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CONCEPT OF LAZUQ (A CLASSICAL UNANI DOSAGE FORM) AND ITS EVOLUTION AS TRANSDERMAL PATCH (A NOVEL DRUG DELIVERY SYSTEM): AN ANALYZATION

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ABSTRACT

Purpose: The goal of this manuscript is to redesign, evaluate and validate the concept of *Lazūq* to increase its; application, efficacy, duration of drug activity, patient compliance, bioavailability, solubility and pharmacological activity and analyze and search its counter form from novel drug delivery system that will make it more stable, provide sustained delivery and protection from physical and chemical degradation and also improve to target at a specific site to reduce unwanted side effects. ***Background:*** *Lazūq* is an ancient *Unani* classical dosage form, the traditional method to prepare this dosage form is that fine powder of drug or drugs is mixed to white part of egg or other mucilaginous substances then spread over already sieved paper or cloth and apply it on affected part. *Unani* system of medicines enriched with lot of formulations of *Lazūq* used in different states of human health e.g., pain, orthopedic conditions and diseases related to throat etc. *Lazūq* finds noteworthy mention in esteemed *Unani* literatures like *Al-Qarabadeen, Kamil-Al-Sana'at, Qarabadeen-e-Azam, Qarabadeen-e-Najam-ul-Ghani* etc. Despite of being an effective and safer dosage form, *Lazūq* has become forgotten for so long, perhaps due to the difficulty in method of preparation and usage. ***Methodology:*** Ancient classical *Unani* literature and concept of *Lazūq* was searched and then analyzed with the today's knowledge of *Transdermal patch; A Novel drug delivery system* to design, develop and evaluate the advanced novel form to *Lazūq*. ***Conclusion:*** After going through the history, course of *Lazūq* and analyzing the concept with novel drug delivery system, it is concluded that *Transdermal Patch* perfectly follows the blueprints of *Lazūq*. The basic purpose of both forms is same with the difference of their genesis with respect to their era. The first inventory form i.e., *Lazūq* has progressed and redesigned as *Transdermal Patch* in the class of *Transdermal Drug Delivery System* with the advancement of pharmaceutical techniques. ***Future prospects:*** Every classical *Unani* drug dosage form should be analyzed with modern novel dosage form and if needed, it must be redesign, develop and converted to increase the efficacy and application of the *Unani* system of medicine.

Index Terms: *Unani, Ilmul Saidla, Lazūq, Transdermal Patch, Transdermal/Novel Drug Delivery System*.

1. INTRODUCTION

The spectrum of *Unani* dosage forms is very broad which has a large number and different types of dosage forms. For instance, if we look for the series related to manuscript only, there are vast inventory class of topical compound formulations in different dosage forms viz., ***Lazūq,*** *Marham, Zimad, Qairooti, Tila, Murawwakh, Nutool, Ubtan, Ghaza, Ghalia, Pashoya, Masooh, Roghan, Ghasool, Kaboos, Norah* etc.[1-10] It is much needed to analyze these *Classical Unani dosage forms* with the *novel drug delivery system* (NDDS); to look counter or advanced form, to develop, redesign and evaluation the classical forms, to give new dimensions to *Unani* system of medicines with the help of modern pharmaceutical innovations and techniques. After going through this review work, it would be easy to understand the importance of novel dosage form in *Unani* system of medicine, conceptual knowledge of *Lazūq* described in *Classical Unani literature* and its evolution and analyzation as *Transdermal Patch*. *Transdermal Patch* are now widely used as cosmetic, topical and transdermal delivery systems. These patches represent a key outcome from the growth in skin sciences, technology and expertise developed through trial and error, clinical observation and evidenced based studies that back to the first existing human records.

2. OBJECTIVE

The goal of this manuscript is to redesign, evaluate and validate the concept of *Lazūq* to increase its; application, efficacy, duration of drug activity, patient compliance, bioavailability, solubility and pharmacological activity. To analyze and search counter form from novel drug delivery system that will make it more stable, provide

sustained delivery and protection from physical and chemical degradation and also improve to target at a specific site to reduce unwanted side effects.

2.1 Importance of novel drug dosage form for *unani* system of medicine

Ancient classical *Unani* literature describes dosage forms for both single and complex *Unani* medications. They have not changed since ancient times, thus one of the primary obstacles facing the *Unani* system is the requirement for dosage forms evaluations based on modern methodologies with the goal to make it agreeable and pleasant for everyone. The use of *Unani* remedies is becoming more and more popular domestically and globally, however this industry is still underutilizing the need. It must start with the fundamentals of experimentation that are required research.

Unani medicines were long disregarded for the development of novel formulations due to processing challenges and a lack of scientific support; however, current phytopharmaceutical research may deal with the requirements of *Unani* medicines in order to incorporate them into novel drug delivery systems. The new formulations are said to offer notable benefits above traditional medication compositions. It must be kept in the mind while transforming that the *Unani* principle must not be compromised in any way by these dosage form modifications.

Now the work that should be done first in the field of *Unani medicinal formulations,* is to provide substantial scientific pharmaceutical experimental base to its philosophy, theories and concepts on the steps of modern parameters. In this way *Unani* medicine could become more authentic and reliable. Encouragements to drug manufacturers, entrepreneurs, and institutions is must for international propagation of *Unani* medicine globally. Registration of products; exports and support for international market is possible when we justify our medicinal products on the scientific pharmaceutical parameters. The development of *Unani* Pharmacy in the present scientific era has been very considering and appreciable. Most pharmaceutical companies have adopted modern techniques and contemporary pharmaceutical equipment for manufacturing their products but still we are lacking very much. Modernization of techniques is very important for delivering effective *Unani* healthcare products; the regulatory authorities should provide guidelines and methodologies for research and evaluation from time to time to ensure the quality, safety, efficacy, cost-effectiveness, utilization, and best practices. The thrust areas of research in *Ilmul Saidla* are a modification of different dosage forms; standardization of single drugs, and compound formulations; scientific validation of every procedure mentioned in *Unani* classical text e.g., *Tadbeer-e-Advia* (detoxification of drug), development of standard operating procedure for a formulation of compound medicine, and as per todays demand the most important work is to redesign, develop and convert *Unani* dosage form with the help of Novel drug delivery system in modern pharmaceutical sciences.[11-16]

To improve aesthetic acceptability, taste and efficacy, reduction in dosage, for acceptance of the inconvenient forms that are not accepted by mass of patients as the first line of treatment should be minimized. Lack of novel drug delivery systems harming the future of *Unani* system of medicine. Therefore, with the help of advanced technology in the field of pharmaceutical sciences, standardization of single and compound drugs and by adaptation of novel drug dosage forms and delivery system, we may take the *Unani* system of medicine at the edge where it must be, and vision of *Hakeem Ajmal Khan* and *Hakeem Abdul Hameed* can be achieved.

2.2 History of *Lazūq* and Its evolution as transdermal patch

Lazūq finds noteworthy mention in esteemed *unani* literatures like *Al-Qarabadeen, Kamil-Al-Sana'at, Al-Qanoon-fil-Tibb, Qarabadeen-e-Azam, Qarabadeen-e-Najam-ul-Ghani,* and other famous *Encyclopedia/Treatises/Books* of *Unani System of Medicine* with respect to pharmacy and treatment written by various *Unani* scholars and having the long history of many centuries.[17-26] It can be considered as band aid that is used in conventional medicine. However, conventional medicine has confined this dosage form only for hemostatic, analgesic and antiseptic, but *Unani* system of medicines is enriched with lot of formulations of *Lazūq* used in different states of human health. The classical *Unani t*ext shows that *Lazūq* has multidimensional use to treat various ailments related to human health, like; for the management of acute and chronic pain of different sites of the body like; (headache, chest pain, abdominal pain, sciatica), diseases related to throat, orthopedic diseases and other conditions.[1,2,9,10] *Lazūq/Laṣūq* (Thick Sticky Drug) is an ancient *Unani* dosage form made up of the drug or drugs dissolved in a suitable solvent to prepare and converted into a thick and sticky form which is then coated upon a piece of paper/cloth to apply on the affected area.[1,2,3,4] Generally, these are pastes, but only the difference is in stickiness. The traditional method to prepare this dosage form is fine powder of drug or drugs mixed to white part of egg or other mucilaginous substances then spread over already sieved paper or cloth and apply it on affected part.[8] According to *WHO international standard terminologies on Unani medicine*, *Lazūq/Laṣūq,* (having Term Id: IUMT-6.2.93) is described as adhesive drug which is spread over a piece of cloth or paper and pasted at affected part of the body and its equivalent term/concept in *English* is *Adhesive Medicine*.[27]

The use of balms, ointments, potions, patches in the form of *Lazūq,* consisting of plant, mineral and animal origin drugs was already popular in ancient *Egypt* and *Babylonian* medicine in ancient *Unani* system of

medicine around 5000-3000 BC.[28-29] Topical treatments that are designated, bandaged, rubbed, or applied to the skin are probably been around since the beginning of human history. Documentary evidence of these techniques, including those found on *Sumerian clay tablets*, have made their use clear.[30] The cosmetic and dermatological items that the ancient *Egyptians* developed included unguents, creams, pomades, rouges, powders and paints for the eyes and nails. They also utilized fats (Mainly animal), oils (Such as castor, olive, and sesame) and scents (Such as bitter almond, peppermint and rosemary) for the cosmetic and dermatological purpose.[31] *Kohl*, a paste used to paint the eyes, was made from the mineral ores of lead and copper.

The most comprehensive ancient pharmaceutical record appears to be found in the *Papyrus Ebers* (1550 BC), which describes over 700 medications and over 800 prescriptions.[32-33] A variety of formulas are included to treat skin disorders such as blisters, burns, wounds and exudation. Powder of Hyoscyamus was mentioned as an agent to be topically applied or taken orally for abdominal discomfort. Other remedies are the first transdermal delivery of drugs for systemic effects, such as topical frankincense application for headache and other type of pain and a substance applied in the form of *Lazūq* to a woman's or man's abdomen to relieve tapeworm related abdominal pain.[34-36]

Medicated plasters (*Emplastra*), which were generally applied to the skin for local conditions, can be traced back to Ancient China (around 2000 BC). These early plasters generally contained multiple ingredients of plant origin drugs dispersed into an adhesive natural gum rubber base applied to a backing support made of fabric or paper. This historical background signifies the concept of *Lazūq* described in *Unani* system of Medicine.[37]

In the 16th Century BC the husk of castor oil plant in water was used for headache.[38-39] Also, the use of *Khardal* (Brassica nigra) has been practice in the form of mustard plaster which was first described by Dioscorides (circa 1st century CE).[40] The mustard plasters have also been used to overcome the condition of vomiting.[38,41-42]

Jalinūs (Galen; 131-200 AD) a *Greek* physician introduced the compounding of *Unani* drugs and other excipients in dosage form. He is widely considered to be "*Father of Pharmacy*". Galen invented cold cream very first time which is certainly his most renowned formula with a composition relatively similar to the one used today.[43] The concept that certain drugs cross the skin appears to have been also applied by *Ibn Sina* (980-1037 AD) an *Unani* physician best known as *Avicenna* within western world along with other renowned *Unani* scholars. In the *Al-Qanoon-fil-Tib* (Cannon of Medicine), he proposed that topical drugs have two spirits or states i.e., *Lateef* (soft) and *Kaseef* (hard). He suggested that when topical products are applied to skin, *Lateef* part penetrates in the skin whereas the *Kaseef* part does not. He also proposed that dermally applied drug not only have local effect but also affects tissue immediately as well as have systemic action. He further proposed that dermally applied drugs not only have local effects but also affect tissues immediately beneath the skin including joints (regional effects) as well as effects in remote areas (systemic effects). One of his topical formulations acting systematically was for conditions where drugs could not be taken orally. One of Avicenna's regional therapies was the use of a *Lazūq* in which *Ghandhak* (Sulphur) was mixed with tar and applied to the skin with a piece of paper applied as backing to keep the formulation in place to treat sciatica, that is, pain arising from the compression of the sciatic nerve felt in the back, hip and outer side of the leg.[1,21,44] Other forerunners of modern transdermal medication include mercurial ointments which were used for treatment of syphilis in late 15th century.

2.3 Introduction To Novel Drug Delivery Systems (NDDS)

It is a novel approach to drug delivery system (the method or process of administrating a pharmaceutical compound to achieve a therapeutic effect in humans or animals) that includes various newer methods of drug delivery like; *Oral controlled release, Large-molecule delivery, Taste masking,* ***Transdermal*** *and* ***topical drug delivery****, Oral fast-dispersing dosage forms, Technology for insoluble drugs, Colon-specific delivery, Intranasal delivery/Pulmonary delivery, Vaginal/rectal delivery, Site-specific drug delivery; Targeting is the ability to direct the drug-loaded system to the site of interest-Implants, Liposomes, Microspheres/Microcapsules, Nanotechnology, Cochleates, Transferosomes, Magnetic microcarriers.* This system employees a variety of rate controlling mechanism including matrix diffusion, membrane diffusion, biodegradation and osmosis. There are two main objectives of drug delivery system and they are as follows: ***Drug Targeting*** (This means to deliver a drug to desired location in body) and ***Controlled Release*** (This state to deliver a drug at desired rate over a desired length of time).[11-14]

It is also important to understand and evaluate different terms used under broad category of NDDS and they are as follows: ***Localized Drug Delivery Device*** (Delivery of drug through spatial control and release directly to the targeted site), ***Modified Release Drug Product*** (a product that alter release rate of drug), ***Extended-Release Dosage Form*** (When absorption of drug is greater than its elimination then that release is extended drug release), ***Sustained Release*** (It is achieved and ensured by slow release of drug over extended or prolonged period of time or at constant release rate. Here absorption is equal to elimination), ***Controlled Release*** (Any drug delivery system from which drug is delivered at predetermined rate for prolonged period of time), ***Delayed Release Dosage Form*** (A dosage form that release a discrete fraction of drug at a time although one portion may

release immediately after administration. For example, enteric coated dosage form), ***Targeted Release of Drug*** (A dosage form that release drug at or near physiological or target site. Target release may be immediate or extended), ***Repeated Action Dosage Form*** (It is designed to release one dose or drug initially followed by 2nd dose of drug latter time), ***Prolonged Action Dosage Form*** (They release the drug slowly and provide continuous supply of drug over an extended period of time).[11-16]

After going through the literature available with respect to *Lazūq* in classical *Unani* text and its evolution and transformation with the advancement of modern technologies, it could be sensed easily that transdermal patch is nothing but the newer advanced dosage form of *Lazūq* described in *Classical Unani* dosage form. So, in the following section, brief description of transdermal drug delivery system is being given to understand and analyze the modern concept of *Lazūq.*

3. Progress of Transdermal Drug Delivery System (TDDS)

Routine use of transdermal drug delivery system became common practice in later 3rd of 20th century when there was more development in drug delivery systems.[33] Topical remedies are used since the origin of man. In 1904, *Schwenkenbecker* generalized that skin was relatively permeable to lipid soluble substance but not to water and electrolytes. However, the ointments were needed to be applied several times a day which concerns remain about exact amount of drug being applied each time. *Dale Wruster* and his student *Sherman Kramer* stated that the absorption can be enhanced or modified by varying the diffusion area of cell by changing the level of skin hydration.[45-46]

The zero-order kinetics (Constant rate of drug release) of transdermal drug delivery has one of the cornerstones in future development of transdermal system. Transdermal system is also used to produce clinical effects as local anesthesia and anti-inflammatory activities deep in the skin. Transdermal drug delivery system is a system having more scope now a days because it's a type of novel drug delivery system that helps to enhance the benefits and drug safety and also have many advantages over other routes of drug delivery.[47] Several examples include the capacity to evade first-pass metabolism in the liver, circumvent the digestive tract and administer continuous dosages of medication over a prolonged duration of time.[48] Intravenous drug delivery is one of those more uncomfortable and infection-prone modes of drug administration. It is challenging to regulate the amount when using the inhalation approach via oral route. Transdermal administration is frequently used to administer medications for ailments like chronic pain, motion sickness, smoking cessation, and hormone replacement therapy because of its advantages over traditional delivery methods.[49-51] It can bypass the first pass metabolism and can also be used for immediate release of drug which also gives high bioavailability and steady plasma drug concentration. TDDS is a developing drug delivery system which is now more explored in last one to two decades. In TDDS the drug is transported to the epidermal and dermal tissues present in the skin for local and systemic therapeutic action.[52]

This system maintains the drug concentration within the therapeutic window for prolonged time period to ensure that the minimum effective concentration or exceed the maximum effective concentration. It has competed with oral route as most successful innovative research area in drug delivery that includes different formulations like ointments, patches and gels etc. In recent years many Novels transdermal formulations are invented for example *Liposomes, Nanoparticles, Micro needles* etc.[53]

3.1 Transdermal patches

Transdermal patches are primarily designed to provide pre-prescribed dose of medications through the skin, which diffuse through different layers of the skin to reach the bloodstream, or the systemic circulation to improve patient convenience and also boost therapeutic efficacy and protection.[54-55] According to definitions, TDDS patches are non-invasive self-contained dosage forms that, when applied topically, release medication through the skin and into the systemic circulation over an extended period of time at a regulated pace. The first pass metabolism can be avoided or bypassed with transdermal patches as compared to oral route. By removing patches from the skin, it is simple to stop the drug's absorption into the circulation. The skin serves as a partition membrane in the transdermal patch mechanism, forming a barrier that regulates the release and absorption of the medication.[52]

They are made with several ingredients and come in various sizes. Transdermal patches have the potential to include potent ingredients that stay on the skin for a long time. In 1979 Scopolamine (Hyoscine) patch for treatment of motion sickness was the first transdermal patch to reach the market by *Alejandro Zaffaroni* through his company *Alza*.[56] In 1985, the nitroglycerin patch was developed for transdermal application for the angina pectoris. A rate-controlling ethylene vinyl acetate membrane is used in the patch, which was devised by Gale and Berggren.[33] Then after these many patches came in market such as fentanyl and diclofenac patches for pain treatment, *Clonidine* in hypertension treatment, *Estradiol patches* and *estradiol combined with norethisterone acetate* for female hormone replacement therapy, *Nicotine* for smoking cessation, *Testosterone* for hypogonadism, *Non-steroidal anti-inflammatory* drug patches, *Insulin* patch for type 2 diabetes mellitus and many more.[33,49-52,54,56] Depending on how the medicine is used, the release time can also vary, ranging from the shortest (up to 9 hours) to the longest (up to 9 days).

An anti-emetic transdermal patch was formulated, designed and developed from *Unani* drugs formulation by *Dr. Mohd Nauman Saleem et al* in 2015-2016, in the

Post-Graduate department of Ilmul Saidla, Ayurvedic and *Unani* Tibbia College, Delhi, University of Delhi. [38] But this could not reach into market as it needs further clinical and market trails still. I (*Dr. Amreen*) am also working on the *Lazūq* and trying to redesign it as transdermal patch for dysmenorrhea with the help of *Unani* drug formulations in the same department with having research entitled as "*Pharmaceutical Design and Development of Lazooq Into a Novel Dosage Form For Dysmenorrhoea*". I wish, I could also redesign and formulate an *Unani* transdermal patch for the dysmenorrhea and could give little contribution for the innovation in traditional *Unani* dosage form.

3.1.1 Various components of transdermal patches[57-65]

3.1.1.1 Polymer matrix

This primarily assists in releasing the medication from transdermal patches that are dependent on or modulated by polymers. The polymer creates an extremely dense matrix as its concentration rises, which slows the drug's release rate. The transdermal medication delivery method is mostly composed of polymers. Both the polymer and the drug's concentration, along with their diverse physiochemical characteristics, influence the drug's diffusion through the matrix and its rate of release. Polymer matrix examples include gelatin, polyvinyl alcohol (PVA), polyvinyl chloride (PVC), hydroxypropyl methyl cellulose, starch, PVP and polyethylene. *Ideal properties of polymer matrix are;* It should not react with drugs and be inert. The medicine and excipients must not cause it to break down. It should not affect the medication's stability. It ought to be simple to access, reasonably priced and must not have any antagonistic effects of any kind. It should not cause any kind of hypersensitivity reaction.

3.1.1.2 Ingredients in action

The most crucial part of transdermal patches is the drug reservoir. Extreme caution should be used when choosing it. Ionized drug molecules have limited skin penetration and permeability; hence they are not good candidates for use in transdermal patch formulation. *Perfect Features of Ingredients;* The active ingredients should not cause skin irritation to humans. Its biological half-life should be brief and must have a strong enough pharmacological activity to be needed. After administration, there should not be any kind of hypersensitive reaction. It ought to have no harmful properties. Drugs should to possess affinity for both hydrophilic and lipophilic phases.

3.1.1.3 Penetration enhancers

These are the compounds that increase skin permeability by improving the skin's ability to metabolize drugs. There are three ways that drugs can enter the skin; polar, Non-polar and mixed. By changing one of these channels, penetration is boosted. Changes in protein structure can also modify the polar route. Lipid stiffness can be changed to modify the non-polar route. *Ideal properties of Penetration Enhancers are:* It should not damage the layer of skin permanently. It should be pharmacologically inert, non-toxic, non-allergic, non-irritant and action specific.

3.1.1.4 Surfactants

These are added when drug used shows hydrophilic character. They enhance polar pathway transport of the drug. Cationic surfactant is not used. They are considered to be most irritating to skin. Example of non-ionic surfactant is *Pluronic F127*. An example of anionic surfactant is *SLS (sodium lauryl sulphate)*.

3.1.1.5 Solvents

The example of solvents used are *Ethanol, Methanol, Glycerol, Propylene glycol*.

3.1.1.6 Plasticizers

They are used to reduce or minimize the brittleness of polymer film. They provide or give flexibility and elasticity to the polymeric film. If plasticizer is used in high concentration, then they make the film sticky and damp. *Ideal properties of plasticizer are;* It should be; easy to handle, cost effective, non-reactive, non-irritant, pharmacologically inert, easily and readily available. It should not affect the stability of drug. Examples are: *Glycerol, Propylene glycol, Dibutyl Phthalate, Polyethylene glycol*.

3.1.1.7 Drug reservoir component

This is a component that contains one polymer or the combination of polymers in various different concentrations and ratios.

3.1.1.8 Backing laminates

This facilitates the giving and receiving support. Drug surfaces that are not in contact with the skin should not be allowed to release. The medication and excipients should work well together. Flexibility, strength, and elasticity should all be considered when choosing. This confers on the transdermal drug delivery system appearance, flexibility, and occlusions. The compatibility of the excipient should be taken into consideration while choosing backing laminates. High flexibility backing laminates are the most appropriate. Example are; *Metallic Plastic Laminates, Polyurethane, Aluminium foil*.

3.1.1.9 Adhesive layer

This layer adheres the transdermal device on surface of skin at proper site and position. *Ideal properties of adhesive layers are:* It should have ability to stick with minimum pressure and non-irritant to the skin. It should not; interfere with release rate of drug, affect solubility of drug.

3.1.1.10 Release liners

These are the protective layer which are removed before the application of transdermal patches on skin. They are helpful to prevent drug loss during storage and

transportation condition. Examples are; *Teflon, Silicon, Polyester* etc.

3.2 Various types of transdermal patches

Following are various types of transdermal patches available generally: ***Drug in Adhesive system (Single Layer Patches, Multi-Layer Patches), Reservoir Matrix, Vapor Patch*** **and** ***Micro-Reservoir System*****.** [65] Among these, reservoir or matrix type of patches are most commercially available.

3.2.1 Drug in adhesive system

Single-Layer Patches: In these, the adhesive layer helps to release the medication from the patch and is also in charge of keeping the different layers of the system to skin attached. The backing laminate and release liner encircle this adhesive as well. The medicine is included directly into the skin contacting adhesive that is applied to the epidermis in these types of patches. **Multi-Layer Patches:** It is composed of multiple layers. The medicine is released immediately from one layer and it is controlled by another layer that releases it from a temporary liner layer and a permanent backing layer. The drug release in this patch is contingent upon the permeability and diffusion capacity of the membrane.

3.2.2 Reservoir type patch

This patch has a distinct medication layer. A liquid compartment holding a drug solution or suspensions is known as the drug layer. Here, a shallow compartment molded with metallic plastic laminates and a polymer-based microporous rate-controlling membrane completely encloses the medication compartment. In this system, the drug reservoir is held between backing layer and the rate-controlling membrane. The drug may be in the various forms like solution, suspension, gel form or maybe dispersed in a solid polymer matrix within the reservoir chamber.[63]

3.2.3 Matrix type patch

The matrix system has a drug layer of semisolid matrix which contains drug in solution or suspension form and dispersed in hydrophilic or lipophilic polymer matrix. This is also called as monolithic device.

3.2.4 Vapor patches

The adhesive layer in this patch has two purposes: it adheres the several layers together and also releases vapors. The essential oils in these vapor patches can be released for up to six hours at a time. The primary and common use of these vapor patches is decongestion. Some vapor patches are designed to improve sleep quality and help people stop smoking.

3.2.5 Micro-Reservoir system

It is combination of reservoir and matrix system. For the manufacturing of the medication in this case, drug particles are first suspended in an aqueous solution of a water-soluble liquid polymer, and the solution is then uniformly dispersed in a lipophilic polymer to generate thousands of microscopic drug reservoirs that do not leach.

3.3 Drug permeation through skin

Absorption of the medication occurs via the sebaceous gland and follicular epithelium. After reaching a stable condition, diffusion through the intact stratum corneum takes place. The two ways that drugs enter the skin are as follows: drugs can enter cells through two different routes, namely transcellular and intercellular, (if they pass through the trans epidermal route). Trans follicular; here, the medication travels through the hair follicles and sweat glands. Despite having a high permeability, this route is not very significant.

3.3.1 Factors affecting the permeation of transdermal patches

There are main three types of factors which affects transdermal permeation and they are as follows: *Physiochemical properties of penetrant, Physiochemical properties of delivery system, Physiological and pathological Skin conditions.*

3.3.1.1 Physiochemical properties of penetrant

Partition Coefficient: The partition coefficient value of 1 or more is ideal for the transdermal drug delivery. **pH Condition:** The pH has an impact on the rate of absorption of acidic or basic drugs, while unaltered drugs have a greater ability to penetrate. Transdermal patches work best at a pH of moderately high. Both high and low pH levels have the potential to destroy or harm skin. **Composition of Drug Delivery System:** This comprises the concentration of different components, including the medication, polymer, plasticizer, membrane thickness, etc. The passive diffusion mechanism of transdermal permeability in mammalian skin is dependent on the concentration of penetrant molecules on the skin surface.

3.3.1.2 Physiochemical properties of drug delivery system

Affinity of Vehicle for Drug Molecule: Solubility in carrier determine the release rate of drug. Mechanism of drug release depends on whether the drug is dissolved or suspended in delivery system. **Composition of Drug Delivery System:** This affects the rate of drug release and also permeability of subcutaneous layer by hydration. **Enhancement of Transdermal Permeation:** The subcutaneous layer is dead in nature. Permeation enhancer can cause physiological changes in subcutaneous layer and increases drug penetration through the skin.

3.3.1.3 Physiochemical and Pathological skin condition

Skin Age: The permeability of fetal and infant skin is more than that of mature adult skin. Therefore, percutaneous absorption of topical steroid is rapid in children's as compare to adults. **Lipid Film:** Formation of thin lipid film of skin occurs by excretion of sebaceous gland like sebum. **Skin Hydration:**

Transdermal permeation can be increased by hydration of subcutaneous layer. **Skin Temperature:** Increased skin temperature enhance the skin permeation rate. It tends to increase the vasodilation of blood vessels in contact with skin. This increases the percutaneous absorption. **Species Difference:** Skin of different mammalian species shows various anatomical differences like thickness of subcutaneous, hair follicles etc.

3.4 Factors affecting the rate of drug release

Following are the various factors the rate of drug release from the transdermal patches and they are as follows: Pore size of rate controlling membrane, Molecular weight of drug, Molecular size of drug, Solubility of the drug and Thickness of the membrane.

3.5 New approaches in transdermal drug delivery system

Following are the various new approaches related to transdermal drug delivery system. These new approaches are emerging and are having a great scope of innovation and development. [65]

3.5.1 Iontophoresis

Iontophoresis is the application of an electrode to facilitate medication absorption through the skin. Here, electricity is applied and the charged electrodes are connected to the drug reservoir. Therefore, the stratum corneum's permeability increases in the presence of electric current, aiding in the enhancement of drug release.

3.5.2 Electroporation

There is formation of small pores with the help of electric pulses in stratum corneum through which drug is transported.

3.5.3 Photomechanical wave

This wave makes stratum corneum permeable to drug by developing transient channel.

3.5.4 Medicated tattoos

They go by the name Med-Tats as well. There is an active medication ingredient in Med-Tats. This is helpful and is used to administer drugs to kids who don't take or think that typical dosage forms are important. Here, the length of the therapy is not set in stone. Thus, the manufacturer provides a color chart that is matched to the patient's tattoo to determine when the tattoo should be removed.

3.5.5 Microneedle

This was seen or observed first in 1976. Micro needle which are 50-100mm long are used. They are penetrated from reservoir to stratum corneum for the drug delivery.

Types of microneedle: There are four main categories of microneedle-based patches that have been developed: solid, hollow, dissolving, and coated microneedles. The particular application and the patient's requirements determine the type of microneedle to utilize.

Solid needles: The simplest kind of microneedles are solid ones, which are made up of solid needles that pierce the skin to form microscopic channels. Usually, these are employed in cosmetic procedures and medication administration.

Hollow microneedles: These microneedles contain a hollow core that makes it possible to inject substances into the skin for transdermal medication delivery and interstitial fluid sampling. ***Coated Microneedles:*** These microneedles are frequently employed for transdermal medication administration because of their coating, which dissolves when it penetrates the skin and releases pharmaceuticals or other substances. ***Dissolving microneedles:*** Often employed for vaccinations and other drug delivery applications, these are composed of components that dissolve in the skin to enable for the controlled release of medications or other substances.

3.5.6 Skin abrasion

Here, there is removal and destruction of upper layer of skin to enhance the permeation of medicament. Such technique is used in treatment of acne, scars, skin blemishes etc.

3.6 General procedure for applying any type of transdermal patches

Following are the steps which should be followed for applying the transdermal patches and they are as follows: Initially wash your hands and area where patch will be applied, make the area clean and sterile, hold the patch so that the plastic backing is facing to side applicator, peel off one side of the patches backing, apply exposed half of patch to the skin (affected part), now then press sticky side of patch against the skin and smooth it down.

3.7 Advantages of transdermal Patches and Transdermal drug delivery system

It helps to maintain the steady infusion of drug for prolonged period of time, act as an alternate dosage form for the patient who cannot tolerate oral dosage forms. It helps to increase the therapeutic value of drug. It acts as a best and convenient alternative for conventional dosage form and also increase the patient compliance. It bypasses the first pass metabolism. It helps to minimize fluctuations in physiological and pharmacological response and decrease side effects due to reduced plasma concentration. It is helpful in administrating drugs having short biological half-life and drug with low therapeutic index. It helps to administer the drug with low melting point and easy termination of drug therapy at any time. The gastrointestinal drug absorption difficulties due to gastrointestinal pH, enzymatic activity and drug interaction with food, drinks and other orally administered drug can be avoided. Drug given orally can be given as transdermal patches if the patient is vomiting or having diarrhea. It is non-invasive and avoid the inconvenience caused by parenteral route. It provides

extended therapy with single application. It helps to reduce inter and intra patient variability. Drug level can be maintained in systemic circulation within therapeutic window. [57]

3.8 Disadvantages of transdermal Patches and Transdermal drug delivery system

Drug with high molecular weight is difficult to penetrate stratum corneum. In this delivery system the drug dose is a limitation factor. If drug which metabolize in liver are given through transdermal route, then results into low bioavailability. The drug causing irritation locally or systemically are not suitable for transdermal drug delivery system. Only potent drugs can be incorporated into transdermal patches due to natural limit of drug entry through skin. [57]

Table 01: Ideal properties of drug for transdermal drug delivery system.[57-65]

Properties	Required Criteria
Aqueous Solubility	>1 mg/day
Dose Deliverable	<10 mg/day
Half Life (Hours)	10 or less
Log P	Between 1-3
Melting Point	<200 degree Celsius
Molecular Weight	< 500 Dalton
Nature of Drug	Non-Ionic and Relatively lipophilic to cross the skin
Oral Bioavailability	Should be Low
pH	5-9
Therapeutic Index	Should be Low

Table 02: General differences between Topical and Transdermal formulation.[64]

Topical formulation	Transdermal formulation
These work on surface of skin and do not reach the blood stream.	These penetrate the skin and enters the blood and also distribute through whole bloodstream. These do not enhance ability of drug molecule but increase drug absorption by prolonged application of patches.
These formulations cannot avoid first pass metabolism	These formulations bypass and avoids first pass metabolism.
There are some chances for occurrence of local skin irritation and rashes.	It can help to minimize adverse drug reactions due to low drug concentration.
Drug when given through topical route just show superficial action.	Here drug penetrates deep inside the deep layers of tissues.
Forms: Cream, Ointments, Lotion, Sprays, Foam, Powder etc.	Forms: Patches, Nano gels, and Pastes.

With the help of following table, differences between topical and transdermal approach is discussed to sense the efficacy and application of both forms.

3.9 Credible application of transdermal patches

Globally researches are going on to take this system at its finest form and approach for the application of transdermal patches for vaccination, diabetic foot ulcer, antibiotic patches, gene therapy, insulin delivery, cardiovascular diseases, hormonal deficiencies, contraception, central nervous system (CNS) disorder, infectious diseases and other conditions.

4. DISCUSSION

Despite of being an effective and safer dosage form with wide range of application in different therapeutic conditions, *Lazūq* has become forgotten for so long, perhaps due to the difficulty in method of preparation and usage. Application of targeted drug delivery system with *Lazūq*: one of the issues is the uncertainty of knowing whether the administered drug will reach the intended organ or area of the body. Therefore, the need of hour is to redesign this existing dosage form into a better and readily available dosage form. Man has always observed the things by five senses, so that ancient physicians did the same to put forth structure and form of *Lazūq*. Ancient *Unani scholars* had given the *form of drugs* based on macroscopic observation and practicality of synthesis with respect to technologies and aid available at their era. But nowadays to observe the things, efficacy and the vision have been reached to nano level with the achievement of time and innovations in science and technology. After reviewing the knowledge regarding the history and concept of *Lazūq* and analyzing its progress as transdermal patch in novel drug delivery system, Unani drug formulated *Lazūq* must be redesign into newer form to make it more applicable that will increase and enhance the *Unani* formulations in terms of; efficacy, duration of drug activity, patient compliance, bioavailability, solubility and pharmacological activity. It

will make *Unani* formulations more stable, provide sustained delivery and protection from physical and chemical degradation. It will improve targeting for a specific site to reduce unwanted side effects, mimic the circadian rhythm of particular diseases in order to optimize a drug's therapeutic power. It will also decrease the dosing frequency and toxicity. Unani scholars/researchers must develop their formulas of *Lazūq* as per the newer approach of the concept i.e. transdermal patch. Simultaneously, specific carriers should be designed for specific drugs (such as nanoparticles, phytosomes, nano molecules, microsphere, ethosomes and liposomes by using bioactive and plant extracts) to make it easier for the usage in transdermal patch. Although TDDS has been approached to its finest form with having variety of dimensions and generation of the different types of patches to deliver the drug, but if we the *Unani* scholars can reach at its first step i.e. transdermal patch, and able to provide our *Unani* formulations as per this newer method, it would be a great milestone for the fraternity of *Unani* system of medicine.[66-67]

5. CONCLUSION

It is now easily understood and concluded that TDDS perfectly follow the blueprints of *Lazūq*. The basic purpose of both forms is same with the difference of their genesis with respect to their era. The first inventory form i.e., *Lazūq* has long course and progressed and redesigned as transdermal patch with the advancement of pharmaceutical techniques. Overpowering benefits of Novel drug delivery system over the traditional drug delivery system are well known. As it is in concern with the drug delivery through the skin the Transdermal Drug delivery system has an effective benefit over the topical method of drug delivery. The transdermal patches with the incorporation of *Unani* drugs extract could play vital role in decorating the concept of *Lazūq.* Now in the emerging world there is more demand of the *Unani* drug formulations. The advancement in drug delivery system is allowing wide range of drugs to be administered through this system. The *Unani* drug formulated transdermal patches may be formed and used in different therapeutic conditions for example, healing of the wounds, any type of injury, skin infection like eczema, arthritis, different type of muscular pain, dysmenorrhea, pelvic inflammatory diseases etc.

6. *Future prospects*

More researches and innovations in *Unani* system of medicine with respect to traditional dosage forms will bring the wide acceptance throughout the globe. Every classical *Unani* drug dosage form should be analyzed with modern novel dosage form and if needed, it must be redesign and converted to increase the efficacy and application of the *Unani* system of medicine.

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