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Lipid-polymer hybrid nanoparticles: Development & statistical optimization of norfloxacin for topical drug delivery system

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ABSTRACT

Poly lactic acid is a biodegradable, biocompatible, and non-toxic polymer, widely used in many pharmaceutical preparations such as controlled release formulations, parenteral preparations, surgical treatment applications, and tissue engineering. In this study, we prepared lipid-polymer hybrid nanoparticles for topical and site targeting delivery of Norfloxacin by emulsification solvent evaporation method (ESE). The design of experiment (DOE) was done by using software to optimize the result, and then a surface plot was generated to compare with the practical results. The surface morphology, particle size, zeta potential and composition of the lipid-polymer hybrid nanoparticles were characterized by SEM, TEM, AFM, and FTIR. The thermal behavior of the lipid-polymer hybrid nanoparticles was characterized by DSC and TGA. The prepared lipid-polymer hybrid nanoparticles of Norfloxacin exhibited an average particle size from 178.6 ± 3.7 nm to 220.8 ± 2.3 nm, and showed very narrow distribution with polydispersity index ranging from 0.206 ± 0.36 to 0.383 ± 0.66. The surface charge on the lipid-polymer hybrid nanoparticles were confirmed by zeta potential, showed the value from +23.4 ± 1.5 mV to +41.5 ± 3.4 mV. An Antimicrobial study was done against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and the lipid-polymer hybrid nanoparticles showed potential activity against these two. Lipid-polymer hybrid nanoparticles of Norfloxacin showed the %cumulative drug release of 89.72% in 24 h. A stability study of the optimized formulation showed the suitable condition for the storage of lipid-polymer hybrid nanoparticles was at 4 ± 2 °C/60 ± 5% RH. These results illustrated high potential of lipid-polymer hybrid nanoparticles Norfloxacin for usage as a topical antibiotic drug carriers.

1. Introduction

Norfloxacin is a fluoroquinolone derivative, differ from quinolones by having fluorine atom at six position and a piperazine moiety at seventh position. It is a broad spectrum antibiotic, has activity against Gram-negative and some Gram-positive aerobic bacteria. Norfloxacin acts by inhibiting synthesis of bacterial deoxyribonucleic acid (DNA) and have bactericidal property. They can be administered through oral route but the oral bioavailability is only 30–40% on a single dose of 200–400 mg [1].

Lipid-polymer hybrid nanoparticles (LPNPs) are emerging nanoparticles drug delivery systems that have advantage of both state i.e. liquid and solid state. LPNPs remains in solid state at body temperature [2], hence incorporation into the carbopol gel make them easy and consistent delivery of the drug to the targeted site. Due to their existent in both state, they showed a control release of drug. LPNPs are polymeric nanoparticle basically composed of three subsequent layers as 1) an inner hydrophobic core layer where the encapsulation of large amount of hydrophobic drug is possible; 2) an interfacial lipid layer that act as a flexible and biocompatible shell; and 3+) an outer hydrophilic polymer stealth layer to enhance the circulation time and stability of the LPNPs [4].

The coexistence of lipid and polymer possessing different physicochemical properties, such as their lipophilic and hydrophilic behavior lead to design a large variety of delivery system, and also have versatile capability of loading varying types of drugs, (Y.W.

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Xiao suggested that LPNPs are the best drug delivery system for the highly hydrophilic drug, because these drug possess the problem of rapid clearance from the body and low therapeutic recovery) [2] as well as they can be easily conjugated with the targeting moiety to deliver a drug to its target site.

Topical infections cover, localized surface infection due to accidental injury, surgery, abrasion and major complication of burns and topical disease covers bacterial infection, plant warts attack, and fungal growth etc. [3]. Topical antibiotics of lipid-polymer hybrid nanoparticles play an important role to deliver drug in such kind of topical infection and disease, due to its controlled and prolonged drug delivery to the surface of the infection, and avoid frequent application of the medicament to the infected and painful area, hence, lead to an increase in patient compliances.

On the other hand making use of biodegradable, biocompatible and non-toxic polymer such as Poly lactic acid have shown great therapeutic potential as a drug delivery system. PLA is a hydrophobic polymer and exhibits a good mechanical strength widely used in the manufacturing of containers, surgical equipment, and other delivery appliances. In this study the PLA is used as a polymer in an optimized concentration to control the release of drug.

The emulsification solvent evaporation (ESE) is a technique in which a primary emulsion oil/water was prepared, where the water act as a non-solvent system for the polymer (PLA) and finally the organic solvent in which the polymer was dissolved were evaporated by using Rota-evaporator. This method also known as 'water in drying' system for the hydrophobic polymer system because the water serves as a non-solvent that enable a hydrophobic polymer to form particle size in a Nano range. In this study the ESE was used to prepare the lipid-polymer hybrid nanoparticles of Norfloxacin to enhance the drug loading to the polymer and lipid core material, so that a controlled release formulation can be obtained.

However, it is challenging to design an optimal formulation with all desirable characteristics for site specific drug delivery of the norfloxacin, hence, an experiment design was used to overcome this problem. This research article provides an optimized formulation development, antimicrobial study, factors that influence the optimized formulation and there related characterization, and future in development of the effective delivery of LPNPs as an emerging tool for the topical drug delivery system.

2. Experimental

2.1. Materials

Norfloxacin was purchased from Sisco Research Laboratory, Mumbai, India. Poly lactic acid was obtained as a gift sample from Sun pharma advanced research company Ltd. Vadodara, Gujarat, India. Soya lecithin (Lipid), stearylamine (charge-inducer), poly vinyl alcohol (PVA), was purchased from Sigma Aldrich, India, Dichloromethane (DCM), Acetic acid (HPLC grade) was purchased from Merck specialties Pvt, Ltd., Mumbai, India. All other analytical grade chemicals were used during experiment. Millipore water (Millipore, Bedford, MA, USA) was used throughout the study.

2.2. Formulation of norfloxacin loaded lipid polymer hybrid nanoparticles

The lipid-polymer hybrid nanoparticles were prepared by emulsification solvent evaporation method firstly described by Gurny 1981 [5]. Briefly, soya lecithin with different PLA ratios (as showed in Table 1) were dissolved in 3 ml of DCM in a beaker and 200 mg of norfloxacin was separately dissolve in 0.3 ml acetic acid, which was further added to the above lipid-polymer (oil) phase. Then 20 ml of PVA (1.5% w/v) solution was used as an aqueous phase and that also act as a stabilizing agent for the formulation. Lipid phase was added dropwise into the aqueous phase under the high speed stirring for 24 h. Leaving continuous stirring of the formulation till total evaporation of organic solvent (DCM) at room temperature (RT). Nanoparticle dispersion was then subjected to sonication at 4 °C using probe sonicatior (PCI Analytics) for each 5 min of cycle leaving rest of 3min in between each cycles of sonication to avoid excessive heat generation that may lead to product degradation [6]. The lipid-polymer hybrid nanoparticles were centrifuged at 14000 rpm for 15 min at 4 °C. The supernatant were discarded and the solid mass were washed thrice with distilled water and then suspended in Millipore water. The LPNPs were lyophilized and stored in a tightly closed container.

2.3. Incorporation of lipid-polymer nanoparticles to the carbopol K-940 gel

Prepared LPNPs were further incorporated into 1% w/v carbopol K-940 gel. Briefly, 0.5% of the carbopol K-940 was dispersed in slight amount of distilled water and stirred continuously to form gel like mass, subsequently volume was made up to 50 ml with distilled water. Then the prepared LPNPs of norfloxacin (20 ml) was incorporated to it using high speed stirring at 1000 rpm for 5 min. The gel was further made alkaline by using 1–2 drop of Triethanolamine (TEA). Then 0.5 ml of glycerin was added to it that act as a humectant. Then the lipid-polymer nanoparticle gel of norfloxacin was left equilibrating for 24 h at room temperature (25 ± 1 °C) [7].

2.4. Experimental design

Design of experiment (DoE) and Response surface methodology (RSM) have been proved to be useful statistical and mathematical tool in experiment modeling and process optimization of the variables which may influence the responses of the designed experiments [8]. In the present study, Box-Behnken statistical (3^2 Full-factorial) design was employed by using Statistica V.10_ software (StatSoft, Inc. USA) to provide an appropriate set of experiment runs [9]. RSM explores the relationship between several independent variables (factors) and one or more dependent variable (responses). In this study, nine LPNPs were prepared to determine the effect of independent variable as concentration of soya lecithin (X1) and concentration of PLA (X2) on responses (dependent factor). The responses that taken in measure were: % entrapment efficiency (Y1), particle size (Y2), and % cumulative drug release (Y3) [20]. Tables 2 and 3 summarizes the experimental run, their coded form and corresponding actual values, and their responses.

2.5. Particle size, polydispersity and zeta potential

The prepared LPNPs were characterized for their particle size (nm), polydispersity index (PDI) and zeta potential (mV) by dynamic light scattering (DLS) method using Malvern Zetasizer Nano ZS (Malvern Instruments, UK) at standard temperature and experimental condition [10]. The average particle size defined as the relative size of the particle in the LPNPs, and a narrow PDI reveals about particle homogeneity in the prepared formulation. The zeta potential value having larger than +30 mV or −30 mV reveals about its maximum repulsion force and long term stability of the prepared LPNPs. All the measures of particle size, PDI, and zeta potential was run trice for 15 cycle by using software.

2.6. Entrapment efficiency (%EE)

The entrapment efficiency (%EE) of the prepared lipid-polymer hybrid nanoparticles was determined by measuring the

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