



ANTI-NEOPLASTIC TRANSDERMAL PATCHES: A NOVEL APPROACH FOR TARGETED DRUG DELIVERY USING NANOCARRIERS IN CANCER THERAPY

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ABSTRACT

Innovative Nano-carrier-based transdermal patches, a wonder of advanced technologies, have received overwhelming endorsement in medicinal applications primarily in the provision of anti-neoplastic drugs. The purpose of this study was to review the limitations of conventional therapeutic initiatives namely chemotherapy, having several adverse effects, including significant inflammation, toxicity, and discomfort. Antineoplastic transdermal patches can be used as a prophylactic treatment method to treat a variety of cancers through the skin. Novel transdermal methods and Nano-carrier formulations have evolved to resolve the skin constraints and delivering the active drug to the underlying tissue of the skin enabling access to the systemic absorption of drugs and eventually get within tumour cells by approaching different targeting mechanisms. The transdermal administration of antineoplastic drugs is a promising alternative for boosting site-specific application, minimizing adverse effects, hepatic first-pass metabolism and promoting therapeutic value. Furthermore, the utilization of nanocarriers serves as a permeation enhancer to broaden the spectrum of medicines accessible for transdermal administration that has emerged as a viable and intriguing option. This review examines the benefits of transdermal delivery for anti-neoplastic drugs to ensure a good insight into their effectiveness in terms of modern clinical demands, to present a highlighted overview of transdermal drug delivery, and seeks to better comprehend the nano-formulations employed in transdermal drug delivery system (TDDS). Conclusively, reflecting the framework for future research and promoting the chemotherapeutic use of transdermal delivery over conventional dosage forms.

Keywords: Transdermal drug delivery system, Transdermal patches, Nano-carriers, Anti-neoplastic drug delivery, Skin barrier, Permeation, Cancer.

1. INTRODUCTION

The transdermal drug delivery system (TDDS) has enlightened to be a promising arena for the scientific breakthrough and patenting of antineoplastic-drug delivery technologies. Discovering novel and creative cancer therapies is a big challenge all around the world [1]. Traditional chemotherapy is a prevalent cancer treatment technique. But, despite working through several methods, it mostly involves destroying cells that develop intensively, including tumours and normal cells, with significant side effects, such as suppression of the bone-marrow, loss of hairs and gastrointestinal problems [2]. Over the last few decades, consequently, a substantial part of cancer-related research has been used towards the development of medications to target tumour cells more precisely than healthy cells. The therapeutic efficacy of

various tumours has considerably enhanced as the variety of approaches for treating cancer has been raised, along with the innovative idea of transdermal nano carrier-based treatment. The FDA authorized transdermal scopolamine for the first transdermal patch in 1979 for preventing travel-related nausea and vomiting. Nicotine patches were also employed for people to avoid bad-smoking habits [3]. Transdermal drug delivery has gained utmost prominence in recent years, which utilizes self-administered transdermal patches, having the property of efficient drug delivery that allows the medicine to penetrate through the intact skin for a regulated timeframe to access a local or systemic impact. Although, it would be advantageous to administer more medicines through patches, the stratum corneum, the outer dermal layer, acts as a prime barrier, preventing transdermal

permeation of most chemicals at therapeutic dosages. The key aspect of the stratum corneum is the protection of the tissues underneath the skin, although it frequently reduces the number of medicines passively receptive to the dermis [4].

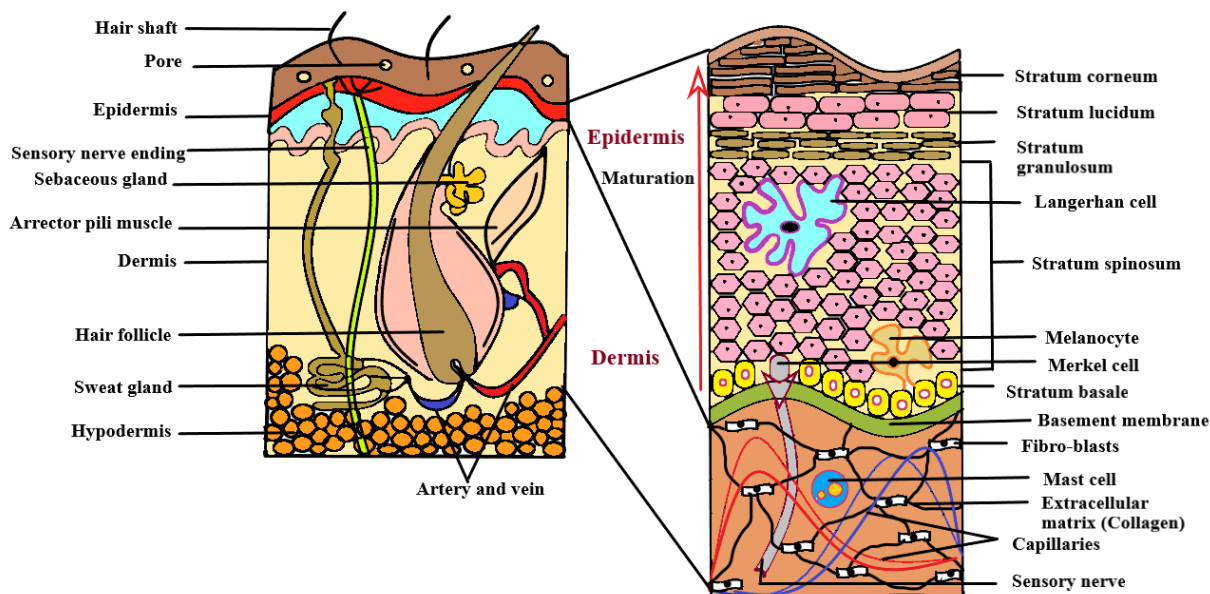
With the advent of novel nanotechnology, difficult-to-penetrate anticancer macromolecules like nucleic acids and proteins may now be administered transdermally via penetration enhancers [5]. Nano-carriers offer a framework for encapsulation and circulation of medicinal products [6,7]. They can prolong the half-life of medicines and cause their aggregation within tumour tissue due to their size, surface features and their activity in enhancing permeation and retention [8,9]. The targeting mechanism, however, shields healthy tissue from drug cytotoxicity that helps to alleviate cancer treatment side effects. For instance, PEGylated liposomes filled with doxorubicin lower its cardiotoxicity than unbound doxorubicin [10].

Nano-carrier formulated transdermal patches have established a new era of anticancer therapy and further study is deemed necessary in conjunction with this area. This review outlines the short overview of the different types of transdermal patches, which are available with consent from the FDA, their structural components,

physicochemical properties and fundamental principles of use of the nanocarrier system in the treatment of cancer, tracing their existing problems and unfolding the path for future research prospects [11,12].

2. SKIN AS A PRIME BARRIER AND ITS ANATOMY

The skin is the prominent outer protective covering and the body's largest organ, forming an essential foundation barrier interface between the body and the external habitat. It covers an area of about 1.5-2.0 m² and around 15% of the absolute body weight of adult human beings [13]. It carries out numerous essential physiological activities such as protection, assurance against exterior physical, synthetic, and biotic aggressors, and thermoregulation thereby aid in keeping the water and homeostatic equilibrium of the body [14]. Besides all the above, scientists have endeavoured to utilize the skin for drug delivery to conquer issues related to conventional methods of medication. This has been a convoluted job because of the exceptionally viable hindrance properties of the skin [15]. To satisfy these functions, three layers of skin are involved: the epidermis (outer layer), the dermis (middle layer), and the hypodermis or the subcutaneous tissue (inner layer).



The skin serving as a formidable barrier, consisting of the epidermis, made up of five layers, each of which plays a role in skin renewal and topmost layer (i.e., the Stratum corneum), acting as a prime barrier; followed by the layer of dermis and hypodermis.

Fig. 1: Schematic representation of the anatomy of skin [16]

2.1. The epidermis

It exists as a peripheral layer of ectodermal origin made of stratified squamous epithelium and confers its barrier

properties [17]. The keratinocytes are the actual physical barriers that undergo dynamic mitotic multiplication in the more profound layers, the

generation of new cells and uprooting the mature cells towards the surface via the process known as cornification, which develops into five distinct sub-layers as Stratum basale, Stratum spinosum, Stratum granulosum, Stratum lucidum, and Stratum corneum [18,19]. The stratum corneum also called the horny layer, is the topmost layer comprising of dead keratinocytes lacking nuclei, packed within lipid grid, and coordinated as different lamellar bilayers thus forming a cornified layer displaying “Bricks and Mortar” arrangement. These profoundly hydrophobic lipids forestall water loss and in like manner block the passage of most topically applied medications, other than those that are lipid-solvent and thus function as a prime barrier of the skin [20,21].

2.2. The dermis

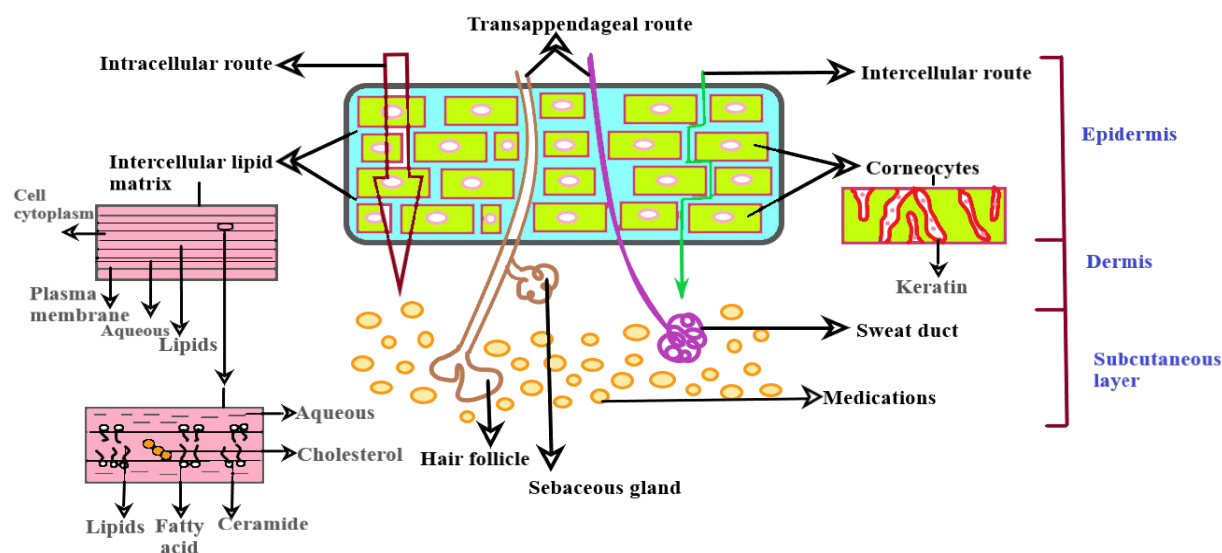
The fundamental framework of the dermis is formed by collagen and elastin and other extracellular networks of proteins by fibroblasts [22,23]. Furthermore, it contained hair follicles and sweat glands for regulating the optimum temperature [24].

2.3. The hypodermis

It is the deepest layer of loosely arranged connective tissues, lying underneath the dermis and incorporates subcutaneous fat in the form of macrophages and adipose tissues that shield and performs adipose homeostasis in obesity [23].

3. ROUTES OF DRUG PERMEATION

As a potential barrier of the skin, the stratum corneum (SC) resists the absorption of the drugs, however, the occurrence of different assimilation pathways enables the drugs access and their delivery into the systemic circulation. Both hydrophilic and lipophilic drugs are retained from these pathways [19]. Different investigations have been led to resolve the available pathways for the drug permeation via the skin and are categorized into two major macro routes. The first and foremost is the trans-epidermal route, that enables the transport of essential drugs from the intact layer of stratum corneum into the systemic circulation and incorporating two pathways i.e., the trans-cellular route where the drug passes across the corneocytes having profoundly hydrated keratin creating a hydrophilic-pathway accessible to polar molecules and the inter-cellular route that allows the diffusion of drug across the continuous lipid matrix creating a lipophilic pathway accessible to non-polar molecules [19,25]. Lipophilic molecules favor the passage along the inter-cellular route whereas the hydrophilic molecules favor the trans-cellular route over the inter-cellular route [26]. Secondly, the trans-appendageal route that ensures the permeation of drugs along the trans-follicular route involving the sweat ducts, sebaceous gland, and hair follicles. It bypasses the passage through the stratum corneum and likewise, is referred to as the shunt pathway [27].



a. Intracellular route-drug passes across the corneocyte, b. Inter-cellular route-diffusion of drug across the continuous lipid matrix, and c. Trans-appendageal route-across sweat glands, sebaceous gland and hair follicles.

Fig. 2: Schematic representation of routes of drug permeation via the skin [28, 29], involving three pathways

4. NANOMATERIAL FORMULATED SKIN PERMEATION

Some molecules travel through these above-mentioned pathways very slowly, and the SC of the skin provides the strongest resistance during transdermal drug penetration. So, it is difficult to reach effective levels of drugs in the deeper layers of the skin and to deliver large amounts of drugs into the blood. Thus, an endeavour in the growth of nanoparticle transdermal drug delivery systems has been taken, which can deliver active ingredients of different molecular weights and lipophilic properties to and through the skin, while protecting them from skin metabolism [30]. Nanotechnology is the technique of producing or

processing macromolecular matter with a particle size of 1-100 nm utilizing an individual atom or molecule. Nano-formulations are an important topic of nanotechnology. Nano-formulations have higher efficiency due to their tiny particle size, medication retention, precision and localized targeting, thus making them suitable for TDDS [31].

4.1. Factors governing Nano-based permeation

Nano-carriers are promising molecules, providing a lot of benefits that make them an excellent medication delivery system. The fundamental factors controlling Nano-permeation are mentioned underneath in Fig.3 [32]:

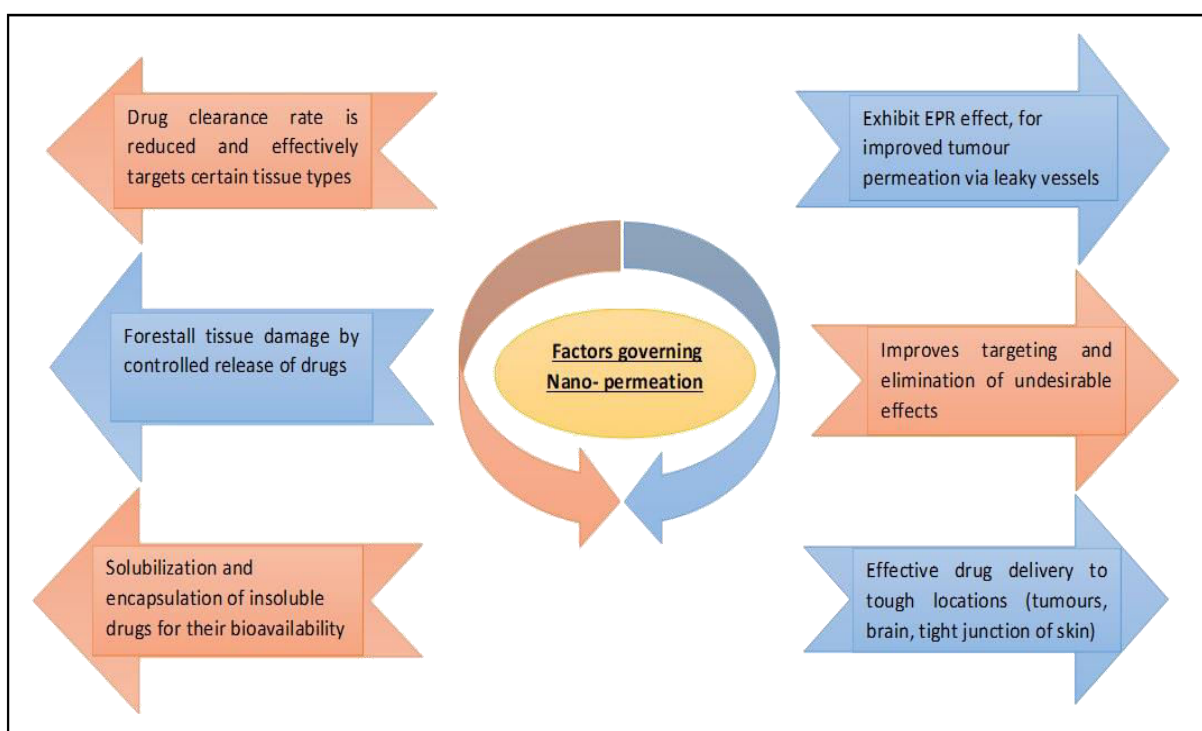


Fig. 3: Illustrative view on the prime fundamental factors that govern the Nano-based permeation of drugs and their efficacy on working as a targeted and controlled drug delivery systems [33, 34].

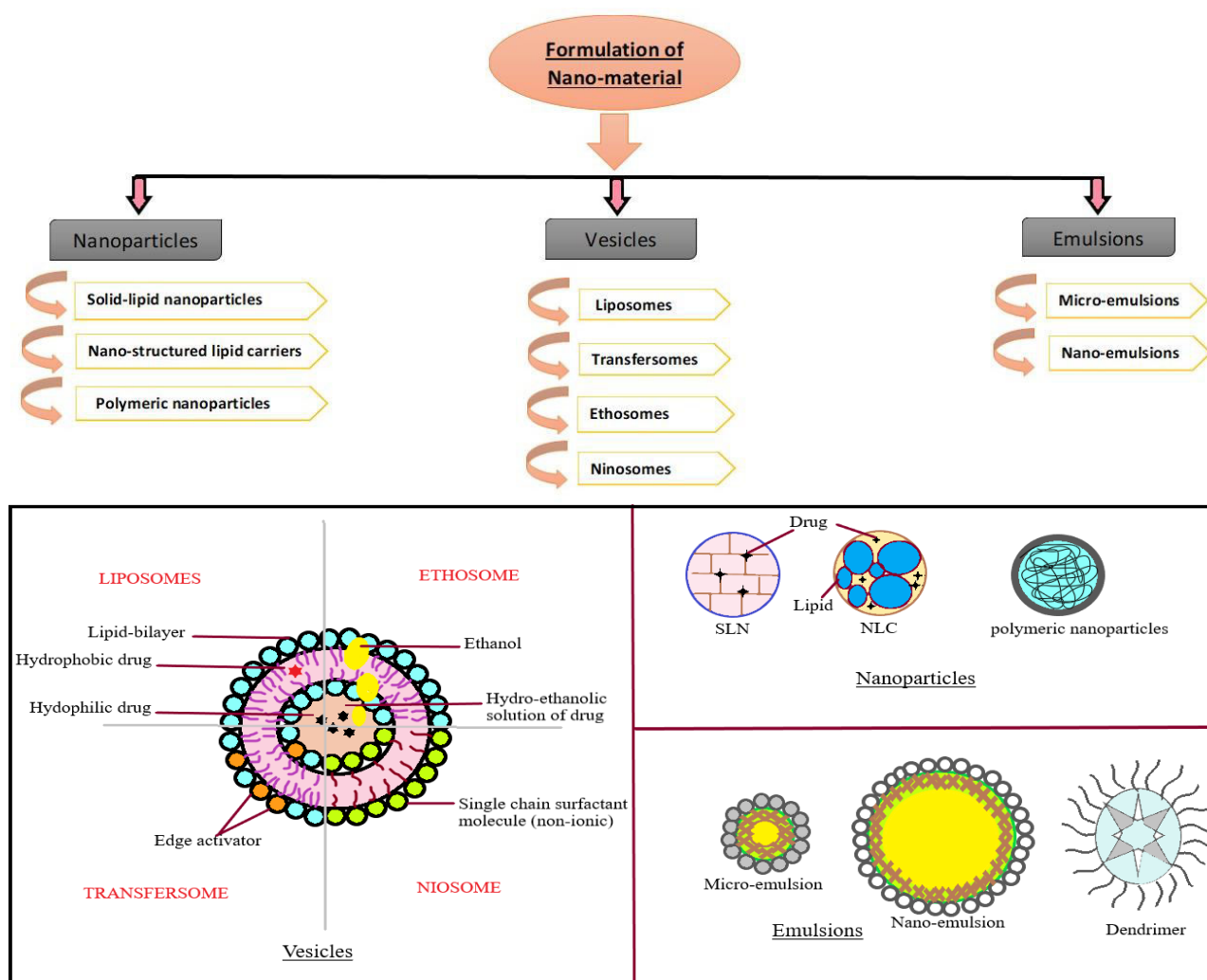
5. TYPES OF NANO-MATERIALS USED FOR DRUG DELIVERY

Nano-formulations for the transdermal drug system can be classified as shown in Fig. 4. The thematic distribution of different types of nano-material formulations used in the transdermal drug delivery system [31].

5.1. Micro-emulsions and Nano-emulsions

Micro-emulsions and Nano-emulsions are two immiscible aqueous phases dispersed in a Nano-metric

dispersive system. Although both systems are low viscosity colloidal dispersions, they are categorised as fundamentally separate formulations despite their apparent similarities [37]. Dispersions with droplet sizes ranging from 10 to 100 nm are known as micro-emulsions. They are thermodynamically stable [38]. In contrast to this, Nano-emulsions can feature droplet sizes as small as 250 nm [39]. They are kinetically stable yet thermodynamically unstable [40].



Nanoparticles employed for transdermal drug delivery system. Nanocarriers adsorb at the skin's surface, forming a film that transports the nanocarrier-loaded medicine into the skin; the smaller the size, the higher the transdermal absorption [35, 36].

Fig. 5: Schematic illustration of assessing smart nanocarriers in the form of vesicles, emulsions and nanoparticles

5.2. Liposomes

Liposomes are structures composed of lipid bilayers that can transport water-soluble medications within the core while also delivering lipid-soluble medications between the bilayers. Liposomes have been frequently employed in transdermal administration. Cholesterol and phospholipids make up these systems. Liposomes are among the greatest therapeutic delivery systems since they are nontoxic and stay in circulation for an extended period of time. They're being utilized to treat cancer and skin melanoma with great effectiveness [41].

5.3. Transfersomes

Cevc et al. in 1992 coined the name "Transfersomes," which are also known as deformable liposomes, elastic liposomes, or ultra-flexible liposomes. Their enhanced

flexibility is due to the addition of a single-chain surfactant i.e., a bilayer softening component, such as sodium cholate, polysorbic acid (also known as an edge activator) [31]. Transfersomes sustain the capacity to pass through minute pores 5 to 10 times smaller than vesicle diameter, as well as their numerous benefits over traditional liposomes for cutaneous distribution, which have been widely addressed [37].

5.4. Ethosomes

Touitou invented ethosomes in 1996 and published them in 2000. Ethosomes are fluidic vesicles that store a large amount of ethanol, phospholipids, and water. They are used to administer drugs transdermally [31]. The principal function of ethanol is to impart flexibility and softness to the membrane of ethosomes to provide a

kind of malleable vesicles with uni-lamellar or multi-lamellar frameworks with lipid bilayer encircling a liquid phase and encapsulated medicines. Thus, allowing them to penetrate underlying skin layers and circulate throughout the body. They may have a broad array of prospects as a result of these factors [27, 41].

5.5. Ninosomes

Ninosomes are attractive drug carriers as they are more stable and lack many of the drawbacks associated with liposomes, such as toxicity and the high value of lipids. The hydrated combination of cholesterol and non-ionic surfactant (such as alkyl ethers, alkyl esters) that are biocompatible and non-immunogenic, leads to the formulation of vesicles that can entrap both polar and non-polar medicine forming an innovative drug delivery method. They can be unilamellar or multilamellar [42,43].

5.6. Solid-lipid nanoparticles (SLN)

Solid lipid nanoparticles (SLN) exist as colloidal nanoparticles with diameters ranging between 50-2000 nm and are composed of emulsifiers and solid lipids. They are well-known for numerous reasons as reliable medication for targeted delivery, non-toxicity, biodegradability and biocompatibility are all factors to be considered. Surface-active compounds stabilize the lipid core, which contains the encapsulated active ingredient [37,44,45].

5.7. Nano-structured lipid carriers (NLC)

Solid and Liquid lipids are combined in the ratio of 7:3 to 9:1 to create nanostructured lipid carriers to forestall the recrystallization of solid lipids by creating a matrix core less organized and lowering the melting point as well [46-48]. NLCs is an improved variant of SLNs, with the same distinctive features as SLNs though a more adaptable core composition that allows for greater payload, improved stability, and ability to operate at low temperature [49].

5.8. Polymeric nano-particles

Polymer-based nanoparticles are colloidal conveyers having a size varying from 10-1000 nm, that solubilize and encapsulate the drugs into a polymer matrix for its transport to the systemic circulation via TDDS [38]. They have received much interest in the field of TDDS because they can conquer some of the restrictions of other lipid systems, such as protecting unstable drugs from degradation and denaturation, releasing

continuously to reduce toxic drug side effects, and increasing the concentration gradient to improve drug percutaneous permeability [46].

5.9. Dendrimers

Dendrimers are potential nanocarriers having a size of 1-100nm and helps in reducing for toxicity and enhancing solubilizing properties of anti-neoplastic medicines and promote targeted delivery of therapeutics [50]. Factors combined with these dendrimers, such as their monodispersal size, multivalence, changing surface functions, solubility in water, and the internally accessible cavity, make them appealing for controlled and targeted drug delivery [51].

6. TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Transdermal drug delivery systems (TDDS), also renowned as transdermal patches or skin patches, have engrossed all the spotlight over the traditional dosage forms. It is a first-generation medication delivery method involving a passive way of distribution. The FDA authorized the first Scopolamine-containing transdermal patch in 1979, for preventing vomiting and nausea during traveling. The Nitroglycerine patches were approved by FDA in 1981, accompanied by Fentanyl and nicotine patch in 1990 and 1991, respectively [52]. A transdermal patch is a self-medicating adhesive patch that is applied topically and brought up a basic idea of controlled drug delivery that delivers a precise dosage into the circulation [53]. Moreover, TDDS not only permits regulated medication delivery but also enables the continuous input of short-lived biological medicines and prevents pulsed entrance into blood circulation, which typically produces adverse reactions [54]. From a large perspective, TDDS refers to all topically applied medicine formulation, designed to transport the active substance into the bloodstream. Furthermore, it eliminates some of the negative consequences of traditional drug delivery systems, such as painful drug supply and first-pass metabolism. As a result, transdermal delivery has sparked a lot of attention in subsequent years and became a major subject of interest [55].

6.1. Merits of TDDS over conventional dosage forms [56, 57]

- Patches can be self-administered by the patients.

- The patch may simply be removed if the toxicity arises from TDDS.
- Avoidance of the first-pass metabolism of drugs via the liver, gastrointestinal system and oral route, resulting in increased drug bioavailability.
- It is a non-invasive and pain-free approach for the continuous delivery of therapeutics.
- Ensures controlled and prolonged administration of medicines with biochemically small half - life and precludes irregular entry into the blood stream.
- Employed as an alternative to the oral dosage forms for those who find it hard to take medications orally.
- Eliminates the severe side-effects of traditional dosage formulations by targeted delivery.
- Improved patient compliance by eliminating several dose intervals.

6.2. Demerits of TDDS [55, 57]

- There is a chance of skin discomfort at the site of medication delivery.
- Only some strong medicines are suited for transdermal treatment.
- Ionic medicines are incompatible with transdermal delivery.
- Several hydrophilic medications are either unable to penetrate through the skin or do so extremely slowly, that leads to reduction in medication efficacy.
- Drug adherence to the skin can lead to dumping dosage.
- The medication causes local edema, many other issues like itching and erythema due to adhesives and other excipients in the patches.
- Patches are only feasible for chronic diseases and not for acute diseased conditions.
- The efficacy of TDDS will be influenced by dermal metabolism.

7. TRANSDERMAL PERMEATION: FACTORS AFFECTING PERMEATION

Taking account of three components, namely the skin, the medication, and the carriers, can be used to build a successful transdermal drug delivery system. As a result, the influencing elements may split into two categories: biological and physicochemical aspects.

7.1. Biological Factors

7.1.1. *The skin's health and age*

Acids and alkalis, as well as a variety of solvents such as chloroform and methanol, cause cellular skin damage and encourage permeation. Furthermore, being a prime barrier, the intact skin of children is more permeable than the adult because toxin absorption via the skin is particularly high. The drug absorption in TDDS is boosted in response of these characteristics.

7.1.2. *Availability of blood*

For TDDS, peripheral blood flow is an important element in medication uptake. Increased blood circulation results in rapid assimilation of TDDS.

7.1.3. *Skin localization and variation between species*

The composition of the skin barrier, skin thickness, keratinization, and the density of appendages differ by regional skin location as well as across species. These variables have a substantial impact on permeation.

7.1.4. *The metabolic rate of skin*

The bioavailability of medicines absorbed via the skin is determined by the metabolic rate. The skin metabolises steroids, hormones, chemical toxic substances, and also some medications.

7.2. Physicochemical Factors

7.2.1. *Skin hydration*

Keeping the skin moist is the key factor in improving skin permeability, which increases considerably when it comes into contact with water. Formulations such as humectant are used in TDDS.

7.2.2. *pH of the skin*

The amount of drug in the skin is determined by the fraction of unionized drugs as only they are compatible for permeation. Dissociation of weaker acids and weaker bases takes place depending on pH and the values of pKa or pKb. When the pH of the skin matches that of the medication, drug absorption is quick.

7.2.3. *Temperature and Diffusion coefficient*

With temperature changes, drug penetration increases tenfold. The diffusion coefficient of the drug drops with a decrement in temperature and at a constant temperature, it depends on the characteristics, medium of diffusion, and the relationship between the drugs.

7.2.4. Partition coefficient

For serious enforcement, the ideal partition coefficient (K) is essential. Drugs having a high K content are unable to pass through the lipid layer of the skin. Additionally, medication with a low K content will likewise not pass through.

7.2.5. Size and structure of molecules

Smaller medications penetrate more readily than larger ones. Therefore, the absorbance of the therapeutic agent is inversely proportional to its molecular mass.

7.2.6. Concentration of drug

If the drug concentration is greater across the barrier, then the flux is larger [58,59].

8. TRANSDERMAL PATCH AND ITS WORKING PRINCIPLE

Previously, the skin was thought to be an impenetrable line of defense, but further research demonstrated the value of skin as a pathway for systemic delivery. TDDS embracethe concept of putting medications into a "patch" that has the potential to be used for transdermal delivery of a wide range of medicinal therapies. Transdermal patches are adhesive drug-containing devices placed on the skin having defined surface areas that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate to reach the systemic circulation. Patch administration is less painful than needles and avoids the chance of infection [60,61]. The following are the several processes in the transit of medicines from the patches to the bloodstream:

- Release of medications from the formulation having drug reservoir to the stratum corneum layer of the skin via the rate-limiting membrane.
- Distribution of drugs over SC through the convoluted intercellular route of lipid.
- Sorption and partitioning of the drug by the SC into the epidermal layer of the skin.
- The capillary network present in the dermal layer allows access of medications to the systemic circulation.
- Finally, affect and foster the response in the target organ [61,62].

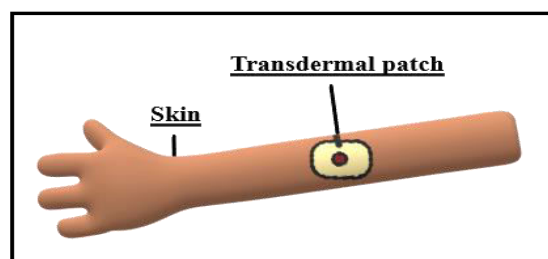
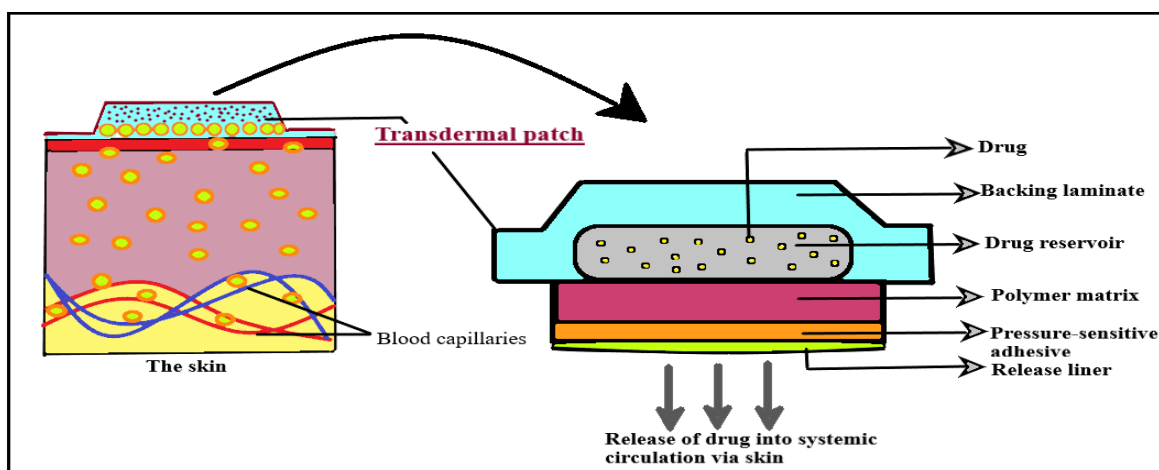


Fig. 6: Illustration of administration of the transdermal patch on the surface of the skin to permit the controlled and targeted delivery of drugs into the systemic circulation using the transdermal patch [57]

9. FORMULATION DESIGN AND COMPONENTS OF TRANSDERMAL PATCH

Transdermal patch is a multi-laminate system comprising of the following components:



Where, the medication is deposited in and adheres to the single polymer layer, after which it is released from the backing laminate layer that maintains the drug reservoir to the polymer matrix and finally to release liner into the systemic circulation via skin. [57]

Fig. 7: Schematic diagram depicting different layers of a transdermal patch

9.1. Polymer matrix

TDDS rely on polymers as their foundation. Drug-polymer matrix is placed between the external impermeable outer backing layer that forestalls drug losses from the retaining surface and the internal rate-limiting layer that also serves as an adhesive. Primarily, it ensures the controlled delivery of drugs at the site of action. For a polymer to be utilized in transdermal patches, it should be safe, stable, cost-effective, easy to construct, patient-friendly and significant quantities of the active agent can be integrated. Its molecular mass and chemical nature must ensure a suitable diffusion of the particular medicine and its release. TDDS polymers are categorized as follows [55,63] :

9.1.1. Natural polymers

It carries derivatives of cellulose, natural rubber, starch, zein, gelatin, waxes, proteins, gums, and so forth.

9.1.2. Synthetic elastomers

It carries synthetic rubbers like silicone, hydrin, butyl, styrenebutadiene, polybutadiene, polysiloxane, nitrile, acrylonitrile, neoprene, and other synthetic rubbers.

9.1.3. Synthetic polymers

It carries polyethylene, polypropylene, polyacrylate, polyvinyl chloride, polyvinyl alcohol, polyamide, polyurea, pyrrolidone, epoxy, and so forth.

9.2. Drug

The medicine needs to be carefully evaluated before constructing a transdermal patch. Some ideal physicochemical and biological qualities of a drug appropriate for transdermal distribution are listed below:

- i. A drug should be fewer than 1000 Daltons in molecular mass and must have a low melting point.
- ii. A drug should exhibit hydrophilic and lipophilic phases of affinity. Extensive partitioning properties make it difficult to administer drugs transdermally.
- iii. The drug must not be harsh and allergic but should be powerful with a short half-life [63,64].

9.3. Other excipients

9.3.1. Pressure-sensitive adhesive

They can be mounted on both the front and rear sides of the patch and also extended outwards. Adhesives ensure the proper attachment between the skin and the patch. They stick firmly to the skin and are swiftly removed. Also, they do not sensitize or irritate the skin. In

addition, drug allowance and supply of permeability enhancers should not be altered and must be compatible with the environment both chemically and biologically. The most often utilised in TDDS are poly-acrylates, polyisobutylenes and silicone based adhesives [64,66].

Table 1: Tabular representation of the chief fundamental properties and characteristics of ideal drug for Transdermal drug delivery systems [65]

Ideal features of drug	Characteristics
Dosage	Below 20 milligrams per day
Half-life	Short (upto10h)
Coefficient of partition	Within -1.0 and 4
Molecular mass	More than 400
Degree of skin permeability	$> 0.5 \times 10^{-3}$ cm/hour
Response from skin	Non-irritant, non-sensitive
Efficacy of therapeutic-index	less
Buccal bioavailability	less

9.3.2. Baking laminate

A good backing layer is flexible enough to allow oxygen and moisture to pass through. The Backing layer should be chemically robust and adaptable to other excipients. In addition, the leaching of chemicals should be prevented. They bind the pharmaceutical reservoir effectively, prevent a medicine from escaping the dosage form, and allow printing. Material of baking laminate protects and support drug and includes metal-plastic laminate; plastic films of-polyethylene, polyvinyl chloride, polyester and so forth [11,55].

9.3.3. Release liner

While storing, the release liner inhibits medication migration into the adhesive and its degradation. Consequently, it is considered as a part of the principal packing component instead of just a part of the active ingredient for supply. It constitutes a base layer that can be non-occlusive or occlusive (e.g., paper fabric, polyvinylchloride, polyethylene), and a release-coated layer comprised of Teflon or silicone [67].

9.4. Permeation enhancers

Stratum corneum serves as a first-line defense of the skin against foreign materials. The fundamental role of permeation enhancers is to effectively reduce the barrier characteristics of the stratum and reverse them when the drug has been delivered, thus enabling medications to

permeate deeper layers and enter the bloodstream [11]. In other words, permeation accelerants improve transport by changing the skin as a barrier to the transit of desired drugs to the target organ. Several features that should be taken into consideration regarding these promoters are mentioned below [66, 68]:

- Biochemical and physical compliance with the medicine and other medicinal products.
- Regulated and reversible boosting activity, also the capacity to operate precisely for the expected time.
- It must be cheap, odour-free, colour-free, non-toxic, patient-friendly as well as non-allergic.
- Should ensure the regain of barrier property when detached from the skin.
- Body secretions, electrolytes, and other endogenous elements must not be removed.
- Permeation enhancers can be categorized into the mentioned categories:

9.4.1. Solvent

Such chemicals potentially improve absorption by the expansion of the polar skin channels and Lipid fluidization. e.g., water alcohol-methanol & ethanol, alkyl methyl sulfoxides, dimethyl sulfoxide, silicone fluid, isopropyl palmitate, and so forth.

9.4.2. Surfactants

Such substances are designed to increase the transit of polar pathways, specifically hydrophilic medicines. A surfactant's capacity to change permeation is dependent on the head and the size of the hydrocarbon chain. Anionic surfactants can enter and firmly react with the skin, whereas, cationic surfactants cannot and are known to be much more irritating. e.g. (Dioctyl sulpho-succinate, Sodium lauryl sulphate), Pluronic F127 & F68, bile salts (Sodium taurocholate & deoxycholate), Calcium thioglycolate, urea, soyabean casein, etc [67,69].

10. CLASSIFICATION OF TRANSDERMAL PATCHES

Transdermal patches are classified into the following types:

10.1. Single-layer drug-in-adhesive

In this approach, the medication is embedded directly into a single polymer layer with sticky characteristics that serve as a reservoir for medication delivery.

Underneath the monolayer lies an impervious backing layer. The medicine is first placed in the polymer layer and attached to it and is finally released from the laminate supporting the drug reservoir [70].

10.2. Multi-layer drug-in-adhesive

The multi-layer medicine-adhesive patch is just like the single-layer method, as the release of the medication is done across both layers. Moreover, it adds another layer of medication-in-adhesive, often kept isolated by a membrane. These patches comprise a medication storage layer and an adhesive, in which the flow of drugs is regulated over a longer time and incorporate a provisional protective layer and a durable backing layer [57,71,72].

10.3. Drug reservoir-in-adhesive

The reservoir transdermal patches have a distant drug layer unlike the patches mentioned above. The layer of the drug is a fluid chamber that has a sticky layer separated from the drug suspension. The backing laminate supports this fix as well. Moreover, the release rate is nil in this sort of mechanism [57].

10.4. Drug matrix-in-adhesive

These patches contain a layer of drug formed by a semi-solid matrix carrying the medication in the form of suspension or solution. It has an adhesive membrane that partly covers the medication layer [60].

10.5. Vapour patch

Transdermal vapour patches contain a single sticky polymer layer with the ability to impart the vapours. These patches are novel and distribute vital oils for up to 6 hours [66].

11. NANO-CARRIER FOR POTENT CANCER TREATMENT

The skin's barrier property is attributed to the stratified brick and mortar structure of keratinocytes, as well as the lipid-soluble nature of the stratum corneum. The core objective of a nanocarrier is to break through the epidermal barrier. To circumvent this barrier, nano-emulsions, vesicular (liposomes, ethosomes, niosomes, etc.) and nanoparticle nanocarriers are being designed [73,74]. Doxil (PEGylated liposome-encapsulated doxorubicin) was the very first liposome-enclosed medication to be certified by the US Food and Drug Administration (FDA) in 1995 for the management of AIDS-related Kaposi's sarcoma, and was subsequently

licensed for ovarian cancer. It was lately certified in the United States for the treatment of breast cancer, as well as in Europe and Canada for treating multiple myeloma in conjunction with Velcade, a proteasome antagonist [75-77].

The micro-nanocarriers are often researched in the field of anticancer chemotherapies to promote solubility, controlled and targeted delivery, as well as to increase skin permeation [78,79]. Taking into account, the severe adverse impact of chemotherapy, anti-neoplastic transdermal administration to localized cutaneous tumours may be a promising technique for enhancing targeted effectiveness and decreasing cytotoxicity [80]. For successful therapy of cancer, a dermal formulation must be patient-friendly and enable the medicine to permeate into the underlying layers of skin to reach the tumour location. Due to inherent qualities such as their capacity to penetrate profoundly through the skin and deliver site-targeting action, this antineoplastic drug penetration is conceivable with nanocarriers. Fortunately, it lessens skin irritation by avoiding effective antineoplastic medications from coming into direct touch with the skin. Furthermore, boost the drug's stability as well [81].

Anti-neoplastic medications should preferably be able to pass through the body's barriers and target the intended tumour tissues with minimum loss of volume or activity in the systemic circulation after delivery to be successful in treatment for cancer. Furthermore, they should be able to selectively destroy tumour cells while causing no harm to normal cells once they reach their target location. These two main techniques are also linked to improved patient survival rates by concurrently boosting intracellular therapeutic concentrations and minimizing dose-restricting toxicity [51]. Biodegradable nanoparticles are widely used in cancer treatments because of their great biocompatibility. The main prerequisites in active targeting are sustainable release and site-specific administration. Another key feature is nanoparticle stability, which allows for extended retention in systemic circulation and, eventually, accumulation in tumours [36].

11.1. Fundamental factors driving Nano-based cancer drug delivery

The fundamental property for administering the drug to the target cancer cells is the capacity of nanocarriers to stay in the blood circulation for a prolonged period without being destroyed. The reticuloendothelial system, like the liver and a spleen, often attracts

traditional surface particles and unmodified nanocarriers in its circulation, depending on their surface size and characteristics. By adjusting their size and surfacing features the destiny of administered nanocarriers may be regulated [82].

11.1.1. Surface property

The surface properties of nanocarriers play a key role in defining their longevity and fate throughout circulation concerning macrophage uptake. The effective approach to avoid getting caught in nano-carriers must possess a hydrophilic surface. This is perhaps performed using two approaches. Initially, an aqueous polymer such as PEG is used to coat the particle surface, and secondly, protecting them from opponents by resisting the plasma proteins [83,84].

11.1.2. Size

Nanocarriers also have the bonus of being able to alter their size, in contrast to their surface properties. Nanoparticles that are utilized as drug carriers should be tiny enough to evade capture by static macrophages stuck in the reticuloendothelial system, such as the liver and spleen, yet be wide enough to prevent fast leaking into the bloodstream [85].

12. MECHANISM OF ANTI-NEOPLASTIC DRUG TARGETING

Therapeutic targeting is described as the delivery of a drug to a specified physiological target cell that requires a certain therapeutic activity. In nanocarrier based cell-orientated release, active or passive techniques have been employed.

12.1. Passive targeting (EPR) effect

Drugs can often be carried to the affected tissue via passive targeting, which relies on the pharmacological carrier's durability in the circulation and the drug-loaded nanoparticles deposition at the targeted site. The defining feature of tumour cells is that they possess damaged blood arteries; resulting in increased vascular porosity. This distinctive property aids macromolecule delivery into tumour tissues. Maeda et al have established that there is enhanced permeability and retention (EPR) activity in the location of inflammation or infection in which excess bradykinin is produced [86]. Duration of the retention time is the distinguishing factor between the inflammatory response of the EPR and that of the tumour. The swelling period is shortened in normal tissues, so, after several days,

swelling might decrease whereas the lymph drainage system is active in tumour cells and this greater vascular susceptibility provides ample nutrition and oxygen for the fast development of cancer cells. Larger particles around 40 kDa will leak out of the tumour vessel and accumulate in the cancerous cells. This EPR effect of drug administration is lacking in normal cells and this peculiar EPR effect of tumour cells are afterward regarded as a breakthrough in the process of tumour-targeting chemotherapy and becomes a paradigm approach for the creation of antineoplastic drugs. Passive targeting lacks the capacity of delivering huge amounts of solutes, as a result, active techniques have emerged as a viable substitute [87].

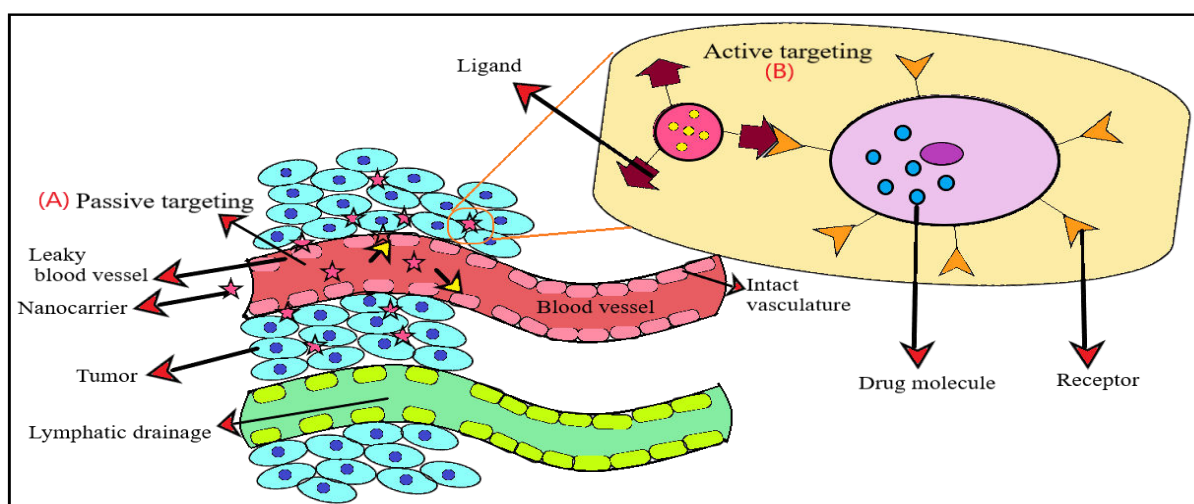
Just as Maeda et al. first discovered the EPR effect in the 1980s, a lot of work has gone into understanding the relevance of this concept in tumour targeting and developing relevant TDDS. Some of these nanocarriers, such as the commercially available Doxil and Caelyx, are currently being employed in health centres, and the EPR effect has become a benchmark in the development of passive tumour-targeted devices [88].

12.2. Active targeting

The adhesion of a specific point to the surface of drug carriers is the basis for active targeting. It uses patterns of molecular detection like ligand-receptors, antigen-antibodies to provide medications to a targeted region

and this powerful contact gives the delivery mechanism more precision. The active technique is also possible by manipulating the physical stimuli (for example, temperature, pH, magnetization, and so forth). When aiming for active targeting method, the targeting ligand is linked to the exterior surface of the nanostructures, which attaches with their binding site receptor at the site of action. The effectiveness of targeting medicine depends on the selection of targeted components that must be readily available and have high affinity and specialized features for binding cell receptors. Folate, transferrin, aptamer, small ribonucleotides or deoxyribonucleotides that may be administered in several geometries and in ligand-binding antibodies, are amongst the potent targeting ligand for treating cancer. Due to overexpression of targeting ligands in tumour tissue, it causes less harm in normal cells, and it is commonly utilized in cancer therapy [89-91].

Nanocarrier's surface properties and its size can be successfully managed to provide both passive and active therapeutic targeting with minimal harmful effects. The inclusion of nanocarriers protects the medication against degradation. This technique may be employed for a myriad of areas of administration, such as transdermal drug delivery, and so forth. The medicine will stay in the appropriate quantity at a specific site for a longer period, resulting in less wasting and more potency [87].



(A) Passive tissue targeting and (B) Active cellular targeting [92] Where, Passive targeting of nanomedicines is performed by their capacity to extravasate out of the leaky tumour vasculature in conjunction with ineffective lymphatic drainage, also known as the increased permeability and retention (EPR) effect. Active targeting is achieved by acquainting nanomedicines with targeting ligands that detect tumour cell markers, hence increasing cell selectivity and uptake.

Fig. 8: Schematic depiction of several pathways for the delivery of medication to tumours via nanocarriers

13. CONSTRAINTS AND FUTURE PROSPECTS OF NANOCARRIER BASED TRANSDERMAL DELIVERY

Nanocarriers are indeed being actively evaluated for various uses in TDDS because skin-patch administration is painless as that of injections, avoids first-pass hepatic metabolism, and can be designed for controlled and steady drug release into blood circulation. As a result, nanocarriers have been explored for application in transdermal delivery of the anti-neoplastic drug. However, several obstacles must be overcome before nanocarriers can be considered a viable substitute to traditional treatment for chemotherapy. The toxicity of nanocarriers is a serious impediment to the formation of an effective anticancer targeted drug delivery. There is indeed a lack of valuable research and norms for nanocarriers, essential to form these systems, including other issues, to provide appropriate categorization, analysis, toxicology, and pharmacological assessments. Because of their small size, optimum surface energy, shape, and composition, they are essential for evaluating the efficacy of nanotechnology for therapy and diagnostic imaging. The toxicity of current nanocarriers is still being reduced and the future upgraded nanocarriers with a limited toxicological profile are being explored.

From the myriad studies performed concerning nanocarriers, it has become apparent that nanocarriers possess the ability to transport medicines across the skin barrier and provide milestone prospective future benefits as transdermal drug delivery systems.

14. CONCLUSION

Traditional cancer therapy is a paramount foundation in the fight against cancer, but there are numerous restrictions associated with the provision and pharmacokinetics of antineoplastic drugs, such as resistivity to anti-cancer medicines, cytotoxicity, and a lack of specificity. The uncontrolled destruction of normal cells, chemotherapy-related toxicity, and acquired immunity against medications generate the need to seek efficient, site-specific treatments. Advanced techniques in pharmacotherapy for the absorption of anti-neoplastic drugs through the skin assist cancer therapies with decreased side effects as well as improved pharmacokinetics. Adhesive dermal patches are the most prevalent type of transdermal medication delivery approach, allowing controlled delivery of potent antineoplastic drugs with enhanced patient compliance. However, the intricate barrier property of

skin limits the entrance of medicines via the transdermal method. For combating this, Transdermal nanocarriers have been formulated to overcome the challenges posed by the skin, allowing treatments to access their target locations more efficiently.

This study addresses approaches that can be utilized to improve the effective transdermal administration of chemotherapeutic agents. Researches have shown that these approaches are promising and might establish new avenues for treating cancer. However, it is pivotal to achieve therapeutic efficacy and broaden the boundaries in the integration of diverse approaches that can ease the development of the transdermal administration of anti-neoplastic drugs and the advent of such a proficient transdermal nano-therapeutic system heralds the important milestone in anti-neoplastic drug delivery. Focusing on the quantity of study and attention, health centres can conclude that transdermal formulations are safer and more efficacious than oral formulations in the near future.

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Conflict of Interests

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