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Polymicellar-based drug delivery systems for use in nanodentistry, oral and cranio-maxillo-facial oncology

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Abstract: Polymer-based therapeutics is a precipitously-growing Research, Development and Innovation (R&D&I) translational field of bioengineering for biomedicine. The last decade has witnessed an exponential rise in interest from Dentistry, in general and Oral Oncology (extending to cranio-maxillo-facial), in particular. Basically, the area comprises the design, development, characterization, evaluation and fine-tuning (refinement) of polymer-drug and polymer-protein conjugates, macromolecular drug delivery systems, and polymeric micelles that incorporate covalently-bound drugs, bioactive agents and polyplexes for controlled pharmaceutic and DNA delivery. Accordingly, tackling drug delivery-related issues, including mode-of-administration, encapsulation efficiency, loading capacity, release pharmaco-kinetics, bio-safety and -efficacy became *key* in nanomedicine and nanoDentistry of today and tomorrow. Herein, nano-sized drug delivery vehicles and carriers can represent a cornerstone in the ongoing efforts for controlled drug development, formulation, optimization and translation from bench-top to chair-side; to the clinic and our patients. Indeed, the self-assembly of amphiphilic polymers, or aggregation colloids (in solution), commonly referred to as polymeric micelles, continue to represent an invaluably desirable and pursued small-scale, easy-to-formulate, -characterize and -sterilize tool in pharmaceutical innovation, mainly, in overcoming critical issues in drug delivery, including low water solubility in biological fluids and poor drug permeability across biological barriers. Yet, challenges, related to post-administration stability and behavior (pre-clinical and clinical) for example, continue to drive the present R&D&I efforts across the World. Dentistry and Oro-Dental Health Care including Oral and Cranio-Maxillo-Facial (Surgery and) Oncology are no exception. Therefore, in this special review, a concise presentation and discussion of the past, present and future of polymer-based micelles and nano-micelles, including characterization parameters, methods of preparation, drug(s) loading/delivery and challenges, is presented, via integrating illustrations of pertinent a range of uses and applications, in an attempt to bridge the gap between biomaterial engineering, pharmaceutics, nano-biotechnology, innovative clinical translation and the curious junior/senior investigator.

Keywords: dentistry; biofilm; oral cancer; chemotherapy; drug delivery; dental caries; tooth-binding; micelle; nanomaterials; nanotechnology; polymer; surgery; cancer; oncology

1. Introduction

Critical Précis- For decades, polymers have been employed for therapeutic applications, mainly, due to the ability to tailor-design the physico-chemico-mechanical characteristics and biological properties of formulations whether via the variation of the incorporated polymer back-bone, molecular weight, hydrophilicity, hydrophobicity, polydispersity (of dispersion), size (micro- and nano-scale), architecture and/or surface chemistry (functionalization and targeting). Indeed, the most recent interventional uses benefiting from the wide array of readily-available biocompatible and biodegradable polymers have this far provided a very attractive platform and "tool-box" favorable for the design and development of novel, innovative and/or alternative polymer-molecule conjugates, suspensions, hydrogels and scaffolds, suitable for bioactive pharmaceutic delivery (cell, protein, gene, drug, anti-microbials, amongst others), tissue engineering, regenerative medicine and cancer. Hence, stomatology, for instance is not a far from such advances and implementations.

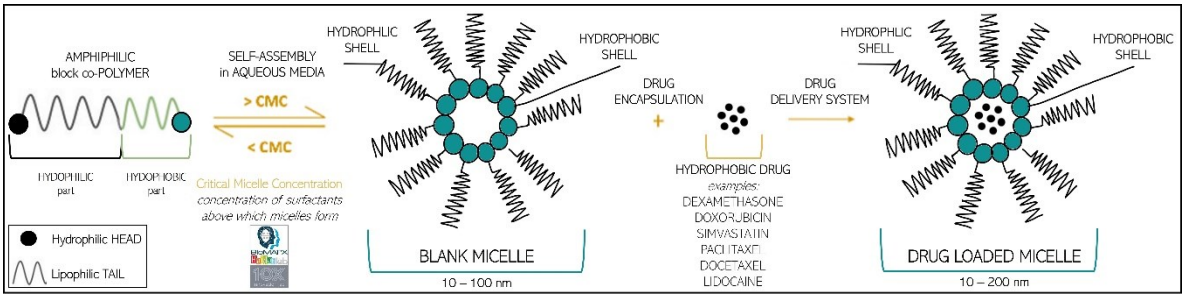

Figure 1. Schematic illustrating the synthesis of a polymer-based micelle for drug delivery.

Nanotechnology and nano-scale drug-delivery materials have become increasingly-popular, in recent years, due to the advantageous versatility and enhanced biological activity whether in biofilm targeting (penetrability), improved drug bio-availability and/or controlled pharmacokinetics and localized vs. systemic dose-response (safety and efficacy of anti-bacterial/-microbial drug-loaded core-shell nanoparticles/nanocapsules and/or nanoMicelles) against dental caries (in treatment as well as prevention), for example. This article aims to familiarize the interested reader with polymer-based nano-biotechnologies, via special focus on the sub-area of polymeric micelles, and the potential applications in the oro-dental field.

2. Nanotechnology and the nano-scale

According to the U.S. National Nanotechnology Initiative https://www.nano.gov/, nanotechnology is defined as the direct manipulation of materials at the nanoscale. Nanotechnology-based approaches for pharmaceutical targeting and drug delivery including liposomes, dendrimers, carbon-based nanoparticles, and micelles are often considered and favorable to enhance the therapeutic efficacy of drug-based platforms and other treatment or therapeutic modalities. Today, amphiphilic aggregates or polymeric micelles, have been shown to be capable of modulating/changing the physico-chemical properties of the encapsulated/loaded drug. Basically, polymeric micelles can be described as the nanoparticles structured as a drug delivery system, with a hydrophobic (core) and a hydrophilic co-polymer (shield or shell) - which are commonly long hydrocarbon chains [1]. Drugs hosted within micelles have shown increased solubility and can be targeted to specific sites thereby improving the therapeutic index of the drug itself. Indeed, in a liquid solution, the amphiphilic particles or molecules (existing separately) function/work as a wetting agent

(surfactant), thereby reducing the tension (air and water interface). The more extra chains added and present on the structure of the micellar system, the better (higher) adsorption resulting at the interface, until the saturation of the bulk solution is achieved [2-3]. Once reached, the formulation faces the "Critical Micellar Concentration" or CMC, described/defined as the minimum concentration of polymers needed to form micelles. This parameter is critical in defining the micellar thermo-dynamic and kinetic stability [1, 4]. Furthermore, it is well known that drug stability as well as the drug-associated adverse (or side) effects can change upon drug loading into a polymeric micelle, thus, it is an important aspect to keep in mind. Herein, amphiphilic di-block [poly (ethylene glycol) and polystyrene], tri-block (poloxamers), graft and ionic copolymers are often considered/used as the traditional polymers in developing polymeric micelles. The hydrophilic part is commonly constituted of poly (ethylene glycol) (PEG) and for the hydrophobic forming materials, polylactid acid and/or polyglycolic acid are included/incorporated. A polyion-complex is often spontaneously formed between oppositely-charged macromolecules or polymers such as positively-charged polyethylene imine and poly (L-lysine) and negatively-charged poly (aspartic acid) and poly (acrylic acid) [1, 5]. The term was first used by James William McBain in 1913, when he analyzed how the conductivity of a solution can change with different (varying) concentrations [5-7]. A list of researchers then proposed different structural models for these nanostructures (McBain, Adam, Harkins, Hartley and Philippoff) focused on diverse techniques to clarify micellar diameter, shape and morphology [7-8]. For instance, in 1949, the theory of Debye, proposed and explained how micelles are created, however, between the years 1950 to 1956, ample researchers (Hobbs, Ooshika, Reich and Halsey) attempted to corroborate the fundamental hypothetical properties, and some of the key aspects rendered missing in the Debye model. Later in the period between 1956 to 1965, different methods emerged (Hoeve & Benson and Poland & Scheraga) focusing on statical mechanics, thereby providing fundamental concepts that were later integrated (and are) into the current models [9, 10]. The Tanford free energy model, emerged as a model to further clarify more about micelles, including the physical and chemical factors, explications about their form, growth and why they remain finite [7]. Micelles (Figure 1) contain a hydrophobic core that can be loaded with a range of different medicines/pharmaceuticals and have a hydrophilic shell that can avoid or prevent bio-substances from dealing with the mononuclear phagocytosis system. During their formation or even later, and depending on the development method used, and characteristic of the medicine/load, micelles can be made, constructed, prepared or formulated via different methods. Those include direct dissolution, dialysis, emulsion with solvent and film hydration (*i.e.* thin-film). Hence, the creation of micelles occurs when the concentration of the block co-polymer grows above the critical aggregation concentration (CAC) or even the CMC mentioned earlier. Indeed, at the CAC, the hydrophobic fragments of block co-polymers turn to associate, thus leading to the realization of the designed/intended core-shell micellar structure [11, 12]; issues further elaborated next.

3. Polymeric micelles

A micelle is an aggregate of molecules in a colloidal solution. Briefly, polymeric micelles, are spontaneously self-assembled structures made or composed of amphiphilic molecules, with two main types of blocks (hydrophilic and hydrophobic) [2]. Between the hydrophobic block, there is an inner field (micellar nucleus) that can solubilize and protect with lipo-soluble drugs (load or cargo), and on the other hand, the hydrophilic blocks generate an external crown with an intimate contact with the exterior [4, 13]. The hydrophobic region of this amphiphilic molecule is the core, and associate together to form the micellar nucleus (ability to concentrate and solubilize lipo-soluble drugs) whereas hydrophilic region is the

shell of the structure (intime contact with the external environment) [14]. The outside of the shell also determines surface charge and is responsible for interactions with bio-components present in the blood and cellular membrane(s). These properties render micelles appropriate for the systemic delivery of water insoluble (hydrophobic) medications and bio-agents [12].

The preparation, solubilization and small (nano-size) scale, render these micellar structures very interesting pharmaceutical carriers, suitable for different administration methods, routes or regimens. Indeed, the use and administration of polymeric micelles could be ocular, nasal, oral (Figure 2) and parenteral (most common), with very low toxicity. Also, are often more stable in an aqueous environment, keeping them stronger (stability), even in concentrations that are below of the CMC (the concentration which micelles form), thereby, prolonging their residency time in the blood flow, an invaluable and highly-pursued clinical feature [2, 4]. Nowadays, the intravenous route is investigated, with interesting results, improving drug bio-availability. It is important to consider the administration route of preference because micelles will face different obstacles. For example, in topical (including intra-oral and dental) administration or application, the interaction of the micelles with the mucosa and serum should be considered. For the intravenous route, factors such as serum, the high dissolution and the local stress in the site of injection, could result in the de-stabilization and consequently result in the disintegration of the formed micelle [15]. Similarity between the drug itself and the dissolution medium can greatly impact and improve drug loading, drug encapsulation, drug inhibition and consequently the chemical stability and bioactivity of the drug. In general, the surface properties of the polymeric micelle impact or influence stability during storage (shelf-life), sterilization and behavior post-administration.

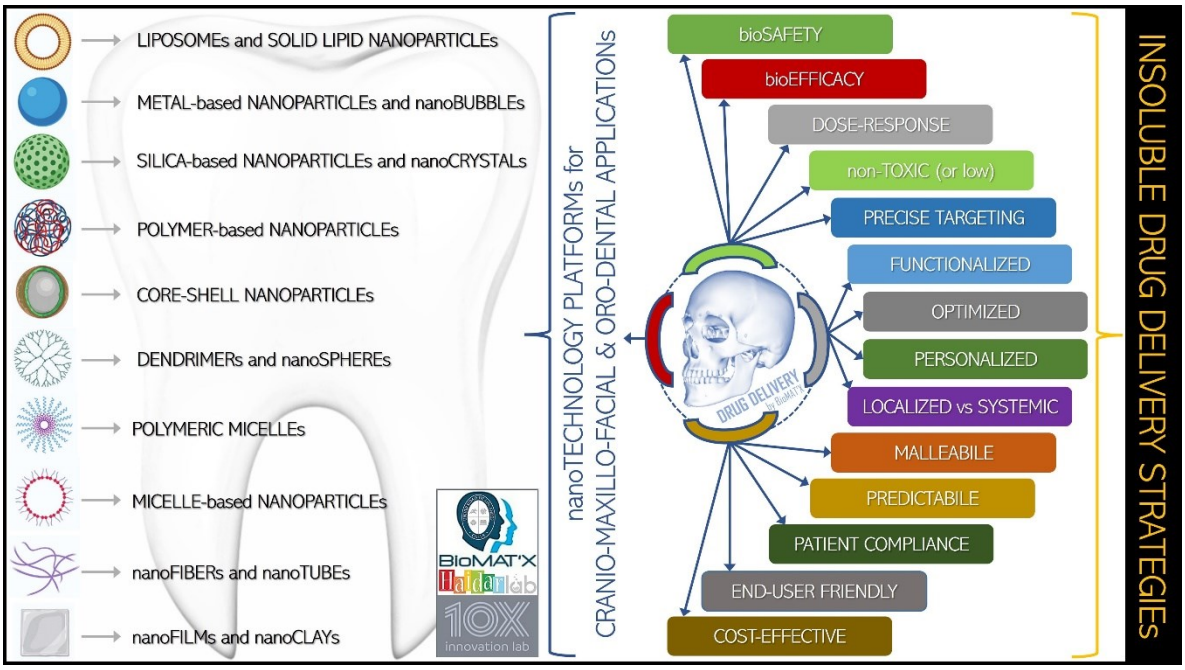

Figure 2. Major nano-scale structures, carriers and bio-systems, and desired properties.

Hence, surface modification strategies are useful and effective in optimizing the size/diameter, surface charge and bio-distribution of the nanocarrier [5]. Those are key design and behavioral parameters requiring more attention, thus, discussed in the following section.

3.1. Polymeric micelles as drug delivery systems: physico-chemico-mechanics

Generally, the size of the micellar nanostructure created will depend on the pursued or intended therapeutic target, hence, considering this aspect, the biodistribution of the nanocarrier is inversely related to the formulated size or diameter. Indeed, polymeric micelles smaller than 100 nm in size, tend to possess enhanced stability, accumulation and permeability in highly-permeable tumors, *i.e.* micellar size (average diameter) contributes to diffusion, cellular uptake, and evading the cellular system defense line (mononuclear phagocytic) [16-18]. The enhanced permeability and retention effects, is the mechanism by which drugs, tend to accumulate in tissues that offer increased vascular permeability (inflammation sites, for example), and these properties are possible when using micelles (also with liposomes and nanospheres), thereby offering desirable application and therapeutic advantages, over other carrier systems [13, 19]. Nevertheless, a larger size would probably increase the release of the loaded compounds [20] (yet, coating with protective shell is possible). Indeed, size control of the transporter or carrier is one of the many desirable advantages and benefits of considering and developing polymeric micelles for drug delivery. Given the small-scale size, avoiding clearance by the kidney and reticuloendothelial system is feasible and evident [2, 21]. Finally, the advantage of the nano-scale (nanoparticles, nanospheres, nanocapsules, amongst other designs and formulations) to be selective (in bloodstream), and then in the target tissues, render them much easier to be controlled and transportable (targeting and fate: biodistribution post-administration) where needed [19]. Further, the form, shape and morphology of these spherical (most often) nano-sized structures, will almost always depend on the hydrophilic-hydrophobic balance of the co-polymer block, which in turn, depends on the hydrophilic volume fraction [21, 22]. Micelles can also be formulated to be worm-, rod- or even disk-like structures. This depends mainly on the polymers used in the structural composition and formulation alongside the environment (pH and temperature). Herein, micellar morphology is key in post-administration behavior prediction, as shape impacts circulation time, biodistribution as well as cellular uptake (and tumor penetration). It is perhaps noteworthy herein to emphasize and remember that biocompatibility, biodegradability and cytocompatibility requirements could limit the choice of polymers available to be involved in creating a poly-micelle [23]. Surface properties (and functionalization possibilities) are therefore impacted as well. Indeed, surface characteristics (that allow or facilitate or direct interaction with biocomponents and regulate stability post-administration) play a role in micellar behavior (and fate). The stability of the micellar structure (block-copolymer) is therefore, a very important factor in determining efficacy and is often dependent on the followed kinetic and thermo-dynamic foundations. Briefly, for thermo-dynamic stability, the co-polymer critical micelle concentration should be high. Herein, this is influenced by the hydrophilic-lipophilic balance. It is usual or expected that an increase in the hydrophobic block length results in a low CMC. On the other hand, with a concentration below or low, such would allow disassembly, and often occurs in a relative rate and will depend on the physical state of the core-shell, interactions between the hydrophobic blocks, the molecular weight of the hydrophobic block and finally, on the ratio of the hydrophilic to the hydrophobic blocks [14, 18, 24]. Surface charge is a key feature to consider as well, where positively-charged micelles are often more muco-adhesive and better in epithelial interactions (especially in transporting the drug load across biological barriers), while neutral micelles can have enhanced mucous-penetrating properties; highly-critical issues for oral and dental applications. Surface functionalization with signaling bio-factors or molecules, for active targeting, is, also common, especially in the oncology and chemotherapeutics arena [14, 18, 24]. Evidently, cellular membranes, in general, are impermeable to a number of external or exogenous materials. Therefore, figuring out a strategy to diffuse drugs into cells or organelles, is therefore, one of the major challenges in drug development and drug delivery, today. Hence, the surface of a polymeric micelle could

host tailored ligands (attached), for a better active vectorization (ability to be recognized from selective cells), as mentioned earlier. Briefly, such supra-molecular organization(s) are created as a product of achieving the optimum balance between the solid bonds that hold the blocks and the reversible energies that build them together [21]. Further, size could be also controlled by the molecular weight of the amphiphilic block, aggregation number (number of amphiphilic co-polymer molecules that conform a micelle), proportion of hydrophilic and hydrophobic chains, quantity of solvent (inside the micellar core), and finally, the selected preparation method and/or process [21, 25-26]. To this end, therapeutic strategies based on intra-cellular systems often require complex genetic engineering and gene therapy systems. Intra-cellular targeting can be achieved via employing methods such as electroporation and micro-injection. Hence, surface functionalization of polymeric micelles, for prolonged or long-term blood residency and circulation (as well as tumor or cancer cell penetration) is to be carefully studied in the design, formulation, and evolution of polymeric micelles [7]. In the subsequent section, several of the most common formulation techniques are described.

To recap, nano-based drug delivery systems employed in oncology and cancer therapy, are often challenged by the release of the loaded anti-tumoral drug with high stability inside the targeted cancer cells. Further, the designed and applied nano-carrier is not to generate any significant toxicity, against the (near and afar) normal or healthy cells. As mentioned, micellar preparation or formulation also depends on the properties of the polymer(s) chosen/used and/or drug(s) incorporated and can be carried out via numerous technical methods. Generally, polymeric micelles are often easily prepared by direct dissolution. This method begins with the dissolution of the co-polymer in water, and continues with stabilization at the adequate temperature, and finally, with the incorporation of the drug(s) into the aqueous medium. Herein, to increase drug loading (for efficient drug delivery), the dissolution method can be combined with higher temperatures (precipitation, emulsification and ultrasonication) or a thin film (thin-film hydration technique) of the drug that can be prepared before the addition of the co-polymer [1, 12, 21]. Once done, the organic solvent is removed, either by dialysis (bag) or via evaporation. Stirring, thermal or sonic treatments could also be used, herein, for facilitating the dissolution step [1, 21, 27]. Remember, drug encapsulation in a polymeric micelle does not “fully” protect it from degradation (over time). Polarity and hydration (degree of), besides interaction with different blood biocomponents (including proteins), are some of the important aspects to be well-considered for the micellar creation [13, 21, 28]. Figure 3 summarizes the traditional or most-common preparation methods. It is worth mentioning that drug loading and encapsulation can be done, either during micellar formation, or afterwards, at a later step, during the preparation or formulation process of the designed / pursued drug delivery system and strategy, depending on the required (and feasible) physico-chemico-mechanical, rheological and biological properties [28]. The “ideal” features of a pharmaceutical delivery system were also shown in Figure 2.

Reiterating, effective micellization environments vary in the solubility of the individual block of the co-polymer. The size or diameter (and structure and characteristics) of the definitive micelle may depend on the preparation protocol of the polymer(s). The choice of solvents, employment of the dialysis procedure, thermal treatment, amongst others, may all influence the formation of polymeric micelles. Therefore, alteration in the experimental process may be chosen to be used in order to modify the core of the resulting micelles. The micellar characteristics and properties are stable once they reside in a solvent that is a solid non-solvent for the core [1, 12, 21]. It is noteworthy that hydrophobic drugs are the most common load, hosted within the core. It is also perhaps worth-mentioning here in that the encapsulant(s), load, cargo and/or drug release will later occur, post-administration, either due to drug(s) diffusion through and outside the micelle or micellar erosion and disassembly.

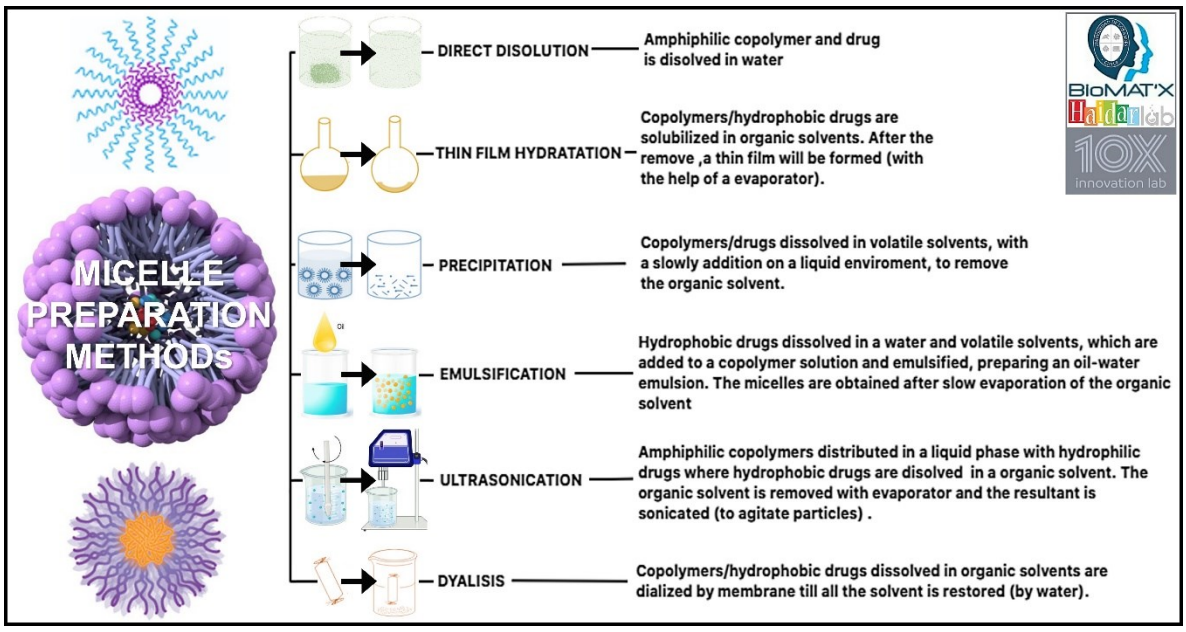

Figure 3. Summary of the most common preparation methods for polymer-based micelles.

To re-emphasize, the design and preparation method of choice, should therefore, always consider optimal thermos-dynamics and superior kinetic stability as the guiding principle and goal for a useful micellar nano-carrier/-delivery system [21]. As nano-carriers, the small size of polymeric micelles, alongside the afore-discussed ease of preparation, render them interesting/desirable for a range of different administration routes and clinical applications. Indeed, polymeric micelles, also, offer the ability to solubilize poorly water-soluble (or insoluble) drugs increasing their bio-availability properties, hence, are often described to have good solubilization and an anisotropic distribution of water (decreasing content via moving from the surface to the core) [15, 29]. Herein, the solubilization process starts with the displacement of the solvent molecules (water), from the micelle core, and then the solubilized drug starts to accumulate in the nucleus of the micelle core, thereby forcing hydrophobic blocks from the region. It is noteworthy that this process results in an increase of the micellar size, mainly due to the development of the core associated with loading a solubilized drug which also depends on degree or strength/level of polarity (dictating location within or closer to surface) [29, 30]. On the other hand, hydrophilic drugs and biomolecules (such as RNA) can also be loaded into polymeric micelles, which form upon the self-assembly of amphiphilic macromolecules, either via chemical conjugation processes (with unimers/RNA condensation) or electro-static interactions (poly-ion complexes, such as via the layer-by-layer or L-b-L step-wise method, as is displayed in Figure 4, depicting the followed protocol in our BioMAT'X R&D&I (HAiDAR I+D+i) laboratory for creating multi-layered shell build-up via bi-polymer adsorption (step-wise deposition) onto/around the core to formulate stable core-shell nanocapsules suitable for the controlled delivery of one or more drugs. Sequential drug release is also feasible to attain with such nano-systems).

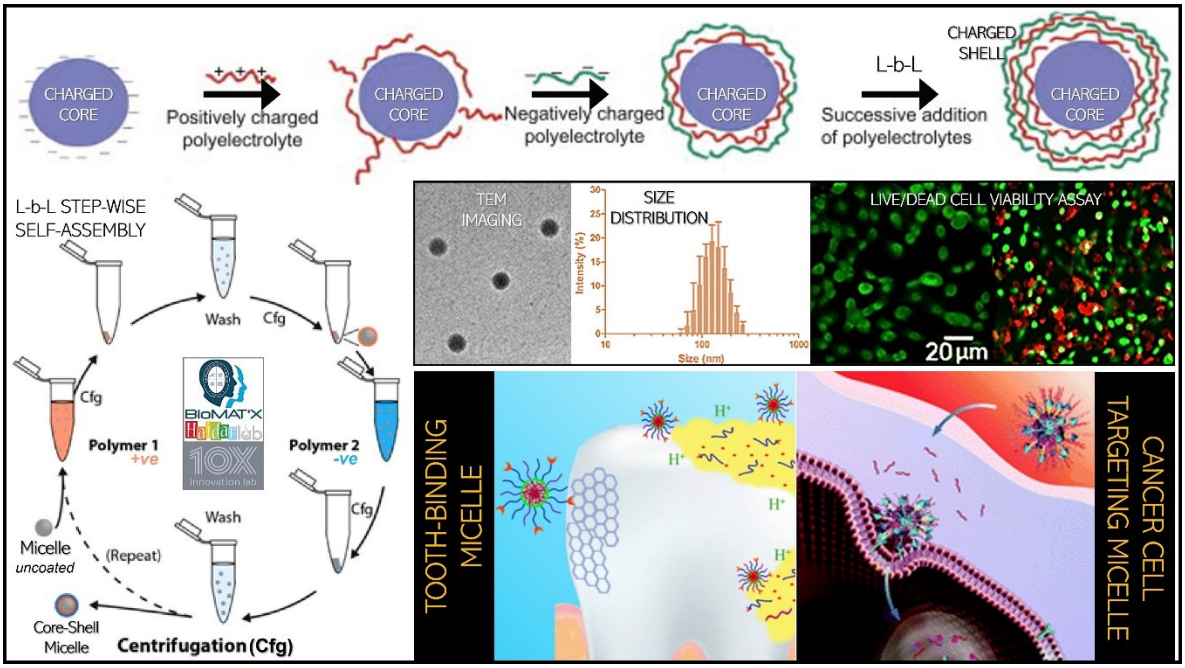

Figure 4. Schematic illustration of the L-b-L technique, characterization, and potential uses.

3.2. PolyMicelles in dentistry: from anti-Caries to anti-bioFilm to anti-Cancer and beyond

Critical Précis- The urging need to realize the full potential of modern clinical and surgical dentistry (extending to oral and cranio-maxillo-facial surgery/oncology, and the craniofacial complex; especially, post-genomic age), opened doors, to demand, pursue and apply the recent advances in polymer, bio-polymer and macromolecular sciences, material chemistry and bioengineering, and nanomedicine, for the design, development, formulation, characterization, optimization/fine-tuning, and translation of innovative bio-nano-technologies. The potential safety and efficacy of natural or synthetic polymers (and composites) have been demonstrated, whilst avoiding many of the common side effects associated with the systemic administration of bioactive agents, for applications such as bone grafting procedures, alveolar ridge augmentation, treatment/management of periodontal diseases (guided tissue regeneration, for example) and in restorative materials, scaffolds, gels, films, carriers, vehicles or matrices for cell-, gene- and protein-based therapies, and in the treatment of acute, chronic and autoimmune-related inflammations, against resistant pathogens (localized/in situ intelligent delivery systems and therapeutic strategies). Despite the wide availability of materials, no single bio-material and/or -polymer possesses all the ideal/adequate physical, chemical, mechanical, cellular, biological and surface characteristics. Remember that although such characteristics of a biomaterial or polymer are often dictated by the bulk properties, the tissue-biomaterial interaction(s) are governed by the surface, which can be easily tailored to specific requirements, *i.e.,* application-driven design.

3.3. Tooth-binding micelles

Microbial adhesion is followed by bacterial growth and colonization, resulting in the formation of a compact yet complex multispecies biofilm matrix; a cause for the most-common oro-dental diseases and conditions that involve microbes adhering to the dentition, oral mucosa or restorative materials [31, 32]. Indeed, in the battle against dental caries and decay, where dental plaque (and multi-species biofilm) is one of the prominent promoters of

caries progression, bacteria Streptococcus mutans (and other organisms) do so via colonizing onto the surface of teeth [31, 32]. Herein, polymeric micelles were suggested as an alternative solution to broad-spectrum anti-microbials (such as chlorhexidine and triclosan) to inhibit the growth or kill cariogenic bacteria. A polymeric micelle was selected to aid in overcoming the poor selectivity of such medications, whilst avoiding any disturbance to the normal or healthy balance of microflora in the mouth. Researchers recently designed, developed and evaluated novel polymeric micelles, loaded with a natural anti-microbial derivative, capable to attach/adhere to the tooth enamel, as a preventive and therapeutic strategy/tool against dental caries. They also deducted that the polymeric micelles facilitated the targeting of the anti-bacterial load, in a set or pre-clinical assays, involving rats fed with a high-sucrose diet [33]. Whilst the acidification of the biofilm (pH) is closely related to the development of dental caries, nanoscale drug-delivery materials can indeed enhance biofilm penetrability and drug bioavailability, as mentioned earlier. Hence, in another recent example, Zhang *et al.* [34] in 2021, synthesized using the atom transfer radical polymerization method, a pH-responsive two-block core-shell nano-micelle, formulated with the capability to deliver the loaded hydrophobic anti-bacterial cargo, directly, into the acidic and mature biofilm. The findings demonstrated that the bedaquiline-loaded nano-micelles were successful in inhibiting the growth of S. mutans, in neutral as well as in acidic environments, with a good bactericidal effect on mature biofilm, yet without any cytotoxic effect on periodontal cells [34]. In another example, micelles were opted as the carrier of choice, to overcome some of the limitations or obstacles in anti-microbial photodynamic therapy or aPDT; a promising too for oral de-contamination; especially resulting from the hydrophobic properties of bioactive agents [35]. Herein, curcumin was incorporated as a photo-sensitizer against Streptococcus mutans and Candida albicans biofilms, reporting a minimum inhibitory concentration (MIC) of 270 μm and 2.1093 μm, respectively, in suspended culture. Micelles, as a delivery vehicle, enhanced the solubility, stability, permeability and controlled the release of the anti-bacterial and anti-fungal Curcumin; another new and potentially-translational advancement in the battle against dental caries and tooth decay [35], afar from the formerly-adapted/-pursued tooth-binding micelles, often tested with HA (hydroxyapatite particles, as a usual tooth surface model) [36].

3.4. Oral cancer cell-targeted micelles

The increased employment of material and biomaterial science, biopolymers, surface chemistries and functional biochemistries, engineering and nanotechnology in medicine, pharmacy and dentistry has led to and driven the design, development and formulation of improved drug delivery systems and polymer-based platforms, for intra-oral use, and beyond.

In cancer, conventional treatment strategies, such as surgery and chemo-radiotherapy (solo or combined), have improved over the past few decades; yet, remain afar from optimal. For decades, orally-administrable anti-cancer nanomedicines have been and continue to be highly desirable, mainly due to the easy-of-use and repeatable administration. Yet, the mouth, often, presents difficulties in drug delivery design, owing to low therapeutic efficacy due to patient-to-patient variations in oral saliva, for example, and the short retention time of dosage forms. Yet, local drug delivery systems have been used for years, as mentioned above, and in particular, herein, have been employed for the local therapy of diseases, affecting the oral cavity itself, and beyond. Muco-adhesive systems are a good example; oral local drug delivery via the oral mucosa can occur through the keratinized mucosa (gingival and hard palate), and non-keratinized mucosa (sublingual and buccal) [37]. Further, nanocapsules as carriers allows for targeted drug delivery, controlled/sustained release drug delivery systems, transdermal drug delivery systems, and improved drug stability and bioavailability. Indeed, drug-loaded polymeric nanocapsules prepared with different biodegradable polymers, such

as alginate, chitosan, hyaluronan, gelatin, and methacrylic acid have demonstrated potential for use as drug delivery systems (polymer-drug conjugates), with good stability, encapsulation efficacy, pharmacokinetics, and overall synergistic bio-performance, leading to the U.S. Food and Drug Administration (FDA) approval in different applications; mainly related to the administration of chemotherapy agents and biomolecules in anti-cancer therapies, whilst evading the side effects related with systemic use [38-41]. For example, the Genexol-Polymeric Micelle conjugate, is/was the first polymeric micelle formulation approved by the FDA; reported to be superior in terms of safety and tolerability, when compared to other marketed formulations. It is comprised of polymeric micelles loaded with paclitaxel [42]. For paclitaxel (TAXOL®) as well, in 2022, a mucous-penetrating and cell-binding polymeric micelle, block co-polymer with poly(ε-caprolactone), have been recently designed and demonstrated, as an alternative potentially-superior therapy to the intravenously-administered PEG-based counterpart or even free drug [43]. Such tactical nano-based drug delivery systems, based on differentiating between healthy and tumor cells, and the promising potential to efficiently produce or lead to novel DNA-based (Small interfering RNA or siRNA delivery to cancer cells) products and solutions have been recently discussed by Charbe *et al.* in a comprehensive presentation of emerging lipid and polymer-based drug delivery systems for nanoncology and nanomedicine [44]. Finally, the potential of polymeric micelles (amongst other nano-scale systems) against oral squamous cell carcinoma (OSCC), the most common type of oral cancer, has been extensively reviewed elsewhere [45], with an insightful focus on the accumulation of multiple genetic mutations in the cells resulting in the damage to the oral epithelial cells [45]. Herein, re-emphasizing that for the successful development and translation of novel oral modalities for cancer therapy designed for emerging cytotoxic agents, enhancement of safety and bioavailability, is a critical pre-requisite. For example, ligand-decorated cancer-targeted cisplatin-loaded polymeric nano-micelles, recently showed promise, demonstrating a rapid intra-cellular uptake and thereby, an enhanced cytotoxic effect (superior apoptosis) in OSCC cancer cells [46]. This study also suggested that actively-targeted micelles will deliver more of the anti-cancer agent to the targeted cancer cell than non-targeted micellar system [46]. Finally, in oral cancer (oral cavity, tongue and oropharynx amongst others, including head and neck cancers) treatment, various nanotechnology-based carrier systems are being investigated, World-wide. Besides polymeric micelles, nano-lipid (liposomes and solid lipid nanoparticles) carriers, nano-emulsions, core-shell nanocapsules, cyclodextrin complexes, metal-based nanoparticles, organic and inorganic nanoparticles, nanocarbon tubes, nanodiamonds and even hydrogels are considered for potential therapies. Herein, therapeutic purposes often demand that the employed micelles (as well as other nano-scale carriers) have the versatile ability to overcome physiological barriers, deliver the load according to the suitable and efficacious dose-response and pharmacokinetic release profile(s), and increase bioavailability as well as permeability, especially for drugs that are poorly soluble or insoluble. All this is required, whilst avoiding or preventing non-specific cell death. Hence, the global purpose is to maximize the bio-safety and -efficacy of the available anti-cancer therapeutic agents; including drugs such as 5-fluorouracil, methotrexate, cisplatin and doxorubicin, commonly-investigated for oral cancer an aggressive malignant tumor that are prone to relapse and metastasize, yet, with the 5-year survival rate remaining at ~ 50%-60% [40, 45-48]. Novel targeted therapeutic drugs and biomolecules will therefore continue to advance and be tested in clinical trials with patients suffering from intra-/extra-oral cancers, to determine selectivity, efficacy, toxicity (programmed) and therapeutic index (+ prognosis); towards genuinely improving the survival rates and the quality of life of cancer patients [48].

4. Limitations and challenges

Nanotechnology is based on the idea of creating functional structures by controlling/arranging atoms and molecules, one-by-one, to achieve specific physical, chemical, mechanical and biological properties. Now, despite that nano-carriers are considered promising in the pharmaceutics, nevertheless, challenge exist and remain to be sorted out, in the clinical field. Three main impediments may restrict considering a polymeric micelle as an effective drug delivery vehicle: low loading capacity, low blood stability and need to clarify the interaction(s) with cell membranes [1]. Herein, the miscibility between polymers and drugs, is necessary to understand in order to increase or further enhance the drug encapsulation and loading. The stability of the micelle into/within the bloodstream, must be guaranteed to deliver the drug into the target cell (conventional micelles are not stable because they are physically assembled) [13]. To enhance this property, it is possible assign/attach specific ligand molecules, to the micellar surface [29]. Via changing the micellar composition and the size of both blocks, it is easy to control properties, including half-life, size and loading capacity. Characterization methods, especially for the drug loading capacity and encapsulation efficiency parameters are invaluable in accumulating sufficient and useful evidence to further employ or incorporate in optimizing the final characteristics of the desired polymeric micelle. Likewise, drug release studies (pharmaco-kinetics, often using the dialysis bag method) are to be performed in order to plot absolute versus cumulative drug release profiles, and evaluate the impact of excipients in drug release kinetics, whether during micellar core-shell formulation, storage and sterilization (quality control), drug loading and encapsulation (by physical entrapment via oil-in-water emulsion or chemical conjugation resistant to enzymatic cleavage), and/or drug release (whether free or targeted delivery), over time, and under specific conditions such as in the presence of stimuli (triggering). New drug release studies, methods, and strategies, such as, voltammetry and turbidimetry, have been recently introduced and are worth exploring [49]. Besides, as with other drug carriers, investigating drug load/release, micellar circulation time and drug delivery fate (or targeting mechanism) are very important aspects, for pharmaceutical or clinical applications of polymeric micelles. To recap, whilst polymeric micelles are in general easy to prepare as well as sterilize, offering favorable solubilization to certain drugs, molecules and agents, lower stability (kinetic behavior) in biological fluids and substrates (such as fluids, cells and tissues) is a challenge. Further, characterization of polymeric micelles might be complicated [50], requiring advanced equipment, tools, and expertise (and combination thereof). This is mostly realized, in pre-clinical models [50], whilst studying the interactions between the utilized bio-polymeric micelles and the bio-environment(s), in vivo.

5. Conclusions

Polymer-based therapeutics is a rapidly expanding area of research, development, and innovation. Yet, the noted exponential growth in the scientific and technological literature should not and does not correlate to clinical translation. This is, in part, can be attributed to the stringent regulatory requirements for approval. Further, scale-up issues persist and therefore, complicate reach to patients and market. Nonetheless, accruing advances alongside the promising results arising from in vitro, in vivo, and clinical trials, hold a promising future for such strategies and solutions. This, indeed, applies to the discussed polymer-drug conjugates in this review. In summary, when compared to micelles in general, polymeric micelles can be considered as the best alternative drug nano-carriers. Generally, polymeric micelles are simple to formulate, stable and favorable/beneficial in loading, encapsulating and delivering a range of bio-drugs and molecules, to their targets, in a controlled (and possibly predictable) manner. The small-scale nano-sized core-shell structure helps offering and tolerating a prolonged half-life in blood circulation, with an adequate infiltrating ability

into different tissues as well as a high translational longevity and potentiality [13, 21, 28]. From a research, development and innovation perspective, it is rendered very interesting that the critical or key physico-chemico-mechanical/rheological as well as cellular/biological properties and behavior of polymeric micelles as active drug delivery systems, can be further controlled via the bioengineering of the incorporated block co-polymers. Thermodynamic stability, especially in mixed polymeric micelles, is attractive for increased blood circulation time applications. Controlled drug delivery/release requires precise and in-depth characterization of the formulated micellar system, alongside, therapeutic efficacy studies (for controlled drug concentration levels, dosing intervals and drug localization/retention within the targeted tissue or zone), pre-clinically as well as clinically. As noted earlier, several clinical trials continue to investigate and search for the '*ideal*' polymeric micelle (in terms of size or dimension, drug-polymer combination and systemic *vs.* localized pharmaco-kinetic profile), to prevent disadvantages of drug loading and avoid unwanted effects [11, 12, 17]. In dentistry, biodegradability is a crucial characteristic, worthy of further investigation.

6. Perspectives

The ideal nano-scaled system would be a "smart" or "intelligent" multi-functional and release-controlled nanoparticulate delivery system capable to concurrently target, image,

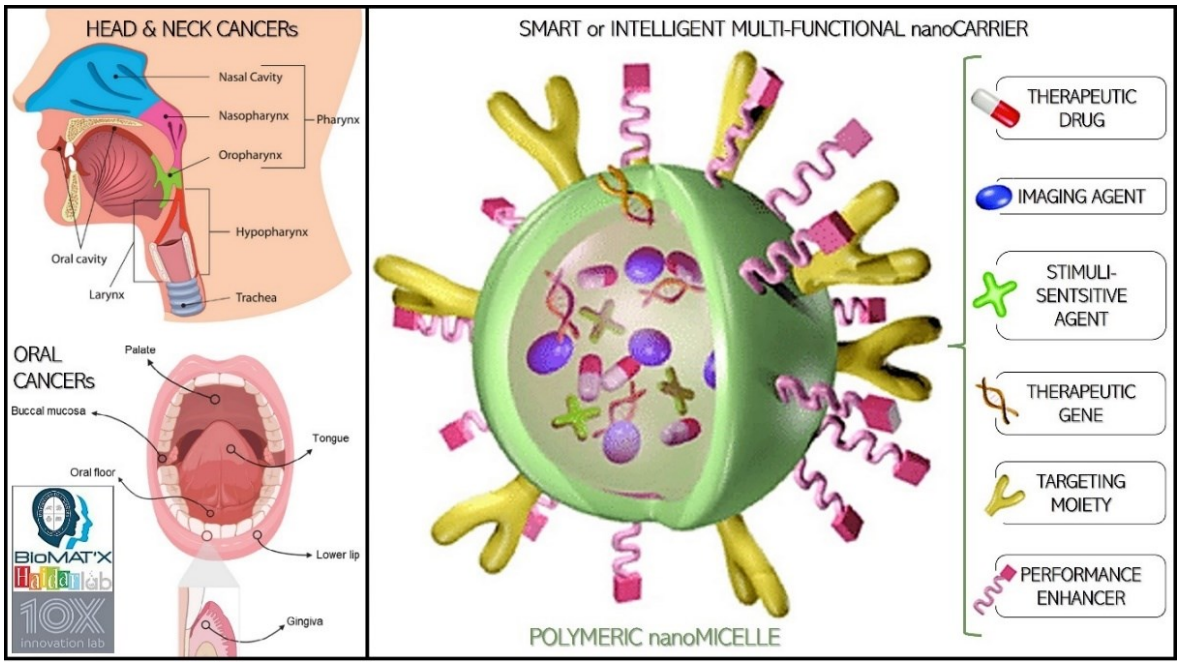

Figure 5. Schematic illustration of future multi-functional nano-carriers.

manage and treat, hence, loaded with one or more drug(s), agent(s) and perhaps a stimulus-sensitive element, and at the same time, is bio-compatible as well as -degradable (Figure 5).

The evolution of polymeric micelles into such multi-functional nano-carriers will become a major subject of interest, with accruing effort and investment, especially from pharmaceutical manufacturers and companies, as well as funding agencies and academic research institutions. Multi-functional nano-carriers envisioned to possess key properties such as: targeting ligand, controlled imaging agent administration and/or triggered bio-pharmaceutical delivery and release, are highly desirable, and would provide superior alternative therapies to a wide array of conditions and diseases. Creating new systems that

could deliver a drug or drugs, into a specific tissue target, localized, with the possibility to be monitored (and track) using a dynamic real-time imaging system, is pursued; specially so, to be able to realize the ultimate fate of the nanoparticles, released load and by-products (bio-distribution) in the human body, and to learn more about any accumulation(s) in non-target organs (liver, kidney, spleen, bone marrow, etc…). The innovation, development, characterization, fine-tuning, optimization and later the translation (bench-top to chair-side/lab to bed) and introduction of such micellar nano-structures to the clinic would advantageously benefit customized and/or personalized therapies (nanoMedicine and nanoOncology applications) that will enhance the bio-specificity, -safety and -efficacy of nano-therapeutic options [13, 23, 26, 30, 40, 49-55]. Without doubt, ongoing advances in nano-scale polymer and drug delivery will be much more promising in the coming years; towards a new era of personalized medicine, precision oncology and individualized dentistry.

Conflicts of interests

The author declares no conflict of interest.

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