plant kingdom, quercetin as a plant-derived flavonoid is widely found in herbal sources, *viz.* apple, onion, pomegranate greens. Owing to high antioxidant properties of the relevant compound, a plethora of biological activities such antiviral, antihistaminic, anti-inflammatory, antibacterial properties have been attributed to the quercetin. Those remarkable activities have been revealed to be linked to its structure. Corresponding to aforementioned properties, the compound is used in the treatment of diabetic foot wounds, acne treatment, skin blemishes, and the elimination of allergic reactions. Critically, as reported in the previous studies, the active substance quercetin used in the nanopolymer has found promising properties in the treatment of COVID-19. In a docking study, the largest protein of COVID-19 was purified and molecules with similar properties were listed as binding affinity to the ACE-2 receptor. The binding energies and 3-dimensional structures of molecules have been investigated and quercetin is included in these molecules.[1] In another publication, it is mentioned as one of the two active agents prescribed for treatment.[2] There

DOI: http://dx.doi.org/10.32571/ijct.1060235 E-ISSN: 2602-277X

are studies mentioned as inhibitors for SARS-CoV-2 infection. It is stated that it inhibits the virus by changing gene expression activities at the genetic level.[3,4]

The most important reason why the molecular suppression technique is preferred in controlled release systems is that the existing interactions can be controlled. This provides the opportunity to control emission levels. Thus, the release time and quantity of your active ingredient can be designed to suit the conditions.[5]

In current studies, it interacts with the active site of the ACE-2 receptor, closing the interaction site of COVID-19 and preventing the virus from entering the cell. It blocks the virus through this way and is predicted to have a protective effect.[6] Apart from this, the virus has effects in terms of blocking protein synthesis and it is stated that it is effective in SARS viruses. Apart from this feature, the anti-inflammatory feature of quercetin enables it to eliminate the side effects that may occur during virus infection.[7] As mentioned in the docking studies in the literature, the quercetin molecule ranks first among the molecules that are predicted to be effective in terms of binding to the receptor with similar morphological structure by isolating the largest protein group of COVID-19.[1]

In this study; the active substance, as clearly revealed to be effective against COVID-19, is combined with the nanomaterial and developed as a controlled release. Within the scope of the project, a controlled release drug that can affect COVID-19 has innovative aspects. The nanopolymer to be used in the study has a biocompatible structure. The active substance of quercetin was imprinted into the nanopolymer by molecular printing method and then controlled release studies were carried out. Scanning electron microscope (SEM) images were obtained for characterization of quercetin imprinted polymeric nanoparticle.

2. MATERIALS AND METHODS

2.1. Materials

Quercetin was provided from Sigma Chemical Co (St. Louis, USA). 2-Hydroxyethyl Metacrylate (HEMA), poly Vinyl Alcohol (PVA), and ethylene glycol dimethacrylate (EGDMA) were obtained from Aldrich (Steinheim, Germany). Potassium persulfate (KPS) was supplied from Merck (Darmstadt, Germany). All other chemicals were of analytical grade.

2.2. Methods

The absorbance values of Azure A and Pb (II)–Azure A complex were determined by using Shimadzu UV–160A ultraviolet/visible spectrophotometer. The atomic absorbance values of Pb (II) ions were measured by using Shimadzu AA 7000 flame atomic absorption spectrometer and a lead hollow cathode lamp.

2.2.1. Synthesis of quercetin imprinted polymeric nanoparticles

Polymeric material was synthesized with molecular imprinted technique for obtaining controlled release material. For this, 0.25 mg/mL Quercetin dissolved 200 microliters of isopropyl alcohol and 25 microliters of AA (Acrylic Acid) was added to solution. After then pre-complex mixture was mixed for 2 hours at room conditions using a magnetic stirrer. 275 mg Poly (vinyl alcohol), the stabilizer was dissolved in 25 mL distilled water. Pre-complex of Quercetin and AA was stopped and added onto PVA solution. 60 microliters of HEMA as monomer and 30 microliters of EGDMA were added into reactor as crosslinker. The last chemical, 45 mL KPS (0.44 mg/mL) was added onto reactor as an initiator. Final reaction mixture was treated with nitrogen gas and mixed in a water bath at 70˚C for 5 hours. At the end of the polymerization, synthesized polymeric material was rinsed two times with distilled water (100 mL) and ethanol to remove the unreacted quercetin imprinted polymeric nanoparticles, initiators and other used chemicals. After that, polymeric polymeric material was dried at 37˚C and then stored at +4 °C until further analysis.[8,9]

2.2.2. Characterization of quercetin imprinted polymeric nanoparticle

Overall structure and the surface morphology of quercetin imprinted polymeric nanoparticles were studied by using a SEM device (Quanta 250 S FEG). For this, surface of the membrane was covered with thin film of gold and was analyzed with different magnifications. Quercetin imprinted polymeric nanoparticles were analyzed with Zeta-Sizer (NanoS, Malvern Instruments, London, UK) for obtaining nanoparticle's size.

2.2.3. Controlled release of quercetin

While the polymeric material with quercetin imprinted was synthesized, washing with water and ethanol was performed after the synthesis to remove chemicals that did not participate in polymerization. During the washing process, the polymeric material suppressed with quercetin is precipitated by centrifuge and the upper phase is discarded. Then, the solvent was added on the precipitate and mixed in an ultrasonic bath. After the mixing process, chemicals that do not react are removed from the environment by precipitation again.

Spectrophotometry was used to determine quercetin. Determining final release concentrations of quercetin imprinted polymeric nanoparticles spectrophotometrically at 372 nm by using a UV-VIS spectrophotometer (Shimadzu, 1601, Japan).

DOI: http://dx.doi.org/10.32571/ijct.1060235 E-ISSN: 2602-277X

The polymeric material suppressed with quercetin for controlled release was kept in pH 7.4 phosphate buffer at 37 degrees at body temperature for a period of one week. The quercetin release amount was determined by taking samples at regular intervals. For this, the polymeric part was precipitated by taking the sample from the solution and centrifuged and analyzed in the upper phase.

3. RESULTS AND DISCUSSION

Herewith the present study, a polymeric material was synthesized using molecularly imprinting technique using quercetin as a target molecule for controlled release system. The novel quercetin imprinted polymeric nanoparticle was characterized through two characterization methods.

3.1. SEM Results

The findings of SEM images revealed that diameter of polymeric materials was about 45-65 nm with a spherical structure (Figure. 1).

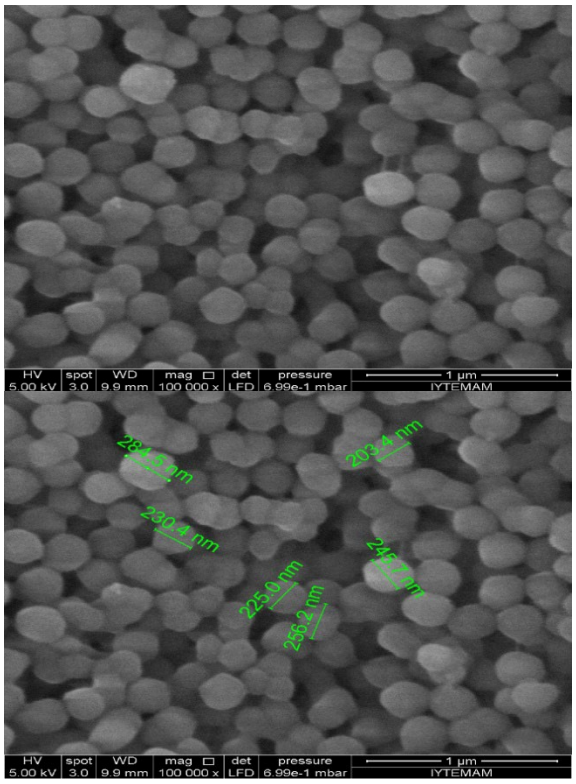

Figure 1. SEM images of quercetin imprinted polymeric nanoparticles.

With respect to the structure of the novel nanoparticle, it is seen that more than one intertwined global structure is together. SEM images are generally not included in the printing studies in the literature.[10-12] It is seen that agglomeration occurs in another polymeric structure.[13,14] When the chemical characteristics of the monomers and target molecules used in the study are considered, aggregation is actually an expected result.

3.2. Zeta-Size Analysis Results

Dimensional analysis of the obtained quercetin imprinted polymeric nanoparticles are given in Figure 2 below.

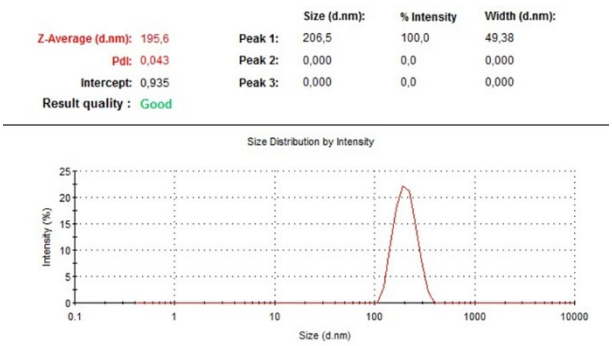

Figure 2. Zeta-Size Analysis of Quercetin imprinted polymeric nanoparticles.

Particle sizes may vary depending on the area of use. As previously reported, the size of another polymeric structure was in the range of 140-210 nm [15]. As mentioned in another publication, particle sizes ranged from 48 nm to 96 nm [16]. Regarding findings of the current study, the quercetin imprinted polymeric nanoparticle shows a scale similar to those in the literature in terms of size. The particles obtained in the study show compatibility with the findings of SEM analysis.

3.3. Controlled Release Results of Quercetin

For the characterization of the quercetin printed polymeric material; after SEM and Zeta-Size analyzes were performed, release studies were carried out to be compatible with the body. For release studies, trials were carried out for one week at body temperature and using pH 7.4 phosphate buffer. Trial results are given in Figure 3.

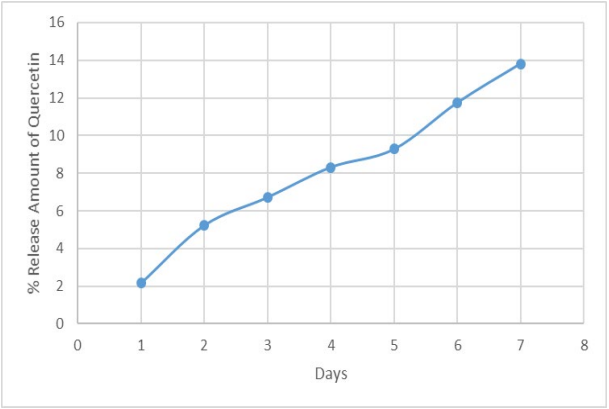

Figure 3. Controlled release results of quercetin from imprinted polymeric material.

DOI: http://dx.doi.org/10.32571/ijct.1060235 E-ISSN: 2602-277X

According to the trial results, there is a certain amount of active substance release every day within a week. According to the 7th day result, it is seen that the material releases the target molecule by 14 %. This shows that the release time may be longer. In a study in the literature, 30 % of the compound was released in a two-hour period. In another study in the literature, there are materials that emit 56-65 % within 24 hours.[17] In another study, it released approximately 70 % in a 7-hour period.[18] However, the emission amount of the quercetin imprinted polymeric nanoparticle developed in the study is very low in comparison to the former reports. Those findings might exert either advantage or disadvantage. Since the release time is long, it can be applied at more intermittent periods. If the amount of active ingredient is low, the application intervals can be more frequent.[19]

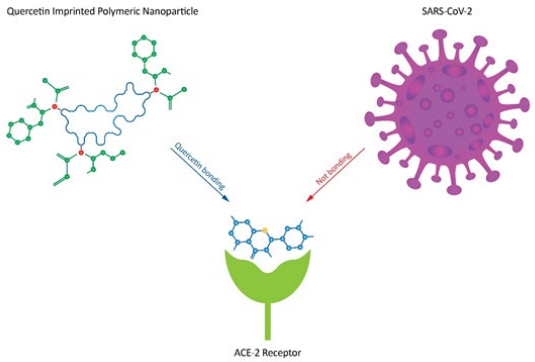

Figure 4. Blocking of ACE-2 receptor with Quercetin imprinted polymeric nanoparticles to avoiding SARS-CoV-2.

As seen in Fig-4; quercetin is released from quercetin imprinted polymeric nanoparticles and ACE-2 receptor is blocked. SARS-CoV-2 virus could not bond with the ACE-2 receptor.

4. CONCLUSIONS

This study includes preliminary trials of the material developed to protect against COVID-19 and treat caught people. The active ingredient quercetin, which is included in the material developed from the study, prevents the binding of the virus by blocking the region where COVID-19 binds in the lungs in literature studies. In addition, since the active ingredient of quercetin has anti-inflammatory effects, it is predicted that it will alleviate the symptoms after the disease. In the study, quercetin printed polymeric material was synthesized by emulsion polymerization method using molecular printing technique. In order to characterize the synthesized quercetin printed polymeric material, SEM images were taken and Zeta-Size analyzes were performed. The SEM images revealed the spherical structure of the particle and Zeta-Size analysis displayed the diameter as 200 nm. Both SEM and Zeta-Size analysis displayed are consistent and compatible with each other. Following characterization analysis, the release studies were made by selecting the values that could be optimum for the body. In the release studies of pH 7.4 phosphate buffer and 37° C body temperature for a week, it is seen that quercetin releases approximately 14% of the printed polymeric material at the end of seven days. It is predicted that the quercetin imprinted polymeric nanoparticle developed can be used practically by inhaler and will reach the lungs and block the binding of the virus to the receptors by interacting with ACE-2 receptors. Since the developed quercetin printed polymeric material has the feature of releasing, it will also be present in the lungs in case of contact with the virus, and can prevent transmission during the day. In addition, it is predicted that in case of contamination of quercetin imprinted polymeric nanoparticle, when the inhaler is used on the way, it can eliminate the inflammation occurring in this area.

ACKNOWLEDGEMENTS

I thank Zafer Zeren for the schematic drawings and graphic design.

Conflict of interests

I declare that there is no a conflict of interest with any person, institute, company, etc.

REFERENCES

1. Khaerunnısa, S.; Kurniawan, H.; Awaluddin, R.; Suhartati, S.; Soetjipto, S.; *Pharmacology & toxicology* **2020**, 20944, 1-14.

2. Sargiacomo, C.; Sotgia, F.; Lisanti, MP.; *Aging (Albany NY)* **2020**, 12, 6511.

3. Glınsky, G.V.; *Biomedicines*, **2020,** 8, 129.

4. Glınsky, G.V.; *Biolocigal and Medicinal Chemistry,* **2020**.

5. Piletska, E.V.; Turner, N.W.; Turner, A.P; Piletsky, S.A.; *Journal of Controlled Release* **2005,** 108, 132-139.

6. Omar, S.; Bouziane, I.; Bouslama, Z.; Djemel, A.; *Biological and Medicinal Chemistry*, **2020**.

7. Alschuler, L.; Weil, A.; Horwitz, R.; Stamets, P.; Chiasson, A.M.; Crocker, R.; Maizes, V.; *Explore (New York, NY)* **2020**.

8. Inanan, T.; *International journal of biological macromolecules* **2016**, 92, 451-460.

9. Türkcan, C.; Somtürk, B.; Özdemir, N.; Özel, M.; Çatalkaya, R.; Aktaş Uygun, D.; Akgöl, S.; *Journal of Biomaterials Science, Polymer Edition* **2019,** 30, 947-960.

DOI: http://dx.doi.org/10.32571/ijct.1060235 **E-ISSN: 2602-277X**

10. O'Mahony, J.; Molinelli, A.; Nolan, K.; Smyth, M.R.; Mizaikoff, B.; *Biosensors and Bioelectronics* **2006**, 21, 1383-1392.

11. Song, X.; Wang, J.; Zhu, J.; *Materials Research* **2009,** 12, 299-304.

12. Xie, J.; Zhu, L.; Luo, H.; Zhou, L.; Li, C.; Xu, X.; *Journal of Chromatography A* **2001,** 934, 1-11.

13. Rahimi, M.; Bahar, S.; Heydari, R.; Amininasab, S.M.; *Microchemical Journal* **2019**, 148, 433-441.

14. Yao, Z.; Yang, X.; Liu, X.; Yang, Y.; Hu, Y.; Zhao, Z.; *Microchimica Acta* **2018,** 185, 70.

15. Patel, G.; Thakur, N.S.; Kushwah, V.; Patil, M.D.; Nile, S.H.; Jain, S.; Banerjee, U.C.; *Nanomedicine: Nanotechnology, Biology and Medicine* **2020,** 24, 102147.

16. Anandam, S.; Selvamuthukumar, S.; *Journal of Materials Science* **2014,** 49, 8140-8153.

17. Lozano-Pérez, A.A.; Rivero, H.C.; Hernández, M.D.C.P.; Pagán, A.; Montalbán, M.G.; Víllora, G.; Cénis, J.L.; *International Journal of Pharmaceutics* **2017**, 518, 11-19.

18. Hazra, M.; *Saudi pharmaceutical journal* **2015** 23, 429-436.

19. Curcio, M.; Cirillo, G.; Parisi, O.I.; Iemma, F.; Picci, N.; Puoci; F.; *Journal of functional biomaterials*, **2012**, 3, 269-282.