Enhancing Topical Pharmacotherapy for Acne and Rosacea: Vehicle Choices and Outcomes

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The choice of vehicle is an important consideration in the treatment of acne and rosacea. Agents used to treat these common conditions may be limited by multiple factors, including poor stability during storage, limited residence time in the skin and follicular unit, and high potential for skin irritation. Novel drug delivery systems have been developed to address these problems, including microencapsulation, liposomal encapsulation, and the use of a variety of nanocarriers. New vehicle technologies for acne and rosacea treatments have appeared over the past 20 years and have somewhat improved stability, tolerability, and possibly efficacy. One of the latest vehicle technologies in acne and rosacea to enhance efficacy, stability, and tolerability is microencapsulation of benzoyl peroxide and tretinoin, which resulted in significant efficacy and good tolerability in patients with each of these two diseases. Other new vehicle technologies include a polymeric form of tretinoin and a microsphere product that combines tretinoin plus clindamycin. It is likely that there will be more reports of clinical success as experience with the rapidly evolving delivery technologies increases. This review summarizes drug delivery systems that have been developed with the aim of improving outcomes for patients being treated for either acne or rosacea. It also focuses, where possible, on formulations that have been evaluated in clinical studies.

KEY WORDS: Acne, rosacea, microencapsulation, vehicle, topicals

Topical agents for acne and rosacea are used as both first-line and adjunctive therapy with oral medications.[1-3] This approach to treatment has important advantages, including the ability to achieve high concentrations of medication to the target tissue and decreasing or eliminating systemic exposure that may lead to adverse events (AEs).[4] Although topical therapy should avoid AEs associated with systemic medication administration, the efficacy, safety, and tolerability of topical therapy is influenced by percutaneous penetration, retention at the target for a sufficient time to obtain the desired therapeutic effect, and avoidance of adverse local reactions that may affect adherence.[5,6] It has been noted that the drug product is only one of multiple components that determine the efficacy and tolerability of topically applied therapies such that the performance of a topical medication is also influenced by characteristics of the vehicle formulation that may influence penetration, permeation, irritancy, and patient preference.[7]

The effects of the active drug ingredient in a topical medication are influenced by the vehicle base employed for delivery (e.g., ointment, cream, lotion, gel, foam, spray), and it has been repeatedly shown that vehicle selection can influence both adherence to therapy and treatment outcomes.[8-11] Drug performance is also significantly impacted by the delivery system in which it is packaged (e.g., microcapsules, liposomes, transferomes, water-in-oil-in-water emulsions, chitosan nanoparticles, solid lipid nanoparticles, cellulose acetate nanofibers, polyvinyl alcohol conjugates, silicone capsules, etc.) prior to mixing with the vehicle.[12, 13] Drug delivery systems have been shown to influence efficacy, tolerability, and adherence for topical therapies.[14-16] Many different delivery technologies have been applied to topical treatments, but only a few have translated into commercial products for dermatologic diseases. This may be due to the inability to economically scale the technology and failure to achieve desired controlled release.[12,17]

This review summarizes drug delivery systems that have been developed with the aim of improving outcomes for patients being treated for either acne or rosacea. It also focuses, where possible, on formulations that have been evaluated in clinical studies.

MICROENCAPSULATION

In general, encapsulation creates a barrier between the medication and the skin. The slow migration of medication from the microcapsules also provides sustained delivery. Microencapsulation techniques typically result in microspheres with a fine coating of inert, natural, or synthetic

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polymeric materials deposited around solid or liquid micronized drug particles.[18] When microspheres are applied to the skin, the amount of free drug in the preparation penetrates the epidermis. Catabolized drug is replaced by continued release of the product from the microspheres.[19] The controlled release of drug from microcapsules has the potential to extend the time over which it is delivered to the skin after a single application and to decrease the risk for very high concentration of the drug to produce local adverse reactions.[20-22]

Microencapsulation can be achieved with a sol-gel process in which drug molecules are entrapped in the inner porosity of a silica-based matrix.[18] In this process, amorphous silica is made by forming interconnections among colloidal particles (the "sol") under increasing viscosity until a rigid network, the silica shell (the "gel"), is formed with pores of submicron dimensions. Drug encapsulation is achieved by a technique known as interfacial polymerization. The process results in a drug core surrounded by a silica capsule shell.[23] This technology has been employed in an effort to enhance the efficacy, tolerability, and compatibility of two drugs that have been used extensively in the treatment of acne: benzoyl peroxide (BPO) and tretinoin. In the combination treatment for acne, encapsulated tretinoin is protected from oxidative decomposition by BPO, which enhances the stability and shelf life of tretinoin. The silica shells also create barriers between both tretinoin and BPO and the skin, which have the potential to decrease the irritation that often follows topical application of BPO or tretinoin. For BPO, skin lipids control the rate of release from the silica capsule since the release mechanism involves migration of the skin's natural secretions through the silica pores into the capsule. The skin lipids dissolve the BPO crystals, carrying it to the skin surface. The controlled release of BPO may be particularly important for the treatment of rosacea. Application of "free" BPO to the skin of patients with rosacea leads to significant skin irritation, such as erythema, burning, and stinging. Microencapsulation has the potential to decrease the occurrence of these AEs and permit use of an agent that has been shown to be efficacious but poorly tolerated in patients with rosacea.[24-27] The combination of microencapsulated BPO and microencapsulated tretinoin and microencapsulated BPO alone have both been evaluated in large-scale, Phase 3 trials, and each has demonstrated efficacy at least equivalent to that for other topical and systemic treatments for these conditions and tolerability comparable to that for vehicle.[28,29]

Microencapsulation has also been employed to enhance the properties of retinol, a vitamin A derivative that has been used to treat acne.[30] This drug is limited by both degradation and toxicity at high concentrations.[31] A sol-gel formulation of retinol has been shown to provide slow release of the drug over several hours. Assessment in healthy volunteers showed that this formulation was less irritating than retinal delivered via microsponge particles and was associated with lower levels of interleukin-1α.[12]

LIPOSOMAL FORMULATIONS

Liposomes. Many different liposomal drug formulations have been developed. These vesicles are formed by ordinary phospholipids found in living systems. They have a hydrophilic environment in the core and a lipophilic environment between the layers of phospholipids.[13] Liposomal drug formulations have been reported to deliver high concentrations of drug to the desired site of action (thus potentially improving efficacy) and to decrease the frequency of local AEs versus unencapsulated formulations.[22,32,33]

Liposomal encapsulation has been used for multiple agents employed in the treatment of acne and/or rosacea. The combination of liposomal BPO gel and liposomal tretinoin gel has been shown to be effective for treatment of comedones, papules, and pustules in patients with acne and had a lower incidence of AEs, including erythema, itching, burning, scaling, and irritation than observed with unencapsulated BPO and tretinoin.[14] Tretinoin-loaded liposomes alone have also demonstrated greater efficacy than free drug in patients with acne, and liposomal BPO has been shown to have a significantly greater antibacterial effect than free drug in patients with this disease.[34,35] More recent studies in experimental animals have demonstrated increased anti-acne efficacy, lower transepidermal water loss (TEWL), and less skin irritation with liposomal BPO plus adapalene versus free drug.[36]

Flexible liposomes. Novel elastic liposomal vesicles are superior to conventional liposomes because of their improved interactions with skin and better drug penetration.[32] These deformable or elastic vesicles are referred to as transfersomes. They are comprised of phospholipids and edge activators, such as polysorbate or sodium cholate, which produce elastic carriers.[37] The constructs are spherical, but they have the ability to deform in shape. Members of this "class" include transfersomes (phospholipids with the surfactant sodium cholate), ethosomes (phospholipids with a high proportion of ethanol), proniosomes and niosomes (flexible non-ionic surfactant vesicles), invasomes (phosphatidylcholine, ethanol, and a mixture of terpene penetration enhancers), and SECosomes (surfactant, ethanol, and cholesterol).[37]

Niosomal formulations have been developed for multiple agents used to treat acne or rosacea, including BPO, tretinoin, clindamycin, and azelaic acid.[38-42] This approach has been shown to lower the doses of BPO and tretinoin required to achieve efficacy in a rat model.[38] Tretinoin has also been encapsulated in pronisomes, and clinical evaluations in human subjects showed greater efficacy and less irritability versus commercial formulations.[43] An ethosome formulation of azelaic acid has been demonstrated to decrease the minimum inhibitory concentration for the drug against *Cutibacterium acnes* from 500 to 250 µg/mL.[42]

Penetration Enhancer-containing Vesicles (PEVs). Another promising variation of liposomal drug delivery combines a permeation enhancer with a flexible liposomal formulation. These constructs consist of phospholipids and penetration enhancers, such as diethylene glycol mono ethyl ether, or propylene glycol. These combinations of ingredients reduce stratum corneum barrier function and improve in vesicular bilayer fluidity.[32,33,44,45] This approach has been employed in a deformable liposomal formulation of tretinoin that also included diethylene glycol monoethyl ether.[45] Preclinical assessment of this tretinoin delivery system indicated that it enhanced penetration of the drug through the skin versus conventional tretinoin cream and resulted in milder hyperkeratosis without hyperplasia, suggesting less skin irritation.[45] A PEV formulation of retinoic acid has been evaluated in patients with acne and demonstrated improved tolerability and patient adherence versus conventional delivery of the drug.[16]

NANOPARTICLES

Nanoparticles, or nanocarriers, like the formulations described above, have multiple potential advantages over conventional drug delivery. These include enhanced solubility of highly hydrophobic drugs, the ability to provide sustained and controlled drug release, increased stability of therapeutic agents, and enhanced delivery of drugs to therapeutic targets (e.g., hair follicles). The most commonly used nanoparticles for topical and/or transdermal drug delivery are polymeric nanoparticles, nano-emulsions, and solid lipid nanoparticles (SLN).[46,47]

Solid lipid nanoparticles. Solid lipid nanoparticles (SLNs) are comprised of a solid lipid matrix that may consist of triglycerides, partial glycerides, fatty acids, steroids, or waxes, and are optimal for protecting unstable drugs and controlling medication release.[48] Solid lipid nanoparticles have been developed for the delivery of multiple agents employed for the treatment of acne and/or rosacea, including BPO, isotretinoin, adapalene, and tretinoin.[49-52] Incorporation of BPO into SLNs provided controlled release and reduced irritation associated with the free drug as demonstrated by results from Draize skin irritation test performed on albino rabbits.[49] A second nanoparticle formulation of BPO has been developed, but it has not yet been evaluated in patients or any *in vivo* or *in vitro* model systems.[53] Formulation of tretinoin in SLNs resulted in significantly superior stability on exposure to light versus free drug.[52] Tretinoin delivered in chitosan-SLNs also has been shown to have improved stability and to retain high antibacterial activity against *C. acnes* and *Staphylococcus aureus*.[54] Delivery of metronidazole via nanoparticles has been shown to provide sustained release of the drug on the skin over a period of eight hours and to decrease systemic exposure to the drug.[55]

Polymeric nanoparticles. With polymeric nanoparticles, the drug is dissolved and attached to a matrix/membrane polymer which increases stability and helps control drug release.[56] Adapalene in polymeric nanoparticles was shown to increase the aqueous solubility of the drug and to provide sustained release versus the commercial formulation *ex vivo* (on human cadaver and porcine ear skin). *In-vitro* studies demonstrated that encapsulation of adapalene significantly reduced the irritancy of the drug to a monolayer keratinocyte cell line (HaCaTs) and reconstituted human epidermis.[57]

Nanoemulsions. Nanoemulsions are colloidal particulate systems in the submicron size range. These carriers are solid spheres, and their surface is amorphous and lipophilic with a negative charge. Similar to other delivery systems, they are aimed at enhancing therapeutic efficacy and tolerability.[58] A nanoemulsion formulation of tretinoin is in development for the treatment of acne.[59] Results from a six-week split-face study in 10 patients indicated that the nanoemulsion formulation reduced inflammatory and non-inflammatory lesions to a greater degree than conventionally delivered drug, but that this difference did not achieve statistical significance.[59]

DISCUSSION

A wide range of technologies have been employed in the development of preparations in an attempt to improve stability, tolerability, and efficacy of topical pharmacotherapy for acne and rosacea. Results from preclinical and small scale clinical studies suggest that many of these approaches have the potential to achieve these goals, but only a small number of the preparations developed have so far reached late stage clinical development. Perhaps this is due to significant limitations encumbering these advanced formulations. A possible limitation to microencapsulation is its inability to create favorable conditions for drug encapsulation or efficiency of encapsulation.[60] Liposomal formulations might be limited by instability due to hydrolysis of phospholipids normally used in their preparation, drug leakage, low reproducibility, polydispersity, toxicity with repeated administration, and capability of inducing immunostimulation and complement activation.[61-63] In addition, liposomes can enhance or reduce skin penetration depending on the molecular weight of the drug and the liposome composition.[64] Other possible difficulties that have been noted with respect to the development of liposomal formulations include restricted drug loading capacity and technical difficulty in obtaining a sterile preparation.[62] There are also limitations with respect to the development of nanoparticle-based formulations, such as requirement for advanced manufacturing technology and particle-particle aggregation resulting from high surface areas, and the potential for hypersensitivity reactions.[65]

CONCLUSION

While limitations exist for all of the delivery vehicles discussed, it is important to underscore important successes that have been achieved in bringing new formulations to the clinic for patients with acne or rosacea. Microencapsulation of BPO and tretinoin with the sol-gel process has resulted in products that have demonstrated significant efficacy and good tolerability in patients with each of these two conditions.[28,29] Results from a large-scale study have shown that a polymeric formulation of tretinoin has a favorable safety and tolerability profile with lower incidences of erythema, dryness, and skin burning than those reported previously for other formulations of the drug.[66] Phase 3 results for a different type of microsphere formulation of tretinoin plus clindamycin have also indicated significant efficacy versus either drug delivered as monotherapy and good tolerability.[67] Greater rates of clinical success are expected as these advanced drug delivery systems continue to improve, which, along with enhancements in vehicle technology, serve to amplify the product's efficacy without sacrificing tolerability.

REFERENCES

1. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945-73.e33.
2. Anzengruber F, Czernielewski J, Conrad C, et al. Swiss S1 guideline for the treatment of rosacea. *J Eur Acad Dermatol Venereol*. 2017;31(11):1775-1791.
3. Del Rosso JQ, Tanghetti E, Webster G, et al. Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS). *J Clin Aesthet Dermatol*. 2019;12(6):17-24.
4. Lewis LS, Steele RW. Updated 24 Sep 2019. What are the advantages and disadvantages of topical antibiotics in the treatment of impetigo? Medscape website. https://emedicine.medscape.com/article/965254-medication#.
5. Tan X, Feldman SR, Chang J, Balkrishnan R. Topical drug delivery systems in dermatology: a review of patient adherence issues. *Expert Opin Drug Deliv*. 2012;9(10):1263-1271.
6. Trottet L, Maibach M. Key factors affecting the efficacy of a topical drug candidate: learnings

from past topical drug development, in Dermal Drug Selection and Development, L. Trottet and H. Maibach, Editors. 2017, Springer: Cham, Switzerland. p. 29-38.
7. Del Rosso JQ, Kircik LH, Zeichner J, Stein Gold L. The Clinical Relevance and Therapeutic Benefit of Established Active Ingredients Incorporated into Advanced Foam Vehicles: Vehicle Characteristics Can Influence and Improve Patient Outcomes. *J Drugs Dermatol*. 2019;18(2s):s100-s107.
8. Mayba JN, Gooderham MJ. A Guide to Topical Vehicle Formulations. *J Cutan Med Surg*. 2018;22(2):207-212.
9. Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. *J Am Acad Dermatol*. 2006;55(4):607-613.
10. Jackson JM, Pelle M. Topical rosacea therapy: the importance of vehicles for efficacy, tolerability and compliance. *J Drugs Dermatol*. 2011;10(6):627-633.
11. Bewley A, Page B. Maximizing patient adherence for optimal outcomes in psoriasis. *J Eur Acad Dermatol Venereol*. 2011;25 Suppl 4:9-14.
12. Shields CW 4th, White JP, Osta EG, et al. Encapsulation and controlled release of retinol from silicone particles for topical delivery. *J Control Release*. 2018;278:37-48.
13. Souto EB, Dias-Ferreira J, Oliveira J, et al. Trends in Atopic Dermatitis-From Standard Pharmacotherapy to Novel Drug Delivery Systems. *Int J Mol Sci*. 2019;20(22):5659.
14. Patel VB, Misra A, Marfatia YS. Topical liposomal gel of tretinoin for the treatment of acne: research and clinical implications. *Pharm Dev Technol.* 2000;5(4):455-464.
15. Prasad S, Mukhopadhyay A, Kubavat A, et al. Efficacy and safety of a nano-emulsion gel formulation of adapalene 0.1% and clindamycin 1% combination in acne vulgaris: a randomized, open label, active-controlled, multicentric, phase IV clinical trial. *Indian J Dermatol Venereol Leprol*. 2012;78(4):459-467.
16. Shamma RN, Sayed S, Sabry NA, El-Samanoudy SI. Enhanced skin targeting of retinoic acid spanlastics: in vitro characterization and clinical evaluation in acne patients. *J Liposome Res*. 2019;29(3):283-290.
17. Moin A, Deb TK, Osmani RA, et al. Fabrication, characterization, and evaluation of microsponge delivery system for facilitated fungal therapy. *J Basic Clin Pharm*. 2016;7(2):39-48.
18. Ciriminna R, Sciortino M, Alonzo G, et al. From molecules to systems: sol-gel microencapsulation in silica-based materials. *Chem Rev*. 2011;111(2):765-789.
19. Arkhireeva A, Hay JN, Oware W. A versatile route to silsesquioxane nanoparticles from organically modified silane precursors. *J Non-Cryst Solids*. 2005;351:1688-1695.
20. Kircik L, Friedman A. Optimizing acne therapy with unique vehicles. *J Drugs Dermatol*. 2010;9(5 Suppl ODAC Conf Pt 1):s53-s57.
21. Lam PL, Gambari R. Advanced progress of microencapsulation technologies: in vivo and in vitro models for studying oral and transdermal drug deliveries. *J Control Release*. 2014;178: 25-45.
22. Vyas A, Kumar Sonker A, Gidwani B. Carrier-based drug delivery system for treatment of acne. *ScientificWorldJournal*. 2014;2014:276260.
23. Erlich M, Arie T, Koifman N, Talmon Y. Structure elucidation of silica-based core-shell microencapsulated drugs for topical applications by cryogenic scanning electron microscopy. *J Colloid Interface Sci*. 2020;579:778-785.
24. Breneman D, Savin R, VandePol C, et al. Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. *Int J Dermatol*. 2004;43(5):381-387.
25. Williamson T, Cheng WY, McCormick N, Vekeman F. Patient Preferences and Therapeutic Satisfaction with Topical Agents for Rosacea: A Survey-Based Study. *Am Health Drug Benefits*. 2018;11(2):97-106.
26. Montes LF, Cordero AA, Kriner J, et al. Topical treatment of acne rosacea with benzoyl peroxide acetone gel. *Cutis*. 1983;32(2): 185–190.
27. Leyden JJ, Thiboutot D, Shalita A. Photographic review of results from a clinical study comparing benzoyl peroxide 5%/clindamycin 1% topical gel with vehicle in the treatment of rosacea. *Cutis*. 2004;73(6 Suppl):11-17.
28. Bhatia, N., et al., Efficacy and Safety of Microencapsulated Benzoyl Peroxide (E-BPO) Cream, 5% in Papulopustular Rosacea: Results from Two Phase 3, Vehicle-controlled Trials, in Fall Clinical Dermatology Conference. 2019: Las Vegas, NV.
29. Del Rosso, J., et al., Twyneo (Microencapsulated Benzoyl Peroxide 3%, Tretinoin 0.1%) Phase 3 Efficacy and Safety: Results from Two Randomized Controlled Clinical Trials, in 16th Annual Maui Derm Conference. 2020: Kihei, HI.
30. Emanuele E, Bertona M, Altabas K, et al. Anti-inflammatory effects of a topical preparation containing nicotinamide, retinol, and 7-dehydrocholesterol in patients with acne: a gene expression study. *Clin Cosmet Investig Dermatol*. 2012;5:33-37.
31. Han HS, Kwon YJ, Park MS, et al. Efficacy validation of synthesized retinol derivatives In vitro: stability, toxicity, and activity. *Bioorg Med Chem*. 2003;11(17):3839-3845.
32. Carita AC, Eloy JO, Chorilli M, et al. Recent Advances and Perspectives in Liposomes for Cutaneous Drug Delivery. *Curr Med Chem*. 2018;25(5):606-635.
33. Latter G, Grice JE, Mohammed Y, et al. Targeted Topical Delivery of Retinoids in the Management of Acne Vulgaris: Current Formulations and Novel Delivery Systems. *Pharmaceutics*. 2019;11(10):490.
34. Rahman SA, Abdelmalak NS, Badawi A, et al. Tretinoin-loaded liposomal formulations: from lab to comparative clinical study in acne patients. *Drug Deliv*. 2016;23(4):1184-1193.
35. Fluhr JW, Barsom O, Gehring W, Gloor M. Antibacterial efficacy of benzoyl peroxide in phospholipid liposomes. A vehicle-controlled, comparative study in patients with papulopustular acne. *Dermatology*. 1999;198(3):273-277.
36. Jain S, Kale DP, Swami R, Katiyar SS. Codelivery of benzoyl peroxide & adapalene using modified liposomal gel for improved acne therapy. *Nanomedicine (Lond)*. 2018;13(12):1481-1493.
37. Babaie S, Bakhshayesh ARD, Ha JW, et al. Invasome: A Novel Nanocarrier for Transdermal Drug Delivery. *Nanomaterials (Basel)*. 2020;10(2):341.
38. Gupta A, Singh S, Kotla NG, Webster TJ. Formulation and evaluation of a topical niosomal gel containing a combination of benzoyl peroxide and tretinoin for antiacne activity. *Int J Nanomedicine*. 2014;10:171-182.
39. Budhiraja A, Dhingra G. Development and characterization of a novel antiacne niosomal gel of rosmarinic acid. *Drug Deliv*. 2015;22(6):723-730.
40. Goyal G, Garg T, Malik B, et al. Development and characterization of niosomal gel for topical

delivery of benzoyl peroxide. *Drug Deliv*. 2015;22(8):1027-1042.
41. Mohammadi S, Pardakhty A, Khalili M, et al. Niosomal Benzoyl Peroxide and Clindamycin Lotion Versus Niosomal Clindamycin Lotion in Treatment of Acne Vulgaris: A Randomized Clinical Trial. *Adv Pharm Bull*. 2019;9(4):578-583.
42. Apriani EF, Rosana Y, Iskandarsyah I. Formulation, characterization, and in vitro testing of azelaic acid ethosome-based cream against Propionibacterium acnes for the treatment of acne. *J Adv Pharm Technol Res*. 2019;10(2):75-80.
43. Rahman SA, Abdelmalak NS, Badawi A, et al. Formulation of tretinoin-loaded topical proniosomes for treatment of acne: in-vitro characterization, skin irritation test and comparative clinical study. *Drug Deliv*. 2015;22(6):731-739.
44. Kumar K, Rai AK Development and evaluation of proniosomes as a promising drug carrier to improve transdermal drug delivery. *IRJP*. 2011;2:71-74.
45. Bavarsad N, Akhgari A, Seifmanesh S, et al. Statistical optimization of tretinoin-loaded penetration-enhancer vesicles (PEV) for topical delivery. *Daru*. 2016;24:7.
46. Goyal R, Macri LK, Kaplan HM, Kohn J. Nanoparticles and nanofibers for topical drug delivery. *J Control Release*. 2016;240:77-92.
47. Raminelli ACP, Romero V, Semreen MH, Leonardi GR. Nanotechnological Advances for Cutaneous Release of Tretinoin: An Approach to Minimize Side Effects and Improve Therapeutic Efficacy. *Curr Med Chem.* 2018;25(31):3703-3718.
48. Mishra V, Bansal KK, Verma A, et al. Solid Lipid Nanoparticles: Emerging Colloidal Nano Drug Delivery Systems. *Pharmaceutics*. 2018;10(4):191.
49. Pokharkar VB, Mendiratta C, Kyadarkunte AY, et al. Skin delivery aspects of benzoyl peroxide-loaded solid lipid nanoparticles for acne treatment. *Ther Deliv*. 2014;5(6):635-652.
50. Raza K, Singh B, Singal P, et al. Systematically optimized biocompatible isotretinoin-loaded solid lipid nanoparticles (SLNs) for topical treatment of acne. *Colloids Surf B Biointerfaces*. 2013;105:67-74.
51. Jain AK, Jain A, Garg NK, et al. Adapalene loaded solid lipid nanoparticles gel: an effective approach for acne treatment. *Colloids Surf B Biointerfaces*. 2014;121:222-229.
52. Ioele G, Cione E, Risoli A, et al. Accelerated photostability study of tretinoin and isotretinoin in liposome formulations. *Int J Pharm*. 2005;293(1-2):251-260.
53. Brammann C, Mueller-Goymann CC. Incorporation of benzoyl peroxide nanocrystals into adapalene-loaded solid lipid microparticles: Part I - Nanocrystalline benzoyl peroxide. *Int J Pharm*. 2019;564:171-179.
54. Ridolfi DM, Marcato PD, Justo GZ, et al. Chitosan-solid lipid nanoparticles as carriers for topical delivery of tretinoin. *Colloids Surf B Biointerfaces*. 2012;93:36-40.
55. Shinde UA, Parmar SJ, Easwaran S. Metronidazole-loaded nanostructured lipid carriers to improve skin deposition and retention in the treatment of rosacea. *Drug Dev Ind Pharm.* 2019;45(7):1039-1051.
56. Kahraman E, Güngör S, Özsoy Y. Potential enhancement and targeting strategies of polymeric and lipid-based nanocarriers in dermal drug delivery. *Ther Deliv*. 2017;8(11):967-985.
57. Ramezanli T, Zhang Z, Michniak-Kohn BB. Development and characterization of polymeric nanoparticle-based formulation of adapalene for topical acne therapy. *Nanomedicine*. 2017;13(1):143-152.
58. Jaiswal M, Dudhe R, Sharma PK. Nanoemulsion: an advanced mode of drug delivery system. *3 Biotech*. 2015;5(2):123-127.
59. Sabouri M, Samadi A, Ahmad Nasrollahi S, et al. Tretinoin Loaded Nanoemulsion for Acne Vulgaris: Fabrication, Physicochemical and Clinical Efficacy Assessments. *Skin Pharmacol Physiol*. 2018;31(6):316-323.
60. Gupta AK, Dey BK. Microencapsulation for controlled drug delivery: A comprehensive review. *Sunsari Tech Coll J*. 2012;1:48-54.
61. Bozzuto G, Molinari A. Liposomes as nanomedical devices. *Int J Nanomedicine*. 2015;10:975-999.
62. Gandhi J, ShahP. A review on current perspectives and recent advances in ocular drug delivery system. *Int J ChemTech Res*. 2018;11:314-326.
63. Wang W, Lu KJ, et al. Nano-drug delivery systems in wound treatment and skin regeneration. *J Nanobiotechnology*. 2019;17(1):82
64. Peralta MF, Guzmán ML, Pérez AP, et al. Liposomes can both enhance or reduce drugs penetration through the skin. *Sci Rep*. 2018;8(1):13253.
65. Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. *J Nanobiotechnology*. 2018;16(1):71.
66. Harper JC, Roberts WE, Zeichner JA, et al. Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris: assessment of safety and tolerability in subgroups. *J Dermatolog Treat*. 2020;31(2):160-167.
67. Dogra S, Sumathy TK, Nayak C, et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin versus their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *J Dermatolog Treat*. 2021;32(8):925-933. JCAD