International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

"Biomimetic Drug Delivery Systems: Nature-Inspired Solutions"

Pratik P.Kudale[*1], Sachin S. Mali[1], Ruturaj T. Pawar[1], Anurag R. Panade[1]
[1]*Ashokrao Mane College of Pharmacy, Peth-Vadgaon, 416112, (M.S.) India*

Date of Submission: 01-05-2024 Date of Acceptance: 10-05-2024

ABSTRACT:
Targeted medication delivery fields are the focus of today's sophisticated drug delivery systems. The enhancement of drug loading capacity in drug carriers, cellular uptake of drug carriers, and the sustained release of pharmaceuticals within target cells are all aspects of innovative drug delivery. Biomimetic hydrogels, biomimetic micelles, biomimetic liposomes, biomimetic dendrimers, biomimetic polymeric carriers, and biomimetic nanostructures are the six categories of therapeutic drug carriers examined in this review. In order to mimic the accumulation that occurs in natural cells, the subject makes use of biomimetic production techniques or biomimetic surface modification techniques. Furthermore, it is evident how these biomimetic strategies improve medication efficiency in focused drug distribution.According to the study, the creation of biomimetic nanocomposite drug carriers has the potential to significantly increase the effectiveness of medications in specific drug delivery systems.
Keywords: Biomimetic, targeted drug delivery, Drug carriers

I. INTRODUCTION:

Otto Schmidt coined the term "biomimetic" for the first time in 1957. The following definition was gleaned from his initial explanation of the topic in relation to biophysics science: "Biomimetics is not so much a subject matter as it is a point of view." It is a method of solving technological issues by applying biological science theory and technology [1]. Additionally, the terms "biomimesis," "biomimicry," "bionics," "biognosis," and "biologically inspired design" are synonyms for the field of biomimetics. Among these, "biomimetics" is the most well-known and practical term [2].

One intriguing approach to treating terminal illnesses like cancer is the use of biomimetics to demonstrate the important problems in pharmaceutics and medicine. Scientists have endeavored to gain a precise understanding of biological systems and processes through recent investigations. Understanding the intricate processes that macromolecular structures (such as the structure of proteins and their biological functions) go through at the cellular and subcellular level aids scientists in drawing inspiration from and imitating these natural processes for use in biomedical applications. The whole knowledge of cell division and growth, metabolic control, intercellular communication, and hormone signaling pathways is included in the idea of biomimesis in cellular processes [3].

The focus of current drug delivery system research is on targeted drug delivery, which allows medications to enter the cytoplasm of certain cells without endangering healthy tissues or organs. Before then, the development of nanotechnology made it possible to encapsulate medications in nanocarriers. Additionally, there has been significant progress in resolving issues with medications that are insoluble, biodegradable therapeutic agents, and drugs that are very hazardous to biological systems. These nanoparticles' modest size also allowed for intercellular diffusion. However, these nanoparticles did not fully apply the targeted release of medications into particular cells [4].

Since 1986, a significant issue involving the circulation duration of nanoparticles in bodily fluid has been the increase of permeability and retention (EPR) effect of nanoparticles for the drug release into tumor cells. The reticuloendothelial system (RES) eliminates therapeutic nanoparticles as unfriendly foreign particles by attaching plasma proteins such as immunoglobulin G (IgG) to their surface. A variety of hydrophilic polymers have been employed to provide nanoparticles a covert coating that enhances their EPR impact and shields them from the immune system. For example, one of the most popular techniques in the last thirty years is the surface coating of nanoparticles using polyethylene glycol (PEGylation). However, the cellular uptake of PEGylated nanoparticles has not occurred and the loaded medicines were destroyed in lysosomes due to the undesired interactions between PEG and target cells and poor endosomal

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

escape (referred to as the PEG problem) [5,6] Proteins, vitamins, peptides, antibodies, and aptamers acting as functional ligands can be added to the surface of PEGylated nanoparticles as a biomimetic approach to overcome their steric hindrance. Target cell features, such as the degree of overexpression of particular receptors on tumor cells, are taken into consideration when choosing the kind of these ligands with a high affinity for receptor-mediated attachment [7,8].

Therefore, biomimetics in sophisticated drug delivery systems just required surface modification with certain amino acids, saccharides, and lipids to establish inherent abilities in biomimetic drug carriers. To be able to replicate natural cells for cellular internalization, it is essential to pay close attention to the fundamental components, size, and form of drug carriers. Furthermore, by biomimetically functionalizing the surface of these nanocarriers with particular biological ligands or moieties that resemble the composition and operation of an external cell membrane, targeted drug delivery within target cells may be achieved [10,11]. Additionally, there are two primary categories of biomimetic drug carriers on the basis of basic materials: synthetic drug carriers, which are biomimetic manufactured nanoparticles with characteristics resembling those of biological materials, and existent biological entities, such as inactivated viral and bacterial vectors. It should be noted that for in vivo therapeutic uses, the second types are safer [4,12].

The control of medication release rate and the application of PEG's stealth feature for immune system stimulation inhibition have been the main concerns throughout the last thirty years. Recent research, however, has focused on methods that can imitate the cellular microenvironment through biomimetic processes, biomimetic drug carrier surface engineering, and bioinspiration from signal pathways that are essential for intracellular communication within the body.In actuality, scientists work toward achieving objectives including enhancing drug carriers' half-lives in circulation and suppressing immunological activation. Additionally, reducing the toxicity effect on the functionality of other healthy live cells and achieving prolonged drug release via the cellular internalization process within target cells could be considered secondary objectives [3,11,13,14].

The six distinct sections of this article introduce the common therapeutic drug carriers used in modern drug delivery systems. The used biomimetic techniques for enhancing therapeutic efficacy and drug release profile within target cells are examined for each area. These distinct components and their uses as drug carriers—biomimetic hydrogels, biomimetic micelles, biomimetic liposomes, biomimetic dendrimers, biomimetic polymeric carriers, and biomimetic nanostructures—are shown in the following. While some studies have been done on the introduction of these drug carriers, a complete assessment of the biomimetic articles has not been done.

1)Biomimetic hydrogels:

A class of hydrophilic polymeric materials, either synthetic or natural, are called hydrogels. Hydrogels can also grow significantly through the absorption of huge volumes of water or biological fluids. This allows the hydrogels to stay in solution in an aqueous environment through the physical or chemical cross-linking of respective polymer chains [16]. These biomaterials also include customizable porosity, biocompatibility, softness, and flexibility as key features. The gel formation conditions are moderate enough to closely mimic those of naturally occurring biological tissues and cells [17]. Changes made to the hydrogel matrix may impart unique characteristics that enable it to react quickly and reversibly to a range of chemical and physical stimuli (such as changes in pH, temperature, and ionic strength), making it suitable for the long-term, sustained release of pharmaceuticals. They can transport biomolecules (such as protein and peptide therapeutics) effectively thanks to this feature.

Biomimetic hydrogels have emerged with the addition of biological recognition sites for covering cellular activities and synchronizing responses to external stimulation. Hydrogels' inert polymer chains should also be customized with specific biological components to enable in vivo targeted medication delivery systems [16]. Furthermore, by incorporating biological cues like proteins, growth factors, and peptides into hydrogel matrices in a spatiotemporal manner, it is possible to imitate the cellular microenvironment and create a unique, controlled drug delivery system that can regenerate tissues [17].

In 2006, Liang et al. [19] used heterogeneous agarose hydrogel to optimize the diffusion of protein (lysozyme and bovine serum albumin (BSA)) at body temperature. It was demonstrated that the general properties of agarose hydrogels, such as their composition, water

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

content, and rheological nature, are comparable to those of live tissues. Using the low-affinity ligand phenothiazine TAPP (the free amine group of 3-(trifluoromethyl-phenothiazin-10-yl) propylamine), Moschou et al. [20] inserted the hinge-motion binding protein calmodulin (CaM) within the bulk of an acrylamide hydrogel network to create stimuli-sensitive hydrogels. When non-covalent cross-links are broken, the hydrogel matrix can easily go into compressive mode or release TAPP, which results in a reversible swelling state. When CAM binds to a ligand of greater affinity, such as chlorpromazine (CPZ), the same mechanism takes place. Hydrogels that are stimulus-sensitive and based on biomimetic proteins can be used to deliver drugs in a responsive manner in response to various chemical stimuli. Biomimetic poly (ethylene glycol)-diacrylate (PEGDA) hydrogels containing ephrin-A1 were created by Moon et al. [21]. In vascular assembly, the angiogenic characteristics of immobilized ephrin-A1 on hydrogel surfaces for the promotion of blood vessel development were investigated. HUVEC (Human Umbilical Vein Endothelial Cells) adhesion and capillary development with lumens were enhanced by the ephrin-A1 onto PEGDA hydrogels. It might continue to be able to promote endothelial cell adhesion.

Fisher et al. [22] conducted research on the use of biomimetic hydrogels for oral therapeutic protein delivery in 2008. Poly(methacrylic acid) grafted poly(ethylene glycol) (P(MAA-g-EG)) made up the hydrogels. As drug carriers, P(MAA-g-EG) can actually cause the lateral disruption of tight junctions, which is the primary barrier to the absorption of this class of medications. Furthermore, the pH-sensitive P(MAA-g-EG) hydrogels did not break down in the stomach, which may have increased the therapeutic protein's transepithelial paracytosis in the intestine. Hydrogels with a peptide base have the potential to replicate the natural extracellular matrix (ECM) interaction and influence cell destiny. Peptide amphiphiles (PAs), which are self-assembling hydrogels, were used to create a peptide hydrogel by alternating hydrophobic and hydrophilic residues. For in vivo drug administration applications, the stability, viscoelasticity, and gelation properties of these new biomimetic hydrogels were enhanced by the production of the biologically-inert peptide amphiphile (PA-S) in conjunction with the bioactive PAs [23].

An alginate polymer chain combination was combined with the adhesion peptide arginine-glycine-aspartic acid (RGD) to create a biomimetic "bioactive cell-hydrogel" for encasing living cells. These unique cell-hydrogel capsules were unique in that they released the medication for an extended length of time in vivo without stimulating the immune system. Additionally, the "cell-dose" biomimetic drug delivery system was self-regulating and offered a particular milieu for regulated drug delivery from immobilized cells [24]. In 2011, Bozzini et al. [25] employed a recombinant human elastin-like polypeptide (HELP) as the primary polymer in a hydrogel that replicated the structure of extracellular matrix (ECM). The enzymatic action of transglutaminase in HELP produced e-(c-glutamyl) lysine linkages via glutamine and lysine sites, which allowed the hydrogel to be cross-linked. Furthermore, there were no harmful effects from these biomimetic hydrogels with satisfactory mechanical stability. The method of modifying recombinant elastin-like protein (ELP) polymer by chemoselective ligation of peptide linkers on hydrogel surface was described by Ravi et al. [26]. For drug delivery applications, the RGD-modified ELP hydrogels may resemble the biological activity of mesenchymal stem cells and endothelial cells.

A biomimetic gelatin–siloxane (GT–S) hybrid hydrogel was made using an easy and environmentally friendly process as opposed to chemical cross-linking, which could be hazardous to living cells. With this approach, the S content and room temperature in the biocompatible solution determine the occurrence of a basic physical cross-link. Under biocompatible conditions, this biomimetic hydrogel with extremely elastic characteristics might be an appropriate carrier for medications, proteins, and biomolecules [27]. By cross-linking maleic acid-grafted dextran with thiolated chitosan, a polysaccharide hydrogel was created. These hydrogels displayed cytocompatibility with fibroblast NIH3T3 cells, swelled nicely, and performed similarly to ECM glycosaminoglycans. Additionally, Gram-positive and Gram-negative bacteria were eliminated by the in situ addition of the antibacterial medication vancomycin to the hydrogel matrix. Therefore, this biomimetic hydrogel could be used as surgical tissue adhesives or as a wound dressing with a controlled drug release mechanism [28].

It is evident that a wide variety of biological cues can be imitated to create biomimetic hydrogels for drug delivery applications. Most of them, nevertheless, are still

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

learning how to employ in vivo treatments techniques. A thorough understanding of natural transport mechanisms and diffusion behavior in biological gel systems is necessary for the controlled and extended release of medicinal bio-macromolecules from gel matrices at body temperature. The development of biomimetic hydrogels suitable for in vivo applications could result from this route. Additionally, hydrogel matrices that mimic the extracellular matrix (ECM) could be produced in order to achieve successful drug localization.Physical and innovative click chemistry approaches are the most biocompatible ways to create cross-linking within a biomimetic hydrogel matrix because they offer precise and easy control over gel formation.

2) Biomimetic micelles:

In chemistry, the term "micelle" generally refers to a structure in aqueous solutions that has a single hydrophobic core encircled by a hydrophilic end. When these supermolecules are used in drug delivery systems, new drug carriers are made that are used to treat diseases like cancer.

Polymeric micelles are the colloidal delivery technology that receives the most attention because of their superior drug modification capabilities [33]. Nanoscale spheres known as polymeric micelles are often created by amphiphilic di- or tri-block copolymers self-assembling in an aqueous medium [33, 34]. The hydrophilic shell interacts with the biological environment and imparts stealth qualities, whereas the hydrophobic (lipophilic) core is used to encapsulate and solubilize hydrophobic substances, such as proteins or DNA. The pathophysiology of the disease, the release mechanism of individual medications in particular areas, and the physicochemical characteristics of the encapsulated drug can all be designed or modified by altering the chemical structure of the block copolymers in micelles. Additionally, the core's chemical structure might be changed to improve drug encapsulation, boost micelle stability, and regulate the rate at which drugs are released from micelles. Additionally, one might create biomimetic micelles to offer more controlled localized drug delivery systems by applying biological moieties or biomimetic base block copolymers via the self-assembly of innovative biomimetic amphiphiles in micellar structure [33, 35–37].

In 2005, Xu et al. [35] developed a biomimetic amphiphile with PEO by utilizing the cholesterol moiety (Chol), which is an embedded component of the cell membrane that regulates membrane fluidity. Driamycin (ADR), a hydrophobic anti-cancer medication, was encapsulated in these Chol-PEO micelles using PEO blocks as the biocompatible shell and cholesterol blocks as the hydrophobic cores. In vitro studies, the Chol-PEO nanocapsules may offer both effective drug loading and the medication's prolonged release characteristics. Similar work was conducted by Xu et al. [36] using poly(2-methacryloyloxyethyl phosphorylcholine) (CMPC) end-capped with cholesterol to create micellar drug carriers. The poly(MPC) phospholipid moiety formed a more biocompatible shell with the human body.

Reversible helix-to-sheet protein folding transition served as the model for Sallach et al.'s [39] (2006) use of protein polymers as copolymer blocks of micelles in drug delivery systems. A protein triblock copolymer formed from elastin-mimetic peptide sequences was created in the micellar structure with the use of recombinant DNA technology. One hydrophilic block served as the center of these biomimetic micelles, while two hydrophobic blocks served as the shell. These biomimetic micelles might react quickly to environmental heat stimuli because of the protein folding transition that was shown in micellar size and compression.

Following these years, no particular and noteworthy uses of micelles were reported until 2010 when PEO was used as the shell and poly(3-caprolactone) (PCL) as the core of biomimetic micelles, or PEO-block-PCL, was developed by Xiong et al. [37] for cancer therapy. To enable it to function as a siRNA carrier and suppress oncogenes in cancer cells, the PCL core was altered by grafting polyamines (spermine). Additionally, viral vectors that give dual peptide functionality (RGD/TAT) micelles were added to the shell to facilitate the effective cellular ingestion of siRNA solely within target cells. Moreover, it was demonstrated that tumor cells exhibited no resistance to doxorubicin (DOX) internalization following the siRNA-mediated inhibition of tumor genes. One biomimetic technique for modifying the micellar structure's endurance was presented by Tang et al. [40]. This technique has broad potential applications in controlled drug delivery. For this reason, cross-links between the micelle cores are created using RAFT (Reversible Addition–Fragmentation Chain Transfer) polymerization techniques under low UV radiation. Thus, there was a notable improvement in the micellar stability

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

in acidic environments, such as the acidic environment of cancer cells.

A dual-functional medication including paclitaxel (PTX), an anti-cancer medication, and siRNA (small interfering RNA), a potent agent that suppresses the tumor's endogenous genes, was created to specifically and successfully suppress the target genes of the tumor. Two therapeutic agents were transferred into target cells simultaneously by forming stable micelle complexes (PTX/DA3-PEI/siRNA) using a micellar carrier made of deoxycholic acid (DA3) and polyethyleneimine (PEI) [41].

In summary, a great number of stable micelles may be created by enhancing the physicochemical characteristics of the biomimetic micellar carrier. A stable micellar structure may shield a loaded medication until it reached its intended location, allowing for straightforward cellular uptake. In order for healthy cells to experience minimal toxicity from medication release that is sustained. The capacity to encapsulate different hydrophobic medications is made possible by the creation of biomimetic multicompartment micelles, which resemble the compartmentalization found in cell membranes. This technique might concurrently release these medicinal substances into the target cells. In vivo applications, the aforementioned strategy appears to be a promising means of more efficiently suppressing cancer cells.

3) Biomimetic liposomes:

Liposomes are spherical vesicles made of phospholipids in a double layer, or bilayer. Liposomes are interesting candidates as medication delivery vehicles because of their lipid bilayer's resemblance to animal or human cell membranes.

By self-assembling in an aqueous solution, cholesterol and naturally occurring phospholipids can form liposomes. Liposomes possess both hydrophobic and hydrophilic properties due to the aqueous center region encircled by the concentric phospholipid bilayer. Moreover, they are biocompatible, biodegradable, and non-toxic, and they can transport hydrophilic and hydrophobic medications in the interior aqueous section and phospholipids, respectively. Different liposome types differ in terms of lipid composition, surface charge, size, and manufacturing process. Additionally, based on their size and the number of bilayers, they are classed as either uniflagellar vesicles (UV) or multilamellar vesicles (MLV) [50, 51].

Liposomes can be synthesized using a technique known as biomimicry, which imitates the biological functions of cells. Additionally, medications or biomolecules could be delivered intracellularly using biomimetic liposomes that are targeted with certain moieties or ligands. Moreover, biomimetic liposomes have the ability to actively or passively release the loaded cargo at a controlled rate in response to a specific stimulus inside the cell microenvironment [53, 54].

Thermal-responsive liposomes were developed in 2001 by Westhaus and Messersmith [55] to encapsulate CaCl2 and release it at body temperature. The production of these biomimetic liposomes was prompted by the quick gelation of Ca+2 with polysaccharides such as protein and alginate. Additionally, CaCl2-loaded liposomes may be used as biomaterials for tissue healing or as an in situ injectable medication. Sakai et al.'s [56] creation of PEG-coated liposomes to the entrapped hemoglobin (Hb-vesicles) allowed for the artificial transfer of O2 in red blood cells. The injection of HbVs at the prescribed bolus infusion rate causes a moderate metabolism in the reticuloendothelial system, according to in vivo experiments. Therefore, Hb-loaded liposomes may be a promising O2 carrier for treating the associated blood illness.

The co-loading of DNA and PTX medication into biomimetic multilamellar liposomes was one way to combine chemotherapy and gene therapy. To achieve this, folic acid (FA)-modified liposomes were co-loaded with the complexes of PEI/DNA (PD) as cationic core and PTX to create FA/PPD cationic liposomes. Next, an anionic multilamellar liposome (HA/FA/PPD) was created by coating the exterior with anionic hyaluronic acid (HA). While FA ligands boosted the simultaneous intercellular release of PTX and DNA within cancer cells, HA coating helped to stabilize these dual-targeting liposomes [61]. In 2016, Cao et al. [62] wrapped the surface of liposomes containing the anti-cancer medication emtansine with membranes from isolated macrophages. The EPR effects for drug internalization within breast cancer cells were enhanced by this ornamentation. These biomimetic liposomes suppress lung metastasis of breast cancer in vivo studies because of their capacity to target metastatic locations.

In conclusion, the biomimetic surface modification of liposomes and the biomimetic liposome fabrication techniques improved the EPR effect, which in turn improved the therapeutic

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

liposomes' ability to target drug delivery. The limited stability of drug-loaded carriers against enzyme degradation is the primary limitation of uniflagellar liposomes for in vivo applications. Another drawback is the early release of medications that have been encapsulated before they reach the target cells. The EPR effect is greatly enhanced by the compartmentalization technique used to create biomimetic multilamellar liposomes. Additionally, these structures can be used to create dual cancer cell targeting carriers by encapsulating several hydrophilic and hydrophobic medications as well as gene therapy agents. Improving the fluidity of the liposomal membrane may facilitate the passage through cellular barriers.

4) Biomimetic dendrimers:

Dendrimers are artificial polymers shaped like trees that can be extended through a sequence of processes and customized to function as drug carriers in drug delivery systems.

Dendrimers are compact spherical, highly branching, three-dimensional macromolecules whose internal repeating units, or generations, arise from a central core [63, 64]. These macromolecules have a predetermined form, size, molecular weight, and monodispersity in addition to many functional groups (exterior reactive terminal groups) on their surface that qualify them as suitable carriers in drug delivery systems. Indeed, medications can be physically contained within the dendritic structure or conjugated to the surface through covalent or electrostatic interactions with the end functional groups [64, 65]. Additionally, dendrimers may increase the bioavailability, biocompatibility, and water solubility of medication molecules [66]. However, before using dendrimers in biomedical applications, it is important to address three aspects of their structure that contribute to toxicity: the charge of the surface, composition, and number of generations. Furthermore, cationic dendrimers exhibit greater toxicity than anionic or neutral ones due to the triggering of apoptosis via cell and organelle membranes [50].

Biomimetic drug carriers can be made by attaching significant moieties to reactive terminal groups on dendrimers' surface, allowing for targeted drug delivery. Furthermore, these macromolecules might be produced by self-assembly with structures resembling natural proteins and the potential to mimic a variety of natural materials thanks to the unique monodispersity of dendrimers [68].

In 2004, Paleos et al. [69] added guanidinium ligands and PEG chains to the outside surface of diaminobutane poly(propylene imine) (DAB) dendrimers. As a result, the amino groups in the physiological media had greater stability and fewer harmful effects due to the simultaneous provision of the stealth cover and targeting feature via biologically acidic receptors. Additionally, in vitro assessments were conducted on the solubility and release characteristics of encapsulated pyrene and betamethasone valerate in this multifunctional dendrimer. By using room temperature ring-opening polymerization (ROP) between β-benzyl-L-glutamate N-carboxyanhydride (BLG-NCA) and the initial amine-ended groups of poly(amidoamine) (PAMAM), Huang et al. [70] produced a biomimetic multi-armed dendrimer. The secondary structure was made more like proteins by the multi-armed PAMAM-PBLG dendrimers, which were easily controlled by a predetermined average size. Additionally, stable globular nanoparticles that served as drug or gene carriers were created by directly injecting these dendrimers into distilled water.

Acryloyloxyethyl phosphorylcholine (APC), which is the outer layer of cell membranes and the terminal zwitterionic part of some lipids, was employed by Jia et al. [75] to alter the cationic surface of PAMAM dendrimers. As a result, the PC ligands reduced dendrimer cytotoxicity and enabled a prolonged release of ADR within the cancer cell. In 2014, Raghupathi et al. [76] presented the facially amphiphilic dendrimers as a distinct field. They demonstrated how most research on the behavior of super molecular drug carriers that are stimuli-sensitive was assessed in relation to certain parameters, such as pH, temperature, and redox conditions, which were the secondary factors that led to biological milieu imbalances. Actually, the behavior of dendrimer assemblies against actual imbalances in biological media, such as enzymatic and non-enzymatic protein stimulations, was studied using the facially amphiphilic dendrimers.

Mekuria et al. [77] compared two PAMAM dendrimers that had been altered to target two distinct ligands—IL-6 and RGD—as therapeutic carriers against cancer cells. In order to achieve this, the pH-sensitive PAMAMIL-6 and PAMAM-RGD dendrimers were loaded with the DOX. The longer IL-6 ligand was shown to give more drug loading, intercellular absorption, and drug transfer via RME into cancer cells in the in vitro experiments.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

As is evident, the primary reason for studying PAMAMs was their intrinsic capacity to improve intercellular drug uptake as the intended drug carrier. However, the primary issues that lead to these dendrimers' harmful effects are the surface cationic charge brought on by amino groups and the number of generations. In order to improve the EPR effect and cellular uptake via RME for in vivo applications, one can therefore expect for the usage of polymeric coating to offer stealth cover and target biological ligand.

5) Biomimetic polymeric carriers:

Certain characteristics of polymeric carriers make them useful for drug delivery applications. These include their ease of nanoscale production, high drug loading capacity, controlled drug release, and surface alteration resulting from active functional groups [41]. Biomimetic polymers are new types of biomaterial carriers that replicate the ways in which cells interact with their surroundings, including endocytosis, cytokine signaling, and cell adhesion. Furthermore, medication transfer across cell barriers within target diseased cells is made possible by the physiologically active constituents of these polymers. Additionally, the right biomimetic polymeric carrier is the one that can extract the necessary cellular response that leads to reaching its target and reduce unspecific interactions on surface cells [78]. The foundational problems to determine the specific drug release mechanism and diffusion model for these polymeric carriers are the optimization of the stoichiometry in polymerization techniques and the design of the biomimetic structure [80].

In 2006, Zhang et al. [81] created a biopolymeric material with a dual-functional feature that could conjugate with biological ligands. It was made of zwitterionic poly(carboxybetaine methacrylate) (polyCBMA) grafted on a gold surface. In fact, by immobilizing the specific protein, it may have a strong resistance against the adsorption of non-specific ones. In this study, immobilization of anti-human chorionic gonadotropin on the surface inhibited the adsorption of hCG (human chorionic gonadotropin). PolyCBMA-based materials are well suited for drug delivery systems and medical diagnostics due to their dual biomimetic activity. In 2007, Duncan[82] synthesized two HPMA [N-(2 hydroxypropyl)methacrylamide]copolymer conjugates, which together resulted in the aromatase inhibitor aminogluthimide and the chemotherapeutic drug DOX. Additionally, it was designed to be specific to a molecular mass so that it could select malignancies through the endocytosis internalization stage. In phase I/II clinical trials, it was the first biodegradable polymer-drug conjugate that was examined.

A surface-based biomaterial, such as starch, was biodegradable and used to create a biomimetic calcium phosphate (CaP) coating. In fact, the balance on osteoblastic/osteoclastic cell line activity at the interface with injured bone was adjusted to regenerate it by mixing sodium clodronate (therapeutic drug) with CaP [83]. By grafting PP-75 (L-phenylalanine stoichiometric grafting) onto the pendant carboxylic acids of a polyamide (poly (L-lysine isophthalamide)), Ho et al. [84] created one biomimetic endosomalytic polymer. The primary features of PP-75 were its small size, which allowed for easy penetration into tumor spheroids and intracellular drug release without harm for other live cells, and its changeable hydrodynamic size, which depended on lower pH. These capabilities may motivate researchers to do additional clinical studies on endosomalytic PP-75's in vivo uses.

Zwitterioni poly(amido amine)s (PAAs) were used by Ekkelenkamp et al. [85] in 2016 to create two different types of PAA nano-gels, from which the best one was selected as a biomimetic and biocompatible polymeric carrier. Lastly, compared to significantly positive surface charge nanogels, PAA nanogels with low dispersity and a negative surface charge had less of an adverse effect on living cells and were therefore more suited as drug carriers.

In conclusion, adding unique ligands or moieties to the surface of polymeric drug carriers may enable intercellular drug release in target cells without impairing the activity of healthy cells. However, because to the strict controls already in place to minimize non-specific interactions in the cell microenvironment, the in vivo application of these biomimetic drug carriers is currently restricted. A comprehensive understanding of the physiological characteristics of modifying ligands and intercellular trafficking channels may lead to the development of biomimetic customized polymeric drug carriers. Additionally, it's critical to optimize the chemical characteristics of synthetic polymers in order to reduce the immunological response mediated by cells.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

II. CONCLUSION:

A cursory look at studies on the creation of biomimetic drug carriers reveals a marked increase in drug efficiency in targeted medication delivery. Indeed, there has been a discernible improvement in the ability of drug loading in drug carriers, drug carrier cellular internalization, and drug release within target cells in a sustained manner.

The creation of biomimetic hydrogels, in which the cellular microenvironments mirrored the extracellular matrix, proved to be extremely effective for localized drug delivery. The physicochemical characteristics of the biomimetic micellar carriers have been improved. Stabilized micellar structures allow for sustained drug release by facilitating cellular absorption and offering total protection for loaded medicines until they reach their target sites. Through an improvement in the EPR effect, the biomimetic modification of the liposome surface and the biomimetic liposome fabrication techniques improved the therapeutic liposomes' ability to target drug delivery. Intercellular drug uptakes for targeted drug transfer have been encouraged in the biomimetic PAMAM dendrimers. Biomimetic polymeric carriers have made endocytosis for intercellular drug release easier. The ability to load pharmaceuticals, cellular absorption, and drug release profile have all been markedly enhanced in the other biomimetic nanostructures based on organic and inorganic materials (nanocomposite drug carriers).

Even though the bulk of research on the uses of biomimetic drug delivery systems was conducted in vitro, the field's rapid advancement in research may eventually lead to successful drug delivery applications for the treatment of diseases that occur in vivo.

REFERENCES:

[1]. J.F.V. Vincent, Biomimetics – a review, Proc. Inst. Mech. Eng. H J. Eng. Med. 223 (2009) 919–939.
[2]. J.F. Vincent, O.A. Bogatyreva, N.R. Bogatyrev, A. Bowyer, A.-K. Pahl, Biomimetics: its practice and theory, J. R. Soc. Interface 3 (2006) 471–482.
[3]. S. Venkatesh, M.E. Byrne, N.A. Peppas, J.Z. Hilt, Applications of biomimetic systems in drug delivery, Expert Opin. Drug Deliv. 2 (2005) 1085–1096.
[4]. C. Vauthier, D. Labarre, Modular biomimetic drug delivery systems, J. Drug Deliv. Sci. Technol. 18 (2008) 59–68.
[5]. Z. Amoozgar, Y. Yeo, Recent advances in stealth coating of nanoparticle drug delivery systems, Wiley Interdiscip. Rev. 4 (2012) 219–233.
[6]. P. Mishra, B. Nayak, R.K. Dey, PEGylation in anti-cancer therapy: An overview, Asian J. Pharm. Sci. 11 (2016) 337–348.
[7]. H. Hatakeyama, H. Akita, H. Harashima, The polyethyleneglycol dilemma: advantage and disadvantage of PEGylation of liposomes for systemic genes and nucleic acids delivery to tumors, Biol. Pharm. Bull. 36 (2013) 892–899.
[8]. S.W. Choi, W.S. Kim, J.H. Kim, Surface modification of functional nanoparticles for controlled drug delivery, J. Dispers. Sci. Technol. 24 (2003) 475–487.
[9]. C. Alvarez-Lorenzo, A. Concheiro, Bioinspired drug delivery systems, Curr. Opin. Biotechnol. 24 (2013) 1167–1173.
[10]. R.A. Meyer, J.C. Sunshine, J.J. Green, Biomimetic particles as therapeutics, Trends Biotechnol. 33 (2015) 514–524.
[11]. Y.-k. Gong, F.M. Winnik, Strategies in biomimetic surface engineering of nanoparticles for biomedical applications, Nanoscale 4 (2012) 360–368.
[12]. S. Guo, L. Huang, Nanoparticles Escaping RES and Endosome: Challenges for siRNA Delivery for Cancer Therapy, J. Nanomater. 2011 (2011) 1–12.
[13]. S.C. Balmert, S.R. Little, Biomimetic Delivery with Micro- and Nanoparticles, Adv. Mater. 24 (2012) 3757–3778.
[14]. N.A. Peppas, Intelligent therapeutics: biomimetic systems and nanotechnology in drug delivery, Adv. Drug Deliv. Rev. 56 (2004) 1529–1531.
[15]. J.-W. Yoo, D.J. Irvine, D.E. Discher, S. Mitragotri, Bio-inspired, bioengineered and biomimetic drug delivery carriers, Nat. Rev. Drug Discov. 10 (2011) 521–535.
[16]. C.-C. Lin, A.T. Metters, Hydrogels in controlled release formulations: network design and mathematical modeling, Adv. Drug Deliv. Rev. 58 (2006) 1379–1408.
[17]. E. Caló, V.V. Khutoryanskiy, Biomedical applications of hydrogels: a review of patents and commercial products, Eur. Polym. J. 65 (2015) 252–267.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 606-617 www.ijprajournal.com ISSN: 2456-4494

[18]. R. Censi, P. Di Martino, T. Vermonden, W.E. Hennink, Hydrogels for protein delivery in tissue engineering, J. Control. Release 161 (2012) 680–692.
[19]. S. Liang, J. Xu, L. Weng, H. Dai, X. Zhang, L. Zhang, Protein diffusion in agarose hydrogel in situ measured by improved refractive index method, J. Control. Release 115 (2006) 189–196.
[20]. E.A. Moschou, N. Chopra, S.L. Khatwani, J.D. Ehrick, S.K. Deo, L.G. Bachas, S. Daunert, Stimuli-responsive Hydrogels Based on the Genetically Engineered Proteins: Actuation, Drug Delivery and Mechanical Characterization, MRS Proceedings, 952, 2011.
[21]. J.J. Moon, S.-H. Lee, J.L. West, Synthetic biomimetic hydrogels incorporated with Ephrin-A1 for therapeutic angiogenesis, Biomacromolecules 8 (2007) 42–49.
[22]. O.Z. Fisher, N.A. Peppas, Quantifying tight junction disruption caused by biomimetic pH-sensitive hydrogel drug carriers, J. Drug Deliv. Sci. Technol. 18 (2008) 47–50.
[23]. J.M. Anderson, A. Andukuri, D.J. Lim, H.-W. Jun, Modulating the gelation properties of self-assembling peptide amphiphiles, ACS Nano 3 (2009) 3447–3454.
[24]. G. Orive, M. De Castro, H.-J. Kong, R.M. Hernández, S. Ponce, D.J. Mooney, J.L. Pedraz, Bioactive cell-hydrogel microcapsules for cell-based drug delivery, J. Control. Release 135 (2009) 203–210.
[25]. S. Bozzini, L. Giuliano, L. Altomare, P. Petrini, A. Bandiera, M.T. Conconi, S. Farè, M.C. Tanzi, Enzymatic cross-linking of human recombinant elastin (HELP) as biomimetic approach in vascular tissue engineering, J. Mater. Sci. Mater. Med. 22 (2011) 2641–2650.
[26]. S. Ravi, V.R. Krishnamurthy, J.M. Caves, C.A. Haller, E.L. Chaikof, Maleimide–thiol coupling of a bioactive peptide to an elastin-like protein polymer, Acta Biomater. 8 (2012) 627–635.
[27]. Y. Xue, L. Wang, Y. Shao, J. Yan, X. Chen, B. Lei, Facile and green fabrication of biomimetic gelatin–siloxane hybrid hydrogel with highly elastic properties for biomedical applications, Chem. Eng. J. 251 (2014) 158–164.
[28]. Y. Zhao, X. Zhang, Y. Wang, Z. Wu, J. An, Z. Lu, L. Mei, C. Li, In situ cross-linked polysaccharide hydrogel as extracellular matrix mimics for antibiotics delivery, Carbohydr. Polym. 105 (2014) 63–69.
[29]. S.Y. Kim, J.-S. Park, Biomineralized hyaluronic acid/poly(vinylphosphonic acid) hydrogel for bone tissue regeneration, J. Appl. Polym. Sci. 131 (2014) (n/a-n/a).
[30]. H.W. Huh, L. Zhao, S.Y. Kim, Biomineralized biomimetic organic/inorganic hybrid hydrogels based on hyaluronic acid and poloxamer, Carbohydr. Polym. 126 (2015) 130–140.
[31]. M. Boffito, E. Gioffredi, V. Chiono, S. Calzone, E. Ranzato, S. Martinotti, G. Ciardelli, Novel polyurethane-based thermosensitive hydrogels as drug release and tissue engineering platforms: design andinvitrocharacterization, Polym. Int. 65 (2016) 756–769.
[32]. L.A. Sawicki, A.M. Kloxin, Light-mediated formation and patterning of hydrogels for cell culture applications, J. Vis. Exp. 115 (2016), http://dx.doi.org/10.3791/54462.
[33]. H.M. Aliabadi, A. Lavasanifar, Polymeric micelles for drug delivery, Exp. Opin. Drug Deliv. 3 (2005) 139–162.
[34]. Z.S. Haidar, Bio-inspired/-functional colloidal core-shell polymeric-based nanosystems: technology promise in tissue engineering, Bioimag. NanoMed. Polym. 2 (2010) 323–352.
[35]. J.P. Xu, J. Ji, W.-D. Chen, J.C. Shen, Biomimetic Amphiphiles for Polymeric Micellar Carrier System, Key Eng. Mater. 288–289 (2005) 465–468.
[36]. J.-P. Xu, J. Ji, W.-D. Chen, J.-C. Shen, Novel biomimetic polymersomes as polymer therapeutics for drug delivery, J. Control. Release 107 (2005) 502–512.
[37]. X.-B. Xiong, H. Uludağ, A. Lavasanifar, Virus-mimetic polymeric micelles for targeted siRNA delivery, Biomaterials 31 (2010) 5886–5893.
[38]. G. Liu, W. Zhuang, X. Chen, A. Yin, Y. Nie, Y. Wang, Drug carrier system self-assembled from biomimetic polyphosphorycholine and biodegradable polypeptide based diblock copolymers, Polymer 100 (2016) 45–55.

[39]. R.E. Sallach, M. Wei, N. Biswas, V.P. Conticello, S. Lecommandoux, R.A. Dluhy, E.L. Chaikof, Micelle density regulated by a reversible switch of protein secondary structure, J. Am. Chem. Soc. 128 (2006) 12014–12019.

[40]. Y. Tang, Z. Liu, X. Wu, G. Liu, K. Yang, Y. Li, L. Lu, Y. Cai, Modulating structural stability and acid sensitivity of photosensitive polymer micelles simply via one-batch UV irradiation, J. Polym. Sci. A Polym. Chem. 50 (2012) 2878–2888.

[41]. Y.L. Jang, U.J. Yun, M.S. Lee, M.G. Kim, S. Son, K. Lee, S.Y. Chae, D.W. Lim, H.T. Kim, S.H. Kim, J.H. Jeong, Cell-penetrating peptide mimicking polymer-based combined delivery of paclitaxel and siRNA for enhanced tumor growth suppression, Int. J. Pharm. 434 (2012) 488–493.

[42]. X. Wang, X. Sun, G. Jiang, R. Wang, R. Hu, X. Xi, Y. Zhou, S. Wang, T. Wang, Synthesis of biomimetic hyperbranched zwitterionic polymers as targeting drug delivery carriers, J. Appl. Polym. Sci. 128 (2013) 3289–3294.

[43]. G. Jiang, X. Sun, Y. Ma, J. Cao, Y. Wang, R. Wang, X. Wang, S. Wang, Hyperbranched polyether surface functionalized with biomimetic zwitterionic polymers as potential drug Release carriers, Soft Matter 150527100759009 (2013).

[44]. Y. Wang, H. Wang, Y. Chen, X. Liu, Q. Jin, J. Ji, Biomimetic pseudopolyrotaxane prodrug micelles with high drug content for intracellular drug delivery, Chem. Commun. 49 (2013) 7123.

[45]. M. Wu, K. Guo, H. Dong, R. Zeng, M. Tu, J. Zhao, In vitro drug release and biological evaluation of biomimetic polymeric micelles self-assembled from amphiphilic deoxycholic acid–phosphorylcholine–chitosan conjugate, Mater. Sci. Eng. C 45 (2014) 162–169.

[46]. H.-K. Yang, L.-M. Zhang, New amphiphilic glycopolypeptide conjugate capable of self-assembly in water into reduction-sensitive micelles for triggered drug release, Mater. Sci. Eng. C 41 (2014) 36–41.

[47]. A.L. Barbarini, D.A. Estenoz, D.M. Martino, Crosslinkable micelles from diblock amphiphilic copolymers based on vinylbenzyl thymine and vinylbenzyl triethylammonium chloride, J. Appl. Polym. Sci. 132 (2015) (n/a-n/a).

[48]. B. Mandal, N.K. Mittal, P. Balabathula, L.A. Thoma, G.C. Wood, Development and in vitro evaluation of core–shell type lipid–polymer hybrid nanoparticles for the delivery of erlotinib in non-small cell lung cancer, Eur. J. Pharm. Sci. 81 (2016) 162–171.

[49]. Y. Wang, J. Wang, T. Wang, Y. Xu, L. Shi, Y. Wu, L. Li, X. Guo, Pod-like supramicelles with multicompartment hydrophobic cores prepared by self-assembly of modified chitosan, NanoMicro Lett. 8 (2015) 151–156.

[50]. C. Cordon, M. Piva, C. Melo, M. Pinhal, E. Suarez, Nanoparticles as platforms of molecular delivery in diagnosis and therapy, OA Cancer 1 (2) (2013 Dec 01) 15.

[51]. A. Akbarzadeh, R. Rezaei-Sadabady, S. Davaran, S.W. Joo, N. Zarghami, Y. Hanifehpour, M. Samiei, M. Kouhi, K. Nejati-Koshki, Liposome: classification, preparation, and applications, Nanoscale Res. Lett. 8 (2013) 102.

[52]. Y.P. Patil, S. Jadhav, Novel methods for liposome preparation, Chem. Phys. Lipids 177 (2014) 8–18.

[53]. R. Chandrawati, F. Caruso, Biomimetic liposome- and polymersome-based multicompartmentalized assemblies, Langmuir 28 (2012) 13798–13,807.

[54]. T.M. Allen, P.R. Cullis, Liposomal drug delivery systems: from concept to clinical applications, Adv. Drug Deliv. Rev. 65 (2013) 36–48.

[55]. E. Westhaus, P.B. Messersmith, Triggered release of calcium from lipid vesicles: a bioinspired strategy for rapid gelation of polysaccharide and protein hydrogels, Biomaterials 22 (2001) 453–462.

[56]. H. Sakai, H. Horinouchi, Y. Masada, S. Takeoka, E. Ikeda, M. Takaori, K. Kobayashi, E. Tsuchida, Metabolism of hemoglobin-vesicles (artificial oxygen carriers) and their influence on organ functions in a rat model, Biomaterials 25 (2004) 4317–4325.

[57]. J. Zhu, J. Xue, Z. Guo, R.E. Marchant, Vesicle size and stability of biomimetic liposomes from 3′-sulfo-Lewis a (SuLea)

containing glycolipids, Colloids Surf. B: Biointerfaces 58 (2007) 242–249.
[58]. J. Zhu, J. Xue, Z. Guo, L. Zhang, R.E. Marchant, Biomimetic glycoliposomes as nanocarriers for targeting P-selectin on activated platelets, Bioconjug. Chem. 18 (2007) 1366–1369.
[59]. J. Gao, U. Reibetanz, S. Venkatraman, B. Neu, Biofunctionalization of polyelectrolyte microcapsules with biotinylated polyethylene glycol-grafted liposomes, Macromol. Biosci. 11 (2011) 1079–1087.
[60]. T. Koklic, Perifosine induced release of contents of trans cell-barrier transport efficient liposomes, Chem. Phys. Lipids 183 (2014) 50–59.
[61]. G.-X. Liu, G.-Q. Fang, W. Xu, Dual targeting biomimetic liposomes for paclitaxel/ DNA combination cancer treatment, Int. J. Mol. Sci. 15 (2014) 15287–15303.
[62]. H. Cao, Z. Dan, X. He, Z. Zhang, H. Yu, Q. Yin, Y. Li, Liposomes coated with isolated macrophage membrane can target lung metastasis of breast cancer, ACS Nano 10 (2016) 7738–7748.
[63]. M. Liu, J.M.J. Fréchet, Designing dendrimers for drug delivery, Pharm. Sci. Technol. Today 2 (1999) 393–401.
[64]. [64] T. Garg, O. Singh, S. Arora, R. Murthy, Dendrimer—a novel scaffold for drug delivery, Int. J. Pharm. Sci. Rev. Res. 7 (2011) 211–220.
[65]. S. Tripathy, M.K. Das, Dendrimers and their applications as novel drug delivery carriers, J. Appl. Pharm. Sci. 3 (2013) 142–149.
[66]. Y. Cheng, J. Wang, T. Rao, X. He, T. Xu, Pharmaceutical applications of dendrimers: promising nanocarriers for drug delivery, Front. Biosci. 13 (2007) 1447–1471.
[67]. B.K. Nanjwade, H.M. Bechra, G.K. Derkar, F.V. Manvi, V.K. Nanjwade, Dendrimers: emerging polymers for drug-delivery systems, Eur. J. Pharm. Sci. 38 (2009) 185–196.
[68]. W.-D. Jang, K.M. Kamruzzaman Selim, C.-H. Lee, I.-K. Kang, Bioinspired application of dendrimers: from bio-mimicry to biomedical applications, Prog. Polym. Sci. 34 (2009) 1–23.
[69]. C.M. Paleos, D. Tsiourvas, Z. Sideratou, L. Tziveleka, Acid- and salt-triggered multifunctional poly(propylene imine) dendrimer as a prospective drug delivery system, Biomacromolecules 5 (2004) 524–529.
[70]. H. Huang, C.-M. Dong, Y. Wei, Biomimetic PAMAM-poly (benzyl l-glutamate) amphiphiles with multi-armed architecture: synthesis, physical properties and selfassembled nanoparticles, Comb. Chem. High Throughput Screen. 10 (2007) 368–376.
[71]. P. Singh, U. Gupta, A. Asthana, N.K. Jain, Folate and folate−peg−pamam dendrimers: synthesis, characterization, and targeted anticancer drug delivery potential in tumor bearing mice, Bioconjug. Chem. 19 (2008) 2239–2252.
[72]. Y.E. Kurtoglu, R.S. Navath, B. Wang, S. Kannan, R. Romero, R.M. Kannan, Poly(amidoamine) dendrimer–drug conjugates with disulfide linkages for intracellular drug delivery, Biomaterials 30 (2009) 2112–2121.
[73]. H. Yuan, K. Luo, Y. Lai, Y. Pu, B. He, G. Wang, Y. Wu, Z. Gu, A novel poly(l-glutamic acid) dendrimer based drug delivery system with both ph-sensitive and targeting functions, Mol. Pharm. 7 (2010) 953–962.
[74]. T. Suehiro, T. Tada, T. Waku, N. Tanaka, C. Hongo, S. Yamamoto, A. Nakahira, C. Kojima, Temperature-dependent higher order structures of the (Pro-Pro-Gly)10-modified dendrimer, Biopolymers 95 (2011) 270–277.
[75]. L. Jia, J.-P. Xu, H. Wang, J. Ji, Polyamidoamine dendrimers surface-engineered with biomimetic phosphorylcholine as potential drug delivery carriers, Colloids Surf. B: Biointerfaces 84 (2011) 49–54.
[76]. K.R. Raghupathi, J. Guo, O. Munkhbat, P. Rangadurai, S. Thayumanavan, Supramolecular disassembly of facially amphiphilic dendrimer assemblies in response to physical, chemical, and biological stimuli, Acc. Chem. Res. 47 (2014) 2200–2211.
[77]. S.L. Mekuria, T.A. Debele, H.-Y. Chou, H.-C. Tsai, IL-6 antibody and RGD peptide conjugated poly(amidoamine) dendrimer for targeted drug delivery of

HeLa cells, J. Phys. Chem. B 120 (2016) 123–130.

[78]. S. Drotleff, U. Lungwitz, M. Breunig, A. Dennis, T. Blunk, J. Tessmar, A. Göpferich, Biomimetic polymers in pharmaceutical and biomedical sciences, Eur. J. Pharm. Biopharm. 58 (2004) 385–407.

[79]. Q. Jin, Y. Chen, Y. Wang, J. Ji, Zwitterionic drug nanocarriers: a biomimetic strategy for drug delivery, Colloids Surf. B: Biointerfaces 124 (2014) 80–86.

[80]. A.C. Lima, C.A. Custódio, C. Alvarez-Lorenzo, J.F. Mano, Biomimetic methodology to produce polymeric multilayered particles for biotechnological and biomedical applications, Small 9 (2013) 2487–2492.

[81]. Z. Zhang, S. Chen, S. Jiang, Dual-functional biomimetic materials: nonfouling poly(carboxybetaine) with active functional groups for protein immobilization, Biomacromolecules 7 (2006) 3311–3315.

[82]. R. Duncan, Designing polymer conjugates as lysosomotropic nanomedicines, Biochem. Soc. Trans. 35 (2007) 56–60.

[83]. A.L. Oliveira, A.J. Pedro, C.S. Arroyo, J.F. Mano, G. Rodriguez, J.S. Roman, R.L. Reis, Biomimetic Ca-P coatings incorporating bisphosphonates produced on starchbased degradable biomaterials, J. Biomed. Mater. Res. B Appl. Biomater. 92B (2010) 55–67.

[84]. V.H.B. Ho, N.K.H. Slater, R. Chen, pH-responsive endosomolytic pseudo-peptides for drug delivery to multicellular spheroids tumour models, Biomaterials 32 (2011) 2953–2958.

[85]. A.E. Ekkelenkamp, M.M.T. Jansman, K. Roelofs, J.F.J. Engbersen, J.M.J. Paulusse, Surfactant-free preparation of highly stable zwitterionic poly(amido amine) nanogels with minimal cytotoxicity, Acta Biomater. 30 (2016) 126–134.