Review Article

Perspective on Solid Lipid Nanoparticles as Drug Delivery System for Infectious Diseases

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Over the years, infectious diseases have significantly contributed to the mortality and morbidity rates in the healthcare system. Conventional treatments have been used for many years to treat infectious diseases, such as oral and topical drug delivery routes. However, these treatments present numerous challenges. The factors such as the solubility of the drug, its size and its molecular weight may affect the efficacy of conventional therapies. Nanotechnology or nanomedicine is one of the novel and promising approaches to overcome these aforementioned challenges for traditional therapies. Solid lipid nanoparticles are a novel approach in the drug delivery system which was first introduced in early 1990s. Their small size, large surface area, high drug loading and the ability to interact with other phases, solid lipid nanoparticles are attractive for improving the performance of pharmaceutical, nutraceutical and other materials. Solid lipid nanoparticles have been proven to be one of the most effective methods of treating infectious diseases (antibiotic-loaded solid lipid nanoparticles). This review emphasizes solid lipid nanoparticles as a delivery system for infectious diseases. Also, it discusses research pertaining to the targeting approach of solid lipid nanoparticles in infections.

Key words: Solid lipid nanoparticles, infectious diseases, targeting approach, controlled release, antimicrobial agents

Infectious diseases have rendered a major influence on both mortality and morbidity rates in the healthcare system over the years. Not only life-threatening epidemics like smallpox, influenza, plague or cholera, but also chronic diseases like syphilis, leprosy and tuberculosis have affected society in recent decades. One of the most prevalent infectious diseases impacting individuals globally is tuberculosis. It originates from the bacteria, *Mycobacterium tuberculosis*, which primarily affects the lungs. Fortunately, it can be treated and cured. Around 10 million cases of tuberculosis were reported in 2019, according to the World Health Organization (WHO) Global Tuberculosis Report 2020[1]. Another infectious disease caused by *Mycobacterium* bacteria, notably *Mycobacterium leprae*, is leprosy. It mostly affects the skin, eyes, upper respiratory tract mucosa, and peripheral nerves. It is treatable with a Multidrug Therapy (MDT). WHO lists 202 256 new leprosy cases as occurring globally in year 2019[2]. Sepsis is a life-threatening illness with an estimated 48.9 million cases worldwide and 11 million deaths annually, according to a new scientific paper, though it is impossible to pinpoint specific figures[3]. Life-threatening infectious disease, malaria arises from parasitic infection caused by *Plasmodium* parasites. Infected female anopheles mosquito can transmit the infection. It is treatable and preventable. In 2019, there were 229 million cases of malaria worldwide, according to the WHO's Global malaria report 2020. That is slightly more than the statistic (228 million cases) in 2018. Additionally, according to the research, 4.09 lakh malaria deaths were reported worldwide in 2019[4]. The most potentially fatal infectious diseases include Human Immunodeficiency Virus (HIV), viral hepatitis and Sexually Transmitted Infections (STIs). A retrovirus identified as HIV attacks the human immune system directly, leading to Acquired Immuno-Deficiency Syndrome (AIDS). Hepatitis is a viral infection that may be

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equally fatal, the liver's inflammation, which also has an impact on its function, is one of the disease's main symptoms. Diseases like gonorrhoea and syphilis are examples of STIs. Bacteria (syphilis), parasites (trichomoniasis), and viruses (HIV) can all cause the development of STIs. According to the WHO, STIs, viral hepatitis and HIV account for 2.3 million deaths annually. This represents 14 % of all deaths due to cancer, digestive illnesses, parasitic and infectious diseases and other causes[5]. Mycosis, an infection caused by fungi, primarily affects the skin. Athlete's foot, yeast infections and other fungal infections are typical examples. According to an editorial that was printed in the journal for unicellular biology and human disease in June 2020, there are 150 million cases of fungal infections worldwide, and roughly 1.7 million deaths have been documented annually[6].

Infectious disorders have long been treated using conventional treatments, such as drug delivery *via* oral and topical routes. These treatments, however, come with a number of challenges. The main obstacle to oral treatment is gastrointestinal degradation, which causes significant active ingredient degradation. Only a limited amount of the active medication eventually reaches the intended site. Drug’s efficacy is decreased as a result of enzyme breakdown and subsequent chemical changes. Hydrolysis, reduction and group transfer are the main inactivation reactions. For instance, group transfer reactions destroy chloramphenicol, macrolides, rifamycin, etc., and hydrolysis typically renders beta-lactam antibiotics inactive[7]. Additionally, additional elements including a drug's size, molecular weight and solubility could influence the extent to which traditional treatments work. For instance, the Blood-Brain Barrier (BBB), an anatomical barrier to drug delivery that only permits tiny molecules with a molecular weight under 400 Da to enter the body. As a result, tiny, highly lipophilic drug molecules are needed to treat brain infections. 95 % of medication molecules are hydrophilic and cannot cross the BBB because of that[8]. It has been reported for medications in Biopharmaceutical Classification System (BCS) classes II and IV to have solubility problems. Amphotericin B belongs to the BCS class IV, while antifungal drugs like ketoconazole and itraconazole fall under the BCS class II. Due to their limited bioavailability, they are less effective. Moreover, antibiotic resistance is a crucial factor to take into account. For instance, antibiotics are administered orally to treat tuberculosis and other microbiological infectious diseases. Their efficacy may decrease as a result of prolonged use due to antibiotic resistance. The specific bacterium alters how it reacts to an antimicrobial agent, which is the cause. Because of this, treating infectious diseases with standard techniques is challenging[9]. One of the main issues with standard antibiotic therapy is the permeability barrier. Due to the permeability barrier made up of two membranes and an active efflux system that protects the cells of these pathogens, the majority of antibiotics are ineffective in the treatment of gram-negative bacteria[10]. Treatment for brain infections must take into account the BBB's permeability[11]. Antimicrobial medications can be prevented from entering bacterial cells *via* efflux pumps; however, if they do enter, these pumps can export the drugs out of the cell. This is one factor contributing to drugs' inadequate penetration into bacterial cells. Drug efflux pumps with multiple drug resistance are the most prominent example of this[7]. The adverse effects, side effects and drug interactions associated with the continued use of conventional therapy are a source of concern. The traditional oral therapy for cutaneous fungal infections may fall under this category. These problems can be treated topically, however prolonged application of topical treatments may have adverse outcomes[12].

In addition, leprosy and tuberculosis MDT may cause adverse drug reactions. Most microbes use a variety of strategies to prevent intracellular destruction. These strategies ultimately prevent phagocytosis and lysosomal degradation, preventing the intracellular killing of pathogens[7]. The use of conventional oral therapy for infectious disorders might result in the unnecessary distribution of medications in healthy tissues, which contributes to drug toxicity and reduces the effectiveness of the treatment. Due to the rapid clearance of drugs from circulation by metabolism or excretion, systemic administration might be challenging. Due to the inefficient systemic absorption of medications, the concentration of active drugs at the target site would likewise be low[13].

One of the newest and most promising solutions for dealing with problems with conventional treatments is nanotechnology or nanomedicine. Numerous different kinds of nanoparticles (inorganic, metal,

polymeric, etc.) nanocrystals, nanotubes, micelles, liposomes, dendrimers, carbon nanotubes, medical nanorobots and more are included in this novel technique. Solid Lipid Nanoparticles (SLNs) are one category out of these nanotechnology categories[14]. SLNs are a cutting-edge method of drug delivery that was initially introduced in the early 1990s. These are first-generation lipid-based nanocarriers (colloidal carriers), which have an exterior stabilizing layer of surfactants, co-surfactants and a solid lipid core inside. These are naturally biodegradable. SLNs are desirable for enhancing the performance of pharmaceutical, nutraceuticals and other materials due to their small size, large surface area, high drug loading and capacity to interact with other phases[15]. Solid lipids, emulsifying agents (to stabilize the formulation and prevent agglomeration), water or any other solvent are used to produce SLNs[16]. APIs like various drugs, deoxyribonucleic acid, proteins and vitamins are combined with emulsifiers into SLNs. Organic salts, surfactants and ionic and non-ionic polymers are examples of emulsifiers. Fatty acids, fatty alcohols, fatty esters, partial glycerides and triglycerides are all examples of solid lipids. In order to produce SLNs, a variety of techniques are used, including High Pressure Homogenization (HPH)-hot/cold, oil/water (o/w) microemulsion breaking technique, solvent emulsification diffusion technique, solvent injection method, water/oil/water (w/o/w) double emulsion method (especially for SLNs loaded with hydrophilic drugs and peptides, insulin, etc.) ultrasonication, supercritical fluid technique[17]. There are various more processes used in the formulation process, including as lyophilization, spray drying, and sterilisation of produced nanoparticles (in the case of parenterals). Following their manufacture, these SLNs are subjected to physicochemical characterisation. Particle size and distribution evaluation, surface charge (Zeta Potential (ZP)), stability studies, particle structure and nature, drug loading capacity, polymorphic behavior, drug release pattern, effects of different enzymes on particles, etc., are all included in this process. Entrapment Efficiency (EE) is frequently expressed as a percentage (% EE). When measuring % EE, the amount of free drug present in the dispersion medium is crucial; by dividing the difference between the drug concentrations in the system and the aqueous phase by the drug concentration in the system, EE can be calculated[18].

Many researchers are interested in SLNs because they have the potential to address the drawbacks of polymeric and liquid lipid-based nanoparticles as well as traditional drug delivery methods. SLNs can be administered in a number of ways, including orally, parenterally, nasally, ocularly, through rectal route etc. These nanocarriers have superior control over the kinetics of drug release (enable regulated or sustained release of drugs), which lowers the frequency of dosage. Drugs that are both hydrophilic and lipophilic can be included into SLNs due to their structural design. They are more efficient against intracellular pathogens because they can more easily permeate cell membranes (due to nanoscale particles). When administered orally, they inhibit the enzymatic breakdown of drugs, increasing the bioavailability of drugs. The stability of active ingredients is also improved by these nanoparticles. They have good biocompatibility since they are biodegradable. They can be produced on large scale, are inexpensive and have minimal toxicity. While preparing these particles, no specific solvent is required (organic solvents are avoided). In comparison to other systems, its manufacturing and sterilisation processes are simple. Compared to polymeric nanoparticles called liposomes, these carriers are less expensive. Polymorphism is less likely to occur when solid lipids are present in the interior core of particles. This ultimately credits the formulation with having good stability. They can accommodate more drug than traditional drug delivery systems. SLNs also have the benefit of being easily modifiable on their surface, allowing them to influence some important biological activities. It can be a useful strategy for systemically administering SLNs. As a result of these benefits, SLNs (antibiotic-loaded SLNs) have been shown to be one of the most successful techniques of treating infectious infections. It eventually avoids issues such as antimicrobial resistance, poor solubility, poor penetration, poor bioavailability and so on[15,16,19].

SLNs FOR TREATMENT OF INFECTIOUS DISEASES

Rifampicin delivery by SLNs:

Chuan *et al.*[20] investigated Rifampicin-loaded SLNs (RFP-SLN) for the treatment of tuberculosis. The traditional oral treatment for the same results in a lower drug efficiency index because drug distribution occurs in both target

cells and healthy tissues. As a result, the amount of drug reaching the target region is insufficient to produce the desired optimum effect. The authors developed and tested RFP-SLNs for mean particle size, Polydispersity Index (PDI), morphology, and EE. *In vitro* and *in vivo* investigations on the cellular absorption of RFP-SLNs by Alveolar Macrophages (AMs) and Alveolar Epithelial Cells (AEC) have been conducted. Below concentration of 20 µg/ml, the cytotoxicity was modest. In addition, when researching the targeting ability of RFP-SLNs, the intracellular concentration of rifampicin was determined. When compared to rifampicin solutions, rifampicin concentrations in AMs were substantially greater than those in AEC after RFP-SLN treatment. This demonstrates that SLNs are more effective in targeting AMs than AEC. The particle size of SLN also influences alveolar macrophage uptake efficiency. AMs were found to efficiently phagocytoze RFP-SLN with a diameter of 829.6±16.1 nm. A further analysis of the selectivity of RFP-SLNs for AMs revealed that after administration of RFP-SLNs, the levels of rifampicin in AMs were higher than in epithelial cells. These overall findings suggest that RFP-SLNs improve targeted drug delivery and absorption, making it a promising alternative to standard tuberculosis therapy. Furthermore, RFP-SLNs were demonstrated to target AMs more precisely[21-23].

Doxycycline-encapsulated SLNs:

Hosseini *et al.*[24] investigated Doxycycline-loaded SLNs (DOX-SLNs) for brucellosis treatment. Brucellosis is an infection caused by an intracellular bacterium *Brucella melitensis*. Treatment of intracellular microorganisms is difficult. Antibiotic administration is the traditional strategy, however it is less effective. DOX-SLNs were developed using the double emulsion or melt dispersion approach. These samples' particle size, ZP and PDI were investigated. The particle size of SLNs was measured at particular time intervals and the size change was not significant. The average diameter of all NPs was 405 nm, whereas it was 299±34 nm in the optimal formulation. Field Emission-Scanning Electron Microscopy (FE-SEM) was used to detect the spherical shape, smooth surface and homogeneous polydispersity of SLNs. According to the encapsulation and drug loading experiments, 8.2 %-11.3 % of doxycycline was loaded on SLN. The percentage of encapsulation ranged from 91.3 %-97.4 %. Differential Scanning Calorimetry (DSC) analysis revealed that there were no free doxycycline crystals left in the DOX-SLNs. The gradual and controlled release of doxycycline from DOX-SLN was demonstrated in an *in vitro* drug release study and an antibiotic sensitivity test (Minimum Inhibitory Concentration (MIC)). The *in vitro* cytotoxicity tests revealed that the concentrations tested were substantially higher than those required to treat infected macrophages. The results of the infection assay showed that DOX-SLN is more effective than free doxycycline. Overall, the results showed that DOX-SLN is more efficient than free doxycycline and that the SLN delivery system may greatly improve drug targeting and controlled release[25,26].

Triclosan targeted delivery by SLNs:

Kakadia *et al.*[27] developed and studied Triclosan-loaded SLNs (TSN-SLNs) in the treatment of skin infections. Traditional topical antimicrobial therapy is less effective due to inadequate targeting and limited access to deeper layers of skin. Initially, the authors used the HPLC method to conduct a chromatographic examination of triclosan. They then used high shear homogenization followed by probe ultrasonication to develop triclosan SLNs using Glyceryl Behenate (GB) and Glyceryl Palmitostearate (GP) as solid-lipids. Surfactants and co-surfactants were used in the formulation to avoid physical instability. The particle size, PDI and ZP of these SLNs were all measured. The speed and duration of homogenization have an impact on particle size reduction. The mean particle size produced by GB-SLNs was found to be greater than that of GP-SLNs. Drug Entrapment Efficiency (% DEE) estimates the percentages of triclosan in SLNs. EE is reduced by lipid crystallisation, high lipid concentration, and greater surfactant concentration than co-surfactant. DSC assessment revealed the homogeneous dispersion of triclosan in SLNs as well as the nanosize of these particles. The crystallinity caused by encapsulation was also assessed using the X-ray diffraction method. Transmission Electron Microscope (TEM) was used to examine the spherical form and nanosize of these SLNs. Under normal conditions, the formulated SLNs were also subjected to a stability investigation. The amount of Triclosan that permeated pig skin was investigated using *in vitro* permeation of the medication. The authors then assessed the triclosan retained in different sections

of skin following permeation using a differential stripping technique. This study found that dermal delivery by SLNs improves drug targeting and penetration into deeper layers of the skin[28-30].

Enrofloxacin-loaded docosanoic SLNs:

Xie *et al.*[31] developed and evaluated enrofloxacin-loaded SLNs in the treatment of Salmonellosis caused by internal *Salmonella* (gram-negative bacterium). Traditional antibacterial therapy has good action and cellular diffusion but limited intracellular retention. The authors used ultrasonication and hot homogenization to produce enrofloxacin-loaded SLNs from docosanoic acid. Under normal atmospheric circumstances, the morphology of these particles was determined. The amount of enrofloxacin present in the nanoparticles following formulation was evaluated by EE and loading capacity. Photon correlation spectroscopy was used to evaluate particle size, ZP and PDI. The cellular absorption of enrofloxacin-loaded SLNs into RAW 264.7 cells (monocyte or macrophage-like cells) was studied using cell culture. There was a substantial difference in accumulation caused by free enrofloxacin *vs.* its encapsulated version. The cellular absorption of SLNs was influenced by particle size and ZP. Increased particle size improved cellular absorption. Though particle net surface charge had an effect on cellular absorption, particle size was the most important factor. Furthermore, the scientists used HPLC to examine the intracellular elimination process of the encapsulated drug, which revealed that the elimination rate for enrofloxacin-loaded docosanoic acid SLNs was lower than the rate for free enrofloxacin. The antimicrobial activity of encapsulated enrofloxacin against intracellular *Salmonella* demonstrated that encapsulated enrofloxacin is more effective against intracellular bacteria than free enrofloxacin. All of these findings demonstrated that enrofloxacin-loaded docosanoic acid SLNs are an effective drug delivery mechanism against intracellular bacteria like *Salmonella*[32,33].

Clarithromycin-loaded SLNs (CL-SLNs) for topical ocular therapy:

Nair *et al.*[34] studied CL-SLNs utilised as topical ocular treatment in illnesses such as endophthalmitis. The ocular drug delivery system is frequently encountered with anatomical, biochemical and physiological limitations. It is challenging to administer drugs to the posterior region of the eye *via* conventional therapy. The design, formulation and evaluation of the therapeutic efficacy of CL-SLNs were all part of this study. The lipids (stearic acid), surfactants (Tween 80) and co-surfactants (Transcutol P) necessary in the formulation were chosen based on clarithromycin solubility experiments. It was determined that the viscosity and partition coefficient (LogP) of the lipids to be employed are also crucial factors. CL-SLNs were subsequently produced using ultrasonication and high-speed stirring. The particle size, PDI and ZP as well as EE and drug loading capacity, were all evaluated and the lipid concentration and sonication time were found to have a substantial effect on the particle size, EE and drug loading capacity. The particle size fell from 413 nm to 113 nm as the sonication period was reduced (particle size range: 113-413 nm). Furthermore, the shorter sonication duration resulted in enhanced drug loading capacity. Surfactant concentration is another element that influences EE. The drug release pattern was first slow and then gradually increased (similar to the sustained release pattern). Drug release is influenced by factors such as lipid and drug melting points, surfactant-lipid and drug-lipid interactions. Penetration studies revealed that the control group had a slower penetration rate, whereas the optimised CL10 (CL-SLNs) had a faster permeation rate. TEM picture depicted drug encapsulation. Albino rabbits were used to test the sample's ocular compatibility. An *in vivo* pharmacokinetic study of clarithromycin revealed that CL10 (SLN) has a longer duration of action than the control group. Data from stability studies revealed that SLNs have strong physical stability under optimal conditions. All of the data showed that CL-SLNs are safe and capable of delivering drugs into the posterior area of the eye[35,36].

Acyclovir-loaded SLNs:

Hassan *et al.*[37] developed and studied acyclovir-loaded SLNs for the treatment of Herpes Simplex Virus (HSV) infection. Authors evaluated the influence of SLNs on the drug's oral bioavailability. Acyclovir is a drug that is used to treat HSV infection. This treatment faces numerous obstacles, such as inadequate oral bioavailability and severe medication reactions. The authors first used ultrasonication and high shear homogenization to create acyclovir-loaded SLNs from glyceryl palmitostearate. The appropriate lipids and

surfactants were determined based on particle size, ZP and PDI. The results showed that the amount of solid lipid and surfactants affects particle size, ZP and PDI substantially. The observed particle size, ZP, and PDI values are 122.72±2.15, -24.37±1.07 and 0.23±0.01 respectively. The observed PDI values indicated that the SLNs were distributed uniformly. TEM was used to examine the particles' spherical form and smooth surface. The drug EE evaluation revealed a high EE due to the sufficient room created by abnormalities in the structure of SLNs for drug encapsulation. Furthermore, DSC was used to calculate the degree of crystallinity (RI), which suggested that the SLNs structure was less organised. This demonstrated SLNs great trapping efficiency. Furthermore, thermal examination revealed that the developed SLNs were solid. *In vitro* drug release studies for SLNs revealed a significant sustained release pattern. In addition, an *in vivo* pharmacokinetic investigation employing Sprague-Dawley rats revealed that SLNs have a longer half-life and better release profile than suspension. SLNs were also found to block the P-glycoprotein efflux transporter in the colon, which boosted drug absorption and permeability. In conclusion, all of the findings revealed that SLNs are both promising and effective methods for overcoming the obstacles of acyclovir traditional therapy[38].

Fluconazole-loaded SLNs (FLZ-SLNs):

El-Housiny *et al.*[39] designed and tested FLZ-SLNs for topical drug delivery in the treatment of Pityriasis Versicolor (PV). Fluconazole is exclusively used to treat PV as an oral antifungal drug, which can have a variety of side effects. Although topical therapy can be advantageous, drug penetration into the skin limits its effectiveness. FLZ-SLNs were developed by the authors employing high shear homogenization and ultrasonication. The measured EE ranged between 55.48±1.21 % and 82.94±1.24 %. Increasing solid lipid concentration reduces crystallinity and increases lipid crystal defects, which boosts EE. The particle size and ZP ranges measured were 292-500 nm and -21-33 mV, respectively. Particle size and ZP are affected by the type of surfactants and lipids utilised. The PDI values were less than 0.3 regardless of the lipids or surfactants used. Overall, the characterisation results demonstrated that the particles were physically stable. The particle's spherical shape and smooth surface, as well as its colloidal size, were observed with TEM. Drug release experiments *in vitro* revealed sustained release. The type and concentration of lipids can have an impact on drug release. The solid-state of FLZ-SLNs at room temperature is suggested by DSC. These formulations were then transformed into gels using carbopol. The gel was found to be smooth and semi-solid, with good spreadability and no syneresis. FLZ-SLN gels were found to have pH values ranging from 5.5 to 6.7, as well as drug content levels ranging from 8 to 9 mg/g. Gel rheological experiments revealed non-newtonian behaviour and thixotropy. These gels were shown to restore their viscosity after application. The regulated release pattern of drug was portrayed in an *in vitro* drug release research of gels and the amount of drug released was observed to be between 53 % and 83 %. The release of fluconazole from the examined gel formulations was found to be slower than that of nanoparticle dispersions. Furthermore, a study on PV patients found that the total eradication of infection after using gel was superior to that after using routinely used cream. Overall, the formulated FLZ-SLN improved skin penetration, reduced adverse effects, and increased efficacy[40,41].

Voriconazole-SLN delivery for testing on *Aspergillus fumigatus* strains:

Kelidari *et al.*[42] developed and tested voriconazole-loaded SLNs (VRC-SLNs) against *Aspergillus fumigatus* strains. Voriconazole is a BCS class II antifungal drug with limited solubility at physiological pH. As a result, the authors developed and tested a voriconazole SLN formulation that can improve drug solubility. Following an initial examination of several lipids, stearic acid and compritol were discovered to be more suited for drug dissolution. Following lipid selection, the scientists used high-shear homogenization followed by probe ultrasonication procedures to prepare VRC-SLNs. These produced particles were then evaluated for particle size and ZP. The lowest particle size and the ZP were found to be 286.6 nm and -15 respectively. A 30 000X magnification FE-SEM revealed that the particles had a nearly spherical form and a restricted size distribution. Antifungal susceptibility studies were also performed on the nanoparticle compositions. The studies revealed MIC values, the MIC50, MIC90 and GM values for voriconazole were 0.25, 0.25 and 0.16275 g/ml respectively whereas the results

for VRC-SLNs were 0.015, 0.031 and 0.009636 respectively. As a result, it can be implied that the therapeutic dose might be reduced in case of VRC-SLNs, lowering the risk of unwanted effects. The overall study indicated that including voriconazole into SLNs can improve formulation performance by boosting voriconazole bioavailability and dissolution rates[43,44].

Clotrimazole (CLZ)-loaded SLNs for treatment of *Candida albicans*:

Carbone *et al.*[45] developed and studied CLZ and Alpha-Lipoic Acid loaded SLNs (CLZ-ALA-SLNs). CLZ is a powerful antifungal agent. Using Alpha-Lipoic Acid (ALA) in conjunction with CLZ may improve the efficacy of CLZ therapy for the topical treatment of *Candida albicans*. The results of the DSC study of CLZ, ALA and their mixture demonstrate the presence of interaction between them. These chemical interactions can be avoided by using a dual-drug delivery system, which increases the synergistic effect of CLZ and ALA. Thus, the scientists used a low energy organic solvent-free phase inversion process (PIT method) to develop SLNs that included both ALA and CLZ independently. Using Dynamic Light Scattering (DLS), the mean particle size, ZP and PDI of uncoated and coated (cationic) SLNs were also measured. Uncoated particles had mean particle sizes ranging from 150-240 nm (unloaded SLN, CLZ-SLN and CLZ-ALA-SLN) whereas cationic SLNs (cSLNs) (coated with cationic surfactant didecyldimethylammonium bromide-DDAB) had mean particle sizes ranging from 75-90 nm. The PDI value for uncoated and unloaded SLNs was less than 0.25 (narrow size distribution), whereas it was larger than 0.25 for cationic unloaded SLNs. Spectrophotometric analysis was also done on uncoated and DDAB-coated CLZ-ALA-SLN to determine the amount of encapsulated drug. CLZ and ALA were both included into SLNs, greatly increasing the PDI values. This increase in PDI values suggested particle homogeneity. When CLZ was added alone or in combination with ALA, particle sizes rose from 150-250 nm. cSLNs (cationic) particle size remained below 100 nm even when loaded with CLZ or CLZ+ALA. The drug's incorporation into the SLN had no effect on the ZP values, indicating uniform drug distribution in the lipid matrix, with % EE values of 96.66 % and 60.66 % for CLZ and ALA, respectively. Evidence demonstrated that cSLNs exhibited higher ZP values than uncoated SLNs, indicating that cationic nanoparticles are more stable. Due to stronger repulsive forces, cationic coating on nanoparticles hinders coalescence. Furthermore, thermal analysis revealed that the lipid matrix of SLN fully dissolved the drug, resulting in its lack of crystallisation. Calorimetric studies also confirmed the solidification of SLN. The regulated release pattern of CLZ and ALA from nanoparticles was demonstrated in an *in vitro* release research. The formulation's antifungal efficacy was assessed using MICs. Cationic SLNs were found to have more potent antifungal action than uncoated SLNs[46,47].

Rifampicin-loaded SLNs for treatment of brucellosis:

Ghaderkhani *et al.*[48] investigated the efficiency of Rifampicin-loaded SLNs (Rif-SLNs) against *Brucella abortus* infection. The authors used modified homogenization or sonication procedures to develop Rif-SLNs and blank SLNs. The particle size, PDI and ZP of these produced formulations were all evaluated. It was discovered that combining 300-400 mg of stearic acid with 100-150 mg of poloxamer produced stable formulations with a minimum particle size of 319.7 nm. As a result, the quantity of stearic acid and poloxamer are almost the only criteria that dictate particle size and stability. Another deciding element in size, stability, PDI and ZP is the amount of lipoid S-100 used. For stable formulations, the PDI and ZP values were 0.204-0.247 and -18.4 to -16.7, respectively. Size, PDI and ZP were all modified by sonication time and cycle number. Rifampicin EE and drug loading were reported to be 95.78 % and 34.2 %, respectively. Rif-SLNs and their components were evaluated using DSC. There are four basic materials that are congruent with Rif-SLN spectral numbers, according to Fourier-transform infrared spectroscopy (drug, matrix, surfactant and cosurfactant). The particle shape was round to oval, the particle size was in the nano range and the surface was smooth, according to FE-SEM. A double drug release pattern was observed, rapid release for the first 4 h, followed by continuous release. Furthermore, no sedimentation, drug leakage or aggregation was seen under normal conditions. The results of the MIC test revealed that Rif-SLNs had twice the antibacterial activity of free Rifampicin. The half maximum Inhibitory Concentration (IC_{50}) values for Rif-SLNs and free

rifampicin were reported to be 161.3 g/ml and 4.66 mg/ml (87/89 g/ml) respectively[49,50].

CONCLUSION

Infectious diseases are a big concern around the world. Although these diseases are being treated on a broad scale using conventional procedures, there are certain restrictions that limit treatment. Nanotechnology may be one of the most promising options to addressing major problems about conventional antibiotic treatment. SLNs are the most advantageous of all nano drug delivery technologies due to their minimal toxicity and large-scale manufacture. These can be manufactured and sterilised. High pressure/shear homogenization-hot/cold, double emulsion or melt dispersion method, ultrasonication and other processes are used to prepare SLNs. They have stronger drug targeting capabilities and more control over drug release kinetics. They have the ability to increase bioavailability as well as permeability, which contributes for improved medication efficacy. Furthermore, the drug loading capacity of SLNs demonstrates their efficacy. The basic structure of SLNs consists of a lipophilic core made of solid lipid (the choice of solid lipid is determined by the drug's solubility) and a coating of surfactants/co-surfactants over it. As a result, these particles can contain both lipophilic and hydrophilic medicines. Any anti-infection medicine (antibiotic, antiviral, antifungal) can be integrated in these SLNs since the space for drug loading and trapping is enough and can hold the maximum amount of drug. Furthermore, because the medication is dissolved in the appropriate solid lipid or solvent, these particles avoid crystallisation of the drug inside. To ensure their stability and efficacy, these drug-loaded SLNs must go through several characterisation and evaluation methods. Particle size, surface charge on particles and PDI are some of the most important elements that determine formulation properties. Smaller the particle size, greater the efficacy of the formulation. Surface charge on particles should ideally be less than -30 mV and more than +30 mV. The ideal PDI is less than 0.5, ideally equal to 0.3. These formulations can be delivered by parenteral, topical or ocular methods. More research is needed to learn more about the biological interactions of SLNs and their commercialisation.

Conflict of interest:

The authors declare no competing interests.

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