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NANOFIBER AND CANCER - AN OVERVIEW OF RECENT DEVELOPMENTS

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ABSTRACT

Cancer is a disease of grave concern. To combat the alarming need to provide an effective treatment methodology, Nanotechnology has become a powerful tool. It aids in achieving target-specific drug delivery to the tumour site. Nanofibers are among such nano-bio materials that can encapsulate antitumor drugs. In this review we tried to enlist various commercial nano-formulations, comprehend electrospinning as a means of developing nanofibers, brief on natural, semisynthetic and synthetic polymers such as Zein, Chitin, Chitosan, Poly-lactic acid, Poly lactic-co-glycolic acid, and Polycaprolactone suitable for nanofiber preparation, and applications of Nanofibers in delivery of a single drug as well as a combination of drugs or theranostic agents in cancer. It also describes three mechanisms of drug release from nanofibers, namely, pH-responsive, thermoresponsive and magnetic-heat composite release. The review tabulates the recent developments enlightening the applications of nanofibers in cancer chemotherapy in the past two decades. Nanofibrous mats are effective systems for localized treatment involving monotherapy, combination therapy, as well as for concomitant delivery of drugs and imaging agent, or genes. They have potential applications in the prevention of post-surgical cancer recurrence. Nanocomposite systems confer the ability to modulate drug release. Systems like nanoparticles which suffer from poor circulation time can be incorporated within nanofibrous mats. With many such unforeseen advantages and merits, Nanofiber becomes a potential nanotechnology driven system that enables patient-centric therapy for grave conditions like cancer.

Keywords *– Nanofiber; Cancer; Electrospinning; Polymer; pH-responsive release; Thermoresponsive release; Magnetic Hyperthermia.*

1. INTRODUCTION

Cancer is the term given for a diseased state with uncontrollable growth and proliferation of cells. Cancer is among the most common health-threats around the world. Its complexity poses difficulty to health-care researchers and patients alike owing to its treatment complications and there is a significant amount of research going on to find a permanent cure or treat its recurrence. The prevailing treatments hold their noted adversities. The existing conventional treatment options are limited by their poor specificity for tumour cells. Chemotherapy results in nausea, alopecia, fatigue, mouth sores, and immunosuppression. Hormonal therapy can lead to weakened bones, headache, diarrhoea, fatigue, hot flashes and problems of the digestive tract. Surgery makes the patient susceptible to infections and pain. Healthy living cells get damaged in radiotherapy. Side effects of immunotherapy

include pain, hypo/hypertension, swelling, headache, redness, soreness, rash, itching, heart palpitation, sinus congestion, dizziness, vomiting, weakness, fever, diarrhoea, and fatigue. There is a need for novel approaches to mitigate such complications and decrease the mortality rate.

Nanotechnology has been achieved a considerable importance owing to size and efficiency. Nano-sized systems offer a higher bioavailability, sustained and controlled release, and targeted drug delivery that is essential in cancer chemotherapy. Nanofibers are among the novel drug delivery systems which see a considerable significance in localized chemotherapy. They come with multiple advantages that offer an edge over conventional system.

The review tries to enlist nanotechnology products which have successfully made it to the market and overviews nanofibers. It covers the credibility of nanofibers as an edge over the conventional drug delivery systems, their production techniques with an emphasis on electrospinning. It describes some of the polymer candidates which can be drawn into nanofibrous systems. The review also discusses nanofiber-based single and multi-drug delivery and three different release mechanisms. We have reviewed and compiled developments encircling nanofibre for the period ranging from 2006 to 2020 [1].

2. NANOTECHNOLOGY

Nanotechnology has led to unforeseen advancement in Cancer research. Nanostructured vehicles are being explored for drug delivery to tumour sites. Nano-drugs have become commercial over the years. Liposomes of Daunorubicin (DaunoXome®), Cytarabine (DepoCyt®), Doxorubicin (Doxil® andMyocet®), Vincristine (Marqibo®), Mifamurtide (Mepact™); Nanoparticle formulations of Leuprolide acetate (Eligard®), Paclitaxel (Genexol® and Opaxio®), Virosomes of Recombinant adenovirus (Gendicine®), are nano-formulations that have successfully made it to the market [2]. Nano-formulations have better penetrability, greater surface area to volume ratio, and can offer features such as targeted delivery, sustained and controlled release, improved bioavailability, etc.

3D scaffolds are widely used as implants in local delivery of drug. This facilitates targeted drug delivery. Nanoparticles, porous scaffolds and self-assembled peptide hydrogels have been used for the said purpose. While as nanoparticles have short circulation time, Hydrogels have poor control over drug release and prone to wash-out of encapsulated drug [3].

3. NANOFIBERS

In recent times, Nanofibers have gained the attention of several researchers. Nanofibers are nano biomaterials that can encapsulate antitumor drugs. Nanofibers are fibers having one dimension in the range of nanometers. These come with several advantages like high mechanical strength, large surface area to volume ratio, flexibility, interfiber porosity, permitting mass transfer and holding adjustable morphology. They are candidates suitable to be utilized as therapeutic patches for biomedical applications.

These patches have topical and implantable applications releasing the drug in a sustained and controlled manner, improving drug efficacy and reducing side effects, thereby improving the life expectancy of the patient. The implant is localized to Tumour site, or tumour cavity formed post-operation, using Magnetic resonance imaging (MRI), to prevent tumour recurrence. Drug loaded nanofibres are also injected intratumorally. Methods such as Phase separation, flash-spinning, melt blowing, drawing, bicomponent spinning, force spinning and electrospinning are used for the fabrication of nanofibers. Electrospinning is the most widely used method due to its simplicity and ease of control on parameters [1-3].

3.1 Preparation of nanofibers –Electrospinning

Electrospinning uses high electric voltage for nano-fiber production. Both molten Polymer and polymer solution are suitable for this technique. The electrospinning assembly mainly includes a high voltage power supply, a spinneret, and a grounded collector.

Electrospinning yields nanofibers with large surface area, small controllable pores and consistency in size which cannot be achieved with conventional techniques. Electrospun fibres can be used in tissue engineering, drug delivery, wound care, pharmaceutical industry, catalytic applications, environmental sciences and biomedical field**.**

An electric field is applied between the collector and the spinneret filled with a polymer liquid. The electric field on exceeding a certain value makes the repulsive force among the charges overcome the surface tension of the polymer liquid. This results in the ejection of a conical charged jet of the polymer liquid from the capillary tip of the spinneret at a fixed flow rate. This cone is called a Taylor cone. This jet is accelerated and stretched. The solvent gets evaporated and an interconnected nanofiber mat gets prepared on the grounded collector which is oppositely charged. By modifying the design of components of the setup, such as spinneret and collector, nanofibers with special properties can be prepared. Other materials like carbon, metals and ceramics have also been successfully electrospun into nanofibers. [4]

3.2 Polymers used for Nanofibers

More than 200 polymers including natural, synthetic, semi-synthetic and copolymers have been deployed till date successfully in electrospinning based on their applications.

3.2.1 Polylactic acid (PLA)

It is a thermoplastic polymer which is biocompatible. Poly-lactic acid and its degradation product, lactic acid both are biodegradable and harmless. The Polylactic acid fibers are suitable to develop implants and sutures. The monomer comes in two forms, L and DL forms. The L-lactic acid form provides mechanical strength to the polymer.

Lactic acid is chiral. It exists as two enantiomers, L- and D-lactic acid. It can be produced by fermentation of molasses, potato starch or dextrose from corn. There is a petrochemical route as well, which results in the production of a racemic mixture. High molecular weight polymer can be developed using two methods, namely Direct condensation, involving solvents under high vacuum and the other method involving the formation of a cyclic dimer intermediate (lactide)—that is solvent-free. The polymer can be extruded into monofilament and multifilament via techniques like melt spinning, dry spinning, wet spinning, and by dry-jet-wet spinning. The economical, eco-friendly, solvent-free process, that is Melt spinning, is achievable, as the polymer can be melted owing to its thermoplastic nature. Dry spinning involves thermal evaporation for solvent removal and wet spinning involves coagulation of the polymer in a fluid that is compatible with the spinning solvent but is not itself a solvent for the polymer. Electrospinning is another technique that can be used for designing surface morphology and establishing porosity in the fiber essential for various biomedical applications whereby nano-sized filaments can be prepared by adjusting the polymer concentration and surface tension of the solution. Other features of the polymer include low moisture absorption, high wicking, low flammability and smoke generation, high resistance to UV, low refractive index, and low density. It can be used to achieve controlled drug delivery by allowing drug release by gradual hydrolytic degradation or via morphological changes in the polymer. The polymer alone or in combination with other biodegradable polymers can offer the provision of adequate support for cell growth and hence can be used in tissue engineering. [5]

3.2.2 Polycaprolactone (PCL)

Polycaprolactone is a Food and Drug Administration (FDA) approved synthetic polymer. It is a biodegradable aliphatic polyester suitable for applications in developing controlled-release drug delivery systems, absorbable surgical sutures, nerve guides, and three-dimensional (3-D) scaffolds that are used in tissue engineering. The polymer exhibits its utility in drug delivery systems like

microspheres, microcapsules, nanoparticles, pellets, implants, and polymeric films. It has high thermal stability useful in achieving melt processing. It is available at a low cost. Polymerization reaction underlying its production is catalyzed by catalysts such as stannous octoate. Low molecular weight alcohols are used to control the molecular weight of the polymer. The polymer is soluble in organic solvents such as chloroform, dichloromethane, carbon tetrachloride, benzene, toluene, cyclohexanone and 2-nitropropane at room temperature, but has low solubility in acetone, 2-butanone, ethyl acetate, dimethylformamide and acetonitrile. It is insoluble in alcohol, petroleum ether and diethyl ether. It can be copolymerized or blended with a variety of polymers. The degradation of this polymer is achieved via hydrolysis of its ester linkages in the human body. Its degradation is slower than that of polylactide. Fibers of this polymer can be developed by methods similar to that of Polylactic acid. Its applications are similar to that of Polylactic acid. The homopolymer degrades over two to four years and the rate of hydrolysis can be adjusted by copolymerization with other lactones or glycolides or lactides. [6]

3.2.3 Poly lactic-co-glycolic acid (PLGA)

PLGA is a Co-polymer of lactide and glycolide. It is known for biocompatibility and biodegradability alongside considerable mechanical strength. It has been fabricated into devices like microspheres, microcapsules, nanoparticles, pellets, implants, and polymeric films. It is produced by copolymerization of lactic and glycolic acid monomeric units. High-molecular-weight polymers and copolymers of glycolide and L- and D-lactides are prepared using ring-opening addition polymerization of their respective cyclic dimers and not by direct condensation of related carboxylic acids, as the latter is a reversible reaction. Based on the ratio of lactide to glycolide, different forms of PLGA can be obtained. All the PLGAs are amorphous and their swelling behaviour, mechanical strength, capacity to undergo hydrolysis are directly influenced by its crystallinity which in turn is directly related to the molecular weight of the polymer. They are normally glassy and have a rigid chain structure giving them mechanical strength required to be formulated as a degradable device. PLGA has a solubility in solvents like chlorinated solvents, tetrahydrofuran, acetone, or ethyl acetate whereas the homopolymers of lactide acid and glycolide acid show poor solubility in such solvents. PLGA can undergo hydrolytic degradation or biodegradation, both in vitro and in vivo, through cleavage of its backbone ester linkages. It can be spun by methods similar to the above polymers and holds similar pharmaceutical and biomedical applications. [7]

3.2.4 Chitin and Chitosan

Chitin and its deacetylated derivative, chitosan is biodegradable and biocompatible polymers. These are non-toxic and exhibit antibacterial activity. They facilitate multiple biomedical applications such as in developing scaffolds in tissue engineering, drug delivery systems, wound dressings, separation membranes and antibacterial coatings, stent coatings, and biosensors. Chitin is the major structural component composing the exoskeleton of arthropods, the main commercial source being crab and shrimp shells. They are also found as a component of cell walls in fungi and yeast.

Chitin has a limitation of poor solubility in common solvents. Hence, its derivative, chitosan is preferred. Chitosan exhibits solubility in acidic, neutral and alkaline solutions. Nanofibers of chitin or chitosan serve a variety of potential applications in areas such as filtrations, recovery of metal ions, drug release, tissue engineering, as a catalyst and enzyme carrier, in wound healing, protective clothing, cosmetics, biosensors, medical implants and energy storage. The protonation of chitosan changes it into a polyelectrolyte in acidic medium. Repulsive forces arise between ionic groups within the polymer backbone when a high electric field is applied during the electrospinning process, which eventually restricts the formation of continuous fibers and results in the production of particles. Also, high viscosity limits its spin ability. This can somehow be resolved through alkali treatment which hydrolyzes chitosan chains decreasing their molecular weight.

This alkali-treated chitosan in 70–90% acetic acid aqueous solution leads to the production of nanofibers with required quality and processing stability. When the concentration of acetic acid in the solvent is decreased, the mean diameter of the nanofibers

increases. Researchers have developed crosslinked, quaternized, galactosylated, chemical derivative forms of chitosan into nanofibers. These nanofibers are promising candidates for the enhancement of absorption of drugs, enzyme immobilization, cell proliferation and wound healing. [8]

3.2.5 Zein

Zein is a polymer with film and fibre-forming properties. It shows antioxidant properties and acts as a promising biopolymer for food and nutritional applications. It serves as a carrier of delivery of many nutrients. It can form encapsulated systems. Zein based nano-materials are used for nanoencapsulation of lipids, essential oils, fat-soluble vitamins, food colourants, flavours; and natural antioxidants. It has shown the ability to improve the bioavailability of folic acid, vitamin D3, curcumin, beta-carotene, and resveratrol. Zein with positive charge can deliver negatively-charged drugs, food, and nutrients. Due to the wide range of isoelectric point for zein, it is suitable to deliver many different nutrients into the body. Zein is eco-friendly. It consists of four components namely, alpha, beta, gamma and delta having different peptide chains, molecular sizes and solubilities. Alpha is the most abundant among commercial zeins. It is soluble in 70-95% ethanol. Beta is soluble in 60% ethanol and insoluble in 95% ethanol and Gamma is soluble in ethanol by a reducing agent.

Commercial zeins have poor water solubility but have a solubility in aqueous ethanol, acetone and alkaline (pH greater than or equal to 11.5) solutions. Zein has a film-forming property, where the films are tough and brittle. Among vegetables, zein can form the strongest fiber. Zein from Corn is a safe and non-toxic and approved for oral use by the FDA. Zein Nano-fibers can be efficient vehicles for sustained and controlled release. However, the risks of zein nanomaterials are yet to be studied and documented.

Other polymers include Polyvinyl alcohol (PVA), Gelatin, silk fibrin, Collagen, Polyglycolide (PGA), Polystyrene (PS), etc. With the world moving towards natural polymers and excipients because of several reasons such as ease of availability, cost-effectiveness, biocompatibility and biodegradable nature, research on nanofiber derived from polymers of natural origin has great scope [9].

3.3 Applications of Nanofibers in Anticancer drug delivery

3.3.1 Drug Delivery

Localized delivery of a drug to the target site is possible using nanofibrous implants. The conventional chemotherapeutic practice has side effects. Healthy living cells fall victim to toxicity alongside tumour cells. Nanofiber based mats on being implanted on cancer site can bring about selective localization of a drug to the target site, eliminating the adversities seen in case of conventional therapies. This will alleviate patient-centric discomfort. Many researchers have performed studies on developing nanofiber implants to be used as preventive therapy for tumour recurrence post-surgery. Yuan et al. incorporated doxorubicin in mesoporous silica nanoparticle composite Poly-L-Lactic acid (PLLA) nanofibers. Herein, the drug entrapped within mesoporous silica nanoparticles is first released at solution state followed by its release from the polymeric fibers to the surrounding medium. The authors discussed the ability of mesoporous silica nanoparticles to enhance dissolution of hydrophobic drugs, which is attributed to high surface area and their phase maintenance of amorphous drugs [10]. Ma et al. incorporated Paclitaxel in porous nanofibers of a blend of Polyethylene oxide and chitosan for prostate cancer. [11] Guo et al. and Sridhar et al. developed nanofibers of curcumin, another anticancer agent from the natural origin [12,13].

Koyakutty et al. developed temozolomide loaded PLGA/PLA/PCL based mats for the treatment of recurrent glioma. The release rate of the drug from the implant in rat glioma was found to be 116.6 µg/day with leakage into peripheral blood being less than 100 ng. The implants showing one month release profile resulted in the survival of 85.7% animals for more than 4 months. However, the implant showing one week release profile resulted in tumour recurrence in 54.6% of animals, leading to a survival of 74 days [14]. Nanofibrous implants can impart sustained and controlled release of the drug.

3.3.2 Multidrug delivery

Many researchers have designed Nanofibrous mats keeping in mind, multi-drug delivery. Combination of two or more drugs is considered essential for chemotherapy, as these combinations may show synergism and avoid resistance which may otherwise develop in monotherapy. Chen et al. reported PLGA based nanocarrier composite nanofibers of Doxorubicin and Hydroxycamptothecin. The amounts loaded were 0.045 mg/100 mg and 0.08 mg/100 mg respectively. The two drugs exhibited synergism in inhibiting HeLa cells in vitro [15]. Chen et al. combined Doxorubicin with the antiphlogistic drug indomethacin and an imaging agent NaGdF4:Yb/Er@NaGdF4:Yb. Nanofiber was prepared by incorporating NaGdF4:Yb/Er@NaGdF4:Yb@mSiO2-polyethylene glycol nanoparticles and doxorubicin into poly(ε-caprolactone) and combining this with indomethacin which is loaded into Gelatin, via electrospinning [16]. Zhang et al. developed Poly-L-lactidenanofibers enclosing Dichloroacetate and oxaliplatin for cervical cancer and tested it on Kunming mice [17].

Research is being led in the direction of Concomitant delivery of drugs, imaging agents and genes. Theranostic applications can be served by incorporating agents that serve the dual purpose of therapeutic activity and imaging, using nanofibrous systems.

3.3.3 Release from nanofibers

Drugs incorporated within nanofibers release via the process of diffusion [1]. There are diverse mechanisms for drug release from nanofibers.

3.3.4 pH-responsive release

The pH-responsive release has been explored to treat colorectal cancer, cancer of gastrointestinal tract, etc. Some polymers show pH-dependent solubility that may allow the release of the formulation in a particular portion of the gastrointestinal tract. Illangakoon et al. designed fibers of eudragit S100 containing 5-fluorouracil, a drug of choice for colorectal, breast, ovarian and gastrointestinal tract cancers. There was a high rate of release of the drug at a pH of 1 owing to its high solubility in acidic conditions, as 5-fluorouracil is basic. Further, it was presumed that the drug release occurred through pores on the shell. The fibers showed two-stage release, where authors predicted in vivo yield of some amount of release in the stomach and more subsequently lower in the GI tract [18]. Aguilar et al. developed pH-responsive polyurethane eudragit L100-55 composite nanofibrous system for paclitaxel to be used as a duodenal stent. The release profile showed higher release at pH 6 than at pH 4, which had no more than 4% of release rate. [19] As per a report, electrospun polyethylene oxide/chitosan/graphene oxide nano-composite nanofiber scaffold released doxorubicin at pH 5.3 and pH 7.4, with faster drug release at former pH due to unstable hydrogen bond interactions between graphene oxide and drug in acidic conditions [20]. Wu et al. developed injectable and pH-responsive silk nanofibrous hydrogels for sustained delivery of doxorubicin for breast cancer. Silk is a biocompatible material. Localized therapy was achieved using silk hydrogels with thixotropic capacities that permitted syringeability and in situ solidification. The system showed 8-week pH and concentration-dependent release. The authors report pH-dependent drug release exhibiting most rapid release at pH 4.5 and the slowest from pH 7 [21]. This type of response can enable the delivery of drug candidates that otherwise have a susceptibility to acidic conditions of the stomach when they are delivered through conventional techniques. Polymers that degrade due to actions of colonic microflora and their enzymes, can also be tested as materials for such nanofibrous systems to cause the release of the drug.

3.3.5 Thermoresponsive release

Thermoresponsive systems release the drug by responding to temperature conditions. *Slemming-adamsen et al* reported use of Poly (N-isopropylacrylamide (PNIPAM), a widely studied thermoresponsive polymer, that undergoes a sharp transition from a hydrophilic state to a hydrophobic state at the lower critical solution temperature. PNIPAMabd gelatin was crosslinked using a combination of N-hydroxysuccinimide (NHS) and 1- ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC). This crosslinked

polymeric system is capable of withstanding swelling and deswelling. The system encapsulated doxorubicin. The system showed burst release in the initial 10 minutes at both room temperature and 40ºC, and this is attributed to the release of surface molecules. However, the release over the next 5 days at 40°C was three times more than the release at room temperature [22]. Zhu et al. reported electrospun aqueous-based blend poly (N-isopropylacrylamide-co-acrylic acid) and regenerated silk fibroin (RSF) nanofibers which showed dual pH and temperature-dependent release. This system depicted behaviour characterized by swelling and shrinkage at different temperature and pH. The composite fibers were seen exhibiting such behaviour when the temperature is increased from 25°C to 40°C. The fibers exhibited hydrophilicity at room temperature and hydrophobicity at higher temperature showing a contact angle of 100.3ºC or 70.0ºC. The fibers exhibited swelling behaviour when pH conditions were altered from 5.7 to 6.6. When there is a rise in temperature to 40ºC, hydrogen bonds between P(NIPAAm-co-AAc) chains (–COOH with –COOH, –COOH with –NHCO, –NHCO with –NHCO) increase. This leads to shrinkage of fibers, squeezing out the material incorporated within. A further increase in temperature to 60ºC leads to an increase in the hydrogen bonding, increasing the release [23]. Che et al described thermoresponsive biodegradable branched caprolactone macro monomeric fibers for concomitant delivery of gene and drug for liver cancer therapy. The drug candidate was paclitaxel and it was encapsulated within the fibers. Further, miRNA-145 was the therapeutic gene candidate that was complexed with nanoparticles of disulfide cross-linked branched polyethyleneimine and coated on the paclitaxel loaded nanofiber [24].

3.3.6 Magnetic-heat composite release

Magnetic nanoparticles have gained widespread interest in cancer treatment, especially, with substantial research on Iron oxide nanoparticles. These nanoparticles, however, hold various limitations such as poor tumour targeting, poor uptake by the tumour, its leakage from dead cancer cells into the surrounding, killing the healthy viable cells as well. As per a report [25], researchers developed electrospun polystyrene nanofibers with high loading capacity, in which these magnetic nanoparticles had been loaded. Due to this high loading capacity, the fiber enables substantial heating of the environment when an alternating magnetic field is applied. This heat generated is called magnetic hyperthermia, and is attributed to the magnetic properties of iron oxide nanoparticles. The fiber does not lose its heating capacity on repeated heating, and at the same time, does not cause the release of iron oxide nanoparticles. Cancer cells when heated undergo inactivation and death. The researchers functionalized the fiber surface with collagen. It was observed that the human SKOV-3 ovarian cancer cells attached well to the fibers and on the application of alternating magnetic field for about 10 minutes, all of these cancer cells were killed. The magnetic field-driven heating served to be a better alternative for the use of a warm water bath. These fibers can be localized at the required site in the body by Magnetic Resonance Imaging.

Some researchers [26] developed a smart hyperthermia nanofiber with which simultaneous heat generation and drug release are attainable. The system enables the on-off switching mechanism for alternating magnetic field generation to achieve skin cancer apoptosis.

The polymer used for developing nanofiber was chemically cross-linkable and temperature-responsive. The fiber was loaded with doxorubicin and magnetic nanoparticles (MNPs).

This chemical crosslinking enables switchable changes in the swelling ratio as a response to the alternating magnetic field, as the heat generated from the magnetic nanoparticles induces the deswelling of polymeric networks in the nanofiber. The release of DOX from the nanofibers is eventually observed. About 70% of human melanoma cells died in only 5 minutes of application of alternating magnetic field in the presence of the magnetic nanoparticles and drug incorporated within the nanofibers, by combined effects of heat and drug. It thus becomes a system enabling manipulation of hyperthermia and associated drug release. Induction of apoptosis is attributed to the synergistic effect of chemotherapy and hyperthermia.

Similarly, a study was performed [27], to assess the potential of doxorubicin hydrochloride (DOX)-loaded electrospun chitosan/cobalt ferrite/titanium oxide nanofibers to exhibit hyperthermia as well as chemotherapy against melanoma cancer B16F10 cell lines. The synthesis of cobalt ferrite nanoparticles was achieved via microwave-assisted heating and the resulting nanoparticles were mixed with titanium oxide nanoparticles to have control over the temperature rise. This mixture along with doxorubicin was loaded into the chitosan nanofibers. The encapsulation efficiency of more than 95% is achievable for Doxorubicin in this system.

A temperature of 44.7°C is achieved 900 seconds after application of alternating magnetic field at a magnetic field strength of 1 kA m−1 and frequency of 290 kHz. Release of DOX from the nanofibers was observed at an acidic pH upon application of the field. The cytotoxicity of chitosan nanofibers was enhanced by simultaneous loading of DOX and cobalt ferrite/titanium oxide nanoparticles into the nanofibers after the application of a magnetic field.

Table – 1: Recent Developments associated with Nanofibers and their applications in Cancer Research

Sr no.	Anticancer Drug	Polymer	Type of Nanofibre	Treatment conditions	Type of cancer it is used for	Type of animal used	Authors' name	Year
1	Docetaxel	Polyvinyl Alcohol	Mucoadhesive, controlled release.	Local	Buccal Cancer	In vitro	Singh et al.	2015 [31]
2	Doxorubicin and Hydroxy-camptothecin	poly (lactic-*co*-glycolic acid) (PLGA)	sustained and controlled release nanocarrier composite nanofibres	Local; Tumor recurrence post-surgery	-	In vitro (HeLa cells)	Chen et al.	2014 [15]
3	Doxorubicin	poly (L-lactic acid) (PLLA)	Sustained release Mesoporous silica nanoparticle composite nanofibre	Local (Reducing High local recurrence rate in breast-conserving therapy.)	Breast Cancer	Female BALB/c mice	Yuan et al.	2016 [10]
4	5 - Fluorouracil	Eudragit S100	pH sensitive	Targeted delivery	Gastro-intestinal Cancer	In vitro	Illangakoon et al.	2015 [18]
5	Doxorubicin	Silk	Thixotropic nanofiber hydrogels with pH and concentration dependent release	Local	Breast Cancer	In vitro Human breast cancer cell line MDA-MB-231. In vivo - Breast tumors bearing BALB/c nude mice	Wu et al.	2016 [21]
6	Doxorubicin	poly (lactic-*co*-glycolic acid) (PLGA)	Drug-loaded multiwalled carbon nanotubes composite nanofiber; controlled release	Local; Post- operative local chemotherapy	-	In vitro	Qi et al.	2016 [28]
7	Doxorubicin	poly (lactic-*co*-glycolic acid) (PLGA)	Drug-loaded multiwalled carbon nanotubes composite nanofiber; sustained and prolonged release	Local; Preventing local cancer recurrence	-	In vitro (HeLa cells)	Yu et al.	2015 [29]
8	Anti-CA19-9 antibodies	Polyamide 6 and poly (allylamine hydrochloride)	Nanofibers of polyamide 6 and poly (allylamine hydrochloride) coated either with multiwalled carbon nanotubes (MWCNTs) or gold nanoparticles (AuNPs) immobilizing anti-CA19-9 antibodies	Diagnosis	Pancreatic Cancer (detection of biomarker CA19-9)	electrochemical impedance spectroscopy	Soares et al.	2017 [30]
9	Doxorubicin	Chitosan	chitosan/cobalt ferrite/titanium oxide magnetic nanofibers	Local using magnetic field	Melanoma	In vitro melanoma cancer B16F10 cell lines.	Radmansouri et al.	2018 [27]
10	Temozolomide	PCL-Diol-b-PU	PCL-Diol-b-PU/Au nanocompsite nanofibers Sustained release	Delivery to Brain	Glioblastoma tumors	In vitroU-87 MG human glioblastoma cells	Mohammad Irani, Gity Mir Mohamad Sadeghi, Ismaeil Haririan.	2017 [33]
11	Doxorubicin	Copolymer of NIPAAm and N -hydroxymethylacrylamide (HMAAm) (poly(NIPAAm- co - HMAAm)).	Magnetic nanoparticle composite crosslinked Copolymer of NIPAAm and N -hydroxymethylacrylamide (HMAAm) (poly (NIPAAm- co - HMAAm)).	Induction of apoptosis by on-off mechanism (heat generation by magnetic field). The System can be incorporated at	Skin Cancer	In vitro human melanoma cell line COLO 679 cells	Young-Jin Kim, Mitsuhiro Ebara, and Takao Aoyagi	2013 [26]

				tumor site during surgery.				
12	Curcumin	Nap-GFFYG-RGD (p-RGD) and NapGFFYG-RGE (p-RGE)	Self-assembling Peptide Nanofiber Sustained release	Hydrophobic drug delivery for targeted treatment of cancer	Liver Cancer	In vitro αvβ3 integrin positive HepG2 liver carcinoma cells and NIH3T3. Animal studies- BALB/c mice male.	Liu et al.	2013 [32]
13	-	Polystyrene	Iron Oxide composite nanofibers functionalized with collagen	Localized therapy using MRI. Association of Cancer cells to fibers. Induction of hyperthermia using an alternating magnetic field for 10 minutes to kill associated cancer cells.	-	In vitro human SKOV-3 ovarian cancer cells	Huang et al.	2012 [25]
14	Doxorubicin	PEO/chitosan/graphene oxide	PEO/chitosan/graphene oxide nanocomposite nanofibrous scaffolds, pH sensitive controlled release	Targeted Drug delivery	Lung Cancer	In vitro A549 cells	Ardeshirzadeh et al.	2015 [20]
15	Paclitaxel	chitosan/polyethylene oxide (PEO)	Porous Nanofibres	Postoperative Chemotherapy	Prostate Cancer	In vitro DU145 prostate cancer cells	Ma et al.	2011 [11]
16	Doxorubicin and Indomethacin	poly(ε-caprolactone) (PCL) and gelatin	Implantable NaGdF4: Yb/Er@NaGdF4:Yb@mSiO2- PEG nanoparticles loaded with antitumor drug doxorubicin incorporated into antiphlogistic drug indomethacin (MC)-loaded poly(ε-caprolactone) (PCL) and gelatin, forming nanofibrous fabric (labeled as MC/UCNPS/DOX)	Localized. Surgically implanted at Tumor site	Un-resectable tumors or metastases cancer.	In vivo Kunming mice	Chen et al.	2014 [16]
17	Curcumin	poly(ε-caprolactone)-poly (ethylene glycol)-poly(ε-caprolactone)	PCEC nanofibers; Controlled release	Localized Implant for post-operative chemotherapy of brain cancers.	Brain cancer	In vitro Glioma 9L cells	Guo et al.	2011 [12]
18	Curcumin and natural extract	Polycaprolactone	Implantable Polycaprolactone nanofibers; sustained release	Implantable preparation/ stent/ localized medical device.	Lung and Breast Cancer	In vitro human breast cancer (MCF7) and lung cancer (A459) cell lines	Sridhar et al.	2014 [13]
19	Doxorubicin	poly (ethylene glycol)–poly(L-lactic acid) (PEG–PLA) diblock copolymer	Amphiphilic poly (ethylene glycol)–poly(L-lactic acid) (PEG–PLA) diblock copolymer nanofibers; forming 'core-sheath' structured drug-loaded nanofibers; three stage diffusion controlled release	Reservoir type delivery system for post-operative localized chemotherapy	-	In vitro	Xu et al.	2008 [34]
20	Daunorubicin	Polylactide	Nanocomposites of polylactide (PLA) nanofibers and tetraheptylammonium-capped Fe3O4 magnetic nanoparticles	Targeted Drug delivery	Leukemia	In vitro leukemia K562 cell lines	Lv at al.	2008 [35]
21	Doxorubicin	poly (L-lactide-co-D, L-lactide) (coPLA) and quaternized chitosan	Nanofibers of poly (L-lactide-co-D, L-lactide) (coPLA) containing quaternized chitosan	Localized therapy; Induction of tumor apoptosis	Breast Cancer	In vitro MCF-7 human breast carcinoma cell line	Ignatova et al.	2011 [36]
22	BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea)	poly (ethylene glycol)–poly (L-lactic acid) (PEG–PLLA) diblock copolymer	Implantable BCNU-loaded poly (ethylene glycol)–poly (L-lactic acid) (PEG–PLLA) diblock copolymer fibers; Controlled release	Localized; Implant for Postoperative chemotherapy	Glioma (Brain cancer)	In vitro rat Glioma C6 cells.	Xu et al.	2006 [37]
23	Doxorubicin	Poly (L-lactic acid)	Implantable Poly (L-lactic acid)/ mesoporous silica nanoparticles composite nanofibers; sustained release	Implants for Postsurgical cancer treatment	-	In vitro HeLa cells	Qiu et al.	2013 [38]
24	DCA and Oxaliplatin	Poly-L-lactide	Implantable time-programmed dual release Poly-L-lactide fibers	Localized therapy; Implant for local cancer treatment following resection	Cervical Cancer	In vivo KunMing mice	Zhang et al.	2016 [17]
25	Curcumin	poly L-lactide	PLLA nanofibres; Sustained release	-	-	In vitro C6 glioma cells and mouse	Thangaraju et al.	2012 [39]

						embryonic NIH 3T3 fibroblast cell lines		
26	Doxorubicin and camptothecin	ZnO/poly (lactic-co-glycolic acid)/gelatin	PLGA/gelatin composite nanofibers encapsulated with mesoporous ZnO nanospheres with decreased burst release.	Implant for treatment of tissue defect after tumor resection.	-	In vitro HepG-2 cells	Wei et al.	2014 [40]
27	Paclitaxel	PLGA	PLGA-based micro- and nanofibers, Sustained delivery	Implant	Brain tumour	In vitro C6 glioma	Xie et al.	2006 [41]
28	Doxorubicin	Polyvinyl alcohol/chitosan	Polyvinyl alcohol/chitosan (PVA/CS) core–shell nanofibers, controlled release	Scaffolding material	Ovary cancer	In vitro human ovary cancer cells (SKOV3)	Yan et al.	2014 [42]
29	Hydroxy-camptothecin	2-hydroxypropyl--cyclodextrin (HPCD) and PELA	Implantable 2-hydroxypropyl--cyclodextrin (HPCD)- poly (dl-lactic acid)-poly (ethylene glycol) (PELA) nanofiber	Intratumoral implantation for local therapy of solid tumours	Lung, prostate, breast, colon, stomach, and ovarian cancer	In vitro HepG2 cells In vivo Kunming mice	Luo et al.	2012 [43]
30	Paclitaxel and miRNA-145	Poly(Ɛ-caprolactone)	Temperature-responsive branched poly (Ɛ -caprolactone) (PCL) macro-monomeric nanofibers coated with Nanoparticles composed of disulfide cross-linked branched PEI (ssPEI) and anti-cancer therapeutic gene miRNA-145 were ; Sustained delivery	Local concomitant delivery of drug and gene	Liver Cancer	In vitro HuH-7 hepatocyte derived cellular carcinoma cell line	Che et al.	2015 [24]
31	Paclitaxel	Polyurethane and Eudragit L100-55	Polyurethane and Eudragit L100-55 composite pH dependent release	Duodenal stent	GI cancer	In vitro fibroblasts (NIH-3T3) cells	Aguilar et al.	2015 [19]
32	Doxorubicin	PNIPAM/gelatin	PNIPAM/gelatin thermoresponsive nanofibers In situ cross linked.	Localized multiple swelling and deswelling	Cervical cancer	In vitro human cervical cancer Hela cells.	Slemming-Adamsen et al.	2015 [22]
33	-	poly (N-isopropylacrylamide-co-acrylic acid) (P(NIPAAm-coAAc)) and regenerated silk fibroin (RSF)	Aqueous based blend poly (N-isopropylacrylamide-co-acrylic acid) (P(NIPAAm-coAAc)) and regenerated silk fibroin (RSF) dual pH and temperature responsive system.	-	-	In vitro	Zhu et al.	2020 [23]

4. CONCLUSION

Nanotechnology has attained considerable commercialization. Marketed formulations containing Nanostructured vehicles like liposomes and nanoparticles have been explored for delivery of drugs like Daunorubicin, Cytarabine, Doxorubicin, Vincristine, Mifamurtide, Leuprolide acetate and Paclitaxel. They come with plenty of advantages like sustained and controlled release and targeted delivery.

Nanofibers are effective nanosized drug delivery systems for anticancer therapy for localized treatment. These mats are effective implants for monotherapy, combination therapy as well as for concomitant delivery of drugs and imaging agent or genes. They have potential applications in the prevention of post-surgical cancer recurrence. There has been remarkable evidence of nanofibers showcasing their ability to deliver drugs for a variety of conditions, including but not limited to Brain tumours, cervical, gastrointestinal, liver, prostate, breast, and ovarian cancers. They possess high mechanical strength, large surface area to volume ratio, flexibility, interfiber porosity and adjustable morphology. Nanofibers can be developed by a number of methods such as Phase separation, flash-spinning, melt blowing, drawing, bicomponent spinning, force spinning and electrospinning. Electrospinning is the most widely used method which is driven by high electric voltage. A number of polymers have widespread utility for nanofiber production, including PLA, PLGA, Chitin, chitosan, zein and polycaprolactone all of which serve several biomedical applications such as in tissue engineering, developing nanofibrous implants, sutures and controlled drug release systems. The drug incorporated within nanofibers can be released at the cancer site through novel techniques that are stimulus-responsive for manipulated drug delivery, based upon the composition of the system. Polymers such as Eudragit, silk, polyethylene oxide/chitosan/graphene oxide nano-composite nanofibrous systems can offer pH-responsive release that is suitable for delivery of the drug via GIT and other similar sites. Incorporation of magnetic nanoparticles within the fibers offers generation

of hyperthermia, which can show synergism with the incorporated drug against the tumour. Thermoresponsive polymers can offer thermoresponsive release.

Nanocomposite systems confer the ability to modulate drug release. Systems like nanoparticles (drug-loaded) which suffer from poor circulation time, can be incorporated within nanofibrous mats. With many such unforeseen advantages and merits that this system holds, Nanofiber becomes a potential new nanotechnology driven system that enables patient-centric therapy for grave conditions like cancer.

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