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Research article

Novel biopolymer spray formulation for drug delivery in precision dentistry

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ABSTRACT

Addressing the growing challenges of periodontal and peri-implant diseases, this study first reports a promising advancement in precision dentistry: an intricately formulated biopolymer spray designed for precise, localized drug delivery during tailored dental procedures. Poly (lactic-*co*-glycolic acid) (PLGA), recognized for its controlled release, biodegradability, and FDA-approved biocompatibility, forms the core of this formulation. Utilizing the double emulsion method, PLGA microparticles (PLGA-MPs) were loaded with dental antibiotics: sodium amoxicillin (AMX-Na), trihydrate amoxicillin (AMX-Tri), and metronidazole (Met). This antibiotic combination was thoughtfully selected to meet the distinctive requirements of the most impacting dental treatments. The newly developed biopolymer spray underwent thorough in-vitro analysis, revealing an optimized release curve for antibiotics over time, guaranteeing sustained therapeutic efficacy, and dose-dependent efficacy, accommodating personalized treatment approaches. The positive outcomes position the novel biopolymer spray formulation the leaders in advancing localized drug delivery during dental procedures. Moreover, the precise application and the tunable formulation meets the concept of precision medicine: in detail, this formulation represents a significant stride in dental therapeutics, significantly contributing to the predictability of dental implantology.

1. Introduction

Dental implants have strengthened their role in the global market as a reliable therapeutic approach for tooth replacement, becoming one of the most performed surgical interventions. On the other side, peri-implantitis has dramatically become the most challenging complication in dental implantology, affecting approximately 15 % of dental implants placed worldwide each year [1]. Peri-implantitis is an inflammatory, multifactorial condition, affecting peri-implant tissues; the bacterial aetiology creates the

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pathogenic environment able to exacerbated the worsening effect raised by other co-factors, such as the incorrect masticatory loading, or the presence of dehiscence between the bone-to-implant surface [2].

Peri-implant inflammation is closely linked to the accumulation of a specific bacterial biofilm; typically, the periodontal pathogens initiate their activity in the soft tissues in contact with dental crown, rapidly progressing towards the underlying peri-implant bone. The progressive bone loss promoted by the bacteria-sustained inflammation is an irreversible process that, if left unmanaged, may culminate in implant failure [3]. Additionally, a wealth of literature confirms that peri-implantitis acts as a non-specific trigger for systemic inflammation, increasing the pathogenic potential of numerous acute or chronic-degenerative conditions affecting organs in districts even far from the oral cavity [4]. Nowadays, various protocols exist for managing peri-implant disease; however, they are mostly based on the symptomatology referred by patients, or on clinical and radiological evidence, often resulting in a tardive and poorly effective clinical management of the advanced/late stages of peri-implantitis [5]. In this landscape, the prevention of peri-implant disease should be considered a successful strategy, by focusing on enhancing the bioactivity of implant surfaces and betting on the potential of personalized therapies to increase therapeutic efficacy while reducing adverse effects.

Drug delivery is a continuously improving technology intertwined with factors such as the nature of the drug, administration protocols, patient clinical conditions, and drug administration. A reliable Drug Delivery System (DDS) stands as a promising therapeutic tool for a groundbreaking approach of oral diseases. DDS is simplistically based on a) biomaterials with exceptional performance, used as drug delivery platforms, and b) an effective formulation capable to face different clinical issues in a single administration [6]. The challenges to develop and validate formulations or technologies designed to optimize the safety and efficacy of drugs can be overcome through the creation of prototypes properly characterized with regard to i) drug delivery rate, ii) release-curve behaviour, and iii) local efficacy over-time [7]. Over the past two decades, there has been a remarkable evolution in controlled DDSs, progressing from macro- and nano-scale devices, to smart and targeted drug delivery systems [8].

In detail, biodegradable polymers have garnered attention within the scientific community for their potential use in biomedical fields; among various polymer types, poly (lactic-*co*-glycolic acid) (PLGA) has emerged as a tunable carrier for drugs, proteins, and other macromolecules such as DNA and RNA [9]. PLGA, a copolymer of lactic acid (LA) and glycolic acid (GA) in varying proportions, undergoes degradation through ester bridge hydrolysis. The degradation rate may depend on environmental factors, especially temperature and humidity. Moreover, the degradation rate is directly contingent on the ratio of the two co-monomers; in fact, an increase in LA content augments the degradation rate [9]. Leveraging its favourable attributes, including biocompatibility, non-toxicity, and malleability, extensive research has focused on employing PLGA in pharmaceutical and medical device materials [9].

Interestingly, PLGA can be engineered into particles with diverse sizes. In this context, polymeric microparticles (MPs) serve as an effective carrier, enhancing the bioavailability and bio-delivery of both lipophilic and hydrophilic drugs. MPs can be tailored for programmable and time-controlled drug release, with fabrication methodologies impacting their size, stability, and drug release kinetics [10].

In our study, we aimed to devise an innovative approach for the creation of a specialized and tunable sprayer system for personalized dental application. Utilizing biocompatible materials, we investigated how to engineer controlled release kinetics of drugs-loaded PLGA-MPs, offering effective drug encapsulation and release.

This system has been ideated, patented and tested for the first time, as reported in our report. In this pilot application, we have loaded the sprayed particles with different antibiotics, to customize and improve the management of the potentially pathogenic infections arising from dental procedures. Furthermore, we envision its potential application in the future for delivering other biomolecules capable of enhancing bone regeneration and healing.

2. Materials and methods

2.1. Bioactive drugs-loaded PLGA-MPs spray formulation

An aqueous solution, designated as solution A (45 % v/v), was meticulously prepared by dissolving 22.5 g of bovine serum albumin (BSA) in 50 ml of deionized distilled water at 37 °C. Then, the solution underwent stirring for approximately 12 h, ensuring the complete solubilization of BSA. Concurrently, a glutaraldehyde (GA) solution of 2 % (v/v), designated as solution B, was prepared by diluting the GA stock solution by 50 % (v/v) with deionized distilled water. Notably, it is recommended to include 0.5 % Tween 20 in solution B. This non-ionic surfactant reduces surface tension and minimizes non-specific binding interactions, thereby stabilizing the suspension and maintaining the formulation's integrity during spraying [11]. For the final formulation, 50 mg of PLGA-MPs (GMP grade with IV 0.28 and MW 54 kDa) were suspended in 1 ml of solution B. Following this, 1 ml of solution A was added, resulting in a final concentration of 25 mg/ml. All materials used for the formulation were sourced from SIGMA.

2.2. Loading antibiotics on PLGA-MPs

Loaded PLGA-MPs were prepared using the double emulsion method [12,13]. Water/oil/water emulsion: 1 g of PLGA (50:50) was dissolved in dichloromethane (5 ml) to obtain an oil phase. The antibiotics selected for our study were amoxicillin (AMX) in specific formulations, and metronidazole (Met). In detail, AMX is commonly used in dental procedures to face infections caused by gram-positive bacteria also supported by some gram-negative bacteria. The sodium amoxicillin (AMX-Na) and trihydrate amoxicillin (AMX-Tri) behave as the most stable solid forms, being ideal candidates for our study [14].

On the other hand, Met is highly effective against anaerobic bacteria: it is a reliable alternative in patients who are allergic to penicillin, as scientific literature has definitely assessed that metronidazole and penicillin are equally effective for the treatment of

dental infections [15].

After this careful evaluation on what antibiotics were strategic to test, AMX-Na and/or AMX-Tri were dissolved in 100 μL of distilled water and added to the oil phase. While the Metronidazole was dissolved in 100 μL of PBS. The mixture was homogenised in a mixer for 2 min at 4000 rpm (LM5 axial impeller mixer). The primary water/oil emulsion was quickly added to a 200 ml bath of polyvinyl alcohol (0.3 %) and homogenised again for 2 min at 2000 rpm. This water/oil/water emulsion was stirred at 300 rpm for 4 h and the MPs were then washed and collected before the lyophilization. Then, the antibiotics-loaded PLGA-MPs were centrifuged for 3 min at 200 rpm to remove the excess of the unbound antibiotics. An automatic aspirator was used without damage to the MPs.

2.3. Microparticles characterization

The fabricated microparticles (MPs) underwent a comprehensive examination of surface morphology through scanning electron microscopy (SEM). In summary, MPs were affixed onto carbon discs (Agar Scientific, UK) mounted on aluminium stubs (Agar Scientific, UK). Then, a gold-coating process was employed using a Balzers SCD 030 gold sputter coater (Balzers Union Ltd., Liechtenstein). Imaging of the MPs was conducted using a JEOL 6060L scanning electron microscope imaging system (JEOL Ltd., Hertfordshire, UK) operating at 10 kV ionizing radiation.

Mean diameter and particle size distribution were also investigated using a Coulter LS230 particle size analyzer (Beckman, UK). The particle size distribution was then determined as a function of particle diffraction and plotted as a function of volume percentage in micrometres. These adjustments include the additional information and maintain clarity in describing the micro-particle characterization process.

2.4. Spraying process

Particle aerosolization was achieved using airbrushes and compressors from airbrushes.com (UK), featuring two separate feeding reservoirs. The first reservoir contained a 45 % (w/v) BSA solution (A), while the second one housed a suspension of PLGA microparticles in 2 % GA (B) and 0.5 % Tween 20. All spraying procedures were conducted at 40 psi in an externally ventilated hood onto a glass slide, involving multiple cycles, each lasting 15 s, until a multi-layered spray coating was achieved. To properly test the spray flow efficacy, we preliminarily sprayed our formulations onto a glass-bottomed dish containing a small amount of coagulated blood, just preliminary to the blood clot formation. We observed by microscopy that spraying from a distance ranging from 10 to 15 cm was the proper protocol to prevent the alteration of the early blood clot in the glass-bottomed dish by the spray flow.

2.5. Release study

The investigation of antibiotic release involved depositing 50 mg of antibiotic-loaded particles following the spraying process, previously reported. The resulting biopolymer film on the glass slide was incubated inside glass vials containing 5 ml of PBS at 37 °C. Release kinetics was meticulously studied by measuring the daily release of antibiotics into the supernatant. Amoxicillin release was

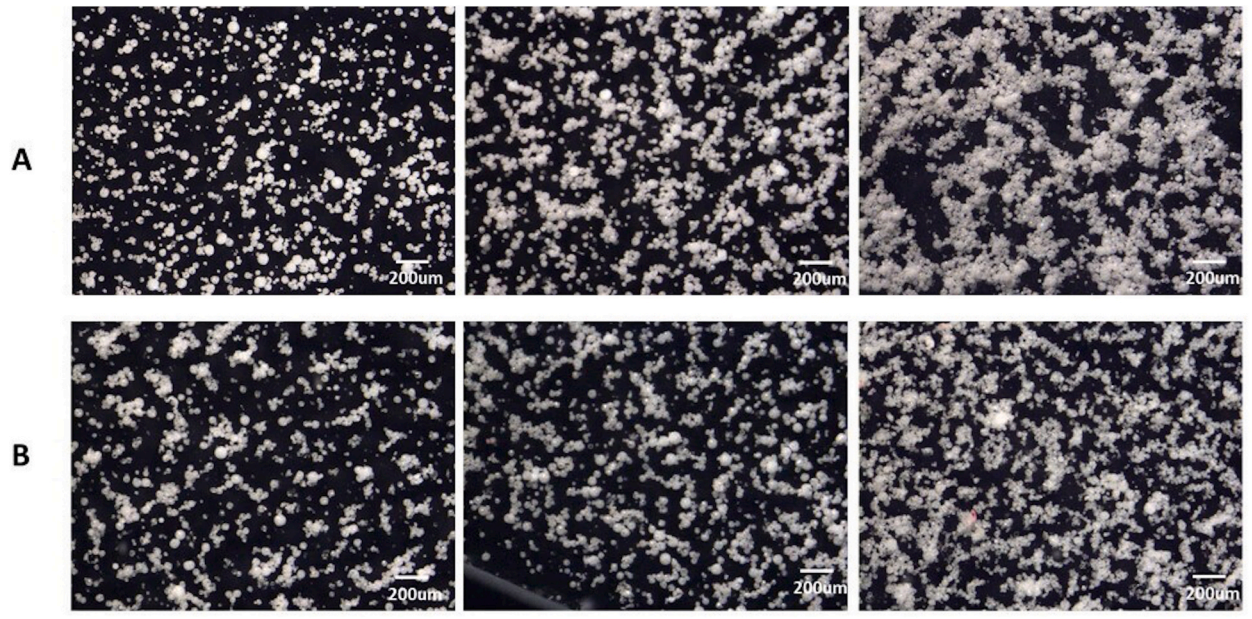

Fig. 1. Film of sprayed biopolymer. **A)** 50 mg of PLGA-MPs suspended in 2 % GA and sprayed with a 45 % BSA solution. B) 50 mg of PLGA-MPs suspended in 2 % GA with 0.5 % Tween 20 and sprayed with a 45 % BSA solution.

quantified utilizing High-Performance Liquid Chromatography (HPLC). The HPLC conditions comprised a C18 ODS thermos column (150 mm, 4.5, 5 μm), with a mobile phase of phosphate buffer pH 2.8 plus acetonitrile (80:20), and detection was performed at 230 nm. For metronidazole quantifications, a spectrophotometer (Tecan i-control - infinite 200Pro) was employed at a wavelength of 320 nm with a reference wavelength of 620 nm.

3. Results

3.1. Bioactive drugs-loaded PLGA-MPs spray optimization

This study focused on optimizing the formulation of a biopolymer film using PLGA-MPs within a sprayable size range of 10–50 μm. Fig. 1A illustrates the suspension of 50 mg PLGA-MPs in 2 % GA, followed by spraying with a 45 % BSA solution, resulting in a stable layer of microparticles. However, this formulation led to the blockage of the sprayer during application, posing a practical challenge. To address this issue, Fig. 1B presents a modified formulation where PLGA-MPs were suspended in 2 % GA supplemented with 0.5 % Tween 20 before spraying with the same 45 % BSA solution. The addition of Tween 20 effectively prevented aggregation and resolved the sprayer blockage, ensuring a consistent and stable film. This adjusted formulation demonstrates enhanced reliability in terms of both continuity and repeatability.

During the optimization process, strategic adjustments included increasing the volume of GA and incorporating Tween 20 to mitigate needle blockage encountered in the initial formulation. Tween 20 acts as a surfactant, facilitating smoother spraying by preventing particle aggregation. The controlled use of PLGA-MPs within the sprayable size range underscores their critical role in achieving efficient and uniform application of the biopolymer film onto the intended substrate.

3.2. Characterization

Particle size analysis highlighted notable differences in distribution patterns among the AMX-Tri, Met, and AMX-Na formulations, as depicted in Fig. 2. Specifically, AMX-Tri-loaded PLGA-MPs (Fig. 2A) and Met-loaded PLGA-MPs (Fig. 2C) demonstrated more uniform size distributions within the optimal sprayable range of 10–50 μm, as shown in Fig. 1. This size range is crucial for ensuring effective dispersion and coverage during aerosolization. In contrast, AMX-Na-loaded PLGA-MPs exhibited a broader size range (10–100 μm) at 1 % loading, with multiple peaks indicating varying particle size populations within the 5 % and 10 % groups, extending up to 200 μm (Fig. 2B). These findings underscore the diverse particle size behaviours observed across different antibiotic-loaded formulations and highlight the critical importance of achieving a suitable size range for efficient spray delivery.

The surface topography and morphology of PLGA-MPs were characterized before and after loading with selected antibiotics using SEM analysis. Fig. 3A and C depict AMX-Tri-loaded PLGA-MPs and Metronidazole-loaded particles, respectively, at concentrations of 1 %, 5 %, and 10 % antibiotic loading. These antibiotic loading concentrations are optimized to maintain effective local concentrations over time, ensuring targeted therapeutic benefits with minimal systemic exposure.

AMX-NA-loaded PLGA-MPs, shown in Fig. 3C, exhibit distinctive characteristics depending on the concentration of AMX-NA. At 1 % and 5 % loading, the particles display a highly porous surface attributed to the presence of sodium, which enhances surface porosity. The 5 % loading formulation shows greater size variability compared to 1 %, as confirmed by size distribution analysis (Fig. 2B). In contrast, the 10 % loading formulation exhibits a markedly different pattern, characterized by large irregular masses and squashed microparticles, indicative of sodium-induced porosity and alteration of particle shape.

These findings underscore the significant influence of AMX-NA concentration on the morphology and surface topography of PLGA-MPs, highlighting the complex interactions between antibiotic loading and particle characteristics.

3.3. In vitro release profiles of antibiotics from PLGA-MPs

The release profiles of the selected antibiotics (AMX-Na, AMX-Tri, and Met) loaded into PLGA-MPs were comprehensively illustrated in Fig. 4A1 and **4B1**. Fig. 4A1 specifically describes the release kinetics of AMX-loaded particles, demonstrating a consistent pattern characterized by an initial burst release reaching approximately 60 % on days one and two across all loading concentrations. This initial release phase was followed by a steady-state release of 5–7% until the completion of the study period.

In contrast, Met-loaded particles in Fig. 4C1 exhibited an initial burst release slightly above 60 % on day one, followed by a steady-state release ranging from 2 to 7% throughout the study duration. The release profile of AMX-Na at 10 % loading was excluded from the study due to significant changes in particle size and morphology observed during the study as seen in Figs. 2 and **3**.

The release kinetics from the sprayed biopolymeric film (Fig. 4A2, 4B2, and **4C2**) showed a slightly slower release profile, attributed to the film barrier, which aids in extending the release duration.

4. Discussion

Due to the increasing incidence of peri-implantitis, the prevention and management of peri-implant disease is becoming a critical issue to minimize its prevalence and increase implant success rates [1]. In this landscape, our work aimed to create a biopolymer film for biomedical applications for targeted drug delivery. Due to its properties, our work has been focused on the use of PLGA as a carrier for selected drugs, including antibiotics.

PLGA is widely used in the fabrication of medical devices because once degraded, the monomeric components (LA and GA) are

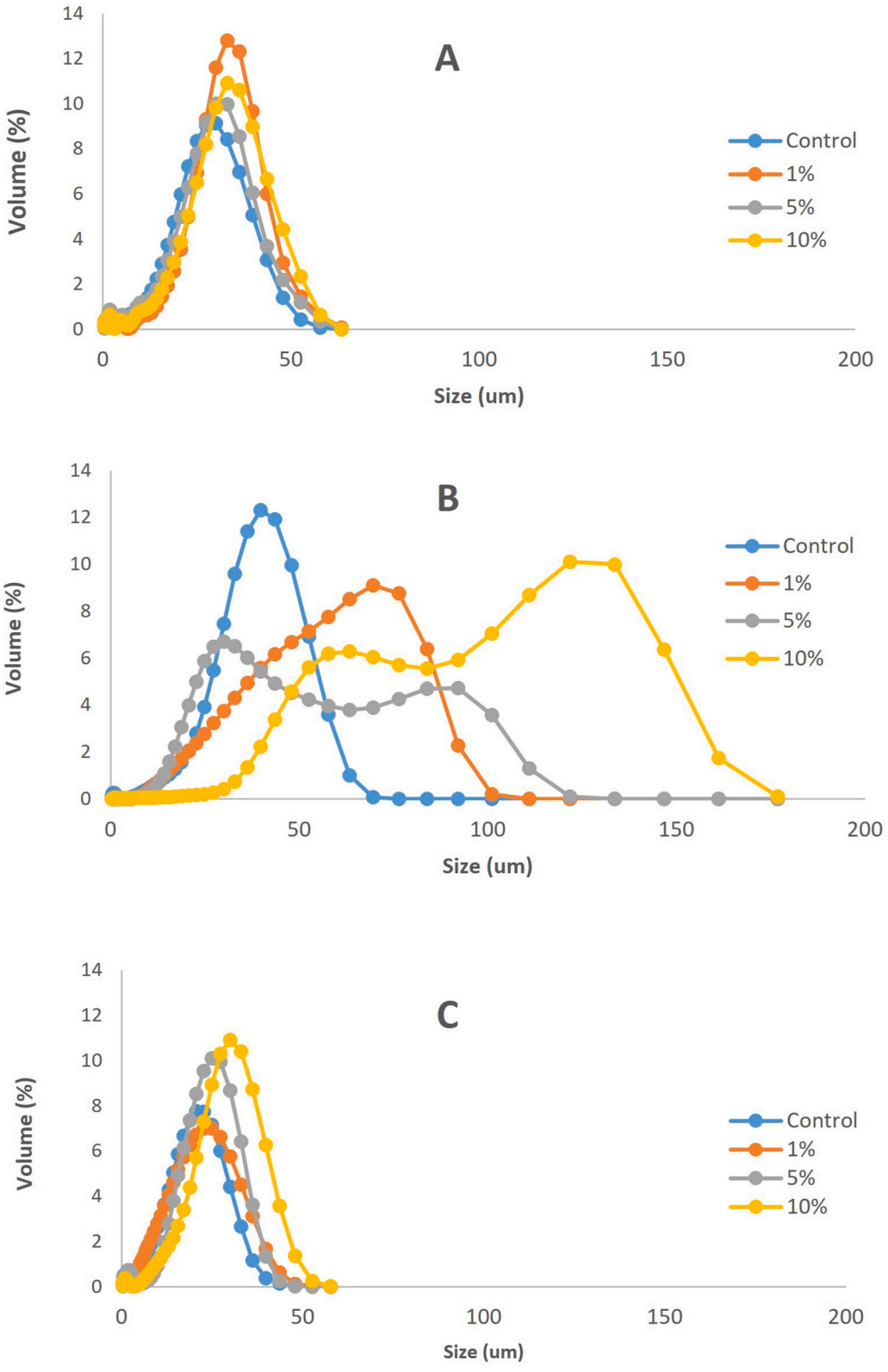

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Fig. 2. Particle Size Analysis by Laser Diffraction Method. **A)** PLGA-MPs loaded with Amoxicillin Trihydrate (AMX-Tri): Size distribution analysis of PLGA-MPs for the control (Blank Control) and those loaded with 1 %, 5 %, and 10 % AMX-Tri. **B)** PLGA-MPs loaded with Amoxicillin Sodium (AMX-Na): Size distribution analysis of PLGA-MPs for the control (Blank Control) and those loaded with 1 %, 5 %, and 10 % AMX-Na. **C)** PLGA-MPs loaded with Metronidazole (Met): Size distribution analysis of PLGA-MPs for the control (Blank Control) and those loaded with 1 %, 5 %, and 10 % Met. These subfigures illustrate the particle size distributions of PLGA-MPs under different formulations, including their respective controls and various drug loadings.

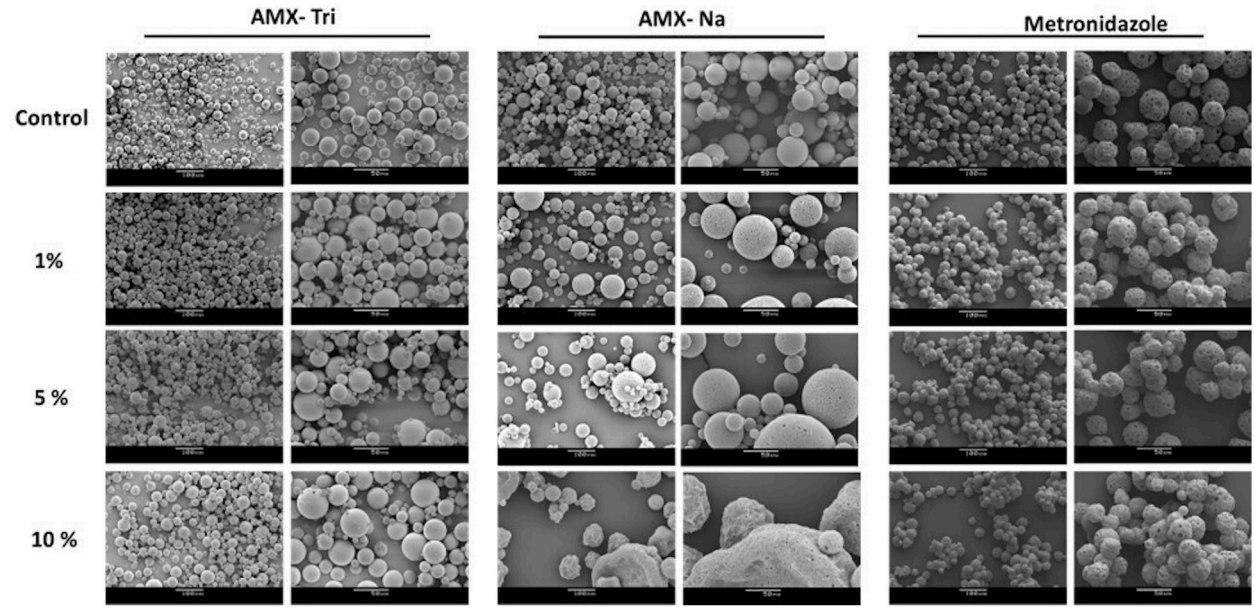

Fig. 3. SEM analysis of PLGA microparticles (PLGA-MPs) loaded with Amoxicillin Trihydrate (AMX-Tri), Amoxicillin Sodium (AMX-Na), and Metronidazole at 1 %, 5 %, and 10 % loading concentrations compared to blank control. The images depict the surface morphology and topography variations induced by different antibiotic loadings, highlighting distinct characteristics such as particle size, shape, and surface porosity.

removed from the body via natural pathways. To date, there is no evidence of systemic toxicity associated with the use of PLGA in drug delivery applications or biomaterials [9].

MPs are widely used as an effective carrier to enhance the bioavailability and bio-delivery of both lipophilic and hydrophilic drugs. They can be loaded with any type of bioactive molecule, such as growth factors, which can be used to regenerate damaged tissue, or antibiotics to treat different infectious diseases. The emulsification-evaporation method is the most common method for creating PLGA-MPs and it involves the preparation of single or multiple emulsions combined with the evaporation of the organic solvent [10]. Specifically, in our study, PLGA-MPs were created using the double emulsion method, following the protocol previously described. This is the main method to encapsulate water-soluble drugs, due to their optimized process, the cost-effectiveness of the instrumentation and the well-controlled process parameters [10].

The biopolymeric film here developed is a spray formulation capable of creating an environment where different molecules can work in a time-depending manner. More in detail, our sprayable formulation provides a gradual and controlled release of drugs and/or growth factors (GF) in the tissue where it is applied (e.g., oral tissues), allowing a better performance of local immunity against bacterial infections, also promoting a faster regeneration of damaged tissues (e.g. bone/periodontal tissues). The bioactive agents we have tested where antibiotics; nonetheless, future applications may involve GFs selected from bone morphogenetic proteins (BMPs), fibroblast growth factors (FGFs), or various mixtures of both. Interestingly, BMPs work by stimulating osteoblast differentiation and promoting tissue regeneration of the bone and cartilage; FGFs are involved in tissue repair, angiogenesis, and the overall wound healing process [16]. With these premises, the future insights related to this new therapeutic tool are focused on its smart capability to simultaneously manage both infected and damaged tissues; our preliminary study, consisting of a solution of BSA, GA and PLGA-MPs loaded with selected antibiotics (AMX-Na, AMX-Tri and Met), showed promising data related on the drug kinetics and its related features. The selection of specific antibiotics was based on clinical considerations; on the other side, we stressed the fabrication-related issues in this first report. Importantly, here we have overcome the issues typically present when drugs are incorporated in the PLGA-MPs; also, the volumetric ratio between the aqueous composition comprising BSA and the aqueous composition comprising GA was determined experimentally. Another important factor was the use of amoxicillin (AMX) and its salts, a broad-spectrum antibiotics of the penicillin family: AMX is particularly suitable for the treatment and prophylaxis of wide-range bacterial tissue infections, especially those infections developing in the oral cavity, or following dental implantology. On the other side, BSA, a cross-linkable protein, forms a solid and continuous film when it is brought into contact with GA at room temperature. The degradation of the

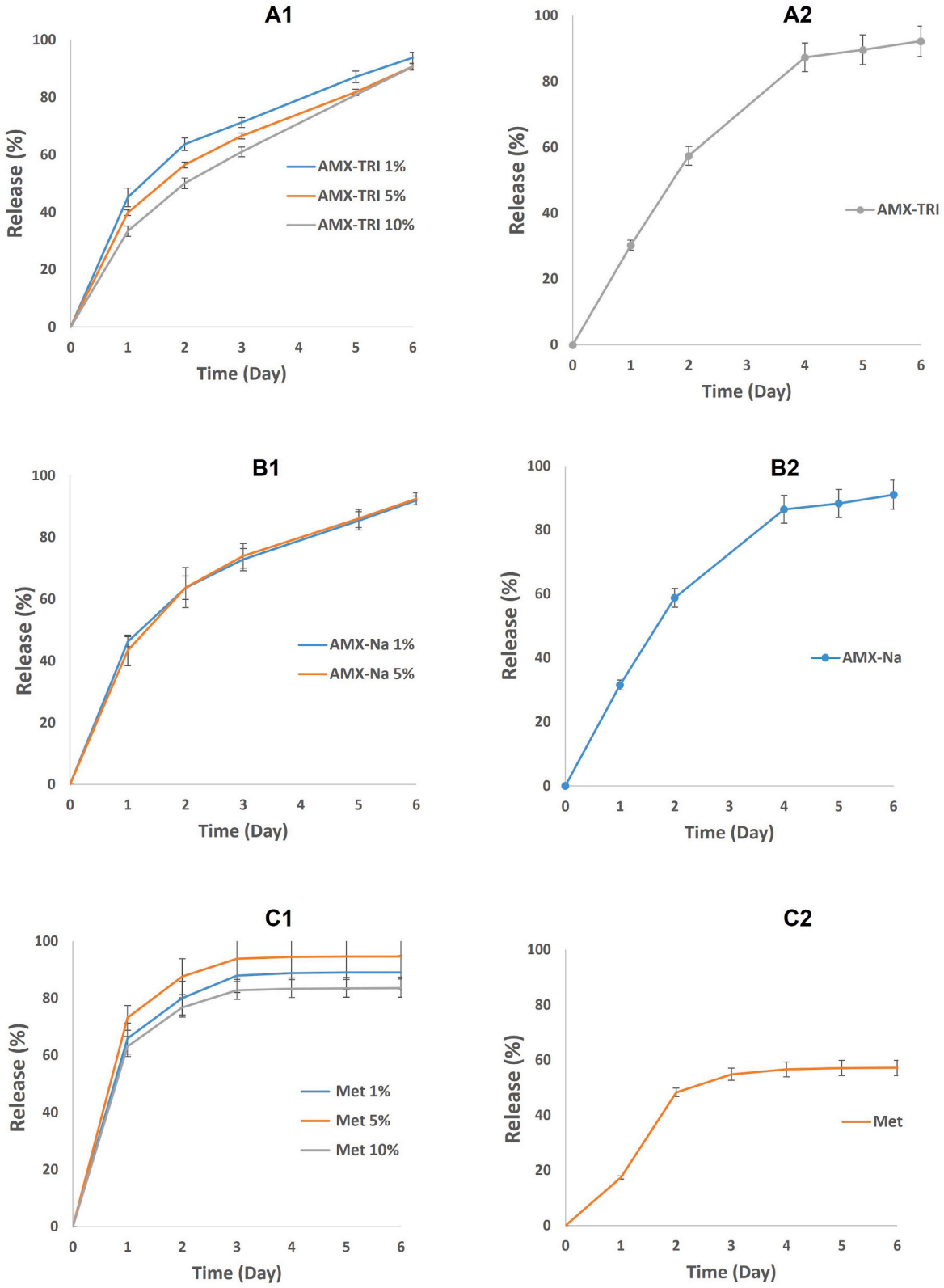

Fig. 4. In vitro cumulative release percentage of Amoxicillin Trihydrate (AMX-Tri) (A), Amoxicillin Sodium (AMX-Na) (B), and Metronidazole (C) from PLGA-MPs. Panels A1, B1, and C1 depict cumulative release profiles of the antibiotics from PLGA-MPs in PBS with varying loadings (1 %, 5 %, and 10 %). Panels A2, B2, and C2 illustrate antibiotic release profiles from the sprayed PLGA-MP biofilm.

chemically crosslinked BSA gel matrix can occur through both enzymatic pathways, facilitated by limited proteases in the oral cavity and salivary enzymes, and non-enzymatic pathways, mediated by the immune system or local inflammatory processes [17]. Solution A and B can therefore be mixed only at the time of use when the biopolymer film is created. The mixing of solution A and B causes the cross-linking of BSA by GA. During this phase, PLGA-MPs (loaded with the selected antibiotic) are embedded in the biopolymer film. In particular, under specific conditions of pressure and temperature (i.e. around 101.32 kPa and 25 °C), the cross-linking phase is rather rapid.

The method proposed here allows for obtaining a biopolymer film in a simple, rapid and ergonomic way, enabling the formation of the film even on surfaces with complex morphology. Moreover, in a humid environment, PLGA-MPs are subject to degradation; thus, the drug encapsulated in them is locally released.

PLGA-MPs before and after the antibiotics loading were observed via SEM. In particular, as shown in Fig. 2, the incorporation of AMX-Na and AMX-Tri in the PLGA-MPs does not seem to significantly modify the homogeneous and fibrous morphology of PLGA-MPs.

In a further phase, after analyzing the dimensions and morphology of the PLGA-MPs (black control and loaded with antibiotics), the release kinetics of the selected antibiotics used here were extensively investigated. More specifically, the release kinetics analysis showed that AMX-Na and AMX-Tri had degradation limitations; this effect was not observed for Met. The *in vitro* release study of AMX-Na and AMX-Tri ended with a lot of technical problems related to the antibiotic instability in the aqueous supernatant. Indeed, AMX is susceptible to hydrolysis which resulted in multiple peaks (degradation by-products) in the HPLC chromatogram, which made the results ambiguous and unusable. In contrast, the diffusion rate of Met loaded in the PLGA-MPs appears to be optimal for a gradual release over time. This characteristic is extremely significant in biomedical applications where the drug is required to maintain long-term activity, including in the treatment of oral pathologies. Thus, the results of the release kinetics of Met are encouraging. Thus, the *in vitro* release study is a crucial test to assess the safety, efficacy and quality of MPs-based DDS [18], but there is no established or regulated standard.

5. Main remarks

The novel biopolymer spray formulation for drug delivery in precision dentistry, as developed in this pilot study, represents a promising biomedical prototype with several key characteristics.

This innovative formulation is administered via aerosolization of a liquid, which, upon application to living tissue, undergoes a hardening process to form a stable film with the mechanical properties necessary for firm adhesion. This film is specifically designed to deliver antibiotics effectively, thereby preventing infections. A significant advantage of this formulation is its ability to provide localized and targeted delivery of antibiotics, minimizing unwanted systemic effects and reducing the need for higher doses to treat infections. The bioactive spray exhibits an optimal release profile for the incorporated bioactive molecules over time, ensuring sustained therapeutic efficacy while mitigating potential side effects associated with systemic administration.

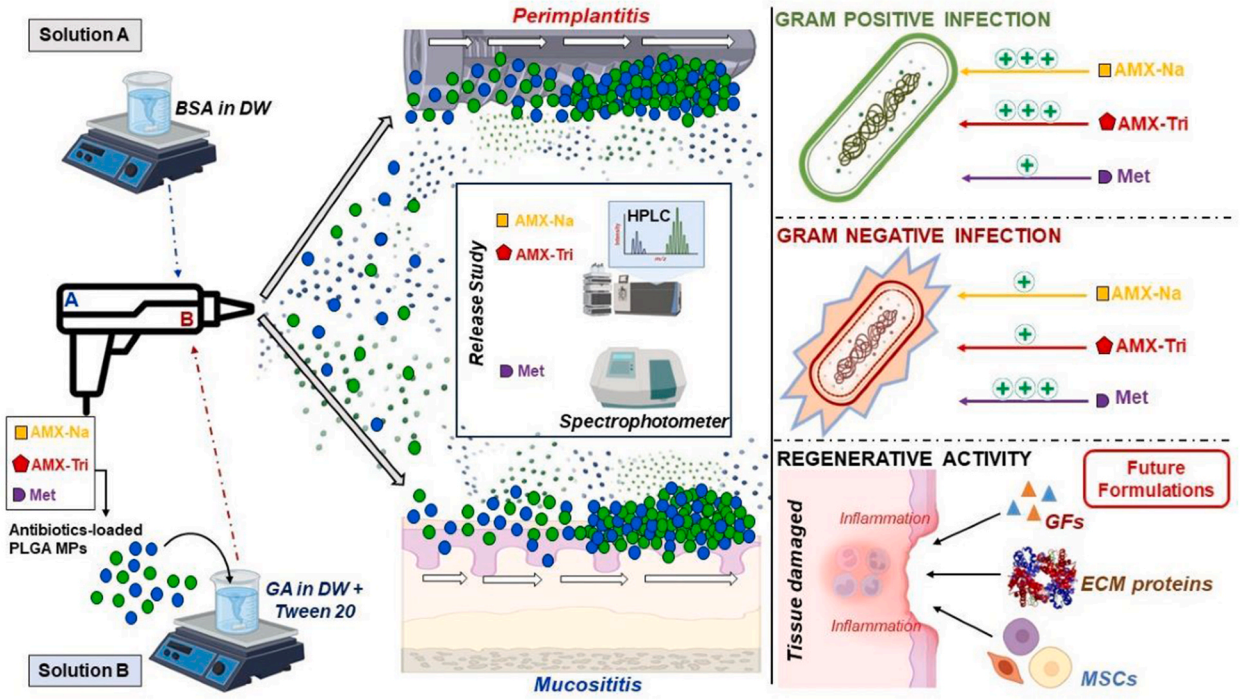

Fig. 5. Schematic overview of the biopolymer spray formulation, study release and potential use in clinical applications.

The formulation employs biocompatible and biodegradable materials, which enhance its safety and efficacy for clinical use. The inclusion of PLGA microparticles is crucial for controlling release kinetics, allowing precise tailoring of the release profile for various payloads. This flexibility makes the formulation suitable for future applications, including the incorporation of growth factors like BMP-2 for bone repair and regeneration. Overall, this biopolymer spray serves as a versatile platform for precision localized delivery in dental procedures.

6. Conclusions

In summary, our study presents a streamlined, rapid, and user-friendly method for creating a biopolymer film (BSA/GA/PLGA-MPs loaded with specific bioactive molecules).

The utilization of PLGA-MPs as carriers for targeted antibiotics (AMX-Na, AMX-Tri, and Met) has demonstrated effectiveness in delivering localized antibiotic therapy throughout the treatment course. This conclusion is supported by our *in vitro* release data, which illustrates sustained antibiotic release profiles over time. Our work successfully demonstrates an efficient strategy for moderating the rate of drug release, a crucial factor in biomedical applications demanding sustained efficacy (Fig. 5).

This research significantly contributes to advancing Drug Delivery Systems (DDS), addressing the imperative need for prolonged drug effectiveness. The focus on biodegradable polymers in DDS holds immense promise for transforming the treatment landscape across various diseases and medical conditions. By elevating drug efficacy, minimizing side effects, and promoting patient compliance, biodegradable polymers emerge as a pivotal force capable of substantially improving healthcare outcomes.

Hence, the exploration of biodegradable polymers stands as an exciting perspective in research and development, offering promising opportunities to propel advancements in medical and pharmaceutical science, with intriguing translational applications in precision medicine and dentistry.

Ethics approval and consent to participate

Not applicable.

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Data availability statement

"The datasets generated and/or analyzed during the current study are not publicly available due to their inclusion in a pending/granted patent [Patent Number: 102018000002841]. This restriction is in place to protect the intellectual property associated with the novel methods and findings described herein."

CRediT authorship contribution statement

Marco Tatullo: Writing – original draft, Validation, Conceptualization. **Benedetta Marrelli:** Writing – review & editing. **Anastasia Facente:** Writing – original draft, Data curation. **Francesco Paduano:** Writing – original draft, Data curation. **Omar Qutachi:** Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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