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REVIEW STUDIES ON THE FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF SOME ANTINEOPLASTIC DRUGS

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ABSTRACT: Cancer refers to a group of diseases characterized by abnormal, unchecked cell growth that spreads to other body parts. Breast, liver, colorectal, kidney, stomach, lungs, and cervical cancer are the most common tumours, with skin cancer (excluding melanoma) being the least common (contributing up to 40 percent of the cases). Surgery, chemotherapy, and other traditional medical methods have several negative side effects, including extreme inflammation and discomfort. As a result, transdermal delivery of the anticancer drug transdermal patch may be beneficial for treating multiple breast cancers via the skin. Transdermal drug penetration using various methods, such as nanocarriers, tactile penetration enhancing tools, chemical penetration enhancers, and newer innovations, such as gels, dendrimers, needle-free injection jets and so on, results in increased patient compliance, scar elimination, and economic benefit. Topical antineoplastic drug delivery is a popular option for increasing site-specific delivery, mitigating side effects, and enhancing therapeutic effects. This study aims to discuss the transdermal delivery of anticancer agents via the skin, which can open up a new frontier in cancer care using nanocarriers.

INTRODUCTION:

Cancer: Cancer is a broad term for a group of diseases characterized by uncontrolled cell growth that spreads throughout the body. The most common cancers are lung, liver, colorectal, prostate, thyroid, breast, and cervical cancers, with skin cancer (excluding melanoma) being the least common (contributing up to 40 percentage of the cases). Surgery and chemotherapy, for example, have many unpleasant side effects, including severe inflammation and discomfort. New transdermal procedures and methods have been established by transporting into the deeper tissues of the skin. Transdermal drug penetration using various technologies, such as nanocarriers, penetration enhancement using essential oils and chemicals and newer technologies, such as liposomes, nanogels, dendrimers, and microneedle leads to improved medication enforcement, scar removal and cost savings. Topical antineoplastic drug delivery is a common way to improve site-specific delivery, reduce side effects, and improve therapeutic effects.

This study aims to develop a transdermal patch that can be used to deliver anticancer drugs transdermally through the skin, which has the potential to open up a new era of cancer treatment [20]. Pravin Shende *et al.*, (2018) [20] have found that Cancer was discovered to be the most prominent family of diseases involving irregular unchecked cell growth that spreads to other parts of the body.

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He observed that Standard medical strategies, such as surgery and chemotherapy, had various detrimental side effects, including extreme inflammation and pain. As a result, found that the antineoplastic agents can be used in pharmacotherapeutic methods to treat a variety of cancers through the skin and to overcome this constraint, new transdermal methods and preparations had arisen in which the transdermal drug penetration using multiple methods, such as nanocarriers, tactile penetration enhancing strategies, chemical penetration enhancers and newer innovations such as gels, dendrimers, needle-free injection jets, and so on results in increased patient compliance, scar removal, and economic benefit.

Finally, it concludes that topical antineoplastic drug delivery was a popular option for increasing site-specific delivery, mitigating side effects, and enhancing therapeutic effects. His aim for this analysis was to provide information on pharmacotherapeutic approaches that can be used to distribute anticancer agents transdermally through the skin, as it could open up a new frontier in cancer treatment. (Shende *et al.* 2018) [29, 30] explored that Cancer is a life-threatening disease contributing to 3.4 million deaths worldwide.

There are various causes of cancer, such as smoking, being overweight or obese, intake of processed meat, radiation, family history, stress, environmental factors, and chance. The first-line treatment of cancer is the surgical removal of solid tumours, radiation therapy, and chemotherapy. The systemic administration of the free drug is considered the main clinical failure of chemotherapy in cancer treatment, as limited drug concentration reaches the tumour site. Most active pharmaceutical ingredients (APIs) used in chemotherapy are highly cytotoxic to cancer and normal cells. Accordingly, targeting the tumour vasculatures is essential for tumour treatment. In this context, encapsulation of anti-cancer drugs within the liposomal system offers secure platforms for the targeted delivery of anti-cancer drugs for cancer treatment. This, in turn, can help reduce the cytotoxic side effects of anti-cancer drugs on normal cells and focuses on the use of liposomes in anti-cancer drug delivery (Olusanya *et al.* 2018).

Skin: Historically, the skin was considered a simple homogenous barrier. However, it is now known to be a highly specialized organ and plays a key role in homeostasis. The epidermis's outermost layer provides the skin's protective properties, safeguarding against chemical, microbial, and physical attacks. The exceptional barrier properties of the skin result in it being a challenging route for the delivery of therapeutic agents. This article reviews strategies developed to enhance the skin penetration of drugs, ranging from conventional approaches, such as chemical penetration enhancers, to those in early-stage development; the human skin is an easily available drug delivery surface. An ideal adult's skin has a surface area of about 2 m2 and receives about one-third of the blood that circulates in the body. Regulated drug delivery has become increasingly relevant in pharma companies over the last 30 years. Per square centimeter of human skin contains an average of 10-70 hair follicles and 200-250 sweat ducts. It is one of the human body's very easily accessible organs.

The ability to use intact skin to administer drugs to the human body has been investigated for many years. Still, the skin is a difficult barrier to the penetration of materials, allowing only limited amounts of a drug to absorb over time. The number of drugs formulated in patches has barely increased over the last decade, and the patch systems have remained relatively unchanged. The majority of the changes have been to optimize the materials used. The identification of drug candidates suitable for formulation as a Transdermal device and the evaluation methods is discussed in this article [92].

The human body's largest organ, the skin, plays a critical role in opioid permeation and penetration. Furthermore, the transdermal drug delivery system (TDDS) is critical for treating dermal diseases and maintaining plasma drug concentrations. To improve TDDS for human use, assessing the drug's percutaneous penetration through the skin is essential. In treating these dermal conditions, various procedures are used to achieve optimal drug entry, permeation, and absorption through the skin. In today's world, the invention of novel prescription dosage formulations for dermal use is a hot topic.

It is, however, critical to assess these approaches to ascertain the bioequivalence and risk of these topically applied products, which eventually enter and are absorbed through the skin. Many skin permeation models are currently being developed and convincingly used in the study of Dermato- the pharmacokinetic (DPK) profile. Different models have been developed to test the TDDS, including *ex-vivo* human skin, *ex-vivo* animal skin, and artificial or reconstructed skin models. The general physiology of the skin, the physiochemical characteristics impacting particle penetration, understanding the models used for human skin permeation experiments, and understanding their implications are all covered in this study [6].

Transdermal Approach: Transdermal drug delivery is a validated technology that contributes significantly to global pharmaceutical care. Since 1980, impressive growth in this field has been observed with many commercial successes; importantly, a new chemical entity was recently developed and approved for transdermal administration without being given in an injectable or oral dosage form. The progress achieved has been based on a clearer understanding of skin barrier function and the physicochemical, pharmacokinetic and physiological factors underpinning the feasibility of transdermal administration. Novel, non-invasive approaches to enhance and control drug transport across the skin are under intensive investigation, and some technologies, *e.g.,* iontophoresis, have reached true maturity. The "local", subcutaneous delivery of drugs (for example, to underlying muscle and other tissues) is gaining increasing acceptance, and new opportunities in this under-subscribed area may be envisaged (Guy 2010).

The transdermal route of administration is a new approach to administering systemic drugs that has several benefits over traditional routes. TDDS is a more expensive alternative to the traditional formulation. It's also significant because of its one-of-a-kind benefit. Regulated absorption, more stable plasma levels, enhanced bioavailability, reduced side effects, painless and fast treatment, and the ease of stopping drug administration by easily removing the patch from the skin are all potential advantages of transdermal drug delivery. The design of a controlled-release transdermal dosage approach is a time-consuming and labor-intensive process. The methods for preparing various forms of transdermal patches are described in this review article [37].

Furthermore, the various methods of transdermal dosage type assessment and advanced growth of TDDS have been studied. Traditional oral delivery formulations have considerable disadvantages, such as low bioavailability owing to hepatic first-pass digestion and a propensity to contain a large fraction of the opioid in the systemic blood supply, necessitating elevated or regular dosing may be both costly and uncomfortable. To address these issues, the transdermal drug delivery system (TDDS) was developed, which would increase the clinical effectiveness and safety of medications by allowing for more accurate (i.e., location-specific) positioning inside the body, minimizing both the size and number of doses. Many medications are now taken orally, but they are not as successful as they can be. To address these issues, a transdermal drug delivery system was created [72].

This article discusses the transdermal drug delivery system and different types of transdermal patches, including the use of polymer as a transdermal drug delivery system, preparation methods, physicochemical evaluation techniques, and the various types of transdermal systems currently on the market. A transdermal patch is a medicated adhesive patch that is applied to the skin and used to inject a particular dosage of the drug into the bloodstream through the skin. This also aids in the recovery of an infected body part.

The patch enables for the secure delivery of medication into the patient, either through a porous membrane surrounding a reservoir of medication or through body temperature melting thin layers of medication embedded in the adhesive, which is a benefit of transdermal drug delivery above other methods such as oral, topical, intravenous, intramuscular, and so on. Transdermal medication delivery allows for regulated drug release into the patient's bloodstream, resulting in less clinical side effects and, in certain cases, increased effectiveness over other treatment types. The key goal of a transdermal drug delivery system is to inject medications into the systemic bloodstream *via* the

skin at a fixed rate with limited differences within and within patients [51].

The factors influencing the suitability of a drug for TDDS are as follows 102:

The potency of the drug - the daily systemic dose should be 20 mg.

- Molecular size - the drug should have an MW of <500 Daltons.
- Lipophilicity - the log P should be in the range 1-3.
- Melting point - should be <200 °C.
- Hydrogen bonding groups should be 2.
- Irritation - the drug should not be directly irritant to the skin.
- Immunogenicity - the drug should not stimulate an immune reaction in the skin.

A predictive rule of thumb is that the maximum flux of drug through the skin should decrease by a factor of 5 for an increase of 100 Da in MW and decrease by a factor of 10 for an increase of 100 °C in melting point. While transdermal drug delivery has made a major improvement to modern medicine, it has yet to achieve its goals as a substitute for oral drug delivery and hypodermic injections.

The clinical use of first-generation transdermal delivery systems for the delivery of thin, lipophilic, low-dose drugs has increased steadily.Second-generation delivery systems like chemical enhancers, noncavitational ultrasound, and iontophoresis are always used to build clinical devices; the capacity of iontophoresis to track delivery rates in a timely manner improves versatility.

Micro needles, thermal ablation, microdermabrasion, electroporation, and cavitational ultrasound are all used in third-generation delivery systems to target the stratum corneum's boundary layer. Micro needles and thermal ablation are being tested in clinical trials to produce macromolecules and vaccines, including insulin, parathyroid hormone, and influenza. Transdermal transmission is poised to dramatically improve its effects on medication using these innovative second- and third-generation enhancement techniques [98]. Patches, often known as transdermal drug delivery systems (TDDS), are dosage types that distribute a therapeutically beneficial volume of the drug through the skin. The detailed morphological, biophysical, and physicochemical properties of the skin must be considered in terms of delivering therapeutic agents across the human skin for targeted delivery. Transdermal delivery is advantageous over injectable and oral routes because it improves patient compliance and avoids first-pass metabolism. Transdermal delivery not only allows for controlled, consistent drug administration but also provides input of drugs with short biological half-lives and prevents pulsed entry into the circulatory system, which may result in unwanted side effects.

As a ready guide for research scientists interested in TDDS, the article provides useful information about TDDS and its assessment process specifics. With technological advancements, the pharmaceutical industry has modernized all of its resources. Previously, we used a convectional dosage form; however, we now use a novel drug delivery method. Transdermal patches are one of the most innovative forms of novel drug delivery, and their benefit is a painless technique of administration of drugs [54]. Kashmira Kathe *et al*., (2017) [36] investigated that for both local and systemic effects, the skin was thought to be an effective route of drug administration.

The effectiveness of topical therapy is determined by the drug's physicochemical properties, the patient's adherence to the treatment regimen, and the system's adherence to the surface during therapy to promote drug penetration. It was discovered that traditional formulations for topical and dermatological administration of drugs have some limitations, such as the inability to penetrate the skin barrier. Topical film-forming systems bind to the body, forming a thin transparent film that delivers active ingredients to body tissue. These were intended as an emollient or protective agent on the skin and for local or transdermal administration of systemic medication. Transparency was a notable characteristic of the polymeric scheme, and it significantly impacted patient acceptance. Finally, film-forming systems

were promising for topical and transdermal drug delivery. The different forms of film-forming systems (sprays/solutions, gels, and emulsions) have also been examined, and their assessment parameters [36]. Sevgi Gungor *et al.*, (2012) [78] have found that transdermal delivery was one of the non-invasive methods for drug administration and realized that Patient compliance was improved and continuous, sustained release of drug was achieved by following the application of transdermal formulation on the skin. Patches, or transdermal drug delivery systems, are dosage forms that distribute a therapeutically effective volume of the drug through a patient's skin at a specified time and pace. Transdermal drug delivery systems can be divided into three main groups: a) adhesive systems, in which the drug is in adhesive, b) matrix-type systems, in which the drug is in a matrix polymer; and c) reservoir systems.

Although there was a difference in the design of transdermal therapeutic systems, several features were common to all systems, including the release liner, the pressure-sensitive adhesive, and the backing layer. There were three critical considerations in selecting a transdermal drug delivery system: adhesion to the skin, compatibility with the skin, and physical or chemical stability of total formulation and components. The adhesiveness of the patches was vital to the product's protection, effectiveness, and consistency. Therefore the three important performance tests to monitor the adhesive performance of patches were tack, shear strength, and peel adhesion.

The choice and design of polymers, adhesives, penetration enhancers, and plasticizers in transdermal patches were also critical because they strongly affected drug release, permeability, stability, elasticity, and wearing properties of transdermal drug delivery systems. He made several considerations in the optimization of a transdermal drug delivery system. The choice and design of polymers, adhesives, penetration enhancers, and plasticizers in transdermal systems were crucial for drug release characteristics as well as the mechanical properties of the formulation [78]. Syeda Ayesha Fathima *et al.*, (2017) [34] investigated common drug formulations that necessitate multidose treatment, with a slew of issues and disadvantages. The design of standard dosage forms should ensure that the correct quantity of medication was administered to the target site correctly.

Apart from medicinal effectiveness, it was the cause of inspiration for the advancement of new drug delivery systems. Redesigning the unit and means was a challenging and lucrative process, so a managed released drug delivery device, a novel drug delivery system, occurs that allows the drug to be released at a fixed pace. Transdermal drug delivery systems, which distribute drugs via the skin to the systemic circulation, may provide controlled drug delivery (Fathima *et al.* 2017). Transdermal patches are also commonly used as surgical, oral, and transdermal delivery devices.

These patches are an important step forward in skin science, technology, and practice, and they were developed through trial and error, clinical research, and evidence-based trials that date back to the dawn of time. This investigation begins with the earliest topical therapies and advances via topical delivery to today's transdermal patches, identifying the early trials, technologies, and drug delivery mechanisms that underpin current transdermal patches and their actives. Following that, the evolutions of various patch designs, their limitations, and the requirements for actives to be used for transdermal delivery are discussed. The properties of currently marketed goods and issues associated with their use, such as variability, protection, and regulatory aspects, are then identified.

The study concludes by discussing the potential of transdermal patches and drug delivery methods through active delivery systems with patches, non-invasive microneedle patches, and cutaneous approaches, such as metered dosage systems [55]. Adherence to prescription psychiatric and nonpsychiatric medicine is a significant problem for individuals with mental illnesses and can lead to negative health effects. Adherence is influenced by various factors, including prescription side effects and ease of use. There is to be a renewed interest in solving challenging dilemmas of protection and commitment to medication as behavioural healthcare gradually focuses on a community paradigm of health delivery. Any of these issues may be solved by using new means of efficiently

administering drugs in novel ways. In the published literature, there has been no mention of the broader application of transdermal patches in psychiatry. This article summarises research results on core concepts driving transdermal distribution mechanisms and the extent of therapeutic application in mental disease, difficulties and benefits [76].

Penetration Enhancersused in TDDS: Properties of an Ideal Penetration Enhancer (Finnin and Morgan 1999)

- Pharmacologically inert.
- Nontoxic, nonirritating, and nonallergenic.
- Rapid onset of action; predictable and suitable duration of action for the drug used.
- Following removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property.
- The skin's barrier function should decrease in one direction only, and the efflux of endogenous materials should not occur.
- Chemically and physically compatible with the delivery system.
- Readily incorporated into the delivery system.
- Inexpensive and cosmetically acceptable.

The transdermal drug delivery route is evolving as a potential route due to its advantages of bypassing the hepatic first-pass metabolism, decreasing side effects and gastrointestinal effects, improving patient compliance as it is a pain-free self-administration for patients, etc. The major setback in this route is the difficulty of the drugs penetrating through the skin, as the stratum corneum (outermost layer of the skin) forms a protective barrier for the underlying tissues from the outer environment. A transdermally delivered drug can only show its action when it can cross the transdermal barrier to reach the systemic circulation help in doing that; the penetration enhancer is the agent which increases the permeability of the skin, which in return maintains the drug level in the blood. Permeation enhancers can be of a chemical type, natural type, and physical type. The present review describes the natural permeation enhancers that can be which be employed for the transdermal permeation of drugs [35]. Natural penetration enhancers have become common because they have many advantages over synthetic alternatives. These include sustainable mass processing from a renewable resource and lower costs based on the extraction method used [86]. The transdermal drug delivery system is an administration route where active molecules are administered through the skin with the advantages of a lesser amount of hepatic first-pass effect, constant plasma drug concentration, and safety. The skin has a barrier function for the passage of medicines and toxic molecules; thus, permeation boosters/enhancers are used to increase medication permeability through the skin. This mini-review reviews recent studies on essential oils that can be used to increase skin penetration in transdermal applications and the possible mechanisms of their effects. Essential oils increase skin penetration by interacting with the stratum corneum (SC).

They were found to be successful in increasing skin penetration of both lipophilic and hydrophilic drugs. Moreover, essential oils do not accumulate in the body since they are volatile and are easily discharged from the body through feces and urine. They are preferred because essential oils are natural, mostly do not damage the skin while increasing skin penetration, are less toxic, and are less allergenic [5]. Tulsi and turpentine oil were evaluated for their ability to increase flurbiprofen transdermal delivery. Flurbiprofen transdermal permeation via the rat abdominal skin was 98.88μg/cm2/h from a binary solvent mixture of propylene glycol (PG): isopropyl alcohol (IPA) (30:70 percent, v/v), which was significantly higher than that of other binary solvent combinations. The 0.71 microg/ml steady-state plasma concentration was substantially lower than the required 3-5 μg/ml steady state plasma concentration.

Consequently, the effects of tulsi and turpentine oil in the standardized binary solvent mixture on flurbiprofen permeation, including the increased drug load, were examined. The flux enhancement factors for turpentine oil and tulsi oil were 2.4 and 2.0, respectively, at a concentration of 5% (v/v); above that, there was no considerable rise in flux. The inclusion of 2% (w/v) HPMC as a thickening

agent gave the patch the necessary consistency while not affecting flurbiprofen permeation volume. The reservoir form of transdermal patch product, which was made by encapsulating the flurbiprofen reservoir solution within a deep compartment made of polyester backing film and micro porous ethyl vinyl acetate membrane, had no effect on flurbiprofen skin permeation by rat skin. Still, flux of formulations containing tulsi oil did.

The effects of penetration enhancers and solvents on the rat skin's anatomical structure were investigated. Unlike solvent-treated and regular control classes, turpentine oil and tulsi oil in an optimized binary solvent mixture has outstanding enhancement properties with reduced skin irritation. The transdermal patches that were developed were discovered to be safe. Compared to orally administered flurbiprofen, the bioavailability of transdermal patch formulations lacking enhancer, tulsi, and turpentine oil formulations improved by 2.97, 3.80, and 5.56 times among albino rats, respectively. Pharmacodynamic experiments in rats with edema supported the findings [100].

Patel and Jani, 2016 [47] investigations aim to formulate and evaluate the biopharmaceutical behaviours of the matrix patch containing Diltiazem hydrochloride (DH) with an attempt to use natural oils as permeation enhancers for transdermal applications. Transdermal patch prepared using 3^2 full factorial designs by solvent evaporation technique by incorporating propylene glycol as plasticizer and ethanol as solvent. Fourier transform infrared spectroscopy (FTIR) was employed to study drug and excipients incompatibility that showed the absence of any chemical interaction. Prepared patches evaluated for physicochemical parameters such as tensile strength, percent elongation, folding endurance, flatness, thickness, hardness, weight variation, percentage moisture loss and uptake, *ex-vivo* permeation study, *in-vivo* skin irritation study, and stability study. The physicochemical and *ex-vivo* permeation studies indicated that Batch A2 containing HPMC K15M and psyllium in the ratio of 2:1 was better compared to all nine batches of factorial designs. Tensile strength, percent elongation, and folding endurance were found to be 4.48 kg/mm2, 21.84±0.335 and 384±3.21, respectively, which showed good mechanical properties of the prepared patch. Penetration enhancing capacity of natural oils (pumpkin seed oil, jojoba oil, tea tree oil, cumin oil, and linseed oil) was determined by performing an *ex-vivo* study using wistar-rat skin. A maximum steady-state skin permeation flux of 239 µg/cm2/h was achieved in batch A2, which contains 20%w/w of pumpkin seed oil.

The highest flux results revealed that pumpkin seed oil enhances the drug's permeation through the skin compared to all essential oils. The release kinetics indicates that the release pattern was diffusion controlled and it follows Higuchi and zero order kinetics. The skin irritation study performed on wistar-rats revealed that the patch was not irritating the skin after 24 h. A stability study was performed according to ICH guidelines and it showed that the transdermal patch of DH containing natural oil was stable at accelerated conditions for six months. This research suggested that transdermal applications of DH improved patient compliance and were a very good alternative to oral administration of DH for the treatment of hypertension [47].

Transdermal drug delivery has been recognized as a possible non-invasive route of drug administration, with benefits such as sustained therapeutic action, reduced side effects, ease of use, and improved patient compliance. However, the development of transdermal products is primarily hindered by the low permeability of the skin. Numerous new chemicals have been synthesized as potential permeation enhancers for transdermal drug delivery to overcome this barrier effect. In this review, we presented an overview of the investigations in this field, and further implications on the selection or design of suitable permeation enhancers for transdermal drug delivery were also discussed [66]. The skin is an important location for drug application for both local and systemic effects.

On the other hand, the stratum corneum is the primary barrier to drug penetration in the skin. Penetration enhancement technology is a difficult advancement that will expand the amount of medications that can be administered transdermally. Chemical and physical methods can also improve drug penetration through the skin. In this study, we addressed chemical penetration

enhancement technology for transdermal drug delivery and possible mechanisms of action. Chemical penetration enhancers are chemical substances that temporarily diminish the skin's barrier and known as accelerants or sorption promoters can enhance drug flux. Several types of enhancers are known Sulphoxides and similar chemicals such as Dimethyl sulphoxides (DMSO), Azone (1-dodecylazacycloheptan-2-one or laurocapran), Pyrrolidones, Fatty acids, Essential oil, terpenes and terpenoids, Oxazolidinones and Urea [96].

Detailed optimization process was carried out to enhance permeation parameters and hence bioavailability, of simvastatin (SMV) transdermal films. SMV solubility was investigated in various oils, surfactants and co-surfactants/ co-solvents. Mixtures of the selected components were prepared to identify zone of nanoemulsion formation that was utilized in Extreme Vertices mixture design to develop SMV self-nanoemulsifying drug delivery systems (SNEDDS) with minimum globule size. Optimized SMV-SNEDDS were included in the preparation of transdermal films. A fractional factorial design was implemented to evaluate effects of the factors on the amount of SMV permeated. The optimized film was investigated for *ex-vivo* skin permeation and *in-vivo* pharmacokinetic parameters.

The optimum SNEDDS formula was 0.09, 0.8 and 0.11 for Sefsol 218, tween 80 and PEG 200, respectively. Fractional factorial design depicted the optimized SMV transdermal film with 2% HPMC and 2% DMSO as permeation enhancer that showed 1.82-fold improvements in skin flux. The pharmacokinetic data showed higher Cmax and almost doubled AUC compared with raw SMV-loaded films. The two-step optimization implemented to optimize and control the experimental conditions for the preparation of SMV-SNEDDS-transdermal film with improved *ex-vivo* skin permeation and enhanced *in-vivo* parameters. (El-Say *et al.* 2015) [57] Anna Otterbach *et al.,* (2021) have found that Dimethyl sulfoxide was a well-known and widely used dermal penetration enhancer and its incorporation in transdermal patches would be highly desirable; however, due to its volatility this was extremely challenging. Here, they reported on the feasibility of a dimethyl sulfoxide (DMSO) containing transdermal system containing estradiol as a model compound. Transdermal patches were prepared from duro-tak 387-2510 containing various DMSO concentrations at different drying temperatures. The resulting patches were analyzed for DMSO content, estradiol and DMSO release, estradiol and DMSO permeation through excised porcine skin and recrystallization during stability testing. He found that drying conditions at 35° to 40° allowed a complete polymer solvent removal while retaining significant amounts of DMSO (≤10 mg/patch).

Estradiol skin permeation increased 4- fold (Jss = 4.12 µg/cm−2 ·h −1) compared to DMSO-negative control (Jss = 1.1 ± 0.2 µg/cm−2 ·h −1). As an additional benefit, estradiol recrystallization was inhibited by DMSO at even the lowest solvent concentrations. He found that Storage stability was limited to 6 months at 25 °C with a surprising discrepancy between DMSO content (significantly lower) and flux (not significantly different). Although the technical feasibility range was relatively narrow, they concluded that such DMSO-containing matrix-type patches could significantly enhance drug permeation through the skin while ameliorating the product stability against recrystallization.

(Otterbach and Lamprecht 2021) [1-7] has investigated that the advent of the transdermal approach led to overcoming drawbacks of conventional dosage forms where the skin is the only barrier to the delivery of drugs through the transdermal route. He realized that the role of penetration enhancers thus becomes commendable as they reversibly alter skin permeation characteristics, assisting transdermal devices in transporting drugs across the skin. The commonly used penetration enhancers were sulfoxides, azones, pyrorroidones, alcohols and alkanols, glycols, surfactants, and terpenes. Finally, he aimed to describe the effect of various penetration enhancers on drug permeation across skin through the transdermal route, which had been used in recent studies and reporting the penetration enhancer that best improves the drug flux [7] Karrie Marren *et al.,* (2011) [87] have explained that Dimethyl sulfoxide (DMSO) was a molecule with a long history in pharmaceutics and was now well established as a penetration enhancer in topical

pharmaceutical formulations. It was currently used in diclofenac sodium topical solution (approved in the United States to treat signs and symptoms of osteoarthritis) and idoxuridine topical solution (approved in Europe for treating herpes zoster). He reviewed the mechanism of action of DMSO as a pharmaceutical penetration enhancer, the characteristics of the molecule that facilitate transdermal drug delivery, and studies of efficacy and safety.

The clinical use of pharmaceutical-grade DMSO as a penetration enhancer was supported by the robust data accumulated over the past 3 decades demonstrating the favourable safety and tolerability profile. Lastly, Dimethyl sulfoxide was a safe and effective mechanism for facilitating the transdermal delivery of hydrophilic and lipophilic medications to provide localized drug delivery. (Marren 2011) Somnath D [87, 16] had an objective to compare and verify the efficacy of Aloe Vera (1 to 3 %) with dimethyl sulfoxide (1 to 3 %) for its penetration-enhancing property for topical delivery of lidocaine.

Carbopol 934 as a gelling agent was used for the preparation of lidocaine gel formulations containing or not dimethylsulfoxide or *Aloe vera* (1%, 2%, and 3%) and evaluated the Gels for physical appearance, rheological behaviour, drug content, drug release and stability. Finally, obtained gel formulations that were good in appearance, homogeneity, and consistency and also the *in-vitro* drug release profiles showed that concentrations of Aloe Vera gel increased in formulations, and the drug release rate increased substantially. It was also observed that the F6 formulation comprised of 3% Aloe Vera as a permeation enhancer exhibited 79.18 % of drug release. Similarly, for formulation F3, which comprised 3% dimethylsulfoxide as a permeation enhancer, the drug release was found to be 84.52%. The last finding found that the use of Aloe Vera may be beneficial compared to synthetic permeation enhancers. Thus, Based on the results of the study, he concluded that the topical gel of lidocaine prepared along with Carbopol 934 by using *Aloe vera* as a natural penetration enhancer at a concentration of 3% can be used to enhance the penetration for lidocaine across the skin. (Bhinge *et al.* 2019) T.N. Engelbrecht *et al.*, (2012) elucidated the mode of action of the lipophilic penetration enhancer isopropyl myristate (IPM) on a molecular scale. They investigated oriented quaternary stratum corneum (SC) lipid model membranes based on ceramide AP, cholesterol, palmitic acid, and cholesterol sulphate containing 10 wt.% IPM using neutron diffraction. His result indicates that IPM affects the lamellar lipid assembly in terms of bilayer perturbation and disordering, then Phase segregation occurs, which indicates that IPM was not likely to mix properly with the other SC lipids due to its branched structure.

He used selective deuterium labeling to localize the penetration enhancer and could successfully prove the presence of IPM in the two coexisting lamellar phases. Finally, he concluded that IPM's mode of action as a penetration promoter was presumably based on incorporation into the SC lipid matrix, extraction of certain SC lipids into a separate phase, and perturbation of the multilamellar lipid assembly [75]. Chunyi Zhao *et al.*, (2016) [44] investigated the effect of isopropyl myristate (IPM), a penetration enhancer, on the viscoelasticity and drug release of a drug-in-adhesive transdermal patch containing blonanserin.

They prepared the patches with DURO-TAKs 87-2287 as a pressure-sensitive adhesive (PSA) containing 5% (w/w) of blonanserin and different concentrations of IPM. And *in-vitro* release experiment was performed with the adhesive performance of the drug-in-adhesive patches with different concentrations of IPM was evaluated by a rolling ball tack test and a shear-adhesion test. The glass transition temperature (Tg) and rheological parameters of the drug-in-adhesive layers were determined to study the effect of IPM on the mechanical properties of the PSA. Finally, the results of the *in-vitro* release experiment showed that the release rate of blonanserin increased with an increasing concentration of IPM. In contrast, the rolling ball tack and shear-adhesion tests showed decreasing values with increasing IPM concentration. The results were interpreted based on the IPM-induced plasticization of the PSA, as evidenced by a depression of the glass transition temperature and a decrease in the elastic modulus. Finally, they found that IPM acted as a plasticizer on DURO-TAKs 87-2287, and it increased the release of blonanserin and affected the adhesive properties of the PSA. (Zhao *et al.* 2016) Ziyi

Wen, *et al.,* (2009) [97] examined the percutaneous absorption properties of daphnetin with chemical penetration enhancers to explore the feasibility of daphnetin as a candidate for transdermal delivery to treat arthritis.

The Permeation experiments were carried out *in-vitro* using 2-chamber diffusion cells in isopropyl myristate (IPM) vehicle using rat abdominal skin as a barrier. Various enhancers were employed, including O-acylmenthol derivatives synthesized in the laboratory and many conventional enhancers. Among the O-acylmenthol derivatives, 2-isopropyl-5-methylcyclohexyl 2-hydroxypanoate (M-LA) demonstrated a significant enhancing effect on daphnetin permeation. He found that the highest degree of enhancement was obtained when NMP combined with Span 80 and the cumulative transport was 667.29 μg/cm2 over 8h and the solubility parameters, vehicle/stratum corneum partition, and diffusion coefficients were calculated to clarify the enhancing mechanism of classic enhancers on daphnetin.

Lastly, he concludes that these findings allow a rational approach to designing an effective daphnetin transdermal delivery system. (Wen *et al.* 2009) [97] Mohd. Yasir *et al.,* (2012) [82] explored that many current medicinal, cosmetic, and agrochemical formulations contained surfactants. Surfactants have been used to improve the transdermal permeation rates of many medications in recent years. Because the major barrier to penetration through the skin is correlated with the outermost stratum corneum layer, the transdermal route can only be used for a few medications. Surfactants influence the permeability of various biological membranes, including the skin. They have the ability to break down lipids in the stratum corneum. The partitioning activity and solubility of the surfactant are both important factors in surfactant penetration into the lipid lamellae of the stratum corneum. Surfactants ranging from hydrophobic agents like oleic acid to hydrophilic sodium lauryl sulphate have been tested to boost drug delivery as permeation enhancers. Finally, assess the function of surfactants as permeation enhancers in transdermal drug delivery of a variety of drugs. (Mohd. Yasir *et al.* 2012). Harneet Marwah *et al.,* (2014) [48] explained that 74 percent of medications are taken orally and are not as successful as they should be. Transdermal drug delivery was created to enhance these characteristics. New regulated transdermal drug delivery systems (TDDS) technologies (electrically-based, structure-based, and velocity-based) have been developed and commercialized for the transdermal delivery of problematic drugs and concluded that this delivery system is capable of transporting the drug or macromolecules painlessly through the skin into the blood circulation at a fixed rate [48].

Plasticizers Use in TDDS: Jirapornchai Suksaeree *et al.,* (2013) [62] have found that the natural rubber latex was a colloidal dispersion of polymer particles in a liquid. It was harvested from rubber trees by a tapping process. Synthetic rubber was one type of artificial elastomer mainly synthesized from petroleum by-products. It has good mechanical properties, thermal stability, and compatibility with petroleum products.

It can undergo much more elastic deformation under stress than most materials and can return to its original size without changing permanently. Many drugs taken via the oral route were often ineffective because of the gastrointestinal tract's first-pass metabolism and drug degradation. Thus, he concluded that transdermal drug delivery systems can improve the disadvantage of orally taken drugs. The significant controlled drug must be released into the systemic blood circulation to target organs via the skin. Here the use of rubber polymers in both natural and synthetic rubber types as a material for transdermal drug delivery systems was reported [62, 26] had aimed to prepare the transdermal patches by a solvent casting method using a varying concentration of polymers i.e., methocel (K15 and K100), ethocel (4 and 10), gelatin, chitosan, eudragit (RL and RS) grade using plasticizer (glycerin and propylene glycol). Here she has taken the ratio of drug to polymers and plasticizer, which was varied, and the effect of formulation variables was also studied. Physicochemical properties, *in-vitro* permeation tests, material uniformity, primary skin irritation studies and FT-IR studies were all performed on the prepared transdermal patches and discovered that the transdermal patch created with Methocel K 100 M had good physical properties. The average weight of patches prepared using glycerin as a

plasticizer ranged from 42.33-67.00 mg, and propylene glycol as a plasticizer ranged from 40.67-67.67 mg. Here, moisture absorption varies from 1.76 to 10.73 for patches formulated using glycerin and 2.28 to 7.97 for propylene glycol patches. The percentage moisture loss from patches prepared using glycerin ranged from 2.75 to 11.54 and 2.87 to 12.02 from propylene glycol. The water vapour transmission rate from patches prepared using glycerine ranged from 0.25 to 0.92 and 0.41 to 1.76. The formulated patch showed the acceptable quantity of medicament ranged from (100.20-101.05%).

Finally, that result met the test content uniformity as per BP (85% to 115%). According to that, the drug was consistent throughout the patches. The formulation PGD was considered the best formulation, since it shows a maximum in-vitro drug release of 43.75 % at 24 h and the drug release kinetics study showed that most formulations followed zero order. Finally, controlled-release transdermal drug delivery system patches were created using polymer combinations; the polymer determined each with a different plasticizer and the drug release rate.

However, release kinetics followed zero order. (Sethi and Mazumder 2018) Chetna Modi *et al.,* (2012) [81] studied that transdermal patch fabrication necessitates close attention to the amount of materials used. It was discovered that transdermal patches have different properties and drug releases due to the varied type of polymers and plasticizers used. Finally, the study aimed to determine the amount of diclofenac transdermal patch that would be needed. When used alone or in conjunction with glycerin or PEG-4000 plasticizer, Hydroxy Propyl Methyl Cellulose has a significant impact on transdermal patches, according to a report [81]. Studied that there were several considerations in optimizing a transdermal drug delivery system and the choice and design of polymers, adhesives, penetration enhancers, and plasticizers in transdermal systems are crucial for drug release characteristics as mechanical properties of the formulation. Besides the other components of transdermal patches, plasticizers also significantly change the viscoelastic properties of the polymers. The reasons for the use of plasticizers in transdermal drug delivery systems were the improvement of film-forming properties and the film's appearance, preventing film cracking, increasing film flexibility and obtaining desirable mechanical properties. Finally, he concludes that the plasticizer type selection and the optimization of its concentration in the formulation should be carefully considered (Gungor *et al.* 2012).

Polymers in TDDS: Veeran Gowda Kadajji *et al.*, (2011) [90] Advances in polymer science have resulted in the creation of novel drug delivery systems, according to the findings. Some polymers were obtained from natural resources and then chemically modified for various applications, while others were chemically synthesized and used. A large number of natural and synthetic polymers were available. In that paper, only water-soluble polymers were described. They had been explained in two categories (1) synthetic and (2) natural. Drug polymer conjugates, block copolymers, hydrogels, and other water-soluble drug-polymer complexes have also been explained. He also discussed the general properties and applications of different water-soluble polymers in the formulation of different dosage forms, novel delivery systems, and biomedical applications [90]. Ndidi C. Ngwuluka, *et al.,* (2014) [63] have found that Naturapolyceutics is a new science and technology framework for designing and developing drug delivery systems that combine natural polymers and pharmaceutics.

Natural polymers, he discovered, are promising in this field because of their biological properties, sustainability, chemical flexibility, and human and environmental friendliness. Pharmaceutical-grade natural polymers need regulatory approval, and robust methods are used to promote their processing. He overviews the processes involved in the eventual use of natural polymers for drug delivery, including extraction, purification, modifications, and characterizations. He discovered that natural polymers, especially modified natural polymers, have a wide range of applications in targeted drug delivery, micro/nano-drug delivery, theranostics, BioMEMs and more broadly in the research and development of highly effective, secure, and high-quality products, demonstrating that natural polymers are polymers of today and tomorrow. As a result, he made the decision to pivot and focused on preparation, intensive testing, and eventual commercialization of more natural

polymers, which are novel and underutilized [8]. The modified/regulated drug delivery system aided in the long-term delivery of the drug and was created to ensure patient safety, efficacy, and enforcement. The aim of the improved drug delivery system, which includes transdermal drug delivery, was to deliver the drug at a defined dose and controlled rate through the skin. Polymers were the cornerstone of the architecture for supplying transdermal systems, and they needed to be robust, non-toxic, cost-effective, and have a long-term drug release. Natural polymers were used as rate-controlling, defensive, and stabilizing agents in general, as well as to reduce dosing frequency and improve the drug's effectiveness by localizing at the site of action. Due to many drug release problems and side effects associated with synthetic polymers, manufacturers are more likely to use natural polymers nowadays.

He discovered that oxidation, diffusion, and swelling are all processes involved in drug release from natural polymers. Natural polymers could be used to achieve controlled drug delivery in the body. Gums, mucilages, resins, and plant waste are natural materials used in conventional and modern dosage forms. As a result, their main goal was to provide a brief overview of the extraction, alteration, characterization, and biomedical applications of traditional natural polymers used in transdermal drug delivery and their future prospective [8] A. S. Mundada *et al.,* (2011) [85] a novel film-forming biomaterial was studied to see whether it could be used to make unit laminate transdermal adhesive matrix systems. The biomaterial Damar Batu (DB) was tested in the preparation of transdermal patches alone and in combination with Eudragit RL100 as a matrix forming agent, and the formed Diltiazem hydrochloride (DH) transdermal patches were analysed for thickness uniformity, weight uniformity, folding endurance, and drug content. For *in-vitro* drug release tests, the USP dissolution apparatus V was used. Modified Franz diffusion cell used for permeation study using excised human cadaver skin. Based on *in-vitro* drug release and *in-vitro* skin permeation profiles, F5 composed of DB: Eudragit RL100 (60:40) and containing 20% w/w DH was chosen as the best formulation for *in-vivo* testing. The results of the *in-vivo* analysis showed that F5 reached a Cmax of around 269.761.52ng/mL in 6 hours and continued to release the drug for another 24 hours. The non-sensitizing and non-irritating properties of the novel biomaterial were demonstrated in a skin irritation analysis. The drug-polymer interaction analysis, which was carried out to see whether the drug and polymer were compatible, revealed that the drug was intact in the formulation, confirming the polymer's compatibility. Finally, the findings of this study suggest that by using a suitable adhesive layer and backing membrane, DB: Eudragit RL100 (60:40) transdermal patches could be used for therapeutic purposes. (Mundada and Avari 2011) [18] analyzed that the transdermal delivery of hormonal therapy had several advantages over the oral route, including the incidence of side effects.

Using the plate casting method and physicochemical parameters, they prepared and screened rate-controlling membranes using Eudragit release liners with hydroxyl propyl methyl cellulose K4M (HPMC K4M) and ethyl cellulose. They also performed preformulation studies (thickness, weight variation, moisture uptake, folding endurance, and moisture loss) with release liners. They decided that Tamoxifen citrate was an ideal molecule for the transdermal reservoir to prepare gel dosage form due to its dosage regimen. Finally, a topical gel, including Tamoxifen citrate, was produced using different proportions of HPMC K4M and Carbopol 934 as gelling agents and Dimethyl Sulfoxide (DMSO) as a penetration enhancer. At the end, rate-controlling membranes were also used to perform Tamoxifen citrate gel diffusion (release liner). Finally, the skin permeation of Tamoxifen Citrate gel was studied using excised rat skin as a barrier [18] Manish Kumar *et al.,* (2018). Their research aimed to use a solvent evaporation method to create a transdermal drug delivery system containing atenolol with various ratios of hydrophilic and hydrophobic polymeric combinations, as well as to investigate the effect of polymer hydrophilicity and hydrophobicity on the physicochemical and drug release characteristics of transdermal patches. Here the solvent casting method has been used to formulate transdermal patches. Hydroxypropyl methylcellulose (HPMC), Polyvinylpyrrolidone (PVP), and Ethylcellulose (EC) in different combination ratios were used as the polymer. Here Propylene glycol was used as a plasticizer.

Permeation enhancers such as span 80 enhanced permeation through the skin. The Franz diffusion cell was used to conduct the *in-vitro* diffusion analysis, which used an egg membrane as a semi-permeable diffusion membrane.

They found that the thickness of all batches of patches varied from 0.32 to 0.39 mm with uniformity of thickness in each formulation. Formulations F1 to F3 had high moisture content varied from 2.07±0.09 to 2.56±0.15 and high moisture uptake value varied from 3.21±0.35 to 4.09±0.38 due to a higher concentration of hydrophilic polymers. He found that the Drug content of all batches ranged between 85.92±1.32 to 95.71±1.42 and the Folding endurance values off all batches were more than 75. Formulation batches F1 to F3 showed higher cumulative drug release varied from 61.34% to 68.11% compared to formulation batches F4 to F6. Finally, they conclude that the higher proportion of hydrophilic polymer in the formulation of transdermal patches gives a higher percentage of drug release from prepared patches.

The study's finding indicates that the hydrophilicity and hydrophobicity of polymer affect the physicochemical and drug release properties of transdermal patches. An optimum proportion of hydrophilic and hydrophobic polymer was required to prepare effective transdermal patches. [22] Mahdie Torkaman *et al.*, (2017) [33] observed that there were considerable numbers of medicines that cannot be dissolved in water or had a little aqueous solubility, which caused problems in their absorption and reduction of bioavailability of them subsequently. Various methods have been developed to increase the solubility of drugs to treat these problems. The study used ethyl cellulose polymers to deliver hydrocortisone acetate drugs. In this way, the solvent evaporation technique was considered to increase the solubility of the drug hydrocortisone acetate. Finally, scanning electron microscopy (SEM) was used to determine the microcapsules' shape and size, and infrared spectroscopy (FT-IR) was also applied to investigate if any change happened in the drug's structure during the microencapsulation process [33]. Eudragit-RL, Hydroxypropyl methyl cellulose K-50, and ethyl cellulose were used to make Tamoxifen-loaded liposomes and a methotrexate-loaded transdermal patch. Using a solvent evaporation process with poly (sebacic acid-co-ricinoleic acid) in various ratios, particle size, drug packing, entrapment efficiency, transmission electron microscopy, differential scanning calorimetry, and X-ray diffraction were all investigated.

Weight, drug quality, moisture content, absorption, folding durability, tensile strength, diffusion coefficient, permeability coefficient, *in-vitro* permeation, and skin discomfort of tamoxifen- and methotrexate-loaded liposomes were studied. The pharmacokinetic and pharmacodynamic parameters of transdermal patches that had been optimized were studied. Transdermal patches showed improved tamoxifen citrate and methotrexate bioavailability compared to the oral path. Regarding bioavailability, tamoxifen-loaded liposomal transdermal patches and methotrexate-loaded transdermal patches may be safer alternatives to commercially marketed formulations.

(Adhyapak and Desai 2016) [38, 17] prepared a transdermal matrix formulation containing different polymer components for topical delivery. *Terminalia arjuna* bark extract-loaded transdermal patches were prepared using a solvent casting technique with different amount of chitosan, and Eudragit RL 100 batches were prepared according to 3^2 factorial designs. The transdermal patches prepared were evaluated for different physicochemical properties, determination of drug content, *in-vitro* diffusion study, *ex vivo* study, skin irritation study, and stability study. Infrared studies indicate the absence of chemical interaction or any changes in the extract's chemical composition during the transdermal patch preparation.

In-vitro diffusion and ex-vivo diffusion studies of optimized batch S3 showed drug releases to 74.56–69.12%, respectively, up to 12 h. Skin irritation study indicates that the extract and excipients used in the patch do not show any irritating effect on the skin. All the prepared transdermal matrix formulations were found to be stable on storage. It concluded that prepared matrix formulations containing different polymer components can be used for transdermal delivery to treat chronic ailments such as cardiovascular disorder [17, 19].

That work aimed to develop and characterize the prolonged-release piroxicam transdermal patch as a prototype to substitute oral formulations, reduce side effects, and improve patient compliance. The patches were composed of film formers Eudragit as a matrix backbone, with PVC as a backing membrane and PEG200 as a plasticizer. Results from X-ray diffraction patterns and Fourier transform-infrared spectroscopy indicated that loading piroxicam into films changed the drug crystallinity from needle to an amorphous or dissolved form. The Piroxicam films were prepared using Eudragit RL100 and Eudragit RS100 as film formers at various ratios from 1:0 to 1:3.

Films prepared solely by Eudragit RL100 showed the toughest and softest film, while other formulations containing Eudragit RS100 were hard and brittle. Drug release kinetic data from the films fitted with the Higuchi model, and the piroxicam release mechanism was diffusion controlled. He found that among all formulations tested, Eudragit RL100 films showed the highest drug release rate and the highest drug permeation flux across the human epidermal membrane then. Increasing drug loading led to an increase in drug release rate, and Eudragit can be used as a film former for fabricating piroxicam films [19].

Using mixed polymeric grades of Eudragit RL/RS, Ashok R. Chandak *et al.,* (2010) [91] aimed to create a matrix-type transdermal formulation of pentazocine. FTIR, DSC, and X-RD were used to describe the potential interaction between the drug and the polymer used. An X-RD analysis shows that the drug state has changed from crystalline to amorphous in the matrix films prepared. The physical parameters and in-vitro dissolution characteristics of pentazocine matrix transdermal films were assessed using Cygnus' sandwich patch holder. The thickness and weight per patch were identical regardless of the Eudragit polymer grades used. *In-vitro* dissolution experiments showed that as the ratio of Eudragit RS (slightly permeable) type polymer increases, the dissolution half-life (t50%) rises, and the dissolution rate constant value falls. The significance of differences in the *in-vitro* dissolution rate profile and pharmacokinetic parameters (Cmax, tmax, AUC(s), t1/2, Kel, and MRT) were statistically tested for these pharmacokinetic studies in healthy rabbits. Finally, he claims that *in vitro* dissolution profiles (DRC and t50%) as well as pharmacokinetic parameters revealed a substantial difference between test products (P) [28].

Since, the early 1980s, buccal delivery of the target substance using mucoadhesive polymers has piqued interest. The advantages of buccal drug delivery have made this route of administration suitable for a wide range of medications. The use of mucoadhesive polymers in buccal drug distribution is highlighted in this study. This article begins with an overview of the oral mucosa, drug permeation mechanisms, and ideal polymer properties before moving on to the hypotheses behind bioadhesive polymer adhesion to the mucosal epithelium.

We also look at the latest age of mucoadhesive polymers, such as thiolated polymers, and the more common mucoadhesive formulations [101] Verma and Chattopadhyay, in 2012, developed mucoadhesive patches for buccal administration of metoprolol succinate and to evaluate their *in-vitro and in-vivo* bioadhesion. The mucoadhesive buccal patches were prepared using solvent casting using two different mucoadhesive polymers. The formulations were tested for *in-vitro* drug permeation, buccal absorption, *in-vitro* drug release studies, and moisture absorption for *in-vitro* and *in-vivo* bioadhesion.

The peak detachment force and work of adhesion for MC5 (sodium carboxymethylcellulose, i.e., Na CMC) patch were 0.87 N and 0.451 mJ, respectively, and the corresponding values for CH5 (chitosan) were 5.15N and 0.987 mJ. Formulation CH5 (prepared with chitosan) showed 67.1 % release, while MC5 (Na CMC) showed a drug release of 81.9 % in 6 h. Basic pharmacokinetic parameters such as Cmax, Tmax, and AUC total varied statistically ($p < 0.05$) when given by the buccal route compared with that of the solution given by the oral route. The results indicate that formulation of suitable bioadhesive buccal patches with the desired permeability is feasible. The development of bioadhesive buccal formulation for metoprolol succinate with a lower dose and few side effects may be attainable. (Verma and Chattopadhyay 2012) Ruiwei Guo, *et al.,* (2011) have used the modified (poly vinyl alcohol) (PVA) gel to create a novel organic-inorganic hybrid film-

forming agent for TDDS, with c-(glycidyloxypropyl) trimethoxysilane (GPTMS) as an inorganic-modifying agent, poly (N-vinyl pyrrolidone) (PVP) as a tackifier and glycerol (GLY) as a plasticizer.

He found that the formulated gels can be added to the skin using a coating process, creating very thin and translucent films in situ that have good performance, a nice feel, and cosmetic appeal. He investigated the main properties of the bioadhesive films generated from hybrid gels. The results revealed that integrating sufficient GPTMS (GPTMS/(PVA + GPTMS) in the range of 20–30%) into the PVA matrix can significantly boost mechanical strength and skin adhesion properties of the resultant film, as well as decrease the crystalline regions of PVA.

Furthermore, he found that the *in-vivo* skin irritation studies revealed that the films did not induce skin irritation after 120 hours of topical use. Finally, it was concluded that bioadhesive films made from organic-inorganic hybrid gels had excellent skin adhesion properties and could be a promising TDDS formulation, particularly when patient acceptability of the dosage type from an aesthetic standpoint was a priority (Guo *et al.* 2011) [88] Yhors Ciro *et al.*, (2019) prepared the polymeric film-based drug delivery systems, which were an exciting and promising option, especially for skin chemotherapeutics.

They conjugate the Polymeric films based on glutathione-chitosan with degrees of thiolation of 4.4, 5.1 and 7.0 percent were synthetized in this study using a casting-evaporation process and methotrexate loading. They used the touch angle and spreading rate calculations to assess the surface properties of these films with Young–Dupré semi-empirical model to evaluate the sessile drop methods and the thermodynamic function of work of adhesion. They measured the methotrexate release *in-vitro* at pH levels of 4.5 and 7.4 to mimic physiological conditions. They found a close link between thiolation degree and hydrophilic surface properties like contact angle and water spreading rate, although adhesion work was not significantly affected. Furthermore, depending on the thiolation degree and the aqueous medium used, he found that these polymer films could regulate methotrexate release by various processes such as diffusion and relaxation. He observed that as the degree of thiolation increased, the release mechanism changed from a primary diffusional form to a relaxation-driven type. Finally, it was concluded that these polymer films could be changed to distribute anticancer drugs locally [10]. The primary goal of this study was to create a new inorganic-organic film. The inorganic form, hydroxyapatite (HAp), was blended well with the organic phase, hydroxyethyl cellulose acetate (HECA), and then the inorganic-organic films were manufactured by evaporating the solvent. Different analytical instruments, such as field emission scanning electron microscopy (FEG-SEM), thermo-gravimetric analysis (TGA) and Fourier transform infrared (FT-IR) spectroscopy, were used to describe the structure and properties of the formed films.

According to the findings, the HAp nanoparticles were well distributed and immobilised in the shaped films. The role of nano- and micropores in the HECA substrate can be due to this. In addition, there was a good relationship between HAp and the HECA matrix. The findings have revealed excellent thermal stability and miscibility. (Azzaoui *et al.* 2015) [59] Varsha Gupta, *et al.*, (2014) [41] have investigated that Ethylcellulose (EC) as a film-forming polymer, polydimethylsiloxane (PDMS) as a pressure sensitive adhesive and propylene glycol and Di-n-butyl-phthalate as penetration enhancers and plasticizers, respectively, were used to create controlled release contraceptive transdermal patches containing centchroman.

Differential scanning calorimetry and the Fourier transform infrared (FTIR) spectroscopic technique were used to determine the drug's physicochemical compatibility with the polymers. The effects of different EC and PDMS ratios on moisture uptake, moisture content, tensile strength (TS), Young's modulus, adhesive strength, water vapour transmission rate (WVTR), and *in-vitro* centchroman permeation via Sprague–Dawley rats abdominal skin using Franz's diffusion cell were studied using a 3^2 full factorial design. She discovered that there would be no major interaction between the drug and the polymers used during the compatibility tests and that incorporating only EC resulted in too hard patches, while incorporating

PDMS resulted in patches with lower TS, increased percentage elongation, WVTR, and Young's modulus. According to statistical studies, independent variables have a major impact on the dependent variable. With r2 40.990, all formulations adopt zero-order release kinetics.

Finally, she effectively prepared the medication in adhesive transdermal patches for non-steroidal contraceptive centchroman to achieve a zero-order release method [89]. William B. Liechty, *et al.,* (2010) [95] have explored that Polymers have played an integral role in the advancement of drug delivery technology by providing controlled release of therapeutic agents in constant doses over long periods, cyclic dosage, and tunable release of both hydrophilic and hydrophobic drugs. From early beginnings using off-the-shelf materials, the field has grown tremendously, driven in part by the innovations of chemical engineers. Modern drug delivery advances were predicated upon the rational design of polymers tailored for specific cargo and engineered to exert distinct biological functions. Here he highlighted the fundamental drug delivery systems and their mathematical foundations and discuss the physiological barriers to drug delivery. The origins and applications of stimuli-responsive polymer systems and polymer therapeutics such as polymer-protein and polymer-drug conjugates were reviewed. The latest developments in polymers capable of molecular recognition or directing intracellular delivery were surveyed to illustrate areas of research advancing the frontiers of drug delivery [95].

Adhesive: Transdermal patches and medicated plasters (patch) represent well-established prolonged-release dosage forms. Even if satisfactory adhesion to the skin is strictly linked to the efficacy and safety of the treatment, nowadays, numerous reports of *in-vivo* 'adhesion lacking' are still addressed to regulatory agencies. The adhesive properties of a patch should be characterized considering i) the ability to form a bond with the surface of another material on brief contact and under light pressure (tack ii) the adhesive's resistance to flow (shear adhesion), and iii) the force needed to peel a patch away from a surface should all be considered when determining the adhesive properties of a patch (peel adhesion). The most commonly used methods for measuring adhesive properties during development studies, as well as patch quality control, are listed in this manuscript. The influence of formulation variables on patch adhesive properties and their possible relationship with the *in-vivo* adhesion performances is also discussed.

Pharmacopeias should consider introducing compendial testing to assay the quality of adhesive patch properties, and regulatory agencies should issue proper guidelines to evaluate these features during development [74]. A novel organic–inorganic hybrid film-forming agent for TDDS was developed by a modified poly (vinyl alcohol) (PVA) gel using γ-(glycidyloxypropyl) trimethoxysilane (GPTMS) as an inorganic-modifying agent, poly (N-vinyl pyrrolidone) (PVP) as a tackifier and glycerol (GLY) as a plasticizer. The prepared gels can be applied to the skin by a coating method and in situ form very thin and transparent films with good performance, comfortable feel, and cosmetic attractiveness. The key properties of the bioadhesive films produced from the hybrid gels were investigated, and the results showed that the incorporation of appropriate GPTMS (GPTMS/ (PVA + GPTMS) in the range of 20–30%) into the PVA matrix not only can significantly enhance mechanical strength and skin adhesion properties of the resultant film but also can decrease the crystalline regions of PVA and hence facilitate the diffusion of water vapour and drug.

Furthermore, the investigations into *in-vivo* skin irritation suggested the films caused non-irritation to skin after topical application for 120 h. In conclusion, the bioadhesive films formed from organic-inorganic hybrid gels possessed very good qualities for application on the skin. They may provide a promising formulation for TDDS, especially when the patient acceptability from an aesthetic perspective of the dosage form is a prime consideration (Guo *et al.* 2011). Transdermal drug delivery is a validated technology contributes significantly to global pharmaceutical care. Since 1980, impressive growth in this field has been observed with many commercial successes; importantly, a new chemical entity was recently developed and approved for transdermal administration without first being given as an injectable or oral dosage form.

The progress achieved has been based on a clearer understanding of skin barrier function and the physicochemical, pharmacokinetic and physiological factors underpinning the feasibility of transdermal administration. The novel, non-invasive approaches to enhance and control drug transport across the skin are under intensive investigation and some technologies, e.g., iontophoresis, have reached true maturity. The "local", subcutaneous delivery of drugs (for example, to underlying muscle and other tissues) is gaining increasing acceptance, and new opportunities in this under-subscribed area may be envisaged [46]. One of the most important components of transdermal drug delivery systems was pressure-sensitive adhesive (PSA). PSA's primary role is to aid in patch adhesion to the skin, but it also serves as a matrix for the drug and other excipients. As a result, PSA affects other essential quality attributes of the TDDS, such as drug delivery, flux through the skin, and physical and chemical stability of the finished product, in addition to patch adhesion. The adhesives used in different forms of TDDS are summarised in this review report [46]. In this review, authors have attempted to propose recent advancements and methods toward developing and assessing transdermal patches of certain antineoplastic medications based on numerous literature review reports.

Chemotherapy in Breast Cancer Using Methotrexate and Tamoxifen Citrate: The commercially available systemic chemotherapy for treating breast cancer has been found to cause severe systemic side effects and threaten patient compliance. The embryological basis of breast skin, highly developed internal lymphatic and venous drainage, and mammary fat layers are all anatomical features that aid in the preferential accumulation of drugs in the breasts after topical application on the breast area. This distinct function is known as localized transdermal delivery, and it may be used to selectively distribute anticancer agents to cure breast cancer while minimizing systemic side effects. However, the therapeutic efficacy of this drug delivery technique is severely restricted by the skin's barrier properties, which reduce anticancer drug permeation. Methotrexate (MTX) is a chemotherapeutic agent used to treat a variety of neoplasms. It is a stoichiometric inhibitor of the dihydrofolate reductase enzyme. We designed and developed a transdermal patch of Methotrexate to act as a drug carrier in this study, and we tested its cytotoxic effect *in-vitro*. The transdermal release of MTX inside the lysosomal compartment is needed for this target drug delivery mechanism [21]. According to their findings, Gae¨lle Jouret *et al.,* (2020) found that cutaneous metastases in breast cancer were also a surgical problem. They observed that the Extramammary Paget's disease, described as an in situ mammary adenocarcinoma of the epidermis, has recently been shown to respond well to oxygen flow-assisted topical administration of methotrexate 5 percent (OFAMTX, 5 percent methotrexate in a carrier solution). He observed that a 51-year-old woman with triple-negative breast cancer who had biopsy-proven skin metastases on her chest decided to take OFAMTX5 percent therapy; that procedure lasted for two weeks and consisted of twice weekly sessions of OFAMTX5% added to a 40 cm2 region of skin. Biopsies of the skin are obtained. He found that the medication was well tolerated at that time, and there were no unpleasant stimuli. After that, the treated region showed post-inflammatory hyperpigmentation for two months after the treatment.

The control skin biopsy revealed no residual metastatic lesions. The patient was now in clinical recovery six months after the operation. Finally, it was concluded that the OFAMTX5 percent was determined to be an alternative skin-directed, painless, patient-friendly, and efficacious adjuvant therapy for breast cancer superficial metastatic lesions [3]. The term "transdermal drug delivery systems" refers to non-invasive or minimally invasive approaches for delivering drugs and vaccines via the skin. Transdermal delivery has several benefits, including easy skin accessibility, which aids patient acceptance, bypassing the gastrointestinal tract, and obtaining extended/regulated release. Women have been waiting for alternatives to oral hormonal chemotherapy for over a decade. Transdermal drug delivery has been developed for contraception and hormone therapy. Tamoxifen citrate has long been a treatment choice for advanced breast cancer, and it's also used as a post-surgical adjuvant. The medicine has also been used to treat menopause. However, one of the drug's side effects is its

proliferative effect on the endometrium. Tamoxifen citrate is a highly lipophilic agent with poor solubility in liquids. Furthermore, oral bioavailability is influenced by first-pass digestion and P-glycoprotein (P-gp) pump efflux in the liver and intestine. As a result, for successful local hormonal chemotherapy, the development of a controlled/sustained delivery system is needed [4]. studied the influence of a tamoxifen-loaded transdermal patch in Dimethylbenzanthracene (DMBA) - induced breast cancer. She developed different formulations containing different concentrations of tamoxifen citrate, poly (SA: RA), glucose, and mannitol and tested in female albino Wistar rats with DMBA-induced breast cancer. Body weight, haemoglobin content, red blood cell, white blood cell, SGPT, and SGOT levels were measured. Compared to illness, treatment of formulations resulted in a reduction in body weight.

In addition, the formulation-treated group significantly improved haemoglobin compared to the disorder group. SGPT and SGOT levels are also declining in type [4]. Mohammed A. Kassem *et al.*, (2018) [25] found that Long-term Tamoxifen treatment is hampered by serious side effects and low selectivity for cancer cells, as per the study. As a result, they decided to create Tamoxifen-loaded span-based nano-vesicles that would deliver maximum efficacy to malignant tissues by using the Box-Behnken design and the effect of three factors on vesicle size (Y1), zeta potential (Y2), entrapment efficiency (Y3) and cumulative percent release after 24 h (Y4) was optimized, and the optimized formula was designed and tested for stability.

For Y1, Y2, Y3, and Y4, they observed the standardized formula values of 310.2 nm, 42.09 mV, 75.45, and 71.70 percent, respectively. The research was carried out using electron microscopy. Even so, the modified formula's cytotoxic activity of both breast cancer cells (MCF-7) and normal cells (BHK) showed improved selectivity (9.4 folds) on cancerous cells, with IC_{50} values of 4.7 1.5 and 44.3 1.3 g/ml for cancer and normal cells, overall. They observed that on cancer cells, the free Tamoxifen provided lower selectivity (2.5 folds) than optimisednano-vesicles, with IC50 values of 9.0 1.1 g/ml on MCF-7 and 22.5 5.3 g/ml on BHK cells, respectively. As a result, with improved efficacy and selectivity, they concluded that the vesicular system was an excellent tool for resolving breast cancer treatment challenges [25] Yu-Ling Lin *et al.*, (2016) [47] have discovered the Tamoxifen citrate to be used for the treatment of early and advanced estrogen receptor (ER) positive breast cancer in both pre-menopausal and post-menopausal people. However, he found that because of its possible side effects, using tamoxifen to suppress endogenous or exogenous estrogen effects regularly can be challenging, so he aimed to create a local drug delivery system to encapsulate tamoxifen and test its effectiveness in terms of skin penetration, drug accumulation, and cancer treatment. He used the cationic liposome-PEG-PEI complex (LPPC) to encapsulate tamoxifen and form the 'LPPC/TAM' for transdermal release. He found that the cytotoxicity of LPPC/TAM was shown to be anaerobic.

Following transdermal therapy, skin penetration, tumour growth inhibition, and organ damage were assessed in xenograft mice. He observed that the average size of LPPC/TAM was less than 270 nm, with a zeta-potential of about 40 mV. He also observed that in all breast cancer cells, LPPC/TAM significantly increased the cytotoxic activity, especially in ER-positive breast cancer cells, and in *in-vivo*, the fluorescent dye penetrating through the skin with quickly collecting in the tumour region was aided by LPPC drug delivery. In mice with BT474 tumours, the transdermal administration of LPPC/TAM prevented tumour development by around 86 percent was concluded. Thus, this LPPC/TAM local therapy did not damage the skin or organs.

The LPPC-delivery mechanism improved skin penetration, drug accumulation, and therapeutic efficacy. Finally, as a result, LPPC/TAM drug delivery may be a useful transdermal option for breast cancer therapy (6, 28). Oukseub *et al.*, (2015) aim was to identify non-toxic, well-tolerated preventative measures for high-risk women and those with carcinoma in situ and found that drug delivery *via* the breast skin is a promising process (local transdermal therapy, LTT). His goal was to test experimental medicines for LTT to prove that LTT can be used for non-steroidal drugs. Oral tamoxifen, transdermal 4-hydroxytamoxifen (4-OHT), or endoxifen gel had applied daily to the

axillary mammary gland which was provided to athymic nude rats for 6 weeks (Study 1). In (Study 2) he compared transdermal telapristone acetate (telapristone) gel to a subcutaneous implant in the same way as in Study 1 in which Mammary glands and blood were obtained through euthanasia. In Study 3, consenting women needing a mastectomy were assigned randomly to either a diclofenac patch applied to the abdomen or a diclofenac patch applied to the breast for three days before surgery. He had taken eight tissue samples and collected venous blood from predetermined locations throughout surgery for each breast. The mammary tissue concentrations of 4-OHT, endoxifen, and telapristone were significantly higher in the axillary glands of gel-treated animals as compared to inguinal glands or systemically treated animals, according to liquid chromatography-tandem mass spectroscopy.

The amounts of plasma in gel and systemically treated animals were similar. Finally, lipophilic drugs can be developed for LTT; although the nude rat is good for drug permeability testing, delivery is systemic; and finally, transdermal treatment of the breast membrane, on the other hand, provides local distribution in humans [58]. Shoei-Loong Lin *et al.,* (2014) observed that tamoxifen citrate, because of the potential for side effects by taking it orally for breast cancer prevention, is of high risk for women and can be problematic at times.

His research aimed to demonstrate transdermal delivery of tamoxifen citrate and phytonutrients for breast safety using a low dose of tamoxifen citrate and analysed 2795 breast MRI photographs from Taiwanese women and categorized them as healthy or unhealthy using the BI-RADS classification system. For at least three months, a fraction of the research patients took hormone supplements containing estrogen components or phytoestrogen; then, these two classes were compared using breast MRI analysis and found to be significantly different. As shown by MRI pictures, breast glandular tissue proliferation can increase by taking too much oestrogen or taking too many phytoestrogen supplements. Due to this proliferation, the possibility of under estrogen therapy, normal breast cells (MCF-10a) showed an improvement in cell proliferation. They used Franz cells with artificial skin membranes to show positive transdermal diffusion using animal urine/feces, blood tests, and subcutaneous skin retention for HPLC analysis to study transdermal absorption through topical application. They successfully showed transdermal absorption of topical tamoxifen and phytonutrients, which may aid in preventing breast cancer in daily estrogen and phytoestrogen users (Lin *et al.* 2014). Isabelle Le Ray *et al.,* (2012) [80] have observed that women with estrogen-positive breast cancers receive endocrine treatment such as tamoxifen and aromatase inhibitors (AI) for 5–10 years. An important side effect of these drugs was vaginal dryness, for which local hormonal therapy (LHT) represents the most effective treatment but was theoretically contraindicated. Their study aimed to assess whether using LHT increases the risk of breast cancer recurrence among women receiving endocrine treatment.

They conducted a cohort study with nested case-control analysis using the United Kingdom General Practice Research Database (GPRD). The cohort included female patients at least 18 years of age who were newly diagnosed with breast cancer and received at least one AI or tamoxifen prescription between January 1, 1998, and June 30, 2008. Patients experiencing a breast cancer recurrence during follow-up were each matched with up to 10 controls based on age, date of cohort entry, type of endocrine treatment received, and duration of follow-up.

Conditional logistic regression was used to estimate rate ratios (RR), and 95 % confidence intervals. A total of 13,479 women were included in the study, of which 2,673 received AIs, 10,806 received tamoxifen, and 271 received LHT. The mean (SD) age at cohort entry was 63.7 (14.1) years, and the mean follow-up was 3.5 (2.6) years. The crude recurrence rate is 25.9 per 1,000 per year. Overall, using LHT was not associated with an increased risk of recurrence (RR: 0.78, 95 % CI 0.48–1.25) compared with non-use. In stratified analyses, LHT did not increase the risk of recurrence among tamoxifen-treated patients (RR: 0.83, 95 % CI 0.51–1.34). In contrast, the risk was not estimable among AI-treated patients s since no patients receiving LHT experienced a recurrence. Finally, they conclude that he use of LHT was not associated with an increase in breast cancer

recurrence among women receiving hormone therapy [80]. Eudragit-RL, Hydroxypropyl methyl cellulose K-50, and ethyl cellulose were used to make tamoxifen-loaded liposomes and a methotrexate-loaded transdermal patch. This is the place to be. Using a solvent evaporation process with poly (sebacic acid-co-ricinoleic acid) in various ratios, particle size, drug packing, entrapment efficiency, transmission electron microscopy, differential scanning calorimetry, and X-ray diffraction were all investigated. Weight, drug quality, moisture content, absorption, folding durability, tensile strength, diffusion coefficient, permeability coefficient, *in-vitro* permeation, and skin discomfort of tamoxifen- and methotrexate-loaded liposomes were studied. The pharmacokinetic and pharmacodynamic parameters of transdermal patches that had been optimized were studied.

Transdermal patches showed improved tamoxifen citrate and methotrexate bioavailability compared to the oral path. In terms of bioavailability, patches may be a safer alternative to commercially marketed tamoxifen-loaded liposomal transdermal patches and methotrexate-loaded transdermal formulations. (Adhyapak and Desai 2016). To combat breast cancer, a liposome-loaded transdermal patch containing methotrexate and tamoxifen citrate will be created. Tamoxifen-loaded liposomes were prepared using a solvent evaporation process with poly (SA: RA), with particle size 418±0.07, drug loading 18.78±2.84 percent, and entrapment performance 90.32±2.30 percent in the optimized liposomal formulation F3. Optimized liposomes were formulated into a finalized form as a transdermal patch using a combination of polymers such as Eudragit RL, HPMC K 50, and ethyl cellulose. Compared to other patches with no skin inflammation, the optimized patch formulation F3 had a better release profile. Formulating a patch's pharmacokinetics and pharmacodynamics profile supports its superiority over other established formulations. This analysis aimed to maximize and evaluate the ability of a Liposome prepared by hot ultrasonication as a methotrexate (MTX) carrier, focusing on the use of factorial architecture. For the Liposome loaded with MTX, preliminary screening and drug/lipid solubility enabled us to choose Witepsol E85 as the solid lipid and Mygliol1 812 as the liquid lipid. Then, using a 3-level, 3-factor Box-Behnken design, and ANOVA analysis, the robustness of the d was demonstrated by the correspondence between the expected values and those tested experimentally. The morphology, scale, zeta potential, entrapment performance, storage stability, *in-vitro* drug release, and cytotoxicity of an optimized MTX-loaded Liposome were investigated. A 252-nm spherical liposome filled with MTX had a polydispersity between 0.06 and 0.02, a zeta potential of 14 mV, and an entrapment efficiency of 87 percent. *In-vitro* release tests showed a rapid initial release of MTX from the Liposome and a delayed release lasting up to 24 h.

The Peppas–Korsmeyer model for physiological and inflammatory settings and the Hixson–Crowell model skin simulation conditions better suit the release kinetics of the optimized Liposome. In fission, no toxicity was detected. As a result, the configured MTX-loaded Liposome could be used as a distribution mechanism. Tamoxifen and methotrexate are prescribed for prophylactic treatment of premenopausal and postmenopausal females with carcinoma. In carcinoma cells, it competes with steroids for steroid receptor-positive cells. Multifocal viscosity, fatty penetration, hepatotoxicity, viscous sphacelus, and blood abnormalities are also possible side effects of this drug. The transdermal patch formulation containing tamoxifen and methotrexate will have lower hepatotoxicity and hemolytic carcinoma and better patient sensitivity to care. This method is important in promoting the pharmacokinetic profile, increasing effectiveness, and reducing toxicity, possibly due to the small particle size that allows them to pass through biological barriers. Nanoparticles should be used as a controlled release mechanism in cancer treatment to reduce the occurrence of multiple side effects. As a result, this research aimed to see how effective tamoxifen- and a methotrexate-loaded transdermal patch were at preventing breast cancer. (Lin *et al.* 2016).

Anti-Cancer Drugs in Transdermal Patch: Ajaz Ahmada *et al.*, (2016) [40] have developed ANV-1, a liposomal formulation for administering an anticancer drug to breast cancer stem cell-like cells, and they also evaluated the pharmacokinetics in an animal model. He paired the anticancer drug ESC8 with Dexamethasone -associated liposome (DXE),

an ESC8-entrapped liposome. Here he expressed NRP-1 at a high level in ANV-1 cells. They also changed the DXE liposome to co-deliver the NRP-1 shRNA-encoded plasmid with the existing DXE liposome to boost tumour regression. He also tested DXE-in NRP-1's vivo efficacy in mice with ANV-1 cells as xenograft tumours, and the tumour growth inhibition was determined by measuring tumour size. He observed that between the DXE-NRP-1 and DXE-Control groups, a substantial gap in tumour volume began to emerge. He also found that DXE-NRP-1 patients had a tumour volume of 4 and 2.5 times less than the untreated and DXE-Control-treated groups, respectively. After Following an intraperitoneal dosage (3.67 mg/kg of ESC8 in DXE), the disposition of DXE was studied in Sprague Dawley rats.

He also used Liquid chromatography and mass spectrometry to assess the plasma concentrations of ESC8 in the DXE formulation and pharmacokinetic parameters. The half-life of ESC8 was found to be 11.010.29 hours. The clearance was 2.103.63 L/kg/h, with the delivery rate being 33.420.83 L/kg. Finally, it was concluded that the DXE liposome formulation is given once or twice daily for clinical effectiveness. Overall, they developed a potent liposomal formulation with a favourable pharmacokinetic and tumor-regressing profile that could sensitize and destroy drug-resistant cancer stem cell-like cells [9] explored that the topical delivery of chemotherapeutics was a promising approach for the management of skin disorders. However, diverse pharmaceutical strategies were essential to penetrate large quantities of drugs into tumor tissue.

Here in, an attempt was made to investigate the use of Derma roller microneedles in combination with doxorubicin HCl (DOX) and celecoxib (CEL) co-loaded liposomes as a potential therapeutic approach for the management of melanoma. DOX/CEL co-loaded liposomes/Gels were prepared and characterized. The results showed that microneedle pretreatment with liposomes gel increased DOX penetration into the skin approximately 2-fold compared with the passive delivery and also observed that Both CEL liposomes and DOX liposomes caused significant growth inhibition on B16 cells. Besides, the DOX/CEL co-loaded liposome was more cytotoxic than the DOX/CEL solution and single drug-loaded liposome. They observed that the transdermal delivery of DOX/CEL co-loaded liposome successfully inhibited subcutaneous melanoma in female BALB/nude mice, and the co-administration of DOX/CEL with liposomes was better and significantly enhanced the antitumor effect more than single-drug-loaded liposomes. Furthermore, Dermarollers treatment before gel application strongly improved the tumor inhibition rate. Finally, they conclude that DOX/ CEL co-loaded liposome delivery via microneedles was a promising strategy for skin tumor treatment with targeting inhibition efficiency and negligible side effects [9].

Michele Atlan *et al.*, (2019) observed that Curcumin was an herbal supplement shown in preclinical studies to have antioxidant, anti-inflammatory, and antitumoral properties that we believe can be harnessed for breast cancer prevention. However, they found that due to its poor absorption when consumed orally, curcumin's anticancer effects have not yet been exploited to their full therapeutic potential. Incorporating existing research that focuses on optimizing curcumin's bioavailability and the latest transdermal delivery technology, they proposed a hypothetical *in-vivo* study to test whether a targeted daily dose of bioavailable curcumin has a cytotoxic effect on cancer cells, potentially reducing the incidence of breast cancer over time. Their ultimate objective was to adopt innovative methods to create curcumin-infused bio-textiles offering transdermal, targeted drug delivery simply through contact with the skin. They used that fabric to create disposable bra inserts for an effortless, daily breast cancer prevention regimen for healthy women. Finally, they conclude that it would be essential that the cost of these inserts remain reasonable. Still, if successful, curcumin was readily available, affordable, and non-toxic and could thus be a preventive measure beneficial for women from all socio-economic backgrounds [12].

Drugs Used in Transdermal Patch: Kapoor *et al.*, (2018) [24] observed that more than 70% of drugs taken orally are found to be less successful than desired. To address this limitation, the transdermal drug delivery system has emerged as a revolutionary area of study. This system aids in the

delivery of drugs and macromolecules via the skin into systemic circulation. The global demand for transdermal patches has now crossed 2 billion pounds. Many medications, such as oestrogen, progestrone, nitroglycerine, and clonodine, have been manufactured as transdermal patches because of their ability to deliver the drug in a non-invasive manner while also overcoming the problems associated with the oral route. Since the drug is delivered at a fixed rate by the Transdermal patches, partitioning the drug from the device to the skin and subsequent penetration across various layers of the skin may be altered by introducing penetration enhancers, which may be physical or chemical in nature.

Finally, he discovered the importance of various chemicals used as penetration enhancers. (Kapoor *et al*. 2018) Shailesh T. Prajapati *et al.,* (2011) [84] observed that due to first-pass metabolism, repaglinide has a half-life of one hour and a bioavailability of 56 percent in the body. The total daily dose of Repaglinide was 16 mg (*e.g.,* 4 mg four times daily depending on meal patterns); thus, regular dosing was needed. Repaglinide sustains release transdermal patches were prepared by varying the grades of HPMC and the concentration of PVP K30 using the solvent casting process. Thickness, tensile strength, folding endurance, percent elongation, percent moisture content, percent moisture absorption, percent drug content, *in-vitro* drug release, *in-vitro* permeation, and drug excipient compatibility were all tested on the prepared formulations. The effect of varying the grades of HPMC (X1) and PVP concentration (X2) on the responses, that is, tensile power, percentage drug released in 1 hr (Q1), 9 hr (Q9), and diffusion coefficient as dependent variables, was investigated using a 3^2 complete factorial design. To determine the kinetics of drug release, *in-vitro* release data was fitted- to different models. For dependent variables, regression analysis and analysis of variance were used.

The F2 statistics between factorial design batches and theoretical profile were used to pick an optimized batch, and it was determined that Batch F6, which included HPMC K100 and PVP (1.5%), had a release rate of 92.343 percent up to 12 h and was found similar to theoretically predicted dissolution profile (f2 = 69.187). (Prajapati *et al.* 2011). This study aimed to develop a matrix-type pentazocine transdermal formulation using Eudragit RL/RS blended polymeric types. The possible relationship between the substance and the polymer was defined using FTIR, DSC, and X-RD. An X-RD study of the matrix films reveals that the drug state has changed from crystalline to amorphous. Physical parameters and *in-vitro* dissolution properties of pentazocine matrix transdermal films were evaluated utilizing Cygnus' sandwich patch holder. The patch thickness and weight were similar regardless of the Eudragit polymer grades used.

In-vitro dissolution studies indicated that the dissolution half-life (t50 percent) increases as the ratio of Eudragit RS (slightly permeable) form polymer increases, whereas the dissolution rate constant value decreases. Relevant formulations were chosen for these pharmacokinetic trials in safe rabbits. Differences in *in-vitro* dissolution rate profiles and pharmacokinetic parameters (Cmax, tmax, AUC(s), t1/2, Kel, and MRT) were analyzed for statistical significance. *In-vitro* dissolution profiling (DRC and t50 percent) and pharmacokinetic properties differed significantly between test items (P 0.01). A quantitatively positive association was discovered between the percentage of drugs consumed by mouth and the percentage of drugs absorbed by the stomach. (Chandak and Prasad Verma 2010).

Nanocarriers in Transdermal Patch: Ravi Kant Upadhyay., *et al.* (2014) [61] have highlighted the various drug delivery systems used for the delivery of pharmaceutical agents, mainly antibiotics, antineoplastic agents, neuropeptides, and other therapeutic substances through the endothelial capillaries (BBB) for CNS therapeutics. In addition, ultrasound is used to deliver therapeutic agents/biomolecules such as proline-rich peptides, prodrugs, radiopharmaceuticals, proteins, immunoglobulins, and chimeric peptides to the target sites in deep tissue locations inside tumor sites of the brain has been explained. In addition, they also show the therapeutic applications of various types of nanoparticles such as chitosan-based nanomers, dendrimers, carbon nanotubes, niosomes, beta-cyclodextrin carriers, cholesterol-mediated cationic solid lipid nanoparticles and colloidal drug carriers, liposomes, and micelles had

been discussed with their recent advancements. They emphasized the need for physiological and therapeutic optimization of existing drug delivery methods and their carriers to deliver therapeutic amounts of drugs into the brain to treat various neurological diseases and disorders. Further, strong recommended in developing nanosized drug carriers/vehicles and noninvasive therapeutic alternatives of conventional methods for better therapeutics of CNS related diseases.

Hence, they conclude that there was an urgent need to design nontoxic, biocompatible drugs and develop noninvasive delivery methods to check post-treatment clinical fatalities in neuropatients which occur due to existing highly toxic invasive drugs and treatment methods (Upadhyay 2014). The author tried their best to review the application of nanocarriers in transdermal patches to treat cancer cells. Several nanocarrier delivery systems have been developed to overcome conventional chemotherapy's limitations and are commonly used for drug delivery to cancer cells. Nanocarriers also increase the solubility, bioavailability and pharmacokinetic properties of chemotherapeutics. Liposomes, polymeric nanoparticles, micelles nanotubes, and other nanocarriers for cancer treatment are either on the market or being tested and analyzed [49]. Regina-Veronicka *et al.,* (2018) observed that advances in nanomedicine had become indispensable for targeted drug delivery, early detection, and increasingly personalized approaches to cancer treatment. They found that nanoparticle-based drug-delivery systems have overcome some of the limitations associated with traditional cancer-therapy administration, such as reduced drug solubility, chemo resistance, systemic toxicity, narrow therapeutic indices, and poor oral bioavailability, and they also observed that the advances in the field of nanomedicine include "smart" drug delivery or multiple levels of targeting and extended-release drug-delivery systems that provide additional methods of overcoming these limitations.

However, more recently, the idea of combining smart drug delivery with extended-release has emerged to develop highly efficient nanoparticles with improved delivery, bioavailability, and safety profiles. Although functionalized and extended-release drug-delivery systems have been studied extensively, there remain gaps in the literature concerning their application in cancer treatment. They aim to provide an overview of smart and extended-release drug-delivery systems for the delivery of cancer therapies and to introduce innovative advancements in nanoparticle design incorporating these principles. Finally, they conclude that with the growing need for increasingly personalized medicine in cancer treatment, smart extended-release nanoparticles had the potential to enhance chemotherapy delivery, patient adherence, and treatment outcomes in cancer patients [23].

Ankita Dadwal *et al.,* (2018) discovered that cancer nanotherapeutics were rapidly evolving and used to overcome many shortcomings of traditional drug delivery systems, including non-specific bio dissemination and targeting, water solubility, and low oral bioavailability. He found that the novel nanoscale targeting methods had been created due to protein engineering and materials science developments, which could give cancer patients new hope. He had done Clinical trials for a variety of therapeutic nanocarriers. The nanoparticles were engineered for optimum size and surface characteristics to boost biodistribution and maximize circulating time in the bloodstream. He observed that the nanotherapeutics were also able to transport the loaded active drug to cancer cells by selectively leveraging to the special pathophysiology of tumours, such as their improved permeability and retention impact. He used active targeting techniques by using ligands or antibodies aimed against particular tumour sites, in addition to this passive targeting process, increasing the specificity of these therapeutic nanoparticles. He observed that drug resistance was another barrier that nanoparticles can help solve or reduce. Finally, he studied multifunctional and multiplex nanoparticles, which were expected to be the next generation of nanoparticles, allowing for more customized and targeted cancer care. (Dadwal *et al.* 2018).

Chiara Dianzani., *et al.* (2014) [69] observed that Nanotechnology, it was noted, entails the engineering of functional structures at the nanoscale, making it appealing to disciplines ranging from materials science to biomedicine. They discovered that nanomedicine, which applies

nanotechnology to extremely specific medical procedures for preventing, diagnosing, and treating diseases, including cancer, was one of the most active research areas of nanotechnology. The researchers also noted that rapid advances in nanotechnology have enabled the integration of multiple therapeutic, sensing, and targeting agents into nanoparticles for the identification, prevention, and treatment of cancer diseases over the last two decades. Nanoparticles can boost the solubility of poorly water-soluble drugs, change pharmacokinetics, increase drug half-life by decreasing immunogenicity, improve bioavailability, and slow drug metabolism.

They can also allow for tunable therapeutic compound release and the delivery of two or more drugs simultaneously for combination therapy. Finally, they discussed recent developments in skin cancer treatment using various forms of nanoparticles for systemic and topical drug delivery. In particular, recent progress in treating basal cell carcinoma, squamous cell carcinoma and melanomas with nanocarriers has been made. (Dianzani *et al.* 2014). RumaMaji *et al.* (2014) have developed and characterized the Four formulations of Tamoxifen citrate loaded polylactide-co-glycolide (PLGA) based nanoparticles (TNPs) and also investigate the internalization by Michigan Cancer Foundation-7 (MCF-7) breast cancer cells. They prepared the Nanoparticles by multiple emulsion solvent evaporation methods. Then the following studies were carried out: drug-excipients interaction using Fourier transform infrared spectroscopy (FTIR), surface morphology by field emission scanning electron microscopy (FESEM), zeta potential and size distribution using a Zetasizer Nano ZS90 and particle size analyzer, and *in-vitro* drug release. They also studied the *in-vitro* cellular uptake of nanoparticles was assessed by confocal microscopy and their cell viability (%).

They found no chemical interaction between the drug and the selected excipients. TNPs had a smooth surface and a nanosize range (250–380 nm) with a negative surface charge. Drug loadings of the prepared particles were 1.5%±0.02% weight/weight (w/w), 2.68% ± 0.5% w/w, 4.09% ± 0.2% w/w, 27.16% ± 2.08% w/w for NP1–NP4, respectively. They also found that a sustained drug release pattern from the nanoparticles was observed for the entire study period, i.e., up to 60 days. Further, nanoparticles were internalized well by the MCF-7 breast cancer cells in a concentration-dependent manner and were present in the cytoplasm, and the nucleus was free from nanoparticle entry. The Drug loaded nanoparticles were found to be more cytotoxic than the free drug. Finally, they concluded that the TNPs (NP4) showed the highest drug loading, released the drug sustainably for a prolonged period and were taken up well by the MCF-7 breast cancer cell line *in-vitro*. Thus they find that the formulation may be suitable for breast cancer treatment due to the good permeation of the formulation into breast cancer [68].

Liposome-Loaded Transdermal Patch: Anjana Ashok Adhyapak *et al.,* (2016) studied Eudragit-RL, hydroxypropyl methyl cellulose K-50, and ethyl cellulose have been used to create tamoxifen-loaded liposomes transdermal patch. Using a solvent evaporation process with poly (sebacic acid-co-ricinoleic acid) in various ratios, particle size, drug packing, entrapment efficiency, transmission electron microscopy, differential scanning calorimetry, and X-ray diffraction were all investigated. The weight, medication content, moisture content, moisture absorption, folding endurance, tensile strength diffusion coefficient, and permeability coefficient of tamoxifen-loaded liposomes were all tested before being inserted into a transdermal patch. She also investigated the pharmacokinetic and pharmacodynamic parameters of transdermal patches. She finally observed that when compared to the oral route, the transdermal patches demonstrated increased bioavailability of tamoxifen and in terms of bioavailability, the tamoxifen-loaded liposomal transdermal patches may be a safer alternative to commercially marketed formulations (Adhyapak and Desai 2016). Himanshu Pandey *et al*., (2016) [50] observed that Liposomes were phospholipid bilayer vesicles that can encapsulate and shield hydrophilic and lipophilic drugs from degradation. Since their discovery in the mid-1960s, liposomes have been widely researched and pique researchers' interest.

He found that liposomes had been widely regarded as the most effective nanocarriers for drug delivery and had entered the industry. Finally, he concluded that various liposomal formulations were currently

on the market for cancer care, with even more on the way. Thus it brought him to a consensus about liposome materials, preparation processes, drug encapsulation mechanism, and possible therapeutic uses of liposomes [50]. Federico Perche *et al.,(*2013) [71] have observed that liposomes were delivery systems used to formulate various therapeutic and imaging agents for the past several decades.

They had significant advantages over their free forms in terms of pharmacokinetics, sensitivity for cancer diagnosis, and therapeutic efficacy. They found that the multifactorial nature of cancer and the complex physiology of the tumor microenvironment requires the development of multifunctional nanocarriers. The Multifunctional liposomal nanocarriers should combine long blood circulation with improving the pharmacokinetics of the loaded agent and selective distribution to the tumor lesion relative to healthy tissues, remote controlled or tumor stimuli-sensitive extravasation from blood at the tumor's vicinity, internalization motifs to move from tumor bounds and/or tumor intercellular space to the cytoplasm of cancer cells for effective tumor cell killing. Finally, they focus on current strategies for cancer detection and therapy using liposomes with special attention to combination therapies (Perche and Torchilin 2013). To combat breast cancer, a liposome-loaded transdermal patch containing methotrexate and tamoxifen citrate will be created. Tamoxifen-loaded liposomes were prepared using a solvent evaporation process with poly (SA: RA), with particle size 418 0.07, drug loading 18.78 2.84 percent and entrapment performance 90.32 2.30 percent in the optimized liposomal formulation F3. Optimized liposomes were developed into an optimized form as a transdermal patch using a combination of polymers such as Eudragit RL, HPMC K 50, and ethyl cellulose. The optimised patch formulation F3 had a better release profile than other patches with no skin inflammation.

Formulating a patch's pharmacokinetics and pharmacodynamics profile supports its superiority over other established formulations. This analysis aimed to maximize and evaluate the ability of a Liposome prepared by hot ultrasonication as a methotrexate (MTX) carrier, focusing on the use of factorial architecture. For the Liposome loaded with MTX, preliminary screening and drug/lipid solubility enabled us to choose Witepsol E85 as the solid lipid and Mygliol1 812 as the liquid lipid. Then, using a 3-level, 3-factor Box-Behnken design, and ANOVA analysis, the robustness of the d was demonstrated by the correspondence between the expected values and those tested experimentally.

The morphology, scale, zeta potential, entrapment performance, storage stability, *in-vitro* drug release, and cytotoxicity of an optimized MTX-loaded Liposome were investigated. A 252-nm spherical liposome filled with MTX had a polydispersity between 0.06 and 0.02, a zeta potential of 14 mV, and an entrapment efficiency of 87 percent. *In vitro* release tests showed a rapid initial release of MTX from the Liposome, accompanied by a delayed release lasting up to 24 h. The Peppas–Korsmeyer model for physiological and inflammatory settings and the Hixson–Crowell model skin simulation conditions better suit the release kinetics of the optimized Liposome. In fission, no toxicity was detected. As a result, the configured MTX-loaded Liposome could be used as a distribution mechanism. Tamoxifen and methotrexate are prescribed for prophylactic treatment of premenopausal and postmenopausal females with carcinoma. In carcinoma cells, it competes with steroids for steroid receptor-positive cells. Multifocal viscosity, fatty penetration, hepatotoxicity, viscous sphacelus, and blood abnormalities are also possible side effects of this drug. The transdermal patch formulation containing tamoxifen and methotrexate will have lower hepatotoxicity and hemolytic carcinoma and better patient sensitivity to care. This method is important in promoting the pharmacokinetic profile, increasing effectiveness, and reducing toxicity, possibly due to the small particle size that allows them to pass through biological barriers. Nanoparticles should be used as a controlled release mechanism in cancer treatment to reduce the occurrence of multiple side effects. As a result, this research aimed to see how effective tamoxifen- and a methotrexate-loaded transdermal patch was at preventing breast cancer [67]. Buddhade Layek *et al.*, (2010) [95] have used the soyaphosphatidylcholine (SPC), cholesterol (CH), and span 20 as key ingredients and developed a safe sustained release liposomal drug delivery mechanism for tamoxifen citrate (TC).

He prepared the liposomes made by forming a thin lipid layer and then hydrating it. He discovered that the overall vesicle diameter was 203.5 19.5 nm, with 21% of the liposomal population having an average diameter of less than 76.72 6.7 nm, and that the polydispersity index of 0.442 0.03 suggested a good vesicular distribution, and that the total drug loading was 53.60 percent of the original volume (34.58 g of drug per mg of lipid). He found that the liposomes stored at 2–8°C were found to be the most stable of the various storage environments, with just 4% of the compound lost during a 5-week storage period while the *in-vitro* release tests of liposomes indicated that 50% of the compound was released in 3 hours (h), and 95% was released in 30 hours (Layek 2010).

Magnetic Nanoparticle Loaded Transdermal Patch: ElaheAttari *et al.,* (2019) [14] have explored a co-precipitation process for developing iron oxide magnetic nanoparticles (MNPs) utilizing arginine capping. They observed that Methotrexate (MTX) was closely connected to nanoparticles, mostly as a novel drug delivery system. They found that these MNP conjugates could be used as a drug delivery vehicle and a contrast material in magnetic resonance imaging. They used nanoparticles for cancer treatment and for the detection of the target. They observed that MNPs formed a covalent bond with MTX and can target cancer cells with over-expressed folate receptors on their surfaces. To produce the nanoparticles, the amide bond was used. They used Transmission electron microscopes, dynamic light scattering, thermogravimetric analysis, differential scanning calorimetry, X-ray diffraction, and Fourier transform infrared spectroscopy to recognize Fe-Arg-MTX. On the contrary, vibrating sample magnetometer research showed that they have exceptional magnetism. Finally, they used Transmission electron microscopes, dynamic light scattering, thermogravimetric analysis, differential scanning calorimetry, X-ray diffraction, and Fourier transform infrared spectroscopy to characterize the pure nanoparticles [12].

Solid Lipid Nanoparticles Loaded Transdermal Patch: Fahima M. Hashem *et al.,* (2014) [60] examined the effect of solid lipid nanoparticles (SLN) containing the poorly water-soluble medication tamoxifen citrate (TC) on the drug's *in-vitro* antitumor action and bioavailability. She made TC-loaded SLN using the solvent injection process, and a lipid matrix of glycerol monostearate (GMS) or stearic acid (SA) as stabilizers, poloxamer 188 or tween 80 was used. She found the highest entrapment efficiency percent (86.07 1.74 and 90.40 1.22 percent) and acceptable mean particle sizes (130.40 9.45 and 243.80 12.33 nm) in TC-loaded SLN (F3 and F4) prepared with GMS and she stabilised it with poloxamer 188. She observed that the *in vitro* release of TC from F3 and F4 had a burst effect at first, then a steady release with antitumor activity and significantly enhances oral bioavailability of TC in rats. She found that the antitumor efficacy of F3 *in-vitro* against the human breast cancer cell line MCF-7 was equal to that of the free drug.

Finally, when comparing the oral bioavailability of TC-loaded SLN in rats to free TC, the findings revealed a 160.61 percent improvement in TC oral bioavailability. Thus it was concluded that incorporating the poorly water-soluble compound TC in SLN retains the *in-vitro* effects, according to the findings [60]. Vivek Avasatthi *et al.,* [42] (2016) prepared a nanogel with methotrexate (MTX) loaded nanostructured lipid carrier (MTX-NLC) and tested its effectiveness in an imiquimod-induced psoriasis model to see whether it could relieve psoriasis symptoms or not. He used a hot-homogenization process to create the MTX-NLC nanogel, which was then developed using a Design of Experiments. He chose Particle size, polydispersity index (PDI), and entrapment efficiency as the essential quality attributes. The antipsoriatic capacity of MTX-NLC nanogel was assessed by using Psoriatic Area and Severity Index (PASI) score and histopathological analysis inside an imiquimod-induced psoriasis model. The particle size of MTX-NLC was configured to be 278 10 nm, with a PDI of 0.231 0.05 and an EE of 22.29 1.23 percent. He found that as compared to MTX gel, MTX-NLC gel had a slower and prolonged release of MTX (47.32 0.94 percent vs. 94.23 0.79 percent) at the end of 48 hours.

Besides that, as the mice's skin returned to normalcy, it greatly decreased the PASI score. At the same time, the MTX gel displayed signs of hyper and parakeratosis at the end of the investigation. Consequently, he concludes that the

recently designed MTX-NLC gel formulation could be suitable for presently offered MTX formulations in treating skin problems (Avasatthi *et al.* 2016).

Microemulsions Loaded Transdermal Patch: E. Monteagudo *et al.,* (2012) [79] have prepared the microemulsions using an advanced realistic approach, characterized and used to load up to 20 mM of Tamoxifen citrate (TMX). They had fascinating drug delivery mechanisms because of their characteristics, such as nanometric mean size and long stability shelf life.

Their findings of inhibiting estradiol-induced proliferation in MCF-7 breast cancer cells *in-vitro* showed an important impact on cell growth, and after incubation with MEs containing 20 mM of TMX, it was found that the number of viable cells decreased by at least 90%. Furthermore, the two formulations containing 10 mM of substance had more than 70% cytotoxic effect. Finally, it was concluded that these findings support the creation of alternative drug administration procedures for oestrogen receptor (ER) positive tumours and ER-negative tumours (Monteagudo *et al.* 2012).

The application of biopharmaceutical concepts to formulation development has revolutionized strategy for dosage form design. Nanotechnology has become an essential element of pharmaceutical sciences and finds multiple applications in drug delivery systems in enhancing the therapeutic performance of drugs. Many of the current "nano" drug delivery systems are pedigree of conventional dosage forms like nanosuspensions, nanoemulsions and nanomicelles. Nanosuspension is an approach to deliver water-insoluble and poorly bioavailable drugs by reducing the size to the submicron range.

Thereby its dissolution rate is increased, hence the bioavailability, where drug dissolution rate is the limiting factor. Nanoemulsions are O/W or W/O emulsions, having droplet sizes from 20-200 nm that are transparent and do not have the tendency to coalesce. Nanoemulsions show great aesthetic appeal and skin feel and find their application in the transdermal delivery of drugs, topical application for systemic drug delivery, oral delivery of proteins, and delivery through parenteral and intranasal routes. Nanomicelles are self-assembling nanosized (usually with particle size within 10 to 100 nm) colloidal dispersions with a hydrophobic core and hydrophilic shell. These are currently used as pharmaceutical carriers for solubilizing hydrophobic drugs and provide a drug delivery platform to be exploited for multiple routes of administration. These nano formulations combine the advantage of maximizing therapeutic benefits with minimized side effects and improved safety since they have enormous potential of being targeted at the cellular level. This review describes various facets of nano drug delivery systems about the formulation, characterization, potential benefits and risks, and pharmaceutical applications in drug delivery [56].

SNEDDS Loaded Transdermal Patch: Simvastatin SNEDDS was created using various oils, surfactants, and co-surfactants/co-solvents. Optimized Simvastatin self-nanoemulsifying drug delivery systems (SNEDDS) were used to create transdermal films (El-Say *et al.* 2015). Work was carried out to establish and test an ultra-fine self-nano emulsifying drug delivery system (UF-SNEDDS) of meloxicam (MLX) to improve its transdermal delivery. The preliminary screening was done to select SNEDDS components based on type IV lipid-based formulations using surfactant and co-surfactant.

The findings suggested that UF-SNEDDS designed for transdermal delivery could be a promising MLX delivery mechanism, with high solubility and increased skin permeation [65]. Osama A A Ahmed optimized glimepiride (GMD)-loaded selfnanoemulsifying delivery systems (SNEDs) for transdermal patch planning. The optimized formulations were tested using an animal model for *ex-vivo* skin permeation, *in-vivo* hypoglycemic function, and pharmacokinetic parameters.

Optimized GMD SNEDs patches were discovered to increase GMD skin permeability and the evaporation rate. GMD skin permeability and the basic pharmacokinetic parameters were found to be improved by optimized GMD SNEDs patches [64].

Polyvinyl alcohol (PVA)-based transdermal films were formulated with saquinavir mesylate SQR-SNEDDS. SQR permeability was optimized and evaluated using the Box-Behnken design. Thickness, tensile strength, elongation, folding

agility, and accelerated stabilization tests were performed on the prepared films. *Ex-vivo* skin permeation and *in-vivo* pharmacokinetic parameters were tested on the optimized video. In contrast to pure SQR-loaded films, SQR-SNEDDS–loaded films had a higher Cmax and doubled the AUC. The films demonstrated improved *ex vivo* skin permeation, increased bioavailability, and circumvented the disadvantages of the oral dosage type [13]. The optimized Febuxostat FBX-SNEDDS primed transdermal film to treat gout, and chronic hyperuricemi may be a good way to boost solubility and skin permeability, resulting in increased patient compliance. The diffusion research revealed increased skin permeation, validated by imaging with a fluorescence microscope. Compared to raw FBX-loaded video, *in-vivo* plasma results revealed a substantial (p 0.05) gap in FBX plasma levels and pharmacokinetic parameters [15].

Evaluation of Transdermal Patches: An average adult's skin has a surface area of about 2 m^2 and receives about one-third of the blood that circulates in the body. For many medications, the transdermal route of administration is ineffective. The rationality of drug selection based on pharmacokinetic parameters and the drug's physicochemical properties are essential considerations when determining a drug's suitability for transdermal delivery [99]. This project aims to apply the response surface approach to producing buccoadhesive Loratadine pharmaceutical wafers (LOR). Experiments were conducted using a 3^{2-}factorial template to assess the effects of buccoadhesive polymer, sodium alginate (A), and lactose monohydrate as ingredients, as well as a hydrophilic matrix former (B) on bioadhesive energy, disintegration time, percent (%) swelling index, and time taken for 70% drug release (t 70 percent). Answer surface plots and contour plots developed by the Design-Expert program were used to investigate the influence of the two independent variables on the response variables. The response variables were optimized using the desirability function. Differential scanning calorimetry, FTIR spectroscopy, and X-ray diffraction (XRD) research were used to validate the stability of LOR and the wafer excipients. The wafers had a strong bioadhesion property, which may be beneficial for maintaining the medication in the buccal cavity, as determined by the TAXT2i texture analyzer. The observed responses matched the experimental values, and Loratadine wafers were developed with less experimental trials and a patient-friendly product thanks to the formulation by design principle. Mara Ferreira *et al.,* (2015) [52] have studied, optimized, and evaluated the ability of nanostructured lipid carriers (NLC) prepared by hot ultrasonication as methotrexate (MTX) carriers, with a focus on the use of factorial architecture. Firstly he took the NLC loaded with MTX; preliminary screening drug/lipid solubility allowed them to choose Witepsol1 E85 as the solid lipid and Mygliol1 812 as the liquid lipid. They used the ANOVA research to verify a 3-level, 3-factor Box-Behnken method; the correspondence between expected values and those tested experimentally verified the robustness of the design.

They optimized the morphology, scale, zeta potential, entrapment performance, storage stability, *in-vitro* drug release, and cytotoxicity of MTX-loaded NLCs. He observed that the NLCs containing MTX had a 252-nm spherical form, a polydispersity of 0.06 0.02, a zeta potential of 14 mV, and entrapment efficiency of 87 percent with its *in-vitro* release experiments showed a rapid initial release of MTX from the NLC, accompanied by a delayed release of up to 24 hours. Finally, they optimized the NLC's release kinetics better matched the Peppas–Korsmeyer model for physiological and inflammatory settings, the Hixson–Crowell skin simulation conditions, and lastly, in fibroblasts, no toxicity was found [52]. Andre Luis, *et al.,* (2016) have discovered that the stratum corneum was responsible for the skin barrier work, which poses a significant obstacle in clinical practice when it comes to cutaneous drug administration. Despite this, many bioactive compounds have been successfully administered *via* cutaneous administration thanks to advancements in the design of topical and transdermal formulations. He observed that to characterize the efficiency of these novel drug delivery systems, *in-vitro* and *in-vivo* tests are needed.This study examines the most widely used approaches for measuring medication cutaneous absorption as a tool for pharmaceutical formulation scientists working on drug delivery systems. *In-vitro* methods for testing cutaneous drug

penetration, such as Franz-type diffusion cell skin permeation assays, cutaneous preservation, and tape-stripping methods, and *in-vivo* evaluations, such as pre-clinical pharmacokinetic trials in animal models, are discussed. He discussed the alternative cutaneous microdialysis methods. Finally, they studied the recent advancements in studies on drug absorption through the skin and the role of skin absorption enhancers, with confocal laser scanning microscopy, Raman C, and other [43].

Anjana Adhyapak *et al.,* (2011) used the solvent evaporation technique to build a matrix-type transdermal drug delivery method for tamoxifen citrate, which was formulated using a particular ratio of eudragit RL100, hydroxypropyl methyl cellulose (HPMC-K15) and ethyl cellulose (EC) and the influence of a binary polymer mixture with a penetration enhancer on physical-chemical parameters such as thickness, folding durability, uniformity of drug content, moisture content, moisture absorption, tensile strength, and *in-vitro* drug permeation was also studied. She carried out the *in-vitro* drug permeation trials using phosphate buffer saline (pH 7.4) in modified Keshary-Chein diffusion cells through female Sprague Dawley rats' skin (PBS). Finally, the stability tests for the chosen formulation were carried out according to the International Conference on Harmonization (ICH) recommendations, and the medication did not show any signs of degradation (Adhyapak and Desai 2011).

The purpose of this investigation was to compare the permeation characteristics of two different compounds (extremely polar and nonpolar), *i.e.*, tritium-labeled water (W) and 14C-labeled 7-hydroxycoumarin (7-OHC), among 16 different species, including human skin. Snake skin exhibited the highest permeability for both W and 7-OHC. Permeability and lag time values of W and 7-OHC across Brattleboro rats and hairless guinea pigs are very close to human skin. Skin thickness in micrometers (full thickness, epidermis and stratum corneum, and stratum corneum) and the number of hair follicles present in each cm2 were determined for each species. There was no relationship between number of hair follicles and permeability values for both W and 7-OHC. The skin thickness (full) was related to the relative permeability values of W, whereas, for 7-OHC, it was not [103].

Biomedical Applications and Future-Perspectives:

Rheumatoid Arthritis: Bhakti Sadarania *et al.*, (2019) worked on low-dose methotrexate (MTX) treatment, which was the gold standard for Rheumatoid Arthritis at the time (RA). They Wrapped the Methotrexate in deformable liposomes and loaded it into a hydroxyethyl cellulose gel in their analysis. They used the Box Behnken statistical architecture to test this system for optimization. Here the Particle scale, entrapment, and *ex-vivo* skin permeation were explored as a function of formulation variables.
They looked at the MTX nanogel's dermal toxicity (acute and repeat dose safety), *in-vivo* biodistribution (using 125I radiolabeled MTX), and therapeutic efficacy (collagen-induced arthritis [CIA] model). The optimized formulation had an appreciable nanosize (110 20 nm). In contrast, the nanogel formulation showed no signs of inflammation or toxicity in dermal toxicity tests. In contrast, in a biodistribution review, the MTX nanogel formulation demonstrated prolonged systemic transmission for up to 48 hours with low concentration in toxicity organs, including the liver, kidneys and stomach.

They conclude that. In the CIA model, the Methotrexate nanogel reduced hind paw swelling, arthritic score, joint injury (histological and radiological examination), and serum cytokines, including TNF- and IL-6. Finally, the optimized MTX nanogel formulation demonstrated skin biocompatibility, continuous systemic delivery, stability and therapeutic efficacy [11].

Colonic Carcinoma: Mansi Paradkar *et al.,* (2018) [27] have aimed to develop and describe colon-targeted methotrexate pellets for the treatment of colonic carcinoma. They used Screening methods to optimize the product and process parameters. They used extrusion spheronization to make the pellets using different ratios of microcrystalline cellulose (MCC) as a spheronizing aid and ethyl cellulose (EC) as a release retardant. They optimized that the Batch P17 containing EC: MCC (3:7) was for core pellets based on physical appearance, sphericity, and percentage *in-vitro* drug release after screening the coating polymers and coating the core pellets with Eudragit S100; they observed the site specificity.

They used the 3^2 full factorial design with the independent variables becoming airflow intensity (X1) and coating time (X2) and the dependent variables becoming physical appearance (Y1) and time taken for 100 percent drug release (Y2). The results found that a coating time of 6 minutes and an airflow rate of 60 cm3 per minute were optimum. One the other hand, *ex-vivo* studies on rat colons revealed a significant connection with *in-vitro* drug release. He observed that Batch B5 showed appropriate physical appearance and percentage *in vitro* drug release up to 17 h, showing sustained release property. The drug release followed Higuchi's model, representing a diffusion pattern for drug release from a pellet matrix. As a result, they conclude that coated pellets could be a good candidate for site-specific Methotrexate delivery to the colon, as they minimize gastric discomfort and thus improve the bioavailability [27].

Psoriasis: Aly A. Abdelbary *et al.,* (2015) [53] found that Psoriasis, a skin disease marked by compromised epidermal differentiation, was commonly treated with systemic methotrexate (MTX), a cytotoxic drug with a long list of side effects.

He aimed of this study was to create topical MTX-loaded niosomes for psoriasis treatment without causing systemic toxicity. He used the thin film hydration to prepare MTX niosomes to accomplish that goal. To statistically maximize the formulation variables, Box-Behnken (BB) architecture was used with Design-Expert tools. They looked at three independent variables: MTX concentration in the hydration medium (X1), the overall weight of niosomal components (X2), and surfactant: cholesterol ratio (X3) (X3). He found that the dependent variables were encapsulation efficiency percent (Y1: EE percent) and particle size (Y2: PS). So under transmission electron microscopy (TEM), the best formulation (F12) had a spherical morphology, an optimal particle size of 1375.00 nm, and a high EE percent of 78.66 percent was observed. Finally, they conclude that in an *in-vivo* skin deposition sample, the MTX from niosomes had the largest percentage of drug deposited (22.45%) and AUC0–10 (1.15 mg.h/cm2) values, which were slightly higher than drug solution (13.87 percent and 0.49 mg.h/cm2, respectively) and the in vivo histopathological tests demonstrated the protection of niosomes applied topically. Thus the findings showed that targeted MTX distribution could be accomplished (Abdelbary and Abou Ghaly 2015).

Neoplasms: Hamed Nosrati, et al. (2018) [31] observed that methotrexate (MTX), a stoichiometric inhibitor of dihydrofolate reductase enzyme, was a chemotherapeutic agent for treating a diversity of neoplasms. In that study, they designed and developed a new formulation of MTX that served as a drug carrier and examined its cytotoxic effect *in-vitro.*

That target drug delivery system depended on the MTX's release within the lysosomal compartment. They first surface coated the iron oxide magnetic nanoparticles (IONPs) with L-lysine and subsequently conjugated with MTX through amidation between the carboxylic acid end groups on MTX and the amine groups on the IONPs surface. They characterized the MTX-conjugated L-lysine coated IONPs (F-Lys-MTX NPs) by X-ray diffraction, thermogravimetric analysis, differential scanning calorimetry, Fourier transform infrared spectroscopy, vibrating sample magnetometer and transmission electron microscopy techniques.

They also compared the cytotoxicity of the void of MTX and F-Lys-MTX NPs to each other by MTT assay of the treated MCF-7 cell lines, and the results showed that the f-potential of F-Lys-MTX NPs was about 5.49 mV and the average size was 43.72 ± 4.73 nm. They observed that the model studies exhibited the release of MTX via peptide bond cleavage in the presence of proteinase K and at low pH. Finally, they conclude that these studies specify that F-Lys-MTX NPs had a remarkable anticancer effect on breast cancer cell lines (Nosrati *et al.* 2018).

Oral Cancer: Bao-Zhong Jin *et al.,* (2017) [21] have focused on developing a methotrexate mucoadhesive patch for oral cancer treatment. Methotrexate-loaded liposomes with a mean diameter of 105.7 137.4 nm and a percentage entrapment efficiency of 54.63.5 were first prepared using the thin film hydration method. They placed the liposomes in an optimized mucoadhesive film, which was defined only by release pattern, thickness, weight, percentage

swelling index, sustained release pattern, and the film's thickness, weight, and percentage swelling index. The formed liposomes distributed in the polymer were tested for cytotoxicity in HSC-3 cells using an MTT assay. They observed that MTX's half maximal inhibitory concentration was lower in the Methotrexate entrapped liposomal film, M LP F7. Finally, when compared to the control group compound, the mitochondria-dependent intrinsic pathway revealed that M LP F7 had induced major mitochondrial membrane potential damage. They observed that M LP F7 accelerated the amount of apoptosis in HSC 3 cells by approximately threefold. Thus they conclude that the increased levels of reactive oxygen species in HSC-3 cells indicate that M LP F7 has a pro-oxidant effect [21].

Anti-Tumor: Dalia S. Shaker *et al.,* (2016) [39] observed that one of the most challenging aspects of using Tamoxifen citrate (TMC) in breast cancer therapy is to achieve a proper target and efficient delivery of sufficient concentration to the adeno carcinoma, thereby minimizing harm to healthy glandular and soft fatty tissue. They proposed Niosomal thermo - responsive hydrogels to solve that issue in TMC. They used Film fluid intake to make niosomes, which were then incorporated into Pluronics thermosensitive gels produced using the cold process; after that, the gelation temperature, rheological activity, and they also tested the *in-vitro* drug release of the hydrogels. Besides that, he also investigated the *in-vivo* anti-tumor activity in Ehrlich carcinoma mice by reporting tumor cell volume regression and TMC tissue distribution. He observed the type and ratio of poloxamers which got modified to attain the optimum gelation temperature (34 to 37 ^{o}C). He found that at low and room temperature the rheological findings showed low viscosity and elasticity values, which greatly improved at physiological temperatures. Tamoxifen citrate was identified after a long diffusion-driven release. Finally it was concluded that the anticancer activity was evidently increased with significant drug retention at the tumour site, according to *in-vivo* data. These encouraging findings indicate that this *in-situ* hydrogel depot has a lot to come (Shaker *et al.* 2016).

Skin Cancers: Amit Bhatia *et al.,* (2012) [73] have found that Tamoxifen (TAM) was a non-steroidal estrogen receptor modulator known for its anticancer activity. Apart from marked breast cancer activity, this drug has also shown potential in treating other cancers, including skin cancer. TAM was reported to be associated with serious side effects primarily due to its systemic distribution. They observed that the localized delivery of this drug in this regard would be highly beneficial concerning safety and efficacy. In their current studies, they investigated the efficacy of topically applied liposome-encapsulated TAM on skin cancer models. The drug was encapsulated in phospholipid-based vesicular systems *viz.* conventional liposomes and elastic liposomes. The incidence of papilloma and histopathological examination was employed to determine the efficacy of the tested formulations. Finally, they demonstrated carrier-dependent strong inhibition of skin carcinogenesis with encapsulated drug vis-à-vis the solution form. And the encouraging findings from the current work construe the immense potential of TAM-loaded liposomal systems in managing skin cancer [73].

Parkinson's disease: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder characterized by a loss of dopaminergic neurons severely in cytoplasmic inclusions and substantia nigra. Several therapeutic agents are available to treat the early and advanced stages of PD. However, the transport of therapeutic actives in to the brain has been a consistent challenge for researchers because of the presence of the blood-brain barrier (BBB). Various novel delivery carriers have been designed to deliver the drugs across BBB, and the systems have been designed to target the drugs and overcome the BBB effectively. In some last decades, transdermal delivery carriers have gained extensive deliberations across the globe. These transdermal systems are depicted to be the most recent modalities in treating PD as they offer constant drug delivery, immediate effect as intestinal absorption in unneeded, and ease of application being a non-invasive technique.

The present review explores the potential of transdermal delivery systems to deliver numerous therapeutic activities researched for PD therapy via the transdermal route. Various trans-carriers such as patches, oil-based nanocarriers, nanoemulsions have been observed to treat PD. The write-up traces the reports on transdermal delivery carriers in PD

and clinical study data to define the feasibility of transdermal carriers [32]. Adherence to prescription psychiatric and nonpsychiatric medicine is a significant problem for people with mental illnesses and can lead to negative health outcomes. Adherence is influenced by various factors, including prescription side effects and ease of use. There seems to be a renewed interest in solving challenging dilemmas of protection and commitment to treatment as mental healthcare increasingly focuses on a community health delivery model. Any of these issues may be solved by using new methods of safely distributing drugs in novel ways. In the published literature, there has been no mention of the broader use of transdermal patches in psychiatry. This article summarises research findings on core concepts underlying transdermal delivery methods, as well as the extent of clinical use in psychiatric disease, difficulties and benefits (Isaac and Holvey 2012).

Targeted Drug Delivery: Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. Targeted drug delivery aims to concentrate medicine in the tissues of interest while lowering its relative concentration in the rest of the body. This improves the efficacy of the while reducing side effects. It is very difficult for a drug molecule to reach its destination in the complex cellular network of an organism. Targeted delivery of drugs, as the name suggests, is to assist the drug molecule in reaching preferably to the desired site. The inherent advantage of this technique has been the reduction in dose & side effects of the drug. Research related to developing targeted drug delivery systems is now a highly preferred and facilitating field of the pharmaceutical world. A quantum dot is a semiconductor nanostructure that is particularly significant for optical applications due to its theoretically high quantum yield. Transdermal devices allow for pharmaceuticals to be delivered across the skin barrier.

Molecules as diverse as small radiodiagnostic imaging agents to large DNA plasmid formulations have successfully been delivered inside FR-positive cells and tissue. (Gupta and Sharma 2011) Delly Ramadon *et al.,* (2021) [2] estimated that transdermal drug delivery systems had tremendous growth as a fascinating research subject in pharmaceutical science. They also found one of the very commonly manufactured pharmaceutical brands on the market.

They observed other delivery routes, such as oral and parenteral, and found drawbacks that can be overcome using these systems. They look at emerging developments and the potential scope of transdermal technology, emphasizing developing a complete knowledge of transdermal drug delivery systems and yield benefits. The report section discussed how each transdermal enhancement approach was used in developing transdermal products. Another of the methods that were used is drug-vehicle interactions, vesicles and particles, stratum corneum modification, energy-driven processes, and stratum corneum by-passing techniques. Transdermal delivery systems have been seen to distribute either primary or secondary metabolite drugs through the proper formulation and construction of active stratum corneum by passing technologies, such as microneedle technology.

They found that Microneedle innovations have proven more stable than other transdermal systems, allowing for intradermal delivery of drugs/ biotherapeutics and therapeutic drug monitoring. Finally, they conclude that Microneedles have been shown to be a successful strategy for improving transdermal delivery systems in that research (Ramadon *et al.* 2021 Jan 20). Nanotechnology has revolutionized healthcare methods in recent years and is expected to have a huge effect on providing improved health facilities. Medical nanotechnology, in this context, refers to the creation, fabrication, control, and application of therapeutic drugs and devices with nanoscale (1–100 nm) dimensions. Nanotherapeutics is gaining growing research interest in the modern medical field due to its groundbreaking implications in drug delivery and gene therapy.

Cancer, diabetes, infectious diseases, neurodegenerative diseases, blood disorders, and orthopaedic issues are all expected to benefit from nano-based drug delivery systems. (Prasad *et al.* 2018). The novel nanotherapeutic potentialities of polymeric nanoparticles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers,

dendrimers, nanocapsules, and nanosponges-based approaches have been highlighted in this report. These nanomedicines' potential applications as Transdermal drug delivery systems in the field of cancer have been thoroughly explored. Nanosystems' regulatory and safety issues, as well as their commercial status, have all been discussed. In conclusion, effectively translating emerging nanotherapeutics as Trandermal patch into commercial products can lead to the expansion of biomedical science. Future viewpoints in this critical area are discussed towards the end of the study.

CONCLUSION: Traditional cancer therapy is important; however, there are many drawbacks to the delivery of antineoplastic agents and their pharmacokinetics, including anti-cancer drug resistance, toxicity, and lack of selectivity. The random damage to healthy cells, the toxicity associated with chemotherapy, and learned susceptibility to it all necessitate the search for reliable, site-specific therapies. Newer methods for delivering antineoplastics across the skin, such as a transdermal patch, allow for more effective cancer therapies with less side effects and a clearer pharmacokinetic profile. This study addresses the old and new approaches that can be used to improve the successful transdermal delivery of cytotoxic agents. Studies have shown that these methods have a lot of promise and could open up a new treatment frontier for breast cancer. However, it is critical to enter these antineoplastic drugs' therapeutic window and broaden the horizons of a combination of therapies that can smooth the development of anti-cancer drug transdermal delivery.

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