Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13020
DOI URL: http://dx.doi.org/10.21474/IJAR01/13020

RESEARCH ARTICLE

NOVEL TOPICAL, REGIONAL & TRANSDERMAL DOSAGE FORMS USING NANOTECHNOLOGY: A REVIEW

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Manuscript Info

Manuscript History
Received: 15 April 2021
Final Accepted: 18 May 2021
Published: June 2021

Key words:-
Novel, Nano, Topical, Transdermal, Dosage Form

Abstract

Purpose: To summarize main findings of topical or transdermal preparation delivered in the skin or eye region using novel nano-technology.

Method: Narrative review of all relevant papers from peer reviewed and high impact journals.

Results: The delivery system of pharmaceutical preparations for skin and eyes are now elevated to novel aerosolized gels, foams, sprays and other forms that are delivered using nano-pharmaceutical dynamics such as Ag nanoparticles,impregnated urethanes, liposomes, nanoemulsions,polymers and nanopolymers. And these trends provide elevation from benefits and limitations of conventional systems such as enhanced spread and permeation, better bioavailability, prolonged efficacy, reduced toxicity and superior stability.

Conclusion: An improved delivery system was made possible by novel discoveries using nano-technology. More and more studies in pharmaceutics are centered on using this technological dynamics to formulate and reformulate drugs that are delivered topically or transdermally.

Introduction:-

Skin is considered as one of the most complex organ in the body. Characterizing the skin would take into consider its specialized cells and multi-functional structures. One character the skin possess is its protective function as a primary defense to mechanical as well as chemical or microbiological invasion. It's morphology actually is one of the reason why dosage forms applied in this organ maybe delivered in various ways: topical, regional or transdermal. With these modes arise challenges of dermatological and pharmaceutical maneuver of products such that the active ingredients as well as the excipients are delivered in the target site of action (Pando et al.,2013).

Topical application is delivery of active ingredient directly into the surface of the affected skin. This can be in various forms some are semi-solids and some are liquids in consistency.(Pando 2013;Chuo 2009). Some are delivered on a local area or deeper region. This are considered regional application such as those in the case of muscle or joint pains. There are emollients, gels, liniments & poultices with essential oils and other active anti-inflammatory or analgesic agents and even counter-irritants that are contained in patches, creams and lotions to provide localized treatment. (Crommelin et al.,2003; Garg et al., 2013). The more complex drug skin delivery is via transdermal application whereby the active component permeates through the dermal layer of the skin, avoiding the

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selective barrier effect of all four epidermal layers and provides systemic action. Nitroglycerin delivery, Vit B12 delivery in patches and creams are an example of how transdermal delivery goes beyond just percutaneous absorption because the permeated active component gets an access to the systemic circulation and bypasses first pass effect (Mazzitelli et al., 2013;Yamaguchi et al.,2018 and Ventre et al.,2018).

All these various dosage forms applied through the skin faces a variety of challenges from pharmaceutical design to bioavailability. Topical dosage forms for example need to have capsule enclosures of the active ingredient so that it will have better bioavailability (Andersson et al., 2013).Others in the formulation has to have a suitable base that will aid in its dissolution, dispersion and delivery (Date et al.,2006). In the case of ointment bases alone, hydrocarbon matrices (Huckzo et al., 1999; Parnami et al., 2013). Accelerants and absorption promoters are essential adjuncts considered specially when penetration, sensitivity, phase separations are considered (Jain et al., 2015; Ting et al., 2004; Walfg 2005). Globule size, rheological and even thermal stabilities are important factors in the design and reformulation of topical and transdermal products (Patel et al., 2012; Kumar et al., 2012; Tanwar 2012)

With these considerations and more, advancements have been rapid and massive to the extent so that topical agents regardless of size of the globules, or the penetrability and stability are no longer such an issue. This is because of the availability of current approaches in optimizing the delivery of active components to the site of action in different delivery forms. Technologies like nano- deliveries (Bala et al., 2004; Karen K et al.,2004), Enhancing agents like polymers such as sodium hyaluronate (John VT et al., 2002; Castelvetro et al., 2004), liposomal agents in spheronized forms and mechanically aided delivery using novel delivery such as gel formulation, aerosolized forms, nano-emulsions, thermal energy, ultrasonography or iontophoresis are some of the latest advances elevating the conventional modes of delivery.

An example of cutting edge technology in topical and transdermal applications are products that are silver-based formulations using novel delivery and nanotechnology. Initially there was a clamor for silver as a good anti-bacterial agent and thus was incorporated in topical preparations the conventional way of just mixing silver in regular ointment and cream bases yielded a not significant result in wound healing. But after a decade the shift to employing a novel technology to deliver silver to the target site of action is crucial thus pharmaceutical maneuvers pave way to making silver novel delivery a breakthrough.

In the case of Diabetes, complications includes development of foot ulcers which are effects of a poor perfusion of blood, an injury or deformity. Wound care and healing then is essential but is made extra difficult due to the elevated high sugar condition that slows the healing process and exposes the patient to microbial contamination. Hence, three controlled clinical studies where made on topical solutions and topical foams where findings show that silver containing foams & solutions did not promote a faster healing process after a month of checking (Vermeulen et al., 2007; Bergin et al.,2006) , though one of the clinical studies expressed that the size of the ulcer was decreased with the silver containing preparation (Vermeulen et al., 2007). In the case of burn patients it is thought that silver topical application may help in hastening the healing process and retarding further infection. But a twenty (20) trials review involving approximately 2000 participants did a comparison of the one with and without silver and results show that there is not enough evidence to support the addition of silver in dressings and creams for burn treatment (Versloot et al.,2010).

Topically applied dermal and transdermal delivery systems finds its advantages in skipping first-pass effect, degradations and frequent dosing. This paper reviews current novel topical & transdermal delivery of active components that will utilize novel drug delivery systems and nanotechnology.

Methods:-

The review was conducted using journal databases in Pubmed, Elsevier, Sciencedirect, Research Gate and MDPI. Search strategies usingwithout limitation, with limitation such as Boolean (with, and and or) ways and year of publication were considered. Keywords such as Novel, Novel Nanoparticles, Novel Nanotechnology, Pharmaceutical Nanotechnology were use plus the qualifier topical, transdermal, regional delivery system. The narrative review criteria includes (1) articles on novel delivery system focused on topical and transdermal application (2). Also that its topical and transdermal application in regions of skin and eye only (3) This novel dosage delivery are products of recent nanotechnologies and development.

Novel Pharmaceutical Nano-Technology Maneuvers:

Novel Delivery of Silver (Ag) using Gel or Aerosolized Foams

Aerosol foams are usually known for their spreadability, texture and higher bioavailability advantages. Latest pharmaceutical maneuver is elevated in such a way that anti-microbials are delivered in gels and foams using impregnation mechanism of active ingredients in polymers and silicones.

Ag in a gel formulation time-kill kinetics

With the aforementioned study reviews that is inconclusive of the benefits of silver in wound healing, the new era in drug formulation of topical products pave the way of the use of novel technological design such aa time-kill kinetics of novel silver containing gel formulation for post-surgical wounds, diabetic wounds and other skin ulcers. The gel form should be administered in a two (2) weeks-time to avoid toxicity and was found to be highly effective in the treatment of infection. An anti-microbial wound gel (CelaCare Technologies) was given in a low dose of a proprietary silver salt combined with acemannan which demonstrated immense healing of ulcers and skin infections (Lee et al.,2015).

Ag impregnated polyurethane

Recent advances include silver chloride impregnated in a novel hydrophilic polyurethane (PU) foam. The elution of silver for 168 hours in a simulated wound and the effect of the foam against opportunistic pathogens such as Staphylococcus aureus (MSSA), Acinetobacter baumannii, Candida albicans, and antibiotic-resistant strains (Methicillin-resistant S. aureus [MRSA] and Vancomycin-resistant Enterococci [VRE]) resulted a high zone of inhibition of 16mm after a day and a reduced viability by a log of four in the direct kill assay. Overall, The technology of delivering silver as a salt and its integration in the polyurethane is found to be an effective wound dressing arresting highly opportunistic pathogens that invades and deters healing of wounds. A logarithmic kill value of six (6)against S. aureus and E.coli, in a 16 hour span contributes to the array of clinical management for wound infection (Percival 2018).

Ag containing foam in soft silicone technology

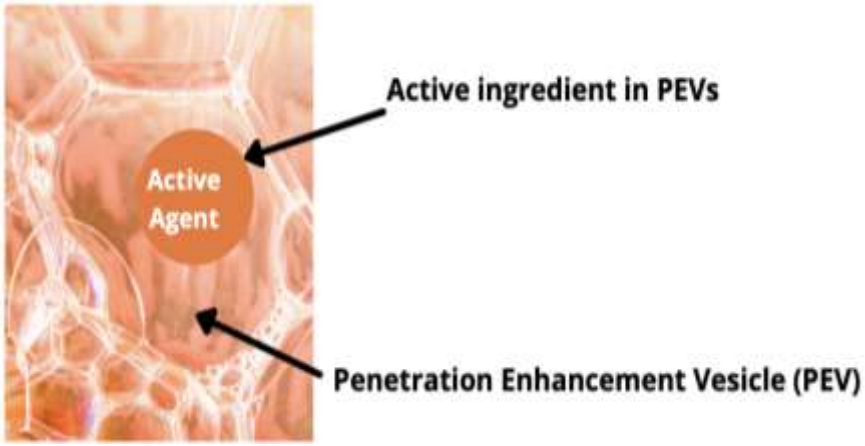
Given the rise of evidence that silver really do possess anti-microbial activity provided that there is a mechanism that will carry the component to the site of action. Another notable technology which makes silver an adjunct in the treatment of skin infections cause by micro-organisms is the Safetac technology. This employs the use of soft silicone mix with a silver impregnated foam dressing developed by Mölnlycke Health Care. Results of this novel mechanism of wound management provides a fast and sustained anti-microbial effect against common opportunistic skin pathogens. This extended the utilization of the Ag impregnated soft silicone foam technology to treatment of acute and long-term wound burns, severe diabetic ulcers and other forms of chronic and cancerous wounds (Davies et al., 2017).

Liposomes

Controlling the delivery of pharmaceutical actives as well as optimizing topical and transdermal effect to the different layers of the skin may be one of the factors considered in ensuring that skin preparations address injuries, wounds and infection. The conventional preparations may have the actives applied on surface but lipid by-layer can be a challenge in perfusion and action. Thus, liposomes are employed to address this as it creates a spherical vesicle. This creates an amphiphilic environment (Schafer-Korting et al., 1994; Brisaert 2001).

Diclofenac delivery by transcutol containing liposomes

Novel delivery using liposomal mechanism via penetration enhancer containing vesicles (PEVs). This is a sophisticated transdermal delivery system by creating a vesicle-skin complex. The transcutol containing PEVs carries the salt forms of diclofenac ingredient to act deep in the dermal layers of the skin. Ex vivo studies of the liposomal PEVs vs the conventional gel on a new born pig skin and results show that skin permeation is superior in PEVs over the traditional gel form (Mancomi et al.,2011)



A visualization of an active agent in a PEV vesicle

Minoxidil Delivery using Liposome (PEVs)

Minoxidil's application for hair growth is renowned. However, the regional delivery to the thick scalp layers poses a challenge in ensuring that minoxidil will illicit it's hair growth function. In the recent researches new liposomal mechanism employs PEVs using a blend of penetration enhancers cineole, Labrasol® - capryl-caproyl macrogol 8-glyceride, anscutol® - 2-(2-ethoxyethoxy) ethanol and Transcutol® - 2-(2-ethoxyethoxy) ethanol and soy lecithin. The in-vitro diffusion research showed that the PEVs dermal delivery provided effective penetration to skin layers with novel enhancers compared to the one without. The Fourier Transform Infra-red Spectrophotometry (FTIR) spectra records formulation of vesicle a clear evidence that the liposomal penetration enhancers efficiently is resuspended and diffused on the layers of the skin (Mura et al., 2013). In another study labrasol improves minoxidil delivery in the cutaneous layer of the scalp as evidence by accumulation in the area (Caddeo et al.,2012). While transcutol PEV loaded in 5-10% resulted to better fluidity than the regular liposomes. And what is important to not is that the zetal potential shows better stability for minoxidil (Mura et al., 2011).

Nanoemulsions

The morphology of skin specially its selective permeability characteristic makes the pre-formulation and formulation studies difficult. Securing that active ingredient is well dispersed in either water in oil or oil in water media. But novelty of nano-emulsion lies in ensuring ultra small droplet mix where thermodynamics is controlled in a special surfactant assisted manufacturing process. While stability is a major concern in traditional emulsion, nanoemulsion's stability is established through nano droplets. Another unique feature of nanoemulsion in skin delivery is that it does not cause clogging of pores instead provides benefits like making skin surface firm and elastic (Yilmaz 2006; Nastiti et al., 2017). Even anti-microbial therapy that employs nanoemulsion can attenuate infections specifically caused by burns or trauma. The reduction of infection is carried by appropriate modulation of the inflammatory dermal signaling (Hemmila et al.,2010)

Ciprofloxacin Nanoemulsions

Anti-microbial treatment is specifically difficult in ocular keratitis. And mostly it is available in ointment bases or solution bases. Through time microemulsions are gaining momentum in pharmaceutics. And recent studies elevated nanoemulsion to treatment of delicate conditions such as bacterial keratitis. This Ciprofloxacin Nanoemulsion (CIP-NE) formulatin was made via homogenization, ultrasonication using oleic acid (CIP-O-NE) complex and Labrafac a lipophile WL 1349 as the oleaginous phase is the Water and Oil combination. This nanoemulsion is glued by two surfactants namely Tween 80 and Polaxamer 188. Both in-vivo and in-vitro results to extensive deep penetration in the cornea. The comparison between the ciprofloxacin nanoemulsion and the regular ciprofloxacin eye solution resulted to the former as an effective delivery system and it features globule stability and dispersibility (Youssef et al.,2021)

Besifloxacin- Loaded Ocular Nanoemulsion

One of the trends in nanoemulsion evolves in using a simple yet highly efficient emulsification at a relatively low energy with a combination of the use of cremohor and Transcutol surfactants and co-surfactants relatively. There

was a comparative efficacy with besifloxacin loaded nanoemulsion from the conventional product. But it is notable that the Besifloxacin-loaded NE shows higher permeation and does not give corneal tissue damage(Kassaee 2021).

Acyclovir Nanoemulsion

Viral infections of skin and eyes are usually treated with acyclovir. The preparations can range to topical, region based like ophthalmic or otic preparations. Drug efficacy has been an issue given concerns on solubility, absorption in the superficial layers of the skin, or isotonicity of solutions. Difficulties associated with opthalmic delivery of acyclovir were addressed in nanoemulsion technology whereby acyclovir pre-formulation solubility testing using Tween 20, Triacetin, and Tramsectol® surfactants and co-surfactants are the loading media for acyclovir nanoemulsion. Acyclovir penetration in nano emulsion in excised bovine cornea showed a sustained drug release and action. While the chorionic test on hens as well as Draize Test showed that ocular administration of the nanoemulsion is safe (Mohammadi et al., 2021). A similar result with a slight difference in the process is the promise of a better acyclovir delivery and action as a nanoemulsion. The results of an acyclovir loaded albumin using desolvation method without an aldehyde glutaraldehyde yielded better permeation through the transcorneal human epithelial tissue (Suwannoi et al., 2017).

Fluconazole pH triggered Nanoemulsion

Skin and eye fungal infection is a primary concern to medical practitioners due to the fact that fungal infections are difficult to treat because of the structure of the cell walls of the fungi that makes it impenetrable and sometimes recurrence of infections happen if treatment is not thorough. Such concern are believed to be address by having nanoemulsion gel. A study of fluconazole as a novel nano-emulsified gel where its release and action is triggered by pH was developed in situ. The formulation includes emulsification with capmul oil phase, a tween surfactant and the usual transcutol secondary surfactant. Polymer solution such as Carbomer 934 solution created a sol which is a the nanoemulsified media for the loading of the active ingredient fluconazole. The research provided a good foundation for further research such that results showed an intensive permeation of the fluconazole phtrigerrednanoemulsion, a long residency time of the emulsion in the cornea and a sustained action for a designated time (Pathak et al., 2013). The use of carbopol as a powerful polymer with biological adhesive property primarily is for the increase contact time of the active ingredient to the eye. The gel-core carbosome formulation showed a nano-size of 339 +/- 5.50 nanometer and an efficiency entrapment percentage of 62%. Compared to regular fluconazole suspension the residency time of the nano formulation of fluconazole has an optimized time of 18 hours and is deemed promising in the ophthalmic delivery of anti-fungal agents (Moustafa et al., 2018). As is the case of a similar active ingredient integrated in a nano – lipoemulsion a prolonged effect was seen when fluconazole was integrated in hyaluronic acid. The hydrogel and liposome showed prolonged and sustained corneal permeability than conventional preparation (Moustafa et al., 2017). In a fungal keratitis case niosomal gel and nanoemulsion using Span surfactant, cholesterol and 1% Carbopol has better ocular bioavailability than solutions and the niosomes extra performed in permeation (Soliman et al.,2019).

Polymers and Nanopolymers

Polymers though are macromolecules presents a versatile feature that is widely use in skin formulation industries. Microcells that is entrapped due to an acrylic acid polymer -water complex allows ease of application, faster and prolonged release with good product stability. Moreover, polymer gels when incorporated with other compounds such as moisturizers and other emollients may have enhanced dermatologic benefits. Such exist in anti-pimple actives like benzoyl peroxide which now high efficacy due to its improved gel based formula (Rouse et al., 2007). PEGylated nanopolymers are the currently marketed nanostructures with an array of application (Farjadian et al., 2018).

Table 1:- Summary of Typical Polymeric Materials in Preparations Applied through Skin and Eyes.

Typical Material	Application	Outcomes	Author(s)
(Nanopolymer) Poly-Lactic Co Glycolic Acid	Biodegradable nano-polymer of an anti-microbial agent	Higher efficiency, greater penetration of the anti-microbial agent and enhance angio-genesis	Vijayan A., James PP, Nanditha CK, Kumar GSV
(Polymer sphere) Chitosan degradable aliphatic natural polymer	Nano-carrier (using spheronize dynamics) of	Ultra-nanosize sphere that crosses the selectively	Zhang Z.,Tsai PC, Ramezanli T., Michniak-

	various dermatological products	permeable membrane. Deeper epidermal penetration	Kohn BB
(Polymeric micelles) methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG-dihexPLA) diblock copolymer	Biocompatible, biodegradable micellar form of delivering tacrolimus for psoriasis patients Micellar delivery of Ciclosporin in plaque psoriasis management Amphilic delivery of azole (cotrimazole, fluconazole, econazole) for fungal infections	Increased bioavailability in a difficult to penetrate cutaneous condition of psoriasis patient. Omits toxicities of ciclosporin in the conventional delivery system. Increased solubility and corneal delivery. Omits systemic toxicities of azole agents, with superior bioavailability and efficacy.	Lapteva M.,MondonK.,Moller M., Gurny R., Kalia YN Lapteva M., Santer V.,Mondon K., Patmanidis I, Chiriano G., Scapozza L., Gurny R., Moller M.,Kalia YN Bachhav YG, Mondon K, Kalia YN, GurnyR.,Moller M.

Anti-microbial Peptide Loaded in Biodegradable Nanopolymer

Wound healing process is a time series process. Any delay in the wound healing exposes an individual to further microbial contamination to opportunistic pathogen. Hence, a formulation that would have sustained wound healing action and good bioavailability could arrest contamination. The novel Poly-Lactic-Co-Glycolic Acid (PLGA) nano-polymer system was entrapped with growth factors and anti-bacterial polymers via solvent diffusion method. Using carbodiimide chemistry the delivery system was optimized. This resulted to a high efficiency penetration, enhanced angiogenesis and a high degree of anti- bacterial action against gram (+) and gram (-) strain (Vijayan et al., 2019).

Polymeric Nano-Particle Delivery for Dermatologic Problems

Permeation enhancement both active and passive are necessary in skin conditions such as psoriasis, contact dermatitis and the like. And natural polymers like chitosan in nanoparticle delivery is enriched with the presence of synthetic and degradable aliphatic polymers. Nanospheres are created when all these polyester or poly acrylates from metabolites such as the tyrosine derived nanospheres. It acts as a nano carrier thus delivering the active ingredients in a selectively permeable skin is enhanced in an ultra-nanosize of 40 mm deep into the layers of the epidermis (Zhang et al., 2013)

Polymeric Micelle Nanocarrier of Tacrolimus

The conventional delivery of topical solutions and topical creams in skin conditions atopic dermatitis in Psoriasis cases has been extremely difficult due to poor cutaneous absorption thereby affecting bioavailability as a whole. The biocompatible methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG-dihexPLA) diblock copolymer creates a micelle biodegradable formulation of about 1% was kept stable for 7 months. The micelle when analyzed using UHPLC-MS/MS showed that the Tacrolimus has better deposition than ointments meanwhile the profiling of Tacrolimus in terms of its bioavailability distribution reaches 400um meter of tissue deep.This validates the improvement of the degree of efficacy tacrolimus may have due to enhanced action and deeper cutaneous penetration of the micellar polymer loaded drug (Lapteva et al., 2014).

Micellar Nanocarriers of Ciclosporin A

Ciclosporin A management of Plaques psoriasis condition presents difficulty in the treatment process due to the systemic nephron and hepato-toxicity ciclosporin presents. A transdermal permeation is a good way to omit those toxicities. MPEG-dihexPLAdiblock copolymer plus the active ciclosporin A creates a micellar formulation which was visualized in confocal microscopy and statistically presents a delivery of spherical nanometer micelles deep into the human skin. Th increased solubility is key as it had a solubility rate increase of 518 fold. Cutaneous delivery was enhanced and images of micelles in corneocytes and inter-corneal regions are evidences of penetration to stratal layers (Lapteva et al.,2014a,b).

Micelle Formulation and Azole Anti-fungals

Anti-fungal administration of azole preparations such as cotrimazole, fluconazole and econazoles are now potentially delivered by passing systemic toxicity effects. Novel amphiphilic preparation using MPEG-hexPLAblock copolymers develop in a micelle solution. Using fluorescein dye the penetration pathways and micellar distribution showed a good micellar loading as it was visualized in a confocal scanning microscopy. Overall MPEG-dihexPLA micelles showed superior cutaneous drug bioavailability and clinical efficacy even in hair follicles compared to branded conventional preparations (Bachhav et al.,2011).

Conclusion:-

Nanotechnologies truly have addressed the pharmacokinetic and pharmacodynamic challenges of the past. Reformulation of our conventional treatments for various skin and eye infections elevated in to BETTER products through maneuvering the formulation via impregnations in nano carriers, use of nano particles, embedment in nano-emulsions, trapping actives in gel polymers, micellar spheres and other nano-technological dynamics are great innovations to Increase drug efficacy by enhancing absorption, targeting regional site of actions, prolonged action and stable preparations.

References:-

1. Andersson M, Holm L, Ridderstrale Y, et al. (2013). Morphology and composition of the spider major ampullate gland and dragline silk. Biomacromolecules 14:2945–52.
2. Bachhav YG, Mondon K, Kalia YN, Gurny R, Möller M. (2011). Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. J Control Release30;153(2):126-32. doi: 10.1016/j.jconrel.2011.03.003. PMID: 21397643.
3. Bala, I., Hariharan, S., Kumar,M.N.(2004). PLGA nanoparticles in drug delivery: the state of the art. Crit. Rev. Ther. Drug Carrier Syst. 21, 387–422.
4. Bergin S, Wraight P (2006). Silver based wound dressings and topical agents for treating diabetic foot ulcers. Cochrane Database of Systematic Reviews. Issue 1. Art. No.: CD005082. DOI: 10.1002/14651858.CD005082.pub2
5. Brisaert M, Grabriels M, Matthijs V, et al. (2001). Liposomes with tretinoin: a physical and chemical evaluation. J Pharm Biomed Anal 26(5-6):909-17.
6. Castelvetro, V., De Vita, C. (2004). Nanostructured hybrid materials from aqueous polymer dispersions. Adv. Colloid Interface Sci. 108–109, 167–185.
7. Carla Caddeo, Maria Manconi*, Donatella Valenti, Anna Maria Maccioni, Anna Maria Fadda, Chiara Sinico (2012). The Role of Labrasol® in the Enhancement of the Cutaneous Bioavailability of Minoxidil in Phospholipid Vesicles, *Research J. Pharm. and Tech. 5(12)*
8. Chuo Y, Kaminska B. (2009). Sensor layer of a multiparameter single-point integrated system. IEEE Trans Biomed Circuits Syst 3:229–40
9. Crommelin DJ, Storm G, Jiskoot W, et al. (2003). Nanotechnological approaches for the delivery of macromolecules. J Control Release 87:81–8
10. Date AA, Naik B, Nagarsenker MS. (2006). Novel drug delivery systems: potential in improving topical delivery of antiacne agents. Skin PharmacolPhysiol 19(1):2- 16.
11. Davies P, McCarty S, Hamberg K. (2017). Silver-containing foam dressings with Safetac: a review of the scientific and clinical data J Wound Care. (Sup6a):S1-S32. doi: 10.12968/jowc.2017.26.Sup6a.S1. PMID: 28594320.
12. Farjadian F, Ghasemi A, Gohari O, Roointan A, Karimi M, Hamblin(2019). Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. Nanomedicine (Lond).93-126. doi: 10.2217/nnm-2018-0120. Epub 2018 Nov 19. PMID: 30451076; PMCID: PMC6391637.
13. Garg T, Singh S, Goyal AK. (2013). Stimuli-sensitive hydrogels: an excellent carrier for drug and cell delivery. Crit Rev Ther Drug Carrier Syst 30:369–409
14. Hemmila MR, Mattar A, Taddonio MA, Arbabi S, Hamouda T, Ward PA, Wang SC, Baker JR Jr (2010). Topical nanoemulsion therapy reduces bacterial wound infection and inflammation after burn injury. Surgery. 148(3):499-509. doi: 10.1016/j.surg.2010.01.001.PMID: 20189619; PMCID: PMC2891388.
15. Huczko A, Lange H.(1999). Fullerenes: experimental evidence for a null risk of skin irritation and allergy. Fullerene Sci Technol 7:935-9
16. Jain N.K., Et. al., (2015)Handbook of Polymers for Pharmaceutical Technologies: Structure and Chemistry
17. Kumar et al., (2012). Pros and Cons of Topical Patches: An Analysis of Precision3's Products. http://www.precision3.com.

18. Karen, K., Tasana, P., Nigel, D.M., Thomas, R (2004). Entrapment of bioactive molecules in poly (alkylcyanoacrylate) nanoparticles. Am. J. Drug Deliv. 4, 251–259.
19. Kassaee SN, Mahboobian MM (2021). Besifloxacin-loaded ocular nanoemulsions: design, formulation and efficacy evaluation. Drug DelivTransl Res. 10.1007/s13346-021-00902-z. Epub ahead of print. PMID: 33575973.
20. Lapteva M, Mondon K, Möller M, Gurny R, Kalia YN (2014). Polymeric micelle nanocarriers for the cutaneous delivery of tacrolimus: a targeted approach for the treatment of psoriasis;11(9):2989-3001. doi: 10.1021/mp400639e.
21. Lapteva M, et al, (2014 a,b,) Targeted cutaneous delivery of ciclosporin A using micellar nanocarriers and the possible role of inter-cluster regions as molecular transport pathways. J Control Release. 2014 Dec 28;196:9-18. doi: 10.1016/j.jconrel.2014.09.021.
22. Lee Y, Atchley DH, Proctor CA, Smith FL, Yi S, Loftis CM, Yates KM (2015). Time-kill Kinetics of a Novel Antimicrobial Silver Wound Gel Against Select Wound Pathogens. Wounds. (12):336-46. PMID: 27447106.
23. Manconi M, Caddeo C, Sinico C, Valenti D, Mostallino MC, Biggio G, Fadda AM (2011). Ex vivo skin delivery of diclofenac by transcutol containing liposomes and suggested mechanism of vesicle-skin interaction. Eur J Pharm Biopharm;78(1):27-35.
24. Mazzitelli S, Pagano C, Giusepponi D, et al. (2013). Hydrogel blends with adjustable properties as patches for transdermal delivery. Int J Pharm 454:47–57
25. Mohammadi M, Elahimehr Z, Mahboobian MM (2021) Acyclovir-Loaded Nanoemulsions: Preparation, Characterization and Irritancy Studies for Ophthalmic Delivery. Curr Eye Res.doi: 10.1080/02713683.2021.1929328.
26. Moustafa MA, El-Refaie WM, Elnaggar YSR, Abdallah OY (2018). Gel in core carbosomes as novel ophthalmic vehicles with enhanced corneal permeation and residence. Int J Pharm.;546(1-2):166-175. PMID: 29778824.
27. Moustafa MA, Elnaggar YSR, El-Refaie WM, Abdallah OY (2017). Hyalugel-integrated liposomes as a novel ocular nanosized delivery system of fluconazole with promising prolonged effect. Int J Pharm;534(1-2):14-24. doi: 10.1016/j.ijpharm.2017.10.007.
28. Mura S, Manconi M, Fadda AM, Sala MC, Perricci J, Pini E, Sinico C (2013). Penetration enhancer-containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil: in vitro evaluation of drug permeation by infrared spectroscopy. Pharm Dev Technol(6):1339-45. doi: 10.3109/10837450.2012.685661.
29. Mura, S., M. Manconi, D. Valenti, C. Sinico, A. O. Vila and A. Fadda (2011). "Transcutol containing vesicles for topical delivery of minoxidil." *Journal of Drug Targeting* 19. 189 - 196.
30. Nastiti, Christofori M R R et al., (2017). "Topical Nano and Microemulsions for Skin Delivery." *Pharmaceutics* vol. 9,4 37. doi:10.3390/pharmaceutics9040037
31. Pando D, Caddeo C, Manconi M, et al. (2013). Nanodesign of olein vesicles for the topical delivery of the antioxidant resveratrol. J Pharm Pharmacol 65:1158–67.
32. Parnami N, Garg T, Rath G, Goyal AK. (2013). Development and characterization of nanocarriers for topical treatment of psoriasis by using combination therapy. Artif Cells NanomedBiotechnol.
33. Patel et al.,(2012). Transdermal Drug Delivery Technology Revisited: Recent Advances. http://www.pharmainfo.net. 22.
34. Pathak MK, Chhabra G, Pathak K (2013). Design and development of a novel pH triggered nanoemulsified in-situ ophthalmic gel of fluconazole: ex-vivo transcorneal permeation, corneal toxicity and irritation testing. Drug Dev Ind Pharm.;39(5):780-90. doi: 10.3109/03639045.2012.707203.
35. Percival SL(2018). Antimicrobial Efficacy of a Silver Impregnated Hydrophilic PU Foam. Surg Technol Int.;32:67-74. PMID: 29529703.
36. Rouse JG, Yang J, Ryman-Rasmussen JP, et al (2007). Effects of mechanical flexion on the penetration of fullerene amino acid- derivatized peptide nanoparticles through skin. Nano Lett 7(1):155-60.
37. Schafer-Korting M, Korting HC, Ponce- Poschl E. (1994). Liposomal tretinoin for uncomplicated acne vulgaris. Clin Investig 72(12):1086-91.
38. Soliman OAE, Mohamed EA, Khatera NAA (2019). Enhanced ocular bioavailability of fluconazole from niosomal gels and microemulsions: formulation, optimization, and in vitro-in vivo evaluation. Pharm Dev Technol. (1):48-62. doi: 10.1080/10837450.2017.1413658.
39. Storm-Versloot MN, Vos CG, Ubbink DT, Vermeulen H (2010). Topical silver for preventing wound infection. Cochrane Database of Systematic Reviews, Issue 3. Art. No.: CD006478. DOI: 10.1002/14651858.CD006478.pub2.

40. Suwannoi P, Chomnawang M, Sarisuta N, Reichl S, Müller-Goymann CC(2017). Development of Acyclovir-Loaded Albumin Nanoparticles and Improvement of Acyclovir Permeation Across Human Corneal Epithelial T Cells. J OculPharmacolTher. 33(10):743-752. doi: 10.1089/jop.2017.0057.
41. Tanwar et al., (2012). Development, fabrication, & evaluation of transdermal drug deliver y s ystem- a review . http://www.pharmainfo.net/reviews/development-f a b r i c a t i o n - a n d - e v a l u a t i o n - t r a n s d e r m a l - d r u g - d e l i v e r y- system-review.
42. Ting WW, Vest CD, Sontheimer RD (2004). Review of traditional and novel modalities that enhance the permeability of local therapeutics across the stratum corneum. Int J Dermatol 43(7):538-47.
43. Ventre A. , Valerio Coppola, Maria Iannone, Paolo A. Netti, Ismaiel Tekko, EnekoLarrañeta, Aoife M. Rodgers, Christopher J. Scott, Adrien Kissenpfennig, Ryan F. Donnelly, Shaheer Maher, DusanLosic, Anne George, Amsaveni Ramachandran (2018). Chapter 2 - Nanotechnologies for tissue engineering and regeneration. Nanotechnologies in Preventive and Regenerative Medicine, Elsevier.
44. Vermeulen H, van Hattem JM, Storm-Versloot MN, Ubbink DT, Westerbos SJ (2007). Topical silver for treating infected wounds. Cochrane Database of Systematic Reviews Art. No.: CD005486. DOI: 10.1002/14651858.CD005486.pub2
45. Vijayan A, James PP, Nanditha CK, Kumar GSV (2019). Multiple cargo deliveries of growth factors and antimicrobial peptide using biodegradable nanopolymer as a potential wound healing system. Int J Nanomedicine14:2253-2263. doi: 10.2147/IJN.S190321. PMID: 30992665; PMCID: PMC6445221.
46. VT John., Simmons, B., McPherson, G.L., Bose, A (2002). Recent developments in materials synthesis in surfactant systems. Curr. Opin. Colloid Interface Sci. 7, 288.
47. Walfg, "The Discovery of the Antioxidant Function of Vitamin E", J. Nutr. 135(3), 2005, 358-366.
48. Yamaguchi T. , Takuji Ishikawa, Yohsuke Imai. (2018) Biomechanics for Pathology and Treatment, In Micro and Nano Technologies,Integrated Nano-Biomechanics, Elsevier, 101-146,
49. Yilmaz E, Borchert HH.(2006). Effect of lipid- containing, positively charged nanoemulsions on skin hydration, elasticity and erythema--an in vivo study. Int J Pharm 307(2):232-8.
50. Youssef AAA, Cai C, Dudhipala N, Majumdar S (2021). Design of Topical Ocular Ciprofloxacin Nanoemulsion for the Management of Bacterial Keratitis. Pharmaceuticals (Basel210. doi: 10.3390/ph14030210. PMID: 33802394; PMCID: PMC7998883.
51. Zhang Z, Tsai PC, Ramezanli T, Michniak-Kohn BB (2013). Polymeric nanoparticles-based topical delivery systems for the treatment of dermatological diseases. Wiley Interdiscip Rev NanomedNanobiotechnol. 5(3):205-18. doi: 10.1002/wnan.1211.