Synthesis and Characterization of pH-Sensitive Smart Patch for Anti- Hypertensive Drug

Author

Maleeha Azhar

Regn Number

360630

Supervisor

Dr. Adeeb Shehzad

BIOMEDICAL ENGINEERING AND SCIENCES

SCHOOL OF MECHANICAL & MANUFACTURING ENGINEERING

NATIONAL UNIVERSITY OF SCIENCES AND TECHNOLOGY

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Dr. Adeeb Shehzad

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2. Name: Dr.Shahid Ali Khan Signature:

3. Name: Dr.Aneeqa Noor Signature:

Supervisor's name: Dr.Adeeb Shehzad Signature:

Date: 11/7/2023

Head of Department

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Date

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Associate Professor
Departmen of Biomedical Engg. & Sciences
School of Mechanical & Manufacturing
Engineering (SMME), NUST
Islamabad

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Copyright Statement

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Abstract

Hypertension is the disease associated to high blood pressure, (140/90 mmHg). One billion people are affected by hypertension globally, and the condition may be responsible for 7.1 million annual fatalities. Poor patient compliance throughout lifelong administration may be the cause of difficulties in the treatment of hypertension. About 50% of hypertension patients do not adhere to their treatment plan, owing to harsh side effects, extensive therapy, and due to lack of memory. The prescribed treatment for hypertension is the use of antihypertensives. Owing to low oral bioavailability and poor gastrointestinal absorption of antihypertensives, a transdermal delivery system is introduced for the sustained release of the drug. Smart patch, comprising of a co-polymer pH-sensitive dissolvable polymer matrix, designed by combining various approaches. The current technology also offers an acceptable alternative using an iterative design process using 3D solid modeling software, followed by 3D bioprinting for the fabrication of prototypes. Six formulations in two different solvents, DMSO and NaOH were optimized and tested for the evaluation of the best combination for the preparation of the polymer matrix of the patch. It was concluded based on physical and chemical analysis that thse CMC-containing matrix proved to be an appropriate option.

Key Words: Transdermal drug delivery, low bioavailability, co-polymer matrix

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List of Abbreviation

- PDC - PVP in DMSO Control
- PNC - PVP in NaOH Control
- PDD - PVP in DMSO Drug
- CDC - CMC in DMSO Control
- CNC - CMC in NaOH Control
- CDD - CMC in DMSO Drug
- CND - CMC in NaOH Drug
- GDC - Gelatin in DMSO Control
- GNC- Gelatin in NaOH Control
- GDD - Gelatin in DMSO Drug
- GND - Gelatin in NaOH Drug
- PVP - Polyvinylpyrrolidone
- CMC - Carboxymethylcellulose
- SEM - Scanning Electron Microscopy
- FTIR – Fourier Transformed infrared spectroscopy
- DMAP- 4-Dimethylaminopyridine
- MMA- Methyl Methacrylate
- TGA- Thermogravimetric Analysis
- XRD- X-ray crystallography

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Chapter 1: Introduction

1.1. Hypertension

1.2. Hypertension, alternatively referred to as high blood pressure, it is medical condition which is persistent, it is marked by raised blood pressure within arterial system [1]. Blood pressure refers to mechanical pressure applied by the circulating blood on the walls of vessels. The measurement is quantified in millimeters of mercury (mmHg) and represented as a combined set of values obtained by dividing systolic pressure by diastolic pressure [2, 3].The systolic pressure is denoted by the magnitude of the force exerted on the walls of the arteries during the contraction and ejection of blood by the heart, whereas the diastolic pressure signifies the force exerted on the arterial walls during the period of cardiac relaxation between heartbeats. Typically, a blood pressure reading of approximately 120/80 mmHg is regarded as within the normal range. Blood pressure over 130/80 mmHg is considered hypertensive when it occurs frequently [3, 4]

1.2. Types of Hypertensions

Hypertension is classified into primary or essential hypertension and secondary hypertension.

1.2.1. Primary Hypertension

Primary hypertension, termed essential hypertension, is the most common form of high blood pressure and manifests gradually over an extended period without any discernible etiology. The etiology of this condition is frequently shaped by confluence of genetic and environmental determinants, including age, familial predisposition, excessive body weight, a sedentary way of life, dietary patterns (particularly excessive consumption of sodium), and psychological stress [5-7].

1.2.2. Secondary Hypertension

In contrast to primary hypertension, secondary hypertension is attributed to an underlying medical condition or the use of certain medications. This form of hypertension may arise due to underlying kidney disease, hormonal imbalance s such as hyperthyroidism caused by increased levels of thyroid hormone or Cushing's syndrome caused by increased levels of cortisol, specific medications such as nonsteroidal anti-inflammatory drugs and oral contraceptives, or drug use [8].

1.3. Associated Complications

Hypertension commonly referred as a "silent killer" because of its tendency to remain asymptomatic until it progresses to more severe stages. Nevertheless, the persistence of elevated blood pressure levels can give rise to severe complications, encompassing [9]:

- Cardiovascular diseases: Hypertension augments the susceptibility to vascular disease, heart failure, coronary artery disease, strokes, and myocardial infarctions [10, 11].
- kidney disease: kidney disease is a potential consequence of prolonged exposure to high blood pressure, as it can result in the deterioration of renal function and hinder the kidneys' capacity to effectively eliminate waste products from the bloodstream. This can ultimately manifest as chronic kidney disease or, in severe cases, kidney failure [12, 13].
- Eye complications: Unregulated hypertension has the potential to inflict harm upon the ocular blood vessels, leading to visual impairment or retinopathy [14, 15].
- Aneurysms: Aneurysms are a potential consequence of chronic hypertension, where the sustained elevation of blood pressure can result in the structural deterioration of blood vessels. This deterioration can manifest as the development of bulges or aneurysms, which possess the propensity to rupture and induce severe internal hemorrhaging, thereby posing a significant risk to an individual's life [16, 17]

1.5. Treatment

The primary objective of therapeutic interventions for hypertension is to effectively decrease and sustain blood pressure levels within a desirable range, thereby mitigating the potential for consequential complications. Treatment options vary from patient to patient based on several criteria, such as the severity of hypertension, the existence of other medical disorders, and the patient's personal preferences [18]. The following are several frequently employed treatment modalities:

1.5.1 Lifestyle Modifications

- One potential approach to addressing health concerns is through lifestyle modifications.
- One potential dietary approach is to adhere to a nutritious eating regimen, such as the DASH diet. This diet emphasizes the consumption of fruits, healthy vegetables, whole grains containing endosperm, germ and bran, lean proteins, and low-fat dairy products

while simultaneously restricting the consumption of sodium, saturated fats, and cholesterol [19, 20].

- Weight management cites practicing sustaining a desirable weight of the body by adhering to a well-rounded dietary regimen and engaging in consistent physical exercise.
- Regular physical activity is important to maintain good health. Engaging in aerobic exercises including walking, cycling, jogging, or swimming for at least 150 minutes per week is recommended [21].
- One of the recommended dietary measures is the restriction of sodium consumption, with a suggested daily intake of fewer than 2,300mg or potentially even lower for some individuals [22].
- Alcohol moderation is referred to the practice of restricting alcohol consumption to moderate levels or abstaining from it entirely [23].
- Smoking cessation is referred to the act of quitting smoking and actively avoiding any form of exposure to secondhand smoke [24].

1.5.2. Medications

- Diuretics: These drugs aid in the kidneys' removal of extra sodium and water, which lowers blood pressure and reduces body fluid content. One example of a thiazide diuretic is hydrochlorothiazide [25].
- Beta-blockers: These drugs work by lowering blood pressure by reducing heart rate and contraction force. They can also be employed in particular instances, such as cases of cardiovascular disease or specific cardiac arrhythmias [26].
- Angiotensin-Converting Enzyme (ACE) Inhibitors: These drugs hamper the formation of angiotensin II, which is a hormone that plays a role in constricting as well as raising blood pressure. Some examples of medications in this category are lisinopril and enalapril [27].
- Angiotensin II Receptor Blockers (ARBs): Much like ACE inhibitors, these ARBs prevent the angiotensin II from relaxing blood vessels and raising blood pressure. Some examples of angiotensin II receptor blockers (ARBs) include losartan and valsartan [27].
- Calcium channel blockers: these drugs help lowering blood pressure by preventing calcium from getting into heart and blood artery cells, thereby relaxing those cells. Some examples

of commonly used medications in the treatment of hypertension include amlodipine and diltiazem [28].

- Additional Medications: In certain cases, supplementary medications such as α-blockers, central α-agonists, direct renin inhibitors, or vasodilators are prescribed [28].

1.5.3. Complementary Techniques

- Stress Reduction Techniques: Exercises like yoga, meditation, and deep breathing can help lower stress levels and regulate blood pressure.
- Complementary: Complementary therapies, such as acupuncture, biofeedback, or herbal remedies, may be investigated by some people as alternative treatments [18].

1.6.1. Integumentary system- drug absorption

The skin is an organ which is adaptable and distinctive, it serves as a barrier between internal and external environments of the body, exhibiting sensory, thermoregulatory, immunologic, and metabolic capabilities. The organ in question is the largest in the human body, with a weight of 9 kilograms and a surface area of 2 square meters in adult individuals [29, 30] . Additionally, it plays an important role in regulating body temperature through the production of sweat and the elimination of waste produced [31] . Injecting drugs through the skin can be categorized into two main methods: topical application and systemic circulation [32].

1.6.2. Functions of the Integumentary system

Integumentary system has a vital role in various essential functions, such as [33]:

- The primary purpose is protection, to mitigate the harmful effects of ultraviolet radiation, as well as to safeguard against potential damage caused by mechanical, physical, and chemical factors.
- Involved in the process of thermoregulation and is responsible for the maintenance of body temperature.
- Involved in the synthesis of vitamin D.
- The function of this barrier is to impede the evaporation of water, thereby preventing its loss.

1.6.3. Anatomy of the Integumentary System

The skin outermost layer is known as the stratum corneum, that serves the dual purpose of preventing water loss and providing protection against potentially harmful substances [34, 35]. The subsequent sections delineate the three crucial layers of the integumentary system.

- Subcutaneous tissue refers to the layer of tissue located beneath the dermis of the skin.
- The dermis and epidermis are two distinct layers of the skin.
- The sebum layer is commonly referred to as the fourth layer skin.

The most superficial layer of the epidermis is the stratum corneum. The stratum corneum in humans is composed of 10–25 layers of corneocytes which are elongated and keratinized. It is composed 40% protein, with 80% of that protein being keratin [36] as shown in figure 1 [37].

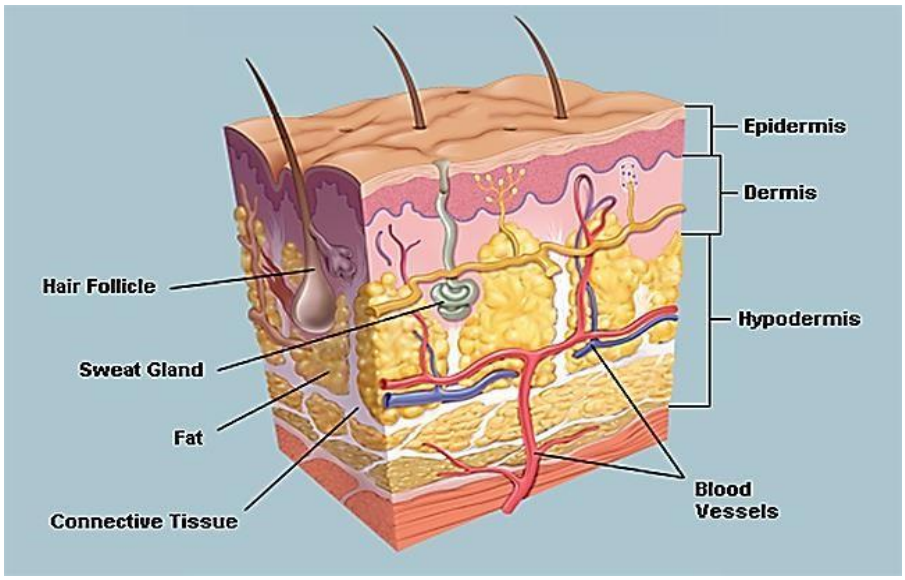

Figure 1.Skin structure shows different layers

The drug penetrates the stratum corneum during topical administration. Ceramides, which are sphingolipids found in the cell membrane, plays an important role in preserving the integrity of the skin structure.There are three significant pathways that are utilized for the transdermal penetration of drugs [38].

- Drug diffusion through cell membranes is facilitated by lipid lamellae.
- Drug transcellular diffusion through the skin is mediated by lipid lamellae and keratinocytes.
- Hair follicles and sweat ducts are also implicated in the diffusion of drug molecules.

1.7. Percutaneous Absorption Pathways

Percutaneous transportation can take place via a variety of pathways, including the intercellular route, the follicular route, and the transcellular route. In the transcellular pathway, molecules are transferred from cell to cell. The follicular route involves the molecular transportation through skin follicles, whereas the intercellular route involves molecular transportation within the gaps between cells [31].

1.8. Drug Delivery Systems

The primary objective of developing a drug delivery system is to facilitate the targeted delivery of a precise dosage of the drug to the intended site of action while ensuring the drug remains active for an optimal duration. The quantity of medication administered is provided within the therapeutic range to attain an appropriate level of drug concentration in the bloodstream. Currently, the primary emphasis in pharmaceutical research lies in the advancement of controlled-release drug delivery systems. This approach is favored due to its ability to mitigate several challenges associated with conventional therapy, such as adverse reactions, excessive dosing, frequent administration, and patient adherence. Extensive efforts have been dedicated to the development of a system capable of delivering therapeutic doses of drugs to targeted regions of the body, to minimize adverse effects and improve bioavailability. Consequently, the objective of this study was to develop transdermal patches to facilitate the delivery of the drug's active components via the skin. This delivery mechanism involves the passage of multiple layers of the skin by drug molecules to achieve systemic circulation. The term "drug delivery system" (DDS) refers to a broad category of physicochemical technologies that allow for the precise and timely introduction of pharmacologically active compounds into the cells, tissues, and also in organs for the purpose of maximizing their therapeutic benefits [38, 39]. That is, DDS encompasses the modes formulation of drug and injecting that effectively transporting the drug maximizing therapeutic efficacy also minimizing any negative effects [40]. Various administration modalities exist depending on the delivery route, including, mucosal administration oral administration, lung inhalation transdermal administration, and intravenous injection. The transdermal drug delivery system (TDDS) is considered a favorable approach among various options. Transdermal drug delivery systems (TDDS) can be described as autonomous and distinct forms of medication that, upon application to unbroken skin, administer the drug(s) at a regulated pace, allowing for their absorption into the systemic circulation [41]. Numerous pharmaceutical active ingredients, such as gene drugs, sex

hormones, and biotechnological drugs, are administered via the parenteral route. This is primarily due to their ineffectiveness when administered orally, as they are susceptible to degradation by gastrointestinal enzymes and the stomach's acidic environment, resulting in limited bioavailability. In order to address these challenges, researchers have put forth novel formulations and administration methods for bioactive compounds, including nasal, vaginal, buccal, sublingual, and transdermal routes [42]. Currently, the oral route of administration is the primary method used, with the majority of drugs being formulated and made available in oral preparations. Undoubtedly, the oral dosage form offers numerous benefits. However, it is not without its limitations, such as diminished bioavailability resulting from hepatic metabolism, commonly known as the first pass effect. Additionally, oral medications have a propensity to cause abrupt fluctuations in blood levels, encompassing both elevated and reduced concentrations. Consequently, this necessitates higher and/or more frequent dosing, which can prove costly and inconvenient for patients [43]. The presence of these concerns necessitates the development of novel dosage forms, such as the Transdermal Drug Delivery System. This system offers potential benefits over traditional oral drug therapy, including avoiding first-pass biotransformation and metabolism, reducing absorption and metabolism variability, enhancing drug bioavailability and efficacy, promoting patient compliance, and facilitating rapid drug delivery termination [44]. The initiation of transdermal drug delivery can be traced back to the early 1950s. During that time period, this particular approach was restricted to a small range of products, such as gels, patches, creams, and ointments. In addition, the use of transdermal drug delivery systems offers significant advantages and convenience. This method effectively regulates drug concentration within the therapeutic range and enhances bioavailability by circumventing the first-pass effect [45].

1.9. Composition of TDDS

The design of transdermal formulations and the types of transdermal formulations available are dependent on factors such as the penetration of drugs and the release of drugs from patches. The primary classifications of transdermal patches include matrix patches, reservoir patches, and single or multi-layer patches [46]. Polymers that are semisolid make up the matrix system. Within the matrix, the medication is either suspended or dissolved. The aforementioned system consists of a backing membrane and an adhesive layer. Drug release has zero-order kinetics. The transdermal medication delivery device under discussion, enables customization of patch sizes and shapes [47].

A medication solution or suspension, which can be either semisolid or liquid, makes up the reservoir system. The drug solution is sandwiched between an impermeable backing membrane and a semi-permeable release liner. Drug molecule release kinetics display zero-order behavior. It asserts that cutting the patches into different forms changes the membrane properties of a reservoir-type patch system, making it difficult to change the geometry of such patches [47]. The adhesive membrane works by joining different membranes and firmly fastening the patch to the skin. To enable the controlled release of the drug molecules to a particular target location, the drug is combined with an adhesive membrane. The aforementioned mechanism consists of a release liner and a temporary backing membrane. The regulated release of the medicine is accomplished via the adhesive membrane found inside multi-layer based adhesive patches. The drug layer forms a separate reservoir for the regulated release of the drug molecules from the matrix of the patch in the setting of single-layer adhesive patches [48].The single-layer system is made up of a temporary release liner and a permanent backing membrane.

1.10.1. Pros of Transdermal Drug Delivery System

Systemic medication effects can be controlled by combining hydrophilic and hydrophobic polymers in a transdermal drug delivery device [49]. Transdermal drug delivery systems (TDDS) are used to transfer existing pharmaceutical treatments for dementia, Parkinsonism, depression, and hyperactivity disorder.

Transdermal, drug delivering patches, can lessen the outburst of gastrointestinal discomfort, drug-drug interactions, and first-pass metabolism. The skin's poor permeability prevents medications from penetrating the body effectively, which hinders the transdermal route's capacity to be used widely [50].

Several strategies are used to address this alerting problem, including physical methods like the use of iontophoresis, administration of chemical enhancers and microneedles introduction. However, these techniques run the risk of impairing the stratum corneum's integrity, which would make it easier for bacteria and foreign objects to enter the skin. A supersaturated system is used in a different strategy [51].

The dermal route is highly advantageous due to the skin's inherent function of impeding the entrance of substances inside the body. However, the primary obstacle within the skin is the stratum

corneum, which serves as the outermost to the epidermis. The stratum corneum is composed of flattened parts of the epidermal cells and the keratins that were previously undergoing active division. It is hygroscopic, meaning it has the ability to absorb moisture, but it is impermeable to water. The SC functions as a resilient and flexible membrane [52].

1.10.2. Cons of Transdermal Drug Delivery System

There are a few drawbacks associated with transdermal drug delivery technology, such as the fact that some compounds and pharmaceuticals utilized in the development of transdermal patches can irritate or swell the skin. For the penetration of pharmaceuticals through a transdermal drug delivery system to reach systemic circulation, a significant amount of time is required. The transdermal drug delivery system exhibits a relatively slow onset of action. Only a certain percentage of drugs are able to penetrate the skin's membrane. The manufacturing expenses for transdermal patches are comparatively higher in comparison to conventional dosage forms. Due to differences in molecular size, hydrophilic and lipophilic properties molecular weight,and dosage of medications, transdermal patches have some limitations in terms of drug absorption [53].

1.11. Active Delivery of the drugs through Transdermal Route

When compared to the administration of drugs through topical application to the skin, external stimuli such as electrical, mechanical, or physical stimulation are known to increase the skin's permeability of pharmaceuticals and biomolecules [54]. Active transdermal delivery, also known as TDDS is reinforced by the right equipment and is a method that is known to deliver medications to the skin in a speedy and reliable manner. Furthermore, this method of enhanced transdermal drug delivery system (TDDS) has the potential to expedite the therapeutic effectiveness of administered medications.

1.11.1. Iontophoresis

Iontophoretic distribution through the skin should more properly be referred to as electrically assisted transdermal delivery. Drug flux through the skin is enhanced by three main mechanisms, of which iontophoresis—also known as electron repulsion, electromigration, or the Nernst-Planck effect—is just one. Other mechanisms include electroosmotic flow [55] and the current-induced enhancement of skin permeation, commonly referred to as the damage effect) [56]. Electroosmotic flow refers to the phenomenon of fluid movement, either as a flux or in bulk, that is generated by

the application of a voltage difference across a charged membrane. Notably, this flow occurs consistently in the same direction as the movement of counter ions. Under physiological conditions, it has been observed that human skin carries a negative charge. As a result, the counter ions associated with the skin are predominantly cations. Consequently, the electroosmotic flow, which refers to the movement of fluid induced by an electric field, occurs from the anode to the cathode. Consequently, the transportation of anions through the cathode is impeded, while the transportation of cations through the anode is facilitated due to the phenomenon of electroosmosis [57].

1.11.2. Microneedles

The utilization of microneedles as a transdermal drug delivery system has earned significant recognition in the field of research. This is primarily because of the advantages it offers in terms of enhancing patient accessibility to drugs, thereby potentially replacing conventional methods of drug administration. Microneedles can be categorized into four distinct formulations: solid, coating, dissolving, and hydrogel. These entities consist of a diverse range of materials, including silicon, metal, polymer, glass, and ceramic [58]. A range of manufacturing techniques are employed to confer distinct shapes, dimensions, and characteristics. Microneedles are undergoing continuous advancements in their development and are being evaluated in clinical trials for the administration of diverse pharmaceutical agents [59]. Numerous studies have consistently indicated positive outcomes when employing this particular system. This technique exhibits the potential to yield therapeutic effects across various disciplines.

1.12. Factors affecting TDDS

There are a few parameters, both biological and physicochemical, that can affect the distribution of drugs through transdermal delivery. Biological parameters encompass various aspects such as flow of the blood, skin-associated conditions, sites of the skin, metabolism of the skin, and species variations. On the other hand, physicochemical factors comprise the hydration level of the skin, partition coefficient, molecular size temperature, diffusion coefficient, and drug concentration [60]. Following are the different factors,which affect TDDS:

1.12.1. Biological factors

- Skin-associated condition:

The penetration of drugs takes place exclusively through the intact integumentary barrier. Acids and alkalis have the potential to cause cellular damage, thereby facilitating penetration. The Percutaneous absorption is also enhanced in pathological conditions affecting the stratum corneum [61].

- Blood circulation:

  Blood circulation has an impact on the process of percutaneous absorption. An increase in blood flow is associated with a decrease in the residence time within the dermis, thereby leading to an increase in the concentration across the skin [62].

- Site of the skin:

  The permeability of skin sites is contingent upon the characteristics as well as on the thickness of the outermost layer of the skin. The rate of absorption of the drug exhibits inter-individual variability among volunteers [62].

- Metabolism:

  Skin metabolism plays a vital role in the activity of the skin, including the biotransformation of drugs and hormones. The bioavailability of a topical substance has an impact not only on its ability to penetrate the skin but also on the absorption of the drug [62].

- Variation in species:

  One notable aspect of species variation lies in the differences observed in mammalian skin, which encompass variations in the thickness, blood flow, hair follicles, density of the sweat glands. These variations ultimately influence the extent to which substances can penetrate the skin [62].

1.12.2. Physicochemical Factors

The physicochemical parameters refer to the measurable properties and characteristics of a substance or system that are related to its physical and chemical properties [63, 64].

- Temperature

  The transdermal drug absorption rate is influenced by fluctuations in temperature. The diffusion coefficient exhibits a negative correlation with temperature, such that a reduction in temperature is associated with reduction in the diffusion coefficient.

- Moisture content:

The skin becomes saturated with water, leading to the absorption of water by the tissue. This results in tissue swelling, softening, and the formation of wrinkles, thereby increasing tissue penetration. The hydration of the outermost layer is a crucial factor in enhancing the transdermal absorption of drugs.

- Diffusion coefficient:

  The diffusion coefficient is a parameter that characterizes the rate at which particles or molecules disperse through a medium due to random thermal motion.

- Diffusion rate:

  The rate of diffusion of drug molecules is contingent upon the physical state in which they exist. The diffusion coefficient is greater in gases and air due to the increased availability of space relative to the size of the molecules.

- Drug concentration:

  The process of drug penetration adheres to the principles of Fick's law of diffusion, wherein the movement of solute is directly proportional to the concentration gradient across the skin barrier.

- Partition coefficient:

  The partition coefficient is a fundamental concept in chemistry and biochemistry that describes the distribution of a solute between two immiscible phases, typically a hydrophobic organic solvent. The flux of drugs is contingent upon the partition coefficient across the stratum corneum. The achievement of a stable partition coefficient is crucial for facilitating the penetration of the drug.

- Dimensions of the drug:

  The topic of interest pertains to the dimensions of molecules. The absorption of a drug exhibits an inverse relationship with its associated molecular size. The penetration rate is higher in smaller molecules when compared to larger ones.

1.13. Problem Area

- Hypertension, commonly referred to as the silent killer, exhibits a notable phenomenon where roughly half of the individuals diagnosed with hypertension fail to adhere to their prescribed treatment regimen due to the presence of intolerable side effects, the complexity of the treatment plan, and a lack of reminders.

- The challenges associated with managing hypertension may arise from suboptimal patient compliance to long-term medication regimens, compounded by the absence of a definitive cure for this condition.
- The majority of antihypertensive medications exhibit suboptimal oral bioavailability and limited gastrointestinal absorption.
- There exists a necessity to devise a strategy to address these aforementioned issues and assist hypertensive individuals in the most optimal manner.

1.14. Research Objectives

- This study focuses on the synthesis and development of a pH-sensitive biocompatible dissolvable patch for transdermal delivery of Losartan Potassium, an antihypertensive drug.
- The transdermal administration of drugs, allowing for their absorption through the skin and subsequent entry into the systemic circulation, offers a convenient method of drug delivery for extended therapeutic treatment in conditions such as hypertension and cardiovascular diseases. This approach effectively addresses the challenges associated with low oral bioavailability and the requirement for regular medication reminders.
- The objective of this study is to explore the advancement of a transdermal drug delivery system (TDDS) that minimizes any potential disruption to the integumentary system.
- To provide assistance to an individual with hypertension who is in an unconscious state or people with Alzheimer's disease or a person in a paralysis condition.

Chapter 2: Literature Review

Transdermal drug delivery systems refer to discrete forms of medication that are applied to intact skin. These systems are designed to deliver drugs across the skin barrier at a controlled rate, allowing for their absorption into the systemic circulation. The drug is administered at an increased dosage within the transdermal patch, which is affixed to the skin for an extended duration [63]. The drug permeates the skin and enters the systemic circulation due to a concentration gradient, with a higher drug concentration in the transdermal patch when compared to low concentration in bloodstream. The composition of transdermal drug delivery systems (TDDS) enables the sustained diffusion of drugs over an extended duration while ensuring a consistent rate of diffusion. Transdermal drug delivery systems (TDDS) are versatile pharmaceutical formulations that may comprise one or multiple therapeutic agents, intended for exclusive application onto the unbroken skin. Patches are topically administered to the skin, facilitating the controlled release of drugs that subsequently permeate through the skin's membranes, ultimately entering the systemic circulation [63]. Transdermal drug delivery systems are well-suited for drugs that possess lower molecular weights and dose sizes, as well as appropriate lipid and water solubility. This route of the drug administration offers the advantage in providing a continuous supply of drugs with short biological half-lives, thereby avoiding the pulsatile entry of drugs into the bloodstream that frequently leads to adverse side-effects.

Basically, transdermal patch refers to a pharmaceutical adhesive type patch that is affixed onto the skin with the purpose of administering a precise dosage of medication through the skin and into the circulatory system. Transdermal patches consist of several essential constituents, including a polymer matrix, backing laminates, enhancers, release-liner membrane, pressure-sensitive adhesives, and additional excipients such as solvents as well as plasticizers [65, 66].

In the contemporary era, significant efforts have been dedicated to the advancement of the transdermal route. However, ongoing progress continues to be made in the domain of TDDS. This transdermal route has been employed since ancient times for the administration of a diverse range of pharmaceuticals. In the historical context, significant contributions have been made through the hypothesis conducted on the resistance to drug permeation through the skin [67].

The role of the stratum corneum in restricting the permeation of drug molecules across the integumentary system. The diffusion coefficient of drug molecules was experimentally

demonstrated in an investigation revealing that numerous drugs exhibit notable permeability through the skin [68]. FDA granted approval for the first transdermal drug delivery system utilizing scopolamine for the treatment of motion sickness in the year 1979 [64, 69]. Nicotine patches were developed by pharmaceutical companies in the year 1980. The patches mentioned in the year 1991-1992 received approval from the Food and Drug Administration (FDA) as documented by Thomas and Finnin in 2004 [70].

Transdermal patches have been developed for the purpose of administering drugs such as scopolamine, estrogen, nitroglycerine, lidocaine, and nicotine through the skin [65]. Transdermal patches are extensively employed in dermal route of administration, topical applications, as well as in cosmetic formulations. The future outlook for DDS and for transdermal patches encompasses the integration of patches with active form of delivery systems, and microneedle patches, allowing for metered dose systems [71]. TDDS demonstrates efficacy in facilitating the transportation of small drug molecules into the systemic circulation via the skin. There are several advantages associated with the use of these therapies in comparison to conventional drug therapy. One notable advantage is their ability to bypass first-pass metabolism and biotransformation processes. Additionally, these therapies are effective in minimizing alterations in drug absorption and metabolism, resulting in consistent drug levels. Furthermore, they have been shown to enhance the efficacy and bioavailability of drugs, improve patient compliance, and enable the rapid administration of medications. The TDDS (Transdermal Drug Delivery System) is composed of three essential components: an adhesive layer, a backing layer, and a release liner. The backing layer provides the polyethylene, polyester, and polyolefin materials with enhanced flexibility, improved appearance, and increased adhesion properties. Additionally, it serves to safeguard against the leaching of excipients. Transdermal drug delivery patches have been specifically engineered to administer drugs at a consistent and controlled rate through the utilization of a membrane that regulates the release of the drug. The adhesive layer is specifically engineered to facilitate the transdermal delivery of medication while exhibiting minimal influence on the rate of drug release. The drug permeates all layers of the patch, leading to saturation and a continuous release of the drug onto the skin. Test-driven development (TDD) exhibits a significant impact on a broader scale rather than being limited to specific domains, making it relevant and applicable across various therapeutic areas. It has the ability to maintain plasma levels within the therapeutic range for an extended duration.

The twentieth century marked the development of dermatological products that utilized oils, fats, scents, fats, nail paints, creams, powders, and more for cosmetic purposes. The Ancient Egyptians employed a kohl paste for the purpose of adorning their eyes, red ochre as a cosmetic for the face, and a combination of lime and oil as a substitute for cleansing creams. In addition, lead-based products were employed for ocular safeguarding, thereby offering a means of protection against infectious agents [72]. It employed a specific formulation consisting of a mixture of tar and sulfur, which was topically applied to the skin using paper as a medium for the treatment of sciatica [73]. Transdermal therapeutic delivery offers several advantages. Firstly, it allows for painless administration of drugs. Additionally, it ensures that patients are unable to self-administer the drug through parenteral means. Moreover, this method eliminates the need for cumbersome delivery devices and the disposal of hazardous needles. Furthermore, transdermal delivery minimizes gastrointestinal effects associated with the drug and reduces peak plasma levels, thereby mitigating potential side effects. Transdermal drug delivery offers advantages for medications that are subject to first-pass metabolism in the liver, exhibit low oral bioavailability, require sustained administration, or are susceptible to degradation by gastric acid [74].

Different modifications of these transdermal patches are available such as single-layer drug-in-adhesive patches. A monolayer of a polymer possessing adhesive-associated characteristics is employed as a reservoir layer for the dispersion of drugs. A backing layer that is impermeable is positioned underneath the single polymer layer. The drug is stored within and exhibits adherence to the polymer layer, subsequently being released from underlying backing layer that provides support to the drug reservoir layer [75]. The transdermal product known as Daytrana® serves as an illustrative instance of a transdermal patch with a drug-in-adhesive formulation, featuring a sole layer and containing methylphenidate. Multilayer transdermal patches are composed of two distinct layers: adhesive layer as well as drug reservoir layer. These patches are designed to regulate the release of drugs over a specific duration of time . Multilayer systems consist of two essential components: a temporary layer and a permanent backing layer. Multilayer patches are employed for the administration of analgesics, pharmaceuticals aimed at promoting smoking cessation, and hormone therapy. These patches enable the sustained release of drugs for a duration of seven days [76]. Vapor transdermal patches are made up of a monolayer layer of an adhesives comprising polymer layer that has the ability to release vapor [77]. There exists a variety of vapor dermal patches that are currently marketed and are utilized for diverse applications. An illustration

of this is the utilization of Nicoderm CQ®, which comprises nicotine-infused transdermal patches that incorporate essential oils. These patches, upon release, exhibit potential efficacy in aiding individuals in their cessation of smoking habits. The introduction of this product to the European market occurred in 2007. Tacura® vapor patches are a variant of vapor mode patches that incorporate oils and are designed for the purpose of alleviating congestion. There are additional variants of vapor patches that can be found in the market, which serve as medications for depression or sedation. The matrix transdermal patch consists of a reservoir composed of either a lipophilic or a hydrophilic polymer matrix. The drug is uniformly distributed within the polymer matrix by positioning the drug-polymer matrix layer on top of a plate with an impermeable backing layer. Matrix dispersion patches, such as Nitro-Dur®, are commercially available products that consist of nitroglycerin and Minitran. These patches are designed to deliver a consistent flow of medication through the skin, even when the skin is undamaged [78].

Chapter 3: Material and Methodology

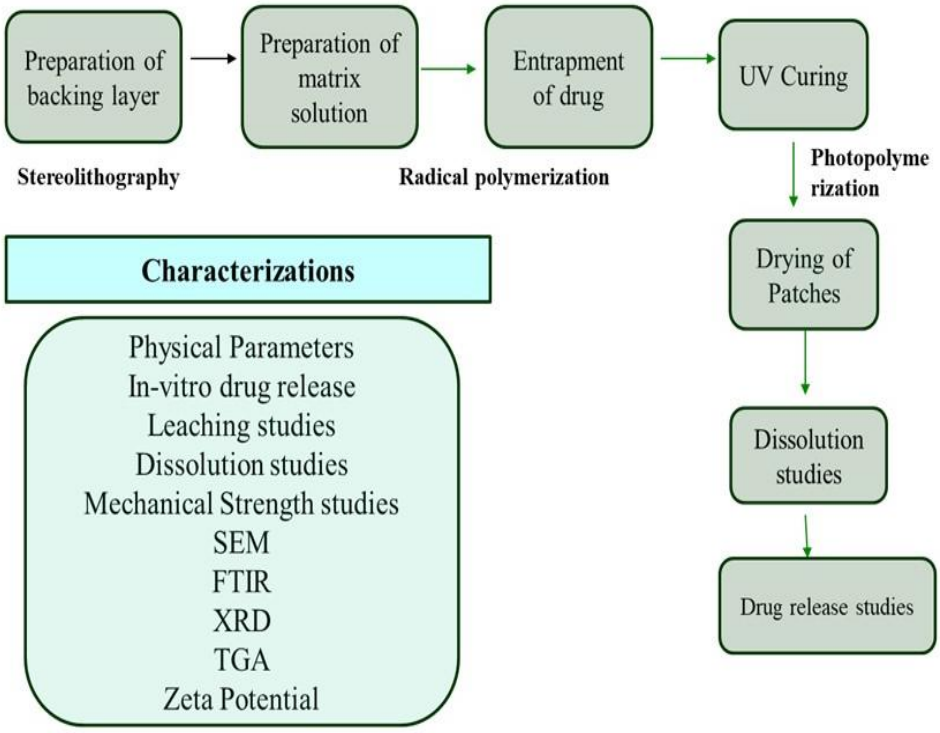

Figure 2: Representing key steps of the methodology

3.1. Preparation of Backing Layer

3.1.1. Designing of a 3D model

A rectangular shaped animation was opted for the device's 3D model. Model programming was ensured by Solidworks2014, Dassault Systems S.A, and was saved in a stereolithography (.stl) file. The model was then imported into the 3D printer's software, and the .stl format was converted to G-code for the printing process.

3.1.2. 3D printing of backing layer

Dental Resin was used as a material for the printing of the layer. According to the CAD designs, the backing layer comprised of two parts:

- 1cm×1cm platform

• 0.5 x 0.5 cm holding slits

The final prototype is given below in Figure.3

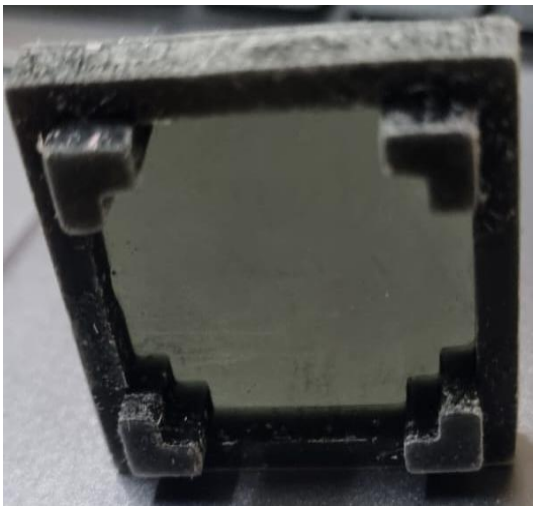

Figure3. Representing backing layer

3.2. Preparation of Polymer Matrix

Three combinations were used in two different solvents, in DMSO, and NaOH.

The following combinations were optimized in both solvents:

1. Carboxymethylcellulose, dextran, methyl methacrylate
2. Polyvinylpyrrolidone, dextran, methyl methacrylate
3. Gelatin, dextran, methyl methacrylate

3.2.1. Preparation of Master mix solution in DMSO

5% dextran solution was prepared by dissolving required dextran in 1% DMSO solution and kept for continuous stirring at 500 rpm, 25°C for a period of one hour until a clear solution was obtained without any precipitation, under an oxygen-free nitrogen atmosphere. After proper dissolution,0.25 grams of DMAP, as a catalyst was added under continuous stirring at 500 rpm, 25°C, for continuous three hours, until no precipitations were observed. After a period of three hours, 322mg of methyl methacrylate was added, under the same conditions, and the reaction mixture was kept under a dark atmosphere under continuous stirring for 48 hours.

3.2.2. Preparation of Carboxymethyl Cellulose Stock Solution

1% of carboxymethyl Cellulose stock solution prepared by mixing 1 gram of CMC powder into 100 ml of distilled water under continuous stirring at 60°C for continuous two hours until a thick and viscous obtained.

3.2.3. Preparation of Polyvinylpyrrolidone Stock Solution

60% polyvinylpyrrolidone stock solution was prepared by adding 60 grams of PVP powder into a beaker containing 100 ml of distilled water under continuous stirring at 60°C, (50 rpm) speed for continuous 3 to 4 hours until a thicker solution without any clump was obtained.

3.2.4. Preparation of Gelatin Stock Solution

A 10% gelatin solution was prepared by adding 10 grams of gelatin powder into 100 ml of distilled water, under continuous stirring for about one hour, until a slightly thicker solution was obtained.

3.2.5. Preparation of Anti-hypertensive Drug (Losartan Potassium) Stock Solution

200mg/ml stock solution was prepared by pouring 200 mg of losartan potassium in 1 ml of deionized water under continuous stirring of about 2 hours, to obtain a clear and translucent solution. The solution was then stored in a refrigerator at 4°C.

3.3. Preparation of Control Patch formulations in DMSO Solvent

3.3.1.CMC/Dextran/MMA

CMC/Dextran/MMA formulation was prepared by pouring 6ml of 1% CMC solution into a beaker containing 6ml of Master-mix solution, as already mentioned above, under continuous stirring at 50 rpm and 60°C in 1:1. The beaker was kept under continuous stirring for about 2 hours, followed by the addition of 1 ml of photo-initiator (Irgacure) for cross-linking, under continuous stirring of about one hour. The solution was then kept in a vacuum desiccator for about 20 minutes for the elimination of air bubbles. The solution was then poured into a glass petri-plate with its surface covered with a hydrophobic sheet. The petri-plate was then placed under a 365nm UV lamp for about 4 hours. After 4 hours, the viscous solution obtained was left for drying. Dried patches were then cut into 1cmx1cm and peeled off.

3.3.2.PVP/Dextran/MMA

PVP/Dextran/MMA formulation was prepared by pouring 6 ml of 60% PVP solution into a beaker containing 6 ml of Master-mix solution, as already mentioned above, under continuous stirring at 50 rpm and 60°C in a 1:1 ratio. The beaker was kept under continuous stirring for about 2 hours,

followed by the addition of 1 ml of photo-initiator (Irgacure) for cross-linking, under continuous stirring for about one hour. The solution was then kept in a vacuum desiccator for 20 minutes to remove any air bubbles that were formed. The solution was then poured onto a hydrophobic sheet, in a glass petri plate. The petri-plate was then placed under a 365nm UV lamp for about 4 hours. After 4 hours, the viscous solution obtained was left for drying. Dried patches were then cut into 1cm x 1cm and peeled off.

3.3.3.Gelatin/Dextran/MMA

Gelatin/Dextran/MMA formulation was prepared by pouring 3ml of 10% gelatin solution into a beaker containing 6ml of Master-mix solution, as already mentioned above, under continuous stirring at 50 rpm and 60°C in a 1:2 ratio. The beaker was kept under continuous stirring for about 2 hours, followed by the addition of 1 ml of photo-initiator (Irgacure) for cross-linking, under continuous stirring of about one hour. The solution was then kept in a vacuum desiccator for 30 minutes to eliminate bubble formation. The solution was then poured into a glass petri-plate. The petri-plate was then placed under a 365nm UV lamp for about 6 hours. After 6 hours, the viscous solution obtained was left for drying. Dried patches were then cut into 1cmx1cm and peeled off.

3.4. Preparation of Drug-loaded Patch formulations in DMSO Solvent

3.4.1.CMC/Dextran/MMA

The same procedure was followed as that of control patch with the modification of the addition of the drug solution under continuous stirring for about 1.5 hours for proper entrapment of the drug into the polymer solution before the step of photopolymerization under UV lamp.

3.4.2.PVP/Dextran/MMA

Same steps of control PVP/Dextran/MMA formulation were repeated, with an addition of drug solution into the polymer solution, under continuous stirring of 1.5 hours, before UV photopolymerization.

3.4.3.Gelatin/Dextran/MMA

Gelatin/Dextran/MMA drug-containing formulations were prepared likewise control formulations, but with a modification of the addition of drug solution under continuous stirring for about 1.5 hours, before putting the solution under UV lamp

3.5.Preparation of Master mix solution in NaOH Solvent

5% dextran solution was prepared by dissolving an appropriate quantity of dextran in 1% NaOH solution and kept for continuous stirring at 500 rpm, 25°C for a period of one hour until a clear solution was obtained without any precipitation, under an oxygen-free nitrogen atmosphere. After proper dissolution,0.25 grams of DMAP, as a catalyst was added under continuous stirring at 500 rpm, 25°C, for continuous three hours, until no precipitations were observed. After a period of three hours, 322mg of methyl methacrylate was added, under the same conditions, and the reaction mixture was kept under a dark atmosphere under continuous stirring for 24 hours.

3.5.1.CMC/Dextran/MMA

CMC/Dextran/MMA formulation was prepared by pouring 6ml of 1% CMC solution into a beaker containing 6ml of Master-mix solution, as already mentioned above, under continuous stirring at 50 rpm and 60°C in 1:1. The beaker was kept under continuous stirring for about 2 hours, followed by the addition of 1 ml of photo-initiator (Irgacure) for cross-linking, under continuous stirring of about one hour. The solution was then kept in a vacuum desiccator for 20 minutes to remove any air bubbles that formed. The solution was then poured into a glass petri-plate with its surface covered with a hydrophobic sheet. The petri-plate was then placed under a 365nm UV lamp for about 4 hours. After 4 hours, the viscous solution obtained was left for drying. Dried patches were then cut into 1cmx1cm and peeled off.

3.5.2.PVP/Dextran/MMA

PVP/Dextran/MMA formulation was prepared by pouring 6 ml of 60% PVP solution into a beaker containing 6 ml of Master-mix solution, as already mentioned above, under continuous stirring at 50 rpm and 60°C in a 1:1 ratio. The beaker was kept under continuous stirring for about 2 hours, followed by the addition of 1 ml of photo-initiator (Irgacure) for cross-linking, under continuous stirring for about one hour. The solution was then kept in a vacuum desiccator for 20 minutes to remove any air bubbles that formed. The solution was then poured onto a hydrophobic sheet, attached to the surface of a glass petri plate. The petri-plate was then placed under a 365nm UV lamp for about 4 hours. After 4 hours, the viscous solution obtained was left for drying. Dried patches were then cut into 1cm x 1cm and peeled off.

3.5.3.Gelatin/Dextran/MMA

Gelatin/Dextran/MMA formulation was prepared by pouring 3ml of 10% gelatin solution into a beaker containing 6ml of Master-mix solution, as already mentioned above, under continuous stirring at 50 rpm and 60°C in a 1:2 ratio. The beaker was kept under continuous stirring for about 2 hours, followed by the addition of 1 ml of photo-initiator (Irgacure) for cross-linking, under continuous stirring of about one hour. The solution was then kept in a vacuum desiccator for 20 minutes to remove any air bubbles that formed. The solution was then poured into a glass petri-plate with its surface covered with a hydrophobic sheet. The petri-plate was then placed under a 365nm UV lamp for about 4 hours. After 4 hours, the viscous solution obtained was left for drying. Dried patches were then cut into 1cmx1cm and peeled off.

3.6. Preparation of Drug-loaded Patch formulations in NaOH Solvent

3.6.1.CMC/Dextran/MMA

The same procedure was repeated as that of control with the modification of the addition of the drug solution under continuous stirring for about an hour for proper entrapment of the drug into the polymer solution before the photopolymerization.

3.6.2.PVP/Dextran/MMA

The same procedure was repeated as that of control with the modification of the addition of the drug solution under continuous stirring for about an hour for proper entrapment of the drug into the polymer solution before the photopolymerization.

3.6.3.Gelatin/Dextran/MMA

The same procedure was repeated as that of control with the modification of the addition of the drug solution under continuous stirring for about an hour for proper entrapment of the drug into the polymer solution before the photopolymerization.

3.7.Adhesive Layer

Silicon Nano-adhesive was used as the adhesive layer of the patch, attached to the holding slits of the backing layer, providing support to the polymer matrix.

3.8.Physical Parameters Measurements

All the patches' films were cut into 1cm x 1cm dimensions and weighed on an electronic weighing balance. Thickness was measured through a micrometer screw -gauge. The following formula was applied to measure the thickness of individual patch films.

The thickness of the film= (Main Scale Reading) + (Circular Scale x Least Count of the Instrument).Other parameters such as, roughness, length, width and angle of reflection of light upon the film were measured through OLYMPUS DIGITAL MICROSCOPE.

3.9.Dissolution Studies

For the dissolution studies of the different patch formulations, sodium citrate buffer adjusted to pH 5 was used as a medium, to match the physiological pH of the skin.

Each patch was cut into 1cm x 1cm, weighed, and dissolved into the sodium citrate buffer.

The percentage of the patch was observed visually after every 10 minutes for a period of 120 minutes.

3.10.Drug Release Studies

Patches were cut into 1cm x 1cm, weighed, and inserted into a beaker containing 7 ml of sodium citrate buffer. Within no time, (3mL) of eluted drug medium was removed for UV spectrophotometer analysis; this volume (3mL) was replaced with fresh buffer to prevent sink conditions. After every 15 minutes, (3mL) of the solution was pipetted out for the UV analysis at 293.5nm and replaced with fresh buffer. The same procedure for all the patches at a time interval of 15 minutes was repeated for consecutive 150 minutes.

3.11.Leaching Studies

CDD patch was fully dissolved in sodium citrate buffer (pH 5), and the drug-containing medium was then analyzed spectrophotometrically to evaluate the leaching of the monomers.

3.12. Material Characterization

3.12.1.Scanning Electron Microscopy

The surface topography and morphology of the patches (CDC and CDD) were investigated by using Scanning Electron Microscopy . The samples were placed onto the specimen mounting stubs and were coated with a thin layer of gold by sputter coater unit JFC-1500 before the analysis to make the patch surfaces conductive in nature.

3.12.2. FTIR Analysis

The FTIR spectral analysis was used to evaluate the chemical configuration of CMC/Dextran/MMA films of both DMSO as well as of NaOH groups, with as well as without the drug, to assess the possible interactions between the compounds in prepared films. The FTIR was

carried out in ATR mode and the analysis at the wavelength range between 4000–800 cm-1. The transmission spectra were recorded to identify any bond stretching or difference in the intensity levels. Essential FTIR software was used to analyze the FTIR spectra of the dissolvable films.

3.12.3. XRD Spectral Analysis

X-ray diffraction analysis is a commonly used technique to study the crystalline structure and composition of materials. When it comes to polymeric films containing antihypertensives, XRD can provide valuable information about the crystallinity and molecular arrangement of both the polymer matrix and the incorporated drug molecules. Prepared film samples of CMC of both DMSO and NaOH groups were mounted in the XRD instrument the data of the acquisition process was initiated. The X-ray beam was directed onto the sample, and the diffracted X-rays were collected by a detector. The detector recorded the intensity of diffracted X-rays at different angles.

3.12.4. Tensile Testing

Samples (1cmx5cm) of all the control patches were placed in the grips of a Universal Testing Machine at a specified grip separation and pulled until failure was observed. Standard method ASTM D638 was followed for this test, and 10mm/min speed was utilized in order to check the UTS point of all the dissolvable films.

3.12.5. TGA Analysis

Thermogravimetric analysis provides information about the temperature range at which the film is stable and what temperature range it undergoes thermal degradation and the corresponding weight loss. A small piece of CDD was placed into the sample holder of the TGA instrument. The initial weight of the sample was measured accurately. The heating program for the TGA analysis was set. The sample was subjected to a gradual temperature ramp from room temperature to a higher temperature, such as 500-800°C, at a constant heating rate (e.g., 5-10°C/min).

Chapter 4: Results

4.1. Physical Parameters Measurements

Following tables represent the physical parameters of the comparison between the DMSO group formulations with the NaOH group formulations.

4.1.1. DMSO Group

Table 1: Physical Parameters of DMSO group films

Patch	Roughness	Width	Height	Angle	Thickness
CMC/Dextran/ MMA	0.041µm	483.2µm	10.0µm	2.38	0.70mm
Gelatin/Dextran/ MMA	3.28µm	515.7µm	20.0µm	1.11	1.47mm
PVP/Dextran/ MMA	2.55µm	540.3µm	39.3µm	4.16	1.66mm

4.1.2. NaOH Group

Table 2: Physical Parameters of NaOH group films

Patch	Roughness	Width	Height	Angle	Thickness
CMC/Dextran/ MMA	0.130µm	894.4µm	66.2µm	4.23	1.04mm
Gelatin/Dextran/ MMA	0.161µm	699.3µm	565µm	38.9	0.58mm
PVP/Dextran/ MMA	5.095µm	300.6µm	363µm	50.4	1.46mm

In both groups, as shown above, CMC-containing patches were smooth in nature and thinner. The thinner the patch, the easier would be its dissolution and hence easier would be the drug release

4.2. Dissolution Studies

In the figure 4, x- axis is representing the time, each formulation of the patch took to dissolve, Y-axis is representing the percentage of each patch remaining. The above groups showed that CMC-containing patches dissolved at a faster rate as compared to other formulations. Gelatin-containing patch of the DMSO group did not dissolve after 120 minutes. While all the formulations of the NaOH group dissolved within 120 minutes.

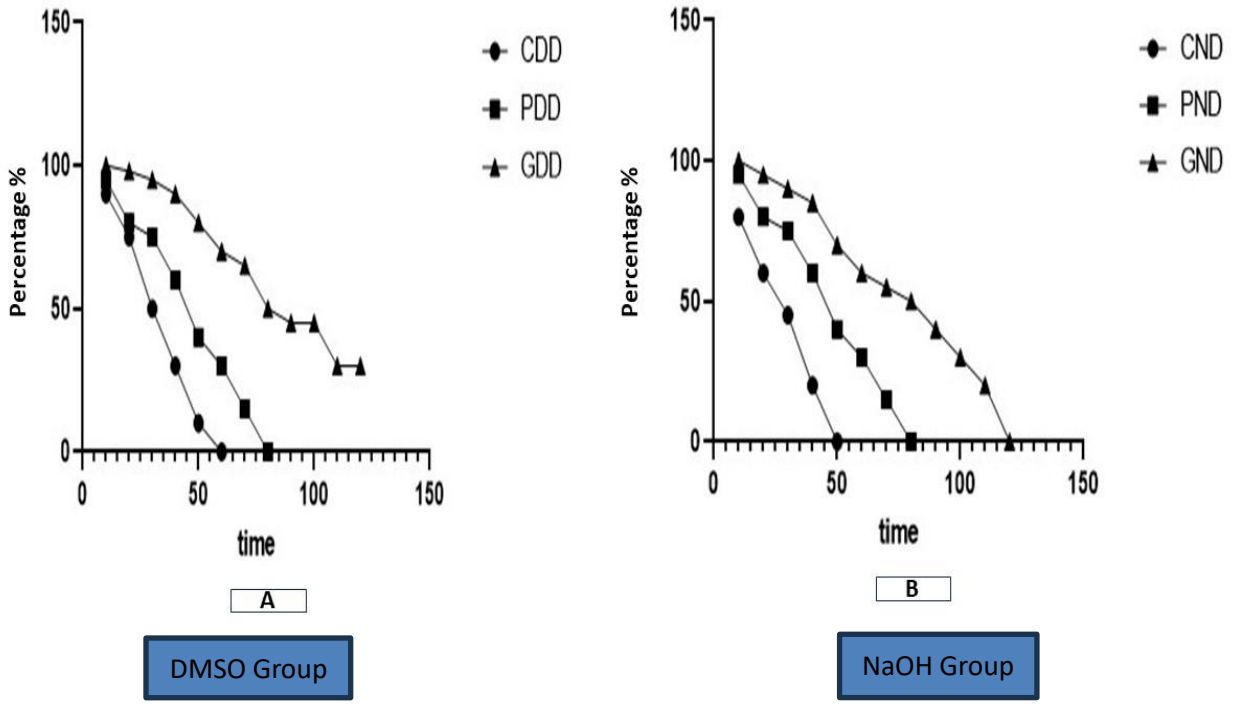

Figure.4. Representing dissolution studies

In the above dissolution studies, it is revealed that CMC-containing patches have the ability to dissolve more rapidly as compared to other formulation patches. PVP-containing patches, dissolved at a moderate rate. While gelatin-containing patches were most time-consuming.

4.3. Leaching Analysis

Figure 5 indicates the overlapping peaks when compared with the absorbance peak of CDD. These overlapping peaks indicate minimum leaching of the monomers and intact polymerization.

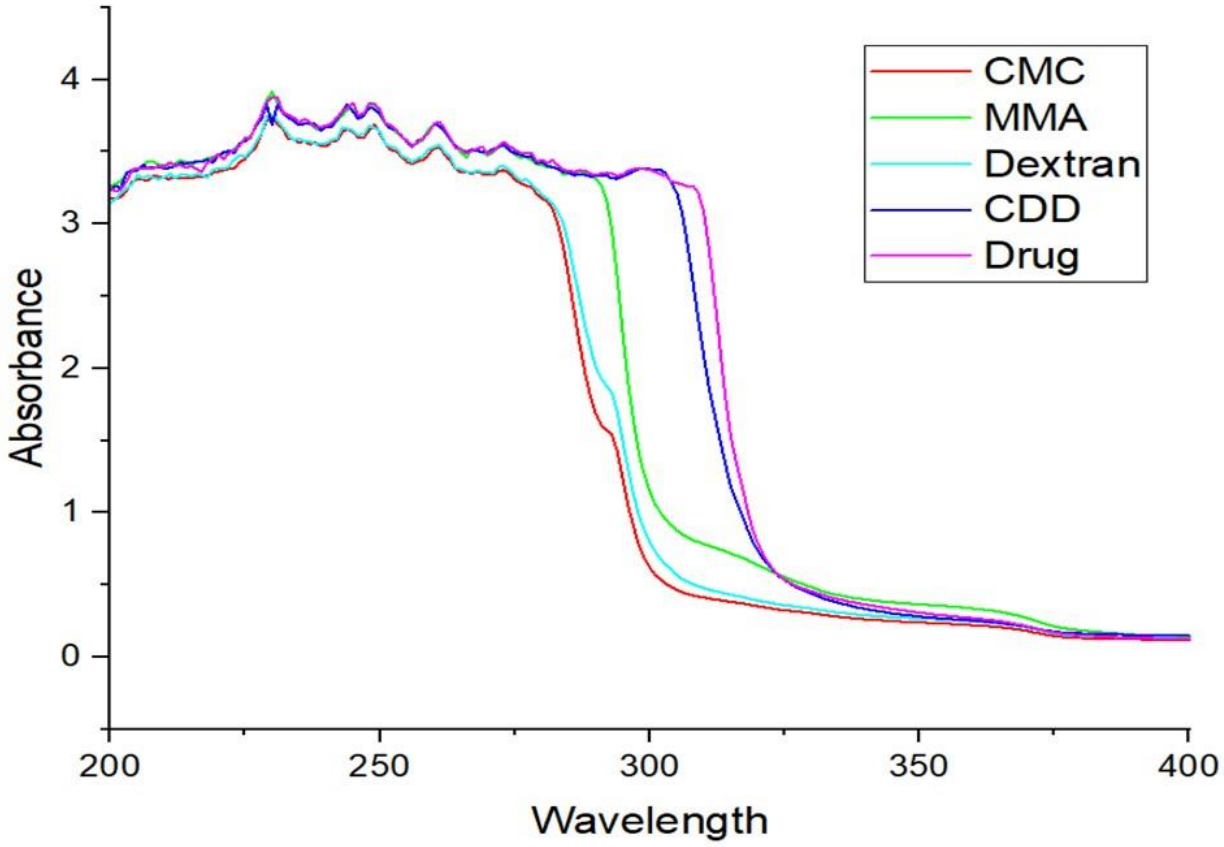

Figure 5. Representing leaching test.

Greater the leaching of the monomers, greater will be the chances of incomplete polymerization and hence greater will be the chances of skin irritancy due to the leached monomers. Absorbance spectra of dug and the absorbance spectra of the CDD is indicating the drug release profile of the CDD patch also.

4.4. Drug Release Profile

The above figure 6 is showing drug release profile of different formulations in DMSO and NaOH solvents. Formulation A, CDD is indicating steady drug release over a time period of 45 minutes. Formulation B, CND showed drug release initially which continued at a constant rate till t=45 minutes. Formulation C, GDD started to release the drug after 45 minutes. Formulation D, GND, showed drug release after 30 minutes. Formulation E, PDD showed that drug release was constant between t = 0 and t = 15 minutes and between t = 30 and t = 45 minutes. Formulation F, GND manifested abrupt release of drug from t = 15 mins till t = 45 minutes.

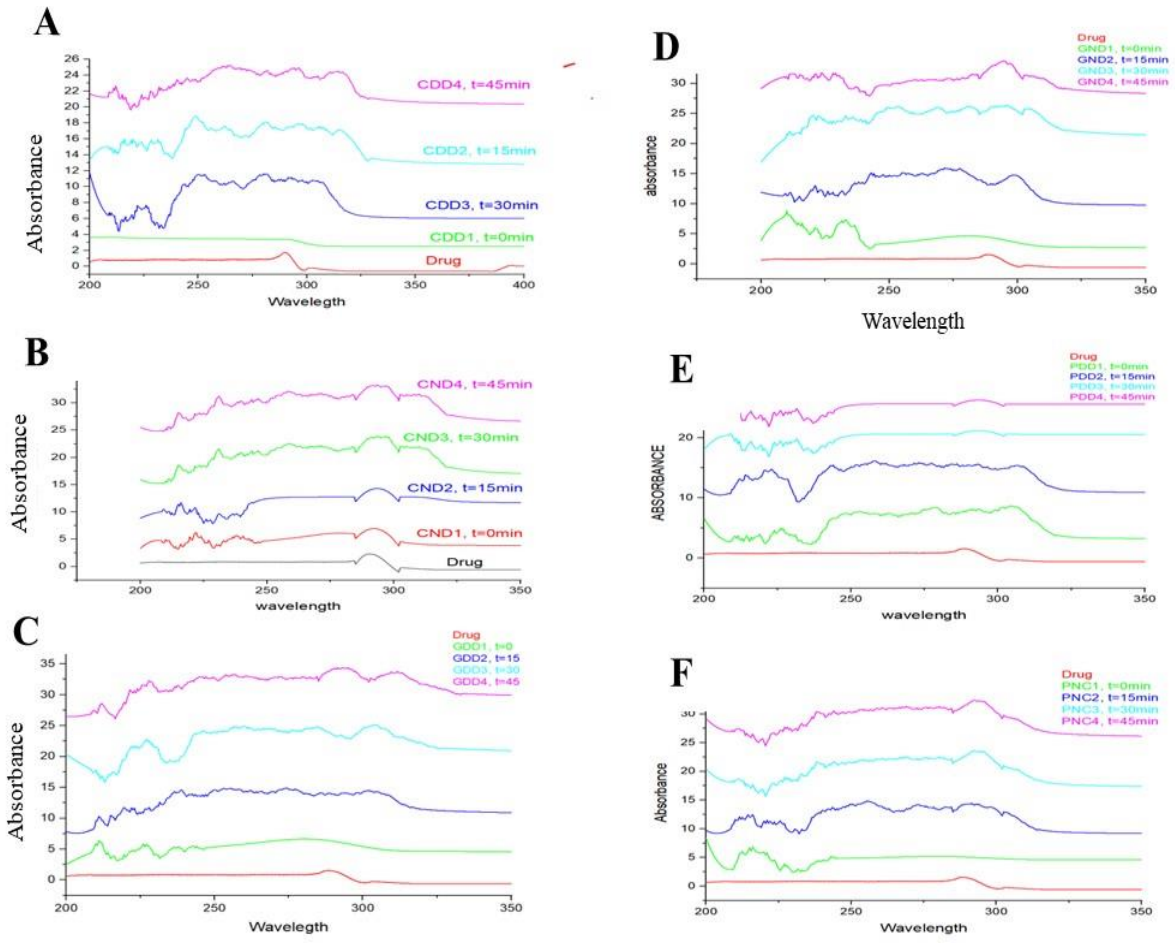

Figure 6. Representing Drug Release Profile

Drug release profile of various formulated patches is indicating that these formulated patches are sufficient enough to be used as an anti-hypertensive patches.

4.5. Material Characterization

Material characterization is important for the selection of the best formulation for the preparation of patch polymer matrix. Material characterization includes following testing techniques.

4.5.1. SEM

Figure 7, is indicating a clear difference between the control group of CMC-Containing Patch and Drug-loaded CMC-Containing Patch. Image B indicates increased pore size, as the molecular weight of the drug is high, and needs more space for the occupation. Image B shows large interconnected pores with irregular geometric mixed with small ellipsoid pores.

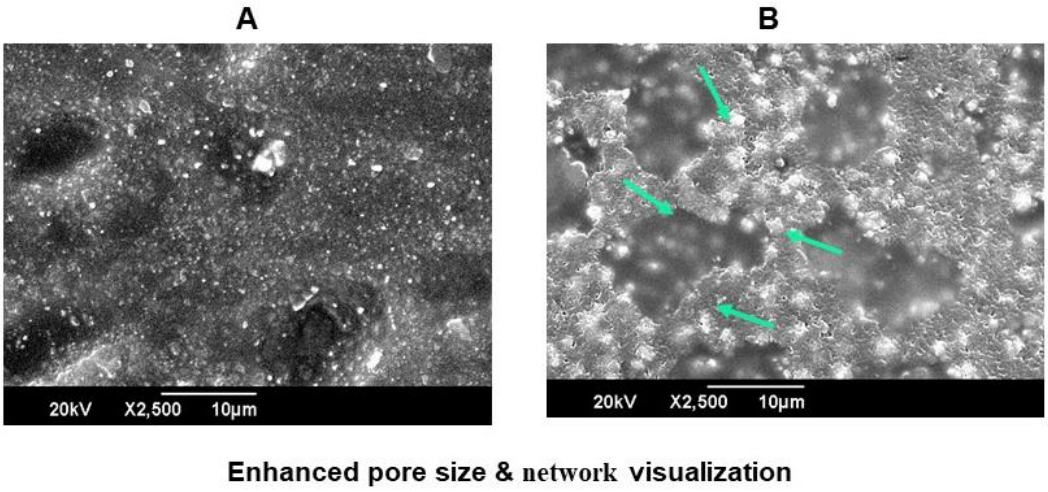

Figure 7. Representing SEM Profile

Large interconnected chains are also observed around the enlarged pores, which may manifest some proportion of the drug molecules, as SEM is a potent imaging method used to view the topography and surface morphology of materials at high magnification.

4.5.2. FTIR Spectroscopy Analysis

The figure8, reveals the FTIR Spectrometry Analysis of CMC-containing formulations in both the solvents i.e., DMSO and NaOH. The combined graph of each solvent group is indicating a change in intensity level. This change in intensity level and phase shift is indicating that the drug interacted with the polymer and underwent structural configurational changes that led to differences in the absorbance and hence transmission. Stretch at the position of (3400 cm-1 – 3434 cm-1) indicates the OH- stretching, OH group is abundant in CMC, dextran, as well as in losartan potassium. While phase-shift at the position of 1627 cm-1 in the CDD, indicates the presence of the drug due to the bonding of the carbon group with the nitrogen group of the drug. While peak at the 2000 cm-1 range is indicating the formation of an unusual functional group, due to the interaction of the drug with the matrix.

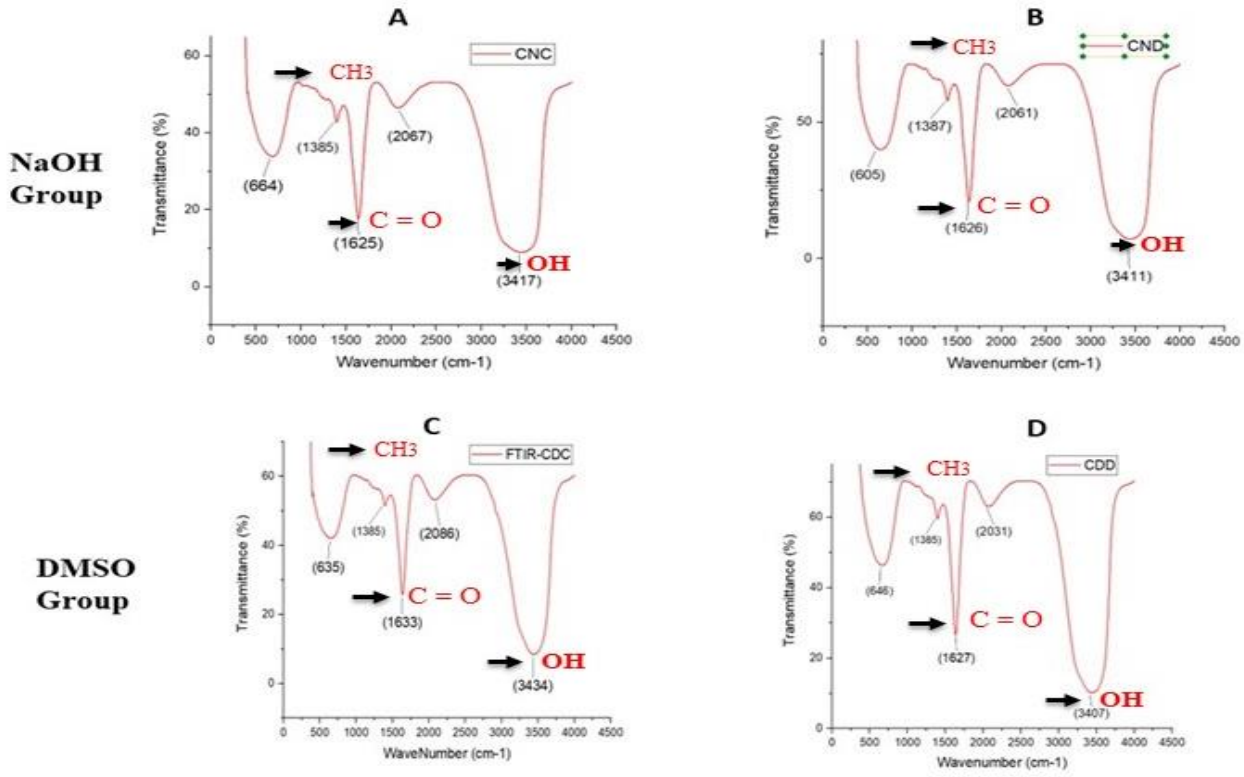

Figure 8. Representing FTIR Analysis

4.5.3. XRD Analysis

Figure 9 represents the X ray diffraction analysis of the CMC-containing formulations. As, XRD can provide valuable information about the crystallinity and molecular arrangement of both the polymer matrix and the incorporated drug molecules. Prepared film samples of CMC of both DMSO and NaOH groups were mounted in the XRD instrument the data of the acquisition process was initiated.

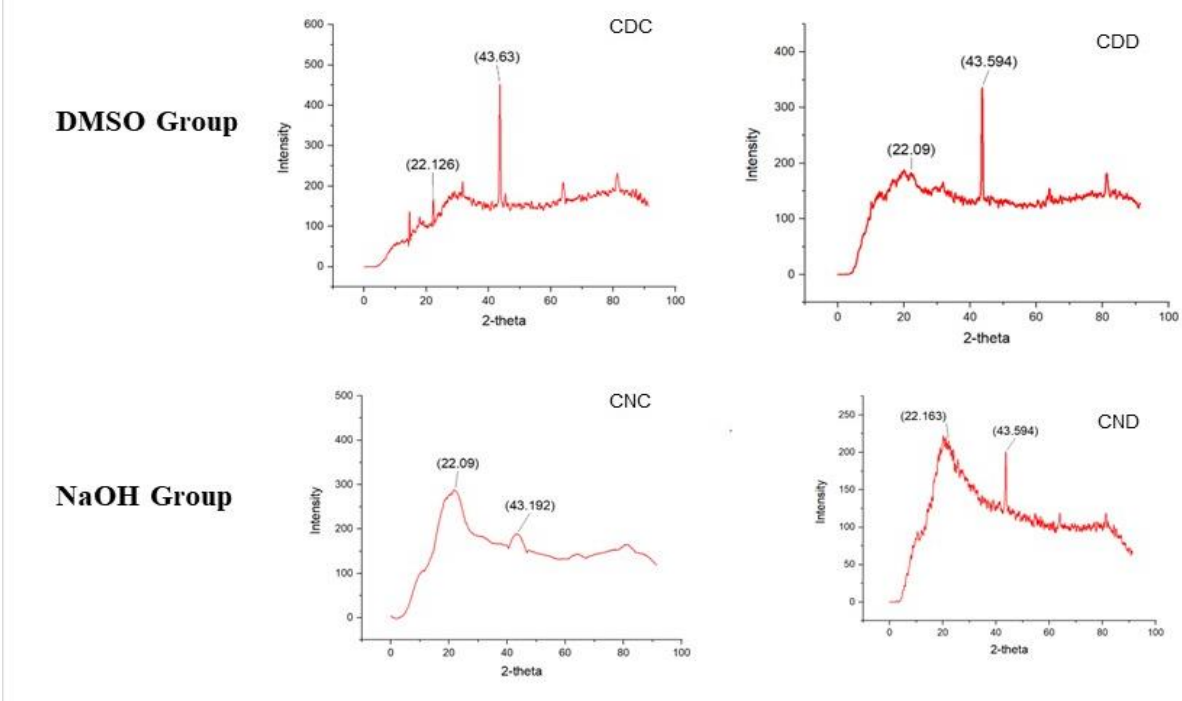

Figure 9. Representing XRD Analysis

XRD peaks at the position of 22 and 43 in the control groups is indicating the presence of CMC and Dextran. While a sharp peak at 11.5 is indicating the presence of drug. Moreover, sharp peaks indicate the crystalline structure of the drug (Losartan Potassium).

4.5.4. Mechanical Strength Analysis

Figure 10 manifests that mechanical strength is estimated by tensile strength test. Standard method ASTM D638 was followed for this test, and 10mm/min speed was used in order to check the UTS point of all the required films.

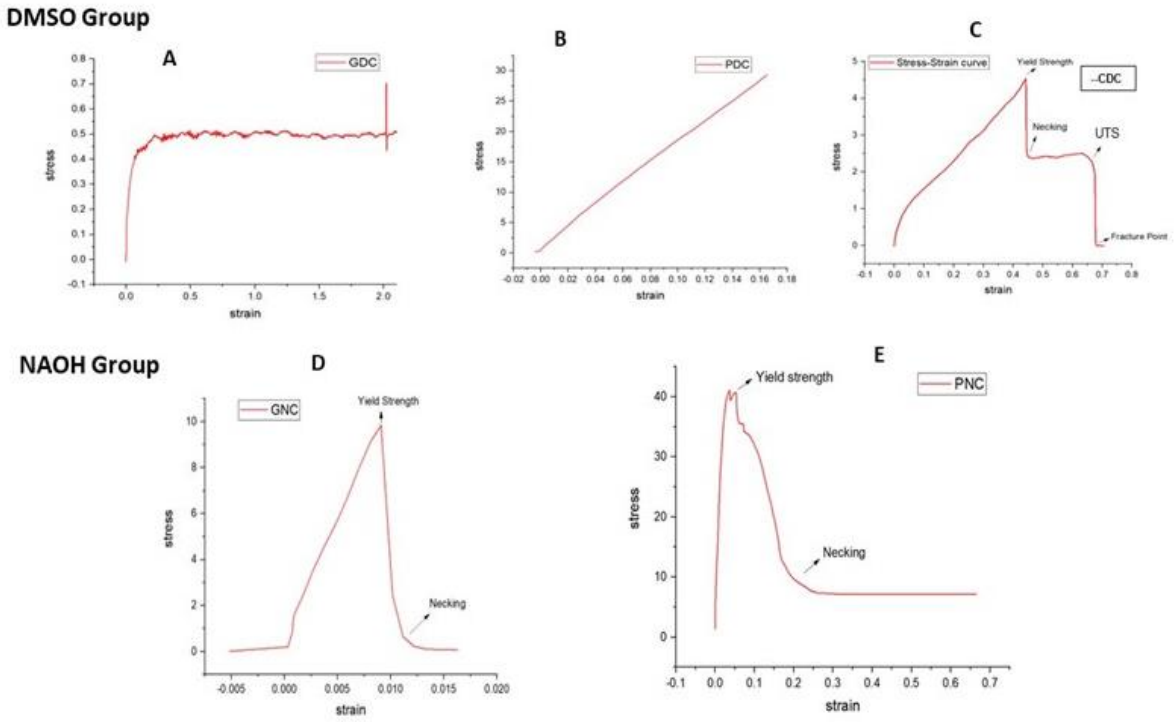

Figure 10. Representing Tensile Strength Analysis

The above groups indicate CDC shows good mechanical properties and is elastic in nature. As films should be ductile in nature and should not be brittle in nature, (C), CDC attaining its UTS (Ultimate Tensile Strength) indicates that the CDC patch is ductile in nature. Necking is the point when the film starts to deform and fracture point is the point when the film fractures i.e,. cannot return back to its shape. While (A) GDC film proved to be most brittle in nature, it got fractured immediately after a small force. (B), PDC indicates that it did not fracture even after applying a large force. It even went beyond the machine's limit. While (D and E) GNC and PNC are indicating the elastic nature of the films but none of them reached their UTS point, UTS point indicates the breaking strength of the films.

4.5.5. TGA Analysis

TGA enables thermal property comparisons between various polymeric films, assisting in the material selection process for particular applications. The outcomes of TGA tests can be very important for enhancing stability, forecasting the performance of polymeric films in diverse applications, and optimising processing settings.

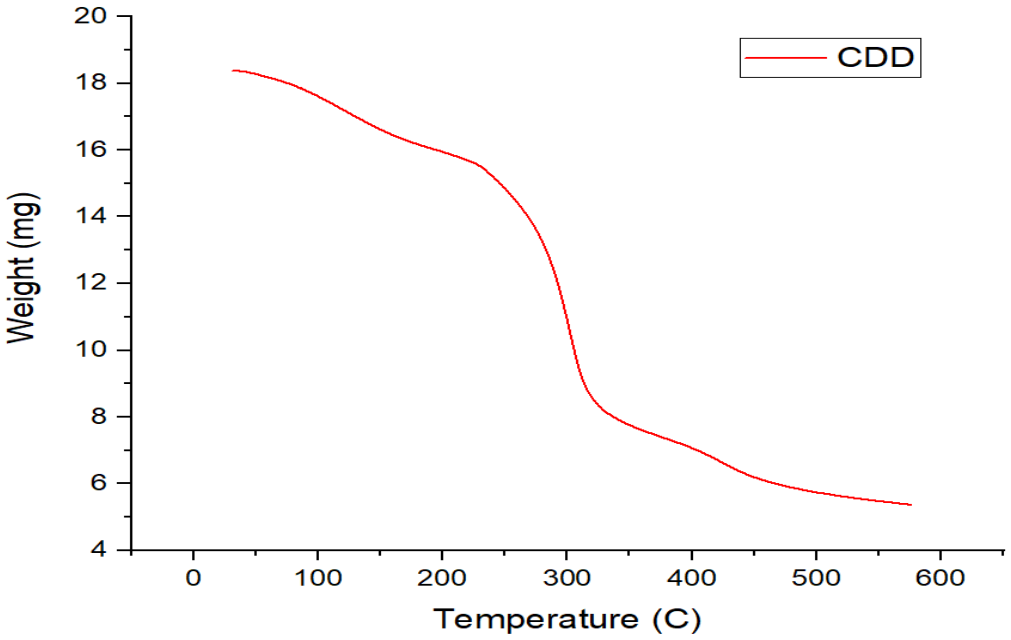

Figure 11. Representing Thermogravimetric Analysis

The sample was subjected to a gradual temperature ramp from room temperature to a higher temperature, such as 500-800°C, at a constant heating rate (e.g., 5-10°C/min).TGA results manifest the less volatile nature of the film till 200°C.CDD film showed minimum weight loss till 200°C and started to increase beyond this temperature. From 200°C to 300°C, an abrupt change in the weight was observed. This manifests that the CDD patch is stable till a temperature range of 200°C.

Chapter 5: Discussion

Hypertension, also referred to as high blood pressure, is a common chronic medical condition marked by excessive blood pressure levels. It affects millions of people globally and poses a serious risk for renal problems, stroke, and cardiovascular diseases. To lower the related health risks and enhance patient outcomes, hypertension must be effectively managed [79]. Traditional treatments for hypertension include pharmacotherapy, which frequently involves oral drugs and lifestyle changes [80]. When lifestyle modifications alone prove to be inadequate, the initiation of pharmacotherapy is considered. Hypertension is frequently managed through a prescribed dosage of oral medications, including angiotensin-converting enzyme (ACE) inhibitors, diuretics angiotensin receptor blockers (ARBs), beta-blockers, and calcium channel blockers (CCBs) [81]. Despite the demonstrated effectiveness of these medications, they are accompanied by a range of constraints, such as suboptimal adherence, potential side effects, and the requirement for frequent administration [82]. In recent years, however, the development of transdermal patches as a novel drug delivery system has received increased attention due to their potential benefits. Transdermal drug delivery systems, such as transdermal patches, have been identified as a feasible alternative for the management of hypertension. These transdermal patches offer a non-invasive and convenient approach to drug delivery, facilitating the controlled and extended release of medication into the systemic circulation via the skin. Transdermal patches have the ability to minimize first-pass metabolism and enhance bioavailability by circumventing the gastrointestinal tract [83].

Losartan Potassium acts as ARBS and is highly soluble in water. This anti-hypertensive drug shows poor gastrointestinal absorption and low oral bioavailability [84]. These were the limitations and the proposed problems that were to be overcome through our study.

Six formulations in two different solvents, DMSO and NaOH were formulated for the patch matrix composition and were comparatively studied to screen the most appropriate formulation. The comparative study was performed based on physical parameters, dissolution studies, drug release profiles, and material characterization analysis, including Scanning Electron Microscopy, Tensile Strength analysis, FTIR spectrometry analysis, X-RAY Diffraction analysis, Thermogravimetric Analysis, and Leaching Test.

Physical Parameters were measured through Digital Microscope (1000X), pinpointing CMC-containing patches being selected due to being thinner and smoother in nature. The thinner the patch film, the easier would be its dissolution. Dissolution studies in acidic Ph also indicated that CMC-containing patches dissolved more easily as compared to other patch formulations. Whereas the drug release profile of all the patches manifested drug release over a time period, CMC-containing, CDD manifested drug release at a steady rate. Based upon all these parameters, CMC-containing formulations in both the solvents, DMSO and NaOH were selected for further material characterizations.

Mechanical Strength Analysis was performed by the standard method ASTM D638 was used in order to check the ultimate tensile strength of all the films. CDC showed good mechanical properties and was elastic in nature while CNC did not show any good mechanical properties. FTIR and XRD analysis was performed to confirm the intervention or possibility of the drug in the polymer film of the CMC-containing patches. And both analyses manifested positive results, confirming the presence of the drug in the patch.

Screening based on physicochemical analysis, a CMC-containing patch in DMSO, was found to be to more appropriate formulation for the patch matrix and was further tested for the leaching analysis as well as for the thermogravimetric analysis, to ensure the safety and stability of the patch.

Chapter 6: Conclusion

Transdermal patches have emerged as a promising antihypertensive drug delivery method. They have a number of benefits over standard oral drugs, such as higher patient compliance, fewer adverse effects, and a more stable drug release profile. Transdermal patches are a non-intrusive and convenient method of administering drugs, as they reduce the frequency of dosing and minimize the chance of drug concentration variations. Developing transdermal patches requires careful consideration of drug properties, formulation design, and patch characteristics to assure optimal drug delivery. So, for the optimization of the patch matrix, six formulations were developed in two different solvents, DMSO and NaOH. Both DMSO group formulations and NaOH group formulations were comparatively studied.

Table 3. Comparison of DMSO group films with NaOH group films

DMSO Group	NaOH Group
Smoother surface	Rougher surface
Thicker film	Thinner film
Regular drug release profile	Irregular drug release profile
High mechanical strength	Low mechanical strength

Both groups were studied based on physical and chemical analysis, and CMC-containing formulations i.e. CDD and CND showed the most appropriate results for further characterizations. By keeping in view the results of material characterization, and in-vito results carried out till now, it can be proposed that CDD, (CMC- containing formulation in DMSO solvent) is a better candidate to be used for the matrix of anti-hypertensive patch.

In conclusion, transdermal patches have emerged as a potentially effective substitute for the administration of antihypertensive drugs. Although more studies and development are required to improve their effectiveness and overcome potential limitations, transdermal patches exhibit significant potential in the management of hypertension and the enhancement of patient outcomes.

6.1 Limitations and Future Aspects

- This research was limited to In-vitro analysis and material characterization, in-vivo analysis is still required.
- Through this research, it was examined the drug release profiles of different composite formulations, but the quantification of drug release is yet to be explored.
- Proper quantification of the drug release and permeation testing through the Franz-diffusion cell is still needed.
- Synthetic adhesive material is used, effect of natural-based adhesive material is still needed to be studied.
- Despite the fact that transdermal patches normally have fewer adverse effects than tablets or injectables, they may cause skin irritation due to the adhesive or the drug they contain.
- Additionally, not all drugs can be administered through transdermal route.
- More research is still needed to explore all the aspects of transdermal delivery system and to further improve it.

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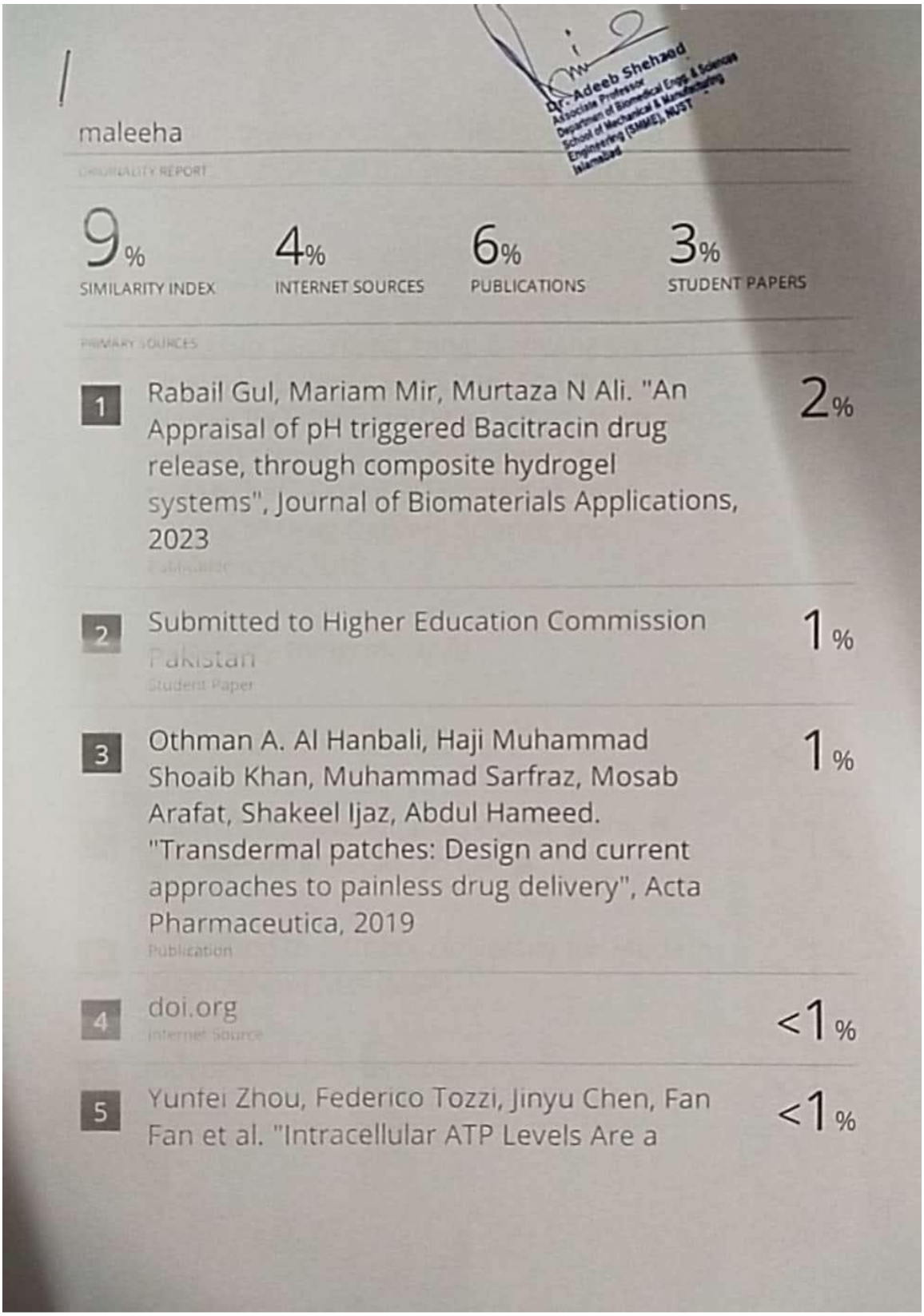

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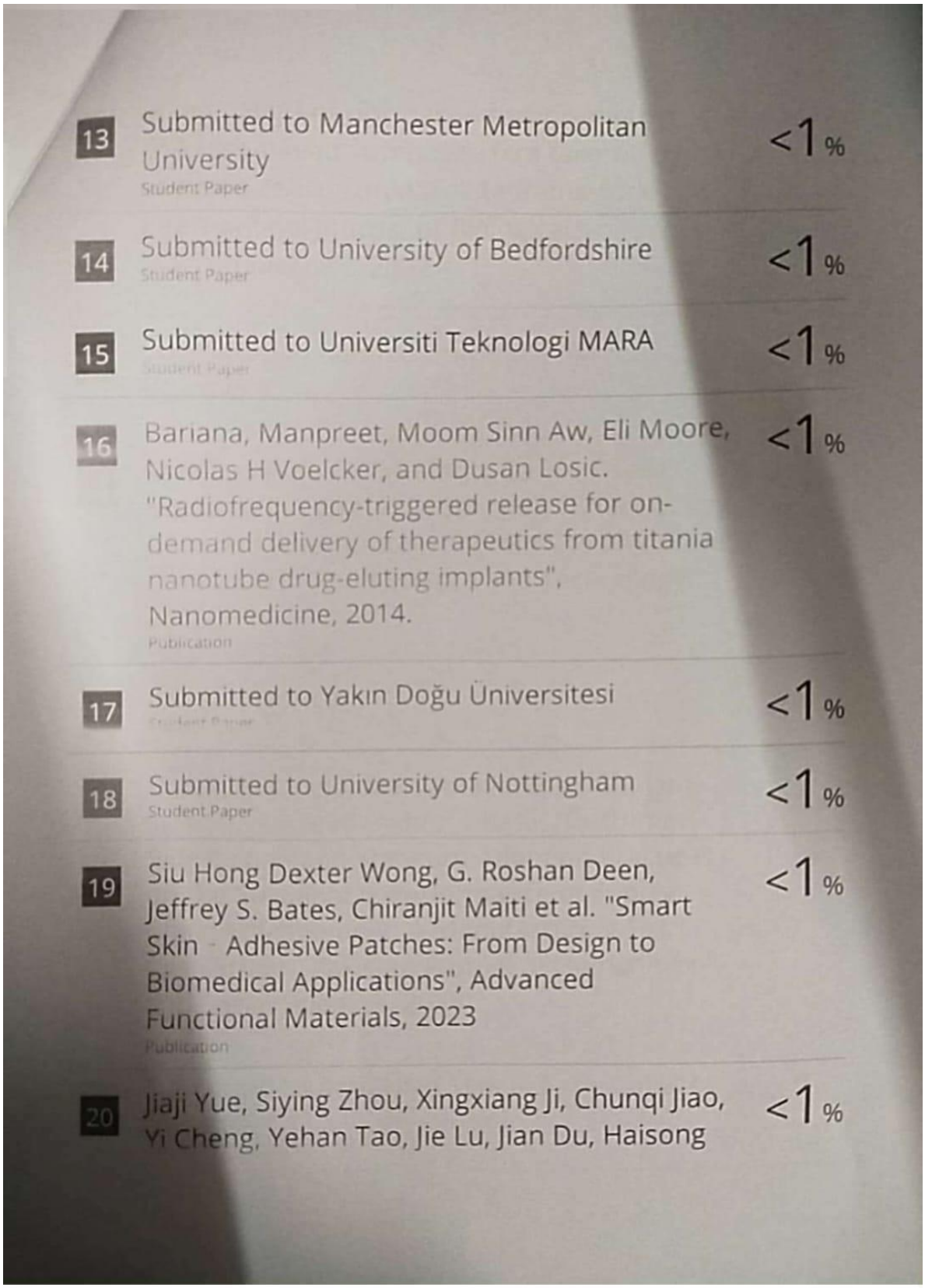

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