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Review article

Plasma treatment as an efficient tool for controlled drug release from polymeric materials: A review

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ABSTRACT

One of the most actively developing fields in modern medicine is controlled drug delivery, an ability to keep optimal concentration of a drug at the desired body location. In particular, the most attention for potential use as drug delivery vehicles is drawn towards biodegradable polymeric materials. This is due to the versatility of tools for their fabrication, as well as due to the need to extract them after implantation being eliminated. In order to enhance polymer characteristics in terms of biocompatibility their surface can be functionalized. Plasma treatment is a method for the modification of material surface properties, which spans a wide range of applications in tissue engineering and regenerative medicine. The main advantage of this method is its ability to modify a polymeric surface without altering the bulk properties of materials, thus preserving original mechanical characteristics. Moreover, plasma modification is well-known for its speed, excluded need for solvents, and scalability. Recently, this approach has been gaining popularity for drug delivery applications. The applications of plasma treatment during the fabrication of drug delivery vehicles include surface activation, enhanced wettability, the fabrication of hydrophobic barrier layer, induced cross-linking and improved drug loading. This review covers the variety of approaches, applied to different polymeric biomaterials, including non-woven meshes, films, microparticles, microneedles and tablets, in order to achieve a controlled drug release. The applications of drug delivery devices with an implemented plasma treatment modification are also described.

1. Introduction

Plasma is a totally or partially ionized gas which consists of various charge carriers such as electrons, ions and radicals, and is overall electrically neutral. Thus, each component within plasma may interact during plasma irradiation. Plasma treatment (or plasma irradiation) is a widely used technique for the effective chemical and physical modification of material surface properties [1–7]. Generally, several common effects of plasma treatment can be determined: cleaning, etching, activation, and cross-linking [2,8,9].

Plasma treatment is widely applied for cleaning of the surface of a studied material of adsorbed contaminants. The cleaning can be performed as a stand-alone process or as a preliminary step before thin film deposition by means of plasma irradiation. The topography of polymeric surface can also be modified by means of plasma irradiation due to its partial etching or degradation process [10–14]. Moreover, plasma exposure can activate a polymer surface by creating new polar functional groups including carbonyl, carboxyl, ether, amine and hydroxyl; thus markedly increasing the free polymer surface energy [10,15–18]. As a result of modified chemical composition, the wetting characteristics and surface adhesion of polymeric materials can also be changed [1,6,16,19–26].

The attractiveness of plasma treatment amongst other conventional surface modification techniques is an ability to alter only surface

Abbreviations: AAc, acrylic acid; AAO, anodic alumina oxide; AC, alternating current; BSA, bovine serum albumin; CASING, cross-linking by activated species of inert gases; CCRF, capacitively couple radio frequency; CVD, chemical vapor deposition; DBD, dielectric barrier discharge; DC, direct current; DCSBD, diffuse coplanar surface barrier discharge; DLC, diamond-like carbon; DEGME, 2-(2-Methoxyethoxy) ethanol; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; EGDMA, ethylene glycol dimethacrylate; GD, glow discharge; HMDSO, hexamethyldisiloxane; HPMCAS, hydroxypropyl methylcellulose acetate succinate; MAA, methacrylic acid; MPC, poly(2-methacryloyloxyethyl phosphorylcholine); MW, molecular weight in g/mol; PA, polyamide; PBS, phosphate-buffered saline; PC, polycarbonate; PCL, poly-(ε-caprolactone); PDMS, polydimethylsiloxane; PECVD, plasma enhanced chemical vapor deposition; PEEK, polyether ether ketone; PEG, poly(ethylene glycole); PET, polyethylene terephthalate; PEU, polyester urethane; PEVA, poly(ethylene-*co*-vinyl acetate); PFO, perfluorooctane; pHEMA, poly-hydroxyethylmethacrylate; PLA, polylactic acid; PLGA, poly(lactic-*co*-glycolic acid); PP, polypropylene; PPBMA, poly-*n*-butyl methacrylate; PU, polyurethane; PVP, poly(*N*-vinylpyrrolidone); RF, radio frequency; TEOS, tetraethyl orthosilicate; Tetraglyme, tetraethylene glycol dimethyl ether; TMDSO, tetramethyldisiloxane; TMCTS, tetramethylcyclo-tetrasiloxane

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properties, up to several nanometers deep, without affecting the bulk characteristics of materials [23]. Moreover, short-time plasma irradiation does not overheat materials, so their destruction may be avoided. The other well-known advantages of plasma treatment, which makes it a favourable surface modification tool for various biomedical applications, are speed, the exclusion of the need for solvents, and practical scalability [2,27,28]. The feasibility of plasma treatment is justified by an ability to obtain ultra-thin films and precise control during the treatment process. The stability and repeatability are also significant advantages of this approach over other surface modification techniques [28] including wet chemistry [29–32] and graft polymerization methods [33–36]. Moreover, in contrast to a distinct dependence on the type of substrate for wet chemistry methods, plasma treatment can be used for a great variety of polymeric materials in order to fabricate thin coatings on their surface [37].

The approach of plasma treatment as a tool for varying the surface properties of synthetic polymeric materials is widely used in tissue engineering [38,39]. In the last decade, this approach has been gaining popularity for drug delivery applications as well [1,6,14,22,23,40–42]. Various drug eluting systems with controlled drug release kinetics using plasma treatment were studied: electrospun mats [43–48], surgical meshes [49], films [50–57], microparticles [58,59], microneedles [10,60], tablets [8,14] and ceramic materials [61–64]. Control over release kinetics in drug delivery devices is governed by the device itself. Therefore, the external factors including gastrointestinal motility and absorption rates do not play a major role in the release of an active agent [65]. The crucial advantages of controlled drug delivery are an ability to keep optimal drug concentration at the desired location, which results in more efficient treatment; increased safety due to the prevention of toxic drug concentrations; a capability to employ drugs with a narrow therapeutic window and a short half-life; and improved convenience for the patients [65].

Drug release from polymeric materials generally occurs via diffusion, although the degradation can be a contributing factor for rapidly biodegradable polymeric systems [23,58]. Plasma treatment can be an extremely efficient tool during the fabrication of drug delivery devices, since it provides an ability to modify the wettability of the surface of polymeric materials. As such, this leads to a modified interaction of the produced material with the medium. The change in wetting characteristics results in varying the diffusion coefficient of an incorporated drug in the polymer. The increased material wettability can also accelerate the degradation rate of a polymer, which in turn also modifies drug release kinetics. However, plasma treatment can be employed for the fabrication of thin hydrophobic films on the surface of a studied polymeric material, thus impeding its degradation and the ensuing drug release [43].

Depending on biomedical application, different release kinetics can be required. For example, rapid release of a drug may be desirable for pain relief or sedative agents, while a sustained and significantly slower release is necessary for hormone and anticancer therapies [58]. Direct applications of plasma treatment for the purpose of altering drug release kinetic include surface activation and enhanced wettability through the introduction of reactive species, and the fabrication of barrier layer by depositing of thin films or cross-linking of polymer chains. An improved drug loading can be referred to as an indirect application of plasma irradiation on controlled drug delivery. Therefore, the practical importance of this work lies in its ability to analyse and compare this variety of plasma treatment application in order to achieve a controlled drug release on different polymeric biomaterials. A wide spectrum of biomedical applications of these biomaterials was also thoroughly discussed.

1.1. Critical plasma treatment parameters

The critical parameters for a plasma modification setup are the following: type of discharge and its power, pressure, treatment time, the presence of gas in plasma chamber, and the flow rate of the gas and precursor [9]. Different plasma treatment methods can be applied for the modification of a material surface [2]. Low temperature short term plasma irradiation is preferred for the surface modification purposes, while high intensity plasma treatment is employed for the surface sterilization and inactivation since it causes cell death.

Conventional chemical vapor deposition is not suitable for the fabrication of thin films for biomedical applications since it is operated at high temperature. However, it is possible to obtain thin coatings at lower temperatures by means of plasma-enhanced chemical vapor deposition (PECVD) [66]. When plasma treatment is used as a tool for thin film deposition, films of a various density and roughness can be obtained depending on the sputtered precursor, type of gas in a plasma chamber and their flow rates [67]. Dielectric barrier discharge (DBD) and glow discharge (GD) are two easily ignited discharges at atmospheric pressure, which are also employed for the surface modification of various polymeric biomaterials [68–71]. In the case of GD, the ignition of plasma occurs in the space between two electrodes, which is filled with the process gas. AC voltage power supply is used to generate DBD, since it requires capacitive coupling. Thus, less energy to form the reactive species in the gas is required, and a substrate can be kept at a low temperature. The homogeneity of produced coatings is maintained owing to a uniform dispersion of nanosecond discharges occurring on the electrode surface. Moreover, atmospheric pressure plasma treatment in general is easier to be processed, since the need for expensive equipment such as vacuum pumps is eliminated [67]. Nevertheless, the majority of researchers use low pressure plasma treatment in their studies since it allows for the formation of more homogenous coatings [10,14,44,48,51–53,58,72–75].

The most used frequencies of applied electric field to induce plasma are radio frequency (RF, generally 13.56 MHz) [43,45,48,51,53,72,74] and microwave (MW, generally 2.45 GHz) [44,76]. Plasma treatment can be performed under pulse [49,75,77–79] or continuous wave discharge [45,51,53,80]. The presence of reactive ions and high photon fluxes in plasma during a continuous-wave mode can cause the degradation of drug molecules. Thus, the choice of a pulsed-wave mode can be justified by the decreased probability of chemical changes to a drug which is incorporated in the treated material [77]. In order to achieve a controlled drug release from biomaterials by means of plasma treatment, most of the modification studies are performed in air [44,47], but experiments in the atmosphere of various gases such as nitrogen [52], oxygen [10] and argon [75] are performed as well.

2. Approaches to control drug release

Several major factors, which influence drug release rate, were observed and analysed including density [74] and thickness of deposited films [43,64,75], the degree of cross-linking [14,52,53], surface wettability [44] and molecular weight (MW) of incorporated drugs [72]. Fig. 1 demonstrates direct applications of plasma treatment for the purpose of altering drug release kinetics from various polymeric systems in a desirable way. The employment of these approaches is discussed in this chapter. One indirect application, which is not illustrated in the figure, is an ability to control delivered drug dosage, which is also crucially important in the process of drug delivery device production. Therefore, a careful choice of plasma irradiation conditions for each particular case is necessitated. Table 1 presents the summarized information of reviewed experimental studies. It highlights major information of each experimental work including the type of studied polymeric material and drug loading technique; applied plasma treatment conditions and release study parameters; as well as the achieved effect of plasma treatment on drug release rate. Potential medical application of each studied polymeric system is also provided in Table 1.

In order to provide a more systematic analysis of published experimental results, times when a certain amount of a drug is released were determined for the studies where it was applicable. This approach