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पेटेंट प्रमाणपत्र
PATENT CERTIFICATE
(Rule 74 Of The Patents Rules)

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फाइल करने की तारीख / Date of Filing	:	22/01/2014
पेटेंटी / Patentee	:	1.Shivani 2.Dr. Amit Kumar Goyal 3.Goutam Rath

प्रमाणित किया जाता है कि पेटेंटी को उपरोक्त आवेदन में यथाप्रकटित A PROCESS FOR PREPARATION MEDICATED NANO PATCH FROM NANOFIBRE AND ITS COMPOSITION नामक आविष्कार के लिए, पेटेंट अधिनियम, १९७० के उपबंधों के अनुसार आज तारीख 22nd day of January 2014 से बीस वर्ष की अवधि के लिए पेटेंट अनुदत्त किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled A PROCESS FOR PREPARATION MEDICATED NANO PATCH FROM NANOFIBRE AND ITS COMPOSITION as disclosed in the above mentioned application for the term of 20 years from the 22nd day of January 2014 in accordance with the provisions of the Patents Act,1970.

एकस्व कार्यालय THE PATENT OFFICE GOVT. OF INDIA भारत सरकार

अनुदान की तारीख : 09/04/2019
Date of Grant :

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, **22nd day of January 2016**को और उसके पश्चात प्रत्येक वर्ष मे उसी दिन देय होगी।
Note. - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on **22nd day of January 2016** and on the same day in every year thereafter.

FORM 2
THE PATENT ACT, 1970
(39 of 1970)
&
The Patent Rules, 2003
COMPLETE SPECIFICATION
(See Section 10 and Rule 13)

TOPICAL NANO-FIBROUS OCULAR IMPLANTS

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THE FOLLOWING SPECIFICATION PARTICULARLY DESCRIBES THE INVENTION AND THE MANNER IN WHICH IT IS TO BE PERFORMED

TECHNICAL FIELD

The present invention relates to polymeric nano sized structures called nano-patch for delivery of therapeutic entities via ocular route. More particularly, the polymeric nanosized structures i.e. nanopatches prepared from nanofibres which are prepared from composition comprising of mucoadhesive polymer or polymeric composites to pass on a therapeutic active compound, thereby assuring a considerable permanence time in the area of application providing a controlled release of the therapeutic active compound.

BACKGROUND OF THE INVENTION

Eye is a small complex multi-compartmental sense and vital organ of the human body. Several bacterial, viral, or other microbiological infection may occur in the eye ailments with different causes. Some common eye infections include conjunctivitis (pink eye), Blepheritis, Hordeolom or Eye Styes, Trachoma, Keratitis. The most common method for treating ocular disorder is delivery of drugs topically (Eljarrat-Binstock et al.; 2010). Conventional dosage forms (solutions, suspensions, ointments and gels) used for the instillation of therapeutic entities is very convenient and easy to use by all age groups. However, these systems have suffers from several associated problems such as poor drainage of instilled solutions, tear turnover, poor corneal permeability, nasolacrimal drainage, systemic absorption and blurred vision (Bourlais et al.; 1998). Currently several alternate approaches have been attempted for the treatment of ocular problems. Several attempts have been made to improve the availability of drugs into the ocular sites like increase the precorneal contact time, minimizing precorneal drug loss through the use of viscosity and penetration enhancers and prodrugs (Kelly et al.; 1989, Jain; 2005). Recently, novel or controlled drug delivery have demonstrated promising potential for increasing the safety and efficacy of drugs to the eye like implants, inserts, colloids, collagen shields, colloidal and vesicular drug delivery systems etc. These systems may overcome the drawbacks of conventional systems like improving the release profile, reducing the toxicity, providing sustained and controlled release of the drugs to the target sites either by prolonging the contact time with ocular surface or by increasing the penetration through membranes (Sahoo et al.; 2008). Various advantages offered by

Ocular inserts over other delivery systems includes increase in contact time and thus improving bioavailability; possibility of providing a controlled and prolonged drug release and thus better efficacy; reduction of elimination in systemic circulation and thus nnwhile rubbing of eyes, interference with vision, difficulty in placement or removal in case of insoluble inserts (Shinde et al.; 2011).

There arises a need to develop very small nano-sized, convenient, comfortable delivery systems for the treatment of ocular disorders. There is no literature known indicating use of nano sized fibrous patches as ophthalmic drug delivery carrier. Nanofibers are sub micron sized fibers whose diameter is 50-500 nm with the prefix nano- meaning a billionth of a basic unit (ten to the minus ninth). Recently, owing to unique combination of mechanical, biochemical and structural properties, nano structures have gained importance in tissue engineering, biosensors, enzyme and cell immobilisation and drug delivery systems. Nanofibers are also used in medical applications, which include, drug and gene delivery, artificial blood vessels, artificial organs, and medical facemasks. The nanofibres of present invention have high-specific surface area, low density, high pore volume, and tight pore flexibility with excellent pore interconnectivity, transparency, higher mechanical strength and superior absorption efficiency. These features make nanofiber a preferred material for development of ocular patch. Present innovation aims at providing nano-sized delivery systems for sustained and controlled release of therapeutics via the ocular route and hence improves patient compliance. The high surface area to mass ratio and high pore volumes with variable pore sizes are the unique properties of nanofibrous ocular implants that provide nanofiber delivery systems a super absorbent with strong mechanical properties while maintaining a very low density. Further the tortuous capillary structure, nanoporous matrix and high fibre density of nanofibrous delivery systems control the release rate of the drugs and hence provide a sustained release of therapeutic drugs at the site of application.

SUMMARY

It is an object of the invention to provide polymeric nano structures such as a patch for ophthalmic drug delivery that can provide a controlled delivery of therapeutics.

In yet another object of the invention is provided a polymeric nano sized structures called nano-patch formed by nano-fibres prepared by a composition comprising a polymer and a therapeutic active compound optionally alongwith a carrier and other pharmaceutically acceptable additives. The nano patch network of the present invention allows mucoadhesive to assure a considerable permanence time in the area of application and thereby provide a controlled release of the therapeutic active compound.

In yet another objective of the invention there is provided a polymeric nanofibrous composition called nano-patch which not only facilitates a release of encapsulated therapeutics/drug over a long period of time, but also facilitates the absorption and retention of the drug at the site of application.

Another aspect of this preparation wherein the polymeric nano sized structure is in the form of a nano-patch meant for topical application on to the ocular cul-de-sac thereby reduced drug loss by nasolacrymal drainage and tear flow and thus reduced the frequency of administration and a lower incidence of visual and systemic side effects.

In another aspect of this preparation the nano-patch is a solid unit dosage form, ensures better in-vitro in-vivo correlation and allows drug termination wherever or whenever feels necessary.

In an aspect of this invention, there is provided a method for preparation of a polymeric nano-sized structure, wherein the nanomatrix nature of the formulation reduce the patient resistance to placing a solid object in the precorneal region, and thereby overcome the limitation associated with contact lens, hydrogels, ocular insert and discs.

DESCRIPTION OF THE DRAWINGS

The particular aspects and the specific advantages of this invention will become more readily appreciated and explained with the accompanying drawings.

FIGS. 1a-1d are photographs of poly vinyl alcohol and alginate-poly vinyl alcohol (PVA) composite nanofibers of the present invention: FIG. 1a is photomicrograph of 8% PVA nanofiber with beads; FIG. 1b is photomicrograph of a representative alginate-PVA composite nanofiber obtained from a polymer solution having an alginate/PVA ratio of 1:5.5 with beads; FIG. 1c is photomicrograph of PVA nanofiber/nanopatch without beads FIG. 1d is photomicrograph of a representative alginate-PVA composite nanofiber without beads.

FIGS. 2a-2d′ are photographs of drug loaded poly vinyl alcohol and alginate-poly vinyl alcohol (PVA) composite nanofibers of the present invention: FIG. 2a is photomicrograph of drug loaded 8% PVA nanofiber/nanopatch with beads; FIG. 2b is photomicrograph of a representative drug loaded alginate-PVA composite nanofiber obtained from a polymer solution having an alginate/PVA ratio of 1:5.5 with beads; FIG. 2c is photomicrograph of drug loaded PVA nanofiber/nanopatch without beads FIG. 2d is photomicrograph of a representative drug loaded alginate-PVA composite nanofiber without beads

FIGS. 3a-3d′ are SEM images of drug loaded poly vinyl alcohol and alginate-poly vinyl alcohol (PVA) composite nanofibers of the present invention: FIG. 2a is SEM images of drug loaded 8% PVA nanofiber/nanopatch with beads; FIG. 2b is SEM images of a representative drug loaded alginate-PVA composite nanofiber/nanopatch obtained from a polymer solution having an alginate/PVA ratio of 1:5.5 with beads; FIG. 2c is SEM images of drug loaded PVA nanofiber without beads FIG. 2d is SEM images of a representative drug loaded alginate-PVA composite nanofiber without beads

FIGS 4 shows drug release profiles of alginate-PVA composite nanofiber/nanopatch in ATF at $37\pm0.5^{O}C$.

Summary

The present invention provides a polymeric nano-sized structure such as a patch called nano-patch for comfortable and controlled delivery of therapeutics constantly over a long period of time. It is a nanofiber based composition for ocular drug delivery.

The polymeric nano-sized structures of present invention are formed of composition comprising a polymer, a therapeutic agent optionally pharmaceutically additives.

In an embodiment, the nano-sized structures have diameters of 50 nm or greater, preferably in the range of 50 to 800 nm. Nano fiber based patch is easy to insert at different places in eye and are more patient compliant. Further, being a solid dosage form it may retain at the site for prolonged period of time and multiple instillation can be minimized.

In the present invention therapeutic agents of particular interest include, without limitation, anti-glaucoma drugs, anti-cataract and anti-diabetic retinopathy drugs, anti-cancer drugs, anti-clotting agents, anti-tissue damage agents, anti-inflammatory or anti-fibrous drugs, antibiotics, anti-viral agents, and other like anticholinergics, anticoagulants, antifibrinolytic agents, antihistamines, antimalarials, antitoxins, chelating agents, hormones, immunosuppressive thrombolytic agents, vitamins, salts, desensitizing agents, prostaglandins, amino acids, metabolites, antiallergenics, the kind of and mixture of any component thereof.

Preferably, polymers are selected from a group consisting of poly vinyl alcohol and sodium alginate. Preferably, poly vinyl alocohol has an average molecular weight in the range from about ranging from 9000 g/mol to 124,000 g/mol and sodium alginate has an average molecular weight in the range from about ranging from 10000 g/mol to 600,000 g/mol.

According to an embodiment of the present invention, the composition for preparing

nanopatch further comprises a mucoadhesive polymer selected from a group of biodegradable and non-biodegrdable polymers consisting of agarose, chitosan, gelatin, Hyaluronic acid, various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate), Synthetic Cellulose derivatives: CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, Methylhydroxyethylcellulose Poly (acrylic acid) - based polymers: CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2- hydroxyethyl methacrylate), poly(acrylic acid-coethylhexylacrylate), poly(methacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid, PEG, poly(alkylcyanoacrylate) and blends and copolymers thereof.

In an embodiment of the invention, the nano-patch is formed by nano-fibres produced by electrospinning a solution comprising a polymer; and active therapeutic component optionally alongwith a carrier and pharmaceutically acceptable additives. Preferably, the solution for electrospinning has a viscosity ranging from 200 – 1000 cps and a surface tension ranging from 43.5 – 46.5 mN/m.

In an embodiment of the invention, the nanofibers are formed from polymer solutions having a concentration of 1—35% w/w.

According to an embodiment of the present invention, the polymer solution comprises a polymer solution comprising of PVA and sodium alginate having a concentration of 5—15% in aqueous phase.

According to an embodiment of the invention, the nano-patch has a length of from about 1 mm to about 30 mm, a width of from about 1 mm to about 30 mm and a thickness of from about 0.001 mm to 2 mm.

Yet according to an embodiment of the present invention, the composition for preparing nanopatch further comprises of an additional therapeutically active agent selected from the group consisting of antibacterial antibiotic agent, synthetic antibacterial agent, antifungal antibiotic agent, synthetic antifungal agent, antineoplastic agent, steroidal anti-inflammatory agent, nonsteroidal anti-inflammatory agent, anti-allergic agent, glaucoma-treating agent, antiviral agent and anti-mycotic agent.

According to an embodiment of the present invention the active therapeutic agent is selected from a group comprising of antibiotics selected from a group aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micronomicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamfenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), .beta.-lactams (e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefÏŠxime, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephapirin sodium, cephradine, pivcefalexin), cephamycins (e.g., cefbuperazone, cefmetazole, cefininox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems,

flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin g benethamine, penicillin g benzathine, penicillin g benzhydrylamine, penicillin g calcium, penicillin g hydrabamine, penicillin g potassium, penicillin g procaine, penicillin n, penicillin o, penicillin v, penicillin v benzathine, penicillin v hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin) or a combination thereof.

According to an embodiment of the present invention, composition for preparing nanopatch further comprises a polymer selected from the group of nondegradable polymers consisting of nylon, polyurethane, polycarbonate, polyacrylonitrile, polyethyleneoxide, polyaniline, polyvinyl carbazole, polystyrene and poly(vinyl phenol) and the group of biodegradable polymers consisting of polyhydroxyacids, poly(caprolactone, polyanhydrides, polyhydroxyalkanoates, polyurethanes, collagen, alginate, chitosan, and hyaluronic acid, and blends and copolymers thereof.

According to an another embodiment of the present invention, the composition for preparing nanopatch further comprises of plasticizers of preferably low volatile substances with average molecular weights between 200 and 400 such as diesters derived from dicarboxylic acids (e.g. sebacic acid, azelaic acid) or from ethylene glycol and propylene glycol, citric acid (tributylcitrate, triethylcitrate) or glycerol (triacetin, tributyrin) and a mixture thereof.

Yet according to an embodiment of the invention said plasticizer is present in a proportion of about 0.1-3 percent by weight by weight of the nanopatch.

Yet according to an embodiment of the invention, composition for preparing nanopatch further comprises of penetration enhancer selected from a group consisting of β-cyclodextrin, sodium lauryl sulphate, sodium glycocholate, sodium deoxycholate, sodium laurate, glyceryl monolaurate peppermint oil, spearmint oil, menthol, pepper oil, eucalyptus oil, cinnamon oil, ginger oil, fennel oil, and dill oil, hydrochloric acid, phosphoric acid, acetic acid, citric acid, lactic acid, oleic acid, linoleic acid, lauric acid, palmitic acid, benzoic acid, poly(alkylene oxide), a polyvinyl alcohol, and a polycarboxylic acid polymer and a mixture thereof

Said penetration enhancers is present in a proportion of about 0.5 – 10 % by weight of the total weight of the nanopatch.

Drug loading techniques can be employed to improve the drug loading efficacy of the developed nanofiber, wherein selected active therapeutic agents are either loaded by active or passive loading techniques.

Nanopatches of the present invention, made up of nanofibres formed by a formulation of pH 5 to 8.5.

According to an embodiment of the present invention, composition for preparing nanopatch further comprising adding a buffer system selected from the group consisting of borate buffers, phosphate buffers, citrate buffers, and combinations and mixtures thereof.

According to an embodiment of the present invention, composition for preparing nanopatch further comprising of tonicity agents selected from the group consisting of dextrose, NaCl, KCl, ZnCl2, CaCl2, and MgCl2.

Nanopatches of the present invention made from nano fibres produced by electrospinning, cross-linking, phase separation, melt fibrillation, gas jet, melts blower or nano litrography.

In yet another embodiment of the invention, the polymeric nano sized structures are made up of polymeric composites comprising biodegradable polymers, non –degradable and natural materials.

In an embodiment of the invention, there is provided a new class of polymeric nanofibers produced by different methods i.e cross-linking, phase separation, melt fibrillation, gas jet, melts blower or nano litrography with unique mechanical and absorbent properties to explore the maximum potential of ocular delivery.

In the present embodiment, nanofibers can be prepared by interfacial polymerization, electrospinning, and forcespinning. The preferred method of fabrication of composite nanofibers was selected to be electrospinning as it provides the most suitable environment for the incorporation of insulin within the polymeric composite nanofibers. In the present invention polymeric nanofibers is fabricated by electrospinning process at variable processing conditions. This technique offers the opportunity for control over thickness and composition of the nanofibers alongwith porosity of the nanofiber meshes using a relatively simple experimental setup. With the enormous increase in available surface area per unit mass, nanofibers will provide favorable conditions for the maximum loading of drugs. The optimization of process for producing fibers involve the in-process testing of the morphology of the nanofibers formed by observing the fibers under an optical microscope for their size, uniformity, density and absence of beads and drops. The

optimized nanofibers are then characterized using various sophisticated analytical techniques such as Scanning Electron Microscopy (SEM), X-Ray Diffraction (XRD), Infrared Spectroscopy (IR), Ultraviolet-Visible Spectroscopy, Differential Scanning Calorimetry (DSC) and Thermal Gravimetric Analysis (TGA). The prepared formulations were evaluated for various parameters like drug interaction studies, physicochemical characteristics, folding endurance, Drug Loading, Entrapment Efficiency, stability studies, in vitro release and permeation studies, in-vitro anti microbial studies, ocular irritation and stability of medicated inserts were also evaluated. The values of physicochemical evaluation revealed that developed nanofibers provide superior film properties with nanometric architecture ranging between 100-800 nm. Developed formulation has demonstrated the sustained release of encapsulated medicaments for the longer period of time. Positive Biocompatibility and toxicity studies have also demonstrated the potential and utility of nanofibrous ocular insert. Thus, nanofibers could be considered as optimum ocular drug delivery system exhibiting great potential in providing controlled drug release than ocular inserts.

In another related embodiment, the composition comprising of polymeric nanofibers or a composite thereof, wherein the nano fiber forming polymer is selected from the group consisting of biodegradable and non-biodegrdable polymers consisting of agarose, chitosan, gelatin, Hyaluronic acid various gums (guar, locust bean gum, xanthan, gellan, carragenan, pollunan, pectin, arabic gum and sodium alginate), synthetic cellulose derivatives, Poly (acrylic acid) - based polymers, PEG and poly(alkylcyanoacrylate)and blends and copolymers thereof.
The mucoadhesive polymer is added to the composition in an amount ranging from l to 99wt% to a total amount of the composition.

In an embodiment of the invention, the nano sized structures of present invention further comprises an additional therapeutically active agent selected from the group consisting of antibacterial antibiotic agent, synthetic antibacterial agent, antifungal antibiotic agent, synthetic antifungal agent, antineoplastic agent, steroidal anti-inflammatory agent,

nonsteroidal anti-inflammatory agent, anti-allergic agent, glaucoma-treating agent, antiviral agent, anti-mycotic agent, anti-cataract, anti-diabetic retinopathy drugs, anti-clotting agents, anti-tissue damage agents, antibiotics, and other like anticholinergics, anticoagulants, antifibrinolytic agents, antihistamines, antimalarials, antitoxins, chelating agents, hormones, immunosuppressive thrombolytic agents, vitamins, salts, desensitizing agents, prostaglandins, amino acids, metabolites, antiallergenics, like and mixtures thereof.

In an embodiment of the invention, the polymeric nano-sized structure is a solid unit dosage formulation and thus, more stable than liquids, with longer expiration dates, easy manufacturing, shipping and handling, less needed shelf space, no preservation requirements, accurate dosage (single dose) and suitable for sustained release preparation.

In another related embodiment, the composition comprising of optional additives wherein the additives comprising is a buffer system selected from the group consisting of borate buffers, phosphate buffers, citrate buffers, and combinations and mixtures thereof and the amount of buffer can range from about 0.1 to 2%, preferably 0.1 to 1%, tonicity agents selected from the group consisting of NaCl, dextrose, KCl, $ZnCl_2$, $CaCl_2$, and $MgCl_2$ or a mixture thereof, the amount of tonicity modifier can range from about 0.1 to 5% to provides an osmolality range of elctrospun solution about 100 to about 300 mOsm/kg.

Preferably the therapeutic agent/drug is dispersed throughout a matrix comprising the nanofiber patch. The invention also provides a nanocomposite wherein the active ingredient is loaded in, or adsorbed to, a carrier comprising the nanofiber patch. Said composition can further contain various additives, to make drug bioavailable and absorbable through the ophthalmic route.

The present invention further includes a composite patch formed by a method which may comprising the steps of: (a) making a mucoadhesive polymer comprising from 2% to 5%

(w/w) preferably sodium alginate; from 5% to 15% (w/w) of nanofiber forming polymer preferably PVA; and from 0.2% (w/w) to 5% (w/w) of drug; and additives, as optional ingredients, is dissolved to prepare a polymer solution (b) electrospinning the solution to form nanofibers.

A composition, which comprises (A) polymer, (B) an active component, as essential ingredients; and (C) a plasticizer, and (D) an a mucoadhesive agent and or (E) additives, as optional ingredients, is dissolved to prepare a polymer solution. Here, (A) to (E) ingredients may be added regardless of order, which is adjusted by those skilled in the art in consideration of properties and the characteristics thereof. The drug could be loaded using various approaches such as active loading or passive loading. Initially, the nanofiber forming polymer solution was optimized preferably PVA in a concentration from 5% to 15% (w/w) and the optimized concentration was considered for the preparation of its composite with mucoadhesive agents and other additives. A fixed amount of drug was then added to it and was stirred for a period of at least 8-10 hours. Then, mucoadhesive agent preferably hydrophilic gums in a concentration from 2% to 5% (w/w) preferably sodium alginate was taken in the optimized ratio for the preparation of the composite and was added to the PVA-drug mixture and stirred overnight. The final solution obtained was then used for electrospinning. All the stirring was carried out at room temperature and all the necessary precautions were observed to protect the formulation from the atmospheric hazards.

A variety of electrospinning processes variables, for example, solution viscosity, the distance between the spinning tip or electrode and the collector, voltage and solution conductivity were optimized in forming the composite fibers of the present invention.

In another related embodiment, process initially involves the preparation of the polymer solution of desired viscosity ranging from 100 – 1000 cps and surface tension ranging from 43.5 – 44.5 mN/m so that it remains feasible for the fabrication of nanofibers.

In the preferred embodiment, the composition comprising of composite polymeric nanofibers composed of polyvinyl alcohol (PVA) (2 – 15% w/w), sodium alginate (0.5 – 5% w/w) and optional additives loaded with gentamycin (0.01-1% w/w).

In brief the process comprising of following steps.

The optimization of the parameters during the preparation of the nanofibers using the electrospinning apparatus was carried out using the following steps:

1. An aluminium sheet of dimensions 16×5 cm^2 was cut and rolled over the collector surface acting as an electrode.
2. The polymer solution to be electrospun was filled within a 3ml syringe with a needle size of 24G×1”0.55×25mm; syringe placed in the cavity provided with the needle placed between the two clips acting as the other electrode.
3. Next, the distance (in cm) between the tip of the needle and the collector was adjusted to the desired value.
4. The piston of the syringe was adjusted such that a small drop of polymer solution was obtained at the tip of the needle.
5. With this, the doors of the chamber were closed and the different parameters such as flow rate, collector speed and potential to be applied were fed into the software along with other details of the sample.
6. The machine was then turned on; with the flow rate controller, the collector rotation controller and the voltage controller turned on in the orderas mentioned.
7. The flow rate (FR) was tried in the range of 0.05-0.15 ml/hr., the tip-collector distance (TCD) & the collector rotation speed (CS) of the collector were fixed at20cm & 2000rpm respectively and the potential applied (PA) was tried between 10-15 KV.

8. Initially the machine was run for a period of 10-15 minutes; the aluminium sheet was taken off from the collector and was checked for any undesired presence of beads or drops along with the presence of nanofibers of small and uniform diameter using the optical microscope.
9. The sheets with any presence of beads or drops were rejected and new combinations of different parameters were then tried. The sheets with no beads or drops, and fibers with small and uniform diameter were taken as a success and a new sheet with the same optimized parameters was electrospunned again.
10. The final sheets obtained were then collected and kept in an air tight box till further use.

As discussed above, the electrospun nanofibers may be formed directly onto a surface of a material such as a film, a woven patch or nonwoven patch. Nonwoven fabrics or patches have been formed from many processes such as for example, meltblowing processes, cross-linking, phase separation, melt fibrillation, gas jet, melts blower or nano litrography etc. Table 1 shows the processing conditions of PVA nanofibers patch.

Table 1- Elecrospinning parameters of Nanofiber nanopatch

Example	Composition (%)	Flow Rate (mL/hr)	Potential (KV)
S1	PVA---- 2% Additives----- 1% DI Water------ 100%	0.05	10
S2	PVA---- 4% Additives----- 2 % DI Water------ 100%	0.05	10
S3	PVA---- 6% Additives----- 3 % DI Water------ 100%	0.05	10
S4	PVA---- 8% Additives----- 4 % DI Water------ 100%	0.05	10
S5	PVA---- 2% S A------ 0.5% Additives----- 1 % DI Water------ 100%	0.05	10

S6	PVA---- S A------ Additives----- DI Water------	4 % 0.75% 2 % 100%	0.05	10
S7	PVA---- S A------ Additives----- DI Water------	6 % 1 % 3 % 100%	0.05	10
S8	PVA---- S A------ Additives----- DI Water------	8 % 1.25% 4 % 100%	0.05	10
S9	PVA---- S A------ Drug---- Additives----- DI Water------	2 % 0.5 % 0.05 % 1 % 100%	0.05	10
S10	PVA---- S A------ Drug---- Additives----- DI Water------	4 % 0.75 % 0.1 % 2 % 100%	0.05	10
S11	PVA---- S A------ Drug---- Additives----- DI Water------	6 % 1 % 0.5 % 3 % 100%	0.05	10
S12	PVA---- S A------ Drug---- Additives----- DI Water------	8 % 1.25% 1 % 4 % 100%	0.05	10
S13	PVA---- S A------ Drug---- Additives----- DI Water------	2 % 0.5 % 0.05 % 1 % 100%	0.1	10
S14	PVA---- S A------ Drug---- Additives----- DI Water------	4 % 0.75 % 0.1 % 2 % 100%	0.1	10
S15	PVA---- S A------ Drug---- Additives----- DI Water------	6 % 1 % 0.5 % 3 % 100%	0.1	10

S16	PVA---- S A------ Drug---- Additives----- DI Water------	8 % 1.25% 1 % 4 % 100%	0.1	10
S17	PVA---- S A------ Drug---- Additives----- DI Water------	2 % 0.5 % 0.05 % 1 % 100%	0.15	10
S18	PVA---- S A------ Drug---- Additives----- DI Water------	4 % 0.75 % 0.1 % 2 % 100%	0.15	10
S19	PVA---- S A------ Drug---- Additives----- DI Water------	6 % 1 % 0.5 % 3 % 100%	0.15	10
S20	PVA---- S A------ Drug---- Additives----- DI Water------	8 % 1.25% 1 % 4 % 100%	0.15	10
S21	PVA---- S A------ Drug---- Additives----- DI Water------	2 % 0.5 % 0.05 % 1 % 100%	0.15	15
S22	PVA---- S A------ Drug---- Additives----- DI Water------	4 % 0.75 % 0.1 % 2 % 100%	0.15	15
S23	PVA---- S A------ Drug---- Additives----- DI Water------	6 % 1 % 0.5 % 3 % 100%	0.15	15
S24	PVA---- S A------ Drug---- Additives----- DI Water------	8 % 1.25% 1 % 4 % 100%	0.15	15
S25	PVA----	2 %	0.15	20

	S A------ 0.5 % Drug---- 0.05 % Additives----- 1 % DI Water------ 100%		
S26	PVA---- 4 % S A------ 0.75 % Drug---- 0.1 % Additives----- 2 % DI Water------ 100%	0.15	20
S27	PVA---- 6 % S A------ 1 % Drug---- 0.5 % Additives----- 3 % DI Water------ 100%	0.15	20

EXAMPLES

Example S1 to S27 illustrates the preparation and characterization of representative polymeric and composite polymeric nanofibers. In these examples, the preparation and characterization of polymeric and composite polymeric nanofibers of the invention is described. The concentration of the nanofiber forming polymer preferably PVA was tried in the range of 2-8 % of weight ratio, the concentration of the mucoadhesive polymer preferably sodium alginate (SA) was tried in the range of 0.5-1.5%, the concentration of the drug preferably gentamycin was tried in the range of 0.01-1% and the concentration of the optional additives preferably buffers and tonicity modifier was tried in the range of 1-5% under different spinning conditions as specified in the Table 1. The stirring time of 6 hours at room temperature was observed for the excipients to dissolve completely in deionised water or any appropriate solvent system thereof. The mixtures were stirred for an additional 3 h and centrifuged to remove air bubbles before use in electrospinning. The electrospinning system was similar to that reported previously (N. Bhattarai, D. Edmondson, O. Veiseh, F. A. Matsen, M. Q. Zhang, Biomaterials 26:6176, 2005). Electrospun nanofibers were collected as a fibrous mat from the collector. The optimization of fibers involve the in-process testing of the morphology of the nanofibers formed by observing the fibers under an optical microscope for their size, uniformity, density and absence of beads and drops. The optimized nanofibers are then characterized using various sophisticated analytical techniques such as Scanning Electron Microscopy

(SEM), Infrared Spectroscopy (IR), Ultraviolet-Visible Spectroscopy and Differential Scanning Calorimetry (DSC). The prepared formulations were evaluated for various parameters like drug interaction studies, physicochemical characteristics, folding endurance, Drug Loading, Entrapment Efficiency, stability studies, in vitro release and permeation studies, in-vitro anti-microbial studies, ocular irritation and stability of medicated inserts were also evaluated.

The fibers were evaluated for their surface morphology characteristics such as diameter, uniformity and density of the nanofibers. The optical micrograph of PVA fibers were first compared with those of the PVA-NaAlg fibers for any change due to the addition of sodium alginate to the PVA solution. Later, the SEM images of PVA-NaAlg fibers were compared with the optical micrograph of the drug loaded PVA-NaAlg fibers to determine any change due to the addition of the drug. The optical micrograph of PVA, PVA-NaAlg as well as drug loaded PVA-NaAlg fibers are shown in the ***figure 1(a), (b) & (c)***. The size of the PVA as well as PVA-NaAlg nanofibers were found to be almost the same (between 200-400 nm[approximately], with the composite nanofibers being slightly of the lower size relatively) but on comparing with the drug loaded nanofiber, there was a significant difference observed in the diameter of the drug loaded nanofiber ranging between 500-700 nm [approximately]. The optical microscope images for the drug loaded fiber are shown in ***figure 2 (a), (b), (c) & (d)***.

The morphology of the electrospun fibers were further analysed by Scanning Electron Microscopy (SEM). At least 10 different positions on the fiber mat at different magnifications were tested to analyze the morphology of the electrospun fibers. A small section of the fiber mat was placed on the SEM sample holder and sputter coated with platinum. Accelerating voltage of 15 KV was employed to take the SEM images. The SEM images were then used for the determination average diameter of the fibers.

The SEM images of composite as well as drug loaded fibers are shown in the ***figure 3 (a), (b,) (c)***. ***& (d).***

The degree of swelling of a nanofiber mat plays a major role in the release of drug from the nanofiber mat. Degree of swelling was found to be more with the unloaded fiber which increased up till the 8^{th} hour and later decreased.

The mucoadhesive strength of the PVA, unloaded PVA-NaAlg and drug loaded PVA-NaAlg nanofibers was calculated using the mucoadhesive force determination apparatus. The observations were that the PVA-NaAlg (unloaded and loaded) nanofibers possessed much higher mucoadhesive strength than the PVA fiber alone. Also, the mucoadhesive strength of the drug-PVA-NaAlg nanofiber was relatively more than the unloaded nanofiber. Mucoadhesion studies showed that the composite nanopatch provides possesses high mucoadhesive strength (764±51.43 N/m^2).

The *in-vitro* drug release profile of drug loaded nanofibers were conducted in ATF pH 7.4 using dialysis bag. The release study of drug loaded formulations of nanofibers nanopatch was repeated three times to check the reproducibility. The release profile indicated that the rate of release was concentration dependent followed by initial brust release and there after a constant amount of approximately 7-10% drug was released at any specific interval of the release study. The in-vitro release profile is presented graphically in the figure 4.

The anti-microbial activity of the developed formulations was carried out against *P.aeruginosa* MTCC No. 1034. The McFarland standard suspension of *P.aeruginosa* MTCC No. 1034 gave a bacterial count of log 4.3 cfu/ml. The different volume of inoculums ware added in 5ml of culture medium and the formulation were placed in the test tubes and the plugged tubes were incubated at 37±1ºC. At periodic time intervals of 0, 2, 6, 12 and 24 hours standard loopfuls from individual tubes were streaked on sterile

nutrient agar plates and incubated at 37±1ºC for 24 h and observed for growth. No growth was seen in any volume of inoculums at the end of 24 hours which shows the efficacy of nanofibers against *P.aeruginosa* MTCC No. 1034 bacterial strain.

Ocular irritation studies in male albino rabbits showed no sign of irritation according to Draize score. in- vivo anti microbiological studies were performed by inoculating P. aeruginosa (10 7 cfu/ml) in right eye of rabbit. The growth of colonies was observed in terms of log cfu/ml at the end of 0, 2, 8, 12 and 24 hour which indicated optimised nanofibers at the end of 5-6 hours exhibited complete eradication or elimination of bacterial conjunctivitis.

The physico-chemical characteristics of the nanofiber formulation particularly including thickness, surface pH, weight uniformity, folding endurance, moisture loss, moisture absorption and swelling index were determined to ensure whether physico chemical behavior comply the physiological requirement of the ophthalmic formulation. The observations obtained for the aforesaid illustration are tabulated in Table No. 2.

Table 2. Physicochemical Evaluation of polymeric nanofiber formulation.

Example	Thickness (mm)	Weight uniformity	Folding endurance	pH	%Moisture absorption	%Moisture loss	% Swelling index
S1	0.058±0.007	4.90±0.42	164.6±4.50	6.9±0.1	9.35±0.21	7.04±0.17	18.4±0.2
S2	0.125±0.009	5.98±0.26	149.3±5.859	6.86±0.05	10.00±0.21	6.91±0.18	17.7±0.173
S3	0.129±0.005	7±0.62	145.3±6.506	7.13±0.05	10.51±0.04	6.74±0.21	17.23±0.11
S4	0.143±0.008	7.81±1.01	129.6±9.01	6.9±0.1	11.71±0.08	6.50±0.14	16.3±0.15
S5	0.149±0.004	7.87±0.49	115.3±12.89	7.23±0.05	12.61±0.04	6.20±0.07	15.93±0.15
S6	0.093±0.03	5.20±0.71	260±4.58	6.96±0.1	9.91±0.06	7.23±0.16	20.93±0.61
S7	0.126±0.01	6.09±0.24	255.3±3.05	7±0.17	10.79±0.02	7.13±0.16	19.03±0.51
S8	0.145±0.01	7.01±0.69	248.6±0.57	6.86±0.05	11.45±0.04	6.96±0.10	18.93±0.45
S9	0.153±0.013	7.84±0.26	239.3±1.52	7.13±0.20	12.08±0.04	6.78±0.10	18.03±0.20
S10	0.163±0.008	7.82±0.44	234.6±2.51	7.06±0.15	12.95±0.04	6.34±0.28	17.1±0.72
S11	0.088±0.023	5.24±0.59	363±2	6.73±0.11	10.77±0.04	7.55±0.03	23.36±0.25
S12	0.142±0.007	6.25 ±0.34	352.6±3.51	7.16±0.25	11.26±0.03	7.41±0.02	22.0±0.47
S13	0.142±0.003	7.37±0.52	341±5	7±0.17	11.91±0.02	7.16±0.09	19.96±0.55
S14	0.149±0.008	7.88±0.16	324.6±4.5	6.96±0.32	12.85±0.02	6.93±0.04	19.06±0.47
S15	0.065±0.008	7.90±0.60	320±2.6	7±0.1	13.23±0.14	6.71±0.16	18.66±0.50

S16	0.013±0.03	6.20±0.71	160±4.58	6.96±0.1	9.81±0.06	7.23±0.16	19.93±0.61
S17	0.126±0.01	6.09±0.24	285.3±3.05	6.8±0.17	10.49±0.02	7.13±0.16	19.03±0.51
S18	0.045±0.01	7.11±0.69	228.6±0.57	6.86±0.05	10.45±0.04	7.06±0.10	19.13±0.45
S19	0.153±0.013	6.84±0.26	239.3±1.32	7.03±0.20	11.08±0.04	6.88±0.10	18.63±0.20
S20	0.063±0.008	6.82±0.44	264.6±2.51	7.01±0.15	11.35±0.04	7.34±0.28	17.19±0.72
S21	0.078±0.023	5.84±0.59	363±2.12	6.83±0.11	11.67±0.04	7.45±0.03	21.36±0.25
S22	0.122±0.007	6.25 ±0.34	252.6±3.51	7.26±0.25	10.26±0.03	7.21±0.02	21.98±0.47
S23	0.132±0.003	7.37±0.52	311±5.76	7.45±0.15	10.91±0.02	7.56±0.09	19.56±0.35
S24	0.199±0.008	7.98±0.16	224.6±4.1	6.56±0.32	11.85±0.02	6.93±0.04	20.06±0.47
S25	0.205±0.008	6.90±0.60	280±1.6	7.13±0.1	12.23±0.15	7.11±0.16	19.86±0.30
S26	0.093±0.03	6.20±0.71	270±4.58	6.56±0.1	10.91±0.06	7.23±0.16	20.93±0.61
S27	0.126±0.01	6.19±0.24	215.3±2.05	7.56±0.17	10.59±0.02	7.43±0.16	21.03±0.51

Claims

1. Polymeric nanofiber based patchs for ocular delivery prepared from a composition comprising a polymer ranging from 5% to 15% (w/w) ; and from 0.01% (w/w) to 5% (w/w) of drug.

2. The nanopatch as claimed in claim 1, wherein nanofibers are produced by electrospinning a solution comprising of a polymer and active therapeutic agent.

3. The nanopatch as claimed in claim 1 or 2, wherein the polymer is poly vinyl alcohol having an average molecular weight in the range from about ranging from 9000 g/mol to 124,000 g/mol.

4. The nanopatch as claimed in claim 1, wherein the polymer is sodium alginate of average molecular weight in the range from about ranging from 10000 g/mol to 600,000 g/mol.

5. The nanopatch as claimed in claim 1, wherein the polymer is in range of 1—35% w/w of total composition.

6. The nanopatch as claimed in claim 1, wherein the polymer is selected from group consisting of biodegradable and non-biodegrdable polymers consisting of agarose, chitosan, gelatin, Hyaluronic acid various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate) Synthetic Cellulose derivatives: CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, Methylhydroxyethylcellulose Poly (acrylic acid) - based polymers: CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2- hydroxyethyl methacrylate), poly(acrylic acid-coethylhexylacrylate), poly(methacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid, PEG, poly(alkylcyanoacrylate) and blends and copolymers thereof.

7. The nanopatch as claimed in claim 1 wherein nanopatch has a length of from 1 mm to 30 mm, a width of from 1 mm to 30 mm and a thickness of from 0.001 mm to 2 mm.

8. The nanopatch as claimed in claim 1, wherein the composition comprises an additional therapeutically active agent selected from the group consisting of antibacterial antibiotic agent, synthetic antibacterial agent, antifungal antibiotic agent, synthetic antifungal agent, antineoplastic agent, steroidal anti-inflammatory agent, nonsteroidal anti-inflammatory agent, anti-allergic agent, glaucoma-treating agent, antiviral agent and anti-mycotic agent.

9. The nanopatch as claimed in claim 1, wherein the composition comprises an additional antibiotics selected from a group aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micronomicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamfenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), .beta.-lactams (e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefÏŠxime, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephapirin sodium, cephradine, pivcefalexin),

cephamycins (e.g., cefbuperazone, cefmetazole, cefininox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems, flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin g benethamine, penicillin g benzathine, penicillin g benzhydrylamine, penicillin g calcium, penicillin g hydrabamine, penicillin g potassium, penicillin g procaine, penicillin n, penicillin o, penicillin v, penicillin v benzathine, penicillin v hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin) or a combination thereof.

10. The nanopatch as claimed in claim 1, wherein the composition comprises a polymer selected from the group of nondegradable polymers consisting of nylon, polyurethane, polycarbonate, polyacrylonitrile, polyethyleneoxide, polyaniline, polyvinyl carbazole, polystyrene and poly(vinyl phenol) and the group of biodegradable polymers consisting of polyhydroxyacids, poly(caprolactone, polyanhydrides, polyhydroxyalkanoates, polyurethanes, collagen, alginate, chitosan, and hyaluronic acid, and blends and copolymers thereof.

11. The nanopatch as claimed in claim 1, wherein the composition comprising of plasticizers, preferably low volatile substances with average molecular weights between 200 and 400 such as diesters derived from dicarboxylic acids (e.g. sebacic acid, azelaic acid) or from ethylene glycol and propylene glycol, citric acid (tributylcitrate, triethylcitrate) or glycerol (triacetin, tributyrin) and a mixture thereof, in a range of 0.1 to 3 % w/w of total composition.

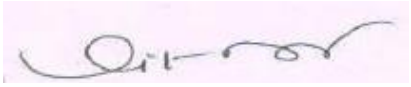
12. The nanopatch as claimed in claim 1, wherein the composition comprising penetration enhancer selected from the group consisting of β-cyclodextrin, sodium lauryl sulphate, sodium glycocholate, sodium deoxycholate, sodium laurate, glyceryl monolaurate peppermint oil, spearmint oil, menthol, pepper oil, eucalyptus oil, cinnamon oil, ginger oil, fennel oil, and dill oil, hydrochloric acid, phosphoric acid, acetic acid, citric acid, lactic acid, oleic acid, linoleic acid, lauric acid, palmitic acid, benzoic acid, poly(alkylene oxide), a polyvinyl alcohol, and a polycarboxylic acid polymer and a mixture thereof in a range of 0.5 – 10 % wt by weight of total composition.

.13 The nanopatch as claimed in claim 1, wherein the composition has a pH ranging from 5 to 8.5.

14. The nanopatch as claimed in claim 1, wherein the composition comprises a buffer system selected from the group consisting of borate buffers, phosphate buffers, citrate buffers, and combinations and mixtures thereof.

15. The nanopatch as claimed in claim 1, wherein the composition comprisesof tonicity agents selected from the group consisting of dextrose, NaCl, KCl, ZnCl2, CaCl2, and MgCl2.

16. The nanopatch as claimed in claim 1, wherein the nanopatch are prepared from nano fibres produced by electrospinning, cross-linking, phase separation, melt fibrillation, gas jet, melts blower or nano litrography.

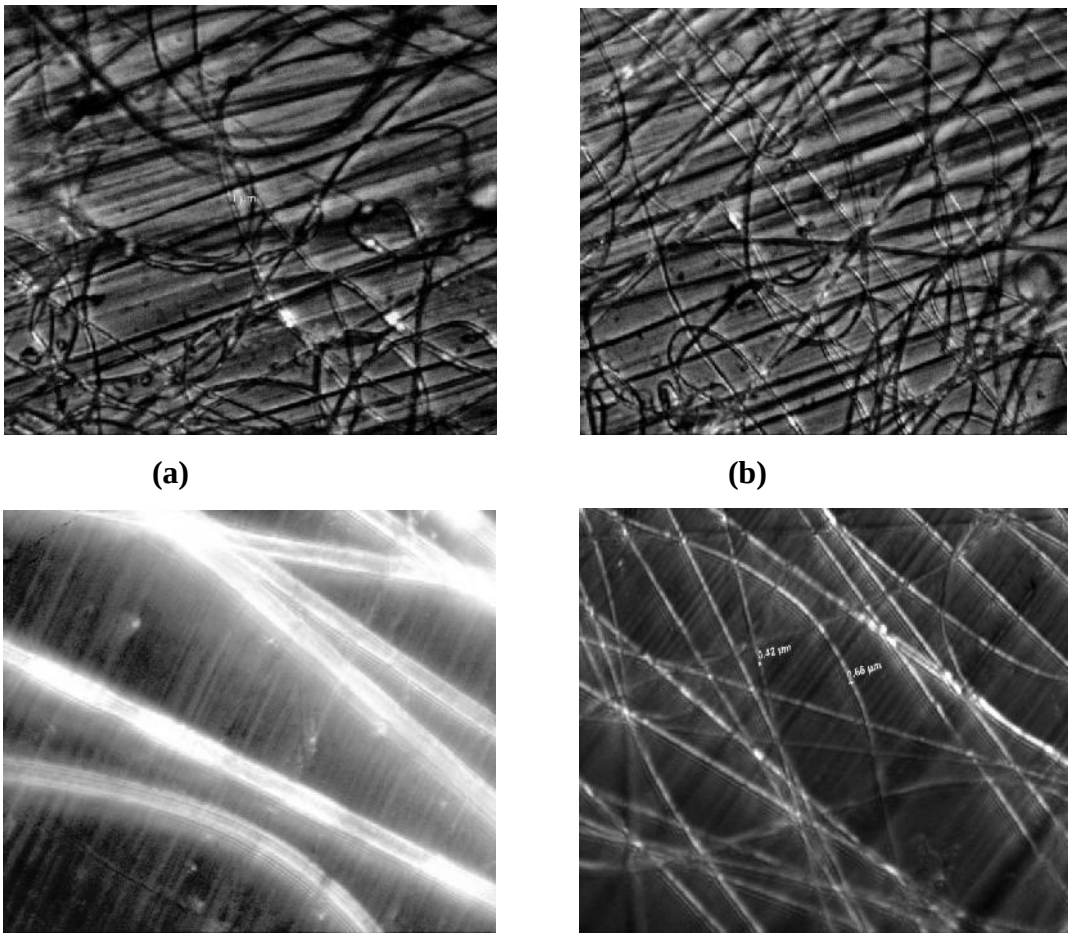


Dated 22/01/2014 **Vikas Asawat**

INPA 1407

Applicants- Shivani
Dr. Amit Kumar Goyal
Goutam Rath

Total no. of Sheets 4
Sheet no. 1 of 4



(a) **(b)**

(c) **(d)**

Figure 1: (a)& (b)Optical Images of PVA & PVA-NaAlg Nanofibers with Beads&Drops, (c)& (d)Optical Images of Uniform & Bead Free PVA & PVA-NaAlg Nanofibers

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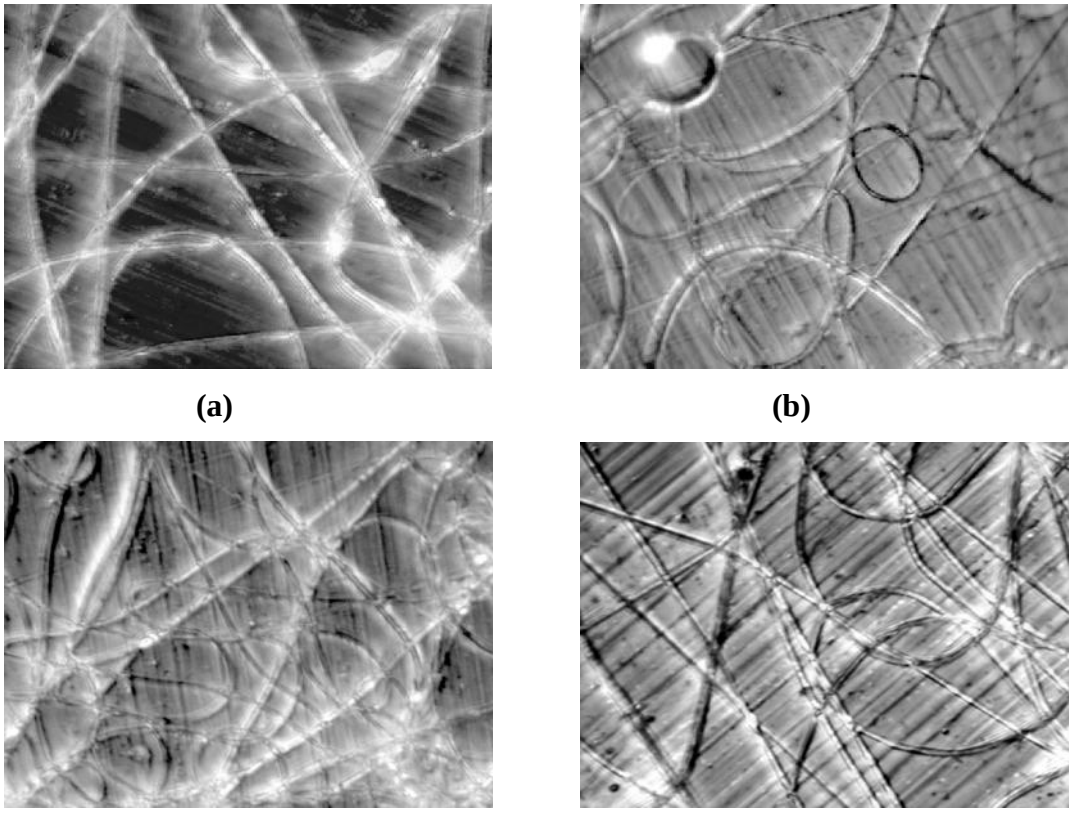

(a) **(b)**

(c) **(d)**

Figure 2 (a) & (b): Optical Images of drug Loaded PVA & PVA-NaAlg Nanofibers with Beads & Drops, (c) & (d): Optical Images of Uniform & Bead Free drug Loaded PVA & PVA-NaAlg Nanofibers.

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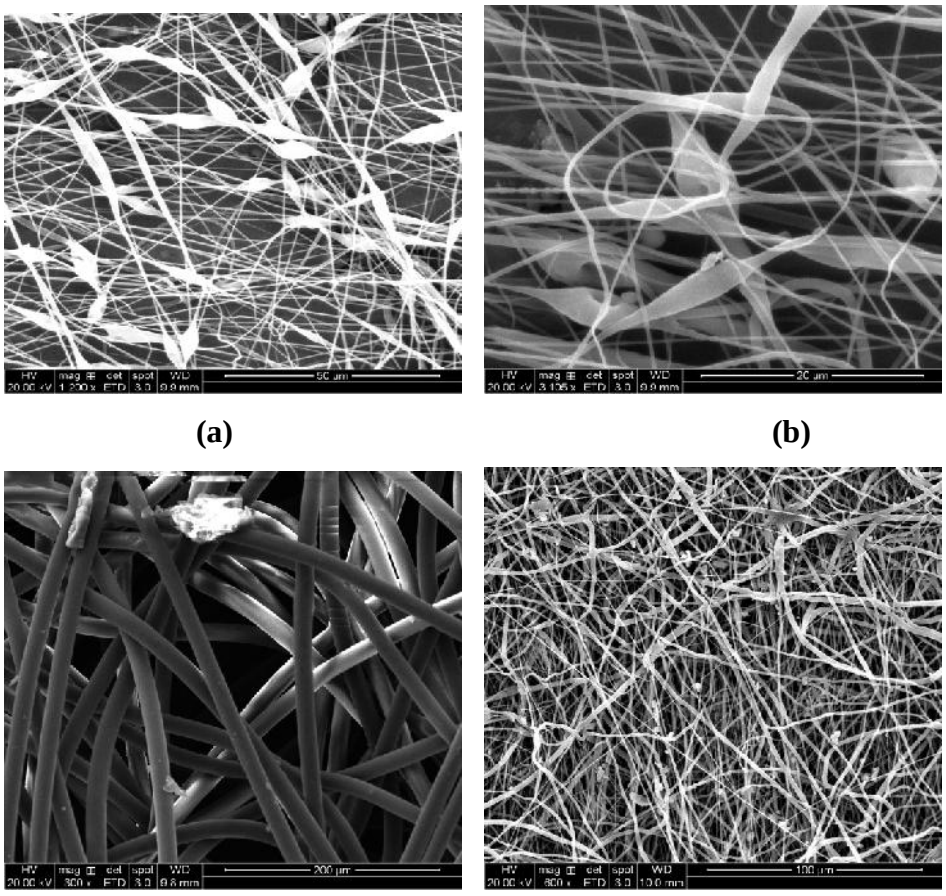

(a) **(b)**

(c) **(d)**

Figure 3 (a) & (b): SEM Images of drug Loaded PVA & PVA-NaAlg Nanofibers with Beads & Drops, (c) & (d): SEM Images of Uniform & Bead Free drug Loaded PVA & PVA-NaAlg Nanofibers.

Dated 22/01/2014

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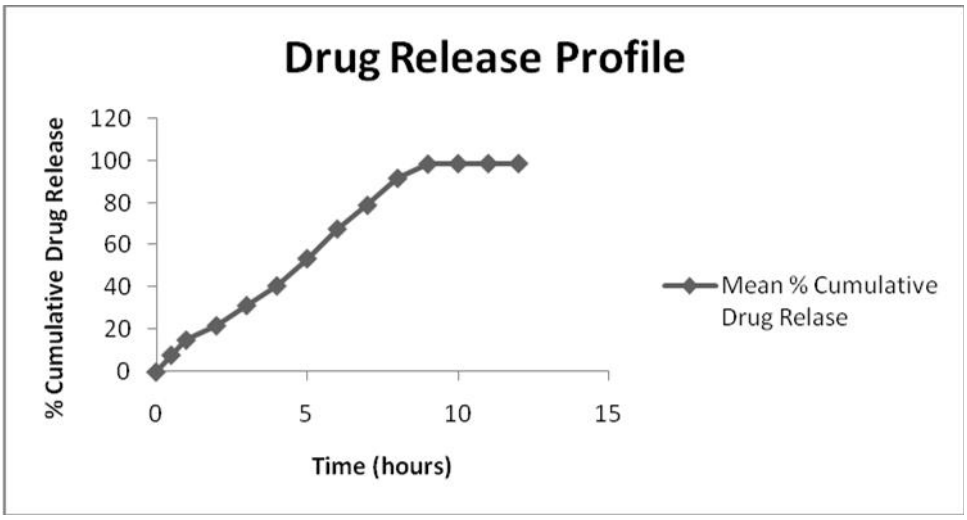

Figure 4: Drug Release Profile of Drug vs. Time

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ABSTRACT

Present invention relates to medicated nano-patch prepared by nano-fibres comprising of biodegradable and non-biodegradable polymer for treating topical, intra-ocular and peri-ocular pathological conditions of the eye. Nano-patch of present invention provides comfortable and controlled delivery of encapsulated therapeutics constantly over a period of several months. The nano-patches are formed of a composition comprising of biodegradable or non-biodegradable polymer, a therapeutic active component and optionally, a plasticizer, and optional additive (s).

Amended Claims: Clean Copy

Claims:

WE CLAIM-

1. Polymeric nano-fiber based patchs for ocular delivery prepared from a composition comprising a polymer ranging from 5% to 15% (w/w) ; drug plasticizers from 0.01% (w/w) to 5% (w/w) , penetration enhancer, buffer system and tonicity reagent.
2. The nano patch as claimed in claim 1, wherein the polymer is poly vinyl alcohol having an average molecular weight in the range from about ranging from 9000 g/mol to 124,000 g/mol.
3. The nano patch as claimed in claim 1, wherein the polymer is sodium alginate of average molecular weight in the range from about ranging from 10000 g/mol to 600,000 g/mol.
4. The nano patch as claimed in claim 1, wherein the polymer is selected from group consisting of biodegradable and non-biodegrdable polymers consisting of agarose, chitosan, gelatin, Hyaluronic acid various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate) Synthetic Cellulose derivatives: CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, Methylhydroxyethylcellulose Poly (acrylic acid) - based polymers: CP, PC, PAA, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2- hydroxyethyl methacrylate), poly(acrylic acid-coethylhexylacrylate), poly(methacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid, PEG, poly(alkylcyanoacrylate)and blends and copolymers thereof.
5. The nano patch as claimed in claim 1, wherein the composition comprises an additional therapeutically active agent selected from the group consisting of antibacterial antibiotic agent, synthetic antibacterial agent, antifungal antibiotic agent,

synthetic antifungal agent, antineoplastic agent, steroidal anti-inflammatory agent, nonsteroidal anti-inflammatory agent, anti-allergic agent, glaucoma-treating agent, antiviral agent and anti-mycotic agent.

6. The nanopatch as claimed in claim 1, wherein the composition comprises an additional antibiotics selected from a group aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micronomicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamfenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), .beta.-lactams (e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefÏŠxime, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalexin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephapirin sodium, cephradine, pivcefalexin), cephamycins (e.g., cefbuperazone, cefmetazole, cefininox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems, flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate

hydriodide, penicillin g benethamine, penicillin g benzathine, penicillin g benzhydrylamine, penicillin g calcium, penicillin g hydrabamine, penicillin g potassium, penicillin g procaine, penicillin n, penicillin o, penicillin v, penicillin v benzathine, penicillin v hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin) or a combination thereof.

7. The nanopatch as claimed in claim 1, wherein the composition comprises a polymer selected from the group of nondegradable polymers consisting of nylon, polyurethane, polycarbonate, polyacrylonitrile, polyethyleneoxide, polyaniline, polyvinyl carbazole, polystyrene and poly(vinyl phenol) and the group of biodegradable polymers consisting of polyhydroxyacids, poly(caprolactone, polyanhydrides, polyhydroxyalkanoates, polyurethanes, collagen, alginate, chitosan, and hyaluronic acid, blends and copolymers thereof.

8. The nanopatch as claimed in claim 1, wherein the composition comprising of plasticizers, preferably low volatile substances with average molecular weights between 200 and 400 such as diesters derived from dicarboxylic acids (e.g. sebacic acid, azelaic acid) or from ethylene glycol and propylene glycol, citric acid (tributylcitrate, triethylcitrate) or glycerol (triacetin, tributyrin) and a mixture thereof, in a range of 0.1 to 3 % w/w of total composition.

9. The nanopatch as claimed in claim 1, wherein the composition comprising penetration enhancer selected from the group consisting of β-cyclodextrin, sodium lauryl sulphate, sodium glycocholate, sodium deoxycholate, sodium laurate, glyceryl monolaurate peppermint oil, spearmint oil, menthol, pepper oil, eucalyptus oil, cinnamon oil, ginger oil, fennel oil, and dill oil, hydrochloric acid, phosphoric acid, acetic acid, citric acid, lactic acid, oleic acid, linoleic acid, lauric acid, palmitic acid, benzoic acid, poly(alkylene oxide), a polyvinyl alcohol, and a polycarboxylic acid

polymer and a mixture thereof in a range of 0.5 – 10 % wt by weight of total composition.

10. The nanopatch as claimed in claim 1, wherein the composition comprises a buffer system selected from the group consisting of borate buffers, phosphate buffers, citrate buffers, and combinations and mixtures thereof.

11. The nanopatch as claimed in claim 1, wherein the composition comprises of tonicity agents selected from the group consisting of dextrose, NaCl, KCl, ZnCl2, CaCl2, and MgCl2.

12. The nanopatch as claimed in claim 1 wherein nanopatch has a length of from 1 mm to 30 mm, a width of from 1 mm to 30 mm and a thickness of from 0.001 mm to 2 mm.

13. Method of preparing nanopatch from nano-fibres forming polymers comprises:

- electrospinning a solution comprising of polymer and active therapeutic component or with a carrier and pharmaceutically acceptable additives

-cross-linking, phase separation, melt fibrillation, gas jet, melts blower or nano litrography

14. The method of producing nano-fibres as claimed in 13 wherein the solution for electrospinning has a viscosity ranging from 200 – 1000 cps and a surface tension ranging from 43.5 – 46.5 mN/m.

15. The method of producing nano-fibres as claim 13, wherein the composition has a pH ranging from 5 to 8.5.

16. The method of producing nano-fibres as claim 13, wherein nano-fibers are produced by electrospinning a solution comprising of a polymer and active therapeutic agent.

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On Behalf of Applicant
Digitally Signed