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ANTI-NEOPLASTIC TRANSDERMAL PATCH: A NOVEL APPROACH IN BREAST CANCER THERAPY

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Keywords:

Evaluation, *In-vivo* studies, Liposomes, Tamoxifen citrate, Transdermal patch

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ABSTRACT: Background: In the present investigation Antineoplastic loaded transdermal patch was formulated using Liposomes, eudragit-RL, hydroxypropyl methyl cellulose K-50, and ethyl cellulose. **Materials and Methods:** Liposomes were formulated by solvent evaporation method using poly (sebacic acid-co-ricinoleic acid) in varying ratios and evaluated for particle size, drug loading, entrapment efficiency, transmission electron microscopy, differential scanning calorimetry and X-ray diffraction. Formulated tamoxifen-loaded liposomes were finally incorporated into transdermal patch and evaluated for thickness drug content, moisture content, moisture uptake, folding endurance, tensile strength diffusion coefficient, permeability coefficient, *in-vitro* permeation, and skin irritation. Optimized transdermal patches were tested for its pharmacokinetic and pharmacodynamics parameters. **Results:** Formulated transdermal patches showed improved bioavailability of tamoxifen when compared to its oral route. **Conclusion:** Tamoxifen-loaded liposomal transdermal patches could serve as a better alternative to existing marketed formulation in terms of bioavailability.

INTRODUCTION: The most prevalent kind of cancer in women, affecting one in eight, is breast cancer. The most evident explanation of an increase in breast cancer cases in industrialised nations is population ageing; in fact, the risk of acquiring breast cancer after age 65 is 5.8 times higher than it is before 65 and 150 times higher than it is before age 30. One of the main causes of cancer-related fatalities in women is breast cancer. Every year, over 1 million new cases are diagnosed.

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The preferred treatment for individuals with all stages of oestrogen receptor positive breast cancer is oral administration of then on steroidal antiestrogens like tamoxifen. A very lipophilic medication is Tamoxifen citrate (TC), [1, 2diphenyl1butenyl] phenoxy) N, Ndimethyl ethanamine 2 hydroxy 1, 2, 3 ropanetricarboxylate, then on steroidal antiestrogen [1]. It could result in negative long-term adverse effects such endometrial cancer or developed tamoxifen resistance.

It is used as the preferred endocrine treatment agent for all stages of breast cancer and has been given US approval for use as a chemotherapy preventative agent in high-risk patients [2]. Tamoxifen taken orally is extensively metabolised in the liver and then excreted in the bile.

It could result in negative long-term adverse effects including endometrial cancer or developed tamoxifen resistance, which would accelerate the growth of the tumour. Increasing blood clotting, liver cancer and ocular adverse effects such retinopathy and cornealopacities are some other negative effects.

Bed dependant reported experiencing these consequences. Using transdermal medication administration, these unfavourable side effects can be avoided (TDDS) [3, 4].

It can have benefits like achieving the required therapeutic concentration of anti-cancer medications at the tumour site and concentrating drug delivery on tumour cells. Dose decrease can reduce systemic adverse effects and medication delivery often can be stopped. The proposed novel prolonged medication delivery method may also make traditional therapy less inconvenient for patients and increase their willingness to accept their treatment [5]. Liposomes are small spheres made of one or more concentrated lipid bilayers that surround an aqueous compartment and have negative long-term adverse effects, including. It can serve as a medication delivery method for TDDS. Transmission electron microscopy (TEM), differential scanning calorimetry (DSC) and X-ray diffraction have all been used to evaluate the tamoxifen-loaded liposomes that were created for this study project (XRD). A transdermal patch containing synthesised liposomes was then evaluated for thickness, drug content analysis, moisture content, moisture uptake, folding endurance, tensile strength, *in-vitro* skin permeation study, *in-vitro* release study and *in-vitro* skin irritation study, followed by *in-vivo* pharmacokinetic and pharmacodynamic studies.

MATERIALS AND METHODS: TC came as a gift from the Indian company Dabur Pharmaceutical Ltd. in Ghaziabad. From Lab Care Ltd. in Bengaluru, Karnataka, India, we obtained beta cyclodextrin, eudragit RL 100, ethyl cellulose, and hydroxypropyl methylcellulose (K 15). The analytical grade of all other chemicals and solvents was obtained from Merck Pvt. Ltd. in Bengaluru, Karnataka, India.

Methods:

Preparation of Transdermal Patch: Ion of liposomes that contain tamoxifen citrate By using the solvent displacement approach, TC loaded poly (sebacic acid/ricinoleic acid [SA: RA]) 50:50 liposomes were created (purchased from Sigma Aldrich, Bengaluru, Karnataka, India). There were four distinct formulation types created, denoted by the letters F1, F2, F3 and F4, with the theoretical loading of TC varying by 5, 10, 20, and 30% w/w of polymer, poly (SA: RA) 50:50, respectively. **Table 1** lists the precise quantities of polymer and medication necessary to produce each type of system [5].

TABLE 1: COMPOSITION OF FORMULATIONS

Formulation	Drug	Polymer	Cryoprotectant	
	Tamoxifen Poly	(SA: RA)	Glucose (mg)	Mannitol (mg)
	Citrate (mg)	7:3 (mg)	14	14
F1	10	190	14	14
F2	20	180	14	14
F3	40	160	14	14
F4	60	140	14	14

After a known quantity of poly (SA: RA) was dissolved in 10 ml of acetone and subjected to a 15-minute magnetic stir, TC was added to the organic phase and swirled for an additional 15 minutes. 40 ml of a 1:1 mixture of ethanol and water were added to the organic phase containing the medication and polymer, which was then stirred at 1000 rpm for 20 minutes. This system functioned normally for 30 minutes. Drug and polymer displacement occurred as acetone, ethanol and water in that sequence as the organic solvent was rapidly removed from the triphasic system using a rotary flash evaporator. The resultant aqueous system was frozen in liquid nitrogen and lyophilized using Christ alpha 1-4 LD plus lyophilizer. Cryoprotectants glucose and mannitol (7% w/w of polymer and medication) were added before lyophilization (Indian Institute of Science, IISc, Bengaluru, Karnataka, India). The objective was to produce poly (SA: RA) lipid nanoparticles of [6, 7] that were free-flowing and fluffy.

Evaluation of Lyophilized Liposomes: Prepared liposomes were evaluated for particle size using Malvern Laser Analyzer Instrument (IISc, Bengaluru, Karnataka, India), drug loading, entrapment efficiency, TEM, DSC and X-RD [8].

Preparation of Transdermal Patch: On the surface of the mercury, transdermal films of TC (5.0 mg/3.14 cm2) were created with various concentrations of eudragit RL, hydroxypropyl methyl cellulose (HPMC K 50) and ethyl cellulose. Drug and polymers in the needed quantity were dissolved in a methanol dichloromethane (1:1) solvent system. Plasticizer was di-n-butyl phthalate (20 and 30% w/w of polymer). The polymer drug solution also contained dimethyl sulfoxide (DMSO) and isopropyl myristate (IPM).

The resulting homogenous solution was poured over a mercury substrate in a circular plane with a uniform surface. The drying process took place over the course of 24 hours, with the rate of evaporation being managed by inverting the funnel over the Petri dish. Aluminum foil was used to wrap the dry films, which were then stored in desiccators. **Table 2** lists the ingredients of manufactured formulations and **Fig. 1** includes images of patches that include drugs.

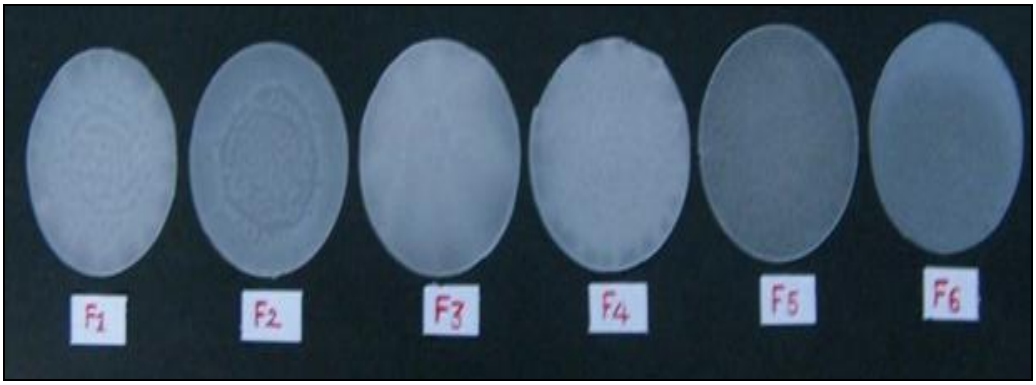

FIG. 1:

TABLE 2: EVALUATION OF TAMOXIFEN CITRATE LIPOSOMES

Formulations	Yield (percentage w/w)*	Drug loading (Percentage w/w±SD)*	%EE (Percentage ±SD)*	Mean particle size (nm±SD)*
F1	66.22	4.79±0.20	93.33±2.26	543±0.02
F2	63.60	9.63±0.49	91.13±1.62	412±0.05
F3	69.41	18.78±2.84	90.32±2.30	418±0.07
F4	74.23	28.18±0.86	92.43±1.72	429±0.12

*Average of three determinations,SD: Standard deviation, EE:Entrapment efficiency

Evaluation of Prepared Transdermal Patches:

Thickness: Utilizing a micrometre gauge, the thickness of the film before and after the permeation investigation was measured (Mitoyoto, Japan). Film was measured at several locations and the mean value was computed [9].

Drug Content Analysis: By taking known areas of the transdermal films at various locations on the film, the uniformity of drug delivery in the films was assessed. The films were dissolved in 2 ml of methanol, subjected to 10 minutes of sonication, and then diluted in phosphate buffer saline (PBS), pH 7.4. Following the proper dilution, solutions were examined spectrophotometrically (ultraviolet [UV] Shimadzu 1700, Japan) for TC at 274 nm using solutions of films made without drugs as a reference to ignore the absorption of formulation ingredients, if any.

Moisture Content: Individually weighed, the produced films were stored for 24 hours at room temperature (30°C) in desiccators with activated silica until a consistent weight was reached. The difference between the starting and final weights relative to the final weight was used to compute the percentage of moisture content.

Moisture Uptake: A weighted film was removed from a desiccator that had been maintained it at room temperature (30°C) for 24 hours and placed in a stability chamber (Lab Care, Mumbai, Maharashtra, India) where it was subjected to 84% relative humidity (RH) until the weight of the film

remained constant. The difference between final and original weight with regard to starting weight was used to compute the % moisture absorption [10].

Folding Endurance: A piece of film (2 cm 2 cm) was cut equally, then folded over and over until it broke. The quantity of folds that the film could withstand at the same location without breaking determined the value of the endurance.

Determination of Tensile Strength: The tensile strength was determined by using dynamic mechanical analyzer (computerized, EPLEXOR 500 N, IISC, Bengaluru, Karnataka, India). Exactly, 2 cm^2 patches of all the formulation were subjected and determined.

Determination of Flux, Diffusion Coefficient and Permeability Coefficient: Through the use of linear regression analysis, the flux of the drug penetrated in the instance of *in-vitro* was determined from the slope of the steady state section of the permeation profile. The lag time was computed using a back extrapolation of the graph's steady state region. According to the equations given below, Diffusion Coefficient (D/h2) and Permeability Coefficient (Kp) were also calculated for the in vitro studies. TLag is the lag time, JSS is the flux at steady state, CD is the concentration in the donor compartment, D is the diffusion coefficient and h is the diffusion path length [11].

***In-vitro* Skin Permeation Study:** For the permeation investigations, female albino rats weighing 150–200 g were used. The anaesthetic ether was used to sacrifice the animals. The test animals' hair was carefully cut short using a pair of scissors and the abdomen region's whole thickness of skin was excised.

The abdominal skin was completely submerged in water heated to 60 degrees for 45 seconds in order to prepare the epidermis for surgery using the heat separation technique. The epidermis was then carefully removed. For permeability investigations, the epidermis was cleaned with water. In a modified Keshary-Chen diffusion cell operating at 32 0.5°C, permeation investigations for various formulations were conducted across the skin of female rats. 3.14 cm2 of effective constant areas are provided by the donor compartment cell's diameter. Adhesive tape (cellophane) was used as the backing layer to apply the 3.14 cm^2 films to the skin. To assure sink conditions and drug stability, the receptor compartment medium (20 ml of phosphate buffer pH 7.4) was utilised. The solution was continually stirred using a magnetic bead while the entire assembly was kept on a magnetic stirrer. At various time intervals, the samples were taken out and replaced with an equivalent amount of diffusion media. At 274 nm, samples were examined spectrophotometrically. To ascertain whether the components of the skin or other excipients of the film interfere in the drug analysis; blank experiment (films without drug) was run using skin as barrier membrane using PBS pH 7.4. When the solution was analyzed at 274 nm for any interfering constituents, the released constituents were amounting to an average of 0.04 ± 0.02% [12].

***In-vitro* Release Studies:** Release of TC from transdermal patch (10% w/w of DMSO as penetration enhancer) was measured using regenerated cellulose dialysis membranes (10 K MWCO, Himedia. Pvt. Ltd, Bengaluru, Karnataka, India). The membranes were washed and equilibrated with 0.1M PBS, and then mounted on Keshary–Chien diffusion cells (receptor volume 20 ml, permeation area 3.14 cm2) by clamping them between the donor and receptor compartments. The receptor compartments were continuously swirled at 100 rpm while being filled with phosphate buffer pH 7.4 and kept at 37 0.5°C. Patch (10–60 mg of medication) was maintained evenly on the donor film, and Parafilm M was used to cover the sample ports (Fisher Scientific, Bengaluru, Karnataka, India). At predefined intervals, samples from the receptor fluid were taken and replaced with an equivalent volume of buffer. The removed samples' drug content was examined using the UV-VIS technique as previously mentioned. Every release study was carried out in three copies.

Skin Irritation Studies: Male Wista ralbino rats weighing 200–225 g were used for the skin irritancy test. The animals were housed in a typical laboratory setting with temperature and relative humidity at 25 1 °C and 55 5%, respectively. The animals were kept in six-animal polypropylene cages with unlimited access to a normal laboratory meal and water. On the day before the experiment, the rats' dorsal side hair was cut with an electric hair clipper.

Three groups of the rats (a total of six) were created. Group I acted as the untreated control group. Group III got 0.8% v/v aqueous solution of formalin as a conventional irritant Group II got a topical 5 mg dose of the TC liposomal patch (33). Each day for up to 6 days, the animals received a fresh application of the TC transdermal patch or fresh formalin solution. Finally, the same investigator consistently rated the application sites using a visual scoring system. According to the level of erythema, the mean erythemal scores (which range from 0 to 4) were reported as follows: Severe erythema (intense redness) = 4, severe erythema (no erythema) = 3, moderate erythema (dark pink), moderate to severe erythema (light red), and hardly visible erythema (light pink) = 0.

Pharmacokinetic Studies: After application, the animals were restrained with hands for five minutes before being put in separate cages. 500 of blood were drawn into 250 heparinized glass capillary tubes and placed into 1.5 ml vials at a number of predetermined intervals (1, 2, 4, 6, 8, 12 and 24 hours) following treatment. Plasma was separated after being centrifuged at 4000 rpm for 10 minutes, and it was then promptly frozen at 20°C until being analysed. The samples were frozen before detection, followed by the addition of 50 ml of n-hexane, 200 ml of acetonitrile, and 200 ml of methanol. The mixture was centrifuged at 4000 rpm for 10 minutes. Injection of the supernatant into the high-performance liquid chromatography was around 50. The analysis employed a Phenomex C8 (250 4.6 mm) 5 column. After that, the samples were processed for analysis as previously mentioned. By gavage needle, the remaining five rats (Group IV) were given an oral dosage of 4 mg/kg TC aqueous solution. For the period of time from 0 to the last measurement point, which was 24 hours, the AUC0-24 was determined using the trapezoidal rule. The concentration time plot was used to determine the maximum drug plasma concentration tmax as well as the peak plasma concentration Cmax [13].

Pharmacodynamics Studies: All animals received a subcutaneous injection of 4 106 MCF7 cell suspension made in standard Dulbecco's modified eagle medium on day 0 to develop a tumour in the dorsal right flank. Animals were randomly assigned to one of four groups when tumours reached a minimum size of 80–90 mm3 on day 19: Group I received no treatment, Group II received a transdermal patch containing 5 mg of TC, Group III received a transdermal patch containing 5 mg of TC in the form of liposomes, and Group IV received an oral dose of 4 mg/kg of TC. The number of mice in each group was five. Groups II, III and IV each received 5 mg/kg of TC. Tumors were measured every day after first dose administered on day 20, till day 28. The tumor volumes were calculated by the following formula as reported earlier: [10] Tumor volume ¼ 0:5 ab2 where *a* = length of tumor mass and *b* = breadth of tumor mass growing on flank of animal. Results were evaluated for statistical significance employing one-way ANOVA (Bonferroni test). The differences in tumor volume were considered statistically significant at $P < 0.05$ [14].

RESULTS AND DISCUSSION:

Preparation and Evaluation of TC Liposomes: By using the solvent displacement approach, TC loaded poly (SA: RA) liposomes were created. The carrier was a polyanhydride-based polymer called poly (sebaciccoricinoleic acid) 5:5. The hydrophobic polymer Poly (SA: RA) 7:3 employed in this work can be used to release both hydrophobic and hydrophilic medicines. It is made of natural fatty acids. In order to speed up particle formation and stop lipid particles from shrinking during lyophilization, glucose and mannitol were utilised as cryoprotectants. Polysaccharides, which the body metabolises through glycolysis and the Krebs cycle to produce carbon dioxide and water and a type of useable energy, were utilised as cryoprotectants and are harmless to humans.

Due to their outstanding results in terms of particle size, entrapment effectiveness and dispersion of these nanoparticles, TC loaded Formulations of F3 and F4 were ultimately chosen for DSC and X-RD experiments. We initially described the physical condition of the drug inside the nanoparticles in order to determine the mechanism of sustained drug release. The melting peak of TC was missing in the DSC thermograms of nanoparticles containing TC, indicating that the medication was disseminated in an amorphous form or dissolution state, according to the DSC thermograms displayed in **Fig. 2**. The medication was shown to be in crystal form by X-ray diffractogram **Fig. 3**. TC

loaded finally, formulations of F3 and F4 were chosen. It was discovered that the range of 61-73% w/w for the percentage yield of the liposomal formulations reported in **Table 2** applied. Comparative loss in F1 is higher than in F4, which could be explained by the relatively high amount of polymer present in F1. Due to the lipid polymer's tendency to attach to the formulation, recovery issues and yield loss may be to blame. To create liposomes, four different medication to polymer ratios were employed. In the poly (SA: RA) of 7:3 based nanoparticles, the drug loading and entrapment efficiency of TC were determined to be between 90 and 93% w/w. The TC's hydrophobicity and insolubility in water, which reduces its entrapment effectiveness, can be used to explain the high entrapment efficiency. Finally, TC loaded Formulations of F3 and F4 were chosen. Since polyanhydrides are generally hydrophobic polymers and liposomal formulwater has a higher percentage yield, it is envisaged that medications with poor water solubility will be more effectively incorporated. We got particles with a size distribution of 400–600 nm. With an increase in TC content, particle size rose marginally. The differences in drug and polymer concentrations as well as the preparation process may be the cause of the observed particle size (mean diameter) variation in the TC loaded poly (SA: RA) nanoparticles. Lipid nanoparticle investigations using a scanning electron microscope are shown in **Fig. 4** together with a typical F3 drug loaded formulation. **Fig. 5** summarises the findings of drug release experiments conducted on all four formulations [15].

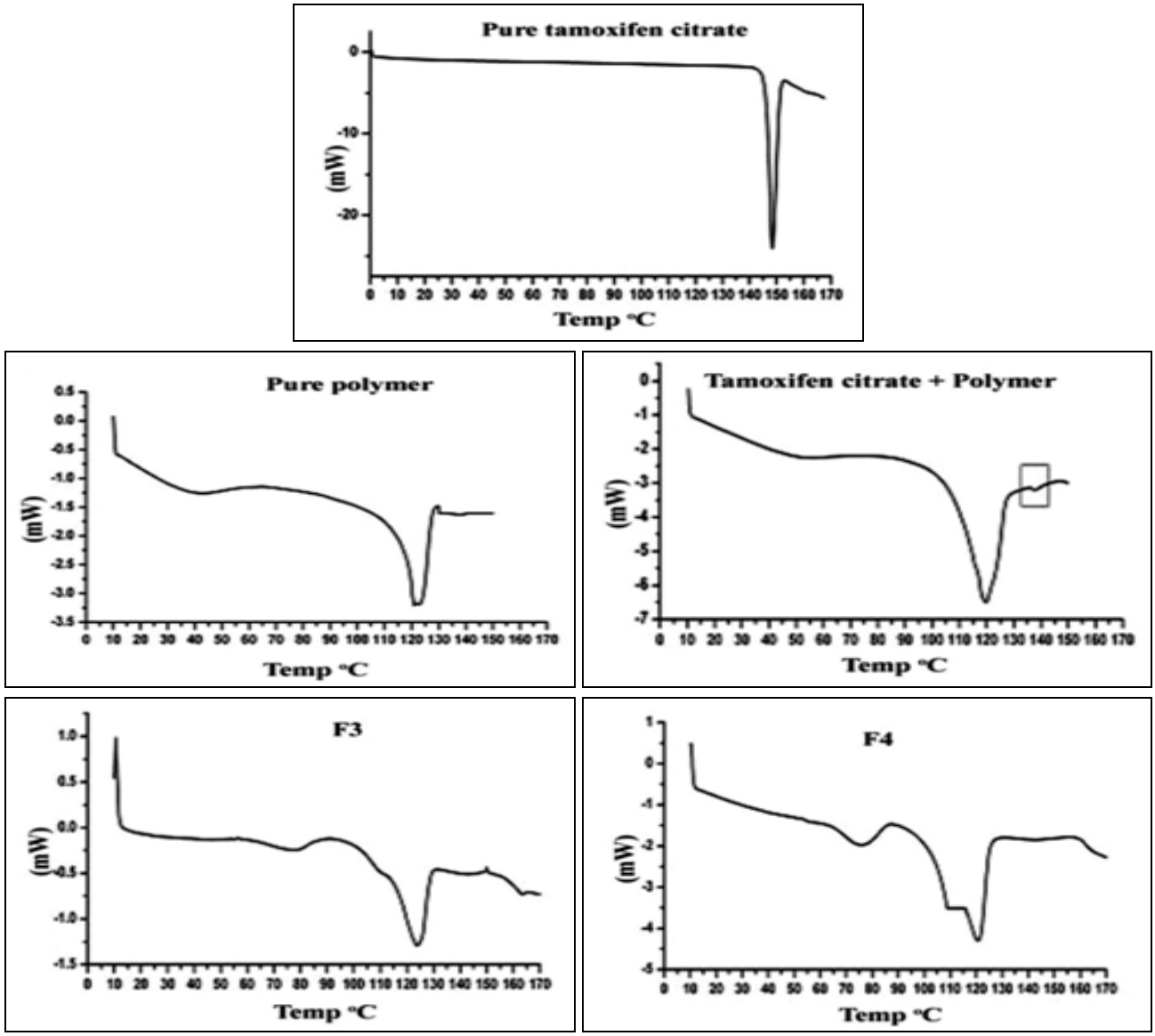

FIG. 2: DIFFERENTIAL SCANNING CALORIMETRYTHERMOGRAMS OF (A) PURE TAMOXIFEN CITRATE (B) PURE POLYMER (C) PHYSICAL MIXTURE (D) F3 AND (E) F4

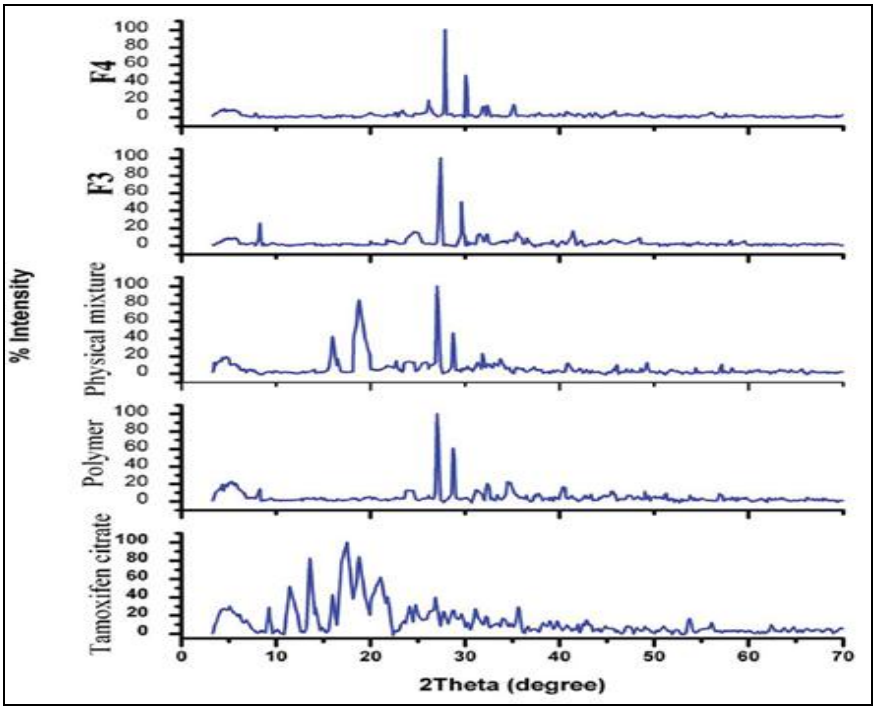

FIG. 3: X-RAY DIFFRACTION PETTERN OF TAMOXIFEN CITRATE, PUNE POLYMER, PHYSICAL MIXTURE, F3 AND F4, RESPECTIVELY

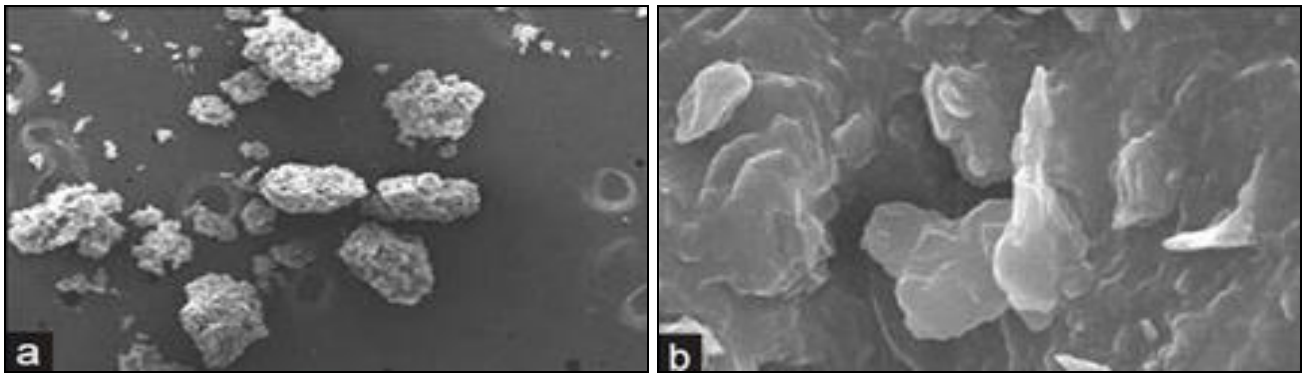

FIG. 4: THE SCANNING ELECTRON MICROSCOPE STUDIES OF LIPID NANOPARTICLES (A) AND TYPICAL F3 (B) DRUG-LOADED NANOPARTICLE IN PATCH FORMULATION

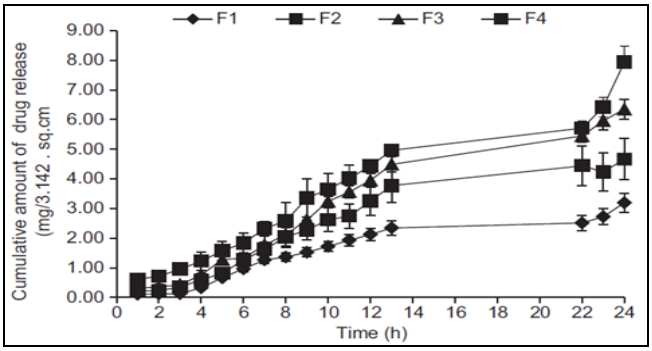

FIG. 5: CUMULATIVE AMOUNT OF DRUG RELEASE OF F1-F4 GET FORMATIONS

Stability Studies: The results of changes in mean particle sizes are presented in **Table 3**. It was worth noting that the TC liposomes did not show any significant changes in either drug content or particle size.

TABLE 3: STABILITY STUDIES OF PREPARED LIPOSOMES SHOWING PARTICLE SIZE AND DRUG CONTENT OVER 90 DAYS

Serial number	Particle Size (nm±SD)	Drug Content (percentage±SD)
Day 0	412±0.05	98.65±1.54
Day 30	411±1.65	99.31±1.02
Day 60	414±2.63	99.34±1.27
Day 90	424±2.15	99.59±1.06

SD: Standard deviation

Preparation and Evaluation of Transdermal Patch: Physical analysis of the formulations revealed that the films were somewhat transparent, indicating that the medication was not fully dissolved but rather was dispersed/suspended in the matrix. The investigations showed that the addition of dibutyl phthalate was set and standardised at

30% weight/weight for formulations F1–F4 and at 20% weight/weight for F5 and F6, respectively. Smooth, homogeneous and flexible films were produced from all of the designed and synthesised polymer compositions **Table 4.**

TABLE 4: FORMULATION COMPOSITION OF TAMOXIFEN CITRATE CONTAINING MATRIX TRANSDERMAL SYSTEMS

Formulations	F1	F2	F3	F4	F5	F6
Tamoxifen citrate (mg)	50	50	50	50	50	50
Eudrajit RL Mg	150	150	60	90	96	95
HPMC-E15 (mg)	-	-	90	60	-	-
EC (mg)	-	-	-	-	4	5
DMSO (w/w) (%)	10	-	10	10	10	10
IPM (w/w)	-	10%	-	-	-	-
DBT µl/w/w (%)	45(30)	45(30)	45(30)	45(30)	20(20)	20(20)
Methanol: DCM (1:2)(ml)	12	12	12	12	12	12

HPMC: Hydroxpropyl methyl cellulose, EC: Ethyl cellulose, DMSO: Dimethyl sulfoxide, IPM : Isopropyl myristate, DBT: Dibutyl phthalate, DCM Dichloromethane.

All the formulation contains 30% DBT except F5 and F6 containing 20% DBT.

Thickness and Uniformity of Weight: According to **Table 5**, thickness of films ranged between 0.106 and 0.127 mm, indicating that formulation factors utilised in the study had no discernible impact on film thickness. The weight uniformity ranged between 135.7 0.7 and 202.2 0.9, and when the Eudragit concentration dropped, the weight dropped as well [16].

TABLE 5: DETERMINATION OF FLUX, DIFFUSION COEFFICIENT AND PERMEABILITY COEFFICIENT

Formulations	(Jss)flux mg/cm^2/h	Permeation coefficient (cm/h)	Diffusion coefficient (cm/h)
F1	0.009±0.02	0.0017±0.001	0.0009±0.002
F2	0.007±0.03	0.0014±0.002	0.0001±0.003
F3	0.054±0.04	0.0116±0.003	0.0018±0.004
F4	0.063±0.05	0.0125±0.005	0.0020±0.001
F5	0.052±0.07	0.102±0.004	0.0020±0.001
F6	0.053±0.06	0.0108±0.003	0.0021±0.002

Average of three determinations were reported (±SD), SD: Standard deviation.

Drug Content Analysis: With a small standard variation (0.61), the drug content ranged from 97.15 to 99.62 in all formulations. The findings of the drug content analysis demonstrated that the technique used to make the study's films could produce films with a uniform drug distribution and a negligible batch variability ($P > 0.001$).

Moisture Content and Moisture Uptake: Studies on moisture content and moisture absorption offer information on the formulation's stability. The findings showed that moisture content and moisture absorption increased as hydrophilic polymer concentration increased (HPMC). Moisture content and moisture absorption values did not significantly alter when penetration enhancers DMSO and IPM were present. A modest increase in both parameters was seen with DMSO. This may be as a result of DMSO's affinity for water. The formulation's low moisture content keeps the films stable and prevents them from becoming entirely dried-out and brittle. It also shields the material from microbial contamination and the bulkiness of the films. Accordingly, the outcomes of physicochemical research on several polymeric films containing tamoxifen suggested combining these polymers to create transdermal films [17].

Determination of Tensile Strength and Folding Endurance: All of the formulations had excellent values for folding endurance and tensile strength, which were between 12.91 0.15 and 13.07 0.09 kg/cm^2 and 38.50 1.29 and 46.00 2.16 kg/cm2, respectively.

Determination of Flux, Diffusion Coefficient and Permeability Coefficient: An essential tool for anticipating how a medicine will act *in-vivo* is the *in-vitro* release profile. **Fig. 6** and **Table 6** display the findings of in vitro skin penetration tests of TC from transdermal patches. When compared to other formulations, the cumulative amount of drug

release from formulations F3, F4, F5, and F6 (2.0 cm^2, area of 3.14 cm2) was (4.278, 4.56, 4.224, and 4.665 mg), respectively. This phenomenon is attributed to the formulations' use of a combination of hydrophilic and hydrophobic polymers.

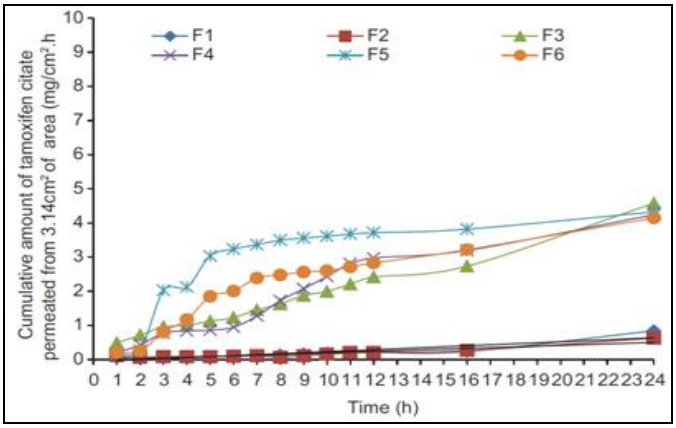

FIG. 6: CUMULATIVE AMOUNT OF TAMOXIFEN CITRATE PERMEATION THROUGH FEMALE RAT SKIN

The cumulative amount of medication that pierced 3.14 cm^2 of rat skin was plotted versus time in patches. When compared to the other two formulations, the flux, permeation coefficient and diffusion coefficient of formulations F3, F4, F5 and F6 were high. The hydrophilic nature of the polymer and its swelling capabilities may be the cause of the rise in these metrics.

Skin Irritation Studies: Transdermal patches made of eudragit RL, HPMC K50, and ethyl cellulose are harmless to skin, according to research on skin irritation. The absence of erythema or edoema on the skin's surface indicates that the patches' formulation is safe for therapeutic usage [18].

Pharmacokinetic Studies: Results of pharmacokinetic investigations are presented in **Table 7**. When delivered transdermally, the medication remained in the rat plasma for 18 h as opposed to 4 h after oral treatment.

Transdermal administration may give prolonged effectiveness with fewer adverse effects since it offers a nonfluctuated and constant distribution of TC into the circulation. For transdermal vs oral delivery, a formulation's relative bioavailability was calculated to be between 0.56 and 0.74. **Table 7** displays the pharmacokinetic parameters that were collected.

TABLE 7: PHARMACOKINETIC PARAMETERS AFTER TAMOXIFEN TRANSDERMAL AND ORAL SINGLE DOSE ADMINISTRATION TO RATS

System	Drug dose (mg/kg)	T_{max}(h)	C_{max}ng/ml	AUC_{0-24}ng/ml	F_{rat} transdermal versus oral
Group l (n=5)					
F1 EH	16.6 mg	1.30	111.85±45	957±387	0.56
F2 EH	16.6 mg	1.20	115.23±85	997±474	0.58
Group ll (n=5)					
F3 HCE	16.6 mg	0.90	112.63±87	1087±870	0.63
F4 HCE	16.6 mg	0.90	108.58±12	1189±666	0.69
Group lll (n=5)					
F5:40:160	16.6 mg	0.80	116.23±33	1425±412	0.67
F6:60:140	16.6 mg	0.60	120.89±78	1258±387	0.74
TC oral solution	3 mg	2.00	097.85±88	308±145	

P<0.05 significant difference from oral BH (unpaired t-test).Dose: All formulations containing 5.0 mg were applied 300±5 g of female albino rats, dose becomes 16.6±0.5mg. In case oral 5-10mg/kg is reported. For 300±5 g equivalent to 3 mg, respectively. TC. Tamoxifen citrate, AUC: Area Under the curve.

Pharmacodynamics Studies: Tumor latency was found to be 16 days after subcutaneous injection of MCF7 cells in *in-vivo* investigations on naked mice. The tumours were separated into four groups at random once they had grown to a size of around 80-90 mm^3 as seen on day 19.

Three different treatments were given to the animals: a transdermal patch containing 5 mg of TC liposomes, an oral formulation, and a transdermal patch. After 23 days, the tumour volumes in Group III receiving the TC liposome patch were considerably lower (P 0.05) than those in the control group's mice as well as those getting the TC oral formulation [19].

When compared to the control group, mice treated with the TC oral formulation and transdermal patch had significantly lower .tumour volumes by day 25 **Fig. 7**. Though one day

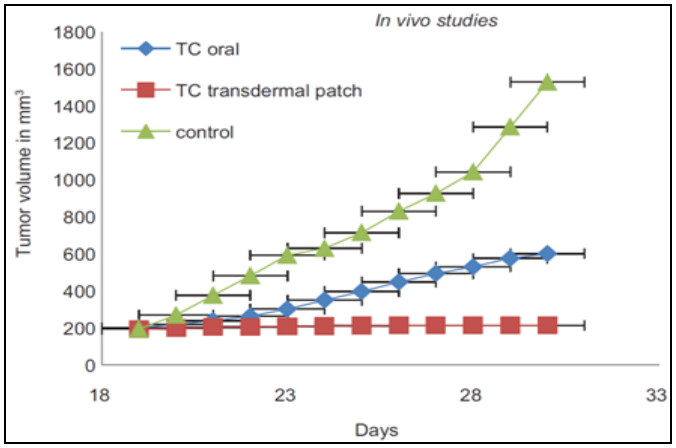

FIG. 7: EFFECT OF TRANSDERMAL PATCH ON TUMOR VOLUME

CONCLUSION: *In-vivo* studies on naked mice revealed that the tumor's latency was 16 days after MCF7 cells were subcutaneously injected. On day 19, when the tumours had reached a size of approximately 80-90 mm3, they were divided into four groups at random. The animals received three different treatments: an oral formulation, a transdermal patch and a transdermal patch containing 5 mg of TC liposomes. After 23 days, Group III mice receiving the TC liposome patch had significantly lower tumour volumes (P 0.05) than mice in the control group or receiving the TC oral formulation. When compared to the control group, mice treated with the TC oral formulation and transdermal patch had significantly lower tumour [20].

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