MULTIFUNCTIONAL COMPOSITES BASED ON ALGINATE HYDROGELS FOR POTENTIAL USE IN WOUND DRESSINGS

Bojana Obradović[1], Jasmina Stojkovska[1,2], Andrea Osmokrović[1], Vesna Mišković Stanković[1], Ivan Jančić[3], Marina Milenković[3]

[1]University of Belgrade - Faculty of Technology and Metallurgy,Belgrade, Serbia
[2]Innovation Center of the Faculty of Technology and Metallurgy, Belgrade, Serbia
[3]University of Belgrade - Faculty of Pharmacy, Belgrade, Serbia

Alginate hydrogels are widely used in wound dressings due to hydrophilicity, biocompatibility, flexibility, and high sorption capacity, providing effective moisture regulation in wounds and inducing rapid granulation and reepithelization of the damaged tissue. However, these dressings are not bioactive so that different methodologies have been investigated to extend functionality of alginate hydrogels.

In the present work, we show several approaches to achieve this aim by addition of different biologically active components. These include incorporation of silver nanoparticles as potent antimicrobial agents (1), bioactive honey components (2), activated charcoal (AC) particles as carriers of therapeutically active agents (3) as well as the use of Zn-alginate hydrogels that release zinc ions (4). The obtained composites were comprehensively characterized regarding composition, cytotoxicity, antibacterial activity, release kinetics of active agents and wound treatment in a rat model.

Ag/alginate nanocomposite hydrogels releasing silver ions and/or nanoparticles exhibited high bactericidal activity against a broad spectrum of standard and multi-drug resistant clinical bacterial strains (*Escherichia coli, Staphylococcus aureus,* methicillin-resistant *Staphylococcus aureus – MRSA, Acinetobacter baumannii* and *Pseudomonas aeruginosa*). Especially interesting results were obtained against 13 clinical isolates of *A. baumannii,* which were completely extinguished over 48 h in 6 cases (2). However, in 3 clinical isolates, antibacterial effects were not noticed implying possibility for development of bacterial resistance to silver. In the treatment of 2nd degree burns in rats Ag/alginate nanocomposites exhibited the same efficiency as commercial medical products (5).

Composite alginate hydrogels with immobilized AC particles impregnated with povidone iodine (PVP-I) as a model therapeutically active agent, were developed with the aim to provide controlled particle release in the wound without actually releasing the adsorbed substance, thus achieving the desired activity without adverse effects by systemic absorption. The composite Ca-alginate hydrogels induced strong bactericidal effects against two standard bacterial strains and clinical multi-resistant wound isolates (*MRSA, E. coli, P. aeruginosa, Enterococcus faecalis* and *Proteus mirabilis*) without releasing PVP-I in the environment (3). Furthermore, composite Zn-alginate hydrogels released zinc ions in addition to AC particles with adsorbed PVP-I, which induced additional microbicidal effects on one wild yeast strain (*Candida albicans*). The obtained bactericidal effects were ascribed to effective adsorption of bacteria onto AC particles and further direct contact with the adsorbed iodine, while the antifungal activity against *C. albicans* was assigned to released Zn^{2+}.

Overall, the developed composite alginate hydrogels have shown high potentials for utilization in variety of multifunctional wound dressings according to the specific needs.

References

1. Obradović B, Mišković-Stanković V, Jovanović Ž, Stojkovska J, Production of alginate microbeads with incorporated silver nanoparticles, patent RS53508-B1, SRB, 2015.
2. Stojkovska J, Petrovic P, Jancic I, Milenkovic M T, Obradovic B. Novel nano-composite hydrogels with honey effective against multi-resistant clinical strains of *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Appl Microbiol Biotechnol. 2019**;** 103: 8529-8543.
3. Osmokrovic A, Jancic I, Vunduk J, Petrovic P, Milenkovic M, Obradovic B. Achieving high antimicrobial activity: composite alginate hydrogel beads releasing activated charcoal with an immobilized active agent. Carbohydr. Polym. 2018; 196: 279-288.

MULTIFUNKCIONALNI KOMPOZITI NA BAZI ALGINATNIH HIDROGELOVA ZA POTENCIJALNU PRIMENU U OBLOGAMA ZA RANE

Bojana Obradović[1], Jasmina Stojkovska[1,2], Andrea Osmokrović[1], Vesna Mišković Stanković[1], Ivan Jančić[3], Marina Milenković[3]

[1]Univerzitet u Beogradu - Tehnološko-metalurški fakultet, Beograd, Srbija
[2]Inovacioni Centar Tehnološko-metalurškog fakulteta, Beograd, Srbija
[3]Univerzitet u Beogradu - Farmaceutski fakultet, Beograd, Srbija

Alginatni hidrogelovi se široko koriste u oblogama za rane zbog svoje hidrofilnosti, biokompatibilnosti, fleksibilnosti i velikog sorpcionog kapaciteta čime obezbeđuju efikasnu regulaciju vlažnosti rane i podstiču brzu granulaciju i reepitelizaciju oštećenog tkiva. Međutim, ove obloge nisu bioaktivne tako da su istraživane različite metodologije kako bi se proširila funkcionalnost alginatnih hidrogelova.

U ovom radu je prikazano nekoliko pristupa ostvarivanju tog cilja dodatkom različitih biološki aktivnih komponenata. Ovi pristupi uključuju inkorporaciju nanočestica srebra kao potentnog antimikrobnog agensa (1), bioaktivnih komponenata meda (2), čestica aktivnog uglja (AU) kao nosača terapeutski aktivnih agenasa (3), kao i primenu hidrogelova Zn-alginata koji otpuštaju jone cinka. Dobijeni kompoziti su sveobuhvatno karakterisani u pogledu sastava, citotoksičnosti, antibakterijske aktivnosti, kinetike otpuštanja aktivnih agenasa i tretmana rana u eksperimentalnom modelu opekotina na pacovima.

Ag/alginatni nanokompozitni hydrogelovi su usled otpuštanja jona i/ili nanočestica srebra, pokazali izraženu baktericidnu aktivnost prema širokom spektru standardnih i kliničkih multi-rezistentnih bakterijskih sojeva (*Escherichia coli, Staphylococcus aureus,* meticilin-resistentni *Staphylococcus aureus – MRSA, Acinetobacter baumannii* i *Pseudomonas aeruginosa*). Posebno interesantni rezultati su dobijeni u kulturama 13 kliničkih izolata *A. baumannii,* gde je u 6 slučajeva postignut potpun baktericidan efekat u toku 48 h (2). Ipak, kod 3 klinička izolata nije postignuto antibakterijsko dejstvo što ukazuje na mogućnost razvoja bakterijske rezistencije na srebro. U tretmanu opekotina drugog stepena na pacovima, Ag/alginatni nanokompoziti su pokazali istu efikasnost kao komercijalni medicinski proizvodi.

Kompozitni alginatni hidrogelovi sa imobilisanim česticama AU impregniranih povidon-jodom kao model terapeutski aktivnom komponentom, su razvijeni sa ciljem da obezbede kontrolisano otpuštanje čestica AU u rani bez otpuštanja adsorbovane supstance kako bi se na taj način postiglo željeno dejstvo bez neželjenih efekata sistemske apsorpcije. Kompozitni Ca-alginatni hidrogelovi su pokazali jake baktericidne efekte na dva standardna bakterijska soja i nekoliko kliničkih multi-rezistentnih izolata iz rana (*MRSA, E. coli, P. aeruginosa, Enterococcus faecalis* i *Proteus mirabilis*) bez otpuštanja povidon-joda u okolinu (3). Isto tako, kompozitni Zn-alginatni hidrogelovi su otpuštali jone cinka uz otpuštanje AU čestica sa adsorbovanim povidon-jodom što je prouzrokovalo dodatno mikrobicidno dejstvo na jedan divlji soj gljivice *Candida albicans*. Dobijeni baktericidni efekti su pripisani efikasnoj adsorpciji bakterija na čestice AU i daljem direktnom kontaktu adsorbovanog joda sa ćelijskom membranom bakterija, dok je antifungalna aktivnost u odnosu na *C. albicans* pripisana otpuštenim Zn^{2+} jonima.

Može se zaključiti da su razvijeni kompozitni alginatni hdrogelovi pokazali veliki potencijal za primenu u raznovrsnim multifunkcionalnim oblogama za rane prilagođenim specifičnim potrebama.

Literatura

1. Obradović B, Mišković-Stanković V, Jovanović Ž, Stojkovska J, Production of alginate microbeads with incorporated silver nanoparticles, patent RS53508-B1, SRB, 2015.
2. Stojkovska J, Petrovic P, Jancic I, Milenkovic M T, Obradovic B. Novel nano-composite hydrogels with honey effective against multi-resistant clinical strains of *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Appl Microbiol Biotechnol. 2019**;** 103: 8529-8543.
3. Osmokrovic A, Jancic I, Vunduk J, Petrovic P, Milenkovic M, Obradovic B. Achieving high antimicrobial activity: composite alginate hydrogel beads releasing activated charcoal with an immobilized active agent. Carbohydr. Polym. 2018; 196: 279-288.