REVIEW

New Drug Delivery Systems Concept in Anaesthesia and Intensive Care—Controlled Release of Active Compounds

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Conflicts of interests

Nothing to declare

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Abstract

With time, medical and pharmaceutical research has advanced significantly. However, one of the major issues is how to administer the active substance. Among these, it counts over- or under-dosage of the active substance, low response to treatment, or increased clinical risk of the patient. An innovative method able to avoid these obstacles is represented by controlled release systems for active substances. The

interest for these systems came with allowing encapsulation in the antibiotic release matrices, local anesthetics, protein or other substances. Moreover, a number of such vehicles are now available to release controlled substances used predominantly in the anesthesia and intensive care unit.

Introduction

A lot of biologically active compounds have been discovered with the developments

in science and research, compounds that can be ideal candidates for the treatment of diverse pathologies. The biological activity depends on the way of administration and on the type of metabolism a certain substance has inside the human body. Active substances administered orally have a pretty low bioavailability, and therefore supplementary administration of the drug is needed at set time intervals, resulting in a lower efficiency, in the risk of underdosage or overdosage, and into a higher discomfort for the patient [1]. Recently new materials have come to light, that are capable of encapsulating the active biological compound in a polymer network and of delivering it into a system (biological or physic-chemical), in a constant manner, and over long periods of time. Much has been taken of the functionalized materials—capable of reaching a target place in the body and to precisely control further aspects: the volume of the entrapped molecule and the concentration of the biologically active compound, resulting in a new field of research: Controlled Drug Release—controlled drug delivery. The chemical materials research field needed for manufacturing the drugs with controlled release is continuously developing because of very strict parameters that need to be met—bioavailability, stimulus response, biodegradability, etc. The release speed of active biological compounds from the systems obtained through various methods can be adapted based on the clinical needs for the treatment by changing certain chemical compounds in the manufacturing process, and therefore reaching the expected therapeutical requirements [1,2]. Controlled release systems from biologically active compounds are devices that allow the administration inside of the body of an active substance, by incorporating it inside them and improving their therapeutic effect by controlling the speed, target place and time of release [3]. Compared to conventional systems, the ones with controlled release allow maintaining an optimal concentration of the active compound that stays between therapeutic limits, without reaching toxic levels and without it being under dosed. The results of experimental studies stand proof for the importance of introducing controlled release systems in the current medical practice [4]. The diversity of controlled release systems can be increased through the biofunctionalizing of particles that are part of the material used when manufacturing the system. In this manner the following can be grafted on the structures of controlled release systems: proteins, lipids, nucleic acids, active substances, and biomacromolecules [5]. The aim of this paper is that of creating a link between poly-

meric biocompatible and bioavailable matrices used for the release of certain biologically active compounds and treatments of interest in the anaesthesia and intensive care units.

Types of Materials Used in Manufacturing-Controlled Release Systems

Because of the high diversity regarding the clinical needs, numerous studies have been carried out in the field of biocompatible materials that could attain the selectivity, metabolism, bioavailability, and biodegradability requirements. Therefore, numerous polymer networks have been developed, that can be successful candidates for carrying biologically active compounds that are of clinical interest. In the following pages we will present some of the materials used for manufacturing-controlled release systems.

Chitosan-Based Hydrogels

Hydrogels are part of the “intelligent” controlled release systems because of their properties: biodegradability, functionality, biorecognition, and permeability [4]. Hydrogels are reticular networks with a high number of hydrophilic groups, with high affinity for water, allowing it to get inside the polymer network. The best results were obtained with hydrogels manufactured out of chitosan because of the body's ability to degrade these structures through enzymatic metabolism [5]. Chitosan is a linear polysaccharide made out of β units— β -(1-4)-D-glucosamine and N-acetic-D-glucosamine, is the ideal candidate for controlled release systems and it is also ranked first in other studies in the field of non-viral vectors such as for DNA genes [5,6]. Because it is non-toxic, stable, biodegradable, and can be sterilized, it can be used for synthesizing different types of hydrogels: liquid gels, powder, films, tablets, microspheres, nanofibers etc. For manufacturing hydrogels one can also use synthetic hydrophilic polymers (poly-N-isopropylacrylamide, poly-vinyl alcohol), but not being fully biodegradable they can lead to local inflammation. Polymers from hydrogels can absorb different quantities of water that can vary from a fraction to thousand times their own mass, depending on the hydrophilic groups present in the network. This physical phenomenon leads to the gel's expansion, which will therefore have common properties with the surrounding live tissues—low superficial pressure, soft consistency. Polymer networks are formed in the presence of the biologically active compound and lead to its encapsulation. The biofunctionalization of the

chitosan-based hydrogels increases their bio-availability though the formation of bionanomaterials with new functions. In 2014, Roberio et al. [7] have synthesized a series of bio hybrids, through the functionalization of crab shell extracted chitosan (CHT) with pectin (PCT) extracted from fruit juice and double layer hydroxides (LDH, $[\text{Mg}_{0.67}\text{Al}_{0.33}(\text{OH})_2]\text{Cl}_{0.33} \times n \text{H}_2\text{O}$ —obtained after the Constantino and Pinnava method from 1998) [7]. Hence, they have obtained a bio-nanomaterial, CHT/LDS-5ASA [7], with new functions that can serve as vehicle for controlled release system used in clinical practice. The release of the active compound is influenced by a series of physical and chemical processes: diffusion, expansion or enzymatic degradation [8,9]. Expansion leads to pores “opening” and to the release of the active substance, while enzymatic degradation destroys the networks and, therefore, depending on the mechanism, leads to the release of the active compound in the system. For example, the release of the biologically active compound based on the biochemical degradation mechanisms of the matrix has the advantage of bioselectivity [7,9].

Choosing the correct material type for the manufacturing of the hydrogel, choosing the type of network and the type of release mechanisms assures a series of pharmacological qualities of the active substance during therapy.

Sol-Gel Siloxane Matrices

The sol-gel process is based on the ability of some hydrolyzable precursors to form metal or semi-metal solid oxides through aqueous processing [10]. The pore-like gel is obtained through the condensation and polycondensation of hydroxylated units obtained through the hydrolysis of a precursor in an acidic or basic environment [10,11]. The silanol (Si-OH) groups will be formed, that through condensation will lead to the formation of siloxanes (-Si-O-Si-), and through maturation and drying lead to the formation of the siloxane matrix. The matrix that will result is a rigid network with pores of under one micrometer and polymer chains with a medium length of over a micrometer [11]. The direct immobilization of the active substance (enzymes, antibodies, proteins, DNA, and ARN) will lead to the physical entrapment that can take place due to the specific properties of siloxane matrices: adjustable porosity, chemical persistency, mechanical and optical stability, normal expandability, thermic stability [12]. Encapsulating the biomolecules without altering their initial

conformation represents the main advantage of the controlled release systems; this property exists due to the recesses that ensure a rigid environment for the encapsulated molecule [13,14]. The size and density of the pores are controlled rigorously during the synthesis in order to eliminate the eventual blockage of molecules inside the matrix, fact that could lead to the alteration of the therapeutic effect [15]. Depending on the precursors, one can obtain different types of matrices (inorganic or hybrid) with different properties: functionality, superficial pressure, controllable porosity, and increased mechanical thermic stability [15–17]. Preda et al. in a study on the entrapment of alkalases in a sol-gel matrix [16], have analyzed the siloxane matrix with the entrapped enzyme thermogravimetrically, in different thermic phases. They have shown that after 500 °C the loss of mass is justified by the total dehydroxylation and by total destruction of the organic compounds, including the enzyme, with a total mass loss of 23%—confirmed by the results from IR analysis. This study has proven the high stability of siloxane matrices capable of entrapping the active substance, and capable of functioning as vehicles for controlled release for the active principle in a system [16].

Amphiphilic Dendrimers

The monomers that are organized under a tree-like shape, around a central nucleus, lead to the appearance of macromolecules called dendrimers [18,19]. Jansen et al. have proven that in the case of dendrimers the immobilization/release of the active compound in the matrix takes place because its specific steric properties [18,20,21]. Dendrimer synthesis is based on two methods: divergent and convergent [21]. Through the divergent method the monomers are assembled from the nucleus towards the periphery, while through the convergent method they are synthesized from the periphery towards the nucleus through some fragments called dendrons. Depending on the number and diameter of the monomers there are different generations of dendrimers (e.g., generation 0—G0, 1.4 nm; generation 4—G4, 4.4 nm). Because of they are multifunctional and due to their particular characteristics, dendrimers can transport biomolecules (chromosomal elements, cytostatic drugs) towards target areas in the body [18,22]. Dendrimers can be functionalized through metal grafts (Au, Ag, Ru, Rh) on the surface of the structure or through grafts of different other molecules (polyethylene glycol, t-butoxycarbonyl) [23].

Carbon Nanotubes

Carbon nanotubes are used especially in the oncology field, in cytostatic therapies. Carbon nanotubes are carbon allotropes with a cylindrical structure [23-26]. Their special properties are given by their biofunctionalization with biomolecules, transforming them in ideal systems for controlled release of active biological compounds [24,26,27]. The development of their application in the field of nano-medicine has been motivated through the fact that bionanostructures are capable of penetrating the cell and of delivering to target the active principle, especially for substances with a low molecular mass [26,28,29].

Cyclodextrines

Cyclodextrines are cyclic oligosaccharides that form macromolecules with tridimensional structures incorporating a high number of exterior hydroxyl groups [1,30]. This structure gives them a hydro soluble exterior structure and a hydrophobic interior, used for the entrapment of the active principle [30,31]. Depending on the composition and on the proportion of saccharide structures there are three different types of cyclodextrines: α -, β -, γ - [32,33].

Controlled Release Mechanisms

The controlled release mechanisms that are characteristic for the systems used in clinical treatments are divided in two categories: physical mechanisms and chemical mechanisms [32]. In the case of physical mechanisms, the release kinetics is only controlled by the structure of the polymer network. In this case the activity of the release system can be increased by adjusting some simple parameters during the manufacturing process, or by choosing a certain type of material. Chemical mechanisms are based on the chemical bonds that grow between the polymer network and the active biological compound, but present the disadvantage that the structure of the active compound is modified, resulting chemical entities that can have unwanted effects [33,34]. For a higher efficacy of the active substance a certain, optimal concentration in the blood (therapeutic index) should be maintained. The therapeutic index (TI) represents the ratio between the maximum admitted concentration (C_{max}) and the minimal concentration required for action of the drug (C_{min}), and therefore $TI = C_{max}/C_{min}$. Each active substance has a specific TI, for example TItrifenilalanina = 20,000, iar TIdig-

itoxin = 2, case in which the value of the therapeutic index become highly valuable [30,33,35]. Among the most widely used physical mechanisms for controlled release is the degrading/dissolving and ion exchange. Degrading or dissolving refers to the destruction of the polymer structure that encapsulates the biologically active compound. The release speed of the biomacromolecules, and implicitly of the polymer structure depends on the water solubility of the polymer [36]. Therefore, the polyglycolic acid and polycaprolactone form networks that, because of low water solubility, are degraded in weeks, or even months—therefore is a rapid release is wanted; one should use materials with high water solubility. The ion exchange I used especially for active substances that have a permanent ion character, that are caught in the polymer network through electrostatic interactions. The biomacromolecule's ion is replaced with another ion, with the same electrical charge in the polymer network, and its delivery to the tissue is hence possible [25,37,38].

The Applicability of Controlled Release Systems to Anesthesia and Intensive Care Units

Transdermal Fentanyl Absorption

Transdermal absorption of active substances offers a series of advantages over the classical administration routes because they are absorbed slowly, in a constant concentration, and for longer periods of time [39]. A series of substances are still administered transdermal, among which we find the following: nitroglycerine, scopolamine, clonidine, lidocaine, estradiol, or fentanyl [40]. The active compound is stored inside the therapeutic transdermal system (TTS), and through the application of the patch the delivery of molecules will begin due to the difference in concentration gradients. Administered through TTS, Fentanyl acts in a minimally invasive manner, after a well-known kinetics, leading to increased patient satisfaction. The molecular weight of the active substance (337 Da), that does not overcome the maximal molecular weight adequate for skin permeability (1000 Da), as well as the fact that fentanyl is soluble in the lipid compartments of the skin (600 times more soluble than morphine), determines a continuous diffusion of the active compound in a safe, non-invasive manner that offers the patient increased comfort during the therapy [41,42]. There are different systems designed for the controlled release of fentanyl: TTS fentanyl-25 that releases 25 $\mu\text{g/h}$, TTS

fentanyl-100 that releases 100 µg/h, and other doses. The delivery system comes as an adhesive patch (reservoir/matrix in which fentanyl is dissolved in ethanol) that will be applied on the skin and will be capable of delivering an optimal opioid concentration for as long as 72 h [39,43,44]. Fentanyl becomes detectable in serum after approximately 60–120 min since the application of the patch and reaches its maximal concentration after 15 h. Depending on the system type, the fentanyl serum concentration can reach 2.6 ng/mL for TTS fentanyl-100 [45–48]. Kress et al. have studied the plasma concentration of fentanyl after applying different types of transdermal release patches (100 µg/h), and they observed that the concentration values for the active substance are equivalent with one another [49]. The clinical effects of fentanyl depend on the dose and on the patient's tolerance to opioids. Transdermal opioid release has proven very efficient in the long term treatment of patients suffering from neoplastic pain, but is also used in the treatment of acute postoperative pain, as well as in other forms of chronic pain [44,45].

Local Anesthetics with Controlled Release

Controlled release systems for local anesthetics have been developed in order to avoid various accidents, in order to assure a longer time of action for local anesthetics (days or weeks), and for avoiding certain methods used nowadays (e.g., epidural catheters that can lead to serious infections) [44,48]. Liposomes, dextrans, cyclodextrines, and biopolymers have all been tested for use in the formulation of such systems capable of releasing local anesthetics for longer periods of time.

Liposomes

Liposomes are made out of lipid or phospholipid molecules with a hydrophilic (head) and hydrophobic (tail) part. They are of great importance because the liposomal mycelia can be encapsulated in concentrated solutions of local anesthetics [45,46,49]. They are biocompatible, biodegradable, and non-immunologic, allowing gradual release of the anesthetic during the slow degradation of the liposomal mycelia. Using these new compounds reduces the systemic toxicity, as well as other adverse effects [48,50]. The increased bioavailability of these liposomal compounds was achieved through polyethyleneglycol grafts. The liposomes functionalized with this technique [25,48] have significant properties

for the interaction with proteins and human cells, and have an important impact on the capacity of controlled release of local anesthetic [48,50,51]. Ilfeld et al., have carried out a femoral block in 14 healthy volunteers using liposomal bupivacaine in different doses (EXPAREL, Pacira Pharmaceuticals, Inc., San Diego, CA, USA) obtaining a variable sensitive blockade and a motor blockade that lasted for over 24 h, for the maximal used dose [52]. Viscusi et al. have studied the pharmacokinetics, sensitive and motor effects for the epidural administration of liposomal bupivacaine (89 mg, 155 mg, 266 mg) versus HCl bupivacaine (50 mg) [53]. The study has shown that though the administration of liposomal bupivacaine 266 mg, the sensitive blockade lasted longer, in comparison to the motor blockade that lasted longer when HCl bupivacaine 50 mg was administered. Slow release bupivacaine was tolerated well when administered epidural, with local pain at injection as side effect that disappeared after 30 days for the majority of the subjects in the study group [53].

Cyclodextrines

Another type of chemical compounds that can be used for the controlled release local anesthetics are cyclodextrines. β-cyclodextrine has a positive impact on increasing bioavailability and decreasing toxicity for local anesthetics. Combining the anesthetics agents (especially bupivacaine and ropivacaine) with cyclodextrines leads to the formation of an extremely advantageous system, offering new properties to the local anesthetic—increased solubility in an aqueous environment, increased chemical stability, and new pharmacodynamic properties. The levobupivacaine—maltozyl-β-cyclodextrine has decreased neurotoxicity of anesthetic agents after spinal anesthesia. There are numerous studies on the combination of anesthetic agents as basic substances or as salts in concentrations of 0.02% with α-cyclodextrine, β-cyclodextrine sau γ-cyclodextrine [33,50,51]. Therefore, numerous systems have been obtained, capable of controlled and gradual release of the local anesthetic—gels, oils, suppositories, or patches. Local anesthetic agents can be associated with other active substances—antihistamines, adrenocorticosteroids etc. [33,50,54].

Biopolymers

A biopolymer with high bioavailability in the human body is the biopolymer formed from sebatic acid and ricinoleic acid in a 2:8 molar

ratio [55,56]. Shikanow et al. have carried out numerous in vitro and in vivo studies on the encapsulation of bupivacaine in a biopolymer, following its release kinetics. The obtained results confirm that controlled release bupivacaine systems can have a longer duration of action, up to 14 days [55]. In parallel they have carried out in vivo studies, sciatic nerve block in lab rats, using the bupivacaine-polymer complex. The study animals were injected with 0.1 mL of the bupivacaine-polymer complex 10% w/w, while for the control they administered the polymer without bupivacaine on the opposite side. In this manner they studied the efficacy, metabolism and elimination of bupivacaine. The controlled release system brought impressive results, leading to an 18 h long motor block [45,55,56]. There are numerous natural or synthetic polymer mixtures, bioavailable and biocompatible, that can form controlled release systems for local anesthetics—polycaprolactone, polyactide, polyesters, hydroxypropyl cellulose, N-isopropylacrilamide, polyvinyl alcohol etc.) [3,55,56]. These polymer systems (micro- and nanoparticles) can exist under different forms—spheres, capsules [56]. The nanoparticles and microparticles in which the active substances are encapsulated considerably reduce the systemic toxicity of local anaesthetics.

Conclusions

Controlled release systems have drawn attention because of the advantages they can bring to clinical practice. In the field of anaesthesia these new discoveries have resulted in the encapsulation of local anesthetic agents and opioids in controlled release matrices, that can significantly reduce the adverse effects associated with the classical administration routes, contributing to drug delivery safety and patient satisfaction.

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