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A Review on Transdermal patch loaded with capecitabine nanopaticles used for breast cancer therapy

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A B S T R A C T

Nanoparticle based drugs are an advanced approach in Cancer treatment using nanoscale particles to deliver drugs more effectively to cancer cell. While minimising damage to healthy cells. Nano particles typically range from 1to 100 Nanometre in size. Breast Cancer is a Leading Cause of Cancer - related deaths in women. To address these challenges, we developed a nanoparticle Mediated Capecitabine transdermal patch for targeted breast Cancer therapy. Polymeric nanoparticles Loaded with Capecitabine Were prepared using Solvent Evaporation method and characterized for size, Morphology, and drug release. Compared to oral capecitabine, the Novel delivery system offers a promising approach for Enhance breast cancer therapy, with potential for improve patient outcomes and quality of life. The Nano particles, Were then incorporated into a transdermal patch, which was Evaluated for in vitro skin permeation pharmacokinetics. Results showed enhanced skin permeation and controlled drug release leading to increased bioavailability and reduced toxicity.

Keywords: Nanoparticle, capecitabine, transdermal patch, breast cancer, targeted therapy

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Breast cancer is the most common cancer in world wide. and this incidence has been increasing over the past 20 years in most countries. Breast cancer is leading cause of cancer related deaths in women. It is a type of cancer originates in the breast tissue. It occurs when abnormal cells in the breast grow and multiply uncontrollably forming a tumour. Currently, standard methods for cancer therapy including breast cancer are surgery followed by chemotherapy, radiotherapy. Both radiotherapy and chemotherapy often fail to treat breast cancer due to side effects. That these therapies incur in normal tissue.[1] In recent years various nanoparticles have been discovered to be able to Selectively target tumour cells without causing any harm to the healthy cells or organs. They fore nanoparticles system targeted drug delivery system have become promising technique. Nanoparticles are defined as particles (1-100nm) with a surrounding outer layer of various organic or inorganic coatings that determine the properties of nanoparticles. Nanoparticles have been popular nanocarriers mainly due to their characteristics such as water dispersity, biocompatibility, and biodegradability. Nanoparticles can be engineered to target specific breast cancer cells, reducing harm to healthy cells. And it increases the solubility and half-life of drug.

Nanoparticles enhance their bioavailability of poorly soluble drugs. Nanoparticles can penetrate deep in to tumours, increasing drug uptake and efficacy. Nanoparticles can release drugs slowly maintaing therapeutic levels over time. It can be used to convert light in to heat killing breast cancer cells.[2]

2. Types of nanoparticles

- Polymeric nanoparticles: Composed of polymers, such as Poly (lactic-co-glycolic acid).
- Lipid-based nanoparticles: Composed of lipids, such as liposomes or solid lipid nanoparticles.
- Ceramic nanoparticles: Composed of ceramics, such as silica or alumina.

Advantages

Targeted delivery: Nanoparticles can be engineered to target specific sites in the body, reducing side effects.

Improved efficacy: Nanoparticles can improve the efficacy of drugs and therapies by delivering them directly to the site of action.

Reduced toxicity: Nanoparticles can reduce the toxicity of drugs and therapies by delivering them in a controlled and targeted manner.

Disadvantages

Targeted delivery: Nanoparticles can be engineered to target specific cells or tissues, reducing side effects.

Improved bioavailability: Nanoparticles can improve the bioavailability of drugs, allowing for lower doses and reduced toxicity.

Enhanced permeability: Nanoparticles can cross biological barriers, such as the blood-brain barrier, to deliver drugs to specific.[3]

Ideal Characteristics

- It should be biochemical inert, nontoxic.
- It should be stable both physically and chemically in In vivo & in vitro conditions.
- Specific Therapeutic amount of drug release must be possessed.
- He preparation of the delivery system should.[4]

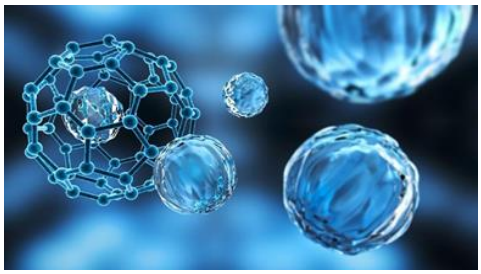

Fig.1 Nanoparticles

Nanoparticle anti-cancer drug combination can improve the efficiency of the therapy by reducing the side effects through targeting specific cancer sites using target ligands. There are various types of Nanoparticles that have been used for Breast cancer targeted Drug delivery system. Capecitabine is a pro drug. Capecitabine is a targeted therapy meaning it specifically targets cancer cells. Reducing harm to cancer cells. Capecitabine is converted to its active form 5- fluorouracil which inhibits DNA synthesis and cell division, leading to cancer cell death[5]. Drugs can be delivered across the skin to have an effect on the tissues adjacent to the site of application. Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by oral route. Bypassing the gastrointestinal tract would obviate the GI irritation that frequently occurs and avoid. First pass in activation by the liver, so these advantages are offered by the currently marketed transdermal products. Transdermal patch is medicated. Adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and in to blood stream. Transdermal patch used to deliver a controlled dose of a drug through the skin over a period of time. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Transdermal drug delivery systems have emerged as a promising alternative, offering improve bioavailability reduced side effects.[6] Transdermal patches are dosage forms designed to deliver drugs through the skin and into the bloodstream. They offer several advantages over traditional oral or injectable medications, including:

Improved patient compliance:

Transdermal patches are easy to use and can be worn for an extended period.

Reduced side effects: By delivering the drug directly through the skin, transdermal patches can reduce the risk of gastrointestinal side effects.

Steady-state plasma concentrations:

Transdermal patches can provide a steady release of the drug, maintaining therapeutic plasma concentrations.[7]

Types of Transdermal Patches

- Single -layer drug-in-adhesive
- Multi-layer-drug-in adhesive
- Drug- reservoir- in adhesive
- Drug- matrix- in adhesive

Advantages

- Avoids chemically hastle GI environment drug degradation in acidic & basic environment is prevented
- No GI distress & the factors like Gastric emptying, Intestinal motility, Transit time, do not effect this route as in oral route
- Avoidance of significant pre systemic metabolism (degradation in GIT or by the liver) therefore need lower dose.
- Allows effective use of drugs with short biological half- life
- Reduced inter & intra patient variability.[8]

Disadvantages

Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.

Higher cost

- Should not use ionic drug.
- May cause allergic reactions.
- A molecular weight less than 500 Da is essential.
- Transdermal therapy is feasible for certain potent drugs only.[9]

Ideal Characteristics of TDDS

- The skin has pH of 4.2 to 5.6, solutions which have this pH range are used to avoid damage to the skin.
- For the therapeutic action of the drug, there is a need of optimum partition coefficient.
- The drug should have a low melting point (less than 2000C) should use.
- Patch size should be less than 40 cm2
- Shelf life up to 2 yrs.
- The half-life t½ of the drug should be short;
- The drug should be non-irritating and non-allergic.
- The drug should be potent with a daily dose of the order of a few mg/days.[10]

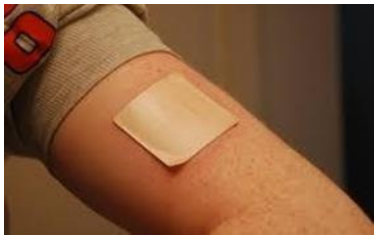

Fig.2 Transdermal patch

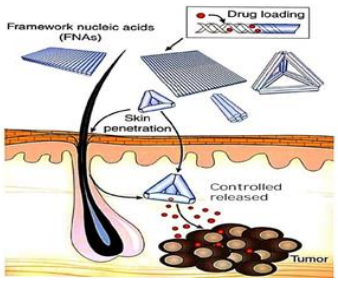

Fig.3 Incorporation drug in to transdermal patch

3. Overview of capecitabine

- Capecitabine is an oral chemotherapy drug used to treat cancer .capecitabine has a low bioavailability to its poor solubility.
- Capecitabine can cause gastrointestinal side effects, such as diarrhea and nausea.so capecitabine nanoparticles are a novel formulation of the drug offering improved bioavailability and targeted delivery to breast cancer.
- Capecitabine nanoparticles have been shown to reduce gastrointestinal side effects, due to there controlled release.

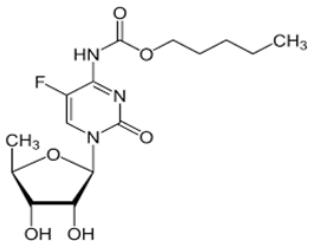

Fig.4. Capecitabine chemical structure

- Molecular weight: 359.350083 (G/mo)
- Molecular Formula: C13H24EN20
- Chemical Name: phentyl N(1(2R 3R, 4R, 5R) 3, 4 dihydroX5methyloxolian,2y1]5Flurop20xoprimidi n4yl) Carbamate
- Description: off white of almost white Crystalline
- Time to peak: Capecitabine: 1.5 hours; 5. Fu: 2hows
- Plasma protein: less than 60%.binding, primarily found to human albumin Metabolism - Extensively metabolized to 5-FU
- Half Life – 0.75 yours
- Melting Point : 110-121°c

Method of Preparation

Nanoparticles

The solvent evaporation method is a technique used to prepare nanoparticles, including those loaded with capecitabine

Solvent Evaporation Method:

- **Dissolution**: Dissolve capecitabine in a volatile solvent, such as dichloromethane or ethyl acetate.
- **Polymer dissolution:** Dissolve a polymer, such as PLGA (poly (lactic-co-glycolic acid)in the same solvent.
- **Mixing:** Mix the capecitabine and polymer solutions to create a homogeneous mixture.
- Emulsification: Emulsify the mixture in an aqueous phase, such as water or phosphate buffer, using an emulsifier like polyvinyl alcohol (PVA).
- Evaporation: Allow the solvent to evaporate, either at room temperature or under reduced pressure, to form nanoparticles.
- **Collection:** Collect the nanoparticles by centrifugation or filtration.
- Washing: Wash the nanoparticles with water to remove any residual solvent or impurities.
- **Lyophilization:** Lyophilize (freeze-dry) the nanoparticles to obtain a powder.[13]

Evaluation of Nanoparticle

Zetapotential

The Zetapotential of a nanoparticle is commonly used to characterized the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (±) 30mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles.

Particle Shape

Scanning electron microscopy characterizes the nano suspension before going for evaluation; the nanosuspension is lyophilized to form solid particles. The solid particles are coated with platinum alloy using a sputter coater.

Particle size

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the in vivo distribution, biological fate, and toxicity and targeting ability of nanoparticle system. In addition, they can also influence the drug loading, drug release and stability of nanoparticles. Currently, the faster and most routine method of determining particle size is by photon-correlation spectroscopy or dynamic light scattering. The

results obtained by photon-correlation spectroscopy are usually verified by scanning or **Polydispersity index**

The polydispersity index was determined using non-imasive back scatter technology which allows samples measurment in the range of 0.6 mm 6μα freshly prepared capecitabine nanoparticles (800 μl) was placed folded capillary cell without dilutionThe measurement was carried out using 4MW He-Ne laser as light source at: a fixed angle of173°C the parameters were med for the experiments like medium temperature 25°C.

Fourier transform in-frared spectroscopy

FT-IR was used to measure changes in chemical structure of the CS, blank nanoparticles, and capecitabine loaded nanoparticle samples. The samples were first lyophilized EYELAFDU-1100 breeze drier, and then ground its homogeneous powders The spectra wer acquired at 400-4000cm wave numbers witha 4cmresolutionutilizing a NEXUS 670FT- spectrophotometerequipped with a diamond Attenuated total reflection cell.

Transmission Electron Microscope

The morphological examination and particle site of the freeze dried capecitabine nanoparticles were determined by TEM. The lyophilized particles (100g) were diluted with deionized water (2 ml) and sonicated for 2 min. The samples were prepared by placing a drop of colloid dispersion for Transmission electron microscopeimage containing Capecitabine nanoparticlesi

Invitro drug release

In-vitro release study of capecitabine nanoparticles was carried out in PBS medium, according to a reported procedure. Dialysis bags (cut off size of 12-14 kDa) were filled with a predetermined amount of each formulation(5-10mg) and put into 40 ml of phosphate buffer solution (pH7.4) used as receptor phase. The receptor phase was stirred and thermal controlled at 37°C. At fixed time interval 2ml of the receptor phase were withdrawn and substinded with fresh buffer. The drug release was assayed spectrophotometrically at the Amax value of 240nm. [14-15]

Preparation of transdermal patch:

Materials Required:

- Active pharmaceutical ingredient (API)
- Polymer matrix (e.g., ethyl cellulose, polyvinyl pyrrolidone)
- Solvent (e.g., dichloromethane, ethanol)
- Plasticizer (e.g., glycerin, propylene glycol)
- Backing membrane (e.g., polyester film, polyethylene film)
- Release liner (e.g., silicone-coated paper)
- Adhesive (e.g., acrylic-based, silicone-based)

Preparation of Transdermal Patch

Step 1: Preparation of API-Polymer Solution

- Weigh the API and polymer matrix according to the desired ratio.
- Dissolve the API and polymer matrix in a solvent.
- Stir the solution until the API and polymer matrix are completely dissolved

Step 2: Addition of Plasticizer

- Add a plasticizer to the API-polymer solution to improve the flexibility and adhesion of the patch.
- Stir the solution until the plasticizer is completely dissolved.

Step 3: Casting

- Cast the API-polymer solution onto a backing membrane.2. Use a casting knife or a pipette to spread the solution evenly.

Step 4: Solvent Evaporation

- Allow the solvent to evaporate, either at room temperature or under reduced pressure.
- Use a vacuum oven or a rotary evaporator to speed up the evaporation process.

Step 5: Drying

- Dry the patch under controlled conditions (e.g., temperature, humidity) to remove any residual solvent.
- Use a desiccator or a drying oven to dry the patch.

Step 6: Lamination

- Laminate the patch with a release liner to protect the adhesive.
- Use a laminator or a heat press to apply the release liner.

Step 7: Cutting and Packaging

- Cut the patch to the desired size using a cutting die or a laser cutter.
- Package the patch in a protective pouch.

Matrix Method

- Capecitabine nanoparticles are incorporated into transdermal patch using a matrix method, a technique that involves dispersing the nanoparticles uniformly throughout the polymer matrix.
- The matrix method is a common approach used in the development of transdermal patches. This method involves dispersing the active pharmaceutical ingredient (API) in a polymer matrix, which is then cast onto a backing membrane.

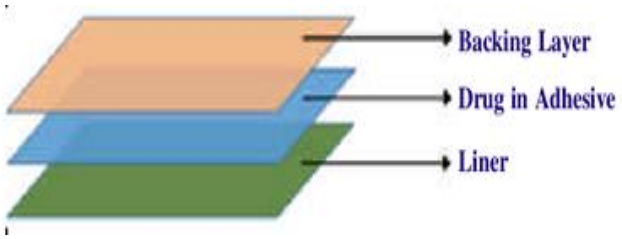

Figure.5: drug-matrix in-adhesive

Backing Layer

- A thin, flexible layer that provides mechanical strength and support to the transdermal patch.
- Materials: Typically made from flexible materials like polyester, polyethylene, or polypropylene.

Drug in Adhesive

- A type of transdermal patch where the active pharmaceutical ingredient (API) is dispersed directly within the adhesive layer.
- Advantages: Simplifies the patch design, reduces manufacturing costs, and can improve patient compliance.

Liner

- A thin, flexible layer that covers the adhesive layer of the transdermal patch, protecting it from contamination and environmental factors until application.
- Materials: Typically made from paper, film, or coated materials.[19

Advantages of matrix method

- Uniform Distribution: The matrix method allows for the uniform distribution of the API throughout the polymer matrix, ensuring consistent drug release.
- Controlled Release: The matrix method enables controlled release of the API, which can be tailored to meet specific therapeutic requirements.
- Improved Bioavailability: The matrix method can improve the bioavailability of the API by enhancing its permeation through the skin.
- Reduced Dose Frequency: The matrix method can provide a controlled release of the API, reducing the need for frequent dosing.
- Enhanced Skin Permeation: The matrix method can enhance skin permeation of Capecitabine nanoparticles, allowing for more efficient delivery.
- Reduced Systemic Side Effects: The matrix method can reduce systemic side effects by providing a localized delivery of Capecitabine nanoparticles.
- Increased Patient Compliance: The matrix method can increase patient compliance by providing a convenient and non-invasive delivery system.

Evaluation of Transdermal Patches

Development of controlled release transdermal dosage form is a complex process involving extensive research. Transdermal patches have been developed to improve clinical efficacy of the drug and to enhance patient compliance by delivering smaller amount of drug at a predetermined rate. This makes evaluation studies even more important in order ensure their desired performance and reproducibility under the specified environmental conditions, these studies are predictive of transdermal dosage forms and can be classified into different types including physicochemical evaluation, in-vitro evaluation, and in-vivo evaluation. After the successful evaluation of physicochemical and in-vitro studies, in-vivo evaluations may be conducted.

Physicochemical Evaluation

Thickness: The thickness of transdermal film is determined by travelling microscope, dial gauge, screw gauge or micrometer at different points of the film.

Uniformity of weight:

Weight variation is studied by individually weighing 10 randomly selected patches and calculating the average weight. The individual weight should not deviate significantly from the average weight (Samanta et al., 2003).

Drug content determination:

It can be determined by completely dissolving a small area (1) cm^2) of polymeric film in suitable solvent of definite volume. The solvent is selected in which the drug is freely soluble. The selected area is weighed before dissolving in the solvent. The whole content is shaken continuously for 24 h in a shaker incubator followed by sonication and filtration. The drug in solution is assessed by appropriate analytical method.

Content uniformity test:

The test is applied as the gold standard to determine chemically the content of active constituent for each unit dose. The test is completed by performing assay to find out the content of drug material contained in polymeric film of the patch. According to USP the procedure consists of two stages. First stage consists of assaying the randomly selected ten units. It is followed by second stage to be performed on twenty more units when the first stage fails. Initially ten patches are selected and content is determined for individual patches. Test passes when all 10 unit doses have content 2 85% and ≤ 115% (RSD<6%). If 9 out of 10 patches have content between 85% to 115% of the specified value and one has content not less than 75% to 125% of the specified value, then transdermal patches pass the test of content uniformity. But if 3 patches have content in the range of 75% to 125%, then additional 20 patches are tested for drug content. If RSD of all the 30 units is <7.8%, not more than one value E outside 85-115%, and no value is outside75-125%, the batch passes the test if not fails the test.

Moisture content:

The prepared films are weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they show constant weight. The percent moisture content is calculated using following formula.

Moisture Uptake:

Weighed films are kept in a desiccator at room temperature for 24 h. These are then taken out and exposed to 84% relative humidity using saturated solution of Potassium chloride in a desiccator until a constant weight is achieved. % moisture uptake is calculated as given below.

Folding Endurance:

Evaluation of folding endurance involves determining the folding capacity of the films subjected to frequent extreme conditions of folding. Folding endurance is determined by repeatedly folding the film at the same place until it break. The number of times the films could be folded at the same place without breaking gives the folding endurance value.

Tensile Strength:

To determine tensile strength, polymeric films are sandwiched separately by corked linear iron plates. One end of the films is kept fixed with the help of an iron screen and other end is connected to a freely movable thread over a pulley. The weights are added gradually to the pan attached with the hanging end of the thread. A pointer on the thread is used to measure the elongation of the film. The weight just sufficient to break the film is noted. The tensile strength can be calculated using the following equation.

Incorporation of Capecitabine Nanoparticles into Transdermal Patch

Step: 1

- Dispersion of nanoparticles: The Capecitabine nanoparticles are dispersed in the polymer [polylactic-co-glycolic-acid]solution using a

suitable method, such as ultrasonication or mechanical stirring.

- Mixing and homogenization: The nanoparticle-polymer mixture is mixed and homogenized to ensure uniform distribution of the nanoparticles. Optimization: Optimize particle size (usually
- <200 nm for transdermal delivery), encapsulation efficiency, and drug release profile.

Characterization: Analyze nanoparticles for:

- Size and morphology.
- Drug-loading efficiency.
- In-vitro release kinetics.

Step-2

Transdermal patch:

- Matrix Design: Choose the appropriate patch matrix (e.g., hydrogel, pressure- sensitive adhesive) to ensure compatibility with the nanoparticles and drug stability.
- Incorporation of Nanoparticles: Disperse capecitabine-loaded nanoparticles into the matrix. patch Fabrication methods.
- Casting method: pour the Nanoparticle matrix Mixture onto a Flat Surface and dry to Form a thin Film
- Coating method: Coat a polymer Film with the Nanoparticle Formulation
- Back Layer: Use an impermeable backing layer to ensure unidirectional drug release.
- Release Liner: Apply a removable layer to protect the patch before application.

Characterization of Transdermal Patch

- Physical characterization: The transdermal patch is characterized for its physical properties, such as thickness, weight, and surface area.
- Pharmaceutical characterization: The patch is characterized for its pharmaceutical properties, such as drug content, release kinetics, and permeation.3.
- Biological characterization: The patch is characterized for its biological properties, such as skin irritation and toxicity.

Step 3: Quality Control and Packaging

Quality control: The transdermal patch is subjected to quality control tests to ensure its quality and efficacy.

Packaging: The patch is packaged in a suitable container, such as a pouch or a blister pack, to protect it from moisture and light.[20]

4. Conclusion

The development and Evaluation of Transdermal patches Loaded with Capecitabine Nanoparticles represent promising approach for breast Cancer therapy. Capecitabine is an oral chemotherapeutic agent has Limited bioavalibility and Side effects. Compare to oral administration the transdermal route, minimizing gastrointestinal toxicity and other systemic adverse Effects. The nanoparticles based Formulation Enhances the therapeutic Efficacy of Capecitabine while minimizing Systemic toxicity and Side effects. Transdermal patches and nanoparticle technology formulation provide a noninvasive and targeted drug delivery method Ensuring Controlled released and improved bioavilability of the drug.

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