Polymeric Coatings for Drug Delivery by Medical Devices

Sanziana Anghel[1,2], Muhammad Arif Mahmood[1,2], Consuela Elena Matei[1,*] and Anita Ioana Visan[1,*]

[1]*National Institute for Laser, Plasma and Radiation Physics, 077125 Magurele, Ilfov, Romania*

[2]*University of Bucharest, Faculty of Physics, RO-77125, Magurele, Ilfov, Romania*

Abstract: An analysis of the current landscape of therapeutics and delivery methods was conducted, aiming the field of drug delivery systems. Drug delivery biodistribution characteristics should be systematically understood, in order to maximize the function of these delivery systems. As a result, this review covers a history of the drug delivery systems, as well as the basic terminology associated with them, with a focus on the usage of polymers in the drug administration systems (particularly in form of coatings) and their application.

New trends in nanomaterials-based drug delivery systems, primarily for cancer treatment, were presented, involving a technology designed to maximize therapeutic efficacy of drugs by controlling their biodistribution profile.

There is a justified need to investigate drug delivery systems in form of thin films because, in comparation to bulk drug delivery system, which have a long and comprehensive history, there is still insufficient and fragmented understanding about the delivery of thin polymeric films, with research limited in general to very specific cases. Our efforts have been concentrated on these specifically polymeric drug delivery systems in the form of coatings. Understanding the dynamic changes that occur in a biodegradable polymeric thin film can aid in the prediction of the future performance of synthesized films designed to be used as implantable medical devices.

Extensive research is required to continuously develop new therapeutic systems in order to achieve an optimal concentration of a specific drug at its site of action for an appropriate duration.

Keywords: Drug delivery, Controlled release, Targeted delivery.

1. STATE OF THE ART

Current drug administration research focuses on the discovery and introduction of new bioactive molecules into therapy, as well as the control of the rate and place of release of commonly used drug substances.

The use of different pharmaceutical technologies to modulate the rate of controlled drug release (controlled drug release) or the release of the substance to the site of action (drug targeting) [1] is a second field of research in full expansion.

When a biodegradable and biocompatible substance, included in the drug formula, is carefully combined with a drug or active agent, the latter is released from the system in a predetermined manner. The active agent release can be continuous and constant (over a long period) or cyclic and in tranches at long intervals.

During drug administration, only a small part of the active substance reaches the site of action, the rest being lost to another tissue, removed before acting on the target tissue, or destroyed before reaching its destination. Over time, researchers in the field have attempted to improve the drug's activity while minimizing side effects by developing drug delivery systems DDS). Thus, drugs and other therapeutic agents are administered to treat specific diseases and disorders with the goal of achieving desired pharmacological effects with causing the fewest side effects possible.

To create nano drug delivery systems, various materials with different structural forms are loaded with drugs. Take into consideration recent approaches, most commonly used drug delivery vehicles (Figure **1**) include nanoparticles (*e.g.*, polymeric, ceramic, and metallic) [2], nanocapsules, liposomes [3], micelles [4] and dendrimers [5] biocomposites, spheroids, beads, gels, hydrogels, microcapsules, films, patches, implants, scaffolds, etc., in which different drugs are loaded [6-8].

As a result, the primary goal of biopolymeric carriers is to deliver drugs to the correct action sites while also protecting them from damage or degradation. The model drug delivery system must be biocompatible, capable of high drug loading, safe and easy to use [7].

A large number of preclinical and clinical studies indicate that they are suitable for the treatment of a variety of diseases [9-11].

*Address correspondence to this author at the National Institute for Laser, Plasma and Radiation Physics, 077125 Magurele, Ilfov, Romania;
Tel: +40 021 457 4550; E-mail: anita.visan@inflpr.ro; consuela.matei@inflpr.ro

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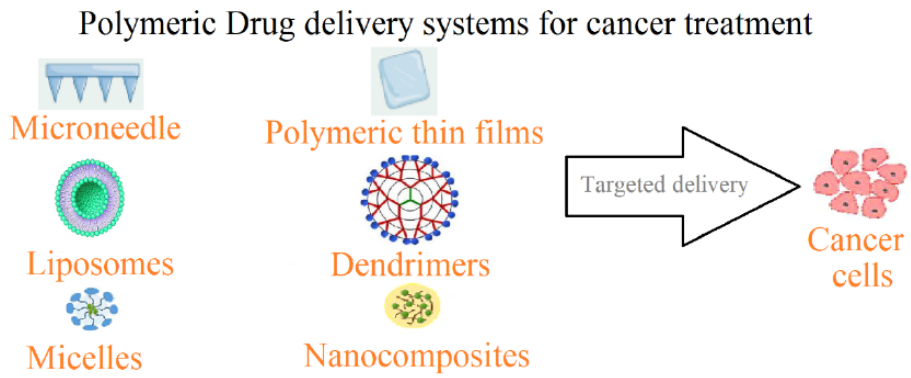

Figure 1: Drug delivery vehicles against cancer.

The field of drug delivery systems in all its forms is vast, so we shall limit in this review to nanobiotechnology-based coatings for drug delivery systems containing polymers for the medical applications, especially in the cancer treatment.

The permanent need to improve the effective delivery of chemotherapeutic agents to cancer cells continuously requires for novel oncology therapeutic approaches. Because of their nonspecific nature, conventional anticancer agents can accumulate in both cancerous and normal cells, therefore, it becomes necessary to create targeted agents that can reduce the systemic toxicity as well as improve the quality of life. Various targeted cancer therapies are discussed with the main focus on DDS in thin film form.

2. SHORT HISTORY OF DDS

Plants have long been used to treat pain and disease. For the treatment of leprosy, the inhabitants of ancient India used a plant called chaulmoogra. The roots of the rauwolfia plant were also used to treat the mental illness by the Indians. The Egyptians used poppy sap to relieve pain.

Initially, people relied heavily on healers, who prepared healing medicines by extracting oils and powders from herbs and spices. Around 4,000 years ago, Egyptian physicians used pills, and ointments to treat various ailments [12]. One of the most important documents on the medicine of the ancient Egyptians is the Ebers papyrus dating from 1500 BC. This document contains 700 magical formulas and remedies on 110 pages of 20 meters long In this papyrus the treatment of cancer, considered by many people as a disease only of our time, also existed in antiquity being described as a tumor against the god Xenus.

After the introduction of opium into medicine, and a few decades after Harvey's description of the circulatory system, the intravenous injections have been given to humans since 1665. Wood have introduced in 1853 the subcutaneous injections, and the modern hypodermic syringe was discovered by Luer in 1884. But long before the studies of Jenner and Pasteur, vaccination and exposure to pathogens has been used in China and India as prevention for measles and other infections [13].

Drugs based on substances extracted from plants and natural minerals found in soils and rocks have been developed by modern scientific medicine. Researchers have discovered that traditional recipes are often more effective because they contain the appropriate active substance. Poppy sap, used by the Egyptians, helps relieve pain because it contains opium. The ancient Egyptians also used moldy bread to heal wounds and infections. Fortunately, today, it is well known that this mold contains penicillin, first discovered by British microbiologist Alexander Fleming in 1928. He observed that the growth of staphylococci in Petri dishes was prevented by the penetration of a certain type of mold called *Penicillium notatum*. In 1940, Chain and Florey resumed their research and were successful in extracting penicillin, the first antibiotic drug discovered. The three researchers were awarded the Nobel Prize in Medicine in 1945.

Meanwhile, prontosil red, the first type of chemical-based antibacterial drug was introduced in 1935. This discovery was based on the idea of the German chemist P. Ehrlich to use chemicals to destroy or inactivate bacteria and other germs in the body, without causing harm to the body [14].

Many antibiotics that are now commonly used to treat infections were discovered in the years that followed. Chloramphenicol and streptomycin were

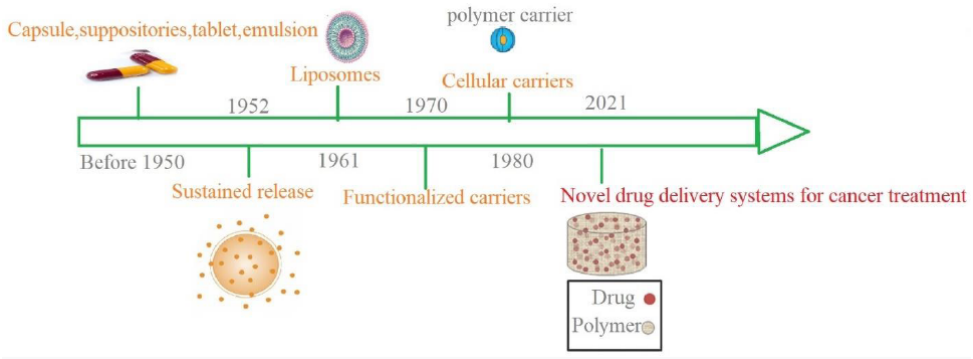

Figure 2: The evolution of drug delivery systems.

obtained from molds and ferns. Other modern antibiotic classes include tetracyclines and cephalosporins.

After 1945, the techniques of production and administration of drugs became increasingly sophisticated as: Wurster technique, encapsulation of liquids in microcapsules, compression and spray coating.

By analogy, the evolution of drug delivery systems from mid-20th to present is centralized in Figure **2**:

When Judah Folkman proposed an original concept of a device for the administration of the active substance in 1964, the field of drug-directed administration began to take important steps toward development. In the late 1960s, chemist Alejandro Zaffaroni founded ALZA company based on Folkman's concept [15].

In 2021, the global market for drug discoveries was worth approximately $ 54 billion, and it is expected to grow even further in the near future. Drug development technologies are critical to the growth of the pharmaceutical industry, as they are the conduit for the introduction of innovative substances capable of revolutionizing medicine. Thus, new approaches to drug design based on polymers and related nanostructures for effective drug delivery are critical , in future medical treatment, especially for cancer therapy. The benefits of nanoscience and nanotechnology advancement and application in therapeutic drug delivery are huge, with the goal of overcoming the undesirable effects of previously administrated therapy and developing treatments for various diseases.

Using Web of Science (http://apps.webofknowledge.com, accessed on 10/18/2021), for the period 2000-2021, a digital survey based on the criteria described in Figure **3** was performed.

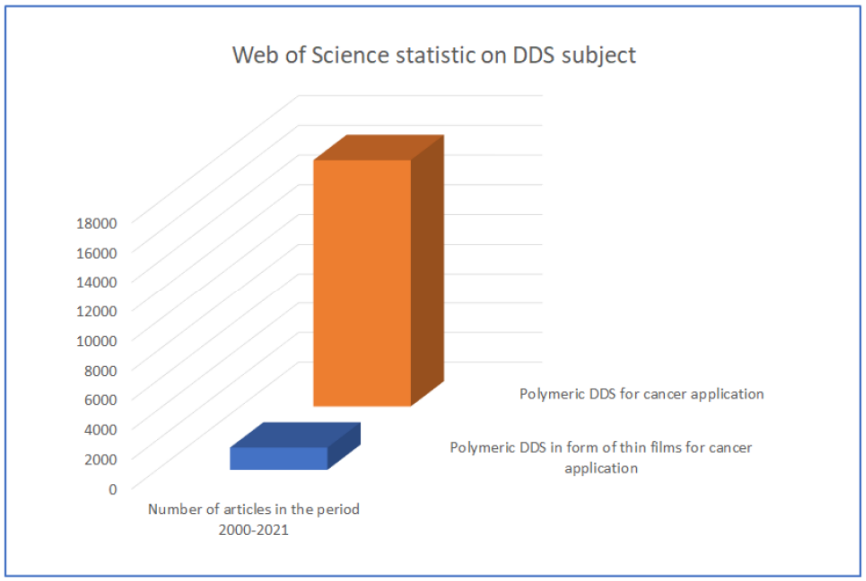

Figure 3: The current state of relevant publications available in the reviewed research field for studies related to polymeric drug delivery systems in form of coatings.

There is still a lack of understanding of polymeric thin films drug delivery systems as according Web of Science Core Collection, the research for papers returned only 150 results. In comparation, during the same period, 333x50=16650 manuscripts on DDS based on other polymeric carriers were published. To limit the search results to the precise phrases, the search terms “polymers thin films drug delivery cancer” and “polymeric drug delivery systems cancer” were inserted in double-quotes. Only abstracts, title and keywords were searched, and it was limited to ISI journal articles. This statistic fully justifies the need for further research into the subject of polymers in form of thin films, which has not been sufficiently evaluated.

3. TERMINOLOGY

Drug administration technology is becoming more sophisticated and current approaches consider factors such as the impact of the pharmacokinetic process on the efficacy of the drug, as well as the significance of the time a drug is administered and delivered to the site of action (biophase) [16].

The most basic definition of a drug known to the entire world is the following: a chemical used in the treatment, cure, prevention or diagnosis of a disease. Some governments define drugs according to the law. In the United States, for example, the Federal Food, Drug, and Cosmetic Act defines drugs as products that must be used in the “diagnosis, cure, mitigation, treatment, or prevention of a disease in man or other animals” [17].

In scientific terms the medicine is defined as a biologically active substance or a combination of substances capable of accomplishing the following:

- recognizing, removing, soothing or preventing the symptoms of a disease;

- recognition or influence of man's or animals' organic structures, organic functions or behavioral typology, as long as these things serve the purpose of medicine [16] .

To be considered suitable, a drug must meet the following criteria: it must have a precise activity, a known mechanism of action, a constant efficacy, no unknown side effects, and must be affordable.

Throughout this chapter the term active substance has been used to refer to substance of chemical, natural or synthetic origin, extractive, vegetable or animal, that when administered to the living organism causes an observable change of a function. Typically, the active substance is combined with excipients in order to achieve the desired biological response (therapeutic effect). The amount of active substance, also known as dose, delivered to the body is determined by the pharmaceutical form administered. In order to produce the desired pharmacodynamic effect, the active substance must reach an effective concentration at the site of action. Many factors influence this concentration, beginning with the administered dose, the rate of absorption based on the route of administration and continuing with distribution and transport, protein binding or tissue localization, activity or inactivity in various compartments.

All of these factors are studied in pharmacokinetic research, which complements pharmacodynamic research, which deals with the action of drugs in the body and its response to contact with the active substance, as well as the definition of the mechanism by which drugs act. Pharmacokinetics quantify the following processes: absorption, distribution, metabolism and elimination. When a specific drug is administered, these pharmacokinetic processes determine the concentration of the active substance inside the body. The speed of the passage and the proportion of the molecules participating in each process are monitored in order to establish the specific pharmacokinetic profile of each substance [18].

DDS are defined as a collection of materials or devices that allow the introduction of a therapeutic substance into the body while improving the efficiency and safety of administration by controlling the rate, time and location of the drug's release into the body. These processes include the administration of therapeutic products, the release of the active ingredient from the medicinal product, and its transport along the biological membrane to the action site [19]. DDS may influence the pharmacokinetic profile of the drug and its side effects.

The pharmacodynamic action and unfavorable side effects of pharmaceutical excipients are frequently dependent on them. Any modification to the pharmaceutical form can lead to a change in the pharmacodynamic action.

Pharmacokinetics considers the body as a multi-compartmentalized system. The entire active substance circuit in the body (from absorption to elimination) involves passage from one compartment to another by crossing a series of biological membranes with varying and complex structures [18]. The

interaction of the active substance with the receptors (place of action) can be achieved in one of the three compartments: the central compartment - blood; the superficial compartment - heart, lungs, brain, organs with which exchanges are fast, and the deep compartment - deep bone organs, placenta, muscles with which exchanges are slower, tumors. Two important mechanisms can be described that emphasize how the active substance reaches the target site: i) active administration and ii) passive administration [16]. The preferential accumulation of chemotherapeutic agents in solid tumors as a result of increased vascular permeability of tumor tissues comparation to healthy ones is an example of passive administration. The surface of the drug transporters can be functionalized with ligaments that are recognized by the receptors on the surface of the cells of interest, which is one strategy that can allow active administration. Since the ligament-receptor interactions can be highly selective, this will allow for more precise control the active substance at the target site [20].

The availability of the drug is represented by three successive phases as is schematically depicted.in Figure **4**.

Another term that refers to the action of drugs is bioavailability. This is the amount of active substance absorbed from the DDS, which becomes available at the site of action and reaches therapeutically active concentrations. Bioavailability is determined by the graphical representation of the concentration of the active substance at the site of action (Cs), that in clinical investigations is considered to be in dynamic equilibrium with the concentration of the active substance in the blood (Cp), as a function of time. (C_p vs. T). The concentration of the active substance at the site of action must be higher than the minimal effective concentration (MEC) but less than the minimal toxic concentration (MTC). This concentration range is known as the therapeutic range and it is depicted below, in Figure **5** [21].

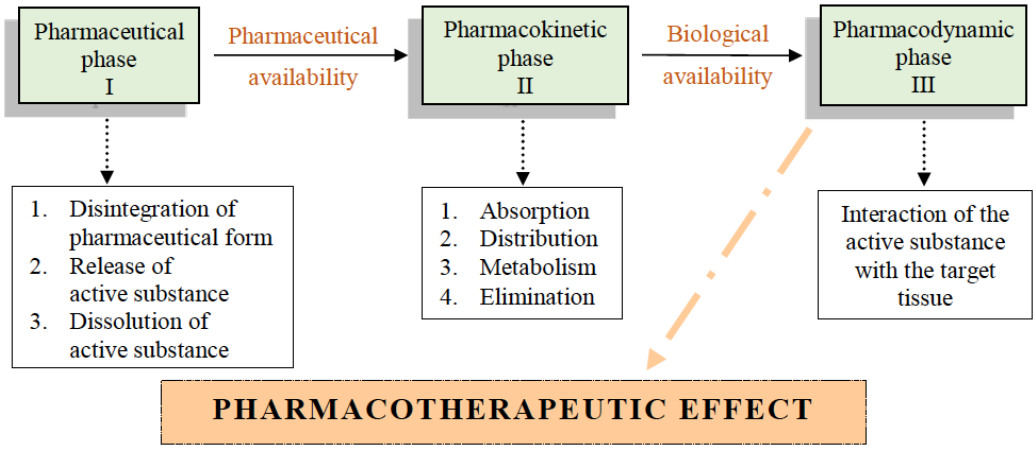

Figure 4: Various stages of drug availability within the body.

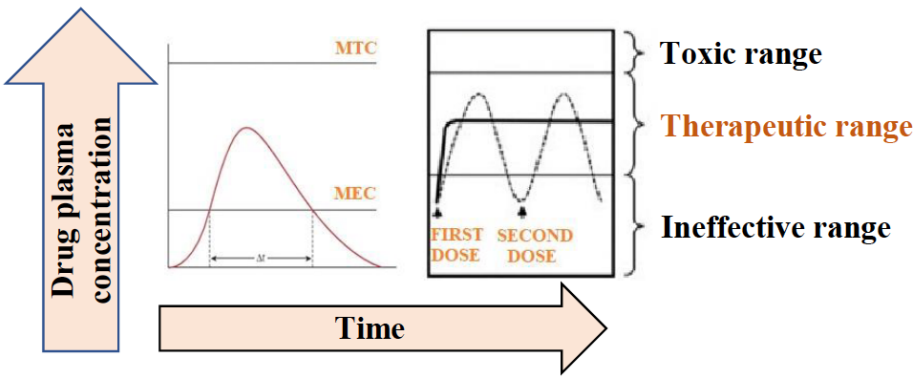

Figure 5: Concentration of the active substance in the blood after administration of DDS. Δt is the interval of the active substance in the therapeutic range [21].

The drug administration routes can be divided into two categories: natural routes and artificial routes.

1. Natural pathways include the application of drugs to the surfaces with which the body comes into contact with the external environment. These are: apparent (conjunctival, nasal, buccal, vaginal) and inapparent (bronchial, tracheal, esophageal, gastric, intestinal and rectal) skin and mucous membranes.

2. The so-called artificial parenteral pathways are those designed to introduce drugs into the body. Examples of parenteral pathways: intradermal, subcutaneous, intramuscular, intravenous, intraarterial, intracardiac, intraperitoneal, intraosseous, intraarticular, intrasinovial, intrathecal, etc.

The correct route of administration is determined by the pharmaceutical form and the advantages / disadvantages of drug administration: the degree of biotransformation in the first intestinal and hepatic passage, absorption, severity of the disease (acute or chronic), the patient's condition, conscious, unconscious or vomiting [16].

4. USE OF POLYMERS IN DRUG ADMINISTRATION SYSTEMS

Biocompatible polymers have become essential components in the production of drug delivery systems. Various natural, semi-synthetic, and synthetic polymers have been used to create various drug delivery systems. In recent years, their use for biological purposes has grown significantly, with applications in tissue engineering, obtaining implants for artificial organs or prostheses, membranes for blood dialysis, elements for conditioning and administration of drugs, in cancer, ophthalmology, dentistry, bone reconstruction and many other fields [22, 23]. The risk of allergic rejection reactions of grafts and prostheses necessary imposed the selection of polymers with anticoagulant surfaces that do not form toxic, allergenic or carcinogenic compounds after biodegradation [24].

A path of development of biocompatible, biodegradable and bioresorbable products with the goal to obtain delayed pharmaceutical forms and transdermal preparations with controlled release of the active substance. Finding and testing new drugs is an expensive and time-consuming process, with each new entrant taking 12 to 15 years to get from concept to product. Dosage forms with targeted administration have multiple advantages in the efficacy and safety of administration compared with those involving immediate administration: the frequency of administration may be reduced, the efficacy of the drug is increased and the intensity of adverse effects is decreased.

Biodegradable polymer-based dosage forms gradually degrade within the body and therefore, these are thus used in the development of drug delivery systems [25]. On the other hand, non-biodegradable polymers are lacking of the recycling facility, and hence, these are rarely used [25, 26]. The most important challenges in the formulation of various biopolymer-based controlled drug delivery system is the rational selection of biopolymers, which necessitate a comprehensive understanding of the surface as well as bulk properties of biopolymers, properties that influence the functionality in achieving optimal therapeutic efficacy [7, 27]. Furthermore, to meet up the above discussed issues, the biopolymeric drug delivery systems require comprehensive biochemical characterizations as long as detailed preclinical assessment [28].

The manner in which a drug is administered can have a significant impact on its efficacy. Some drugs have an optimal concentration range within which they provide the greatest benefits are obtained, and concentrations below this range may be toxic or fail to produce therapeutic effects. On the other hand, slow progress in demonstrating the efficacy of treatment for some diseases has suggested the need to produce multidisciplinary systems for the directed administration of the active substance in tissues. As a result, new ideas for control of pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition and drug efficacy have been implemented. New approaches, known as controlled drug delivery systems (CDDS) [20], are based on interdisciplinary concepts that combine polymer science, pharmacology, bioconjugate chemistry and molecular biology. These systems are constantly evolving, with the goal of minimizing drug degradation or loss, thereby preventing toxic effects and increasing the availability and amount of drug accumulated in the specific area.

Because the choice of dosage form is frequently influenced by how the drug is administered, the release of the active substance makes the difference between success and failure. Polymers that are administered at a controlled rate due to polymer diffusion or degradation over time are used in continuous release of the active substance (Figure **6**) [29, 30]. The most

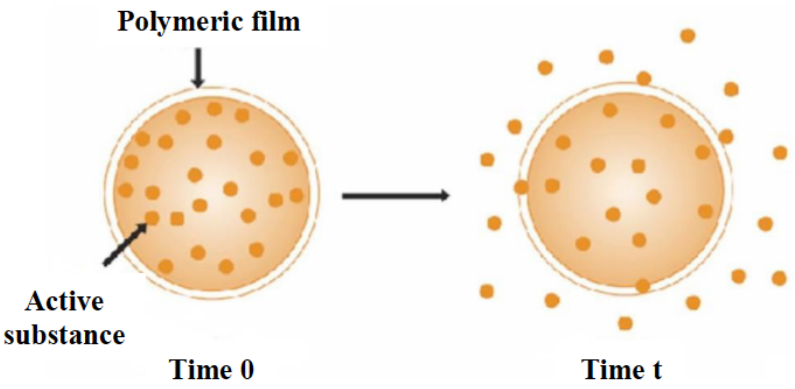

Figure 6: Schematic representation of a system for diffusion of the active substance [30].

commonly used method is repeated administration because it mimics how the body naturally produces hormones such as insulin. This is accomplished through the use of carrier polymers that react to specific stimuli (exposure to light, changes in temperature and pH). Attaching biomolecules capable of recognizing specific cells to the surface of nanoparticles containing therapeutic agents can sometimes achieve precise targeting. In the absence of such recognition centers on their surface, targeting is less precise and drug carriers are used instead of particles or macromolecules. Such aggregates accumulate preferentially in tumor cells, whose cell membrane is more permeable than healthy ones, allowing for efficient local transport. Polymeric nanoparticles can be injected intravenously and used to transport drugs to the target organs via the circulatory system due to their small size. Particles, both intravenously and non-polymeric colloids, are removed from the circulation by the liver and spleen, and a solution to avoid the reticuloendothelial system, for example, must be found to facilitate transport to the tumor tissue.

For decades, polymers have been used as excipients in the compositions of tablets and capsules [31-33], as promoters of blood circulation constantly moving in the parenteral route [34, 35]. They can now provide advanced and sophisticated functions, such as controlling the active substance in medicines [36].

Drug carriers include soluble polymers, micro- and nanoparticles embedded in synthetic and natural polymers, insoluble or biodegradable, microcapsules, cells, lipoproteins, liposomes and micelles. They can degrade over time, be reactive to stimuli (such as pH or temperature), with a specific target (they can be conjugated with antibodies against certain characteristic components of the surface of interest).

Polymer-based conveyor systems enable a slow controlled release of the active substance into the body as well as its precise targeting to the inflamed or tumor-forming site. The term "pro-drugs" (<prodrugs>) describes a transport system consisting of macromolecular transporters that undergo a transformation inside the body, thus releasing the active substance. Polymeric prodrugs are created by combining biocompatible polymeric molecules with appropriate drugs. Polymers used in therapeutics are being studied in a variety of ways, including macromolecular drugs, polymer-drug complexes, polymer-protein complexes, and polymeric micelles containing covalently linked drugs [1].

Polymers have specific properties that are not found in low molecular weight compounds. The chemical influence of a single molecule can extend from a few angstroms to dozens of angstroms, allowing the control of 3D (or 4D, if time is considered) compounds. The spatial influence of the polymers can be extended even further due to their intermolecular cooperation. A simple example of this ability is the capacity of polymers to restrict the diffusion of low molecular weight compounds into the matrix [37]. The simple manipulation of polymer water solubility by increasing chains length with copolymers and other groups results in a variety of materials that can improve drug administration efficiency.

Systems containing polymers or dendrimers are described in literature as:

- prolong the duration of action of drugs by incorporating the active substance into matrices [37], hydrogels [24, 38] or microcapsules [39];
- distribution of the active substance in the direction of tumors [40];

- allow the absorption of the active substance in the gastrointestinal tract [41];

- ensures the availability of the active substance only when there is a defined modification in temperature / pH or when it is activated by an enzyme [42, 43].

To achieve biomedical goal, the used polymers must be biocompatible at least on the surface. The biocompatibility and / or biodegradability of polymers are determined by both the functional groups and the structure. Biocompatible polymers used in biomedical applications must be biodegradable in general, and the products of their biodegradation must not be harmful to the body. Biodegradable polymers (usually referred to as bioerodible or bioresorbable), can be of synthetic or natural origin. *In vivo* hydrolysis of such polymers should produce non-toxic alcohols, acids or other low molecular weight products that are easily eliminated from the body. High molecular weight polymers with hydrolytically unstable bridges can be bioeroded by removing crosslinked chains, while water-insoluble

Table 1: Various Drug Delivery Systems Employed Against Various Cancer Types

Polymeric *Drug* Delivery System	Cell Line Tested	Cancer Type	Reference
PLGA nanoparticles – *Ferulic acid*	NCI-H460 non-small cell lung carcinoma cells	LUNG	[45]
PLA-PEG nanoparticles – *Luteolin*	H292 lung cancer cells		[46]
PEG-PLA polymer micelles – *β-Lapachone and Paclitaxel*	A549 human lung adenocarcinomic cells		[47]
MPEG and PCL star shaped micelles – *Honokiol*	CT26 murine colon carcinoma cells	COLORECTAL	[48]
Polymer (either EC, PCL or PLGA) nanoparticles – *Thymoquinone*	CT26 murine colon adenocarcinoma cells		[49]
Curcumin nanoparticles anchored with C_{18}PMH-PEG on the surface	CT-26 colon cancer cells		[50]
PLGA nanoparticles – *Curcumin*	A2780CP ovarian cancer cells	OVARIAN	[51]
MPEG–PLA nanocarriers – *Honokiol*	A2780 human ovarian cancer cells		[52]
PHEMA nanoparticles – C*urcumin*	SKOV-3 ovarian cancer cells		[53]
Curcumin-Alginate-chitosan-pluronic composite	HeLa cervical cancer cells	CERVICAL	[54]
SFCS polymer nanoparticles – *Curcumin*	MCF-7 human breast adenocarcinoma cell line and MDA-MB-453	BREAST	[55]
Lipid nanoparticles containing TPGS and phosphatidylcholine – *Silibinin*	MDA-MB-231 breast cancer cells		[56]
PAMAM dendrimers – *Gallic acid*	MCF-7 human breast adenocarcinoma cell line		[57]
PLGA nanoparticles – *Apigenin*	A375 skin melanoma and HaCaT keratinocytes	MELANOMA	[58]
RGD-modified liposomes – *Combretastatin A-4* and *Doxorubisin*	B16 and B16F10 melanoma cells		[59]
PLA-PEG nanoparticles – *EGCG*	Mel 928 melanoma cells		[60]
PLA-PEG-PSMA ligands – *EGCG*	LNCaP human prostate adenocarcinoma cells and PCa prostate cancer cells	PROSTATE	[61]
PLA- PEG nanocarriers – *EGCG*	PCa prostate cancer cells		[62]
TPGS – *Berberine* nanosuspension	HepG2 hepatocellular carcinoma cells	HEPATOMA	[63]
mPEG/PLA micelles – *Dihydroartemisinin*	KB human oral cancer cells	ORAL	[64]
Chitosan nanoparticles – *Ellagic acid*	KB human oral cancer cells	ORAL	[65]
TPGS liposomes – *Emodin*	L1210 mouse lymphocytic leukemia cells and K562 myeloid leukemia cells	LEUKEMIA	[66]
Chitosan nanoparticles – *Nobiletin*	RAW264.7 Abelson murine leukemia virus-induced tumor cell lines		[67]
mPEG-PCL nanoparticles – *Resveratrol*	C6 glioma cells	GLIOMA	[68]
mPEG–PCL nanocarriers – *Ursolic acid*	SGC7901 gastric cancer cells	GASTRIC	[69]

polymers can be converted to soluble polymers by ionization, protonation or hydrolysis of side groups. This type of conversions do not significantly affect their molecular weight.

Polymers used in medical applications must have critical properties that will be the key to success. As a result, when selecting polymers for CDDS, it is very important to establish a list of desired properties and then to identify the most important critical properties. CDDS must release the active substance at the desired rate and in the decided order for clinical success. After the active substance is released, the polymeric transport components must swell (or not), degrade (or not), dissolve (or not), or be taken up (if necessary) [44].

5. POLYMERIC DDS FOR MEDICAL APPLICATIONS

Although there has been progress in cancer research in many areas, still its efficacy has been limited by a number of challenges that pose difficulties in clinical translation for the treatment of various types of cancers. Because cancer is a genomically unstable disease, next-generation sequencing data can be a novel technology for revealing the inside molecular machinery in cancer cells. Currently, very few nanodrugs are available to treat cancer, with the main reason being the unknown reason of toxicity of nanoformulations. Thus, advancements in nanomedicines through material improvement and smart nanomedicines design can offer promising anticancer therapeutics.

Coated microneedles have two principal functions. One is to pierce skin and the second one is to deliver the desired drugs applied on the surface of microneedle. The maximum drug dose is less than 1 mg and this is the reason for limiting the development of coated microneedles [70]. Using Layer-by-layer coating techniques to further increase the drug loading, coated microneedles were necessary to dip or spray by aqueous solution with high viscosity. Through the use of electrostatic attraction, negatively charged DNA or virus were absorbed on positively charged microneedle easily to attain microneedle coating [71]. Because of the wide range of coated drugs, glazed microneedles were confirmed as a versatile device, due to the extensive scope of coated drugs (small molecules, macromolecules, vaccines, DNA, micron-scale particles) [72-75]. The different shapes of glazed microneedles are made to promote permeation and drug loading. Comparing with previous fabrication techniques, such as micromolding and Lithographie, Galvanoformung und Abformung (LIGA) technique, those methods often suffered from cumbersome master templates and tedious preparation processes, thereby lacking the versatility of fabrication steps and the capability of changing design quickly. Pere *et al*. [76] employed 3DP technique to create pyramid and cone microneedles designs for the delivery of insulin [76]. Microneedle arrays integrated with 3DP are modeled in a one-step manner to feature microneedles with different geometries rapidly. This efficient method for the mass production microneedle patches holds great promise for commercial applications.

Particularly, microneedle devices have been designed to support the anti-tumoral therapies, either by triggering the anticancer immunologic responses (*e.g*. antigens, immune adjuvants, genetic material) or to deliver anticancer compounds (*e.g*. drugs and nanoparticles) [77-81]. Apart the property of temporally controlled release, these microneedles have also the advantage of increased delivery of drugs in the deeper regions of the tumors, minimizing the leakage to adjacent tissues and the side effects, in the same time allowing different drug combinations in a single therapy, in the quest to develop new drugs and tune the anti-tumoral effect [82-86].

A new and promising class of DDS is based on conjugated polymers which have fascinating optoelectronic properties and are easily controlled electrochemically, properties that widens their area of applications also to bioactuators, biosensors, neural electrode coatings, or even tissue scaffolds for tissue engineering. Mainly investigated for biomedical use were the systems based on polyaniline, polypyrrole, and polythiophene derivatives, the first two being shown to be able to deliver a variety of drugs (especially including anions). The polypyrrole (PPY), for example, was tested with loadings of different drugs (anti-inflammatory, antibiotics, antipsychotic) but the prospects for clinical use are clearly dependent on their biocompatibility [87]. Extensive research on the biocompatibility and cytotoxicity of PPY nanoparticles fabricated by the oxidative polymerization route was performed and the initial findings show that at high concentrations the PPY nanoparticles are toxic to primary mouse embryonic fibroblasts, mouse hepatoma (MH-22A) cells, and human T lymphocyte Jurkat cells, negatively affecting the cell viability/proliferation, but the toxic effects cease for concentrations lower than 9.7 μg/ml [88]. When the PPY was chemically synthesized, the results showed that the particles did not induce any detectable

cytotoxic effect on mouse peritoneum cells, or any allergic response, nor did they affect the spleen, kidney and liver indexes, or affect the immune-related haematological parameters [89]. Moreover, deposited onto gold-plated glass slides, PPY proved to be not toxic to mouse bone marrow-derived stem cells, the substrates maintaining stem cell attachment and proliferation [90]. Further improvement of the PPY-based coatings could bounce forward the development of implantable electronic devices, overcoming the problem of the mechanical mismatch between the inorganic substrate and the soft tissue, diminishing the adverse reaction at the implantation *in vivo* and mediating the release of the selected choice of drugs.

Irina Negut *et al.* [91] investigated the potential of biomimetic thin films made by means of matrix-assisted pulsed laser evaporation (MAPLE) for releasing combinations of active substances as flavonoids (quercetin dihydrate and resveratrol) and antifungal compounds (amphotericin B and voriconazole) embedded in a polyvinylpyrrolidone biopolymer; the antifungal activity of the film components was evaluated using *in vitro* microbiological assays. Using a pulsed KrF* excimer laser source, thin films were deposited and structurally characterized using atomic force microscopy (AFM) and Fourier transform infrared spectroscopy (FTIR). Appling an optimum laser fluence of 80 mJ/cm^2, high-quality thin films with chemical structures similar to dropcast ones were created. Utilizing MAPLE technique, bioactive substances were included within the polymer thin films. The results of the *in vitro* microbiology assay, using two fungal strains (*Candida albicans* American Type Culture Collection (ATCC) 90028 and *Candida parapsilosis* American Type Culture Collection (ATCC) 22019), revealed that voriconazole was released in an active form from the polyvinylpyrrolidone matrix. The findings of this study indicate that the MAPLE-deposited bioactive thin films have a promising potential for use in designing combination products and devices, such as drug delivery devices, and medical device surfaces with antifungal activity.

Thin films have been investigated for vaginal drugs and peptide delivery [92, 93]. Surgical implants are frequently made of biodegradable polymers and are created using techniques such as compression, molding extrusion, and injection molding. The rate of reproducibility of release profiles of such systems is very high. But they require surgical implantation because of its size, which can limit its applicability and use. Vaginal rings, made up of silicone rubber, is the example of such device, that has been designed to release birth control drugs in controlled manner for a period of months [94]. Films are generally obtained using mucoadhesive polymers and have been investigated for treatment of STD, infections, etc [92, 95]. However, the use of films is limited due to their inability to distribute the drug in the vaginal tract.

Film formulations are typically made up of the active pharmaceutical ingredient (API), water soluble polymers, plasticizers, fillers, color, and flavor [93]. Polymers used for films should array optimum peel, shear and tensile strengths. Polymer choice and polymer molecular weight can deeply impact properties of the film such as mechanical strength and disintegration time. Plasticizers are commonly used in thin film formulations to provide flexibility and ensure acceptable texture. Disintegration agents can be used to improve of the film's fast dissolving property [96].

Rodica Cristescu *et al.* [97] demonstrated that matrix-assisted pulsed laser evaporation (MAPLE) has many benefits compared with conventional methods (*e.g.*, dip-coating, spin coating, and Langmuir-Blodgett dip-coating) for manufacturing coatings containing pharmacologic agents on medical devices. As a particularity of this technique, the thickness of the coating that is applied to the surface of the medical device can be tightly controlled. MAPLE was used in this study to deposit rapamycin-polyvinylpyrrolidone (rapamycin-PVP) thin films onto silicon and borosilicate optical glass substrates. Alamar Blue and PicoGreen studies were applied to measure the metabolic health and DNA content of L929 mouse fibroblasts as measures of viability and proliferation. Compared to a borosilicate glass control, the cells on the MAPLE-deposited rapamycin-PVP surfaces exhibited 70.6% viability and 53.7% proliferation. The analyze of the obtained data indicate that the antiproliferative properties of rapamycin were maintained after MAPLE deposition.

Bioadhesive films for vaginal drug delivery have been created for reasons of their rapid drug release, enhanced bioadhesive property, negligible vaginal leakage and messiness, the potential for discreet use, low cost, and ease of insertion without an applicator [98, 99].

In comparation with semi-solid formulations such as creams and gels, bioadhesive thin films are effortless for vaginal insertion and the exact drug dose can be administered without dose leakage. This dosage form has been used for vaginal administration of the

contraceptive/antimicrobial agents, antifungal drugs and the nucleotide reverse transcriptase inhibitor for HIV patients [92, 100, 101]. Vaginal films are utilized to deliver biomolecules like proteins, monoclonal antibodies, and siRNA [102]. Itraconazole was also loaded into the bioadhesive film for vaginal delivery to treat vaginal candidiasis, with the expectation that the drug would remain in the vagina for extended periods of time [100].

The difference between partial pressure of oxygen in healthy and diseased cells or tissues can be used to create a stimuli-sensitive drug delivery system with hyperthermia application. As an example, in cancer the partial pressure of oxygen decreases from periphery to the center of tumors, resulting in a change in tumor microenvironments as compared to normal cells, allowing tumor-specific drug delivery to use this difference as the trigger to release the drug. In one study, an azo linker-incorporated amphiphilic polymer, consisting of carboxymethyl dextran-black hole quencher 3 (BHQ3), was attempted to target cancer therapy. Because of the presence of azo bonds in BHQ3, which reduces in a hypoxic environment, this polymer conjugate system loaded with doxorubicin, an anticancer drug, was found to release the drug under hypoxic conditions. These polymeric nanoparticles demonstrated hypoxia-responsive release of doxorubicin in tumor tissues.

Also, 2-nitroimidazole derivative conjugated carboxymethyl dextran was explored to load doxorubicin and observed to release drug under hypoxic conditions. In the same time, the rate of release of drug was based on the partial pressure of oxygen in cells and tissues in *in vitro* and *in vivo* experiments indicating high tumor accumulation and antitumor efficacy [103, 104]. In another study, the same research group created hypoxia-sensitive block copolymer composed of PEG and poly(ε-(4-nitro) benzyloxycarbonyl-L-lysine) to formulate hypoxia-responsive micellar system loaded with doxorubicin drug. The results showed that drug was released intracellularly in hypoxic cells, indicating a high potential of the system for use in cancer treatment [105].

Targeting can be accomplished in some cases by using the same distribution-controlled polymer system that has the built-in property of target-specific distribution. Polymer surfactants as block copolymers of PPO and PEG modify the distribution of colloidal carriers in the body [106, 107]. The alteration in distribution relies on the capability of the surfactant polymer to exchange absorption of protein on the surface of the particle. We can consider one example of the target specific approach, the local drug delivery to the colon, and site-specificity can be ensured by the presence of bacteria only found in colon to cleave the polymer linkages and release drug [94].

Anita Visan *et al.* [108] proposed a multidrug combination therapy for local and sustained delivery of tetracycline with antimicrobial action, while simultaneously inhibiting the drug's resistance mechanisms and promoting bone regeneration and growth.

Biodegradable coatings based on poly (lactic acid-co-glycolic acid), PLGA, are representing the versatile and safe candidates for surface modification of implantable biomaterials and devices, providing additional tunable ability for topical delivery of desired therapeutic agents. In O. Gherasim *et al.* [109] study, Ibuprofen-loaded PLGA coatings (PLGA/IBUP) were generated by dip-coating and drop-casting combined protocol. The composite materials showed long-term drug release under biologically simulated dynamic conditions. Reversible swelling phenomena of polymeric coatings happened in the first two weeks of testing, followed by the gradual matrix degradation and slow release of the therapeutic agent. Irreversible degradation of PLGA coatings resulted after one month, due to copolymer's hydrolysis (evidenced by chemical and structural modifications). The cumulative release of IBUP after 30 days of dynamic testing, was comparable to 250 mu g/mL. Exceptional cytocompatibility was revealed on human-derived macrophages, fibroblasts and keratinocytes. The findings show that PLGA/IBUP coatings have a promising potential for surface modification of medical devices such as metallic implants and wound dressings

Valentina Grumezescu *et al.* [110] study reports on the deposition of polyvinylpyrrolidone/ antibiotic/isoflavonoid thin films by the matrix-assisted pulsed laser evaporation (MAPLE) method as anti-adhesion barrier coatings, on biomedical surfaces for better resistance to microbial colonization. The thin films were analyzed by Fourier transform infrared spectroscopy, infrared microscopy, and scanning electron microscopy. *In vitro* biological assay tests were carried out to assess the effect of the thin films on the development of biofilms formed by Gram-positive and Gram-negative bacterial strains. *In vitro*, biocompatibility tests were done on human endothelial

cells examined for up to five days of incubation, via qualitative and quantitative methods. According to the findings of this study, the laser-fabricated coatings are biocompatible and resistant to microbial colonization and biofilm formation, making them viable candidates for biomedical devices and contact surfaces that would otherwise be susceptible to contact transmission.

CONCLUSIONS AND PERSPECTIVES

On the entire process of drug delivery evolution, various strategies and technologies have been adapted as new therapeutic modalities aiming either to improve the efficacy or to reduce side effects compared to current patented systems. As a strategy, nanotechnology could be implemented in developing new drug delivery systems with increased effectiveness, safety, and patient compliance, reduce healthcare costs that can be ultimately expand drug markets. A very-good understanding of drug release kinetics from biomimetic drug carriers constitutes the primary focus and subsequent demonstration of easy scale-up of the formulations with favorable pharmacokinetics and toxicity profiles could augment the translation of research findings into practical therapeutics. A continuous collaborative effort among multidisciplinary domains such as materials science, engineering, physics, medicine and pharmaceutics helps to translate novel laboratory innovation into commercially viable medical products.

LIST OF ABREVIATIONS

Abbreviation	Meaning
3DP	3D Printing
AFM	Atomic Force Microscopy
API	Active Pharmaceutical Ingredient
BHQ3	Black Hole Quencher 3
CDDS	Controlled Drug Delivery System
Cp	Concentration of the active substance in the blood
Cs	Concentration of the active substance at the site of action
DDS	Drug Delivery System
DNA	Deoxyribonucleic Acid
E. coli	Escherichia Coli
EC	Ethyl Cellulose
EGCG	Epigallocatechin 3-gallate
FTIR	Fourier Transform Infrared Spectroscopy
HeLa	Human Epithelial Carcinoma
HIV	Human Immune Virus
IBUP	Ibuprofene
LA	Localized Adherence
LIGA	Lithographie, Galvanoformung und Abformung (German acronym for Litography, Electroplating and Molding)
MAPLE	Matrix Assisted Pulsed Laser Evaporation
MEC	Minimal Effective Concentration
mPEG	Monomethoxy poly (ethylene glycol)
MPEG	Methoxy poly (ethylene glycol)
MTC	Minimal Toxic Concentration
PCL	Poly (ε-caprolactone)
PEG	Polyethylene Glycol
PHEMA	Poly(2-hydroxyethyl methacrylate)
PHO	Poly(9,9-dioctylfluorene)
PLA	Polylactic acid
PLD	Pulsed Laser Deposition
PLGA	Poly (lactic acid-co-glycolic acid)
PSMA	Prostate-specific membrane antigen
PVP	Polyvinylpyrrolidone
RGD	Arginylglycylaspartic acid
S. aureus	Staphylococcus Aureus
SFCS	Silk fibroin and chitosan
siRNA	Small interfering RNA
TPGS	D-α-tocopheryl polyethylene glycol 1000 succinate
Wt.%	Percentage by Weight

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