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Formulation And Evaluation of Transdermal Patches of Anti-Cancer Drug Containing Natural Penetration Enhancer.

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ABSTRACT
Transdermal drug delivery systems (TDDS) provide sustained, non-invasive, and controlled release of drugs, enhancing bioavailability while reducing systemic side effects. Aim: This study focuses on the formulation and evaluation of gemcitabine transdermal patches using natural penetration enhancers to improve anticancer efficacy. Transdermal drug delivery system can be defined as the topically administered medications in self- contained, discrete dosage forms of patches which when applied to the skin deliver the drug, through the skin portal to systemic circulation at a predetermined and controlled rate over a prolonged period of time in order to increase the therapeutic efficacy and reduced side effect of drug. TDDS maintains drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.

INTRODUCTION:

Novel drug delivery systems (NDDS) are designed to improve bioavailability by transporting drugs directly to the site of action, thereby reducing side effects and improving therapeutic efficiency. Among these, nanoparticles have attracted attention due to their high surface area, ability to cross biological barriers, and potential to enhance dissolution and stability of drugs, ultimately leading to better bioavailability and reduced toxicity[1].

Transdermal drug delivery systems (TDDS) represent a promising NDDS, offering sustained and controlled drug release through the skin into systemic circulation while bypassing first-pass metabolism[2,3]. These systems maintain plasma concentrations within the therapeutic window and improve patient compliance by reducing dosing frequency. Several drugs such as nicotine, nitroglycerin, and estrogen have already been successfully delivered via transdermal patches[4].

TDDS offer advantages including avoidance of gastrointestinal degradation, non-invasiveness, and rapid termination of therapy by patch removal[5]. However, limitations such as skin impermeability, potential irritation at the application site, and restriction to potent drugs still exist[6]. To overcome these barriers, natural penetration enhancers have been explored to improve drug permeation and therapeutic efficacy[7].

The present study focuses on the formulation and evaluation of gemcitabine-loaded transdermal patches using natural penetration enhancers, aiming to achieve sustained release, improved bioavailability, and reduced systemic side effects.

Types of Transdermal Drug Delivery System:

a) Single layer drug in adhesive: In this type

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the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi -layer drug in adhesive: This type is also similar to the single layer but it contains an immediate drug-release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner- layer and a permanent backing.

c) Vapour patch: The patch containing the adhesive layer not only serves to adhere the various surfaces together but also serves as to release the vapour. The vapour patches are new to the market, commonly used for releasing the essential oils in decongestion. Various other types of vapour patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system: In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non-porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug (Patel and Shah 2018).

e) ***Matrix system:***

i. Drug-in-adhesive system: This type of patch is formulated by mixing the drug with adhesive polymer to form drug reservoir. It then followed by spreading on an impervious backing layer by solvent casting or melting method. The top of the reservoir is protected by an unmediated adhesive polymer layers. It may further be categorized into single-layer and multi-layer drug-in- adhesive. The system is considered to be compatible with a wide variety of drugs. Moreover, the system is competent to deliver more than one drug in a single patch. It offers advantages in reduced size and thickness and improved conformability to the application site, helping drive patient preference.

ii. Matrix-dispersion system: The drug is dispersed homogenously in a hydrophilic or lipophilic polymer matrix. It is then altered into a medicated disc with the definite shape and thickness. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Micro reservoir system: The system consists of microscopic spheres of drug reservoirs which releases drug at a zero order rate for maintaining constant drug levels. Micro reservoir system is a combination of reservoir and matrix-dispersion system. The aqueous solution of water soluble polymer is mixed with drug to form a reservoir. It is then followed by dispersing the solution.

homogeneously using high shear mechanical force in a lipophilic polymer to form thousands of microscopic drug reservoirs. Cross linking agents are added to stabilize the thermodynamically unstable dispersion by in-situ cross-linking the polymer **(Kanoun, 2023).**

Basic component of TDDS:

Both matrix patches and liquid reservoir patches comprise of various components. Some are similar in both classes, while others are type-specific. The common components include:

1. **Backing Films:** Backing films play a vital role in the transdermal patch and also while using the system. The role of the film is to protect the active layer and safeguard the stability of the system, and to affect skin permeation and tolerance, depending on occlusion or breathability. In order to avoid any type of incompatibility the release liner must be fully inert to the ingredients. It must also be flexible, comfortable and must have good affinity with the adhesive and excellent printability. The most common release liners are polypropylene, polyesters, PVC and nylon.

2. **Release Liners:** An anti-adherent coating will be covering the release liners. The role of the release liner is to protect the system when it is in the package, it will be removed just before the application of TDDS to the skin. Release liners play an important role in the stability, safety and affectivity of the patch. Care should be taken to choose the release liners. An incorrect release liner will not

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permit the easy release of the patch, and can interfere with the active(s) or other components, thereby reducing its shelf life. The most common films used as release liners are paper-based, plastic film-based and composite films. The two major classes of coating are silicones and fluoro-polymers.

3. **Pressure Sensitive Adhesives:** For both types of TDDS, pressure-sensitive adhesive (PSAs) play an important role, by serving as the matrix that carries the active like additives and permeation enhancers and the means for making the patch stick to the skin. There are three categories in PSAs: rubber-based, acrylic in the form of acrylic solutions, emulsion polymers or hot melts, and silicon PSAs. For each category there are several sub-categories that give the required flexibility to the patch.

4. **Penetration Enhancers:** These are the completely different chemical substances that belong to the same family by characteristics. They increase the permeation rate by several times of the active ingredient through the skin. This enhances the feasibility of a system, because most of the actives do not enter the skin in the required dosage through a relatively small area. Sometimes a combination of these ingredients is needed to create the correct enhancing effect (Kesarwani *et al.,* 2013).

5. **Micro porous or Semi-Permeable Membranes:** Porous membrane is a special type of membrane mostly used in all liquid transdermal patches and some of the matrix type patches. Its role is to regulate the flow of the semi-solid content from the liquid reservoir, and to act as a rate limiting membrane for the systems. The ability of the membrane depends on the design of the system, size of the active component and the need to have rate-limiting factor in order to satisfy the release and absorption characteristics of the system. Permeation rate depend on chemical composition.

Methods: Patches were prepared by solvent casting method with polymers (HPMC, PVP), plasticizers, and natural enhancers. Evaluation included organoleptic studies, solubility, FTIR, thickness, folding endurance, drug content, and in vitro drug release using Franz diffusion cell. Results: The optimized formulation (TPF-5) exhibited good physicochemical properties, 95–98% uniform drug content, and sustained release (up to 11 h). Kinetic analysis indicated zero-order release with Higuchi diffusion mechanism. Conclusion: Gemcitabine- loaded transdermal patches incorporating natural penetration enhancers provide an effective alternative for anticancer drug delivery with potential clinical applications.

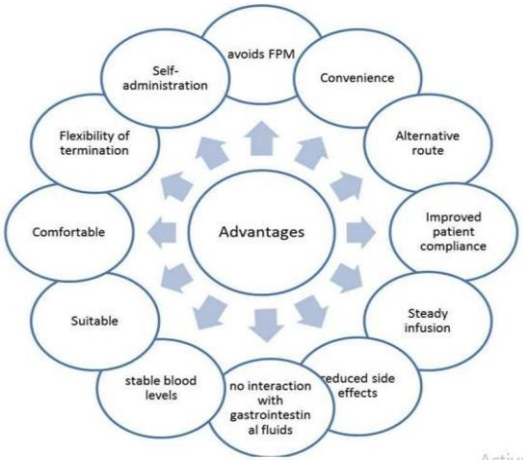

Figure 1: Advantages of TDDS

MATERIALS AND METHODS:

Transdermal patches were prepared using solvent casting method with hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), glycerol, and natural enhancers (e.g., Aloe vera). Prepared patches were evaluated for physicochemical properties (organoleptic, thickness, weight variation, folding endurance, drug content), compatibility studies (FTIR), and in vitro release using Franz diffusion cell in phosphate buffer (pH 7.)

Selection of drug and excipients: Gemcitabine was chosen as a model anticancer drug due to its short half-life and need for sustained release. Natural penetration enhancers such as eucalyptus oil and aloe vera were incorporated for improved skin permeability, while HPMC and PVP served as film-forming polymers. PEG-400 and glycerin acted as plasticizers, with ethanol and water as solvents.

Pre-formulation studies: Solubility studies were performed in methanol, ethanol, DMSO, and water to determine a suitable medium. The melting point was determined by the open capillary method. UV–visible spectrophotometry was used to identify λmax and construct a calibration curve for drug quantification. FTIR analysis was performed using the KBr disc method to assess compatibility of drug and excipients.

Formulation of Transdermal patches: Matrix-type patches of Gemcitabine were prepared by solvent casting technique. Polymers (HPMC,

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PVP, or Eudragit L) were dissolved in methanol, followed by addition of drug, plasticizer, and permeation enhancer. The solution was cast in petri dishes, dried at room temperature for 24 h, and stored in a desiccator. Six formulations (TPF1–TPF6) were developed with varying polymer ratios.

Determination of λ max: Solution was scanned under UV-Vis Spectrophotometer and λ max was determined. It was found to be as per the monograph.

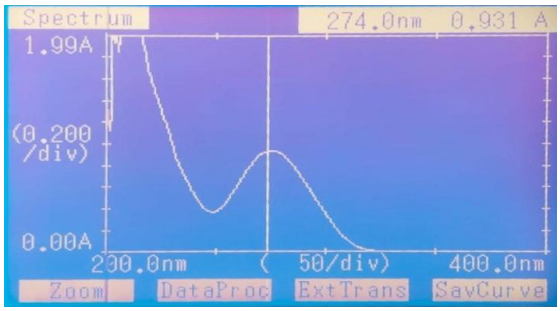

Figure 2: λ max of Gemcitabine

Lambda (λ) max:
The purpose of determining the λ max of Gemcitabine is to identify the wavelength at which the drug exhibits maximum absorbance, which is essential for accurate quantitative analysis in UV spectrophotometry. A stock solution of Gemcitabine was prepared by dissolving 1 mg/mL of the drug in methanol. From this, a working standard solution of 100 µg/mL was obtained through appropriate dilution with the same solvent. The working solution was then scanned over a wavelength range of 200–400 nm using a Shimadzu UV-Visible Spectrophotometer (Model 1700). The wavelength corresponding to the highest absorbance was recorded as the λmax, and this value was used for further spectrophotometric analysis such as the preparation of calibration curves and drug release studies (Ali *et al.*, 2022).

Evaluation of Patches:
Patches were tested for folding endurance, tensile strength, thickness, and drug content uniformity. Drug content was estimated by dissolving the patch in methanol and analyzing at λmax (270 nm).


Figure 3: UV spectrophotometer

In-vitro drug release studies:
Drug release was assessed using Franz diffusion cells with cellulose acetate membranes and phosphate buffer (pH 6.8) as receptor medium at 32 ± 0.5 °C. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically.

Kinetic modeling:
Release data were fitted to zero-order, first-order, and Higuchi models to determine release mechanism. The optimized formulation demonstrated sustained release with good fitting to zero-order kinetics and Higuchi diffusion model.
Zero: order kinetic model – Cumulative % drug released versus time.
First: order kinetic model – Log cumulative percent drug remaining versus time.
Higuchi's model: Cumulative percent drug released versus square root of time.
Zero order kinetics = $A_t = A_0 - K_0 t$
First order kinetics = $\text{Log } C = \log C_0 - K_t / 2.303$
Higuchi's Model = $Q = [D\epsilon / \tau (2A - \epsilon C_s) C_{st}]^{1/2}$

Table 1: Composition of Transdermal patch

Ingredients	Formulation batches					
	TPF1	TPF2	TPF3	TPF4	TPF5	TPF6
Gemcitabine (mg)	100	100	100	100	100	100
Polyethylene glycol (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Polyvinylpyrrolidone (mg)	-	-	-	150	200	250
Eudragit L (mg)	150	200	250	-	-	-
Tween 20	0.1	0.1	0.1	0.1	0.1	0.1
HPMC (mg)	200	200	200	200	200	200
Methanol	10	10	10	10	10	10
Glycerin	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

RESULTS AND DISCUSSION
All patches exhibited uniform thickness, good flexibility, and drug content within 92–98%. FTIR spectra indicated no significant drug–excipient interactions. In-vitro release studies showed sustained release up to 11 h, with optimized formulation (TPF5) releasing 92.8% of drug content. Drug release followed zero-order kinetics with Higuchi diffusion mechanism.

Table 2. Evaluation of Gemcitabine Patches

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Formulation	Thickness (mm)	Folding Endurance	Drug Content (%)	Release at 10 h (%)
TPF1	0.20 ± 0.01	170 ± 5	92.4 ± 0.5	81.2 ± 1.2
TPF2	0.21 ± 0.02	185 ± 6	94.6 ± 0.4	85.7 ± 1.5
TPF3	0.22 ± 0.01	190 ± 4	95.8 ± 0.6	87.1 ± 1.8
TPF4	0.23 ± 0.02	200 ± 7	96.3 ± 0.7	90.5 ± 2.0
TPF5	0.23 ± 0.01	205 ± 5	97.6 ± 0.6	92.8 ±1.3
TPF6	0.24 ± 0.01	198 ± 6	96.2 ± 0.5	91.4 ± 1.4

DISCUSSION:

Transdermal patches are an effective system for delivering drugs through the skin into systemic circulation, providing controlled and sustained drug release. In this study, Gemcitabine transdermal patches were developed using the solvent casting method with HPMC as the primary polymer, polyethylene glycol as plasticizer, and suitable permeation enhancers.

Pre-formulation studies confirmed the solubility of Gemcitabine in methanol and DMSO, with partial solubility in ethanol and water. The drug's melting point was recorded as 180 °C, confirming purity. UV analysis showed linearity between 5–30 µg/mL at λmax 270 nm, with an R^2 value of 0.981, suitable for quantitative estimation. FTIR analysis confirmed no drug–excipient interactions, ensuring compatibility.

Six formulations (TPF1–TPF6) were prepared with varying excipient ratios. Evaluation parameters included folding endurance, tensile strength, elongation, drug content, and moisture content. Folding endurance was satisfactory in all formulations, confirming optimum flexibility. Tensile strength varied between 0.42–0.61 kg/cm³, with higher HPMC and PVP content leading to stronger patches. Percent elongation was within 35– 42%, while TPF5 showed the least elongation. Drug content across patches ranged between 78.67–89.78%, with TPF5 recording the highest at 89.78%. Moisture content ranged between 1.16–3.16%, increasing with higher polymer concentration.

Among all formulations, TPF5 was identified as the optimized batch due to its superior flexibility, drug content, and overall performance. It was further selected for in-vitro release and kinetic studies, which confirmed its potential for sustained drug delivery.

Conclusion

Gemcitabine transdermal patches prepared using natural penetration enhancers showed effective drug loading, flexibility, and sustained release. The optimized formulation (TPF5) demonstrated 92.8% release over 11 h, indicating potential for improved therapeutic efficacy and patient compliance in cancer therapy. The main objective of this work was designed to prepare and evaluate the Gemcitabine Transdermal patches. This formulation will deliver therapeutically effective amount of drug across the skin when it placed on skin. After preparation, the patches were stored in freeze condition, and given for further evaluation. The prepared Transdermal patches of TPF1, TPF 2, TPF 3, TPF 4, TPF 5 and TPF 6 formulations were evaluated for physical and chemical properties like tensile strength, folding endurance, % elongation break test, thickness and drug content. From all evaluation results, TPF 5 formulation was found to be best formulation. These developed Transdermal patches were evaluated for the drug release study in pH 7.4 phosphate buffer using membrane diffusion method. The release of the drug from TPF 5 formulation as found to be 95% in 11 hours. The study successfully developed gemcitabine-loaded transdermal patches using natural penetration enhancers. The optimized patch demonstrated sustained drug release, improved permeation, and potential for reducing systemic side effects. These findings suggest that transdermal delivery of anticancer drugs could be a promising alternative to conventional routes, improving therapeutic efficacy and patient compliance.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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