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REVIEW ON MODIFIED TRANSDERMAL DRUG DELIVERY SYSTEM FOR CYTOTOXIC AGENTS

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ABSTRACT

Cytotoxic agents is primarily administered to cancer patients via oral, parenteral and topical routes. The use of transdermal drug delivery could potentially be a better alternative to decrease the dose frequency and severity of adverse or toxic effects associated with oral or parenteral administration of cytotoxic agents. The transdermal delivery of drugs has shown to be advantageous for the treatment of highly localized tumors in certain types of breast and skin cancers. In addition, the transdermal route can be used to deliver low-dose of drug.

The aim of this study was to develop and evaluate the transdermal patches of the cytotoxic agents. The patches were prepared by solvent casting method using different ratios of polymeric systems the polymers used in the formulation should be inert, biologically safe, and chemically compatible with both the system's excipients and the active pharmaceutical ingredient to give the prolong drug's release and to Improve the permeability will use the physical penetration enhancers like iontophoresis technique .

Key Words: Cytotoxic Agents, Transdermal Drug Delivery, Ionotophoresis

1-INTRODUCTION

Every year, millions of individuals die from cancer, an abnormal condition of cells that leads to unchecked cell division and aggressive tumour's (1). Although skin cancer can take many various forms, it is the most common type worldwide. UV rays, ionizing radiation, and certain chemicals that cause cancer are among the etiological factors that are contributing to its rising incidence (2). The most common malignant illness, especially among Caucasians, is skin cancer, which is estimated to affect over a million new cases nationwide per year (3). Skin tumours are classified into two groups: non-melanoma skin cancer (NMSC) and melanoma skin cancer (MSC) depending on their cellular origin and clinical appearance (4). BCC and SCC are the two primary subtypes of non-malignant squamous cell carcinoma (NMSC). The most prevalent kind of cancer in people is NMSC. Most frequent type of skin tumour, accounting for 80–85% of all NMSC, is BCC. Worldwide, two to three million new cases are reported year (4, 5).

5-Flourouracil was initially developed in 1957 and was found to be beneficial in the treatment of various tumour's, such as those affecting the layer of skin, colon, and breast, as well as dermatological disorders, such as actinic keratosis, benign tumours, nail psoriasis, fungicides for mycosis, and porokeratoses (6, 7). Fluorouridine triphosphate, fluorodeoxyuridine monophosphate, and fluorodeoxyuridine triphosphate are among the active compounds of 5-FU that are produced when it enters the cell.These compounds then disrupt normal nucleic acid activity, leading to the targeted death of rapidly reproducing cells (8). Considering 5-FU's strong polarity, low bioavailability, and reactivity for cell membranes, and there are a number of delivery options. 5-FU desire include transdermal drug delivery and nanocarrier, which would be a superior substitute to reduce the frequency of doses and the intensity of harmful or toxic effects related to parenteral or oral administration (9,10). Only 8–20 mints is the total half-life of 5-FU.Consequently, 5-FU may be able to be transported by the transdermal route to the desired area of activity (10).

Often called "transdermal patches" or "skin patches," via transdermal drug delivery devices (TDDD) are dose forms that are meant for penetration into a patient's bloodstream and distribute a therapeutically effective quantity of medication through their skin (11). There are a number of benefits that transdermal drug delivery (TDD) has over oral medication administration. These consist of reduced systemic adverse effects, patient compliance, non-invasive delivery, and first-pass metabolism

bypass (12). The goal of transdermal treatment techniques is to continuously and regulated deliver medication through the layer of skin to the bloodstream. (13). Medicines with limited biological half-lives can also be continuously injected via transdermal route, avoiding the systemic circulation's pulsed entry, which commonly causes undesirable adverse effects (14).

Since 5-FU is a class 3 medication that is low permeable but highly soluble, we must raise its permeability. To do this, we employ the iontophoresis technique. Iontophoresis uses an electric field to administer drugs locally and systemically in a non-invasive manner. The chosen medication can diffuse through the layer of skin, mucous membrane, enamel, dentin and various tissue. Compared to traditional methods of delivery, Ten to two thousand times more medicinal compounds are given. Its foundation is the theory that positively charged drug ions, or cations, are drawn to the cathode by an electric field and are repelled by the anode, or positive electrode. The anode is followed in turn by negative ions (anions), which the negative electrode (cathode) rejects. Small and hydrophilic compounds are ideal for use in iontophoresis (15). The iontophoresis system consists of two separate electrodes which are: the returned electrode and the drug-delivery electrode. It also has a power supply. The drug-delivery electrode is attached to the surface of the target tissue, either within or in close proximity to the drug formulation. Placing the returned electrode on adjacent boring tissue helps to close the electric circuit and facilitate the flow of electric current. Iontophoretic medicines are mostly transferred across biological barriers by electromigration and electroosmosis. During the electromigration process, drug molecules migrate through biological tissues in the direction of the oppositely-charged returning electrode due to the repulsive attraction between the drug molecules and the drug-delivery electrode. The drug molecules are transmitted by the convective solvent flow in the electroosmosis process, which is triggered by an induced potential difference on the surface of charged tissues (16, 17).

2-Type of skin cancer

The human skin is a highly diversified organ in the body and is composed of three layers: the dermis, hypodermis, and epidermis. Several layers comprise the epidermis: stratum granulosam, stratum spinosam, stratum lucidum (SL), stratum corneum (SC), and stratum germinativum shown in figure 1. SC is the main barrier, made up primarily of lipids and corneocytes that stops the body from losing too much water. It also serves as the main pathway for environmental chemicals to be absorbed via the skin. Skin is made up of different kinds of cells that can develop into malignant or benign cancerous cells. Depending on where they originated, several forms of skin cancer have different names. But consideration is also given to their clinical behaviour. Melanoma and non-melanoma skin cancers (NMSCs) are the two categories into which skin malignancies fall. Figure 2 depicts several types of skin cancer. Squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and Merkel cell carcinoma (MCC) are the three kinds of nonmelanoma skin cancer (18).

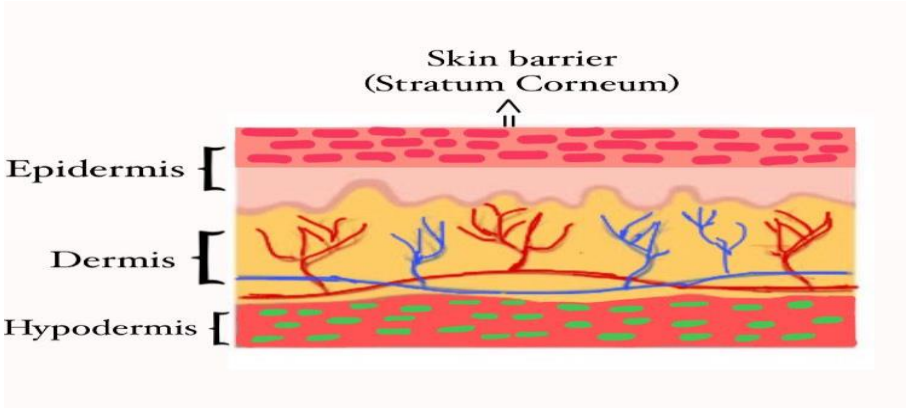

Figure 1 shown the skin's layer

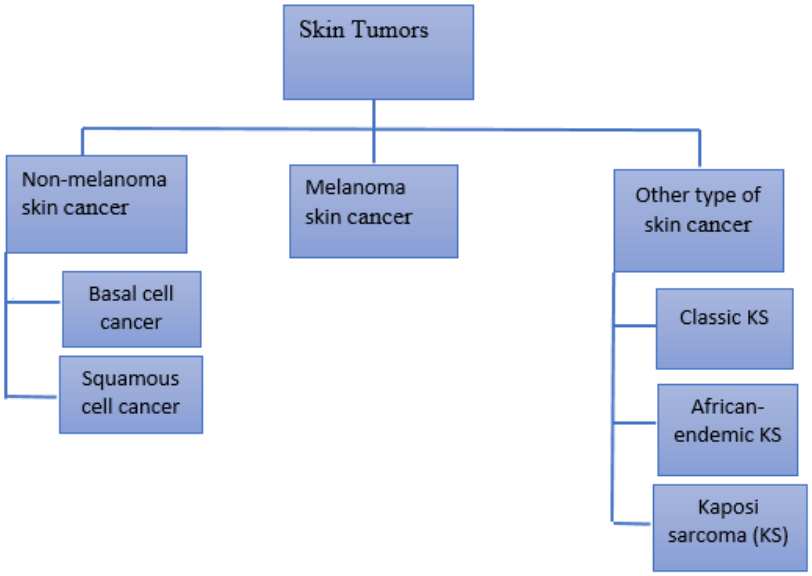

Figure 2: Skin tumors classifications

2.1 BCC or basal cell carcinoma

The most prevalent type of skin cancer that is not melanoma, basal cell carcinomas (BCCs) represent approximately eighty percent of all keratinocyte carcinoma types found in clinical settings. BCCs, which are produced from keratinocytes that resemble epidermal basal cells, are also the least aggressive type of non-melanoma skin cancer. BCC resembles a flesh-colored pearl that looks like a pinkish patch of skin or a pimple. BCC is caused by sun exposure, particularly in areas of the body that are exposed to the sun, such as the regions of the face, neck, head, legs, arms, and belly. BCC grows in bone structures and nerves and can go throughout the body. BCC is sometimes known as cancer that is not melanoma. Every year, BCC impacts a minimum of two to three million individuals. The death rate at BCC is minimal. It can be healed with straightforward treatments like radiation therapy and tropical drugs like 5-fluorouracil (19).

2.2 squamous cell cancer (SCC)

Roughly sixteen percent of cases of skin cancer are SCC. The incidence of SCC is significantly correlated with lifetime cumulative sun exposure. SCC is a cutaneous invasion caused by a malignant tumour of epidermal keratinocytes. There could be significant local tissue loss, and advanced stages of metastases through haematogenous or lymphatic dissemination are possible. Depending on variables including the size, location of the tumours, underlying health issues, and cell differentiation, the estimated total metastasis rate ranges from 3% to 10%16. SCC can show in a variety of ways clinically, but any lesion that does not heal after being exposed to the sun should raise suspicions. Papules, plaques,

nodules, and smooth, hyperkeratotic (crusty), or erosive lesions are examples of clinical signs. The tumor could start out as a rough, erythematous, scaly papule or spot. And could develop nodules, occasionally with a plaque or warty surface. Tumour bleeding may occur without much provocation. The tumour eventually becomes ulcerated and infiltrates the surrounding tissue. The majority of the lesion may occasionally be below the skin's surface. When tiny SCC lesions are appropriately and promptly removed, the prognosis is usually quite good. Non-invasive and invasive (poorly differentiated) tumours are examples of SCC variations. Local lymph nodes and skin are the primary places where the malignancy spreads, and then it moves on to adjacent organs. SCC is more prone to spread and may need major surgery if it develops in scars, behind the ears, or along the lip's vermilion border. Before being diagnosed, almost one-third of lingual or mucosal malignancies had spread (20).

2.3 MCC or Merkel cell carcinoma

Merkel cell cancer (MCC), also known as basic cutaneous neuroendocrine tumour's, is an unusual skin tumour with a rapid clinical progress. Despite being uncommon, MCC is becoming more common; this is most likely due to advancements in diagnosis as well as worldwide population ageing. According to statistics from the Surveillance, Epidemiology and End Results (SEER) database, the rate of MCC raised from 0.5/100,000 people in 2000 to 0.7/100,000 people in 2013. Similar findings have also been recorded from Europe and Australia. Just 4% of MCC instances involve individuals younger than 50, and the frequency of MCC rises steadily with each extra decade of life. The majority of patients with the cancer are Caucasian, and the cancer is more common in regions nearer the equator, indicating a possible link between UV exposure and the development of the disease. Moreover, patients with B cell malignancies and transplant recipients are more likely to acquire MCC. Specifically, it has been estimated that for individuals with chronic lymphocytic leukaemia, the standardised incidence ratio of MCC is 15.7. When MCC affects older people with fair skin, usually appears like a single, not painful, violaceous or reddish intracutaneous nodule that rapidly expands after being exposed to the sun. Although an improved prognosis is linked to MCC shrinkage, little is known about the molecular mechanisms causing the initial tumour to go (21).

2.4 Melanoma

Two percent of all diagnosed skin lesions are melanoma, making it the least frequent type of skin cancer. Since melanoma is a malignancy that needs to be reported, its incidence is well documented. Melanoma in situ (MIS) refers to melanoma in its early stages. Cells have limited potential for metastasis at this stage and are restricted to the epidermis. Within MIS, there are two different forms: lentigo maligna melanoma (LMM) and lentigo maligna (LM). Procedures with broad 0.5–2 cm margins is a reliable treatment for primary cutaneous melanoma and MIS. Except in cases when surgery is not an option or the cosmetic result is not desired, there is limited need for topical treatments due to the efficacy of surgical treatment regarding initial melanoma and the risk of disease metastatic. Compared to cutaneous melanoma, when treating in situ/in transit illness or precancerous lesions (dysplastic nevi), topical treatments are used more frequently. An increasing number of clinical trials report difficulty recruiting participants and early termination. Therefore, at this time, the FDA has not approved any topical medications for the treatment of melanoma or associated precancerous lesions (22).

3- Epidemiology

Approximately 600,000 cases are reported to occur each year, over one-third of tumor cases in the Us Kingdom are nonmelanoma skin cancers (NMSCs). The most frequent cancers that affect white people annually are NMSCs. Out of the 600 000 instances, roughly 500 000 are basal cell carcinomas (BCCs) and between 100,000 and 150,000 are squamous cell carcinomas (SCCs). The ratio of standardized BCC to SCC is approximately 4:1.2. Compared to malignant

melanoma, non-malignant squamous cell carcinoma (NMSC) (BCC and SCC) is 18–20 times more common. NMSC is becoming progressively more. Populations of Caucasians in Australia, Canada, the US, and European have experienced 3-8% average annual growth in NMSC since the 1960s. However, because NMSC is frequently left out of typical cancer registries or is only partially included, there are few incidence statistics on NMSC with high epidemiological quality (23).

4- Risk factor

There are several risk factors for every kind of skin cancer. However, risk factors that are not biological (modifiable) and biological (non-modifiable) are two important variables linked to the etiology of many cutaneous malignancies shown in figure 3 (24).

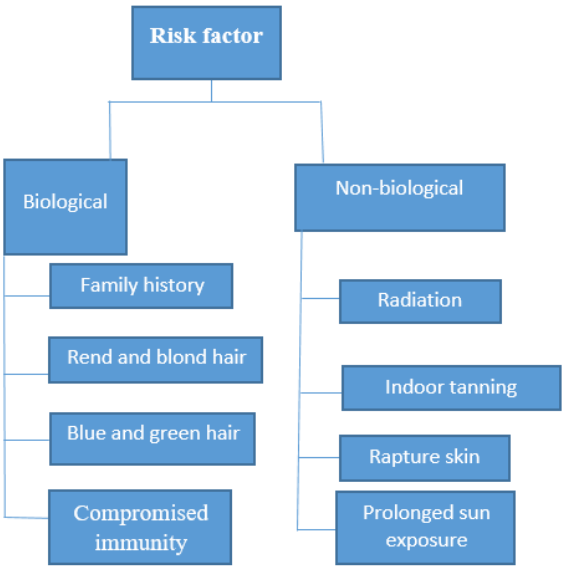

Figure 3 shown the risk factor

5- Prevention

Limiting UVR exposure by "avoiding sun exposure," "seeking shade," wearing UV-protective clothing, and topically applying sunscreen lotions is the primary preventive advice for NMSC. Beyond the traditionally recognised sun protection factor (SPF), which primarily focuses on UV-B radiation, there has been a renewed focus on sun protection in recent times. However, modern sunscreen solutions also seek to shield against UV-A rays and various other visible light wavelengths, including "highenergy blue light," in order to prevent skin damage caused by light. Moreover, secondary chemo-prevention of KC using systemic drugs such nicotinamide, COX-inhibitors, or extracts from Polypodium leucotomas is developing, particularly for high-risk groups like organ transplant recipients, albeit there is little proof of its effectiveness. The effectiveness of various preventative strategies can still not be easily compared, for instance, it is still unknown whether applying sunscreen or donning a hat will provide "more" protection. This problem is likely to continue because there are so many distinct kinds of photo-induced skin damage (25).

6- Skin cancer detection and diagnosis

As seen in Fig 4, Beverly described in this part the principles and detection processes associated with skin cancer diagnosis. Moreover, the existing used technique and method for diagnosing skin cancer was described (19).

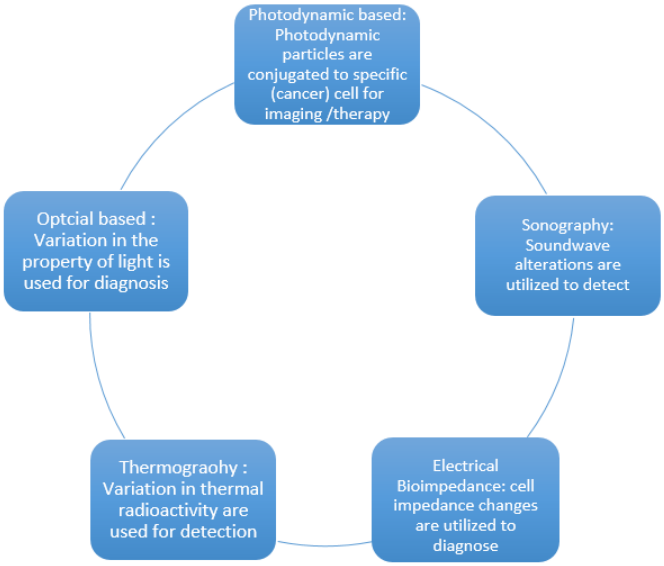

Figure 4 shown principles of skin cancer detection

7- 5-fluorouracil

5 Fluorouracil (5 FU) is a medication that inhibits metabolism is an analogue of pyrimidine. It was first developed to prevent tumour cells from growing by preventing the production of DNA and RNA, which results in cell death (26). Nevertheless, 5-FU is a strongly polar molecule with limited bioavailability and affinity for cell membranes; hence, the drug's bioavailability is mostly dependent on its affinity for biological membranes and its ability to dissolve in aqueous solutions. The FDA's Biopharmaceutical Classification System, which includes drugs with limited permeations through biological membranes and high affinity for physiological membranes, classifies 5-FU as a Class-III medicine. This is due to the polar property of 5-FU, which may reduce its affinity for cell membranes and so restrict its absorption. Because of this, when 5-FU is administered topically, healthy skin tissues absorb it poorly. Conventional 5-FU formulations usually require a high dosage to achieve the desired clinical result because 5-FU has minimal affinity for biological membranes. The 5-FU molecule is more soluble in polar solvents than nonpolar ones, as indicated by its octanol–water partition coefficient of − 0.89 and pKa of 8.02. With a pKa of 8.02, 5-FU Should dissolve more readily in water in solutions with a pH of more than 8 (27).

Overall action mechanism through mechanisms that negatively impact RNA and DNA synthesis and function, 5-FU exerts its cytotoxic effect. 5-FU penetrates the cell via the same assisted transport pathway as uracil and undergoes three biotransformation’s : (1) fluorouridine triphosphate (FUTP), which affects the processing and function of RNA by competing with UTP for incorporation; (2) fluorodeoxyuridine triphosphate (FdUTP), which damages DNA by competing with dTTP for incorporation; and (3) Fluorodeoxyuridine Monophosphate (FdUMP) inhibits the enzyme thymidylate synthase,which preventing the conversion of deoxyuridine monophosphate to deoxythymidine monophosphate and so decreasing DNA synthesis. The above metabolites collectively eventually cause more cancer cells to die (28, 7).

For the treatment of different tumors, 5-FU is offered as an oral medication, an injectable (50 mg/mL), and topical cream (0.5%, 1%, 4%, and 5%). According to human pharmacokinetic studies, the oral intake of 5-FU is insufficient. Additionally, due to hepatic metabolism, 5-FU has a short terminal half-life (8–20 min), which

means that transdermal application might be able to transport 5-FU to the intended area of activity (29, 10). It was preferable to use 0.5% cream rather than 5% cream in the topical cream formulation because the 0.5% 5-FU formulation is more tolerant, requires a single daily application, and causes less skin irritation. However, when the 5% 5-FU formulation was used twice daily for up to 28 days, the lower concentration resulted in noticeably less internal absorption. (30, 8).

8. Transdermal Administration of Medicines:

At 15% of the overall weight of the person, the layer of skin is the biggest organ in the human body. The total surface region varies between 1.5 and 2.0 square meters based on anatomy and the sex. Maintaining homeostasis requires proper skin function, which is considered an essential protective layer. The layers that make up the stratified organ of the skin, which is separated from its outer layer to the inside, are the stratum corneum, viable epidermis, dermis, and underlying hypodermis. When it comes to morphology and function, each of these layers is unique. Unfortunately, the tough barrier known as the stratum corneum (SC) makes it extremely difficult to administer many medications through the skin. Therefore, in order for a medicine to be administered at a rate that will allow for the achievement of the appropriate plasma concentration, the skin's barrier nature must be changed. The skin is traditionally thought of as a highly impenetrable layer that protects the body from harm. Transdermal drug delivery, or TDD, and intradermal drug delivery, or IDD, are terms used to describe the ability of this particular organ to carry different drug molecules into the layers of skin and then into the circulatory system. Typically referred to as "patches". Many penetration enhancement strategies, which can be generally divided into chemical and physical procedures, can increase the bioavailability of a medicine applied transdermally (31, 32).

Transdermal administration is self-administered and allows the medication to act locally or systemically by passing through undamaged skin for a certain amount of time. Drugs can be administered via transdermal patches in a dissolved lipid condition to attain the required efficacy. The United States approved the initial transdermal scopolamine system in 1979.

(33). Because TDD systems are non-invasive, simple to use and stop, do not require professional administration, Since they prevent medications from being metabolized by liver first-pass metabolism, stomach pH, and digestive enzymes and have controllable dose-dependent adverse effects, they are thought to be patient-friendly. Furthermore, they support the management of very confined tumours in some types of skin and tumour’s in breasts. Since transdermal delivery can be utilized to create cancer vaccines and administer low-dose chemotherapy when taken over a long duration, it additionally becomes a practical and compliant route of administration for patients (34, 10).

9. Transdermal patch categories

9-1 One-layer medication-in-adhesive:

The medicine is additionally held in place by this device's adhesive coating. The layer of the glue on this kind of patch releases the medication in addition to holding the system's several layers together and the skin in place. There is a backing and a temporary liner lined up on the exterior of the adhesive layer shown in figure 5 (35).

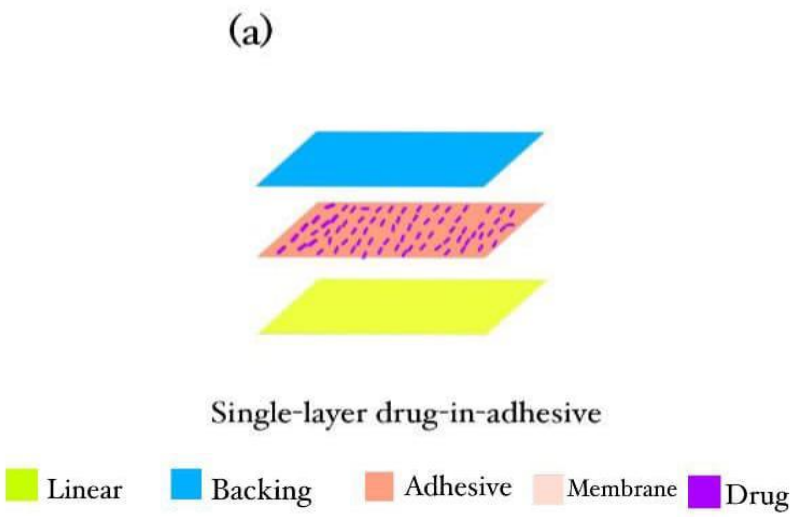

Figure: 5 Shown the One-layer medication-in-adhesive

9-2 Several layers medication -in-adhesive

The medication release mechanism is the same for both adhesive layers as it is for the single layer device. Conversely, the multilayer system incorporates a further layer of drug-in adhesive Material, typically (though not always) divided by a membrane. Two layers surround this patch: a permanent backing layer and a transient liner layer as shown in figure 6.

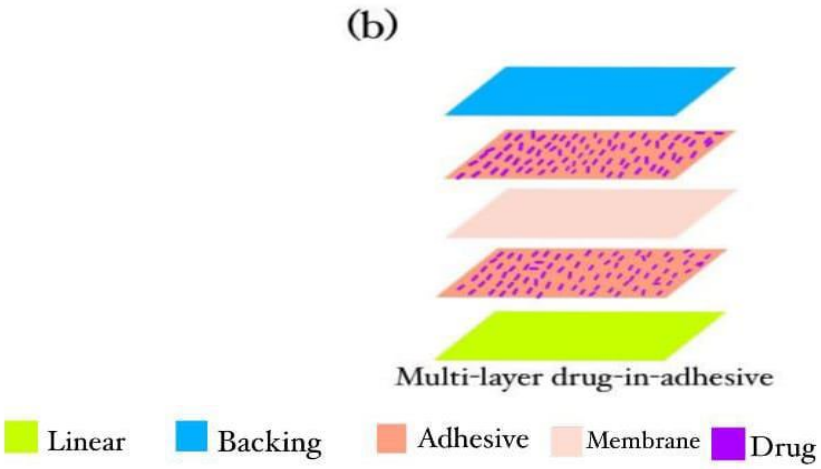

Figure: 6 Shown the Several layers medication -in-adhesive

9-3 Reservoir structure

This approach places the drug reservoir between a rate-controlling layer and a not permeable backing layer. The drug may be released via a microporous or nonporous rate-controlling membrane. Within the drug reservoir compartment, the medication may be administered as a gel, suspension, solution, or suspension or as a solid polymer matrix shown in figure 7.

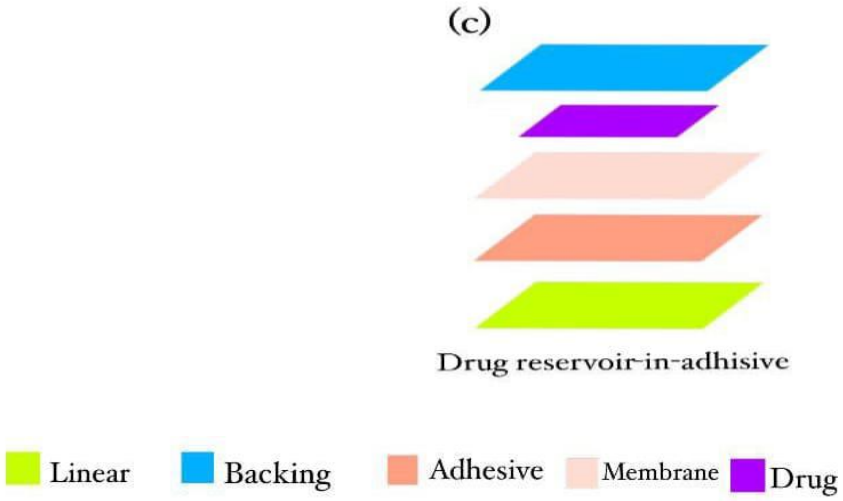

Figure: 7 Shown the reservoir structure

9-4 Matrix dispersion method

This kind involves a water-friendly or lipid-soluble polymers matrix with the drug evenly distributed throughout. Fixated to an occlusive base plate is a drug-containing polymer disc within a compartment composed of a backing layer impermeable to pharmaceuticals. As an alternative to covering the drug reservoir's face with adhesive, a rim of adhesive is applied around its perimeter shown in figure 8.

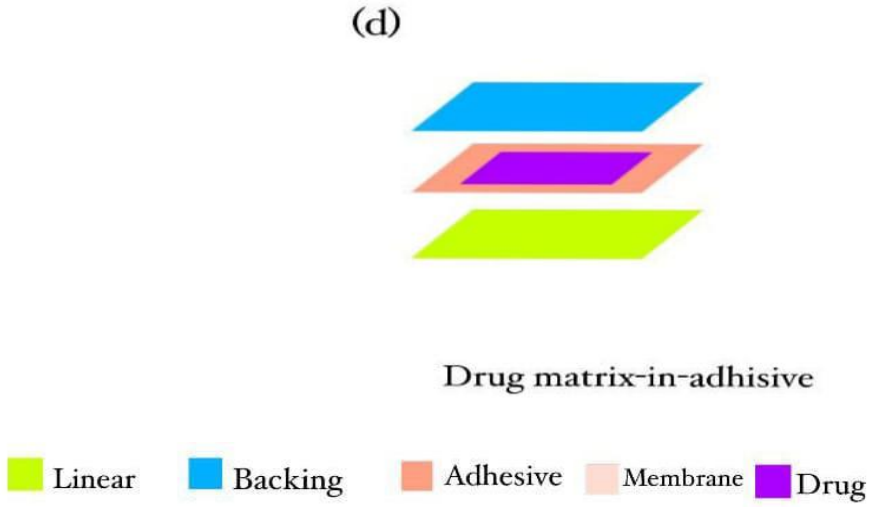

Figure: 8 Shown the matrix dispersion system

10- Iontophoresis

One non-invasive method to improve medicine delivery is iontophoresis, which employs an electric field. By applying an electric current, the process allows ions to penetrate the body more deeply (36) .One of the physical technique to improve medicine administration is iontophoresis. A simple and non-invasive technique for encircling a drug reservoir with a low-level of electric charge to facilitate the drug's passage through surrounding biological barriers and into the intended cells and organs is shown in Fig 9. In order to drive the medication to pass through nearby biological barriers and into the intended cells and organs. A power source and a minimum of two electrodes, referred to as the anode and cathode— the iontophoresis system— which consists of the drug-delivery electrode and the returning electrode. Into or next to the medication preparation on the target cells surface is where the drug-delivery electrode is positioned. The returning electrode is put on nearby cells to make sure the electric circuit is closed and that current can pass. (37, 38, 17). Diffusion, migration, or electroosmosis of the drug over a concentration gradient via the skin

are the mechanisms involved. In electro-osmosis, the bulk of the fluid flows in the same direction as the counterions. Iontophoresis is predicated on the idea that fluid mobility occurs without concentration gradients (39).

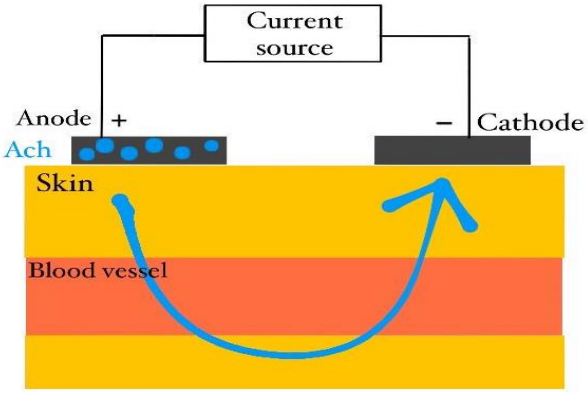

Figure 9 Scheme of iontophoresis technique

11- Materials and Procedures

Materials

5- Fluorouracil was purchased from Mumbai's Loba Chemie Pvt. Ltd, Maharashtra. Eudragit S100 (ES100), polyvinyl pyrrolidone (PVP), ethylcellulose (EC), and hydroxypropyl methylcellulose K100M (HPMC K100M) were acquired from Karnataka college of science. (40)

12- Procedures

1. Preformulation investigations for medications.
2. Transdermal patch formulation.

12.1.1. Organoleptic characteristics

White to practically white, odourless, crystalline powder. (41, 42, 43)

12.1.2. Determination the degree of melting temperature

The range of melting temperature with decomposition: 282–283 OC. (42)

12.1.3. Construction of standard calibration curve for 5-Fluorouracil

Suitable dilutions were prepared to produce a solution of 5-fluorouracil in buffered phosphate solution (pH 7.4) at 2, 4, 6, 8, and 10 µg/ml doses. A UV-visible spectrophotometer was used to measure the absorbance of 5-FU in buffered phosphate solution (pH 7.4) at 264 nm. The absorbance was plotted on the vertical axis and the concentration on the horizontal axis to create the standard curve. (44)

12.1.4. Compatibility Studies

A key phase in the preparation of all dosage forms through pre-formulation is the drug-excipient compatibility study. Drug stability, bioavailability, safety, and therapeutic effectiveness can be influenced by the chemical and physical interactions that take place between excipients and medicines. Drug compatibility studies are conducted using FT-IR spectrum analysis, which measures the drug's physical combination at the functional group region (4000-400 cm-1). To guarantee uniform mixing, the physical combination was made by directly mixing the mass ratio of one to one in a glass mortar (1:1). The 5-FU was mixed with four milligrams of the equivalent amount of the excipient. (45)

12.2 Formulation of Transdermal patch

Solvent casting was used to create 5-fluorouracil skin patches (Figure 10). The copolymer PVP/HPMC and the polymers EC/ES100 had varying weight ratios in the formulations. Ten milliliters of the casting mixtures were made by dissolving 25 mg of 5-fluorouracil, a particular weight of the polymers, and 25% w/w glycerol as a plasticizer in the appropriate solvent, methanol. The mixture used for casting was then transferred into 8-cm-diameter glass Petri plates and allowed to cure for a full day at temperature of the room. After the patches were peeled off, two centimeter squares were cut. The patches were covered with aluminum foil, sealed with self-sealing covers, and dried for a further 48 hours in desiccators containing sodium sulfate (40).

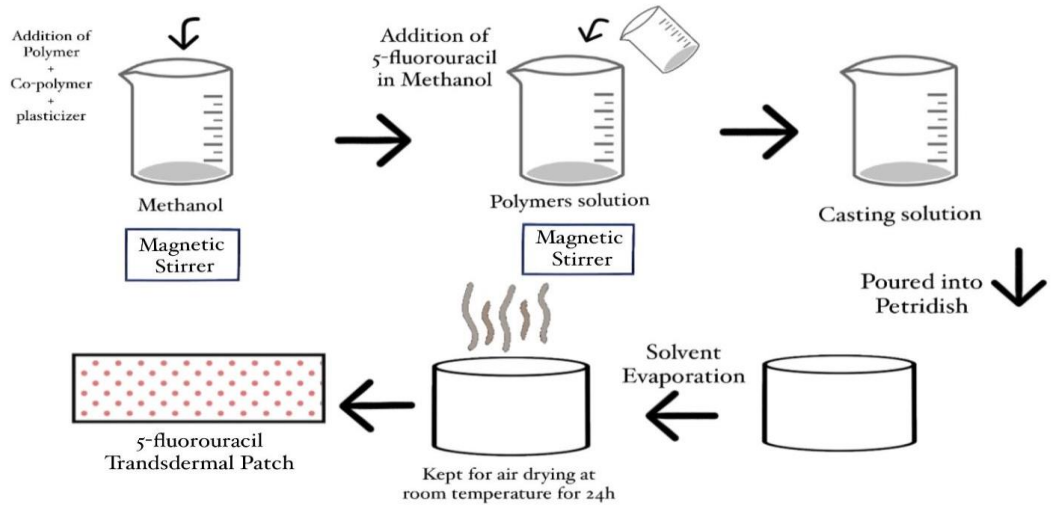

Figure 10. The preparation procedures for the 5-fluorouracil transdermal patch.

13- Evaluation parameter

I. Patch thickness

A digital micrometre is used to measure the wall thickness of the patch filled with drugs at multiple sites. Next, to guarantee the patch's thickness, the mean thickness and standard deviation are calculated.
. (35)

II. Weight variation

Each formulation's ten patches were weighed separately, and the average weight was determined. There shouldn't be a large difference between the individual and average weights. (46)

III. Folding endurance

A certain (2x2 cm) section of the strip was cut consistently, then folded repeatedly till it cracked. The folding strength rating was calculated by folding the film a certain number of times in the same spot. Either causing the film to break or develop obvious cracks. (47)

IV. Percentage of moisture content

A desiccator containing anhydrous calcium chloride was used to keep three randomly selected films for a full day at room temperature. Each film was weighed individually. After a predetermined amount of time, the films were weighed once more until their weight became consistent. (48)

Percentage moisture content = [Initial weight- Final weight/ Final weight] ×100

V. Content of drugs

By slicing a piece that measured one centimetre in diameter and dissolving it in phosphate buffer PH7.4, it was determined. After that, the mixture is filtered using a filter material and the appropriate technology (UV or HPLC procedure) is used to determine the drug content. Three distinct samples' averages are represented by each value. (35, 49)

VI. Flatness

Both side will assess each patch's level of flatness. Each patch will be assessed by both side for levelness. Every strip's length is measured, with variations allowed for since restriction is represented by uniform flatness, with 0% constriction being equal to 100% flatness. (50)

VII. Surface pH

It is employed to ascertain whether the pH shift could have any unintended consequences. The large intestine can become irritated by either an acidic or basic environment. After taking the patch, it was put in Petri dishes that had been soaked with 0.5 millilitre of distilled water at room temperature and departed for thirty minutes. By contacting the

electrodes with the patch surface, we used a pH meter to measure the pH. (51)

VIII. Percentage of moisture absorption

The weighing films need to be stored at 84% relative humidity in a saturated potassium chloride solution in a desiccator for a whole day at room temperature. Weigh again after a day. Using the following formula, find the percentage of moisture uptake. (35)

Percentage moisture absorption = [Final weight- Initial weight/ initial weight] ×100

IX. Swelling study

The produced transdermal patches were measured (W1) one at a time and incubated at 37±0.5 °C in separate agar gel (2%) plates. From the petri dish, the patches were taken out every fifteen to sixty minutes, and any excess water was gently scraped off the surface using paper for filters. The equation that followed was used to determine the swelling value after the enlarged portions (W2) were reweighed. (47)

Swelling value = W2 − W1 % W1 x 100

X. investigation of in vitro release

These patches were used to study the in-vitro medication release utilizing the USP class II dissolving laboratory device (Electro lab TDT-06L). It was agitated at 25 rpm and heated to 37±0.5o C (Bazigha et al., 2011). For the purpose of medicine release, the adhesive impermeable polyester backing layer was applied to one side of the patch while the other was left unattached. The patch was placed between the 50Kda (Hi medium) dialysis membranes to prepare the assembly for the release process test. To keep the assembly from drifting, a piece of glass slide was used as support. Using dialysis closing clips, the tube for dialysis containing the patch was secured from both ends. After that, the tubing was put in a dissolving apparatus that held 500 milliliters of 0.5% SLS solution-containing Solution of phosphate buffer (pH 7.4). Sink conditions were upheld for the duration of the investigation. Samples were collected in 5ml aliquots at pre-arranged and examined with a UV-Visible Spectroscopy at regular intervals set to analyze at λmax 250nm against a blank. (48)

XI. In-vitro permeation study

The drug's penetration and distribution from the skin into the body was measured in the release studies using the Franz diffusion cell. The data on medication release from each dosage form was analyzed by using many mathematical equations such as Higuchi's model, which gave the following expressions: First order is the log cumulative percent of drug left over time versus time, and zero order is the cumulative percent of drug released versus time, and cumulative drug release based on period squared. In order to ascertain the mechanism of releasing medicines from preparations, the information was inserted as log cumulative percent of drug released vs. log time into Korsmeyer Peppa's model. (46)

XII. Study on skin reactions

Fit rabbits weighing between 1.2 and 1.5 kg on average can be used for tests of skin sensitivity and irritation. The rabbit's dorsal surface (50 cm2) must first be cleaned, and then the hair must be shaved off. Representative compositions should be applied to the skin following a rectified spirit surface cleansing. After a 24-hour period, the skin should be assessed and graded into five groups according to the degree of the skin injury. (35)

XIII. Stability studies

Transdermal films were packed in aluminium foils and stored for three months, within a humidity chamber that is configured in compliance with ICH guidelines to be 40±2°C and 75±5% RH. (48)

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