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Recent advances in magnetic electrospun nanofibers for cancer theranostics application

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ABSTRACT

Cancer theranostics is a recent concept that aims to combine in the same device diagnostic and therapeutic features. Magnetic nanoparticles (mNPs) are commonly used as a critical part of these systems due to their ability to respond to an external magnetic field. Consequently, mNPs can generate heat when an alternating magnetic field is applied and enhance image contrast in magnetic resonance. However, direct administration of mNPs intravenously or directly in the tumor can lead to undesired side effects because of mNP elimination by macrophages or leakage to healthy tissues. Therefore, mNPs can be retained in a polymeric nanofibrous mesh, thus preventing misplacing or loss of mNPs. Furthermore, these magnetic nanofibers can be directly implanted in the tumor site, thus ensuring high mNPs loading and higher magnetic response. In addition, polymeric nanofibers produced by electrospinning are frequently used to maintain a sustained drug release in the tumor site. Therefore, a magnetic polymeric nanofiber produced by electrospinning is an ideal nanosystem for cancer theranostics application. This review summarizes the most recent developments of magnetic nanofibers produced by electrospinning for cancer theranostics applications.

1. Introduction

Cancer is a significant burden on modern society, being the second cause of death worldwide. According to the most recent data from Globocan, in 2020, approximately 19.3 million new cases were diagnosed. In the same year, almost 10 million deaths worldwide were caused by cancer diseases [1]. Despite this terrible scenario, cancer treatment and diagnostic have been significantly improved over the last decades, resulting in an increase of 5-year prevalence and survival rates. However, several limitations are still associated with current treatments. Additionally, the increasing incidence and higher disease heterogeneity motivate cancer research, focusing on a better understanding of the disease, and developing new and improved strategies for cancer early diagnostic and effective treatment [2].

New devices have been developed in recent years aiming at combining in the same platform diagnostic and therapeutic features, i.e., theranostics devices. These theranostics devices are designed to act as a personalized approach, leading to faster and more effective diagnostic and treatment of a disease, namely cancer [3]. New and improved materials, particularly nanomaterials, have been used to produce theranostics devices for cancer. In particular, nanofibers have attracted considerable attention as drug delivery systems for localized cancer treatment. Nanofibers are included in one-dimensional nanomaterials, i.e., nanomaterials with two dimensions within the nanoscale [4]. Therefore, nanofibers exhibit several advantages for biomedical applications: large specific surface area, tunable porosity, flexible surface functionality, among others [5]. Electrospinning is a widely used technique to produce nanofibers. This simple and low-cost technique can process different types of materials (polymer, ceramic) and electrospun nanofibers have been used in various areas, including cancer theranostics applications [6]. In this context, electrospun nanofibers are typically used as localized drug delivery systems. Once loaded with an anti-cancer drug, nanofibers can provide a sustained drug release at the tumor site. Additionally, nanofibers can be implanted directly at the tumor site following surgery, thus reducing the risk of local recurrence of cancer [7].

Magnetic nanoparticles (mNPs) have a significant potential for application in cancer theranostics due to their ability to respond to an external magnetic field. Consequently, mNPs may be used for cancer treatment as magnetic hyperthermia agents or triggers for drug release and cancer diagnostic as imaging probes [8–10]. Magnetic nanofibers can be composed of only magnetic materials or magnetic nanoparticles embedded in a polymeric fiber. The latter is the most explored

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architecture, mainly using electrospinning as the preferable technique to produce magnetic nanofibers [4].

This review will give an overview of the most recent advances in the development of cancer theranostics nanosystems based on electrospun nanofibers and magnetic nanoparticles. A brief overview of electrospinning technique will be given, followed by the typical application of electrospun fibers in cancer theranostics. The following subsection includes a short description of mNPs properties and their functionality for cancer theranostics applications. Finally, the most recent advances in magnetic electrospun nanofibers are given. It is not our intention to provide a complete description of the electrospinning process and mNPs properties. For that, the reader is invited to read review papers dedicated to these matters [5,11,12].

2. Electrospinning technique

Polymeric nanofibers can be produced by various methods, including physical, chemical, and biological ones. From the available physical methods, electrospinning is the most used technique because it was the first method used to produce polymeric nanofibers [13] and its numerous advantages. These advantages include its simplicity and low cost, avoids the use of heat during fiber production, the possibility of modifying the nanofibers, and easy incorporation of drugs or other bioactive substances [11]. Electrospinning technique (Fig. 1) processes a polymeric melt or solution to produce nanofibers with high surface area, controlled porosity, and controllable size [7]. The method is based on applying a high voltage to a needle (attached to a syringe containing the starting material), thus inducing charges at the liquid surface, leading to a strong electric field between the needle and the collector. Above a critical voltage, the surface tension of the liquid is surpassed by the repulsive electrostatic force, ejecting a charged jet of fluid towards the collector. When the material is collected, an interconnected web of nanofibers is obtained as a consequence of solvent evaporation (if the starting material is a solution) or solidification (if the starting material is a melt) [13,14]. The final architecture of the fibers is determined by instabilities (whipping or splitting) of the polymeric solution caused by Coulomb interactions in the charged fluid. Therefore, the final fiber architecture can be tailored by adjusting the processing parameters during electrospinning process [11,15].

2.1. Processing parameters

The processing parameters that primarily affect fiber morphology and diameter can be divided into three main groups: solution properties, processing parameters, and environmental conditions. Solution properties include polymer concentration, viscosity, surface tension, conductivity, dielectric constant, and solvent volatility. Polymer solution concentration and viscosity are closely related and interdependent [15]. A minimum solution concentration is required for fiber formation during electrospinning process. Low concentration tends to produce electrospray or beaded fibers, which is directly related to low viscosity. Viscosity increase due to higher polymer concentration leads to an increase in chain entanglement among the polymeric chains. These entanglements aid in overcoming surface tension, thus producing uniform beadless fibers. Ideal viscosity values are reported between 1 and 215 Poise to produce uniform electrospun fibers, although most studies report good fiber production between 1 and 20 Poise [16]. Polymer molecular weight mainly affects solution viscosity and fiber morphology. High molecular weight polymers tend to cause extensive chain entanglement, thus producing uniform and larger fibers [17]. Polymer solution conductivity is mainly dependent on intrinsic polymer properties, solvent, and ionizable salts. An increase in electric conductivity tends to decrease fiber diameter [18]. However, above a critical point, it may prevent the formation of Taylor cone and fiber formation. Highly conductive solutions become very unstable in the presence of strong electric fields, resulting in a dramatic bending instability and a broad diameter distribution [19].

As for the processing parameters, the applied voltage directly affects the dynamics of liquid flow, with significant consequences to fiber morphology (particularly its diameter). Typically, an increase in the applied voltage leads to smaller diameter fibers due to increased charge repulsion in the polymer jet. However, above a critical value (which depends on the polymer solution), irregular and beaded fibers can be formed [20]. The capillary tip to collect distance will determine the evaporation rate and the whipping or instability interval, resulting in different fiber morphologies. Usually, a distance between 10 and 20 cm is needed to produce homogenous fibers without defects. However, this distance is intimately dependent on the electric field [21]. The flow rate determines the amount of polymer solution available at the needle tip to form the Taylor cone. There is a critical flow rate to produce uniform

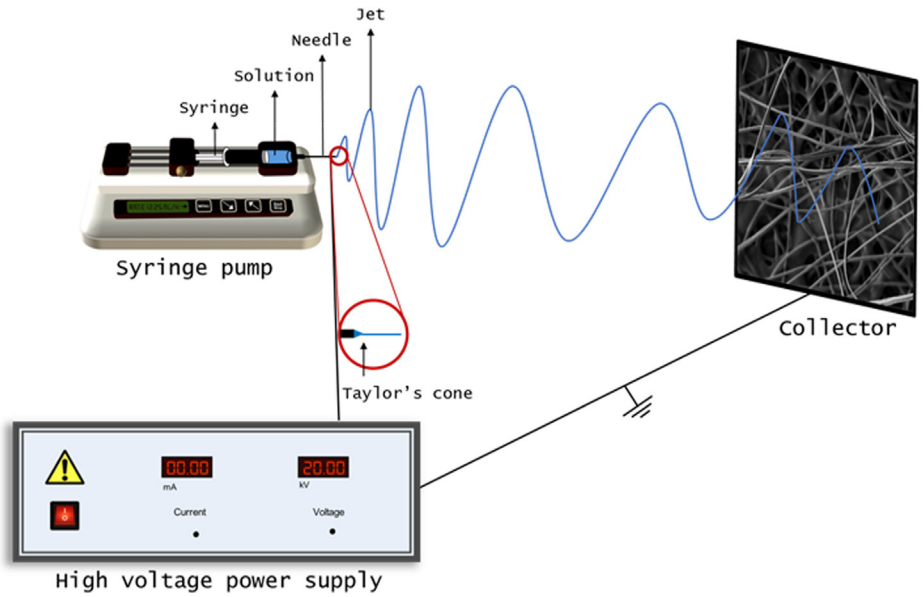

Fig. 1. Schematic representation of the electrospinning process including a high voltage power supply, a syringe containing the polymeric solution attached to the needle, a syringe pump, and a collector where the polymeric fibers are deposited (Reprinted from Ref. [4] with permission from Elsevier).

beadles electrospun fibers depending on the polymer solution properties. When the flow rate increases, the fiber diameter tends to increase as well. An increase in flow rate increases the electric current and decreases the surface charge density. The increase of volume being accelerated towards the collector can lead to incomplete solvent evaporation, originating bead formation, and irregular fibers [22].

Environmental conditions are determined mainly by relative humidity and temperature, directly related to solvent evaporation and fiber morphology. Nevertheless, these conditions are dependent on the chemical nature of the polymer [21]. Low humidity results in a higher solvent evaporation rate, originating thinner fibers. Higher temperatures can have the same effect. However, in some cases, the opposite effect can be observed. For example, Pelipenko et al. [23] demonstrated that an increase in relative humidity leads to thinner fibers composed of a blend between poly(vinyl alcohol) (PVA) and poly(ethylene oxide) (PEO). Other authors also reported the same effect in plain PEO fibers. In fact, in hydrophobic polymers, an increase in humidity can disrupt fiber morphology due to water condensation at the fiber surface, leading to pore formation [21].

2.2. Application in cancer treatment and diagnostics

Electrospun fibers produced using biocompatible and biodegradable materials have several advantages for biomedical applications. Electrospinning has been used as a processing technique to create cancer theranostics devices mainly due to the possibility of incorporating a wide range of biofunctional compounds into a nanostructure through a simple approach [24]. For cancer treatment, the potential to have carriers for local and targeted delivery of drugs, proteins, nucleic acids, and cells supports the application of electrospun membranes. These membranes are usually implantable systems with unique advantages like high and adjusted dosage at the tumor site, decreased side effects in adjacent tissues, and the possibility of effectively controlling drug release [6].

Different polymers can be used to encapsulate bioactive compounds for cancer treatment purposes. Depending on the polymer chemical composition, the final nanofibrous membrane can have stimuli-responsive properties, providing a higher degree of control over drug release rate and mechanisms. Both natural and synthetic polymers can be processed by electrospinning technique. Natural polymers include polysaccharides (chitosan, cellulose, among others) and their derivatives, proteins (gelatin, collagen, among others), and DNA. On the other hand, synthetic polymers that can be manipulated to match the desired properties include, for example, poly(lactic acid) (PLA), poly(lactic-*co*-glycolic acid) (PLGA), PEO, poly(ε-caprolactone) (PCL) [25]. PLA is widely used for biomedical applications due to its biocompatibility and non-toxic properties. Furthermore, due to its compatibility with bioactive compounds, PLA is an efficient matrix for controlled drug release through predictable kinetics. Zeng et al. [26] produced poly(l-lactide) (PLLA) nanofibers through electrospinning to evaluate the encapsulation efficiency and kinetics of drug release using three model drugs: paclitaxel, doxorubicin hydrochloride, and doxorubicin (DOX). Both paclitaxel and doxorubicin are lipophilic, while doxorubicin hydrochloride has a hydrophilic nature. The authors observed a preferable encapsulation of lipophilic drugs, with release kinetics following nearly a zero-order kinetics dependent on polymer degradation. Doxorubicin hydrochloride had a preferable localization at the fiber surface, leading to a burst release dictated by diffusion. Similarly, when curcumin is loaded into PLLA fibers, the release rate is mainly dictated by polymer degradation, leading to a slow and controlled release of this anti-cancer drug [27]. In a different study, Zhang et al. [28] produced a multilayer nanofiber mat using PLLA loaded with two different drugs (oxaliplatin and dichloroacetate) in distinct layers (Fig. 2A–C). This multilayer system can be implanted in the tumor site following resection (Fig. 2 D), demonstrating a synergistic effect between two drugs and the reduction of toxicity to adjacent healthy tissues throughout 30-days.

PLA is often used in combination with poly(ethylene glycol) (PEG) to produce an amphiphilic diblock co-polymer that can be processed by emulsion electrospinning, originating fibers able to incorporate both hydrophilic or lipophilic drugs. Xu et al. [29] used this technique to incorporate doxorubicin into PEG-PLA nanofibers and evaluate the

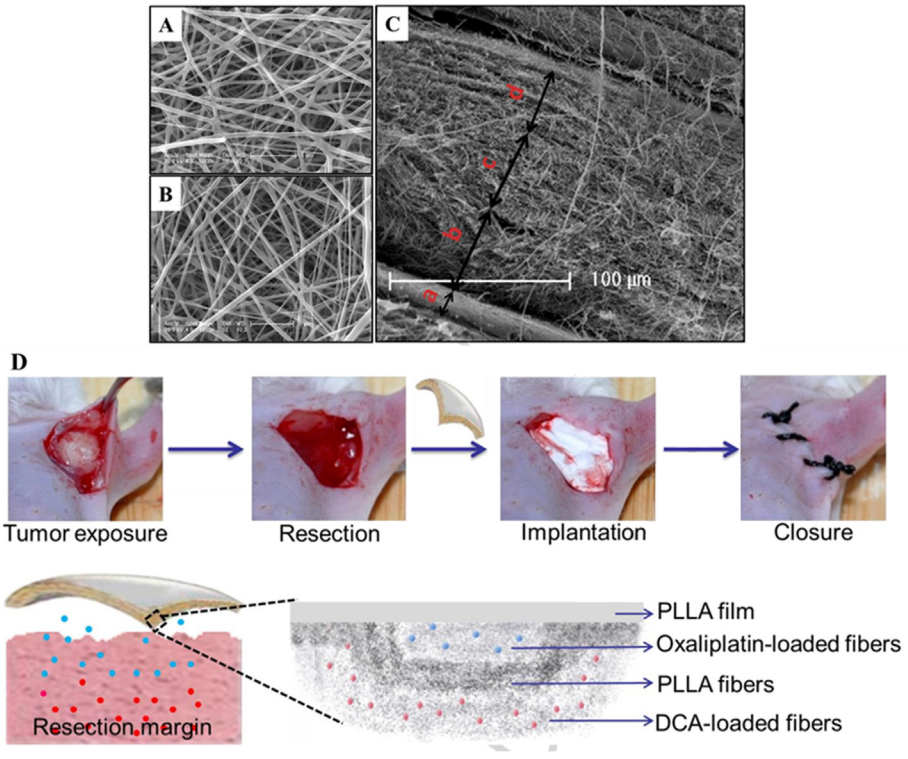

Fig. 2. Scanning electron microscopy (SEM) of PLLA fibers containing dichloroacetate (A) or oxaliplatin (B); C) cross-section of the multilayer PLLA mat containing a PLLA film layer (a), a layer containing oxaliplatin (b) followed by a plain PLLA layer (c), and a dichloroacetate-containing layer. D) Schematic representation of the experimental outline of *in vivo* studies using the multilayer PLLA mat: following cervical carcinoma resection, the PLLA multilayer mat is implanted (Reprinted from Ref. [28] with permission from Elsevier).

release mechanism. Using DOX as a model drug, the authors found that the drug was homogeneously dispersed in the fiber core, forming a core-shell nanofiber (Fig. 3 A, B). The drug release mechanism could be divided into three parts, in which the first one showed a slower release rate compared to the second part, although in both cases, the release mechanism was based on Fick's second law. The authors concluded that these amphiphilic nanofibers could act as a drug reservoir leading to a controlled and slower release rate. The same fiber architecture was used to obtain a sustained release of 2-hydroxypropyl—cyclodextrin for local treatment of hepatic tumors [30].

Natural polymers are also commonly used to produce electrospun nanofibers for cancer treatment purposes. Ignatova et al. [31] encapsulated DOX in a nanofibrous mat composed of quaternized chitosan and PLA (Fig. 3 C, D). The authors evaluated the antitumoral effect of these membranes against a human cervical cancer cell line (HeLa) and a human breast cancer cell line [34], demonstrating that cell death is mainly achieved by apoptosis. A similar nanofibrous membrane caused a significant reduction in Graffi cell viability *in vivo* through the same cell death mechanism. Moreover, the combination of doxorubicin with quaternized chitosan significantly reduces the adverse side effects [35].

Other polymers are also used to produce electrospun nanofibers as controlled drug delivery systems for cancer treatment. For example, Rasouli et al. [36] demonstrated that co-encapsulation of curcumin and chrysin into PLGA-PEG nanofibers leads to a synergistic antiproliferative effect against T47D breast cancer cells, compared to single-drug loaded nanofibers. In a different study, Stanzione et al. [37] used PCL to encapsulate titanocene trichloride, demonstrating a drug release profile unrelated to polymer degradation, with potential for local treatment of cancer. Another research team developed a nanofibrous system based on PVA nanofibers with dacarbazine encapsulated for recurrent glioblastoma treatment. The produced electrospun nanofibers demonstrated a high drug loading, with sustained drug release and antiproliferative effect [38].

Although most studies reporting the use of electrospun nanofibers for cancer theranostics application use magnetic nanoparticles (which will be discussed further in this review), some authors used gadolinium complexes as magnetic resonance image (MRI) contrast enhancers. Jin et al. [32,33] prepared core-shell fibers composed of a PEO core and a Eudragit S100 shell (Fig. 3 E – G). Eudragit is a pH-sensitive polymer often used as a coating for oral administration, thus avoiding drug release in the stomach. These core-shell electrospun fibers were loaded with Gd(III) diethylenetriamine pentaacetate hydrate and indomethacin. The hybrid system demonstrated sustained release at pH 7.4 as opposed to acidic pH. Additionally, proton relaxivities were similar to those of pure gadolinium complex, demonstrating the potential application for cancer colon theranostics (Fig. 3 H).

More detailed information on the application of electrospun nanofibers in localized cancer treatment can be found in Refs. [6,7,25].

Electrospun nanofibers can also be used as biosensing platforms for cancer diagnostic. Recently, electrospun nanofibers functionalized with a specific marker are being used for early detection of circulating tumor cells (CTCs) [39]. Chen et al. [40] produced TiO_2 nanofibers by electrospinning, followed by calcination. The TiO_2 nanofibers were functionalized with bovine serum albumin (BSA) to inhibit non-target cell adhesion, and a specific peptide (asparagine-glycine-arginine – NGR) was used to capture the target CTCs. The results demonstrated a high capture sensitivity and efficiency using low concentrations of CTCs in simulated blood samples. In a different work, PLGA nanofibers were functionalized with streptavidin for specific detection of biotinylated ant-CD45 antibody-labeled white blood cells. Demonstrating a high capture efficiency, the microfluidic platform integrated with functionalized nanofibers produces a negative sorting device for early detection of non-small cell lung cancer [41].

3. Magnetic nanoparticles for cancer theranostics

In the last decades, nanotechnology has revolutionized the development of new materials with potential applications in various fields. For biomedical applications, nanotechnology is used to design and engineer new devices, particularly for precision medicine. These nano-devices aim to improve diagnostic precision and treatment outcomes [42]. Typically, nanoparticles, defined as nanostructures with at least one dimension below 100 nm, are used to produce nano-devices for biomedical applications [43]. The ability of mNPs to respond to the application of an external magnetic field enables their use in nano-devices for a multitude of biomedical applications [4]. Magnetic nanoparticles can be composed of pure metals, their oxides, or metal alloys. mNPs of pure metals usually present higher magnetization than metal oxide ones. However, these pure metal mNPs are highly sensitive to oxidation and may be toxic to the biological systems [10,12]. Magnetic alloys are typically composed of iron or cobalt with another metal to enhance the magnetization of the final mNP. Nevertheless, the magnetic properties of alloy mNPs are

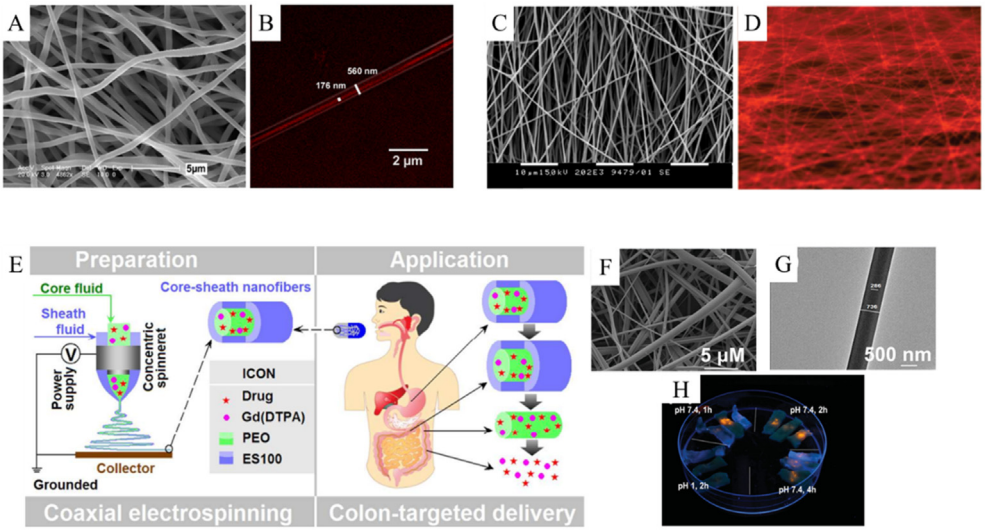

Fig. 3. A) SEM images of PEG-PLA nanofibers loaded with DOX 3 wt%; the presence of DOX at the fiber core was confirmed by confocal microscopy (B) (Adapted from Ref. [29] with permission from Elsevier). C) SEM image of electrospun fibers composed of quaternized chitosan and PLA loaded with DOX 6 wt%; in this case, the presence of DOX was confirmed by fluorescence microscopy (D) (Adapted from Ref. [31], Copyright (2010) American Chemical Society). E) Schematic representation of the production of core-shell nanofibers composed of Eudragit S100 shell and PEO core, and its applicability for oral administration (Reprinted from Ref. [32], Copyright (2016) American Chemical Society); F) SEM and G) Transmission electron microscopy (TEM) images of the core-shell pH-sensitive nanofibers; H) Core-shell nanofibers under UV irradiation following immersion in different pH conditions; rhodamine B was used as a model to illustrate enhanced release at pH 7.4 (Adapted with permission from Ref. [33], Copyright (2016) John Wiley and Sons).

highly dependent on the relative composition of each metal and the synthesis method [12]. Metal oxide NPs are typically chosen for biomedical applications due to their superparamagnetic properties, biocompatibility, and chemical stability under physiological environment. Metal oxide mNPs containing iron include magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3), and other ferrites (MFe_2O_4, where M = Co, Mn, Ni, Zn, among others). Particularly for cancer theranostics application, superparamagnetic properties are preferable. A superparamagnetic NP rapidly changes its magnetic state upon application of an external alternating magnetic field; once the field is removed, the mNP have zero coercivity and present no hysteresis. This phenomenon occurs below a critical size, where the particle behaves like a paramagnet instead of individual atomic magnetic moments [10,44].

3.1. Preparation of magnetic nanoparticles

Magnetic nanoparticles can be synthesized using different approaches, from chemical methods (chemical co-precipitation, thermal decomposition, hydrothermal synthesis, among others) to physical methods [4], including laser pyrolysis techniques [45], microorganism or bacterial synthesis [46]. Chemical methods are usually preferred to obtain nanometric monodisperse magnetic nanoparticles with adequate surface chemistry and magnetic properties for biomedical applications [10]. A recent new method for mNPs synthesis is by using a microfluidic device. Using these systems, it is possible to obtain 4 nm mNPs with narrow size distribution due to an efficient control over the reaction parameters [47].

Following synthesis, mNPs designed for biomedical applications typically require a coating step to achieve the required colloidal stability in an aqueous environment. Due to their nanometric size, mNPs tend to aggregate or agglomerate in an aqueous medium, which predominantly affects their magnetic properties. To avoid this undesired consequence, mNPs are typically stabilized using different types of molecules, including small organic molecules (e.g., oleic acid), macromolecules (both natural – chitosan- or synthetic - PVA), and inorganic materials (e.g., silica). In addition to prevent aggregation or agglomeration, mNPs coating can also be used for further functionalization with a bioactive agent, thus conferring additional functionality to the nanosystem [4,48].

3.2. Application in cancer theranostics

The unique magnetic properties of iron oxide nanoparticles, particularly superparamagnetism, are one of the most attractive features for their application in cancer theranostics. In this sense, three main functionalities are found in mNPs for cancer theranostics application: contrast agents for MRI, treatment through magnetic hyperthermia, and magnetic drug delivery. MRI is extensively used for cancer diagnostics by measuring the nuclear relaxation of atoms in the body following the application of a strong magnetic field. Using this diagnostic technique, it is possible to differentiate soft tissue and observe physiological phenomena using a non-invasive method. Superparamagnetic nanoparticles can enhance the nuclear relaxation of water protons, mainly by changing the transverse (T2) relaxation, leading to a darker contrast [49]. Several formulations of iron oxide nanoparticles were clinically approved for cancer diagnostic through MRI in the last decades. The primary approved applications included liver and spleen (Feridex I.V.® – USA and Endorem™ – Europe), lymph node, bone marrow, carotid atherosclerotic plaques (Sinerem®/Combidex®) imaging. Some formulations were also clinically approved for MRI imaging through oral administration, mainly directed for bowel imaging (Lumirem®, GastroMARK®, Abdoscan®). However, these formulations were withdrawn from the market recently due to low competitiveness compared to gadolinium-based contrast agents [50–52].

Magnetic hyperthermia is based on applying an alternating magnetic field to a tumoral area containing magnetic nanoparticles. The alternating magnetic field induces heat generation by mNPs, which is instantly transferred to the tumor cells. If the temperature is maintained at a temperature above 42 °C for sufficient time, tumoral cells will be destroyed [53,54]. Since 2010, a formulation containing 15 nm iron oxide nanoparticles coated with aminosilane (Nanotherm®) was approved for the treatment of glioblastoma multiform by magnetic hyperthermia in the European Union. The rationale for Nanotherm® application is by direct injection in the glioblastoma tumor, followed by application of an external alternating magnetic field until a temperature of about 44.6 °C is achieved. Simultaneously, clinical trials are being performed in Europe and the USA to use the same formulation for pancreatic, prostate, breast, and esophageal cancer treatment [55–58].

Current chemotherapeutic regimens are usually administrated via intravenous injection, leading to systemic distribution. The presence of such toxic drugs in healthy cells and tissues leads to adverse side effects. Drug delivery systems aim to deliver the drug precisely to the target site, therefore avoiding systemic distribution. mNPs application in drug delivery systems takes advantage of the magnetic responsiveness to control the release of the drug [59]. Typically, an external high-gradient magnetic field directs the magnetic nanosystem to the target site. Using this technique, magnetic nanosystems demonstrated a higher accumulation in the tumor site in mice bearing CT26 colon carcinomas [60] and lung tissue [61].

4. Magnetic nanofibers for cancer theranostics

A critical issue when designing magnetic nanoparticles for biomedical applications is their biological fate following intravenous injection. Typically, mNPs are internalized by cells via endocytosis, followed by degradation in lysosomes, resulting in the release of metal ions. When using iron oxide nanoparticles, the iron ions are eliminated via endogenous iron metabolism pathways [62,63]. Depending on their size and surface properties, mNPs can be rapidly eliminated from the bloodstream following intravenous injection. To avoid particle loss before reaching the target site and to ensure a high concentration of mNPs suitable for cancer theranostics application, mNPs can be incorporated into nanostructured systems. These nanostructured systems can be directly implanted or injected into the tumor site, ensuring a localized treatment, thus decreasing negative side-effects to healthy tissues [4].

Nanofiber polymeric membranes incorporating magnetic nanoparticles possess the polymeric matrix's mechanical properties but the ability to respond to a static or alternating magnetic field. Furthermore, confining magnetic nanoparticles into a polymeric fiber produces a multi-core system, i.e., the polymeric nanofibers contain multiple magnetic cores incorporated. Therefore, the number of incorporated particles and their magnetic properties do not change over time, thus ensuring a constant response to an external magnetic field during the treatment interval [64].

Electrospinning technique constitutes a simple technique to incorporate inorganic nanoparticles directly inside a polymeric matrix. It enables the possibility of simultaneously processing a mixture of different polymers, or of polymers and small organic molecules as, for example, a drug. Therefore, the composition and properties of the final nanofibrous membrane can be easily tunned during electrospinning, including mechanical properties, porosity, and swelling, among others [64].

4.1. Natural polymer-based nanofibers

Different types of polymers can be used to incorporate magnetic nanoparticles, from natural polymers to synthetic ones. Chitosan, a biopolymer derived from chitin, was used by Lin et al. [65,66] to produce magnetic nanofibers. The authors evaluated the effects of mNPs location in heat generation during magnetic hyperthermia assays (Fig. 4 A, B). The results demonstrated that these non-cytotoxic magnetic nanofibers could increase the temperature up to 45 °C, therefore having potential for cancer treatment (Fig. 4 C). Radmansouri et al. [67] also used chitosan nanofibers to encapsulate titanium oxide and cobalt ferrite. These

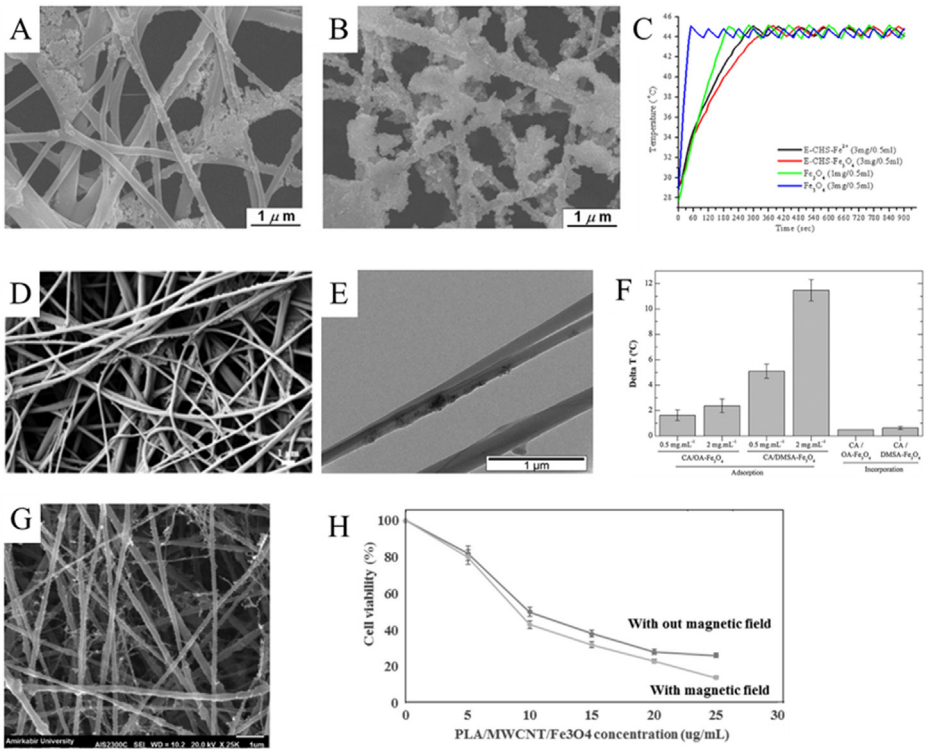

Fig. 4. A, B) SEM image of magnetic fibers composed of chitosan and iron oxide nanoparticles with different preparation methods; C) magnetic hyperthermia results demonstrate chitosan magnetic nanofibers' ability to achieve and maintain a hyperthermic temperature (Adapted from Ref. [65] with permission from Elsevier). D, E) SEM and TEM images of cellulose acetate nanofibers containing iron oxide nanoparticles adsorbed at fiber surface and incorporated inside the fibers, respectively; F) magnetic hyperthermia results enhancing the importance of mNPs location in the generated heat when an alternating magnetic field is applied (Adapted from Ref. [70] with permission from Elsevier). G) SEM image of PLA nanofibers containing multi-walled carbon nanotubes and iron oxide nanoparticles; H) K562 cell viability after synergistic treatment of daunorubicin release and magnetic hyperthermia, demonstrating the effect of application of an alternating magnetic field (Adapted from Ref. [71], Copyright (2016), with permission from Taylor & Francis Ldt.).

magnetic nanofibers loaded with doxorubicin demonstrated that doxorubicin release was enhanced by applying an alternating magnetic field, leading to *in vitro* cell death using melanoma cancer B16F10 cell lines. Chitosan is often used in combination with synthetic polymers such as PCS. Amini et al. [68] produced CS-grafted-PCL nanofibers using electrospinning. Theses nanofibers were loaded with plain bioactive glass (BG) and magnetic bioactive glass (MBG) together with cisplatin. These composite nanofibers were evaluated for combinatory treatment of chemotherapy and magnetic hyperthermia in MG-63 osteosarcoma cells. The results demonstrated an absence of cisplatin burst release from the composite nanofibers, whereas a controlled released occurred tailored by temperature and pH. The fastest release rate was observed at 43 °C and pH of 5.5, demonstrating the synergistic effect of heat generation by mNPs and drug release. Abasalta et al. [69] used a combination of carboxymethyl CS and PCL to produce core-shell nanofiebrs through electrospinning incorporating doxorubicin and nichel ferrite. The results demonstrated a sustained DOX release tailored by pH and magnetic field presence, with promising results for breast cancer treatment.

Using a cellulose derivative, cellulose acetate, Matos et al. [70] produced magnetic fibers by incorporating or adsorbing magnetite nanoparticles in the biopolymer nanofibers (Fig. 4 D, E). The magnetic nanofibers demonstrated outstanding potential for cancer treatment through magnetic hyperthermia, with a significant enhancement of the generated heat when mNPs are adsorbed at the fiber surface (Fig. 4 F).

As above-mentioned, PLA is a commonly used polymer to produce electrospun nanofibers for cancer theranostics applications. Hosseini et al. [71] used PLA electrospun nanofibers incorporated with multi-walled carbon nanotubes and magnetite nanoparticles for leukemia K562 cancer cells (Fig. 4 G). The authors used daunorubicin as a model drug and demonstrated *in vitro* a synergistic cytotoxic effect between localized chemotherapeutic treatment and an applied magnetic field (Fig. 4 H). Using a different approach, Awada et al. [72]

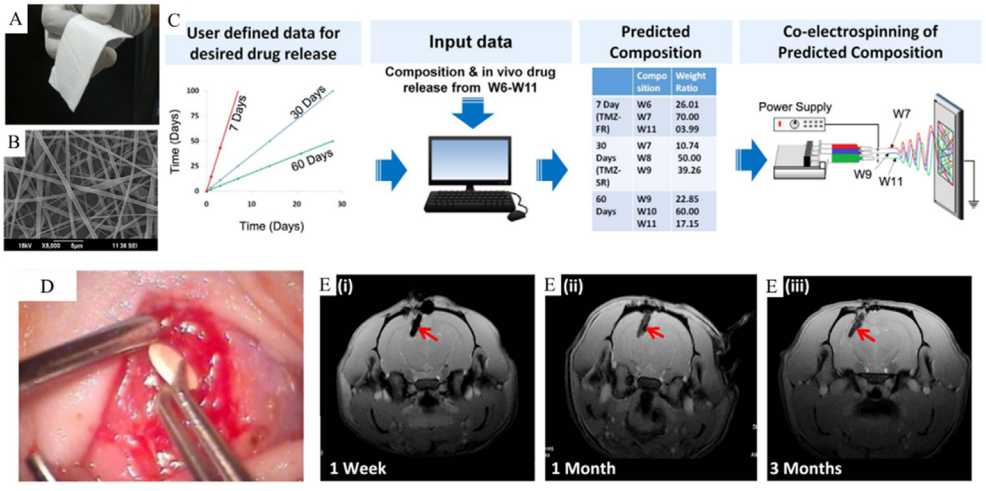

Fig. 5. Photograph (A) and SEM image (B) of the polymeric blend composed of PLGA, PLA, and PCL; C) Schematic representation of the data model used to produce the most efficient polymeric blend, depending on initial drug release data; D) Photograph of polymeric mesh implantation, and the respective T2-weighted MR images of the polymeric mesh implanted in orthotopic rat glioma over throughout three-months (Reproduced with permission from Ref. [75], Copyright (2017) Springer Nature, CC BY 4.0).

functionalized the surface of PLA electrospun nanofibers to enhance the controlled anchoring of mNPs. The obtained magnetic nanofibers exhibited a core-shell structure with mNPs located at the nanofiber surface. Thoroughly characterization showed that the size and nature of mNPs were not altered during grafting, thus avoiding undesired aggregation of mNPs inside the fiber. Preliminary *in vitro* results demonstrated that these magnetic nanofibers are not cytotoxic and can be used to enhance T2 contrast in MRI. Perera et al. [73] used the infusion gyration technique, a spinning technique alternative to electrospinning, to produce magnetic PVA nanofibers. Using acetaminophen as a model drug, the authors could control drug release using magnetic actuation. Nikolaou et al. [74] used PLLA and PEO incorporated with oleic acid-coated Fe_3O_4 NPs to produce microrods through electrospinning technique. These microrods can be magnetically guided to achieve higher deposition in selected areas within the lung. Additionally, these magnetic microrods enable localized lung cancer treatment through a combination of magnetic hyperthermia and chemotherapy. Ramachandran et al. [75] performed a systematic study to produce an electrospinning nanofibrous membrane from a blend of three polymers: PLGA, PLA and PCL (Fig. 5 A, B). The authors studied different polymer ratios with temozolomide incorporated. Each blend was tested in orthotopic brain-tumor to evaluate drug release kinetics. Different release kinetics were obtained depending on polymer ratio, from hours to months (Fig. 5 C). *In vivo* results in orthotopic rat glioma demonstrated a sustained release over one month with negligible release to peripherical blood. Additional, over 85% of rats had a long-term survival. Additionally, the presence of mNPs in the polymeric blends allowed treatment monitoring by MRI (Fig. 5 D, E).

4.2. Synthetic polymer-based nanofibers

Tiwari et al. [76] used PCL, an FDA-approved semi-crystalline polymer, to produce magnetic nanofibers for combined chemotherapy and thermotherapy (Fig. 6A–C). The nanosystem included carbogenic quantum dots as the detection component, and doxorubicin as a model drug, in addition to iron oxide nanoparticles as the magnetic component. With an alternating magnetic field application, over 90% of HeLa cells died through a combination of the generated heat and induced drug release. The synergistic effect of these magnetic nanofibers as compared to individual treatments demonstrated the potential for cancer treatment. In 2018, Demir et al. [77] produced PCL magnetic nanofibers with a high load of mNPs (Fig. 6D–F) and compared the incorporation of a hydrophobic (Nile Red) and a hydrophilic (Rhodamine-B) dye. The results showed that the presence of mNPs influenced dye release, particularly of the hydrophilic one. However, no significant differences were observed for the hydrophobic drug. Niiyama et al. [78] went further in this topic and developed PCL electrospun fibers loaded with magnetic nanoparticles and paclitaxel as an implantable system. This nanofibrous system was implanted in tumor-bearing mice (NCI–H23 cells), demonstrating that the composite system delivers a more effective synergistic treatment than paclitaxel or heating alone (Fig. 6G–J).

More recently, Suneet et al. [79] produced magnetic electrospun PCL fibers to produce a bandage for skin cancer treatment. *In vitro* results using HeLa cells demonstrated a high efficiency in cancer treatment

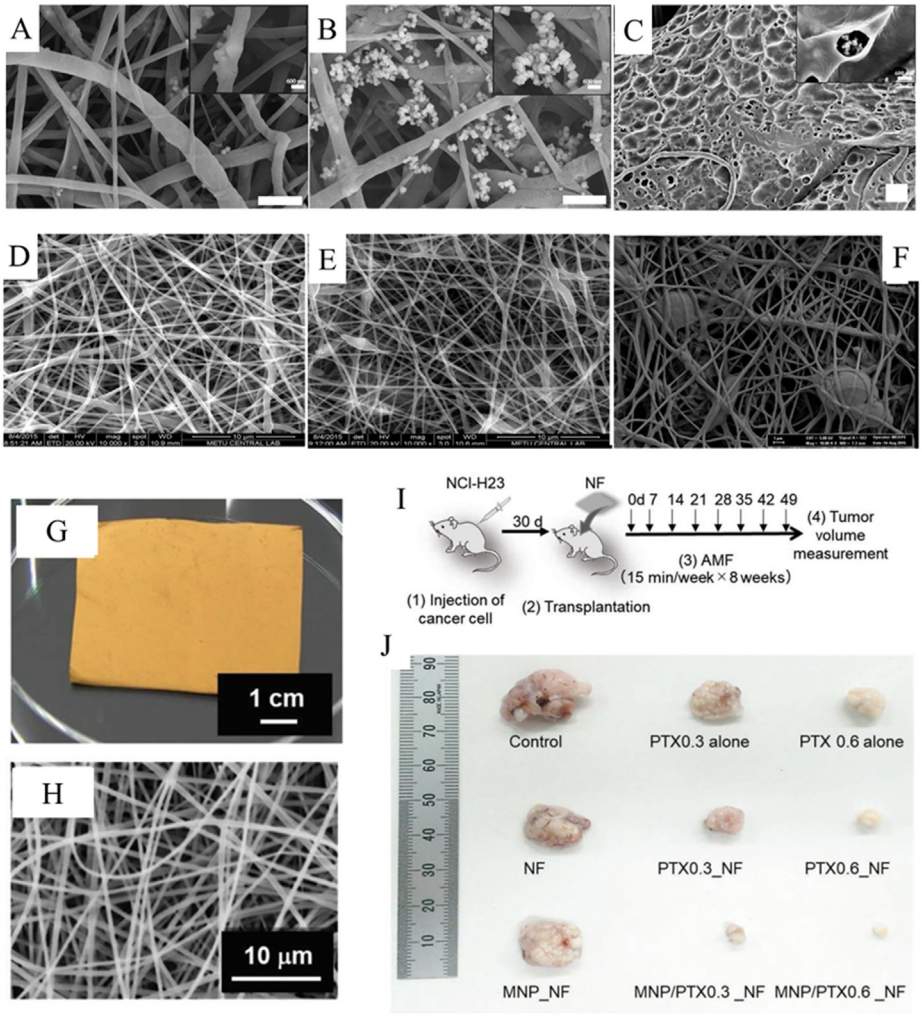

Fig. 6. A - C) SEM image of PCL magnetic nanofibers produced by electrospinning with different surface textures: smooth, rough, and porous, respectively. Scale bar 20 μm (Adapted with permission from Ref. [76]. Copyright (2016) John Wiley and Sons). D – F) SEM image of PCL nanofibers with increasing amounts of mNPs: 1:25, 4:25 and 16:25 (mNP:PCL weight ratio) (Adapted with permission from Ref. [77], Copyright (2018) Springer Nature). G, H) Photograph and SEM image of PCL nanofibrous membrane with mNPs and paclitaxel incorporated; I) scheme of the *in vivo* protocol performed to evaluate the magnetic membranes efficacy for cancer treatment using tumor-bearing mice; J) Ex vivo photographs of resected tumors from tumor-bearing mice following 60-days of combinatory thermo and chemotherapy using the magnetic PCL membranes (Adapted with permission from Ref. [78], Copyright (2019) John Wiley and Sons).

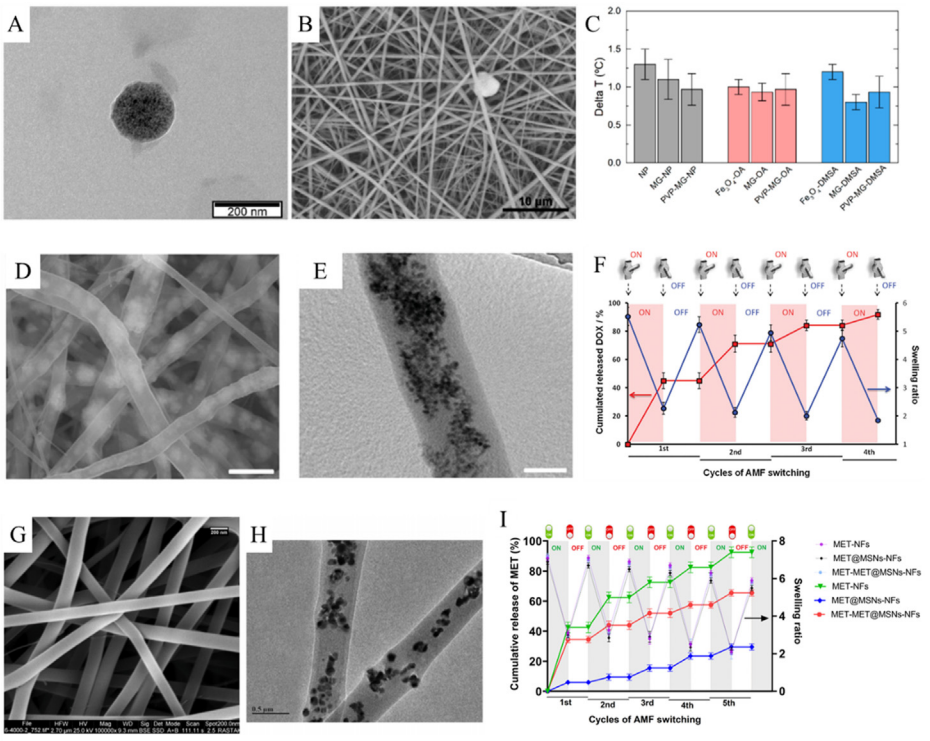

Fig. 7. A) TEM image of PNIPAAm microgel containing iron oxide nanoparticles; these hybrid microgels were confined in PVP nanofibers through colloidal electrospinning (B) and demonstrated potential for magnetic hyperthermia application (C) (Adapted with permission from Ref. [83], Copyright (2021) MDPI, CC BY 4.0). D, E) SEM and TEM image of nanofibers from a co-polymer of NIPAAm and HMAAm containing mNPs; this system demonstrated an on-off switchable and reversible heat profile when an alternating magnetic field is applied, associated with a significant change in its swelling ratio because of the thermoresponsiveness of the co-polymer; DOX release occurs as a consequence of the swelling ratio change (F) (Adapted with permission from Ref. [86]. Copyright (2013) John Wiley and Sons). G, H) SEM and TEM images of nanofibers from a co-polymer of NIPAAm and HMAAm containing mNPs, mesoporous silica nanoparticles, and metformin (MET); this system also demonstrated a reversible heating profile as a consequence of the application of an alternating magnetic field. The consequent changes in the polymeric fiber swelling ratio led to a controlled MET release (Adapted from Ref. [87] with permission from Elsevier).

through magnetic hyperthermia conjugated with DOX release. Serio et al. [80] incorporated DOX and Fe_3O_4 nanocubes in electrospun PCL nanofibers for combinatorial treatment of cervical cancer. They demonstrated a synergistic effect between magnetic hyperthermia and chemotherapy as a promising approach for cervical cancer treatment.

Other synthetic polymers like polyurethane [81], polystyrene [82], and polyvinyl pyrrolidone (PVP) [83] are also used to produce magnetic nanofibers by electrospinning. In the latter, thermoresponsive microgels composed of poly(*N*-isopropyl acrylamide) (PNIPAAm) containing mNPs were incorporated using the colloidal electrospinning technique (Fig. 7 A-C). Colloidal electrospinning is similar to traditional electrospinning, but instead of a precursor polymeric solution, it uses a precursor colloidal solution [84,85]. These fibers generated heat under the application of an alternating magnetic field, thus demonstrating the potential for magnetic hyperthermia application. The combination of stimuli-responsive polymers with magnetic nanoparticles produces smart systems with significant application in cancer theranostics. Kim et al. [86] used a co-polymer of NIPAAm and *N*-hydroxymethyl acrylamide (HMAAm) to produce an on-off system capable of changing its swelling ratio under the application of an alternating magnetic field (Fig. 7 D-F). The heat generated from the incorporated magnetic nanoparticles induces the physical changes in the thermoresponsive polymer. This composite system can be used as a remotely controlled on-off drug release system. Using the same thermoresponsive polymer, other research group incorporated both mNPs and paclitaxel using electrospinning. The resultant nanofibrous membrane demonstrated synergistic thermo-chemotherapeutic effects without significant adverse side effects in mouse lung cancer model. Similar results were obtained in B16F10 skin melanoma cells (Fig. 7 G-I) [87].

In another study, the authors produced novel catecholic nanofibrous membranes by electrospinning a mussel-inspired polymer (poly(methyl methacrylate-*co* dopamine methacrylamide)) (MADO). Following iron oxide nanoparticles incorporation, the smart nanofibers were tested for

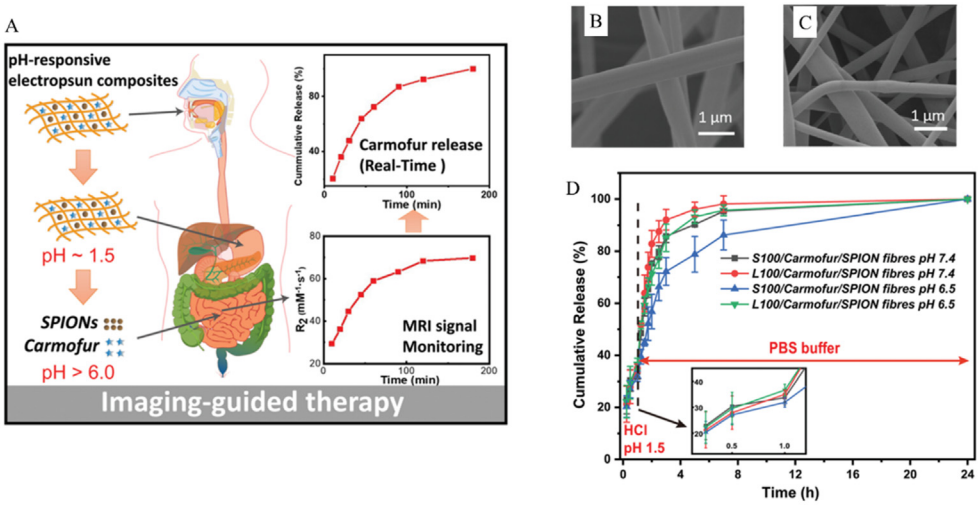

Fig. 8. A) Schematic representation of the pH-responsive magnetic system composed of Eudragit L100 or S100 containing mNPs for oral administration and specific delivery at the colon for cancer theranostics application; B, C) SEM images of the magnetic nanofibers produced from Eudragit L100 and S100, respectively; D) this system releases carmofur specifically in pH conditions similar to small intestine and colon; additionally, the presence of mNPs allow treatment monitoring and drug release quantification through MRI, a non-invasive imaging technique (Reproduced from Ref. [90] with permission from the Royal Society of Chemistry).

cancer treatment through the synergistic effect between magnetic hyperthermia and chemotherapy. This smart nanosystem could release bortezomib in a pH-dependent manner while maintaining an efficient cyclic heating performance. Moreover, these nanofibers can be monitored following direct implantation in the tumor using the MRI modality [88]. Using the same approach, the authors demonstrated similar results using PLGA instead of MADO [89].

Zhang et al. [90] used two pH-responsive polymers, Eudragit L100 and S100, co-polymers of methacrylic acid and methyl methacrylate only soluble in water in a specific range of pH, above pH 6.0 or pH 7.0, respectively (Fig. 8). These two polymers were electrospun in the presence of iron oxide nanoparticles, thus protecting the mNPs from the acidic conditions in gastric fluid. Carmofur, a chemotherapeutic drug commonly used for colon cancer treatment, was used as model drug. The results confirmed the protective effect of Eudragit fibers, leading to a specific release of carmofur in pH conditions similar to those found in the small intestine and colon. Due to the presence of mNPs, the authors found a relation between proton relaxation changes and drug release, enabling drug release quantification through MRI.

4.3. Opportunities and challenges of electrospun magnetic nanofibers

Nowadays cancer is of the major burns of mankind. On the other hand, precision and personalized approaches are becoming the major purpose to achieve early diagnostics, effective treatments and minimum side effects. In this context, a device that can be implanted in a target site, manipulated externally, and tailored for a specific patient is desired. Magnetic electrospun nanofibers can be easily implanted in the tumor site and remotely activated to achieve a personalized treatment. Moreover, the presence of magnetic nanoparticles enables treatment monitoring through MRI.

In a different feature, electrospun nanofibers have been recently used for specialized diagnostic methods such as detection of CTCs in blood, allowing early detection of cancer. Additionally, functionalization with specific markers supports the use of electrospun nanofibers in different biosensoring devices. The major advantages of an electrospun nanofiber-based system is its flexibility, low cost and large scale production, biocompatibility, and availability of different polymers that can be chosen according to the desired application.

Nevertheless, the major limitation of electrospun magnetic nanofibers is their early stage of development. Most studies only report *in vitro* or *in vivo* studies. However, several natural-derived or synthetic polymers used to produce magnetic nanofibers are already approved by the FDA for other medical applications. Therefore, it is expected a smoother path for clinical translation of magnetic electrospun nanofibers for cancer theranostics application.

5. Conclusion

Current cancer treatment and diagnostic struggles are to provide the most efficient course of treatment without causing severe side effects and to diagnose the disease in its extension as early as possible, also allowing further treatment monitoring. Therefore, a nanosystem able to combine both treatment and diagnostic features is ideal to fulfill such purposes. Electrospun polymeric nanofibers have demonstrated to be effective vehicles for long-term local chemotherapeutic drugs release, thus preventing severe side effects and cancer recurrence. The addition of magnetic features in the form of magnetic nanoparticles enables additional functionalities. First, thermotherapy and chemotherapy can be combined locally, often resulting in a synergistic therapeutic effect. Second, the magnetic nanosystem can be remotely controlled, acting as an on-off switch. Third, the presence of mNPs allows treatment monitoring by MRI, even allowing the quantification of the released drug in some cases. These hybrid nanosystems are still not clinically approved for cancer theranostics. However, current research includes numerous *in vitro* and *in vivo* results that demonstrate the high potential of electrospun magnetic/polymeric nanofibers for cancer theranostics application.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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