Silver Sulfadiazine Encapsulated in Lipid-Based Nanocarriers for Burn Treatment

Article *in* Journal of burn care & research: official publication of the American Burn Association · June 2017

DOI: 10.1097/BCR.0000000000000602

CITATIONS
5

READS
518

3 authors:

Hanie Razavi
University of British Columbia
7 PUBLICATIONS **25** CITATIONS
SEE PROFILE

Mohammad Hassan Darvishi
Tehran University of Medical Sciences
9 PUBLICATIONS **61** CITATIONS
SEE PROFILE

Sajjad Janfaza
University of British Columbia
18 PUBLICATIONS **119** CITATIONS
SEE PROFILE

Silver Sulfadiazine Encapsulated in Lipid-Based Nanocarriers for Burn Treatment

Hamideh Razavi,* Mohammad Hasan Darvishi,* Sajjad Janfaza†

Burn injuries are at risk of bacterial infection because of the damaged skin and reduced immune responses. Silver sulfadiazine, a potent antibacterial agent, is considered as a standard therapy for burn treatment. Recent advances in nanotechnology have had an immense impact on drug delivery systems particularly in burn healing. Lipid-based nanocarriers have been considered as efficient drug delivery systems for burn treatment. This review presents a comprehensive overview of silver sulfadiazine-based nanocarriers and their application in the conservative healing of burn wounds. (J Burn Care Res 2017;XXX:00–00)

INTRODUCTION

Structure and Function of Skin

Human skin, largest vital organ in the body, is a complicated multifunctional structure that is very efficient in fulfilling its task like sensory input, protection, and thermal regulation. The epidermis, dermis, and hypodermis are 3 major layers of mammalian skin. Epidermis, the uppermost layer, is a stratified squamous keratinized epithelium and contains mostly keratinocytes but also melanocytes, Merkel cells, Langerhans cells, and other resident immune cells.[1–3]

The stratum corneum, the outer layer of skin, is a highly organized structure containing horny corneocytes (completely keratinized dead cells), embedded in a lipid matrix and provides rigidity of the skin. The dermis, containing collagen, glycosaminoglycans, and elastin fibers, is immediately underneath the epidermis and provides elasticity and tensile strength to the skin. Subcutaneous layer or hypodermis is the innermost and fatty layer of the skin that is made of loose connective tissue with adipose tissue.[4,5]

*From the *Nanobiotechnology Research Centre, Baqiyatallah University of Medical Sciences, Tehran, Iran; and †Young Researchers and Elite Club, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran.*

Address correspondence to Sajjad Janfaza, Young Researchers and Elite Club, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran. Email: s.janfaza@modares.ac.ir.

1559-047X/2017

DOI: 10.1097/BCR.0000000000000602

Routes of Skin Penetration

The transepidermal and transappendageal are 2 typical routes through which applied therapeutics transport across the skin.[6]

The transepidermal route is a significant pathway by which most drugs, especially compounds with small molecular weights, penetrate the skin. On the other hand, due to hair follicles and sweat glands only have a little contribution to the total surface area of the skin, the appendageal pathway is not considered as a main route for permeation.[7]

Transepidermal route includes 2 pathways: transcellular pathway, in which drug molecules pass through either corneocytes or lipid matrix, and intercellular pathway that involve penetration of drugs (mostly lipophilic or nonpolar drugs) across the lipid bilayers present among the corneocytes.[8] The skin penetration routes are presented in schematic form in Figure 1.

SILVER SULFADIAZINE

Burn is a painful event that can affect several organ systems as well as the skin and may cause morbidity and mortality. Although great progress has been made in this field, burn is still a serious problem in the world and a catastrophic event with patients suffering long hospitalization and rehabilitation.[9]

Topical application of ointments is usually used for treatment of superficial burns. The lipid component of the ointment reduces drying and accelerates the healing of the skin. In severe burns, one of the basic problems is bacterial colonization and infection.[18]

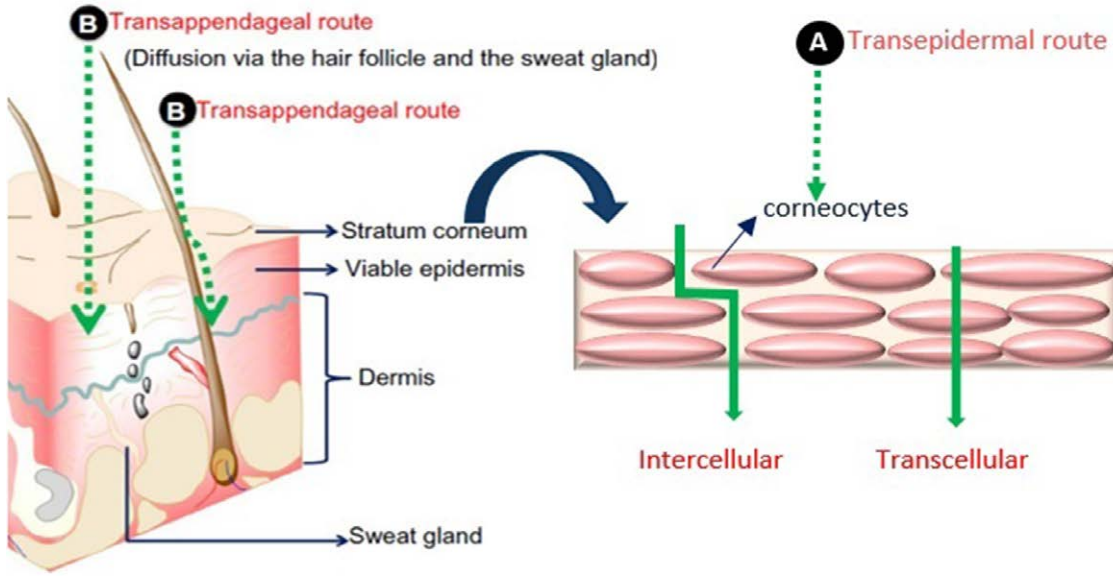

Figure 1. Schematic of skin penetration routes.

During the second half of the 20th century, topical antimicrobials containing silver for burn care introduced.

Silver sulfadiazine (SSD) was introduced by Charles Fox, Jr. SSD with trade name of Flammazine® is considered as the first choice and as "the accepted standard" for either prophylaxis or treatment of burn wound infections.[19]

SSD has several advantages such as controlling microbial colonization in burn wounds, thus preventing the development of invasive infections. It is affordable to cover large burns with SSD and prevent infection in damaged areas of the skin.[20,21] The chemical structure of SSD, which consists of silver (Ag) and sulfadiazine, is displayed in Figure 2.

SSD 1% cream exhibits broad-spectrum antimicrobial properties toward most gram-positive such as *Staphylococcus aureus* and gram-negative bacteria such as *Escherichia coli, Enterobacter, Klebsiella*, and *Pseudomonas aeruginosa*. Also, it has exhibited to be effective against some fungi and yeasts such as *Candida albicans*.[22]

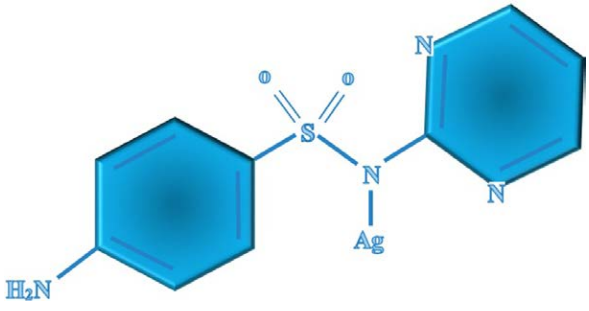

Figure 2. Chemical structure of SSD. SSD, silver sulfadiazine.

SSD has substantial disadvantages in treatment of burns like the formation of a pseudoeschar layer on the burn wound, which delays the wound healing. Other limitations of SSD include the need for frequent dressing changes at least once daily since it loses its silver ions early and induced fear and pain, especially in children. A cytotoxic effect of SSD has also been clearly demonstrated on keratinocyte as well as fibroblast resulting in a slowing down of the healing rate, increased skin problems after healing, renal toxicity, leukopenia, bacterial resistance to SSD, and adverse reactions.[19,23] Another problem of SSD is its low solubility that restricts its application in both hydrophilic formulations and aqueous environment.[24]

NANOCARRIERS

Nanocarrier systems have many different types that could be utilized for targeted drug delivery by various routes of administration, controlled release or sustained release of the encapsulated drugs at the active site, improvement of bioavailability and solubility of the drugs, and also reduction of therapeutic side effects.[25] Commonly, drug loading occurs by either adsorption onto carrier particles or entrapping in it.[26] Biodistribution of nanocarrier systems and their biological effects depend on many parameters, such as their size, surface charge, and hydrophobicity. Nanocarriers for drug delivery applications must be prepared of nontoxic, biocompatible, and biodegradable materials.[27]

Nanopharmaceutical delivery systems provide considerable potential advantages, such as enhanced skin permeation and offer over conventional approaches for topical treatment of various skin disorders.

Some nanocarriers like lipid-based nanocarriers can enhance the solubility of hydrophobic medicine to improve their efficacy resulting in reduced doses of medication. They are also able to deliver both hydrophilic and hydrophobic molecules and prevent them from degradation.

Nanocarriers also offer considerable advantages for burn treatment. For instance, nanocarriers used for burn treatment can release the antibacterial drug locally with suitable release rate (at therapeutic levels). They accelerate wound repair, with minimizing the risk of burn wound infection.

On the other hand, many properties of nanosystems should be investigated before using them as drug carriers. For example, nano-sized drug carriers often tend to interact with each other or with biomolecules in the surrounding environment. As a result, the nanocarriers' physicochemical properties alter in contact with biological environment. So, it is essential to minimize the potential interactions through precise manipulation of nanosystems, for example, surface charge adjustment and surface modification. Advanced research and development is required to overcome the problems associated with forming nanocarrier systems.[27]

The objective of a number of studies have been focused on synthesis of various vesicular lipid nanocarriers like liposomes, cubosomes, niosomes, and solid lipid nanoparticles (SLNs) containing SSD to determine their efficacy to prevent bacterial growth and biofilm formation.

Liposomes

Liposomes, membrane-like spherical vesicles, are composed of lipid bilayers surrounding aqueous compartments. Liposomes were first formulated and reported by Alex Bangham and have been widely used as pharmaceutical nanocarriers.[28]

Liposomal nanocarriers, the most successful drug delivery system, are particularly favorable because they are nontoxic biocompatible vesicles and have been approved by the FDA for medical applications. They have an advantage in safety because they consist of phospholipids, which are biocomponents. They are poorly immunogenic carriers with good payload capacity and can be made in different sizes. Moreover, liposomes are able to entrap both hydrophilic and hydrophobic drugs.[29]

The first study on liposomal SSD was published by Lichtenstein et al.[30] They investigated spectrophotometric assays for the determination of SSD and assessment of the efficiency of SSD encapsulation. They showed that SSD-loaded liposomes have potential benefits over the free SSD.

The efficacy of liposomes containing SSD to prevent growth of relevant human pathogens including *S. aureus, P. aeruginosa, E. coli*, and *Bacillus subtilis* has been studied by Taylor et al.[31] Their liposomal nanocarriers are composed of endogenous phospholipid dipalmitoylphosphatidylcholine, dioleoylphosphatidylethanolamine, and lauric acid. The results indicated that all liposomes reduced bacterial growth better than the commercially available antibiotic SSD.[31]

Cubosomes

Cubosomes (Cubs) are biocompatible liquid crystalline nanocarriers made of certain amphiphilic lipids in definite proportions with typically 100 to 200 nm in size and pore size about 5 to 10 nm. They possess a unique nanostructure consisting of 3-dimensional curved bicontinuous lipid bilayer and 2 congruent, nonintersecting water channels.[32]

When compared with liposomes, cubosomes can entrap larger amounts of drugs with various physicochemical properties.[33]

Several features of cubosomes have made them ideal drug delivery carriers. Cubosomes have great potential for entrapment of various active molecules such as hydrophilic compounds (can be enveloped within the water channels), the lipophilic ones (can be loaded into the lipid bilayers), and the amphiphilic molecules (may partition at the interface of lipid and water). They can protect drugs from physical and enzymatic degradation. Cabs are able to solubilize poorly water-soluble drugs. They can be used for controlled or sustained release.[34]

In 2014, Morsi et al.[20] prepared and characterized SSD-loaded cubosomes. Then, they formed cubosomal hydrogels (cubogels) by incorporation of optimum formulae in hydrogels of chitosan, carbopol 934, or chitosan/carbopol mixture.

In vitro study of cubosomes containing SSD has demonstrated that cytotoxicity of SSD can be minimized by controlling the release of SSD and decreasing the SSD dose to 0.2% caused a significant decrease in cytotoxic effect of silver.

In vivo histopathological study results displayed that cubogels based on chitosan and carbopol 934 were successful in deep second-degree burn treatment.[20]

Niosomes

Niosomes were developed and patented by L'Oréal in the 1970s and 80s. The first niosomal formulation was introduced by Lancome in 1987 and have been widely applied in pharmaceutics as a demanding tool to improve the delivery of many drugs.[35] Niosomes are vesicles formed by self-assembly of hydrated and synthetic nonionic surfactants such as sorbitans or polysorbates. Nonionic surfactants are inexpensive, nontoxic, and can be found in wide variety. Types of surfactants affect encapsulation efficiency, mechanical properties, stability, and toxicity of niosomes.[36]

In fact, they are nano-sized vesicles with a bilayer structure that have a hydrophilic core shielded from 1 or multiple hydrophobic lipid bilayer. This unique structure can encapsulate both oil-soluble compounds as well as water-soluble drugs and display some advantages including less production costs, higher chemical stability against oxidation, and hydrolysis and cause less allergic reactions.[37]

Dharashivkar et al[38], in 2014 reported an improved delivery system based on niosomal formulation of SSD for the treatment of burn sepsis. The current conventional SSD creams need to be applied 2 to 4 times a day and each reapplication requires removal, which is very painful. Accordingly, they developed novel niosomal formulation of SSD with sustained release once a day in order to improve the patient compliance. Also, they evaluated the influence of surfactant structure, the hydrophilic–lipophilic balance of a surfactant, and molecular weight on SSD entrapment efficiency. Niosomes were prepared through the ethanol injection method and by using different nonionic surfactants like tweens, spans, and cholesterol. In addition, fixed quantity of SSD was added in all the niosomal batches, then entrapment of SSD in niosomes were optimized.

Results indicated that among all the surfactants used, the niosomes containing span 60 had highest entrapment and more sustained release (98.14% over 28 hours). Span 60 with a longer saturated alkyl chain in comparison with other spans yields higher entrapment efficiency for niosomes.

In addition, it has been found that the surfactants chain length affect the release of SSD from the niosomes. With increasing chain length of surfactants, more sustained release of SSD for longer duration obtained. Besides chain length, another parameter that can affect the release of SSD is phase transition temperature of surfactants. Span 60 niosomes with high phase transition temperatures illustrated a decreased permeation of SSD.

In vitro antimicrobial survey exposed that 1% and 0.5% optimized niosomal formulation of SSD in comparison with 1% conventional cream has a superior zone of inhibition; 14 and 12 mm zones of inhibition were observed for niosomal SSD and conventional dosage form, respectively.

Moreover, in another study, thin film hydration method was used for preparation of niosomes. They prepared SSD (0.5% wt/wt) niosomal gel containing Span 60 as a nonionic surfactant and 1.6% carbopol 934 as the gelling agent.[39]

Results of in vitro permeation study revealed slower release of SSD from niosomal gel that might be because of slower diffusion of entrapped drug out of the gel matrix. Thereby, compared with niosomes and commercially available formulations in market, niosomal gel showed more sustained release of SSD, which would result in decreased dosing frequency, reduced trauma of the patients, and improved patient compliance.

In vitro antimicrobial study against *S. aureus* showed 21 mm zone size for SSD niosomes and 17 mm zone for marketed cream.[39] Therefore, their antibacterial activity was superior.

Besides, in vivo study demonstrated that the wound-healing activity of SSD niosomal gel was more effective than 1% wt/wt creams available in the market even when applied 1 time a day; thus, faster burned wound healing can be achieved using SSD niosomal gel.

The same group in 2014 evaluated the effect of aqueous and organic solvents used for preparation of niosomes on the entrapment efficiency of SSD.[40] SSD-loaded niosomes containing span 60 and tween 60 with cholesterol were prepared by ethanol injection methods while keeping the drug quantity constant, then optimized to get the high level of entrapment and sustained release. Optimized niosomes showed the sustained release of 98% over approximately a day while marketed formulation released the same amount after 8 hours.

Based on the in vitro study, niosomal SSD showed high antimicrobial activity against *S. aureus* and exhibited larger zone of inhibition (18 ± 1.0 mm) compared with conventional cream (14 ± 0.5 mm). In addition, incorporation of drug in the organic phase can considerably enhance entrapment efficiency of the niosomes.

Solid Lipid Nanoparticles

SLNs were introduced as a drug delivery system for addressing the drawbacks of traditional colloidal dispersions, in the early 1990s. The core of SLNs consist of a lipid with a high melting point and is covered with outer shell containing amphiphilic surfactants in which drug can be efficiently incorporated. They

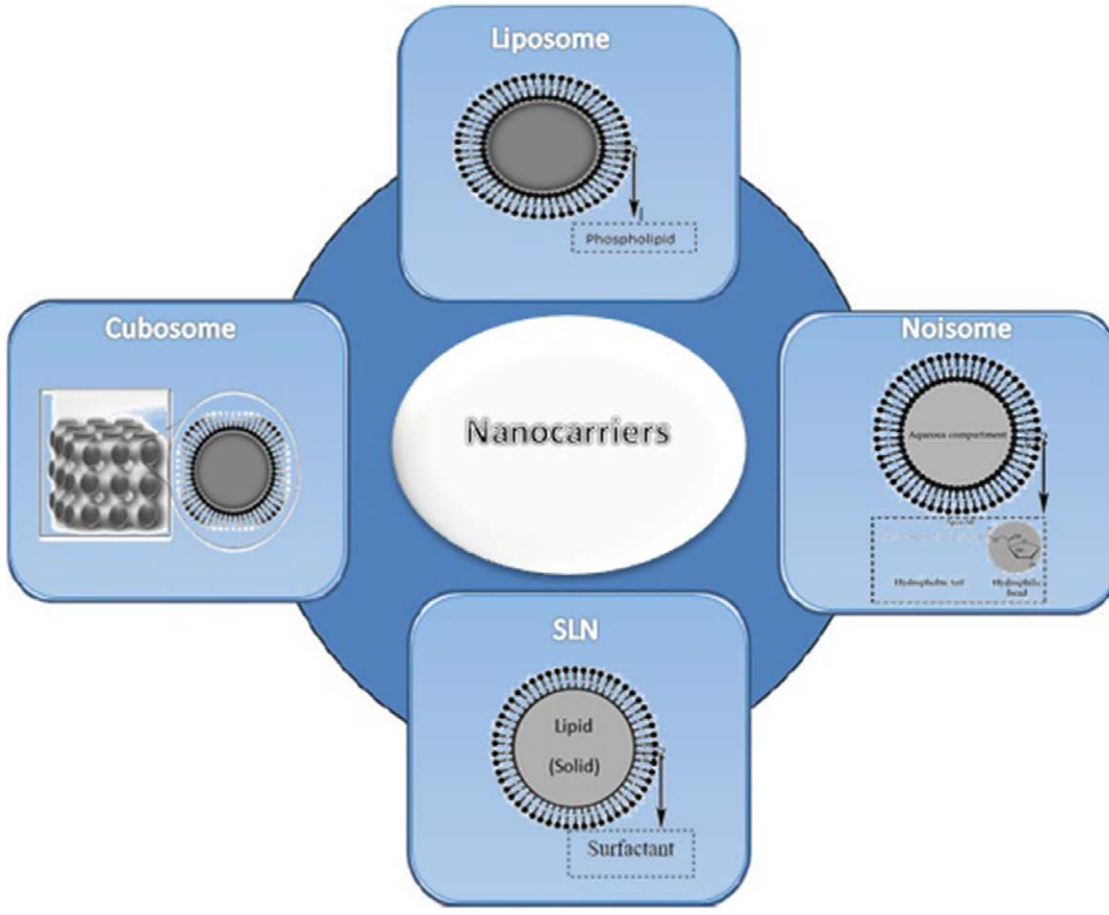

Figure 3. Four lipid-based nanocarriers employed for SSD delivery. SSD, silver sulfadiazine.

are commonly matrices of lipids, which is solid at room and body temperature. SLNs with a mean size between 50 and 1000 nm have a potential for the delivery of lipophilic and hydrophilic drugs.[41] Some main advantages of SLNs are

- The possibility of production on a larger scale and their production is quick and efficient
- Utilization of physiologically acceptable lipid and biocompatible surfactants to prepare SLNs that makes them suitable in living systems and therefore, less stringent regulatory requirements
- From SLN degradation, no acute toxic effects are expected
- SLN formulations can remain stable for a long time
- They can deliver a high content of the drug, so improved pharmacokinetic properties
- In transdermal administration, they can adhere to the surface and stay a long time on the stratum corneum layer by forming a dense hydrophobic film
- Protection of unstable drugs against degradation[42,43]

In 2013, Dellera et al[24] focused on wound dressings by SLNs containing SSD and platelet lysate for the treatment of skin persistent lesions.

SLNs were prepared using ultrasound and hot homogenization techniques. Then, SLNs-loaded wound dressings based on chitosan glutamate or hydroxypropylmethyl cellulose were prepared. Biocompatibility and antimicrobial activity of SSD-loaded SLNs was evaluated. Moreover, elasticity (tensile measurements), resistance to penetration, hydration, and bioadhesion properties of wound dressings were investigated.

The result of their work demonstrated that this dressing can improve the antimicrobial activity of SSD and wound healing. Furthermore, the in vitro assays presented encapsulation of SSD in SLN that can protect fibroblasts and keratinocytes from toxicity of SSD.[44] Figure 3 pinpoints the above-mentioned nanocarriers structures.

CONCLUSIONS

Recent advances in nanotechnology have had an immense impact on various fields of studies from

energy to medicine.[45] Nanocarriers have been widely fabricated, investigated, and used in drug delivery, particularly in burn healing. The SSD-loaded nanocarriers have been used to control and minimize the risk of burn wound infection and accelerate wound repair.

Evidence discussed in this review shows that SSD encapsulated in lipid-based nanocarriers such as liposomes, cubosomes, niosomes, and SLNs has great advantages in healing of burns compared with the commercially available antibiotic SSD. For instance, research manifested that the formulation of SSD nanocarriers enabled avoiding the cytotoxic effect of silver by controlling the release of SSD and decreasing the dose of drug administered to patients while improving efficacy of the treatment. Beside, due to faster treatment times, which usually result in a shorter length of hospital stay, a noteworthy improvement in achieving patient's satisfaction has been observed.

We hope the information in this review will be useful in developing new lipid-based nanocarriers for burn healing.

REFERENCES

1. Herdina AN, Plenk H, Jr, Benda P, et al. Correlative 3D-imaging of Pipistrellus penis micromorphology: validating quantitative microCT images with undecalcified serial ground section histomorphology. J Morphol 2015;276:695–706.
2. Kirwan H, Pignataro R. The skin and wound healing. Pathology and Intervention in Musculoskeletal Rehabilitation 2015;25.
3. Razavi H, Janfaza S. Ethosome: a nanocarrier for transdermal drug delivery. J Paramed Sci 2015;6(2).
4. Sharma AM, Uetrecht J. Bioactivation of drugs in the skin: relationship to cutaneous adverse drug reactions. Drug Metab Rev 2014;46:1–18.
5. Vidlářová L, Hanuš J, Veselý M, Ulbrich P, Štěpánek F, Zbytovská J. Effect of lipid nanoparticle formulations on skin delivery of a lipophilic substance. Eur J Pharm Biopharm 2016;108:289–96.
6. El Maghraby GM. Stratum corneum lipid liposomes: drug delivery systems and skin models. Percutaneous penetration enhancers chemical methods in penetration enhancement. Springer; 2016:111–119.
7. Lane ME. Skin penetration enhancers. Int J Pharm 2013;447:12–21.
8. Ng KW, Lau WM. Skin deep: the basics of human skin structure and drug penetration. Percutaneous penetration enhancers chemical methods in penetration enhancement. Springer; 2015:3–11.
9. Harats M, Peleg K, Givon A, et al. Burns in Israel, comparative study: demographic, etiologic and clinical trends 1997-2003 vs. 2004-2010. Burns 2016;42:500–7.
10. Hostler D. Scorched skin. A guide to prehospital burn management. JEMS 2015;40:57–61.
11. McDougal WS, Slade CL, Pruitt B. Manual of burns. Springer Science and Business Media; 2012.
12. Li J, Zhang YP, Zarei M, et al. A topical aqueous oxygen emulsion stimulates granulation tissue formation in a porcine second-degree burn wound. Burns 2015;41:1049–57.
13. Landry A, Geduld H, Koyfman A, Foran M. An overview of acute burn management in the Emergency Centre. African J Emerg Med 2013;3(1):22–29.
14. Panahi Y. A herbal cream consisting of Aloe vera, Lavandula stoechas, and Pelargonium roseum as an alternative for silver sulfadiazine in burn management. Asian Biomedicine (Research Reviews and News). 2012;6(02):273.
15. Wang X, Zhao Q-s, Zhao C-l, Guo H, Peng S-w, Wu J-h. Effect of Chinese medical herbs-burn liniment on deep second degree burn in rats. African Journal of Traditional, Complementary and Alternative Medicines 2014;11(6):92–104.
16. Moravvej H, Hormozi AK, Hosseini SN, et al. Comparison of the application of allogeneic fibroblast and autologous mesh grafting with the conventional method in the treatment of third-degree burns. J Burn Care Res 2016;37:e90–5.
17. Elijah IE, Komak S, Finnerty CC, Herndon DN. Pediatric burns. Pediatric critical care medicine. Springer; 2014:277–286.
18. Prevention B. Outpatient burns: prevention and care. 2012.
19. Heyneman A, Hoeksema H, Vandekerckhove D, Pirayesh A, Monstrey S. The role of silver sulphadiazine in the conservative treatment of partial thickness burn wounds: a systematic review. Burns 2016;42:1377–86.
20. Morsi NM, Abdelbary GA, Ahmed MA. Silver sulfadiazine based cubosome hydrogels for topical treatment of burns: development and *in vitro/in vivo* characterization. Eur J Pharm Biopharm 2014;86:178–89.
21. Sheckter CC, Van Vliet MM, Krishnan NM, Garner WL. Cost-effectiveness comparison between topical silver sulfadiazine and enclosed silver dressing for partial-thickness burn treatment. J Burn Care Res 2014;35:284–90.
22. Li P, Wu L, Li B, Zhao Y, Qu P. Highly water-dispersible silver sulfadiazine decorated with polyvinyl pyrrolidone and its antibacterial activities. Mater Sci Eng C Mater Biol Appl 2016;60:54–9.
23. Heo DN, Yang DH, Lee JB, et al. Burn-wound healing effect of gelatin/polyurethane nanofiber scaffold containing silver-sulfadiazine. J Biomed Nanotechnol 2013;9:511–5.
24. Dellera E, Bonferoni MC, Sandri G, et al. Development of chitosan oleate ionic micelles loaded with silver sulfadiazine to be associated with platelet lysate for application in wound healing. Eur J Pharm Biopharm 2014;88:643–50.
25. Yordanov G. Nanocarriers for antibiotics. New Delhi, India: Daya Publishing House; 2014:124–134.
26. Hanafi A, Kamali M, Hasan Darvishi M, Amani A. Evaluation of loading efficiency of azelaic acid-chitosan particles using artificial neural networks. Nanomed J 2016:169–178.
27. Shetab Boushehri MA, Lamprecht A. Nanoparticles as drug carriers: current issues with *in vitro* testing. Nanomedicine (Lond) 2015;10:3213–30.
28. Wilson CM, Magnaudeix A, Naves T, Vincent F, Lalloue F, Jauberteau MO. The ins and outs of nanoparticle technology in neurodegenerative diseases and cancer. Curr Drug Metab 2015;16:609–32.
29. Unida S, Ito Y, Onodera R, Tahara K, Takeuchi H. Inhalation properties of water-soluble drug loaded liposomes atomized by nebulizer. Asian J Pharm Sci 2016;11(1):205–206.
30. Lichtenstein A, Margalit R. Liposome-encapsulated silver sulfadiazine (SSD) for the topical treatment of infected burns: thermodynamics of drug encapsulation and kinetics of drug release. J Inorg Biochem 1995;60:187–98.
31. Taylor E, Kaviratna A, Banerjee R, Webster TJ. Vesicular lipid nanoparticles (liposomes) for the treatment of medical device infections. In: MRS proceedings. Cambridge University Press; 2011; 1316: mrsf10–1316.
32. Azhari H, Strauss M, Hook S, Boyd BJ, Rizwan SB. Stabilising cubosomes with Tween 80 as a step towards targeting lipid nanocarriers to the blood-brain barrier. Eur J Pharm Biopharm 2016;104:148–55.

33. Luo Q, Lin T, Zhang CY, et al. A novel glyceryl monooleinbearing cubosomes for gambogenic acid: preparation, cytotoxicity and intracellular uptake. Int J Pharm 2015;493:30–9.
34. Karami Z, Hamidi M. Cubosomes: remarkable drug delivery potential. Drug Discov Today 2016;21:789–801.
35. Jain AP, Sharma P, Pandey P, et al. Niosome a novel approach for drug delivery system: an overview. Asian J Pharm Sci Res 2013;3(5):18–30.
36. Ritwiset A, Krongsuk S, Johns JR. Molecular structure and dynamical properties of niosome bilayers with and without cholesterol incorporation: a molecular dynamics simulation study. Appl Surface Sci 2016;380:23–31.
37. Chuah L, De Silva L, Saravanan M, Fu J. Preparation and optimization of tocotrienol rich fraction (TRF)-loaded niosomes. Asian J Pharm Sci 2016;11(1):56–57.
38. Dharashivkar S, Sahasrabuddhe S, Saoji A. Silver sulfadiazine niosomes: a novel sustained release once a day formulation for burn treatment. Int J Pharm Sci 2014;6(1):611–16.
39. Dharashivkar SS, Sahasrabuddhe SH, Saoji AN. Niosomally encapsulated silver sulfadiazine gel for burn treatment. J Microencapsul 2015;32:137–42.
40. Dharashivkar S, Sahasrabuddhe S, Saoji A. Effect of few formulation variables on entrapment efficiency of silver sulfadiazine niosomes. 2014.
41. Hao J, Wang F, Wang X, et al. Development and optimization of baicalin-loaded solid lipid nanoparticles prepared by coacervation method using central composite design. Eur J Pharm Sci 2012;47:497–505.
42. Xia X. Dissolving the rocks: solubility enhancement of active pharmaceutical ingredients using mesoporous silica. 2014.
43. Bae KH, Lee JY, Lee SH, Park TG, Nam YS. Optically traceable solid lipid nanoparticles loaded with siRNA and paclitaxel for synergistic chemotherapy with in situ imaging. Adv Healthc Mater 2013;2:576–84.
44. Sandri G, Bonferoni MC, D'Autilia F, et al. Wound dressings based on silver sulfadiazine solid lipid nanoparticles for tissue repairing. Eur J Pharm Biopharm 2013;84:84–90.
45. Mahyad B, Janfaza S, Hosseini ES. Bio-nano hybrid materials based on bacteriorhodopsin: potential applications and future strategies. Adv Colloid Interface Sci 2015;225:194–202.