Nanoformulations for Topical Diseases

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Abstract: This study is to provide a complete idea about nanoformulations for topical medication delivery. Nanotechnology is a novel area in the field of medicine, especially pharmaceuticals for safe and targeted drug delivery. The medication concentration in the carrier is increased which increase the flow of drugs into and out of the skin. Both hydrophobic as well as hydrophilic medications and have the ability to release them in regulated manner for an extended period of time. The examples provided show that this field of study has a lot of potential and have a significant impact on clinical results as well as the development of new drugs.

Keywords: Nanoformulations; Skin; Topical Drug delivery

1. Introduction

Nanotechnology is a relatively new and quickly evolving technology that reduces the size of a material particle to that of a single atom, molecule, or cluster of molecules. The study of particles with a diameter of less than 100 nanometers is involved. [1] It covers topics as nanoparticle medication drug delivery and molecular nanotechnology and nanovaccinology applications. [2] These nanoformulations are intended to provide an effective, specific and flexible therapeutic choices. Nanotechnology-based devices and pharmaceuticals are more efficient, tailored, flexible and cost-effective.

1.1 Dermatology

Skin is the largest organ in the human body with total surface area around 2m². The skin is a fantastic vehicle via nanomaterials can be studied for drug administration, both in terms of active component delivery and efficacy. The skin's defense mechanism protects not only the physical body but also the immune system, metabolism, and UV rays. [3] The outermost layer is epidermis, around 50-150 m thick, the inner layer is dermis, about 250 m thick and subcutaneous tissue is about 50-150 m thick. The epidermis lacks blood vessels and nutrients so it is must to diffuse across the dermal-epidermal junction that keep epidermis alive. The five layers that make up the stratum corneum (basal layer) are stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum germinativum. The epidermis without the stratum corneum is known as viable epidermis. [4] The stratum corneum, the epidermis' outermost layer (15-20 m), is important for the skin's barrier function. Corneocytes are stiff, desmosome-linked epithelial cells, embedded in lamellar structure created by intercellular lipids. The basic skin permeation resistance presented by peculiar organization, which prevents molecules larger than 500 Da from passing through. [5] Keratinocytes, melanocytes, merkel cells and Langerhans cells may all play a role in the healthy function of epidermis. Keratinocytes develop and travel upward through a process known as keratinization i.e. from the basal layer to the outermost layer. Appendages such as pilosebaceous units, apocrine and eccrine sweat glands are present in addition to foregoing cellular components. The outer layers of the stratum corneum, known as the stratum disjunctum, are primarily desquamated. The stratum corneum is totally replaced depending on the anatomical region and age to preserve its optimal protective characteristics. [6] Passive diffusion is used to transport substances across the stratum corneum. There are three possible routes: transcellular, intercellular, and appendageal. [7]

1.3 Various skin disorders and their origin

Skin disorders	Types					
Bacterial skin	Impetigo: a contagious bacterial skin infection					
disease	forming pustules and yellow crusty sores.					
	Cellulitis: a common and potentially serious					
	bacterial skin infection.					
Fungal skin	Superficial: caused by dermatophytes, non-					
disease	dermatophyte molds as well as yeasts.					
	Deep: occur from primary infection of skin or					
	from cutaneous dissemination due to systemic					
	infection. E.g. Sporotrichosis, Mycetoma and					
	Chromomycosis					
	Systemic: yeast penetrate beneath the surface of					
	skin and cause infection.					
	e.g. Histoplasmosis, Blastomycosis					
Viral skin	Herpes Simplex Virus (HSV) Infection: virus					
disease	causing contagious sores, most often around					
	mouth and on the genitals.					
	Eczema herpeticum: painful, blistering rash					
	caused by the herpes simplex virus.					
	Herpetic whitlow: painful infection of finger					
	caused by herps virus.					
	Herpes gladiatorum: skin infection caused by					
	herpes virus type-1.					
Inflammatory	Atopic dermatitis: appearance of rashes on skin					
skin disease	Psoriasis: thought to build an immune system					
	problem. Triggers include infections, stress and					
	cold.					

2. Designing of topical drug delivery system

Topical administration medications encompass a wide range of therapeutic purposes. They have certain physicochemical features, such as high lipophilicity and poor water solubility, despite having different molecular structures. The log octanol/water partition coefficients [log P] of medicines should be greater than 6.0. The rate and extent of drug administration are sufficient to achieve therapeutic local concentrations in a timely manner and provide long-term

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pharmacological action. [8] In comparison to any other route of drug administration, the effects of formulation on absorption characteristics are substantially stronger with topical medication delivery. [9] The target biologic membrane's barrier function presents a significant difficulty for optimal therapy. Drugs with poor skin/nail/cornea penetration have lower local bioavailability and effectiveness. The nail, corneal, stratum corneum, mucosal barriers have different morphologies, yet all obstruct drug transport significantly. The barrier function is primarily influenced by the epithelial architecture physicochemical composition. For delivery efficiency and therapeutic impact, drug diffusion affinity and interactions between formulation excipients and membrane components are responsible. As a result, formulations and medications should be better designed and changed to pass through certain biologic barriers. [8]

3. The need of nanotechnology in Skin Infection

In recent years, the prevalence of fungal yeast infections, including resistant infections, has grown. Nanotechnology incorporation provides better skin penetration, long lasting effects, controlled drug release, enhance stability and many more. [10, 11]

4. Conventional approach

The traditional topical medicines are mainly designed to deliver the medicament locally rather than systemically. Traditional remedies are said to work on the skin's surface. Traditional topical skin care involves the application of ointments or lotions. When drugs from these preparations are applied to the skin, they partition, resulting in a highly concentrated layer of active substance that is quickly absorbed. [12] It could also cause side effects including irritation and allergic reactions. Uncontrolled evaporation of the active substance and an unpleasant odor are further disadvantages. [13] For medications to be effective, they must first reach the site of action in a considerable amount and then remain at the site in an effective concentration for a period of time. Although the skin, as the outermost organ, is easily accessible for medication application, this does not imply that the drug has an easy route to its target. Penetration enhancers, such as dimethylsulfoxide or propylene glycol leads, have been used to promote medication penetration across the skin layers. Penetration enhancers boost drug transport through the epidermal barrier, but they also increase undesired side effects due to increased drug levels in the blood. Penetration enhancers have been linked to irritative or even hazardous adverse effects, raising concerns about their usage in topical medication administration. [14,15]

5. Treatment strategies based on nanomedicines

5.1 Liposome

Liposomes are phospholipid-based vesicles with concentric lipid bilayers that contain an aqueous phase and are high in phosphatidylcholine. The capacity to localize medications at the site of action, biodegradability, biocompatibility, enhanced deposition within skin, and protection of drug molecules from the inactivating effects of external circumstances are all advantages of liposomes for the treatment of topical infectious illnesses. [16-22] Liposomes also have the advantage of overcoming limited stratum corneum permeability, resulting in increased antimicrobial molecule permeation via the skin layers while lowering systemic absorption [23]. The presence of phospholipids in liposomal systems causes bilayer fluidity in the stratum corneum to be disrupted, lowering skin barrier characteristics.

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Table 1: List of various Nanomedicines for the treatment of Topical Infectious Disorders along with their composition and target pathogen

			<u> </u>		
Delivery System	Type of Infection	Composition	Studies	Study Findings	References
Liposome-loaded usnic	Bacterial	Gelatin, usnic acid,	In vitro and in	Liposomal system showed the development	24
acid combined with	infection which	phosphatidylcholine,	vivo studies	and maturation of granulation tissue and scar	
gelatin membrane	is result of	propylen		repair as compared to silver sulphadiaizine	
	lesions and burn			ointment	
Terbinafine	Onychomycosis	Phospholipon 90 G,	In vitro release	Formulation proved to be a promising system	25,26
Hydrocholride	(fungal infection)	Lipoid S 100,	and ex vivo	for ungual drug delivery due to better	
(TBFHCL)- loaded		Lecithin, Cholesterol	permeation study	accumulation at the infection site	
liposomal gel			across the nail		
			plate		
Itraconazole (ITR)-	Keratitis caused	Phospholipid,	In vitro and in	Liposomal system demonstrated better	27
loaded liposomes	by Aspergillus	Cholesterol	vivo studies	antifungal activity than the unencapsulated	
	flavus			drug	
Ketoconazole (KTZ)-	Fungal infection	Phospholipid,	In vitro and in	KTZ- loaded DL acted as a drug depot for	28
loaded Deformable		cholesterol and	vivo studies	effective in fungal infection	
liposomes (DL)		Sodium dodecyl			
		sulfate			
Idoxuridine (IDU)-	Herpes Simplex	Phosphatidylcholine	In vitro, ex vivo	Study suggested improvement of therapeutic	29
loaded liposomal gel	infection (HSV)	and cholesterol	and double-blind	efficacy of IDU entrapped in liposomes in	
			clinical studies	treatment of HSV-1 and HSV-2 patients	
Ethosomes	Fungal infection	Phospholipon 90 G,	caused In vitro	Ethosomal gel formulation	30
		Lipoid S	release		
Econazole (EN)-	Fungal infection	Sov-bean	In vitro and ev	EN ethosomal gel showed controlled drug	31
loaded nanoethosomal	Pungai infection	phosphatidylcholine	vivo studies	release and better antifungal activity	51
		and ethanol	vivo studies	release and better antifungar delivity	
Munirocin (MP)	Burn related	Phosphatidylcholine	in-hydrogels In	Superior bioadhesiveness and sustained	32
loaded linosomes	infections	chitosan hydrogel	vitro release	release profile in hurn therapy	52
roaded hposoilles	miccuons	cintosan nyuroger	vitio icicase	release prome in burn therapy	

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Silver nanoparticle	Infected deep	Silver nanoparticles,	Cytocompatibilit	SNP-CMC could be ideal for the treatment of	33
loaded amorphous	wounds	carboxymethylcellul	y and	deep infected wounds	
hydrogel (SNP-CMC)		ose	antimicrobial	_	
			activity		
Lipidic Nanoparticles	Cutaneous	Compritol 888 ATO,	In vitro and ex	NLCs provided a good skin targeting effect	34
Fluconaozole loaded	candidiasis	Oleic acid, Egg	vivo studies	and sustained release resulting in effective	
solid lipid		phosphatidylcholine,		treatment of cutaneous fungal infection	
nanoparticles (SLNs)		Pluronic F-68			
and nanostructured					
lipid carriers (NLCs)					
Emulsion Pseudolaric	Fungal infection	Isopropyl myristate,	In vitro and ex	ME enhanced in vitro permeability, in vivo	35
acid (PA) loaded		Cremphor EL,	vivo studies	dermal bioavailability and antifungal activity	
Microemulsion (ME)		Transcutol P,			
based hydrogel		Carbopol gel			
Itraconazole (ITR)	Superficial skin	Acconon CC400,	In vitro studies	The system proved good alternative to	36
loaded ME	infections	Acconon Sorb20,		conventional antifungal therapies against	
		Capmul, Tween 40		superficial fungal infection	
Acylovir (ACV)	Cutaneous	Transcutol, Labrafac,	ME In vitro and	The system resulted in suppression of	37
loaded	Herpetic Infec	Tween 20, Span 20	in vivo studies	herpetic skin lesions	
	tions			_	
Eucalyptus oil	Staphylococcus	Eucalyptus oil,	In vitro and skin	The studies suggested the non-	38
nanoemulsion (NE)	aureus (SA) and	Triton X-100 and	safety studies	irritant nature and higher wound contraction	
	Methicillin	Tween 80		rate with respect to control and neomycin	
	resistant			treated rats	
	Staphyloccocus				
	aureus (MRSA)				
	infection				

5.2 Ethosomes

Ethosomes are deformable vesicles that contain a high concentration of ethanol and water and are made up of phospholipids (phosphatidylcholine, phosphatidylserine, and phosphatidic acid). The inelasticity of phospholipids and high ethanol content helps them to squeeze through skin pores, resulting un deeper penetration and significant transdermal flux in the skin bilayers. [39,40] Because of their high ethanol concentration and malleability, ethosomes have the potential to improve medication penetration across the strong keratinized stratum corneum barrier. [41]

5.3 Transfersomes

Transfersomes are a type of liposome that is made up of natural phospholipids such phosphatidylcholine plus a single-chain surfactant that functions as an edge activator. [42,43] The aqueous core of these liposomal systems is surrounded by a lipid bilayer that incorporates both hydrophilic and hydrophobic molecules. Deformable liposomes had previously been reported to have the intrinsic ability to enhance the in vitro delivery of various medications and to penetrate intact skin in vivo for the treatment of various topical infections, according to a number of studies. [44-46]

5.4 Solid Lipid Nanoparticles (SLNs)

SLNs (sub-micron colloidal carriers) are sub-micron colloidal carriers (50nm-1m) made up of physiological lipid distributed in water/aqueous surfactant solution. SLNs have a number of advantages, including controlled drug release, improved drug stability, the ability to incorporate hydrophobic and hydrophilic drugs, biocompatibility and biodegradability, and increased skin hydration due to greater occlusivity, making them effective for the treatment of

topical infections. [47,48] The use of lipidic nanoparticles for topical drug delivery in skin conditions is an outstanding tool in the dermatological sector. The carriers' antibacterial capabilities are due to their large surface area, which allows for increased drug penetration into bacterial cell walls, the creation of an occlusive film on the skin's surface, and biocompatibility with tissues. [47]

5.5 Nanostructured Lipid Carriers (NLCs)

The second generation of lipidic nanocarriers, NLCs, were created to address the shortcomings of SLNs, such as limited drug loading and drug leakage during storage due to lipid polymorphism. [48] NLCs are made up of a mixture of solid lipid(s) and liquid lipid(s), resulting in a less precise crystalline structure that allows for increased drug integration. [49-52] Successful formulations and evaluations of various medications for skin disease therapy have been reported in the literature, demonstrating the relevance of NLCs for cutaneous illnesses and infections. The tiny size of lipidic carriers ensures direct contact with the SC barrier, allowing more medication to penetrate the skin. [53-57]

5.6 Polymeric Nanoparticles

Polymeric nanoparticles are colloidal particles with a diameter of less than a micron that are used to encapsulate active medicinal ingredients within a polymeric matrix or adsorb to the surface. [58] Improved drug bioavailability, larger loading capacity, ability to localize at infectious target sites due to increased permeability, and the surface of nanoparticles can be easily chemically modified with either drug moieties or targeting ligands are all advantages of polymeric NPs as carriers for topical infections. [59]

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5.7 Lipid-Polymer Hybrid Nanoparticles (LPHNPs)

LPHNPs are sophisticated nano-drug delivery systems made up of liposomes and polymeric nanoparticles that have been hybridized. The hybrid nanostructures were created to overcome the shortcomings of both systems, such as low drug loading capacity, high initial burst release, drug

5.8 Microemulsion and Nanoemulsion Microemulsions

(MEs) are transparent, isotropic monophasic systems with low interfacial tension made up of two immiscible liquids. When compared to traditional vehicles, ME as a possible delivery method has the possibility to improve topical medication delivery of both hydrophilic and lipophilic components. [64-68] It's an excellent carrier for increasing in vitro skin permeability because it contains permeation enhancers as a formulation component and has a small globule size. In comparison to the aqueous suspension. griseofulvin, an antifungal medication included as ME, showed 7-times higher drug permeability and 48-times higher skin deposition. [69]

5.9 Hydrogel

The three-dimensional network of hydrophilic polymers held together by covalent bonds or cohesive forces is known as a hydrogel. Because of their biocompatibility, drug dispersion within the matrix, and high degree of control gained due to the polymer's unique properties, these swelling polymeric systems have piqued interest in the field of controlled drug delivery. [70] Hydrogels have traditionally been utilized to deliver hydrophilic medicinal molecules with excellent solubility in both the hydrophilic hydrogel matrix and the aqueous solvent swelling. Hydrogels have been extensively studied as carriers for antibacterial, antifungal, and antiviral medicines in topical applications. [71]

5.10 Silver nanoparticles

(SNPs) are ultrafine particles with a diameter of less than 100 nm and a silver content of 10000–15000 atoms. They are made by converting metallic silver into ultrafine particles. [72] The advent of antibiotic resistance has reignited interest in silver compounds, which cause bacterial cell death by modifying the structure of the cell wall and nuclear membrane. Silver also binds to the thiol groups of bacterial respiratory enzymes, halting respiration and killing the bacterium. [73] Topical ointments and lotions containing SNPs have been widely utilized to prevent infection in burns and open wounds. [74]

6. Conclusion

Infectious diseases caused by a variety of microorganisms, as well as some inflammatory diseases, provide considerable problems and are a developing research area. The advent of extremely resistant microorganisms has made combating the onus of topical infections even more difficult. The type of infection and the state of the skin layers determine the answer to this serious problem. Due to inadequate skin permeability and retention, traditional formulations such as ointments and creams have failed to produce the necessary leakage, polymer cytotoxicity, and the production process' use of hazardous organic solvents. [60] High structural integrity, stability, prolonged release from the polymer core, biocompatibility, enhanced drug loading capacity, and targeted drug delivery are all advantages of LPHNPs. [61-63]

therapeutic impact. The formulation scientists are on the lookout for the optimal drug delivery mechanism to boost the medicine's local concentration at the preferred spot, limit side effects, and overcome pathogenic resistance. The use of nanotechnology for drug delivery has resulted in a number of significant advancements in the pharmaceutical sector.

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