Utilization of Liquid Crystals for Transdermal Drug Delivery System

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
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Declaration

It is hereby declare that,

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The project titled "Utilization of Liquid Crystals for Transdermal Drug Delivery System" submitted by Madhurza Mitra Mazumder (18146049) of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on February 16, 2022.

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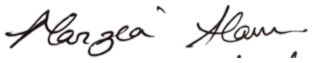

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I, Madhurza Mitra Mazumder, hereby certify that the following criteria are fulfilled for the manuscript "Utilization of Liquid Crystals for Transdermal Drug Delivery System":

1. This material is my own original material of review that has never been published beforehand.
2. The study does not include any animal or human trial.
3. All of the sources those are utilized are correctly credited (correct citation) along with a proper and justified reference.

Abstract

The following review paper addresses certain theoretical features of liquid crystals, such as liquid crystal forms and phases, as well as lyotropic liquid crystals and nanoparticles in transdermal drug delivery systems. The possible reasons behind the probability of using LLC (Lyotropic Liquid Crystal) along with LCNPs (Liquid Crystal Nanoparticles) successfully for the creation of nanocarrier drug delivery has been also explored but the focus of this review is on the topical and transdermal applications of these systems. Altogether, the current review paper studies the achievements of distinct phases of liquid crystals for transdermal drug delivery mechanism has been described and investigated in depth by which, an end result has been accomplished that liquid crystals may soon be the preferred medicine delivery system as well as these methods have the ability to revolutionize the sector for dermatological diseases.

Keywords: Liquid Crystals, Lyotropic Liquid Crystal, Transdermal Patch, Nanoparticles, Drug Delivery pathways, Inflammation.

Dedication

Dedicated to my beloved parents and respected supervisor

Acknowledgement

First and foremost, I would like to express my gratefulness to my supervisor, Ms. Marzia Alam, for her unwavering support of my studies and project work, as well as her patience, inspiration, excitement, and vast knowledge and her advices which was invaluable during the review and drafting of this thesis.

Last but not least, I would like to express my gratitude to my family, particularly my parents for always supporting me and stand beside me during hard times.

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List of Acronyms

LC Liquid Crystal

LLC Lyotropic Liquid Crystal

TDDS Transdermal Drug Delivery System

LCNP Liquid Crystal Nanoparticles

SAXS Small-Angle X-ray Scattering

WAXD Wide-Angle X-ray Diffraction

DSC Differential Scanning Calorimetry

XDR X-ray Diffraction

FTIR Fourier Transform Infrared Spectroscopy

NMR Nuclear Magnetic Resonance

ATR-IR Attenuated Total Reflectance-Infrared Spectroscopy

CXB Celecoxib

LCGs Liquid Crystalline Nano-organogels

TET Tetrandrine

Chapter 1

Introduction

1.1 History of Liquid Crystals (LCs)

In the early twentieth century, liquid crystals have been controversial among scientists, and the material remain an inquisitiveness for nearly six decades. Friedrich Richard Reinitzer (1858-1927), who is known as a horticulturist from Austria, is the first to discover the concept of LC phase while researching cholesterol compounds from carrots. While performing the experiment, Friedrich Richard Reinitzer notices that at 145.5° Celsius, the white-colored cholesterol benzoate powder (saturated fat) has melted into something like a hazy liquid that is bright blue-violet in color. Following the procedure, when it is heated to 178.5° Celsius, the hazy part has evaporated and transformed into a transparent liquid that was pale blue in color. It is clearly visible that lengthy linear structure like substances (crystalline-like feature) is present in LC nanoparticles, whereas relatively brief spatial structure is nonexistent (liquid-like feature) and the pigment of this part of an emerging has been called mesophase, varies with temperature and evaporates in the shift, but it can sometimes remain in the crystalline phase due to rapid freezing. The situation has been subsequently taken over by German scientist Otto Lehmann, who realizes that he has discovered a novel phenomenon and has been in a position to do investigation into it as well as LC substance is first seen under a polarizing optical microscope (POM) by him, who hypothesizes that they flow like isotropic fluids and have some intrinsic characteristics comparable to solids. He calls it 'flowing liquid' at first, then 'liquid crystal' later. Friedel, a French physicist, has been developed it further, and the term "mesomorphous state" is coined from the Comes from the greek "Mezos," which means "middle," because LC is the intermediary phase between isotropic fluids and crystallographic substances. As soon as liquid crystals are introduced in regular life, Pierre-Gilles de Gennes

(1932-2007) has been awarded the Nobel Prize in Physics in 1991 for exploring that methods developed for investigating sequence manifestations in simple models can be universally applied to more intricate states of matter, in particular liquid crystals and polymeric materials. (Prakash et al., 2020)

1.2 Types and Phases of Liquid Crystals (LC)

Because of their precise and persistent drug release characteristics, liquid crystals (LCs) are one of the most broadly utilized transporters for drug delivery as well as these have the physical properties of liquids and some of the structural qualities of crystalline solids because they are self-assembled organized mesophases. (Hu et al., 2021) Generally, liquid crystal (LC) structures can be subdivided into two categories that are thermotropic and lyotropic mesophases respectively.

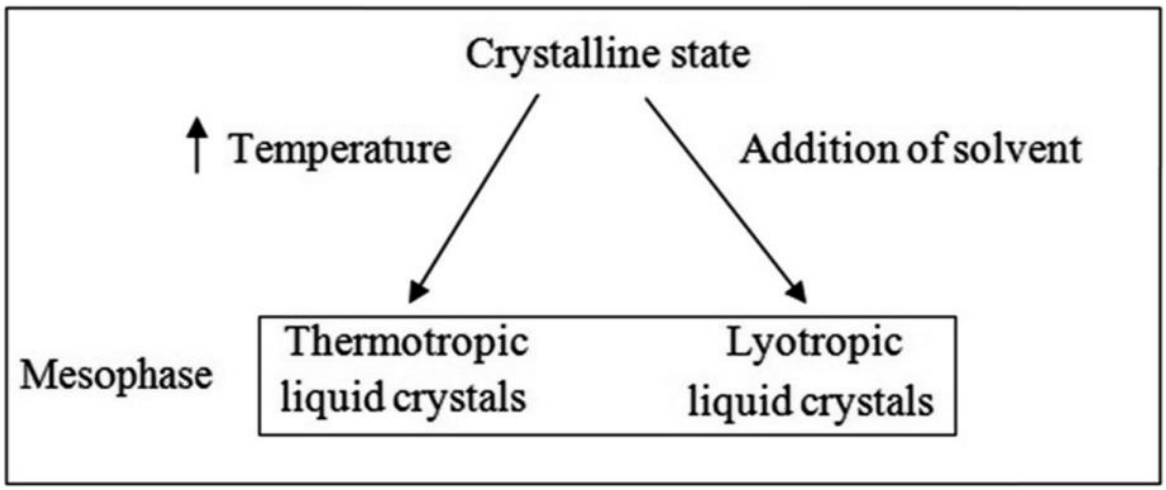

Figure 1: Phase transition to form mesophase (Adaptated from (Shete et al., 2021))

1.2.1 Thermotropic Liquid Crystal

The preponderance of thermotropic liquid crystals are made up of shaft molecules and are classed as nematic, smectic, or cholesteric and these form when a crystalline solid is heated or an isotropic liquid is being freezed. The simplest liquid crystalline phase under thermotropic liquid crystals is the nematic phase in which the molecules sustain lengthy coordination. (Rajak

et al., 2019) Moreover, thermotropic LC requires a hard central core (typically aromatic) and a flexible outer moiety (usually aliphatic groups) and this property divides thermotropic LCs into calamitic and discotic mesogens. The creation of a thermotropic liquid crystal is certain throughout an ambient temperature when pure substance commences dissolving rather than the predicted solid-melt phase transition. (Shete et al., 2021)

1.2.2 Lyotropic Liquid Crystal

Lyotropic liquid crystals, also referred as lyotropics or lyomesophases, are amphiphilic component combinations in a medium at specific temperatures and concentrations. The temperature as well as the configuration of the organic molecule, and the moisture ratio are the motivating factors behind the development of lyotropic mesophases. (Rajak et al., 2019) It is important to note that hydrolysis of shaft molecules culminates in diverse morphologies such as conical and sphere. To be more precise, triglycerides, fatty acids, carbohydrates have been thoroughly researched as main ingredients for lyotropic liquid crystals, providing highly organized way as well as stable crystalline intracellular nanostructures that have continuously assisted to protracted drug delivery frameworks. Following moisture absorption, lipids develop mucilaginous phases with a specific structure, which can be used to absorb medicines which is why LLCs are classified as lamellar, hexagonal, or cubic based on their characteristic interiors. (Shete et al., 2021) The degree of bending has been generated by the configurations of the amphiphiles as well as the ratio of the size of the head group to the aliphatic chain that plays a significant role in determining phase shapes. Lamellar phases, for instance, develop at low deformations and hexagonal phases are formed when the surfactant molecules form columnar structures that pack in hexagonal arrays as the deformations increases. In addition, the creation of micellar structures occurs as the curve increases more. (Gaisin et al., 2010) Lastly, longitudinal curvilinear bilayers and a pair of cross linking non-intersecting aqueous channels

are found to be separated by each other to compensate the cubic phase structure. (Rajak et al., 2019)

1.3 Classification of Lyotropic Liquid Crystal (LLC) Phases

Lyotropic Liquid Crystals (LLCs) can be divided into lamellar, cubic, hexagonal, spongy type, and other structures. Their shapes and chemical properties are comparable to those of cell membranes. For example, allowing medications to pass through the stratum corneum during transdermal drug delivery process promote drug transdermal penetration. Due to the presence of both lipidic and aqueous domains, LLCs can encapsulate both hydrophilic and microscopic hydrophobic molecules as well as macromolecules as drug carriers, such as peptides, polysaccharides, and nucleic acids. Furthermore, these demonstrate a thermodynamically nanostructure and the possibility for drug release that is both sustained and controlled. Moreover, LLC structure is significantly influenced by amphiphilic molecular structure, component concentration, solvent properties such as refractive index, saltiness, etc. and environmental parameters such as temperature, pH, light, CO2, etc. (J. Liu et al., 2021) Additionally, LLCs, which are based on the identity of amphiphilic molecules in excess water, have gotten a lot of attention as a drug delivery system, are influenced by many factors, including temperature, pH, light, magnetosphere, amphiphilic kind, moisture content, and additives. As a result, changing the preparation conditions can result in desirable phase structures and intelligent carriers, as well as the option of leveraging heat to induce liberation. Researchers have been able to make the transition the hexagonal mesophase to the bicontinuous cubic phase by controlling the temperature above or below physiological temperature.

1.3.1 Lamellar Liquid Crystals

While facing the water layers, surfactant particles are vaulted in tail to tail formation which can rotate. Because of the incorporation of aqueous as well as drug particles into the polar layer

where harmonized particles are introduced in favor of non-polar layer, the flat layer's thickness gets enlarged. Notwithstanding the presence of a large number surfactants concentrations, their phase remains aqueous and their crystal-like structure is maintained. (Huang & Gui, 2018)

1.3.2 Cubic Liquid Crystals

The structure of cubic liquid crystals are distinctive and typical as well as compromise along with a curved lipid bilayer that have thick consistency of approximately 3.5 nm and independent as well as water channels that are non-criss-crossing, additionally, a large interfacial area is present in the cubic channel. In Spite of having a thick consistency than other mesophases, cubic shaped crystals have a disadvantage of low flow property. Moreover, diverse compartments in cubic liquid crystals comprise different medications of hydrophilic and lipophilic type, with hydrophilic drugs situated in a close area of the aqueous channels and lipophilic drugs are found to be located in the lipid bilayer mostly. (Rapalli et al., 2020) However, unlike other liquid crystals, despite of the complete dilution process, cubosomes remain stable and can be easily included into the formulation. Even if it offers a number of advantages, including ease of preparation along with a maximum medicine stuffing magnitude as a consequence of having crystalline cubic structure, due of the great amount of water in it, it is unable to assimilate extremely water-soluble medicines. (Garg et al., 2007)

1.3.3 Hexagonal Liquid Crystals

Because of the adjoining excessive amount of water and stabilizer, an out spreading of nanoparticle formation is seen into hexagonal liquid crystals that result in a colloidal distribution called hexosomes. However, the proportion of non-polar as well as, polar solvent supplied have been seen to be kept in a minimal quantity. In comparison to the lamellar phase, the hexagonal phase is stiffer. A polarized light microscope can easily identify the texture of both lamellar and hexagonal structures. Hexagonal liquid crystals have a characteristic texture

that resembles that of a fan. Furthermore, phase transition in hexagonal and inverse hexagonal molecules is mostly influenced by the solvating agent's polarity as well as the molecule itself. (Rapalli et al., 2020)

1.4 Analytical Approaches to Designate the Phases of Liquid Crystals

Especially the liquid crystal nano-materials illustrate the discrete physicochemical properties such as changes in size and shape, alternate characteristics among stability, purity and solubility for which, here are few comprehensive analytical techniques to investigate liquid crystalline phases which is needed to ensure proper quality, and security as well as development, are discussed below. (Silvestrini et al., 2020) First of all, X-ray diffraction (XDR) has been known as the fundamental investigation method for liquid crystalline phases. By introducing this specific tool, the chemical features of specific substances, all varieties of phases of liquid crystals as well as accommodation of crystallinity can be differentiated with the standard. Because of having extended range in the structural characteristics of liquid crystals, different properties of patterns are seen to be produced through electromagnetic radiation of an appropriate wavelength. (Rajak et al., 2019) Characteristics of the scattered X-rays indicate the arrangement of the crystalline material using Bragg's Law is used to determine the features as well as the adaptation of materials of liquid crystal. This law indicates that:

$$2d \sin\theta = n\lambda,$$

Here,

n= Works as an integer

λ= Represents the wavelength

θ= The angle of scattering

d= Indicates the interspace between planar

Furthermore, small-angle X-ray scattering (SAXS) is another electric spread based approach which works alongside the available compact electrons of the sample besides considering the variation in electron density of object and vehicle. A function of shifting has been expressed in this technique which is:

$$q = 4\pi\sin\theta/\lambda$$

Here,

λ= Wavelength of the active beam

2θ= The angle which is scattered (Silvestrini et al., 2020)

Moreover, an uncomplicated and faithful approach has been used which is none other than polarized microscopy by which a detailed investigation of liquid crystal phases can be done. Different phases of liquid crystals show different characteristics in this microscopical technique. For example, underneath a polarized prism, the lamellar phase generally exhibits patchwork motifs, however the hexagonal phases illustrate non geometrical structures as well as, the gloomy background of the cubic phase has been detected due to not showing any double reflection of the microspheres solutions. In spite of having advantages, it sometimes shows adverse effect of deterioration of the sample due to interconnection of several imaging approaches. (Rajak et al., 2019)

Besides, several spectrometric approaches have indeed been intensively investigated, with the goal of determining the physicochemical characteristics of liquid crystals along with nanoparticles. One of them is most well-known technique which is nuclear magnetic resonance (NMR) that has a purpose of analysing liquid crystal phases through reciprocity electromagnetic rays accompanied by atomic nuclei. By reason of the breakdown timescales seem to be susceptible to fluctuations in regional intermolecular interconnectivity and molecular mechanics specifically in liquid-crystalline systems, NMR has been used to analyze

and track the distribution pathway of dispersed particles at the mesophase interface. This approach has also seen to evaluate the wavelength associated to the corresponding intensity as well as the timetable by which the atoms can readjust to the surrounding temperature including, utilizing the collected data to disclose the sample's structure. On the other hand, Fourier Transform Infrared Spectroscopy (FTIR) approach is available to evaluate the actions of spectra in thermal as well as medium infrared field and it is also feasible to explore the various connections of hydrophobic and hydrophilic substances integrated in the liquid-crystalline in order to determine their orientation in the aquatic or lipid regions.

Last but not the least, Differential scanning calorimetry (DSC) is utilized to find out something about phase inversion frequencies and liquid crystalline phase permanence and such approaches have been used to gain information regarding potential combinations in between mesophase-encapsulated treatment in LCNPs. (Silvestrini et al., 2020)

1.5 Physiology of Skin

Combination of ectoderm (epidermis) and mesoderm (dermis) develop the skin that serves as a protective lining against the external atmosphere and also plays a function in regulating body temperature, metabolism, and fluid and electrolyte control. The epidermis is the skin's outermost layer and depending on the level of keratinocyte development, the epidermis is split into four primary layers. The stratum corneum is the epidermis' outer part. Corneocytes are cells under startum corneum that have abandoned their nuclei and cytoplasmic components as well as have very insoluble cornified envelopes generated by the cross-linking of soluble protein precursors. The stratum corneum maintains homeostasis by a succession of well-balanced events that rejuvenate and replenish exfoliated cell layers. (Menon et al., 2012) The hypodermis, also known as the subcutaneous layer, is the skin's lowest layer and is made up of a network of fat cells that connects the skin to the body's underlying tissues, such as muscles

and bone which is why, the hypodermis' main tasks are physical shock protection, heat insulation, and support and conductance of the skin's vascular and neurological signals. (Alkilani et al., 2015) On the other hand, interstitial and cellular elements are involved for the development of the dermis. Coronary arteries, lymphatic canals, and nerve cells are also present in the part. Lipocytes make up the subcutis, which is the skin's inner lining. Moreover, fat lobules are produced from this, which are separated from one another by fibrous lining epithelium. The link between these two compartments is strengthened by bundles of fibers that originate in the dermis and extend into the subcutis. (Lai-Cheong & McGrath, 2017)

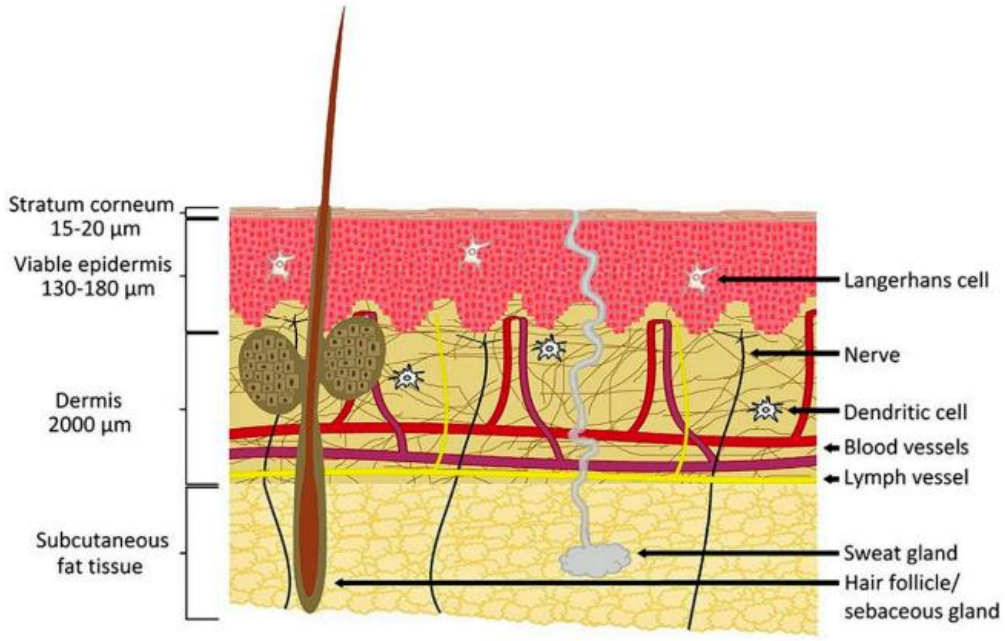

Figure 2: Layers of Skin (Adaptated from (Alkilani et al., 2015))

1.5.1 Transdermal vs. Intradermal Drug Delivery System

Transdermal absorption of bioactive components over the epidermis for systemic dispersion is referred to as transdermal delivery. Most importantly, transdermal patches, for example, are used to deliver medicine which is given as a patch or an ointment that is injected into the bloodstream and has a systemic impact. Along with that, transdermal drug delivery is a potential therapeutic delivery strategy that can be used to compensate the drawbacks of

conventional medication delivery systems such as oral and injectable methods and this mode of administration allows for both simple and painless drug delivery as well as a long-term release profile with fewer side effects. Furthermore, a thorough examination demonstrates that transdermal distribution has certain advantages over oral administration or hypodermic injections because transdermal diffusion avoids the digestion and first-pass metabolism of the active medication in the gastrointestinal tract and liver. (H. Lee et al., 2018)

On the other hand, the word "Intradermal" means administration of pharmaceutical ingredients within or into the dermis of the skin. Intradermal medication administration has become more widely acknowledged as a possible answer to many of the problems that new and existing therapies confront by allowing more effective administration of small molecules, biologics, and vaccines, as well as enhanced bioavailability. Nonetheless, technical obstacles in delivering intradermal injections, which need specialized training and have poor consistency, continue to limit the widespread use of this route of delivery. (Dr. S. Boris, Dr. R. sahan, 2018)

1.5.2 Permeation of Liquid Crystals (LC) through Skin

Permeation through skin is primarily divided into two types which are firstly transcellular and secondly intercellular. Most commonly it has been proved that, the infiltration of LC in the skin through the medium of intracellular route. Additionally, peptide enzymes along with a stansted cell agitator has been introduced to segregate the lipids which are present in the stratum corneum. Normally, the surrounded cells that are seen in the intercellular portion as well as liquid crystals and lipids, have been well known for controlling moisture deprivation as well as, coating the skin and imparting lubrication. The stratum corneum is thought to include lipids, which would form a bilayer and reflecting on the characterization of the human stratum corneum, several model epidermal lipids were generated. Using the model lipid combination to generate a bilayer culminated in a thoroughly heterogeneous matrix of liquid fats, amorphous

solids, and water and after putting into consideration some few critical components, the model would construct a bilayer. Additionally the pH of the skin is the most essential component which is between 4.2 and 6.0. Because of the acidic nature of the skin, carboxylic acids are partially saponified and do not exist as acids. As a result, the skin contains a combination of soaps and carboxylic acids. (Suhaimi & Rose, 2016)

1.6 Aim of the study

The main aim of the study is to understand the importance of liquid crystals in transdermal drug delivery system along with other contemporary systems that include oral, ophthalmic and injectable drug delivery system. Understanding the interconnection between skin and liquid crystals and the mechanism plays a very vital role to understand the whole topic. The main objective of the study focuses on the most known and prominent technology which is lyotropic liquid crystal nanoparticles in various skin diseases such as burn, fungal infection, cancer as well as psoriasis and the available drugs used in transdermal drug delivery including liquid crystal. Last but not the least, knowing the challenges along with future perspectives of the topic is a vital focus of the study.

Chapter 2

Methodology

This review is based on recent and important research papers and articles from journals with high impact factors. A thorough search of peer-reviewed publications, clinical trial papers, and articles is conducted. Basic and supplementary material is gathered from several books to supplement the review study.

In this circumstance, about more than 50 papers have been initially sorted, and 41 of those is carefully examined in order to generate this review study. Following search engines have been used to collect data for this paper which are Research Gate, Science Direct, PubMed, Elsevier, etc. in which the major publications include Nature, Journal of Medicine, Science, Drug Development and Delivery, International Journal of Drug Delivery, Nanomaterials, Journal of Molecular Liquids, Drug Design, Development and Therapy, Advanced Drug Delivery Reviews, Journal of dermatological treatment etc. In depth screening of the journals has been followed by narrowing down to the possibly recent and relevant ones along with qualitative method of secondary research is utilized to organize the non-clinical data with their findings to create an ideal quality review on “Utilization of Liquid Crystals for Transdermal Drug Delivery System”. Finally, the Mendeley software has been employed as the reference manager to uphold the credit of the work of the original authors.

Chapter 3

Transdermal Drug Delivery System

Transdermal drug delivery system (TDDS) is convenient for local or systemic delivery of therapeutics with simplified administration along with the affordability even outside healthcare centers. It helps to diminish patient burden engendered by intravenous administration as well as minimisation of the first pass effect by the liver and delivery of therapeutic drugs with constrained ratio along with convenience of preventing administration. (Tomoda & Makino, 2014)

3.1 Kinetics of Transdermal Drug Delivery System

The kinetics of skin permeation is needed to be understood in order to create effective TDD systems. The evaluation of percutaneous absorption of substances is a vital phase in appraising the transdermal drug delivery system and here, the penetration of chemicals into various layers of skin and permeation across the skin into the systemic circulation is referred to as percutaneous absorption. Molecules are absorbed through the skin in a step-by-step procedure which includes firstly, the term penetration involves the insertion of a substance into a specific surface of the skin. After that, the stratum corneum is subdivided into the aqueous feasible epidermis. Then, diffusion of the substances into the upper portion of dermis through the viable epidermis occur. The term Permeation is introduced onwards that indicate the movement of substances through one layer to another that is practically and structurally distinct from the very first. Finally, the whole process end with absorption which mean the process of a substance getting absorbed into the bloodstream.

Furthermore, for transdermal patch delivery system, the pharmaceutical substance is held in a reservoir (storage type) or incorporated in a liquid or mucilaginous reservoir. According to Fick’s law of diffusion, until the concentration gradient diminishes, pharmaceutical substances

has the ability of being transmitted through into the skin. An approximation of the drug structure's optimum flow across the skin surface is the basic foundation point for assessing the kinetics of release of the drug from a transdermal patch.

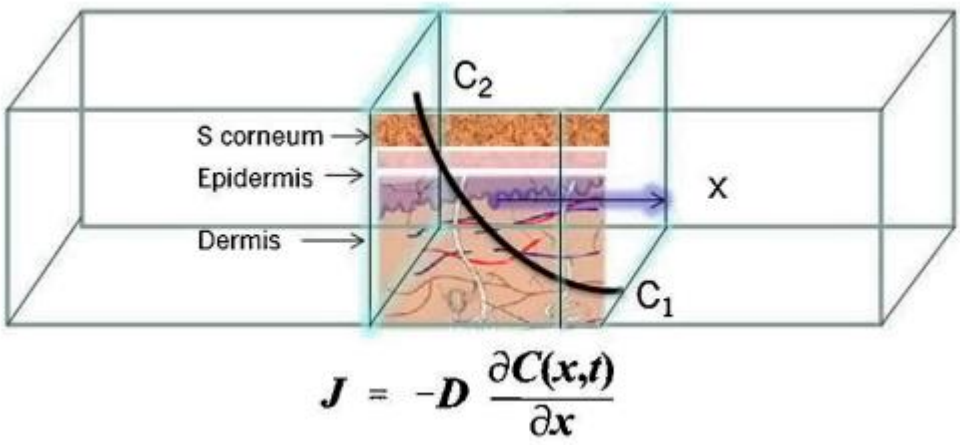

Figure 3: Description of flux across the skin from a transdermal patch (Adapted from: (Alkilani et al., 2015))

On the above figure, flux across the skin as seen through a transdermal patch has been indicated where,

J= Molecular flax

C_1= Concentration of the active substance in the patch

C_2= Concentration of the active substance in the body

D= Diffusion coefficient

T= Diffusion time

L= Diffusion depth in cross-sectional area (Alkilani et al., 2015)

3.1 Features of Liquid Crystal in Nanoparticle Form During Transdermal Administration Through Mechanistic Route

Because of having resemblance between stratum corneum of skin and liquid crystal formulation, the formulation containing LC exhibits finer as well as recommendable hydration along with distribution than emulsion. To be more precise, among all other phases of liquid crystals, cubic phase is considered as more purposive in the company of stratum corneum while initiating a lipid combination that contains cubosomal characteristics in lipid stratum corneum by storing cubosome which release the drug in a well-controlled manner. During topical use, this cubic phase shows a bio-adhesive feature that enhances the penetration across skin as well. Moreover, simultaneously, LC contains lipid and surfactants of amphiphilic kind that enhance the drug permeability by ease the exposure of LC to skin. For bringing down the negative repercussions as well as the enhancement in low systemic absorption, liquid crystals nanoparticles are found to be encapsulated in specific drugs for interconnecting the stratum corneum of skin. Furthermore, by showing the reservoir characteristic, water in liquid crystals helps the tissues to minimize the dehydration. For example, in an experiment, it has been discovered that for diclofenac sodium which is going to use for transdermal administration, liquid crystals of hexagonal phase has been constructed while diminishing the maximum amount of reflectance as well as by metamorphosing an infrared process for scrutinize in-vitro penetration. This test has manifested the transformation of skin lipid from a hexagonal matrix to a liquid disordered disposition which has called cubosome uncertainty which enhances diclofenac sodium penetration as a consequence. (Rapalli et al., 2020)

3.2 Liquid Crystal in Nanoparticle form in Various Dermatological Diseases

For transdermal drug delivery approaches mostly from the nano-formulation sector, delivery systems are used in various form in which one of the convenient way is liquid crystalline phases that have gained a high amount of attention and have been extensively studied for use in drug delivery. Because of topologies of LC and stratum corneum are identical, liquid crystal-based compositions have more hydration and easier diffusion than emulsions. As liquid crystals are amphiphilic in nature and have a presence of surfactant, these can enhance the connectivity with stratum corneum as well as leading to increased drug absorption. (Rapalli et al., 2020)

3.2.1 The use of Liquid Crystal Nanoparticles for Burn Therapy

Burns are considered to be the most agonizing abrasion of skin which is why the remedy requires a quick ease to get relief from the devastating pain. For topical distribution of pirfenidone via spraying treatment for wound healing enhancement and scar minimization, hyaluronic acid is mixed with lyotropic liquid crystal and because of having a minimal viscosity and high water uptake ability, it is easy for spraying and easy to absorb the wound exudates. A thoroughly in-vivo experiment has been done on a model containing a severe wound caused by burn and the result is found satisfactory as it has showed outstanding wound healing capabilities as well as scar prevention. The liquid crystal nanoparticles' (LCNPs) spraying therapy produce a gel on the wound surface with a complicated stiffness comparable to healthy skin that has seen to be worked to maintain the dressing in place as well as liquid crystals enhance the anti-inflammatory activity of hyaluronic acid by limiting its decomposition. Therefore, lyotropic liquid crystal based spray dressing in comparison to alternative dressings, has sped up the healing process and reduced inflammation by controlling collagen along with a successful and promising drug delivery method and has enabled

researcher’s new insights into the prevention and therapy of profound partial thickness burn damage. (Chen et al., 2020)

3.2.2 The utilization of Liquid Crystal in the Form of Nanoparticles in Fungal Contamination

As tolnaftate is considered to be insoluble in liquid form, the cream of liquid crystalline has been accelerated the penetration of epidermal site as well as has found to be effective in many fungal pathogens by showing antimycotic action and has further synthesized, modified, and assessed through various tests such as organoleptic characteristics, homogeneity test, sensitivity test, pH, viscosity management, spreadibility, attenuated total reflectance infrared spectroscopy (ATR-IR), in Vitro Anti-Fungal Studies as well as in vitro drug release studies. Recently, liquid crystalline systems have replaced traditional dosage forms because they offer greater possibilities for the development of less soluble medicines with faster diffusion rates. The current study's findings reveal that a formulation of liquid crystals cream containing 1% tolnaftate works well as a topical delivery mechanism as well as the viscosity, drug concentration, and drug release profile of the liquid crystalline cream formulations are found acceptable. (Jyotsna et al., 2018)

Moreover, in spite of being the first and effective commercialized drug, Terconazole (Tr) is not used to treat cutaneous candidiasis because to low skin permeability and difficult physicochemical characteristics which is why the use of new lecithin-integrated liquid crystalline nano-organogels (LCGs) is being introduced to improve the physicochemical properties of Tr so that it can be used on the skin to treat cutaneous candidiasis. After the intensive investigation of all physicochemical parameters such as pH, rheological behavior, size of the particles, in-vivo, and in-vitro antifungal activity and being ended up with a result

that the produced formulation has increase in permeability when compared to a typical hydrogel. (Elnaggar et al., 2016)

Last but not the least, Miconazole Nitrate-based cubosome hydrogels have been developed to deliver Miconazole Nitrate for topical use from the findings of the experiments such as in-vitro release, ex vivo permeation and microbiological studies and the produced cubogels offer a lot of potential for topical drug delivery as well as after 8 hours, the produced dispersion has released 100% of the medication, compared to 44.8 percent in the commercial formulation. (Ka Khalifa & Khalifa, 2015)

3.2.3 Liquid Crystal in the form of Nanoparticle to treat Acne

A frequently seen chronic inflammation in skin that includes the pilosebaceous region result in acne problems mostly during adolescence. To prevent this, Erythromycin in cubic form which are nanomaterials that really are self-assembled liquid crystalline particles of surfactants and triglycerides with the appropriate proportion of water are introduced to use topically. Surface morphology, particle shape or size, encapsulation performance, and also in vitro drug release study, are all measured in the manufactured cubosome dispersion while integrating carbopol 934 at various doses into the optimum formulation resulted in cubosomal gel formation. Additionally, homogeneity, pH, viscosity, spreadability, drug content study are all assessed on the produced gel. The findings of the study has revealed that innovative cubic vesicles, also known as cubosomes, can easily penetrate the skin and enhance medication retention over time as well as, cubic nanoparticles (cubosomes) is being mixed into gel formulation can be used as a topical gel to treat acne and bacterial infections. (Jain, 2018)

3.2.4 The use of Liquid Crystal as remedy in Melanoma Cancer

Cancer is considered to be the most severe disease overall and when it comes to skin cancer, malignant melanoma is known as the most fatal and frightful where patients can enlarge

metastases with a lifespan of highest 5 to 6 years only because of the severity of skin cancer. Cubosomes are a type of nanoparticle that takes advantage of some lipids' natural inclination to self-aggregate in water, producing backward cubic bicontinuous liquid crystalline structure. Tumor-targeted nanoparticles have indeed been developed for the contemporaneous integration of medicines and diagnostic agents, with the intention of providing the best possible therapeutic efficacy at specified sites in the body while minimizing detrimental consequences. The orchestrated polymer-free, monoolein-based cubosomes are co-stabilized by a mishmash of phospholipids that play a key role for enhance formulation biocompatibility and biodegradability as well as propylene glycol, the last one attempting to play a dual role in the preparation, being both a hydrotrope and a humectant, and the propylene glycol impacted cubosome physicochemical properties, enabling the maximum nanocarrier stability. Consequently, the discoveries has reported further contributed to the design and development of a new generation of sustainable drug delivery nanocarriers with a cubic structure of liquid crystal for use in melanoma skin cancer therapy. (Bazylińska et al., 2018)

In addition, because of the poor penetration of photodynamic therapy (PDT) in skin cancer, a newly generated delivery approach has been introduced with lyotropic liquid crystal. Despite the fact that liquid crystalline vehicles have always had the ability to carry medicines into the skin, few research have used this form of transporter to convey photosensitizing drugs (PS) externally employing PDT and to that purpose, reverse hexagonal phase nanoparticles containing this PS are produced, and their topical applications in vitro and in vivo are assessed. Further to that, a delivery method has been investigated which has outstanding features for use in topical PDT of melanoma, including such fine particle size (below 200 nm) coupled with low cytotoxic effects for natural skin fibroblast cell's cell line and being managed to improve PS accumulation by deeper layers of the skin, in which neoplasic and non-neoplasic tumours actually happen in inflammatory conditions. (Petrilli et al., 2013)

3.2.5 Liquid Crystal in Nanoparticle form for Psoriasis

Psoriasis is a common inflammatory condition that causes skin infections as well as a deterioration in the barrier function even, scalability can also occur as a result of an uneven formation of the stratum corneum and uncontrolled keratinocyte production. Regardless of the fact that psoriasis is indeed hardly alarming and threatening, because of skin being the human body's vast and most prominent biological structure, it retains a public exclusion which means the patient with infection feels shame for public meeting and this condition worsened with time, resulting in highly deep as well as trifling spot that is red in color across the skin outer surface area. For the beneficial thinking of society, liquid crystalline nanoparticles that are stuffed with tacrolimus have been introduced by the scientists to treat this disease. The consequences of liquid crystal nanoparticles which are packed with tacrolimus, in membrane permeability and retention in vitro, as well as in vivo psoriasis-like skin inflammation, are investigated in a study by investigating particle size and entrapment efficiency of monoolein-based nanoparticles. The application of LCNs has resulted in a considerable increase in the amount of tacrolimus penetrated and retained in a skin permeation and retention trial. (Thapa & Yoo, 2014)

Moreover, cubic phase structures with an oleic acid/propylene glycol connection has lessened edema throughout times, implying that they influence Celecoxib (CXB) release and penetration and the developed liquid crystalline devices could be used to deliver CXB to the skin. In the aerosil-induced rat paw edema paradigm, the CXB-loaded liquid crystalline systems successfully minimize edema formation, indicating that these formulations are suitable for CXB transdermal delivery. Moreover, the anti-inflammatory efficacy of CXB is affected by the systems' composition and liquid crystalline structure, with CXB-loaded cubic phase systems being more effective than CXB-loaded hexagonal phase systems of GMO-W containing oleic acid (OA) and propylene glycol (PG) as additives. (Dante et al., 2018)

3.2.6 Liquid Crystals for Peptide Delivery

In order to tackle topical *Pseudomonas* infections, glyceryl monooleate (GMO)-based liquid crystals offer a promising responsive delivery strategy for alginate lyase and gentamicin. A research work has been conducted by scientists which have presented that, to cure *Pseudomonas* biofilms, the enzyme that is called as glycoside hydrolase which means alginate lyase along with antibiotic, such as gentamicin, has been incorporated into liquid crystals that shows response to infection, are susceptible to *Pseudomonas* infection for glycoside hydrolase and antimicrobial combination. The presence of *Pseudomonas* causes the release of alginate lyase along with gentamicin especially from glyceryl mono-oleate liquid crystals that has reduced the biofilm of mucoid *Pseudomonas aeruginosa*. After that, two days apart, the anti-biofilm activity of the liquid crystals formulation has been comparable to the conventional solution which has indicated the developed formulation delivered stimuli-responsive treatment for *Pseudomonas* infections on the skin. (Thorn et al., 2018)

Furthermore, freeze-dried and re-hydrated liquid crystalline nanoparticles after stabilized with disaccharides for drug-delivery of the plectasin derivative AP114 antimicrobial peptide has been investigated. According to the conducted research findings, trehalose is the optimum lyo-protectant for sustaining a mono-modal particle size distribution of LCNPs generated by powders as the trehalose formulation has performed best in terms of antibacterial efficacy among the antimicrobial peptide (AP114)-containing formulations. The release of AP114 and antibacterial activity are dramatically boosted when the hexagonal phase's lattice parameter has been raised. The approach including heat-treatment of the particles to minimize vesicle content may be more suitable for encapsulation and distribution of low molecular weight, heat-stable medicines. (Boge et al., 2018)

Furthermore, antimicrobial peptides (AMPs) are commonly considered to be viable antibiotic replacements as pH-targeted nano composites have the ability to increase the treatment

effectiveness of AMPs by preferentially concentrating their antibacterial properties to infectious sites while safeguarding them from disintegration and reducing off-target detrimental effects. Additionally, the lipid and peptide contents of these nanoself-assemblies, can be modified to manage the pH range in which it can undergo desired structural and surface charge modifications using the generated OA/GMO/LL-37 partial phase diagrams at different pHs as a reference which are critical for the future development of smart lipid nanocarriers with programmable pH-triggered nanostructures for pH-guided AMP administration in pathologies. (Gontsarik et al., 2021)

3.2.7 Liquid Crystal Nanoparticles for Atopic Dermatitis

In adolescent, commonly a skin condition has been faced named atopic dermatitis that is mostly known as atopic eczema as well as a systemically debilitating chronic diseases for which, traditional topical formulations for example, moisturizer and ointments are available in the market for sale. However these formulations do not allow the medicine to reach the deeper layers of the skin. New tactics for optimizing skin-specific nanoparticulate systems to treat atropic dermatitis can be investigated with the help of adaptable nanocarriers in combination with novel administration routes. (Akhtar et al., 2017) Moreover, in another study, scientists assessed KIOM-MA-128 which is considered as a newly produced herbal medicine to treat atopic dermatitis that has been studied in conjunction with monoolein (MO) cubosomes which is known as an in-vitro skin permeation enhancer of KIOM-MA-128. It has been discovered that the physical characteristics of MO cubosomes are very specific which is 10-100 nm in size as well as contain black and white threads, which is why cubosomes penetrate the skin more easily than KIOM-MA-128 suspension. (Rapalli et al., 2020)

3.3 Liquid crystal containing drugs which are used in Transdermal Drug Delivery System

As usefulness of liquid crystals is developing day by day rapidly, there are many drug that are particularly has been produced for the treatment of skin diseases, has been listed out. Moreover, Lyotropic liquid crystals are used to provide various genres of medicines for skin problems along with different indication as well as having separate mesophases. Some of these drugs has been listed below for the better understanding that how much prominent using LC is:

Table 1: LLC and LCNPs have been employed in skin conditions in topical, transdermal, and subcutaneous skin treatments. (Adapted from: (Silvestrini et al., 2020))

Drug	Skin Application	Mesophases
Bupivacainahydrochloride	Analgesia	Transition
Celecoxib	Works against inflammation by improving skin penetration	Hexagonal and Cubic
Chlorin e6 and meso-Tetraphenylporphine Mn(III) chloride	Skin cancer such as Melanoma skin cancer through fast skin penetration	Cubic
Cyclosporin A	Helpful against psoriasis	Hexagonal
Cetylpyridinium chloride and Poly-hexamethylene biguanide	Works against skin infection	Lamellar and Cubic
Fluconazole	Works to prevent cutaneous candidiasis while accelerating skin penetration.	Cubic

Finasteride	Works against scalp diseases such as alopecia	Hexagonal and Cubic
Genistein	Fight againt skin cancer while improving skin penetration	Lamellar
Itraconazole	Antifungal	Lamellar
Ketoconazole	Antifungal	Hexagonal
Metronidazole	Defend skin infection through fast skin penetration	Hexagonal
Naltrexone	Against inflammation through sustained release	Hexagonal
Paenol	Helpful to prevent skin inflammation along with skin cancer by improving skin penetration	Cubic
rhEGF	Work against severe wounds as well as accelerate sustained release along with maintaining stability	Cubic
siRNA TyRP-1	Active against long term skin condition such as vitiligo	Hexagonal
Tacrolimus	Works against Psoriasis as well as inflammation by improving skin penetration.	Cubic

Triptolide	Accelerating the generation of tissue through sustained release	Cubic and Hexagonal
Zinc phthalocyanine tetrasulfonate	Active to prevent skin cancer by improving the photodynamic therapy.	Hexagonal, Lamellar and Cubic
Vaccines containing peptide	Sustained delivery by penetrating the skin	Cubic
VEGF	Tissue Regeneration through sustained release	Cubic

Chapter 4

Other Drug Delivery Systems that use Liquid Crystal

Not only in transdermal drug delivery system, but also, liquid crystals are now widely used in oral, injectable and ophthalmic drug delivery system.

4.1 Oral Drug Delivery System

Because of its noninvasiveness, having a high rate of patient compliance, easy to handle, and therefore not requiring specialized aseptic conditions, oral medication delivery is considered to be a popular method of administration. However, before being absorbed into the systemic circulation, several medications that has been taken orally meet many physiological, pharmacological, and metabolic barriers that reduce their therapeutic efficacy. Although numerous drug transportation methods have been introduced based on nanocarrier or lyotropic liquid crystals conducive to the convention of oral drug delivery system have been proposed in recent years and are showing promising results, they are still a long way from being used in the field. (Martins & Santos, 2020) To be more precise, lyotropic liquid crystals (LLCs), in which, mainly the cubic crystal phase separation, may actually demonstrate preferable for oral delivery for some specific reasons such as firstly, the configuration might safeguard the drug against deterioration in the gastrointestinal (GI) pathway as well as the lyotropic property of the cubic phase with a hydrophilic area that have greater solubility, facilitates a direct interactions with the endothelial cell surface and can traverse the aqueous layer, increasing the performance for permeability throughout the endothelial cell membrane. During the digestion and absorption of lipid molecules, LLCs are comprised of an oil phase and a solubilized micellar phase in the GI tract's physiologic environment, which enhances therapeutic solubility and dissolution rate in the lumen. Enhanced apical to basolateral (luminar side) permeability observed that is caused by excessive inhibition of drug metabolism due to the production of cubic nanostructures.

(Rajabalaya et al., 2017) In addition, it has been highlighted by scientists that liquid crystals in the shape of nanoparticles has significantly used as an oral drug delivery system mainly for liver specific distribution. The phase inversion temperature (PIT) approach are used to produce the LCNPs incorporated with the peptide-based treatment which is a new hepatitis C virus NS5A inhibitor, BMK-20113, in this study, which has a requirement of minimal amount of energy as well as a short processing time and the particle sizes of the LCNPs were roughly 100 nm, together with the structure is determined to be orthorhombic lateral packing of crystallography with a lamellar liquid crystal structure. The whole process is conducted through various methods such as SAXD and WAXD analysis (Small- and Wide-angle X-ray diffraction), TEM (Transmission Electron Microscopy) analysis, DSC (Differential Scanning Calorimetry) analysis, in-vitro dialysis, particle size analysis, tissue distribution studies and Pk studies. (D. R. Lee et al., 2016) For example, when taken orally, quercetin, a hydrophobic medication, typically shows instability physiologically, but an LC formulation comprising soy phosphatidylcholine (SPC) and glycerol dioleate (GDO) significantly solubilize quercetin in a nonaqueous SPC and GDO mixture, resulting in physiological stability. Remarkably, the drug has facilitated an enhanced unit cell dimension of the reversed micellar cubic phase with a low SPC concentration and the LC nanostructure has been found to improve hydrophilic drug absorption kinetics and has demonstrated to increase bioavailability by extending stomach absorption. (Rajabalaya et al., 2017)

4.2 Ophthalmic Drug Delivery System

The pharmaceutical scientist's most mesmerizing and demanding delivery mechanism is ocular medication administration as the eye's particular shape, function, and biology make it highly impervious to outside chemicals and the formulator must find a way to get beyond the eye's protective barriers without inflicting long-term tissue damage. These types of impediments have a significant impact on ocular medication bioavailability. The quick and broad removal

of conventional eye drops from the eye is the fundamental challenge in ophthalmic medication delivery systems. To circumvent the issues has caused by static and dynamic barriers, innovative pharmaceutical drug delivery concepts including iontophoresis, liquid crystal nanoparticles, liposome biocompatible gels, liquid crystal gels, and retinal inserts have been developed over the years. (Kumari, 2019) The choice of the most promising route of administration for ophthalmic distribution is largely determined by the target tissue. The most conventional examples of ocular drug delivery are local, local retinal that includes subconjunctival, intravitreal, retrobulbar, and intracameral and systemic. (Üstündağ Okur et al., 2020) A significant variety of new drug delivery technologies, such as liposome nanoparticles and microemulsion, have indeed been applied to the eyes to prolong the retention time of the eyes, minimizing treatment repetition and enhancing bioavailability and among these, introduction of in situ gel has become new type of ophthalmic drug delivery system. The bioavailability and biocompatibility of the medicine are vastly enhanced when compared with eye drops whilst using the liquid crystal gel precursor preparation as well as the liquid crystal gel exhibited superior prolonged effect in the in vitro drug release studies tests, avoiding the drawbacks of recurrent administration. The moisture level of cornea along with the draize test also shows that the preparation is less irritating to the eyes and suitable for ocular administration and the pre-corneal residence time analysis revealed that the preparation has displayed excellent adhesion properties. (Wu et al., 2021) On the other hand, in comparison to tetrandrine (TET) solution, a revolutionary new glyceryl monoolein, poloxamer 407, incorporating liquid crystalline nanoparticles (LCNPs) for the ophthalmic delivery system of tetrandrine (TET) has showed improved pre-ocular retention time and increased optical bioavailability. Cellular uptake, drug encapsulation capability, drug usage, zeta potential, particle shape and size, polydispersity index and crystalline matrix phase, all are investigated in this research of TET-loaded liquid crystal nanoparticles (LCNPs) as well as a dynamic

dialysis approach has been used to determine in vitro drug release from the LCNP system. (R. Liu et al., 2016)

4.3 Injectable Drug Delivery System

Because of the characteristics of Liquid Crystals' performance in the presence of liquid medium, increases aqueous solubility and modulates dissolution rate and this particular system can be used in injectable drug delivery applications. Specifically, organogels are mainly composed of liquid amphiphilic lipids which thus expand in water to produce lyotropic liquid crystals of distinctive kinds. Structure-modified surfactants such as oleylglycerate and phytanylglycerate, which form viscous lyotropic liquid crystal (LLC) phases in excess water and provide sustained release matrices for depot drug delivery of paclitaxel, irinotecan, glucose, histidine, and octreotide by forming reverse hexagonal phase which is why injections made by using microemulsion which are formed by liquid crystals, can prolong the drug release. (Shete et al., 2021) For its long-term drug release characteristics, liquid crystal technology has significantly emerged as a promising injectable sustained release (SR) preparation. An injectable liquid crystal-forming system (LCFS) is developed utilizing sorbitan monooleate (SMO) which is a significant liquid crystal-forming material for injections, and the feasibility of using a therapeutically relevant sustained-release formulation has been investigated through various tests such as in-vitro release test, the thorough investigation of pharmacokinetic and pharmacodynamics characteristics along with statistical analysis, Cryo-transmission electron microscopy (Cryo-TEM) and polarized optical microscopy. As an outcome of the tests, when deployed for SR injection of leuprolide acetate for patient, the LCFS is thought to provide a sufficient therapeutic impact in terms of safety, ease of preparation, and suitability of controlled release qualities as well has predicted to replace conventional repository injections. Additionally, the developed LCFS for SR injections in liquid form is also anticipated to be used for the controlled drug release of a vast scope of medications, especially

in low molecular active compounds to large molecular pharmaceuticals like peptides and proteins. (Ki et al., 2014)

Furthermore, injectable in situ forming gel that is based on lyotropic liquid crystal has been introduced for the persistent postoperative/postsurgical analgesia. ISFG (in situ forming gel) which is based on lyotropic liquid crystal (LLC), dynamically gelatinizes from the reaction mixture to the substantial gel with such a lamellar-hexagonal-cubic phase transformation induced exclusively by moisture absorption, is a revolutionary intravenous sustained release method that has already previously emerged that starts off as a solution for administration before transforming into a gel at the injection site. (Mei et al., 2018)

Chapter 5

Beneficial Aspects of Utilizing Liquid Crystals in Transdermal Drug Delivery System

Nanoparticles are getting popular in the arena of transdermal drug delivery system since they have the opportunities to alleviate the shortcomings of traditional lipid-based approaches, such as safeguarding hazardous medications from deterioration and thermal degradation as well as generating continuous drug release to lessen negative impacts. The basic beneficial aspects of liquid crystals that can be present in both hydrophobic and hydrophilic drugs, in transdermal drug delivery includes a vast mechanical strength as well as not having any shape changing problem which can execute both targeted and controlled release of the drug. (Jeong et al., 2021)

The clarification of physical-chemical and morphological characteristics, as well as the interactions with the living organism, is not only difficult but also vital work in the biomedical sector, whether in the management or diagnosis of disorders, which is why, it has been witnessed numerous research approaches that are ingrained in LLC research. Both LLCs and LCNPs have numerous advantages for usage as effective drug delivery systems via various modes of administration. The advantages of LLC along with LCNP nanostructured systems includes the trapping of molecules with various physical along with chemical characteristics, protection from internal and external influences and additionally, because LCNPs can be modified structurally and chemically, these can be adapted to the route of administration and the disease of interest. Moreover, inflammation, infections, autoimmune illnesses, cancer, photoprotection, tissue regeneration, repellent protection, hormone therapy, and immunization have all been successfully treated for topical skin application by using both LLC and LCNPs. The feature of high affinity of liquid-crystalline mesophases with the skin, which makes it more

porous and fluid as well as the biocompatibility of its components, account for the wide range of uses. A more precise and reliable as well as an in-depth analysis of the behavior and interactions of LLCs and LCNPs with cellular membrane can lead to the development of smarter and safer systems, allowing for precise control over the dermal or transdermal distribution of pharmaceutical products in the professional qualifications and diagnostic circumstances. The study of their kinetic behavior in damaged or diseased skin is another significant element that enables the use of these systems in the topical delivery of therapeutic medicines. There are several research that have looked into how damaged skin's permeability might vary, which is an important factor to consider when designing topical drug delivery systems and the alternatives to in vitro or ex vivo models that resemble healthy and pathological skin for better understanding of these challenges and improved drug delivery through these systems include in vitro or ex vivo models that mimic healthy and pathological skin. Last but not the least, it is expected that LLCs and LCNPs will gain market share in illness treatment technology, as well as skin care and cosmetic applications, during upcoming years. (Silvestrini et al., 2020)

Chapter 6

Future Prospects of Liquid Crystal

The liquid crystals along with nanoparticles have shown a very promising and succeeding future in the sphere of drug delivery. Proteins and peptides that are mainly hydrophobic and hydrophilic particles, can be shifted easily because of the potentiality of liquid crystals. It is known that the structural advantage of liquid crystal has always been favourable for enhancing the release profile of drugs. Topical application on skin surface has been seen to improve along with its occlusive nature and permeability due to the lipid characteristics as well as due to the nano-size. The highest concern which is maintaining the non-toxicity of the formulation is incorporated with the biocompatibility and biodegradability of amphiphilic lipids. According to possible findings, liquid crystalline nanoparticles could be used as a medicine delivery vehicle for acute to chronic cutaneous illnesses. (Rapalli et al., 2020)

The growth of the transdermal drug delivery system (TDDS) sector in the regional and abroad drug delivery system industry has grown rapidly in recent years, as demonstrated by an expansion in studies that has conducted, copyrights, and economically accessible products from different companies and research institutes. Microparticles, liquid crystal nanoparticles, and lyotropic liquid crystals are also increasing in popularity among TDDS technologies, since they complement the limits of current simple application and patch administration approaches to improve therapy efficiency and effects. Last but not the least, manufacturing and commercialization methods are being developed for various types of skin diseases as well as genetic diseases, infectious and localized infectious diseases, as well as spearheading advances in vaccination and supporting patient preference for self-administration of drugs for long-term treatment, with judicious implementation of latest technologies, such as 3D bioprinting. (Jeong et al., 2021)

A few of the medications that are manufactured as liquid crystals are in the preclinical developmental stage and thus are listed below:

Table 2: List of LC drugs which are still in preclinical or clinical stage. (Adaptated from:(Bala et al., 2021))

Drug Name	**Characteristics**	**Activity**
Apatone	This is comprised of two nontoxic substances which includes LC compound and sugar, is currently being investigated for a clinical trial.	Competence for treating late-stage prostate cancer.
Tolecine	This a new anti-cancer liquid crystals medication that is being developed, is now in the preclinical stage.	It has strong anti-neoplastic properties, as well as antiviral and antibacterial properties and selective for tumor cells.

Chapter 7

Challenges of Using Liquid Crystal in Drug Delivery

Inspite of having tremendous advantages in different sectors such as transdermal, oral, opththalmic and injectable drug delivery systems, the usage of liquid crystals (LCs) for therapeutic purpose has a few drawbacks. First of all, a major challenge is, lyotropic liquid crystals form spontaneously when amphiphilic lipids come into contact with too much water, as well as, thermodynamically stable liquid crystalline formation occur and the main objection of this is whether the LLCs will preserve their nanostructure and characteristics when the temperature is changed or not which was proved in a study in which, despite the presence of extra water, such a system produced the cubic phase at lower temperatures but transitioned to the hexagonal phase as the temperature climbed and addition of oleic acid and vitamin E acetate, the LLC systems decreased these transitions. Moreover, local or systemic toxicity as well as a shorter release pattern are only a few of the negative aspects that make using LCs in drug delivery difficult, especially for long-acting medicines, for which, a simulation investigation was able to reduce this problem by selectively alkylating the medication, using tryptophan and releasing it from the cubic phase with various geometries and the findings stated that, increasing the alkyl chain length can prolong the release, and modifying the alkyl linkage type and charge can also affect the release. Furthermore, the proportion of surfactants and co solvents has employed may change the value of medicine that can be delivered through an LLC, yet, utilizing excessive amounts of these two ingredients may be dangerous, limiting the number of combinations which can be deployed. Finally, the influence of its structure on long-term storage, particularly at low temperatures, is one of the main concerns in the use of LCs. (Rajabalaya et al., 2017)

Chapter 8

Conclusion

The significance of using liquid crystals including the usefulness of lyotropic liquid crystals nanoparticles' acceptance in transdermal drug delivery system has been thoroughly brought up in the above written project paper named "Utilization of Liquid Crystals for Transdermal Drug Delivery System". Despite the fact that now in almost all aspects of drug delivery systems such as injectable, ophthalmic and oral, liquid crystals are used but it has shown a prominent result and beneficial aspects in transdermal drug delivery system by working on various dermatological diseases such as burn, acne, psoriasis, atopic edema, melanoma cancer, peptide delivery etc. because of having resemblance between stratum corneum of skin and liquid crystal formulation, the formulation containing LC exhibits finer as well as recommendable hydration along with distribution. Moreover, notwithstanding numerous benefits in areas such as transdermal, oral, ophthalmic, and injectable drug delivery systems, the use of liquid crystals (LCs) for therapeutic purposes has a few limitations, according to the findings, for which various industrial production and corporatization techniques are being developed for a range of different skin maladies, genetic abnormalities, highly contagious and regionalised infectious diseases, as well as spearheading breakthroughs in immunization and continuing to support patient quality of life for self-administration of drugs for long-term treatment.

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