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(54) **Title:** THE ART, METHOD,MANNER PROCESS AND SYSTEM OF FIBROUS BIO-DEGRADABLE POLYMERIC WAFERS FOR THE LOCAL DELIVERY OF THERAPEUTIC AGENTS IN COMBINATIONS

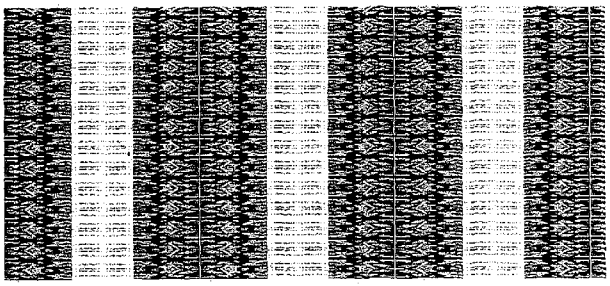

Figure 1: Schematic diagram showing microscopic structure, made of different polymer fibers loaded with different drugs separately.

(57) **Abstract:** The present invention is related to flexible, fibrous, biocompatible and biodegradable polymeric wafer consisting of more than one polymeric fibres, each one loaded with different therapeutic agents having mutually exclusive synergistic activity. The wafer is capable of delivering the drugs locally in to the deceased site like tumor, inflammation, wound etc in a controlled and sustained fashion for enhanced therapeutic effect. The combination of drugs loaded in the wafer is chosen in such a way that the second or consecutive drugs will enhance or improve the therapeutic effect of the first drug

WO 2013/124869 A2

1. TITLE OF THE INVENTION - ***"The art, method, manner, process and system of fibrous biodegradable polymeric wafers for the local delivery of therapeutic agents in combinations"***

PREAMBLE TO THE DESCRIPTION COMPLETE SPECIFICATION

The following specification describes the invention

The Invention relates to the -***"The art, method, manner, process and system of fibrous biodegradable polymeric wafers for the local delivery of therapeutic agents in combinations"***

ABSTRACT

The present invention is related to flexible, fibrous, biocompatible and biodegradable polymeric wafer consists of more than one polymeric fibers, each one loaded with different therapeutic agents having mutually exclusive synergistic activity. The wafer is capable of delivering the drugs locally in to the diseased site like tumor, inflammation, wound, etc in a controlled and sustained fashion for enhanced therapeutic effect. The combination of drugs loaded in the wafer is chosen in such a way that the second or consecutive drugs will enhance or improve the therapeutic effect of the first drug.

FIELD OF INVENTION

The present invention is related to fibrous, flexible, biodegradable and biocompatible polymeric wafers engineered using electrospinning or rotary jet -spinning techniques, intended for the delivery Of combination of therapeutic agents, for example anti-neoplastic drugs, locally to the diseased site in a controlled and sustained fashion. The wafers are made of electrospun or rotary jet-spun fibers Of fiber diameter averaging between 1Onm - 50000nm, with beaded or non-beaded, porous or non-porous, cylindrical or ribbon shaped, hollow or solid, aligned or non-aligned morphology. More specifically the wafer consists of two Or more kinds of electrospun fibers; each loaded with different drug molecules in such a way that the release kinetics of each fiber is optimal for the drugs loaded within and aids an optimal and combinatorial activity. The optimum release kinetics is achieved by using two different polymers or blend of polymers or polymers with different molecular weight or polymers that have altered monomer ratio. The polymeric fibers are made of simultaneous/sequential/co-spinning of single or multiple or cross-linked or blends of biodegradable polymers. Along with improving local bioavailability and sustained release of the drugs within, these drug delivery wafers can significantly reduce the systemic toxicities and associated adverse events.

BACKGROUND

Current methods for drug delivery have very limited utility because of their inability to deliver drugs locally to a specific organ or tissue in clinically significant doses. Most conventional drug delivery methods can only aid a small concentration of the drug to reaches the specific target location because of wide drug distribution, high plasma-protein binding, low bio-availability and short half life. Also most chemotherapeutics being hydrophobic in nature will tend to form aggregates and get cleared from the circulation very fast. Most of the anti-neoplastic agents need to be administered repeatedly in high systemic concentrations for effective therapy causing toxicities even to the normal cells. Most of these problems can be effectively addressed by using local drug delivery devices that will provide a sustained and controlled delivery of drugs delivery in desired fashion.

Local drug delivery is very important in case of highly isolated organs such as brain where blood brain barrier will act as an additional barrier. Central Nervous System tumors, for example Glioblastoma (GBM) are one of the important disease that require local drug delivery mostly. The standard of care therapy for GBM is surgical resection of the tumor followed by chemotherapy and/or radiation therapy. Complexity in complete tumor resection and limitations faced by supporting therapies make its cure very difficult and the median survival rate still remains less than 12 months. Despite the remarkable increase in the number of anti-cancer drugs discovered, chemotherapy for CNS tumors still phases apparent ineffectiveness due to unique environment of brain. Brain, being one of the most important as well as delicate organ, is protected by specialized mechanisms; and the important one being the Blood Brain Barrier (BBB). It significantly reduces the permeability of capillary walls to effectively block large molecules and peptides to get into the brain. In addition the blood cerebrospinal fluid barrier and blood tumor barrier also work to reduce the permeation of drug molecules into the brain. Hence molecules having very small size (<400Da) with electrically neutral and lipid soluble nature only can pass through it and most chemotherapeutic agents excludes from this category. Even in the case of small drug molecules which have limited permeability to BBB, achieving their clinically significant concentration locally in the tumor site for the effectiveness of chemotherapy necessitates administration of very high systemic doses. This can lead to systemic toxicities and other adverse drug events, necessitating dosage limitations ultimately causing treatment failure. Most of the potent chemotherapeutic drugs like DNA alkylating/intercalating agents, anti-angiogenic agents, cytokines, small molecule inhibitors, DNA alkylating agents etc., fall on this category.

In order to circumvent these problems regarding brain drug delivery, various strategies have been developed by the researchers, like changing the drug design for increased permeability, disrupting the BBB temporarily, localized drug delivery etc. In these methods, local drug delivery using biocompatible polymeric devices or microchips is one of the most important therapeutic strategies that shows promising outcome in cancer management. Gliadel® turned into the first locally implantable polymeric drug delivery device approved by FDA. Gliadel® is made of pCPP-SA (poly[bis(p-carboxyphenoxy)propane-co-sebacic acid] polymer incorporating 3.8% wt/wt carmustine (BCNU; 1,3-bis(2-chloroethyl)- 1-nitroso-urea) and provides an effect means of its direct delivery. These devices are implanted into the cavity resulting from the surgical resection of the tumor. Gliadel thus can provide sustained release of BCNU approximately up to 3 weeks and has shown its effectiveness to improve the patient survival significantly. This local chemotherapy can be used along with other conventional therapies like radio-therapy without causing any limitations to them. Although Gliadel® therapy provides benefits to cancer management; they possess limitations due to their extreme brittle nature, handling difficulties and inability to provide extended sustained release.

Recent studies also prove that tumors develop different mechanisms for drug efflux, ROS scavenging, DNA repair etc to prevent or overcome the damage caused by chemotherapy. In order to avoid these limitations combinatorial therapeutic approaches were introduced, which combine conventional chemotherapeutic agents with drugs that inhibits the cell's drug resistance mechanisms. For example Temozolomide, a potent chemo-drug, acts by alkylating DNA bases mostly in 0 6 position of guanine residue. These altered bases will cause miss-pairing during DNA replication leads DNA repair associated cell death. But, cancer cells (eg., glioma) over express MGMT protein that can remove these alkyl groups and helps the cells for survival. A clinically accepted combination therapy to such cancer uses 06-Benzyl guanine, a substrate analogue, that irreversibly inhibit MGMT enzyme and thereby making the cells sensitive to temozolomide. Success of such combinatorial approach primarily depends on achieving clinically significant concentrations of both drugs locally in the tumor site in a desired fashion. For example, in this case the therapy will be highly efficient if 06-BG is applied just before TMZ administration. Also temozolomide, being very short-lived (half life is 1.8 hrs) in physiological conditions, should be administered repeatedly in high doses for desired treatment effect causes signi ficant systemic toxicities and related adverse drug-effects.

This can be overcome by delivering these drugs locally in the tumor site using drug delivery wafers. Success of such a drug delivery device depends on many factors including stability of the drugs loaded, drug-loading efficiency, achieving sustained release with desirable release kinetics etc. Gliadel® like device made of simple incorporation of these drugs cannot achieve these properties necessary for the combinatorial treatment approach. Also clinicians face difficulty with their highly-brittle and non-flexible nature. These factors demand a flexible device that can deliver the combination of drugs in derided and sustained fashion for optimal treatment efficacy. The emerging field of nanotechnology offer great promise for such drug delivery applications. For example, in the above mentioned case, the optimum drug deliverys can be achieved by electrospun/rotary jet-spun wafers with flexible nature and tenable degradation kinetics.

PRIOR ART

Even though many local drug delivery (or drug eluting) devices have been developed world wide to treat diseases like cancers especially brain cancers, there exist a very few devices made of biodegradable polymers giving a sustained drug release. One of such important FDA approved drug delivery device is Gliadel®. Gliadel® is used for treating recurrent and advanced forms GBM by delivering DNA intercalating agent Carmustine, a nitrosourea. These devices are made by mixing the drug (3.8% wt/wt) with pCPP-SA polymers and making discs by applying pressure pelletizing and aid release up to 3 weeks. Even though Gliadel® improves the survival of the GBM patients, it possesses disadvantages regarding low drug release period, brittle and delicate nature and resulting difficulties in surgical implantations. One of such another polymeric drug delivery device is DC bead®. It is produced from biocompatible polyvinyl alcohol (PVA) hydrogel that has been modified with sulphonate groups for the controlled loading and delivery of chemotherapeutic drugs and in trans-arterial chemoembolisation. They occludes the blood flow to the target tissue and delivers a local and sustained dose of the loaded drug (e.g. Doxorubicin, irinotican etc.) direct to the tumor.

US patent No. 5846565 is directed to biodegradable polymeric drug delivery devices consists of reservoirs which release drugs for extended period while at the same time preserving the bioactivity and bioavailability of the agent. US patent No. 0 192487 is directed to a system and related method for delivering the anti-tumoral agent cannustine or other types of diagnostic or therapeutic agents into the brain of a patient with a brain tumor includes an insertion device, a skull mount, and a refonnulated geometry of the carmustine compound (or other material) optimized for use in the insertion device and for maximized biodegradation time.

Electrospinning has shown effective for loading a therapeutic substance in a polymeric matrix for creating micron-scale drug delivery systems. US. Pat. No. 7,7 12,765 is directed to a drug-containing polymeric membrane wherein the active drugt is an antibiotic. The system is used to lessen the risk of post surgical infections. However, there is no teaching or suggestion of using anti-neoplastic agents to a non-woven nanozied polyester matrix. US patent No. 030388 l is directed to electrospun fiber compositions comprising one or more polymers and one or more nerve growth factors on the surface of elctrospun film, or a tube. US patent No. 027684 l is directed to biodegradable drug eluting polymer threads or fibers of solid or hollow kind loaded with single or multiple therapeutic agents giving sustained-release of the therapeutic agent on implantation in patients. It is also said that the fibers may be coated to carry another drug. US patent 038936 is directed to a drug delivery systems characterized by an electrospun biodegradable resorbable polymeric fiber matrix with at least one therapeutic agent incorporated into the fibers and applying it for delivering a chemotherapeutic agent to body cavities from which a tumor has been excised and for strengthening weakened blood vessel walls. US patent No. 029 1182 is also directed to locally implantable drug delivery device consists of drug loaded fibers wherein the drugs are in their particulate form. Also the first and second drug is loaded in the inner rad ial portion and outer radial portion of the same fibers. Us Patent No. 0 166854 is directed to elctrospun matrices for delivery of hydrophilic and lipophilic compounds, describes simultaneous spinning of up to six different polymers.

US patent No. 7374774 is directed to electroprocessed material made by simultaneously electroprocessing a natural protein polymer and two synthetic polymers. The invention is directed to novel compositions consist of an electroprocessed material and a substance, their formation and use. The electroprocessed material can, for example, be one or more natural materials, one or more synthetic materials, or a combination thereof and is used for the delivery of single or multiple substance like therapeutic or cosmetic substances or other compounds, molecules, cells, vesicles within an organism. US patent No 0009949 is directed to a stent scaffolding composed of a plurality of fibrous structural elements, wherein the fibrous structural elements are composed of a network of polymer fibers, wherein the fibrous structural elements include particles that are encapsulated within the fibers, partially encapsulated within the fibers, and entrapped between the fibers of the fibrous layer.

Even though various local drug delivery devices were prepared and studied by the researchers worldwide, there is only little literature available which deals with drug delivery using electrospun or rotary jet-spinning method. Also, most of the literature deals with delivery of a single chemotherapeutic agent. Liao et al have studied the Preparation, characterization, and encapsulation/release studies of a composite nanofiber mat electrospun from an emulsion containing PLGA. Ranganath et al have studied Paclitaxel-loading in biodegradable electrospun polymeric implants in the form of microfiber discs and sheets and investigated its efficiency against malignant glioma. They fabricated wafers of PLGA fibers having submicron size diameter loaded with pacletaxel. Xie et al also studied pacletaxel loading in electrospun PLGA fibers and its effects on C6 Glioma both ***in vitro*** and ***in vivo.*** He also studied PLA/PLGA electrospun fibers for local delivery of cisplatin.

Even though biodegradable polymeric fibrous or elctrospun devices were used in few of the prior arts for localized delivery of single or multiple therapeutic agents, fibrous wafers made up of two different kinds of polymeric fibers loaded separately with two different drugs capable of releasing the two in a controlled and sustained fashion for $\geq$1 month for enhanced combinatorial approach are not reported. Furthermore, in our method, the polymers and solvent used are chosen critically for the optimal loading, stability, sustained release of the encapsulated molecules and required release kinetics for combinatorial chemotherapy.

Accordingly, there exist no prior art on the preparation and use of flexible, handy, fibrous, biodegradable and biocompatible polymeric wafers consists of more than one type of polymeric libers, each loaded separately with different therapeutic agent aiding combination therapy and also capable of delivering the drug in a controlled and sustained fashion for ≥ one week and up to many months, locally in to or to the vicinity of the diseased area or tissue for local drug delivery applications. Even in prior arts detailing drug delivery wafers with two or more different polymer fibers loaded with drugs, there exist no suggestion obtaining the optimum release kinetics needed for the combination therapy, also there is no suggestion in criteria for choosing the drug-combinations for synergistic therapeutic effects because of mutually exclusive activity.

SUMMARY OF THE INVENTION

The present invention is regarding a flexible, biodegradable and biocompatible fibrous wafer made up of at least two different kinds of polymeric fibers and each loaded separately with different therapeutic agents for local combination drug delivery. These different kinds of polymeric fibers can provide optimum release kinetics needed for the combinatorial action of therapeutic drug loaded within. This fibrous wafer can be implanted in to tissue resected cavity or in the vicinity of the diseased tissue to provide a sustained and controlled release of the drug ≥ one week. In some specific cases drug resistance of cancer, the drugs loaded in the different polymer fibers are chosen in such a way that the second drug will improve effectiveness of the first drug either by enhancing the cytotoxic effect of the first drug or by inhibiting the pathways or molecules responsible for the cells resistance against first drug. This unique locally implantable polymeric wafer can improve conventional therapy by providing clinically significant doses of drugs in the diseased site such as cancer, inflammation, wounds, autoimmune disease, surgically resected areas, etc by aiding sustained and controlled release of the drug.

DEFENITIONS

The term "**polymeric fibers**" as used herein refers to that fibers formed electrospraying or rotary jet-spinning of polymer solution , measuring diameter about 10nm-50,000 nm, preferably 10 -1OOOnm, most preferably around 1-250 nm in **size.**

The terms "**biodegradable**." refers to the degradation or disassembly of **a** polymer by action of a biological environment **by the way** of linkage breakdown **by** mechanisms such as hydrolysis, enzyme, pH or temperature degradation.

The term **"loading"** as used herein refers to uniform or non uniform incorporation of monomeric or aggregated forms of the therapeutic agent inside or outside or throughout or though the surface of the polymer fibers.

The term "**chemotherapeutic agent**" or "**chemo-drug**" or "**drug**" or "**therapeutic agent**" as used herein are similar and refers to compound or molecule which produces a beneficial or useful for cancer treatment.

The terms "**controlled release**", "**sustained release**" and similar terms are used to denote a mode of delivery of the therapeutic agent that occurs when the agent is released from the polymeric wafer at an ascertainable and manipulatable rate over a period of time, rather than dispersed immediately upon application. Controlled or sustained release **may** extend for hours, days or months, and may vary as a function of numerous factors. In the present **invention,** the important determinant of the rate of delivery is the rate of hydrolysis of the linkages **between and** within the **units** of **the** polymer. The rate of hydrolysis in turn may **be** controlled by the factors like the composistion of the wafer, polymer used, its molecular weight, monomer ratios, hydrophilicity, **fiber** diameter, **presence** and **absence of** beads, fiber porosity **etc.** Other factors include implant **size,** length of **the electro spun fibers, acidity of the** medium, solubility **of** the active agent in the matrix, molecular weight and **charge density of the active agent.**

The term mutually exclusive synergistic activity means the therapeutic effect by the combination of drugs are enhanced or much better than that of individual drugs as the activity of one drug helps to improve the effect of another drug .

FIG URE CAPTIONS:

Figure I: Schematic diagram showing microscopic structure, made of different polymer fibers loaded with different drugs separately.
Figure 2: Schematic showing different steps involved in wafer making through electrospinning method
Figure 3: SEM images showing different morphology of polymeric fibers obtained electrospinning technique
Figure 4: SEM image showing microscopic fiber morphology of TMZ and 06-BG co-loaded PLA-PLGA/PLGA wafer.
Figure 5: EDS mapping results showing uniform distribution of drugs throughout polymeric fibers
Figure 6: FTIR results showing interaction of TMZ with PLA-PLGA blend polymeric matrix
Figure 7: Graph showing near - zero order temozolomide release shown drug loaded wafer.
Figure 8:1 Graph showing near - zero order 06-Benzylguanine release shown drug loaded wafer.
Figure 9: Cell attachment studies of bare and drug-loaded wafers showing effective inhibition of cell attachment and proliferation by the drug loaded wafers.
Figure 10: *In vitro* live-dead assay results showing effective cell growth inhibition by the drug loaded wafers. Cells were seen live and attached (in green fluorescence, due to esterase activity) in the bare wafers (Upper panel) where as no cells were attached onto drug-loaded wafers (Down panel).

DETAILED DESCRIPTIONS OF THE INVENTIONS

The main features of the inventive drug delivery wafer are the flexibility, easy handling, biodegradability, biocompatibility and tunable drug release kinetic making it capable for local-combinatorial drug delivery. As the wafer is intended for the combinatorial delivery of two or more chemotherapeutic agents, achieving release kinetics optimal for each drug for its maximal effectiveness is very important. In most combination therapies the respective therapeutic agents are administered sequentially. For example combination chemotherapy for glioma with Temozolomide and 0 6 Benzylguanine necessitated prior administration of 0 6 BG before TMZ for its optimal effect. Also, temozolomide being very short lived with a half life of 1.8hrs in physiological conditions necessitated repeated administration. Existence of blood brain barrier also necessitates administration of high systemic doses for achieving clinically significant drug concentration in the tumor site. These will ultimately results in systemic toxicities and other related adverse drug events. But this combination chemotherapy can be achieved by local delivery of therapeutic agents through sustained release drug delivery devices with tunable drug release kinetics. Electrospinning and rotary jet-spinning, are two versatile techniques yielding flexible wafres of polymeric fibers, can be used for

In a preferred embodiment of the said method the combinatorial therapeutic effect is achieved by combining a conventional chemotherapeutic agent along with a supporting drug, which enhances the toxicity either by enhancing the cytotoxicity of the conventional drug or by inhibiting the molecular mechanisms and molecules responsible for the resistance against first drug by the cells. In such a local delivery approach using electrospun or rotary jet-spun wafer, the conventional chemotherapeutic agent is loaded in one type of polymeric fiber and the supporting drug will be loaded in second type of polymeric fibers.

In a proffered embodiment of the said method in which, the enhanced cytotoxic effect is achieved by combining Temozolomide and 06Benzyl guanine wherein 06BG (an MGMT inhibitor) is loaded in the fibers having faster degradation and faster release kinetics and TMZ is loaded in fibers with comparatively slow degradation and release kinetics. Hence, these wafers will release TMZ onto MGMT inhibited cells for better therapeutic effect.

In yet another embodiment of the said method, the effective combination therapy is achieved by delivering a DNA intercalating agent (Eg., Carmustine) along with its drug resistance inhibitors like AGT inhibitor, PARP inhibitor etc.

In a preferred embodiment of the said wafer wherein the fist polymer fiber is prepared using a single/multiple/cross-linked/or blended polymers chosen from the group containing poly glycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), glycolide/trimethylene carbonate copolymers (PGA/TMC); poly-lactides (PLA), poly-L-lactide (PLLA), Poly-DL-Iactide (PDLLA), L-lactide/DL-lactide copolymers; lactide/tetramethyl-glycolide copolymers, poly-caprolactone (PCL), poly-valerolacton(PVL), poly-hydroxy butyrate (PHB), poly vinyl alcohol (PVA) poly-hydroxy valerate(PHV), polyvinylpyrrolidone (PVP), Polyethyleneimine (PEI) and lactide/trimethylene carbonate copolymers, chitosan, carboxymethyl chitosan, chitin, pollulan, etc., or blends thereof.

In a preferred embodiment of the said wafer wherein the first polymer fiber is loaded with a drug chosen from the following group containing paclitaxel, rapamycin, cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, cisplatin, hydroxyurea, leucovorin calcium, tamoxifen, flutamide, asparaginase, altretamine, mitotane, procarbazine hydrochloride, mechlorethamine, thioguanine, carmustine, lomustine, temozolomide, melphalan, chlorambucil, streptozocin, methotrexate, vincristine, bleomycin, vinblastine, vindesine, dactinomycin, 6-MP, daunorubicin, Lenalidomide, L-asparginase, doxorubicin, tamoxifen etc

In a preferred embodiment of the said wafer wherein the second polymer fiber is prepared using a single/multiple/cross-linked/or blended polymers chosen from the group containing poly glycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), glycolide/trimethylene carbonate copolymers (PGA/TMC); poly-lactides (PLA), poly-L-lactide (PLLA), Poly-DL-Iactide (PDLLA), L-lactide/DL-lactide copolymers; lactide/tetramethyl-glycolide copolymers, poly-caprolactone (PCL), poly-valerolacton(PVL), poly-hydroxy butyrate (PHB), poly vinyl alcohol (PVA) poly-hydroxy valerate(PHV), polyvinylpyrrolidone (PVP), Polyethyleneimine (PEI) and lactide/trimethylene carbonate copolymers, chitosan, carboxymethyl chitosan, chitin, pollulan, etc., or blends thereof.

In a preferred embodiment of the said wafer wherein the second polymer fiber is loaded with a drug chosen from the following group containing MGMT or AGT inhibitors like 06-Benzyl guanine, cell cycle/check point inhibitors like polo-like kinase (PLK) inhibitor (e.g. volasertib), cyclin dependent kinase (CDK) inhibitors (e.g. seliciclib, indirubin etc.,), topoisomerase inhibitors (e.g. adriamycin, camptothecin, etoposide, idarubicin, irinotecan, topotecan, mitoxantrone etc.,), microtubule inhibitors (e.g. docetaxel, vincristine etc.,), antimetabolites (e.g. decitabine, gemcitabine, fludarabine etc.,), telomerase inhibitors, DNA & RNA replication inhibitors (e.g. clarithromycin, cytarabine, mitoxantrone HC1 etc.,) dihydrofolate reductase inhibitor, HDAC inhibitor, Bcl-2 and TNF-a inhibitors, PARP inhibitors, MAPK inhibitors, PI3K/Akt/mTOR inhibitors, integrase and protease inhibitors, Wnt/Hedgehog/Notch inhibitors, cAMP, lipide signaling inhibitors (e.g. PKC, PIM etc.,), TGF-β inhibitors, tyrosine kinase inhibitors such as epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, platelet derived growth factor receptor (PDGFR) inhibitors, fibroblast growth factor receptor (FGFR) inhibitors, Rous sarcoma

oncogene/Breakpoint cluster region/Abl (Src-bcr-abl) inhibitors, Insulin-like growth factor 1 receptor (IGF-1R) inhibitors, FLT-3, HER-2, STAT5, c-Kit, c-Met, ALK, ETA receptor inhibitor, HIF inhibitor, Syk inhibitor, Tie2 kinase inhibitor and the like), Vascular disrupting agents (e.g. plinabulin), antioxidant inhibitors like diethyl-dithiocarbamate, methoxyestradiol, 1-buthionine sulfoximine, 3-amino-1,2,4-triazole and the combinations thereof.

In a preferred embodiment of the said wafer wherein the optimum release kinetics needed for each drug is achieved by loading them in separate polymeric fibers having different degradation kinetics.

In a preferred embodiment of the said wafer wherein the different degradation kinetics for each kind of fibers is achieved by using polymers or polymer blend with differed degradation or by using same polymers with different molecular weight or by using same polymers with altered monomer ratio. For example PLGA (85:15) will have extended degradation than that of PLGA (50:50). Also a polymer with higher molecular weight will degrade slow compared to same polymer with a lower molecular weight. The degradation of polymers will depend on factors such as the rate of hydrolysis of the linkages between and within the units of the polymer. The rate of hydrolysis in turn may be controlled by the factors like the composistion of the wafer, polymer used, its molecular weight, monomer ratios, hydrophil icity, fiber diameter, presence and absence of beads, fiber porosity etc. Other factors include implant size, length of the electro spun fibers, acidity of the medium, solubility of the active agent in the matrix, molecular weight and charge density of the active agent.

In a preferred embodiment of said fibrous wafer, the polymer fibers are formed by a preferred method chosen from electrospinning or rotary jet spinning in co-spinning, sequential spinning , simultaneous spinning fashion as specified for the optimal release of the incorporated drugs.

Fig. 1 refers to the schematic diagram showing internal microscopic structure and alignment of polymeric fibers in an electrospun wafer. The wafer will be made up of two different kinds of polymers, each loaded with different drugs, separately. The two polymers are chosen in such a way that the polymers should have different degradation nature to provide optimum release kinetics for the drugs loaded within.

Referring to the schematic given in Fig. 2, for the preparation of flexible and biodegradable fibrous wafer, in step-l, polymer solution-I containing drug-I (e.g., PLGA (85:15)/PLA blend containing 20 % wt/wt TMZ) and polymer solution-II containing drug-II (e.g., PLGA(50:50) containing 10% wt/wt 06-BG) are co-electrospun to yield polymeric wafers. The electrospun polymeric wafers thus formed are then lyophilized for 96 hrs to remove any residual solvent in it. The lyophilized wafers are then processed in aseptic conditions for desired shape and quantity.

Fig. 3. refers to some of different type of polymer fiber morphology that can be obtained during electrospinning or rotary-jet spinning. The morphology can be threadlike, plain, ribbon type, beaded, porous etc. These fiber morphology will have profound effect on the drug release kinetics. For example, porous fibers will provide a burst and fast drug release as the porous nature will aid more solvent diffusion into the wafer and also by providing more surface area for drug elution.

In relation to the above method of preparing embodiment, the polymeric fibers showed an average diameter of ~2μιτι as shown in figure 4. The fiber diameter can be varied from 10nm to 50,000 nm depending on the polymer concentration, solvent, applied voltage, tip-target distance etc in the case of electrospun wafers.

In yet another aspect of the above mentioned embodiment, the polymer fibers have shown uniform distribution of drugs throughout the fibers (Fig. 5). Uniform drug distribution is considered very important for controlled drug release. Existence of drug molecules as aggregates in fibers in a non-uniform nature will cause un-co(itrolled drug release behavior

The e!ectrospray was carried out. under ambient temperature, pressure **and** 55±5% humidity, by applying a potential of between 10-15 KV using a high voltage supply. The electrospun wafers were collected carefully **and** lyophilized for 96hrs to remove any residual solvent and stored at low temperature, away from light **and** humidity.

Example 2: PLA:PLGA-PLGA electrospun wafer loaded with Carmustine and 06-Benzylguanine: Sequential electrospinning

In this example preparation of electrospun wafer loaded with (Carmustine) BCNU and 0 6 Benzyl guanine (06BG) is descried. In this wafer 06BG is loaded in fibers of PLGA [poly(lactic-co-glycolic acid (50:50)] and BCNU in fibers of PLA-PLGA (85 : 15) blend. PLA-PLGA(85 : 15) blend was prepared by dissolving the two polymers in acetone in 1:1 ratio and added with 20% wt/wt BCN U to it. 10% wt/wt 06BG solution was prepared mixing the drug in PLGA(50:50) solution. The two different solutions were taken in two separate syringes and the electrospray was carried out in a sequential manner to get a final wafer consisting of intermittent layers loaded with the two drugs. In the first step the BCN U containing PLA-PLGA blend solution was electrosprayed using a potential of 13-14KV at ambient temperature and pressure to a grounded metallic surface. After sufficient quantity of first layer formation, 06BG containing PLGA(50:50) solution was electrosprayed on to the first layer at a potential of 10KV. This process was repeated several times to get final wafer consisting of intermittent layers loaded with BCNU and 0 ^BG. The electrospun wafers were removed from the metallic surface and lyophilized for 96hrs to remove any residual solvent and stored at low temperature, away from light and humidity.

Claims:

1. We claim a flexible and biodegradable polymeric wafer system made up of more than one polymeric fiber, each one separately loaded with different therapeutic agents, having mutually exclusive synergistic activity, for their controlled localized delivery against any disease such as cancer, inflammation, wounds, neurodegenerative disorders, etc.
2. The composition of claim 1, wherein the polymer fiber-1 is made from single or blended or cross linked polymers, at least one from the group of poly glycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), glycolide/trimethylene carbonate copolymers (PGA/TMC); poly-lactides (PLA), poly-L-lactide (PLLA), Poly-DL-Iactide (PDLLA), L-lactide/DL-lactide copolymers; lactide/tetramethyl-glycolide copolymers, poly-capro lactone (PCL), poly-valerolacton(PVL), poly-hydroxy butyrate (PHB), poly vinyl alcohol (PVA) poly-hydroxy valerate(PHV), polyvinylpyrrolidone (PVP), Polyethyleneimine (PEI) and lactide/trimethylene carbonate copolymers, chitosan, carboxymethyl chitosan, chitin, pollulan, etc., their blends or combinations thereof.
3. The composition of claim 1, wherein the polymer fiber 1 will be loaded with a potent therapeutic agents chosen from and not limited to the group of paclitaxel, rapamycin, cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, cisplatin, hydroxyurea, leucovorin calcium, tamoxifen, flutamide, asparaginase, altretamine, mitotane, procarbazine hydrochloride, mechlorethamine, thioguanine, carmustine, lomustine, temozolomide, melphalan, chlorambucil, streptozocin, methotrexate, vincristine, bleomycin, vinblastine, vindesine, dactinomycin, 6-MP, daunorubicin, Lenalidomide, L-asparginase, doxorubicin, tamoxifen, antibiotics, antiseptic agents, anti-inflammatory drugs, such, ibuprofen, diclofenac, growth factors, phytochemicals such as curcumine, pipperlongumine, methyljasmonate, plumbagine, or combinations thereof.

In yet another aspect of the above mentioned embodiment, the bare polymeric fibers (PLA-PLGA Belnd), drug loaded fibers (PLA/PLGA-TMZ) and pure drug (TMZ) shows distinct FTIR pattern as depicted in figure 6, shows the successful incorporation of the specific therapeutics in the nanomedicine construct. The incorporation and the effective drug loading will be depending on the interaction between the drug and the matrix forming material. For example, a drug having weak or no interaction toward the carrier polymer will mostly remain as separate entity on the voids of the electrospun wafers as aggregates and will cause burst release. But, on the other hand the drug having firm interaction towards its carrier molecule will be incorporated mostly throughout the fibers and will provide a much stable and extended release.

In yet another aspect of the same embodiment loaded with TMZ and 06BG, both TMZ and 06-BG were released in a controlled and extended manner with near-zero order release kinetics as shown in Fig. 7 & Fig. 8 respectively. The wafer provided release for both drugs for more than 1 month. Since these wafers are implanted to the tumor resected cavity at the time of tumor removal, it is desirable that they provide maximum extended drug release.

In yet another aspect of the same embodiment, the cell attachment studies on the wafer showed effective inhibition of cell attachment and cell growth by the drug loaded wafers. Fig. 9 depicts the SEM images results of cell attachment studies. The left panel refers to SEM images of cells attached to the bare wafer. The bare wafers aided good attachment for the U87MG glioma cells and the cells appeared in their normal stretched morphology. But, the drug loaded wafers effectively prevented any cell attachment and the cells were appeared small and round without proper attachment to the matrix, as depicted in the right panel of Fig 9.

In yet another aspect of the above embodiment, the cell death induction by the drug delivery wafers is depicted in figure 10. Upper panel depicts the confocal microscopic images of live and attached cells on to bare wafer as seen by the green flurescence due to the esterase activity in live cells; where as the lower panel depicts the confocal microscopic images of the drug loaded wafers, where no cells were seen attached or proliferating. Bare PLA/PLGA wafers act as a good supporting matrix for the cells to be attached, whereas the TMZ and 06-BG eluted from the drug loaded wafers prevent the cells from attaching into the matrix and inhibit the proliferating.

The authors have invented a flexible, biodegradable and biocompatible polymeric-fibrous drug delivery device in which different drugs for combination chemotherapy can be loaded in different kinds of polymer fibers having different degradation kinetics ultimately aiding controlled and sequential/simultaneous delivery of the drugs for enhance anticancer effects. The design of the nanomedicine is in such a way to simultaneously carry two different drugs and deliver it specifically and in a controlled fashion to the tumor cells in desired concentrations. The targeting is achieved by a specific biomarker ligand conjugated to the nanomedicine construct.

Examples

Example I: PLA-PLGA electrospun wafer loaded with Temozolomide and 06-Benzylguanine: Co-electrospinning

In this example preparation of electrospun wafer loaded with DNA alkylating agent temozolomide (TMZ) and AGT inhibitor 0 6 Benzyl guanine (06BG) is descried. In this wafer 06BG is loaded in fibers of PLGA [poly(lactic-co-glycolic acid (50:50)] and TMZ in fibers of PLA (Poly lactic acid). For the effectiveness of TMZ-06BG combinatorial therapy, 06-BG should be delivered prior to TMZ; and is the reason for its loding in PLGA (50:50). PLGA with faster degradation kinetics will release 06BG loaded within it and TMZ will be released slowly from PLA fibers. PLGA solution in acetone premixed with 10% wt/wt 06BG and PLA solution premixed with 20% wt/wt TMZ are taken in two different syringes and electrospun simultaneously at a rate of 3ml/hr to a grounded metal surfaceThe tip to target distance was maintained as at 13cm throughout the experiment.

4. The composition of claim 1, wherein the polymer fiber-2 or more is made from single or blended or cross linked polymers, at least one from the group of poly glycolic acid (PGA), poly(lactic-co-glycolic acid) (PLGA), glycolide/trimethylene carbonate copolymers (PGA/TMC); poly-Iactides (PLA), poly-L-lactide (PLLA), Poly-DL-lactide (PDLLA), L-lactide/DL-lactide copolymers; lactide/tetramethyl-glycolide copolymers, poly-caprolactone (PCL), poly-valerolacton(PVL), poly-hydroxy butyrate (PHB), poly vinyl alcohol (PVA) poly-hydroxy valerate(PHV), polyvinylpyrrolidone (PVP), Polyethyleneimine (PEl) and lactide/trimethylene carbonate copolymers, chitosan, carboxymethyl chitosan, chitin, pollulan, etc., their blends or combinations thereof
5. The composition of claim 1, wherein the polymeric fiber-2 or more is loaded with drug molecule chosen from the group of MGMT or AGT inhibitors like 06-Benzyl guanine, cell cycle/check point inhibitors like polo-like kinase (PLK.) inhibitor (e.g. volasertib), cyclin dependent kinase (CDK) inhibitors (e.g. seliciclib, indirubin etc.,), topoisomerase inhibitors (e.g. adriamycin, camptothecin, etoposide, idarubicin, irinotecan, topotecan, mitoxantrone etc.,), microtubule inhibitors (e.g. docetaxel, paclitaxel, vincristine etc.,), antimetabolites (e.g. decitabine, gemcitabine, fludarabine etc.,), telomerase inhibitors, DNA & RNA replication inhibitors (e.g. clarithromycin, cytarabine, mitoxantrone HCI etc.,) dihydrofolate reductase inhibitor, HDAC inhibitor, Bcl-2 and TNF-ct inhibitors, PARP inhibitors, MAPK inhibitors, P13K7Akt/mTOR inhibitors, integrase and protease inhibitors, Wnt/Hedgehog/Notch inhibitors, cAMP, lipide signaling inhibitors (e.g. PK.C, PIM etc.,), TGF-|3 inhibitors, tyrosine kinase inhibitors such as epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor receptor (VEGFR) inhibitors, platelet derived growth factor receptor (PDGFR) inhibitors, fibroblast growth factor receptor (FGFR) inhibitors, Rous sarcoma oncogene/Breakpoint cluster region/Abl (Src-bcr-abl) inhibitors, Insulin-like growth factor 1 receptor (1GF-1R) inhibitors, FLT-3, HER-2, STAT5, c-K.it, c-Met, ALK, ETA receptor inhibitor, HIF inhibitor, Syk inhibitor, Tie2 kinase inhibitor and the like), Vascular disrupting agents (e.g. plinabulin), antioxidant inhibitors like diethyl-dithiocarbamate, methoxyestradiol, l-buthionine sulfoximine, 3-amino-l,2,4-triazole or the combinations thereof.
6. The composition of claim l, wherein the different kinds of fibers are prepared by simultaneous or sequential or co - electrospinning or rotary jet spinning method.
7. The composition of claim 1, wherein the polymer fibers have an average diameter between !-50000nm
8. The composition of claim 1, wherein the polymer fibers are porous or non-porous, beaded or non-beaded, uniform or non-uniform, solid or hollow, or ribbon-shape in nature
9. The composition of claim 1, wherein the two different fibers has different release kinetics.
10. The composition of claim 11, wherein the different release kinetics are achieved by using different polymers or combinations of polymers or by using same polymers of different molecular weight or by using polymers of different monomer ratio.
11. The composition of claim 1, wherein the drugs loaded in the fibers is in their pure molecule form or in their slated form or in their nano-encapsulated form.
12. The composition of claim 1, wherein the fibers are randomly oriented fibers
13. The composition of claim 1, wherein the fibers are aligned fibers.
14. The composition of claim 1, wherein the polymer fibers form a flexible wafer.
15. The flexible wafer of claim 14 is placed near to or wrapped-over or inserted within the diseased area such as tumor, inflammation, wounds, autoimmune diseases, surgically resected regions, etc

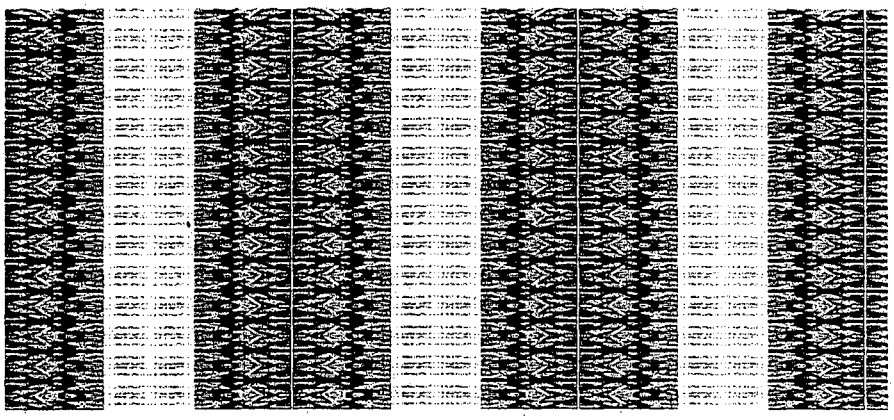

Figure 1: Schematic diagram showing microscopic structure, made of different polymer fibers loaded with different drugs separately.

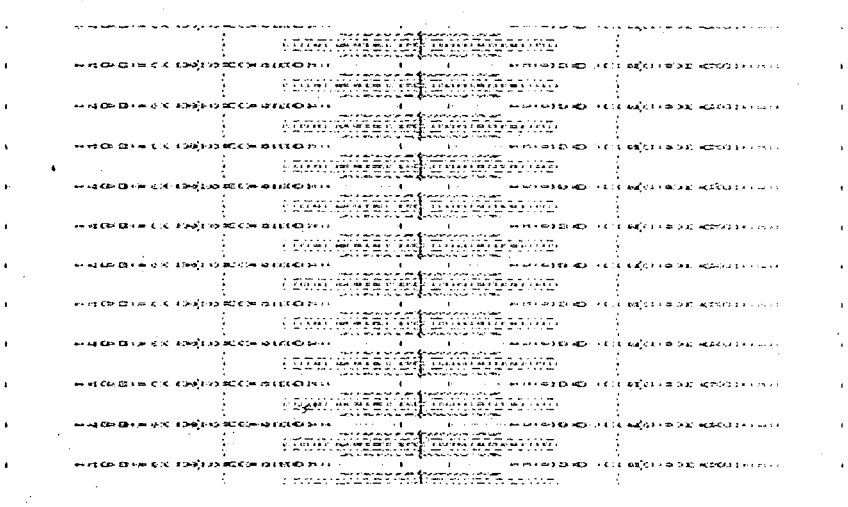

Figure 2: Schematic showing different steps involved in wafer making through electrospinning method

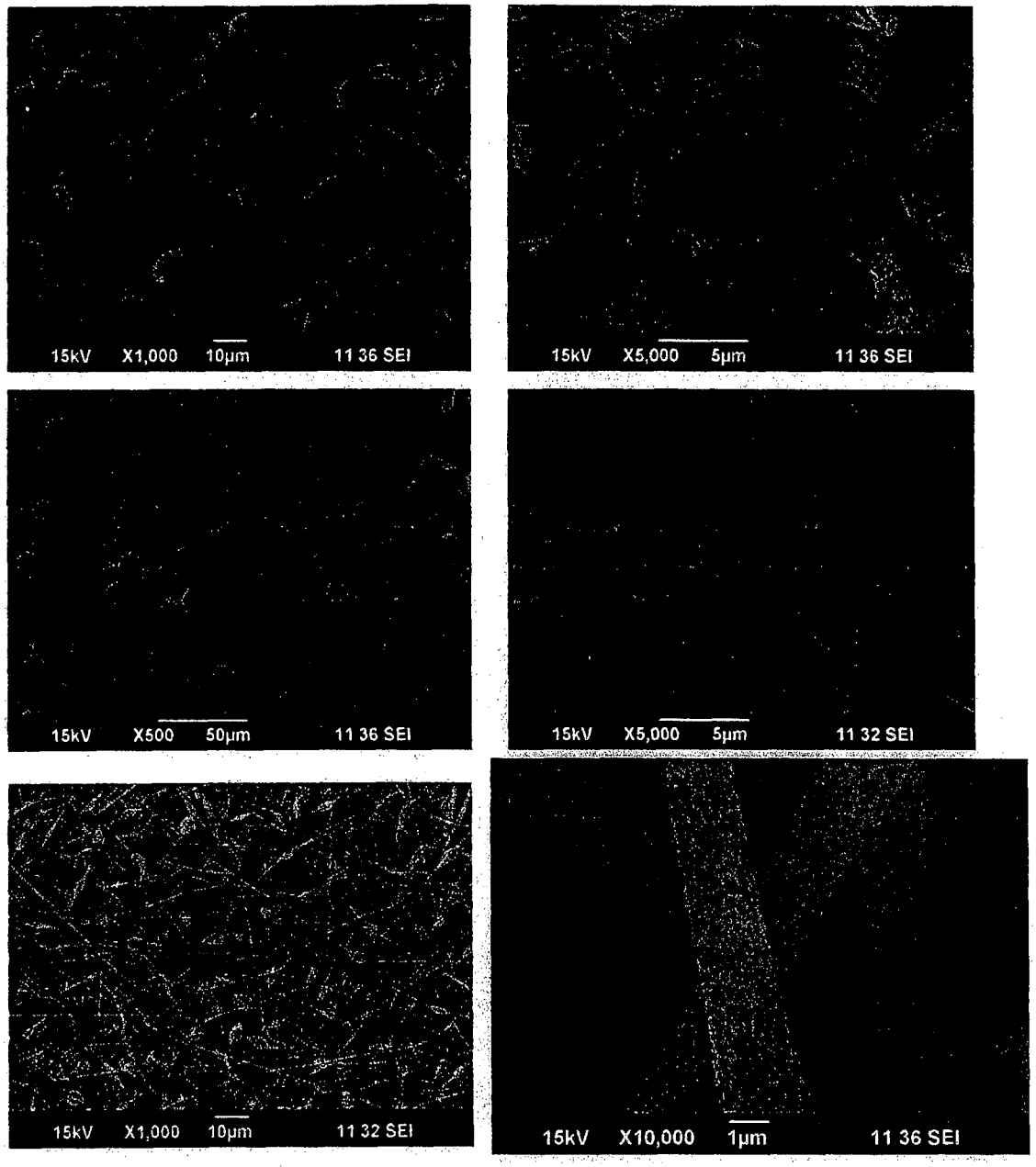

Figure 3: SEM images showing different morphology of polymeric fibers obtained electrospinning technique

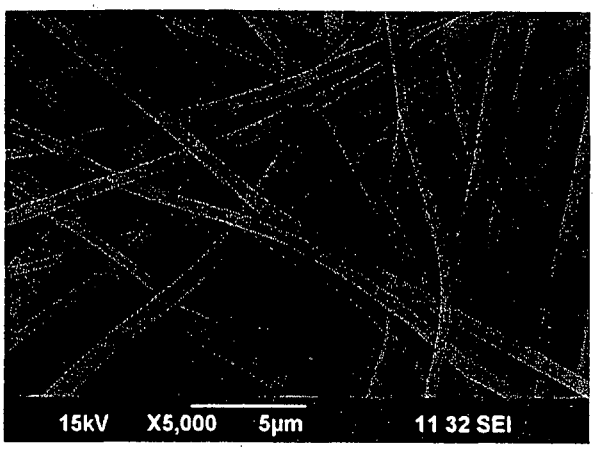

Figure 4: SEM image showing microscopic fiber morphology of TMZ and O6-BG co-loaded PLA-PLGA/PLGA wafer.

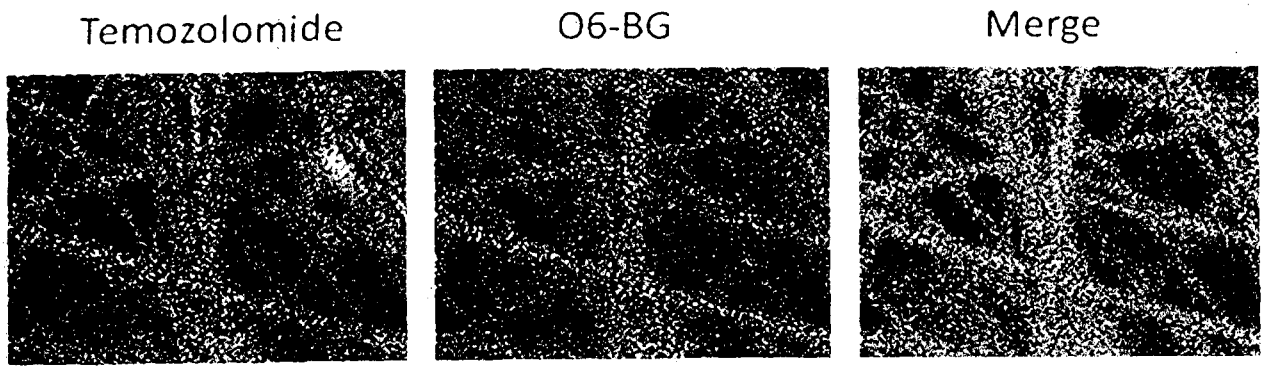

Figure 5: EDS mapping results showing uniform distribution of drugs throughout polymeric fibers

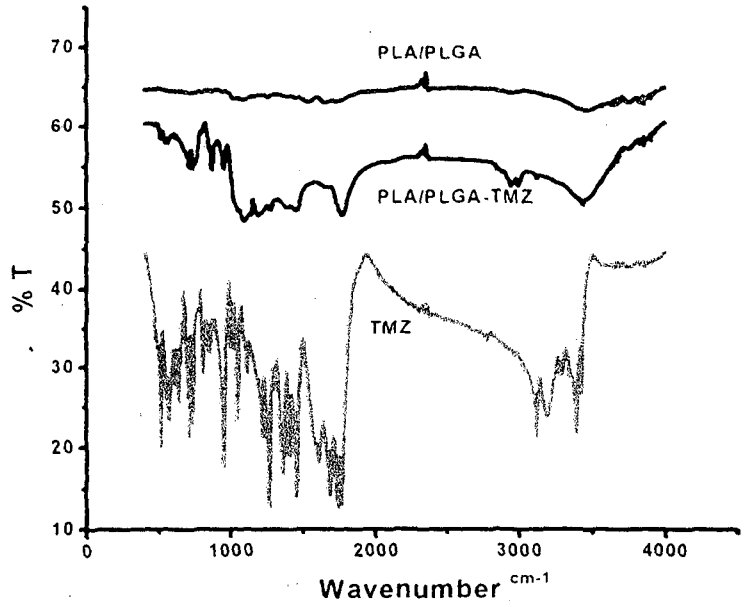

Figure 6: FTIR results showing interaction of TMZ with PLA-PLGA blend polymeric matrix