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Experimental and theoretical investigations of *Lantana camara* oil diffusion from polyacrylonitrile membrane for pulsatile drug delivery system

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ABSTRACT

Porous composite membrane of polyacrylonitrile (PAN) and *Lantana camara* essential oil was synthesized by solvent casting method. Stability of oil in PAN solution was measured by XiGo nano tool indicating constant relaxation time of 1487 time/s. Pore size of few microns confirmed by electron microscopy was supported by atomic force microscopy indicating roughness factor of 0.9 nm. Contact angle of 2° inveterates superhydrophilicity of the composite membrane. Membrane showed excellent antibacterial activity against both Gram-positive *Bacillus subtilis* and Gram-negative *Escherichia coli* with a 7–10 mm zone of inhibition. *In vitro* release of *Lantana* oil from the composite membrane was carried out in isotonic phosphate buffer solution (pH = 7.4). *Lantana* oil was released for 9 h, lag time of 3 h with constant 33% release confirmed PAN membranes as potential system for pulsatile drug delivery applications. Diffusion of E-caryophyllene (antibacterial component of oil) which was studied through molecular simulation using Material Studio software ensued diffusion coefficient value of $1.11 * 10^{-9}$ m^2/s. Biocompatibility of the composite membrane was assessed by mouse embryonic fibroblast cell line (NIH 3T3) through MTT assay indicating more than 91% viable cell even at 200 μg/mL concentration. Such membranes can be efficiently used in biomedical applications as antibacterial and antifungal agent.

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1. Introduction

Controlled drug delivery systems aim to uphold plasma concentration of drugs within the therapeutic window for a longer period of time, thereby ensuring sustained therapeutic action [1]. Controlled and targeted delivery approach of therapeutic compounds, which involves multidisciplinary scientific approach, has the potential to radically improve disease outcomes. Nanotechnology enhances the therapeutic efficacy by altering the solubility of hydrophobic drug, prolonging drug half life, decreasing degradation during circulation, reducing potential immunogenicity, and releasing drug in sustained or stimuli triggered fashion promising to increase the efficacy while decreasing unwanted side effects [2]. Pulsatile drug delivery system (PDDS) is the sustained and controlled release of drug at substantially constant release rate per unit time/stimuli, thus managing the disease while minimizing the treatment side effects. It delivers the drug at specific time as per the physiological need of the disease resulting in enhanced therapeutic efficacy and compliance. PDDS is also classified as time controlled release in which the drug is released at specific time interval and stimuli induced release in which release is controlled by stimuli like pH or enzymes present in the intestinal tract and systems regulated by external stimuli like magnetism, ultrasound, electrical effects and irradiation. PDDS is used in the treatment of asthma, cardiovascular diseases, arthritis, hypercholesterolemia and peptic ulcer [3]. Lyon and his co-workers, which studied pulsatile release of insulin from thermoresponsive poly(N-isopropylacrylamide-co-acrylic acid) microgel thin films prepared by layer-by-layer (LbL) polyelectrolyte assembly, hypothesize that subjection of film to many thermal cycles enables the embedded peptide to solubilize and subsequently partition through the film layer and this release is controlled by the film thickness [4].

Polyacrylonitrile (PAN), an engineering polymer, was extensively used as high performance filters/adsorbent for removing toxic chemicals [5], electronic devices [6], military/civilian protective clothing systems [7], super hydrophobic surface application [8], composite application [9], antibacterial and medical application [10], optoelectronics and photonic devices [11] and energy storage application [12] due to their enhanced thermal stability, high mechanical properties and chemical resistivity [13]. The strong electrostatic nature of PAN enables it to readily attract microbes and dust particles [14] resulting in the formation of biofilm and dysfunction of the membranes. Such allied problems

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are over-ruled by functionalizing PAN surface by anti-bacterial moieties such as antimicrobial peptides [15], antibiotics [16], enzymes [17], quaternary ammonium salts [18], N-halamine compounds [19] *etc.* Apart from all these bizarre properties, biocompatibility, semipermeability and limited solubility of PAN membranes help it to find potential application in drug delivery like hemodialysis and wound dressing [20]. Essential oils (EOs)/ethereal oils are the complex mixtures of volatile compounds produced as secondary metabolites in aromatic plants, stored in cavities, canals, epidermal cells, secretory cells or glandular trichomes and extracted from various parts of the plant [21]. EOs and/or their components are highly used in medicinal and plant pathology as well as in food industries to control microorganisms which are pathogenic to consumers and responsible for food spoilage [22]. Essential oils of thyme, cinnamon, bay, and clove are known to possess antimicrobial activity [23]. Essential oil or their main components not only possess wide range of antibacterial properties, but also of insecticidal, antiparasitic, antifungal, antiviral and antioxidant properties. But these essential oil constituents are not potent enough to all the aforementioned medicinal properties as single components, sometimes they cause negative organoleptic effects when added in sufficient amounts to provide an antimicrobial effect and other effects. Hence the use of EOs embedded in biocompatible polymeric membrane came into practice. Salmieri and Lacroix investigated the antiradical property of oregano essential oil in alginate/polycaprolactone film which could find potential application in food industry to prevent lipid oxidation in food systems [24]. Oussalah et al. studied the antimicrobial and antioxidant effects of milk protein based film containing oregano and pimento essential oil on beef's muscle meat wrapped and stored for 7 days. Oregano based film showed effectiveness against antimicrobial property while pimento based film exhibited effectiveness against antioxidant activity [25].

The present work focuses on immobilization of anti bacterial essential oil of *Lantana camara* (Verbenaceae) in PAN matrix through a facile technique to form *L. camara*–PAN composite membranes which is not reported elsewhere. *L. camara* is a notorious weed ornamental plant with varied medicinal properties and is extensively used in traditional medicines as carminative, antispasmodic and antirheumatic agents. It also exhibits antibacterial, antifungal, antioxidant, nematicidal and insecticidal properties [26]. The major components of *Lantana* oils are germacrene D (19.8%), E-caryophyllene (19.7%), bicyclogermacrene (11.7%), and α-humulene (9.3%) contributing ~60.5% of oil content [27]. Stability of the oil in PAN matrix was monitored using XiGo analyzer. Gram positive and Gram negative bacteria are great threat to the public health and result in increasing mortality and morbidity [28] *Escherichia coli* (Gram negative) is responsible for urinary tract infection, food poisoning, gastroenteritis and neonatal meningitis while *Bacillus subtilis* (Gram positive) is responsible for causing disease in immuno-compromised patients, consequently, the antibacterial efficacy of the composite membrane was examined systematically against these pathogens. Superhydrophilicity of the composite membrane responsible for antibacterial property was measured by drop shape analysis system. Chemical interactions of the anti-bacterial moiety *i.e.* E-caryophyllene with polymeric membrane and its diffusion from the membrane were studied by molecular dynamics simulation. Semicrystalline nature of PAN allows the encapsulation of oil in the amorphous part. Such semipermeability of the membrane allows the drug to ooze out in a controlled fashion as the burst release of the *Lantana* oil leads to the release of large quantity of oil leading to cytotoxicity. The super-hydrophilic nature of the membrane protects itself against the cell adsorption.

2. Experimental

2.1. Materials

Polyacrylonitrile ($\overline{M_W}$: 150,000), dimethyl sulfoxide (DMSO), and anhydrous sodium sulfate were purchased from Sigma Aldrich, India and phosphate buffer solution (PBS) (pH = 7.4) was from Thomas Baker. DMEM (Dulbecco's Modified Eagle Medium) containing 10% fetal bovine serum (FBS) was purchased from Gibco, India. Bacterial strains' Gram-negative (*E. coli* MTCC-1650) and Gram-positive (*B. subtilis* MTCC-441) were used for antibacterial evaluations. The mouse embryonic fibroblast cell line (NIH 3T3) which was obtained from National Centre for Cell Science (NCCS), Pune was used for cell viability test.

2.2. Extraction and characterization of oil

Shade dried leaves (1 kg) of *L. camara* were subjected to hydrodistillation in a conventional Clevenger type apparatus for 10 h to extract the essential oil. Light yellow color oil (0.92 g, <1% yield) obtained by decantation was dried over anhydrous sodium sulfate and stored at 4 °C. Essential oil composition was determined using Shimadzu GC-2010 coupled with Perkin-Elmer Turbo Mass spectrometer using a PE-Wax (30 m × 0.32 mm i.d., film thickness 0.25 μm) column. Oven temperature initially kept at 70 °C was raised to 120 °C at 2 °C/min and was then raised to 240 °C at 3 °C/min; injector temperature was maintained at 250 °C and helium acted as carrier gas for the molecular ions. EO constituents were analyzed by mass spectrometer (ion trap at 220 °C; manifold at 80 °C and transfer line at 240 °C). The MS fragmentation pattern was checked by matching with NIST mass spectral libraries.

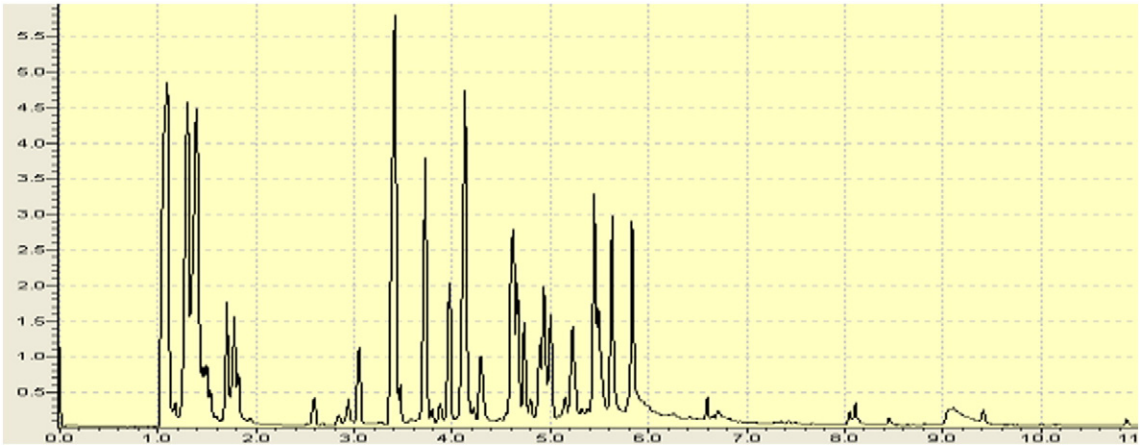

Fig. 1. GC profile of *Lantana* oil.

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