POLY(SEBACIC ANHYDRIDE) MICROPARTICLES LOADED WITH CURCUMIN FOR PULMONARY PURPOSES

Konrad Kwiecień[1]*, Katarzyna Reczyńska-Kolman[1], Daria Niewolik[2], Katarzyna Jaszcz[2], Elżbieta Pamuła[1]

[1] AGH University of Science and Technology, Faculty of Materials Science and Ceramics, Department of Biomaterials and Composites, A. Mickiewicz Av. 30, 30-059 Kraków, Poland
[2] Silesian University of Technology, Department of Physical Chemistry and Technology of Polymers, M. Strzody str. 9, 44-100 Gliwice, Poland
*e-mail: kkwiecien@agh.edu.pl

Abstract

Microparticles (MPs) made of fast biodegrading biomaterials, loaded with drugs, are considered a superior treatment method for pulmonary infections. One of the promising biomaterials for obtaining such a drug delivery system (DDS) is poly(sebacic anhydride) (PSA) due to its favourable degradation kinetics and mechanism.

In this paper, we present a study of manufacturing MPs from PSA loaded with curcumin (CU) for pulmonary purposes. MPs were manufactured by oil-in-water emulsification; their morphology and size distribution were evaluated using optical microscopy, while the encapsulation efficiency and drug loading were obtained by the fluorometric assay. The cytotoxicity of the MPs, both the empty ones and loaded with CU, was analysed by in vitro tests with BEAS-2B human lung epithelial cells. To this end, metabolic activity by AlamarBlue assay and fluorescent staining (DAPI/eosin) of the cells were performed.

The MPs produced were round, regular in shape with diameters in the range of 1-5 μm and of yellow colour originating from CU. The CU encapsulation efficiency ranged from 42% to 55% and decreased with a higher CU ratio. The drug loading ranged from 4% to 11% and increased at a higher CU ratio. Both empty and CU-loaded MPs did not show a cytotoxic effect at concentrations up to 10 μg/ml.

Keywords: *poly(sebacic anhydride), curcumin, drug delivery system, pulmonary infections, polymeric microparticles*

[Engineering of Biomaterials 162 (2021) 7-12]

doi:10.34821/eng.biomat.162.2021.7-12

Introduction

Chronic obstructive pulmonary disease (COPD) is a life-threatening lung dysfunction. It is believed to be the third major cause of mortality worldwide, which led to the death of 3.17 million people in 2015 (5% of all deaths) [1]. COPD patients suffer from acute exacerbations, half of which are of bacterial origin. Such events occur usually 1.5-2 times a year for patients with moderate to severe lung obstruction, and most of them require hospitalization [2]. Conventional therapy is based on oral or intravenous administration of antibiotics. The relatively small portion of the drug reaching the alveolar region of the lungs is the cause of using high doses that lead to multiple side effects mostly in the gastrointestinal system, liver, and kidneys [3]. Moreover, such treatment leads to gaining resistance to antibiotics by the bacteria and, in consequence, reduces the number of potent antibiotics to be used to treat future exacerbations [4].

Among the possible solutions, fast biodegrading polymeric microparticles (MPs) acting as drug carriers in the inhaled drug delivery systems (DDS) are considered a treatment method for pulmonary infections that could ensure the therapeutic effect without severe side effects and at lower risk of developing resistance to antibiotics [5]. Poly(sebacic anhydride) (PSA) is regarded as a suitable material for this purpose. It is superior to other degradable polymers, e.g. poly(lactide-*co*-glycolide) (PLGA), because of its fast degradation kinetics according to the surface erosion mechanism. PSA undergoes an almost complete decomposition after several days of incubation in an aqueous environment [6-8].

Drug carriers for pulmonary purposes delivered by inhalation have to meet several requirements. First, their diameter size should be optimal: too large carriers cannot reach the deep regions of the lungs, whereas too small carriers are removed while exhaling. The beneficial diameter size range in which a significant pulmonary deposition occurs is 1-5 μm [9]. However, the exact values are highly dependent on breath-holding while inhaling. For inhalation with and without breath-holding the maximum values were determined as 1.5-2.5 μm and 2.5-4 μm, respectively [10]. Another study confirmed that the MPs of such diameters have the highest alveolar deposition [11]. Moreover, the interactions between the carrier and the drug should support a high encapsulation efficiency. Physicochemical properties of the drug, the matrix and their compatibility strongly influence the drug loading capacity [12,13].

As it is not possible to eliminate antibiotics from COPD exacerbations treatment, it is important to reduce their doses without losing therapeutic effects. One approach to obtain that is to combine antibiotics with quorum sensing inhibitors (QSIs) [14,15]. Briefly, such substances inhibit bacterial activity and prevent bacteria from creating biofilm, making them more sensitive to antibiotics and the components of the patient's immune system [16]. Curcumin (CU) is an example of QSI, which is also a widely used colouring factor in the food industry. CU is also used in various studies for fluorescent labelling [17,18], enabling measurements of encapsulation efficiency by fluorometric assays. It was also shown that antibiotics used for pulmonary therapies (i.e. gentamycin, azithromycin) combined with curcumin show enhanced germicidal properties [19].

Therefore, in this study, we designed a novel inhalable DDS consisting of PSA MPs loaded with CU for the treatment of exacerbations in COPD patients. We characterised the PSA MPs properties and behaviour in contact with model human lung epithelial cells.

Materials and Methods

PSA was obtained by two-step melt polycondensation, as previously described [8]. Sebacic acid (10 g) was refluxed in acetic anhydride (1:10 w/v) under the nitrogen flow for 40 min. After this time, the excess of acetic anhydride and acetic acid formed in the reaction was removed under vacuum. The remaining diacyl derivative of sebacic acid (prepolymer) was heated at 150ºC for 2 h with constant stirring under vacuum (0.1 mm Hg) and nitrogen. PSA in the form of a solid material was obtained with a yield of more than 90%. The obtained polymer was stored in a freezer. The thermal properties of the polymer were investigated using the 822^e DSC Mettler Toledo differential scanning calorimeter. The sample was tested in a temperature range of -70ºC to 250ºC at a heating rate of 10ºC/min. The structure of PSA was studied by the ^{1}H and ^{13}C NMR spectroscopy (Varian UNITY/INOVA spectrometer (300 MHz)) ^{1}H NMR ($CDCl_3$, ppm) δ: 2.40 - 2.50 (m, 4H, -CH_2C(O)OC(O)-), 2.22 (s, 6H, CH_3C(O)OC(O)-), 1.55 - 1.74 (m, 4H, -CH_2CH_2C(O)OC(O)-), 1.22 - 1.44 (m, 8H, -CH_2-). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.53 (C=O, anhydride), 35.18 (-CH_2C(O)OC(O)-), 28.80 (-CH_2CH_2C(O)OC(O)-), 24.10 (-CH_2-).

The molecular weight (M_w) of PSA was determined in methylene chloride by gel-permeation chromatography (GPC) using Agilent Technologies Infinity 1260 chromatograph that was equipped with a refractive index detector and calibrated with polystyrene standards. The sample was pre-filtered prior to analysis. The evaluation of M_w by the ^{1}H NMR analysis was calculated on the basis of dependence shown in eq. 1:

$$M_w = n_{SA} \cdot M_{SA} + M_{end\ groups} \quad (1)$$

where: M_w - molecular weight, n_{SA} - number of repeating unit of PSA, M_{SA} - molar mass of repeating unit of PSA, $M_{end\ groups}$ - molar mass of end groups in polyanhydride equal to 102 g/mol.

The n_{SA} parameter was calculated from the ^{1}H NMR spectra as the intensity ratio between PSA protons and end groups protons as in eq. 2:

$$n_{SA} = \frac{I_{[1H]SA}}{I_{[1H]end\ groups}} \quad (2)$$

where: $I_{[1H]SA}$ - intensity of one PSA proton, $I_{[1H]end\ groups}$ - intensity of one proton of end groups.

MPs were manufactured using solid-in-oil-in-water emulsification (S/O/W). As a solid phase (S) different amounts of CU (Sigma-Aldrich) – 3 mg, 6 mg, and 12 mg per batch (5, 10, and 20 mg / 100 mg of PSA, respectively, equal to CU:PSA ratio of 1:20, 1:10 and 1:5, respectively), were used. As an oil phase (O), a PSA solution in dichloromethane (DCM) (Chemland) – 20 mg/ml was prepared. As a water phase acted the (W) poly(vinyl alcohol) (PVA) (Mowiol® 4-88, M_w = 31 kDa, Sigma-Aldrich) solution in ultra-high quality water (UHQ-water) – 80 mg/ml. Before the process, all the O and W phases were cooled in ice. The CU portions were dissolved in 3 ml of the PSA solution in DCM using an ultrasound probe (1 min, amplitude 40%, pulsation workpause 10 s – 5 s; SONICS Vibra cell). The 20 ml of the W phase was placed on the magnetic stirrer (JEIO TECH Multichannel stirrer) at 1500 rpm. Then, 3 ml of the O phase was poured into the W phase with constant stirring. The organic solvent was being evaporated for 4.5 h under constant magnetic stirring. The suspension of MPs was then collected and centrifuged (MPW-351R) at 15000 rpm for 10 min to remove the PVA excess from the MPs; the process was repeated 3 times. The water after the first 2 centrifugations was collected for encapsulation efficiency studies. Then, the MPs were freeze-dried for 24 h (Martin Christ Alpha 1-2 LDplus) and stored at -20ºC.

The morphology of the MPs was evaluated using an optical microscope (ZEISS Axiovert 40 CFL), and the diameter of the MPs was measured using ImageJ software (n = 1000).

The encapsulation efficiency of CU was determined in the supernatant after the MPs centrifugation using a fluorometric assay. The samples of the supernatant were diluted with dimethyl sulfoxide (DMSO) (POCH S.A.) in a volumetric ratio of 1:10 to dissolve residual CU. CU in known concentrations (0-100 µg/ml, step 10 µg/ml) was dissolved in the same mixture water:DMSO (1:10) for the preparation of the calibration curve. The linear relationship was evaluated in the range 0-20 µg/ml CU.

The samples of both calibrations and supernatants diluted in DMSO were placed in a black 96-well TCPS plate (100 µl/well, n = 3 for each sample). Measurements at excitation wavelength 485-412 nm and emission wavelength 590-510 nm were made using the plate reader (FluoStar OMEGA, BMG LabTech).

The encapsulation efficiency was determined as:

$$\textit{Encapsulation efficiency} = \frac{\text{encapsulated CU}}{\text{initial CU addition}} \cdot 100\% \quad (3)$$

and the drug loading was determined as:

$$\textit{Drug loading} = \frac{\text{encapsulated CU}}{\text{MP mass}} \cdot 100\% \quad (4)$$

BEAS-2B human lung epithelial cells (ATCC, CRL-9609™) were used to evaluate the biological properties of the developed MPs system. The cells were cultured in cell culture flasks in Dulbecco's modified Eagle's medium (DMEM) with 10% volume of fetal bovine serum (FBS) and 1% mixture of penicillin (10,000 U/ml) and streptomycin (10 mg/ml) (all chemicals from PAN Biotech). Before the experiment, the cells were seeded in a 96-well TCPS plate (10 000 cells/well in 100 µl medium) and incubated for 24 h at 37ºC and 5% CO_2. Then, the medium was replaced with the suspension of empty and CU-loaded MPs (CU:PSA equal to 1:10) at different concentrations from 0 to 1000 µg/ml.

To test cell metabolic activity, an AlamarBlue assay (resazurin-based, Sigma-Aldrich) was performed. The MPs were sterilized by 40-minute exposure to UV radiation. After the 24 h incubation of the cells with MPs, the suspensions were removed and the cultured cells were washed with Dulbecco's Phosphate Buffer Saline (DPBS) (PAN Biotech). The resazurin reduction based viability assay (AlamarBlue, Sigma-Aldrich) was conducted by filling each well with 150 µl of 10% AlamarBlue solution in DMEM and 3 h incubation at 37ºC. The fluorescence was then measured using the fluorometer (FluoStar OMEGA, BMG LabTech) at the excitation wavelength 544 nm and the emission wavelength 590 nm. The relative reduction of resazurin was evaluated using the equation:

$$RR = \frac{F_{sample} - F_0}{F_{100} - F_0} \quad (5)$$

where: RR - resazurin reduction, F_{sample} - fluorescence measured for the sample, F_0 - fluorescence measured for the DMEM-AlamarBlue mixture incubated in empty wells (0% relative resazurin reduction), F_{100} - fluorescence measured for DMEM-AlamarBlue mixture completely reduced in an autoclave (100% relative resazurin reduction). The statistical significance of the obtained differences was evaluated with ANOVA and the *post hoc* Tukey HSD test.

The 4',6-Diamidino-2-Phenylindole (DAPI, Sigma Aldrich) and eosin (Thermo Scientific) fluorescence staining was performed to evaluate the cell morphology. Before staining, the MPs suspension was removed from the wells, the cells were washed with DPBS with the addition of Ca/Mg ions (PAN Biotech), and the cells were fixed with 4% paraformaldehyde (Sigma-Aldrich) for 15 min. The cells were then washed 2 times with DPBS-Ca/Mg, incubated in the 0.1% Triton X solution (Sigma Aldrich), and again washed 2 times with DPBS-Ca/Mg. The preserved cells were incubated for 5 min in the eosin solution (0.5 % (w/v) in acidified ethanol, Sigma Aldrich), washed 5 times with DPBS-Ca/Mg and incubated in the DAPI solution for 15 min, and washed 3 times. Finally, the observations were made on a fluorescent microscope (ZEISS Axiovert 40 CFL) with ZEISS HXP 120 C metal halide illuminator.

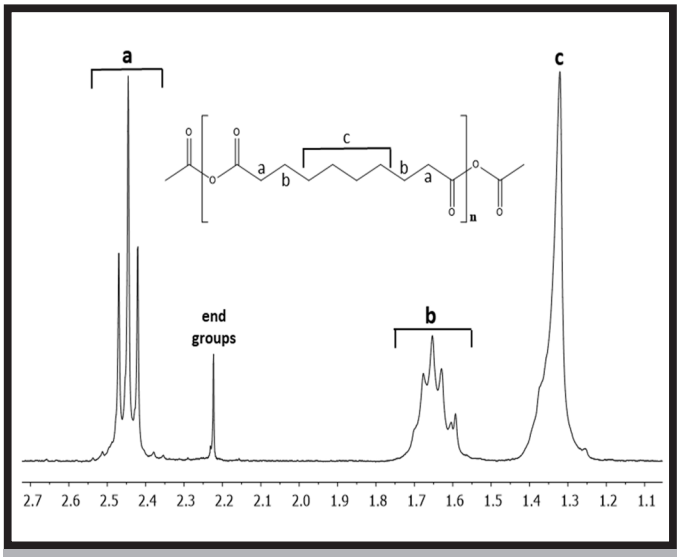

FIG. 2. ^{1}H NMR spectra of PSA.

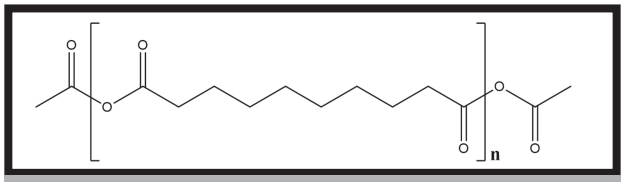

FIG. 1. Chemical structure of PSA.

Results and Discussions

Poly(sebacic acid) structure and properties

Poly(sebacic acid) (PSA) was obtained by melt polycondensation of sebacic acid with the use of acetic anhydride. The structural formula of PSA is presented in FIG. 1.

The obtained polymer was a solid crystalline material, with a melting temperature T_m = 82ºC. The relative crystallinity estimated by dividing the determined heat of fusion of PSA (ΔHm = -94,6 J/g) by theoretical value (-115 J/g) was equal to 80%. The polymer was found to be soluble in chlorinated and partially in aromatic solvents, but insoluble in water, ethanol, acetone, diethyl ether, hexane, THF and DMSO. To determine the structure of PSA, the ^{1}H NMR spectra (FIG. 2) and ^{13}C NMR spectra were made. The successful synthesis of polyanhydride was confirmed by the anhydride bond formation. The presence of the signal at δ = 169.53 ppm (in the ^{13}C NMR spectrum), assigned to carbonyl carbon atoms in anhydride, and the signal at δ = 2.40-2.50 ppm (in ^{1}H NMR spectrum), assigned to methylene protons close to anhydride groups, confirmed the formation of anhydride bonds.

The molecular weight of PSA was calculated from ^{1}H NMR and determined by GPC. The molecular weight calculated from ^{1}H NMR was approximately 10,000 Da, which corresponded to a polymer consisting of ca. 50 repeating units, whereas the one determined by GPC was 10800 Da. It indicates a good correlation between the obtained molecular weights.

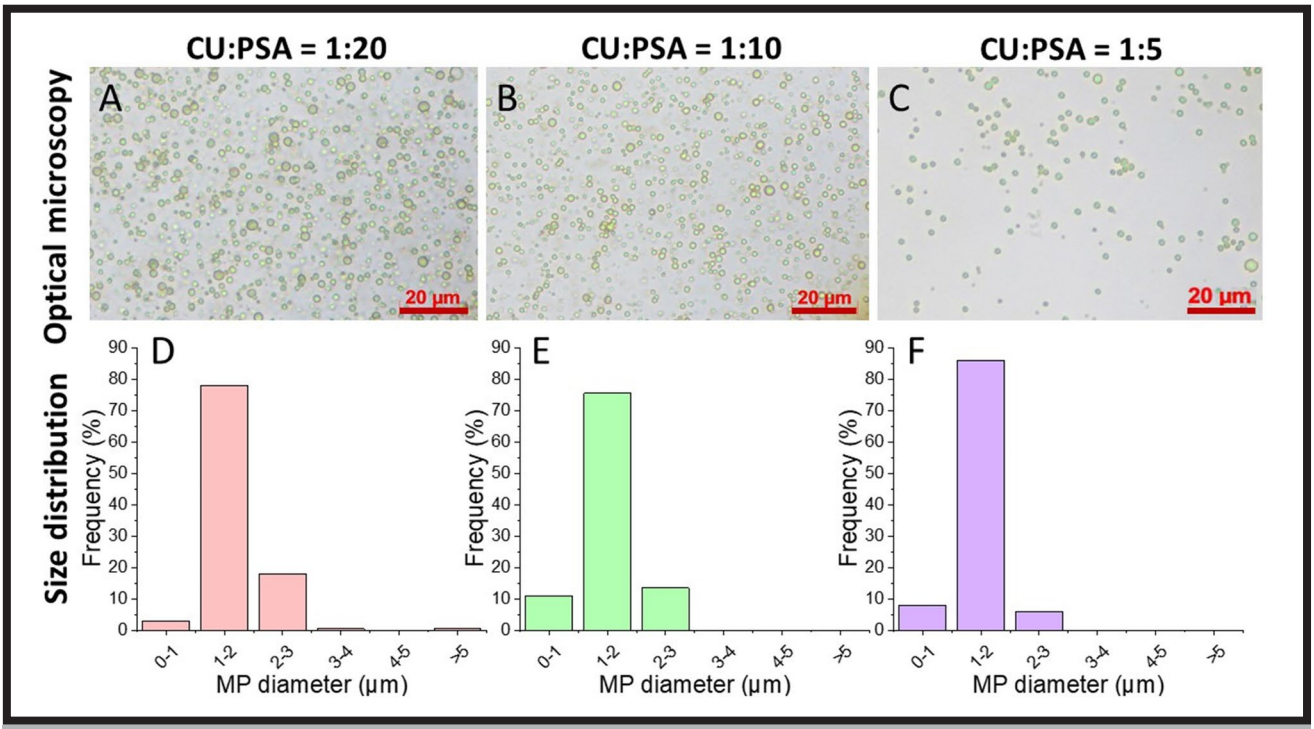

FIG. 3. Morphology (A, B, C) and size distribution (D, E, F) of PSA microparticles with different concentrations of curcumin to PSA (weight ratio): 1:20 (A, D), 1:10 (B, E) and 1:5 (C, F) – pictures from the optical microscope and histograms of diameter size distributions.

Microparticle morphology and size

The manufactured MPs were spherical in shape and yellow from the encapsulated CU (FIG. 3 A-C). In all the cases, the majority of the MPs had diameters in the range of 1-2 μm. The number of MPs with diameters exceeding 5 μm was negligible. There were some MPs with the diameter smaller than 1 μm (FIG. 3 D-F). Yet, in each case, more than 90% of the MPs were in the appropriate size for administration via inhalation [9]. However, to obtain the best pulmonary deposition, the MPs could have slightly larger diameters to fit more to the range of 1.5-2.5 μm [10]. The median size gradually decreased with an increasing CU:PSA weight ratio (median: 1.53 μm, 1.48 μm, and 1.43 μm for CU:PSA equal to 1:20, 1:10 and 1:5, respectively).

Encapsulation efficiency and drug loading

The encapsulation efficiency and resulting MPs loading was evaluated for all the batches. For the 1:20 and 1:10 CU:PSA ratio, we obtained the encapsulation efficacies without significant differences ($\alpha = 0.05$) – 54.6 ± 1.0% and 55.0 ± 2.6%, respectively. At the 1:5 ratio, the efficiency decreased significantly ($p < 0.001$) to 42.8 ± 0.7% (FIG. 4A). However, the drug loading increased significantly ($p < 0.001$) at each subsequent higher CU ratio – 4.5 ± 0.1%, 7.9 ± 0.4%, and 11.0 ± 0.2% for 1:20, 1:10 and 1:5 CU:PSA ratio, respectively (FIG. 4B). Although the process was less efficient at a higher CU ratio, the final drug loading was much higher. The encapsulation efficiency was satisfactory but not very high, so future work may focus on improving that value. In the other studies, for similar MPs made out of PLGA for different biomedical purposes, the encapsulation efficiencies were higher, e.g. around 67% for lipid-PLGA hybrid MPs [20] and up to around 95% for PLGA MPs with electrospray droplet formulation [21]. On the other hand, the most important value is the drug loading, and manufacturing the MPs that consist of the drug in 11% mass is a promising result that confirms a good CU-PSA compatibility. For comparison, in [20] the drug loading was evaluated as 1.85 ± 0.19%. All of the MPs glowed intensively in green colour under a fluorescence microscope (FIG. 4C), indicating that the CU was effectively and uniformly encapsulated within the MPs.

***In vitro* tests of microparticles**

The BEAS-2B cells were cultured for 24 h and then the MPs (empty or CU-loaded, obtained at CU:PSA ratio 1:10) suspensions (concentrations: 0.1, 1, 5, 10, 50, 100, 500, and 1000 μg/ml DMEM) were added to the wells. To evaluate the viability of the cells incubated in contact with the MPs for 24 h, the metabolic test AlamarBlue was performed on both the empty MPs and CU-loaded MPs. The fluorescent staining by DAPI/eosin was performed to assess the cell morphology.

AlamarBlue tests did not show a cytotoxic effect up to 10 μg/ml for both empty (FIG. 5A) and CU-loaded MPs (FIG. 5B). Above this concentration (up to 100 μg/ml), a gradual decrease in the cell viability was observed. The reduction of resazurin decreased by 23.8% for 50 μg/ml and by 35.5% for 100 μg/ml for the empty MPs suspensions, and by 22.4% for 50 μg/ml and by 36.1% for 100 μg/ml, as compared to the control. For the highest concentrations of MPs (500 and 1000 μg/ml) the viability decreased rapidly by 90.3% for 500 μg/ml and by 98.4% for 1000 μg/ml (empty MPs), and by 70.3% for 500 μg/ml and by 84.8% for 1000 μg/ml. These results were consistent with the DAPI/eosin staining. The cells cultured in contact with MPs looked similar in each well with a low concentration of MPs suspension. For 50 μg/ml and higher concentrations, a significant amount of the stained MPs residue was visible in each well, with a decreasing number of cells. The cells nuclei were DAPI stained in all cases. The cytoplasm was stained with eosin; however, it was properly stained only up to the 50 μg/ml MPs concentration. For concentrations of 100 μg/ml and 1000 μg/ml, the signal from the MPs residues was too strong. We chose DAPI (blue staining of cell nuclei) and eosin (red staining of the cytoskeleton) to avoid overlapping of green colour from the MPs (FIG. 4C). However, this was not sufficient, as the residues of degraded MPs, which were not removed during washing, absorbed eosin, resulting in a very intense red glow, much brighter than the cytoplasm of the cells stained by eosin. Zhang et al. [22] tested a PSA-based polymer, synthesized with poly(ethylene glycol), nanoparticles *in vitro* in contact with L929 and MCF-7 cell lines and obtained no cytotoxicity up to 220 μg/ml. The cytotoxic effect observed in this study at lower concentrations could result from the high sensitivity of BEAS-2B cells.

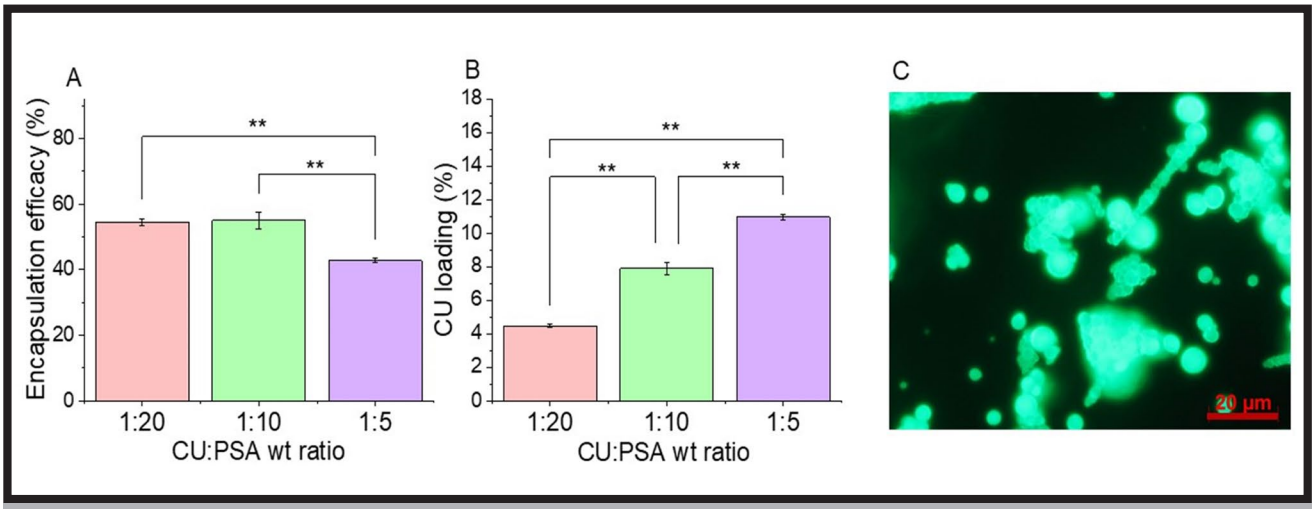

FIG. 4. Encapsulation efficiency (A), CU loading in the PSA MPs (B), and a picture from the fluorescent microscope (MPs obtained with CU:PSA ratio of 1:10) (C); * - $p < 0.01$, ** - $p < 0.001$ – the significance levels, according to ANOVA and post hoc Tukey HSD test.

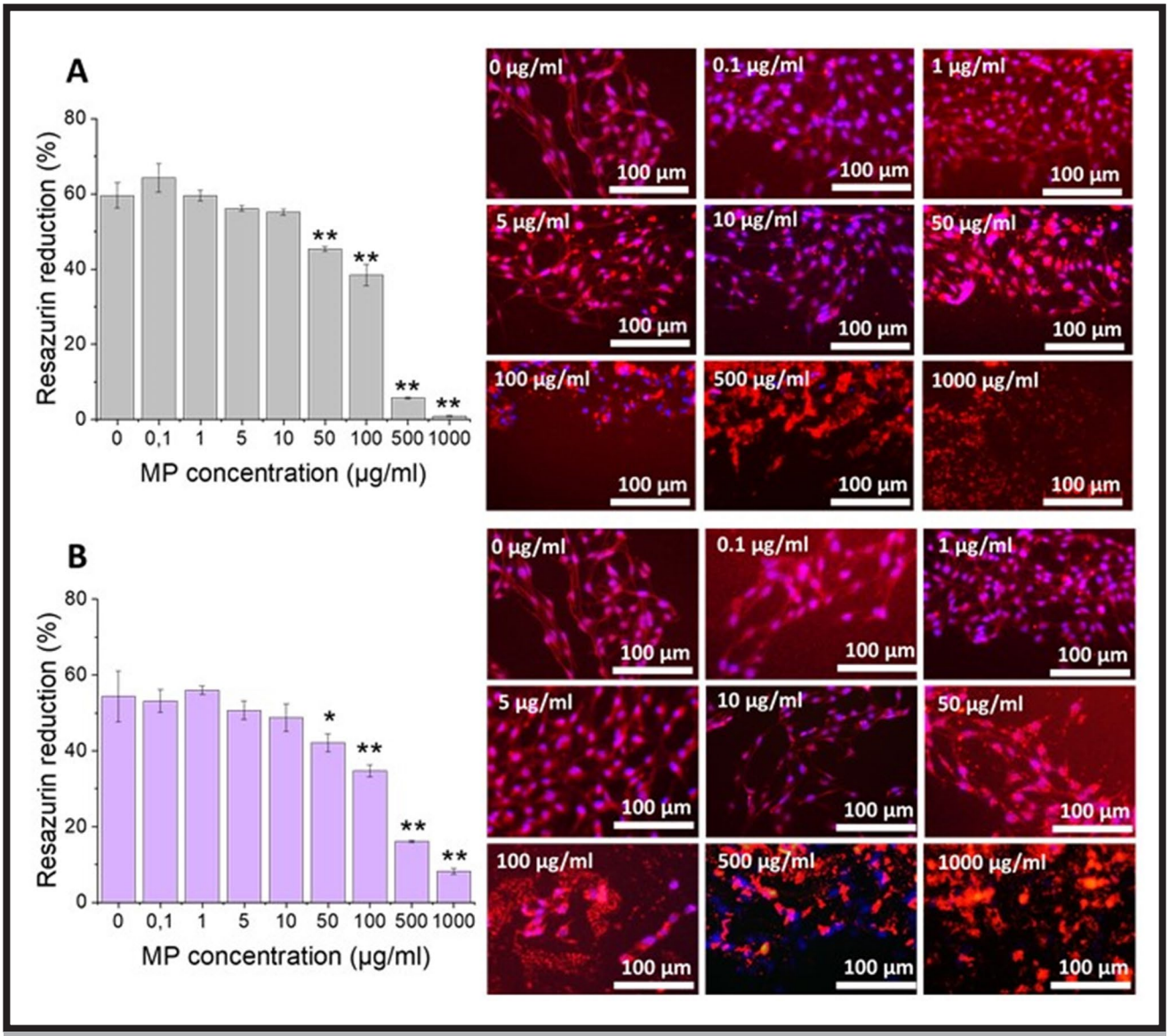

FIG. 5. Cytotoxicity test results – AlamarBlue (left) and DAPI/eosin fluorescent staining (right). A – empty MPs, B – CU-loaded MPs; * - p < 0.01, ** - p < 0.001 – significance levels, according to ANOVA and the post hoc Tukey HSD test.

The AlamarBlue results indicated that CU-loaded MPs were less cytotoxic than the empty ones: the difference in viability at 50 µg/ml was less significant for the CU-loaded MPs. However, the AlamarBlue is a fluorescent test. Therefore, there is a possibility that the evaluated resazurin reductions for the CU-loaded MPs overlapped with the signal of the MPs residue unwashed from the well. Such an effect is possible. As it was previously proved, pure CU influences the BEAS-2B cells negatively, and the influence decreases while the CU is encapsulated within the liposomes [23]. On the other hand, overlapping should be observed at a significant level only for the wells where the relatively high concentrations of MPs were applied (i.e. 500, 1000 µg/ml). At these concentrations, the pictures from the fluorescent microscope showed a significant amount of MPs residues that could influence the measurements. Below these concentrations, the significant overlapping is much less probable. However, this conclusion should be confirmed in the future by evaluating the background from the CU-loaded MPs residue at the analysed concentrations.

Conclusions

This work aimed to manufacture the cytocompatible CU-loaded PSA MPs with the 1-5 µm diameter size f, the narrow size distribution, and the sufficient CU loading. Three batches of the MPs were prepared using different ratios of CU to PSA: 1:20, 1:10, and 1:5. In all the samples, more than 90% of the MPs had diameters in the range of 1-3 µm, meeting the size and uniform distribution conditions for administration via inhalation. Additionally, all the MPs were spherical and of yellow colouration resulting from the CU encapsulation.

The encapsulation efficiency was satisfactory in the range of 42-55% and decreased with a higher CU:PSA ratio. On the other hand, the CU loading increased at a higher CU ratio from 4.5 ± 0.1% to exquisite 11.0 ± 0.2%.

The cytocompatibility tests did not show a toxic effect at the low concentrations of MPs in the suspension (up to 10 µg/ml). Above that concentration, the viability of the cells gradually decreased for both the empty and CU-loaded MPs. However, the cells in contact with CU-loaded MPs showed a slightly lower decrease in their metabolic activity, indicating that the presence of CU decreased the system toxicity.

To sum up, it was possible to manufacture the MPs from PSA in the proper sizes for pulmonary administration that are loaded with CU in a sufficient ratio. Such MPs appear to be safe for human lung epithelial cells (BEAS/2B) up to 10 μg/ml. The surface of a single well was 0.33 cm^2 which is approximately 10^6 times smaller than the surface area of the human lung, indicating the cytocompatible limit of the MPs to be administrated at around 30 g. Moreover, the limit of MPs concentration per surface unit should be higher *in* vivo, as the cells in the tissue are densely packed. Therefore, the cytotoxicity evaluated in this study should not be a limitation for pulmonary purposes. However, this is only an estimation. Without the aerodynamics study of the MPs using a cascade impactor, it is not possible to determine the exact amount of the MPs that would reach the alveolar region. The example of such a study [24] showed that the alveolar deposition of an inhalable aerosol with particles in the diameter range of 4.70-5 μm could be estimated at around 7.7-11.5%. Therefore, future studies will focus on the following methodological aspects: 1) determining the fluorescent background of the degraded MPs residue in the AlamarBlue test, 2) choosing another cell visualisation method to prove the superior cytocompatibility of CU-loaded MPs to the empty ones, and 3) eliminating the signal overlapping from the MPs during fluorescent microscopic observations, as by eosin staining. Moreover, the future work will focus on the further increase of the CU loading within the PSA MPs or MPs obtained from other polyanhydrides and the co-encapsulation of CU and antibiotics in one formulation, accompanied by evaluating its germicidal properties.

Acknowledgements

This study was supported by the National Science Center, Poland (project No. 2019/35/B/ST5/01103) and by the Program "Excellence Initiative – Research University" for the AGH University of Science and Technology.

ORCID iDs

K. Kwiecień: https://orcid.org/0000-0002-9504-1205
K. Reczyńska-Kolman: https://orcid.org/0000-0002-5266-9131
D. Niewolik: https://orcid.org/0000-0003-2472-3943
K. Jaszcz: https://orcid.org/0000-0003-4883-8278
E. Pamuła: https://orcid.org/0000-0002-0464-6189

References

[1] J.B. Soriano, A.A. Abajobir, K.H. Abate, et al.: Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 5(9) (2017) 691-706, doi: 10.1016/S2213-2600(17)30293-X.
[2] C.F. Vogelmeier, G.J. Criner, F.J. Martinez, et al.: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med 195(5) (2017) 557-582, doi: 10.1164/rccm.201701-0218
[3] J. Marchant: When antibiotics turn toxic. Nature 555(7697) (2018) 431-433, doi: 10.1038/d41586-018-03267-5.
[4] R. Hershberg: Antibiotic-Independent Adaptive Effects of Antibiotic Resistance Mutations. Trends in Genetics 33(8) (2017) 521-528, doi: 10.1016/j.tig.2017.05.003.
[5] A.K. Thakur, D.K. Chellappan, K. Dua, M. Mehta, S. Satija, I. Singh: Patented therapeutic drug delivery strategies for targeting pulmonary diseases. Expert Opinion on Therapeutic Patents 30(5) (2020) 375-387, doi: 10.1080/13543776.2020.1741547.
[6] J. Fu, C. Wu: Laser light scattering study of the degradation of poly(sebacic anhydride) nanoparticles. Journal of Polymer Science Part B: Polymer Physics 39(6) (2001) 703-708, doi: 10.1002/1099-0488(20010315)39:6<703::AID-POLB1044>3.0.CO;2-B.
[7] Z. Deng, A. Schweigerdt, A. Norow, K. Lienkamp: Degradation of Polymer Films on Surfaces: A Model Study with Poly(sebacic anhydride). Macromolecular Chemistry and Physics 220(15) (2019) 1900121, doi: 10.1002/macp.201900121.
[8] K. Jaszcz: Synthesis and Characterization of New Functional Poly(ester-anhydride)s Based on Succinic and Sebacic Acids. Macromol. Symp. 254(1) (2007) 109-116, doi: 10.1002/masy.200750817.
[9] M. Paranjpe, C.C. Müller-Goymann: Nanoparticle-Mediated Pulmonary Drug Delivery: A Review. International Journal of Molecular Sciences 15(4) (2014) Art. 4, doi: 10.3390/ijms15045852.
[10] P.R. Byron: Prediction of Drug Residence Times in Regions of the Human Respiratory Tract Following Aerosol Inhalation. Journal of Pharmaceutical Sciences 75(5) (1986) 433-438, doi: 10.1002/jps.2600750502.
[11] J. Heyder, J. Gebhart, G. Rudolf, C.F. Schiller, W. Stahlhofen: Deposition of Particles in the Human Respiratory Tract in the Size Range 0.005-15 μm. Journal of Aerosol Science 17(5) (1986) 811-825.
[12] S.R. Shah, A.M. Henslee, P.P. Spicer. et al.: Effects of Antibiotic Physicochemical Properties on Their Release Kinetics from Biodegradable Polymer Microparticles. Pharm Res 31(12) (2014) 3379-3389, doi: 10.1007/s11095-014-1427-y.
[13] Z. Huang, S.N. Kłodzińska, F. Wan, H.M. Nielsen: Nanoparticle-mediated pulmonary drug delivery: state of the art towards efficient treatment of recalcitrant respiratory tract bacterial infections. Drug Deliv. and Transl. Res. 11(4) (2021) 1634-1654, doi: 10.1007/s13346-021-00954-1.
[14] V.C. Kalia: Quorum sensing inhibitors: An overview. Biotechnology Advances 31(2) (2013) 224-245, doi: 10.1016/j.biotechadv.2012.10.004.
[15] M. Whiteley, S.P. Diggle, E.P. Greenberg: Progress in and promise of bacterial quorum sensing research. Nature 551(7680) (2017) 313-320, doi: 10.1038/nature24624.
[16] T. Defoirdt, G. Brackman, T. Coenye: Quorum sensing inhibitors: how strong is the evidence? Trends in Microbiology 21(12) (2013) 619-624, doi: 10.1016/j.tim.2013.09.006.
[17] E. Akbari, O. Akhavan, S. Hatamie, R. Rahighi: Curcumin as a green fluorescent label to revive the fluorescence property of functionalized graphene oxide nanosheets. Journal of Drug Delivery Science and Technology 45 (2018) 422-427, doi: 10.1016/j.jddst.2018.04.010.
[18] A. Kumar, L. Li, A. Chaturvedi, J. Brzostowski, et al.: Two-photon fluorescence properties of curcumin as a biocompatible marker for confocal imaging. Appl. Phys. Lett. 100(20) (2012) 203701, doi: 10.1063/1.4717753.
[19] S. Bahari, H. Zeighami, H. Mirshahabi, S. Roudashti, F. Haghi: Inhibition of Pseudomonas aeruginosa quorum sensing by subinhibitory concentrations of curcumin with gentamicin and azithromycin. Journal of Global Antimicrobial Resistance 10 (2017) 21-28, doi: 10.1016/j.jgar.2017.03.006.
[20] P.-C. Li, S.-C. Chen, Y.-J. Hsueh, et al.: Gelatin scaffold with multifunctional curcumin-loaded lipid-PLGA hybrid microparticles for regenerating corneal endothelium. Materials Science and Engineering: C 120 (2021) 111753, doi: 10.1016/j.msec.2020.111753.
[21] S. Yuan, F. Lei, Z. Liu, Q. Tong, T. Si, R.X. Xu: Coaxial Electrospray of Curcumin-Loaded Microparticles for Sustained Drug Release. PLOS ONE 10(7) (2015) e0132609, doi: 10.1371/journal.pone.0132609.
[22] J. Zhang, Y. Liang, N. Li, et al.: Poly(ether-ester anhydride)-based amphiphilic block copolymer nanoparticle as delivery devices for paclitaxel. Micro Nano Lett. 7(2) (2012) 183, doi: 10.1049/mnl.2011.0580.
[23] T. Zhang, Y. Chen, Y. Ge, Y. Hu, M. Li, Y. Jin: Inhalation treatment of primary lung cancer using liposomal curcumin dry powder inhalers. Acta Pharmaceutica Sinica B 8(3) (2018) 440-448, doi: 10.1016/j.apsb.2018.03.004.
[24] J. Fiegel, L. Garcia-Contreras, M. Thomas, et al.: Preparation and in Vivo Evaluation of a Dry Powder for Inhalation of Capreomycin. Pharm Res 25(4) (2008) 805-811, doi: 10.1007/s11095-007-9381-6.