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DEVELOPMENT AND CHARACTERIZATION OF TAMOXIFEN SPANLASTIC VESICLES FOR TARGETED CANCER THERAPY

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Abstract:

The present study was aimed at the development and characterisation of Tamoxifen-loaded spanlastic vesicles for targeted cancer therapy through transdermal delivery. Tamoxifen is widely used in the treatment of hormone-dependent breast cancer, however, its conventional oral therapy is associated with poor bioavailability, first-pass metabolism, and systemic side effects. To overcome these limitations, spanlastic vesicles were formulated as elastic nanocarriers to enhance drug permeation, entrapment, and controlled release. Tamoxifen spanlastic were prepared using non-ionic surfactants and edge activators by suitable vesicle preparation techniques and further incorporated into a gel base for transdermal application. The prepared formulations were evaluated for particle size, zeta potential, pH, viscosity, spread ability, entrapment efficiency, in vitro drug release, release kinetics, and stability studies. The particle size of the formulations ranged from 238 to 301 nm, indicating nanosized vesicles suitable for enhanced skin permeation. Zeta potential values ranged from −21 to −31 mV, confirming good vesicular stability. The pH values of all gel formulations were found within the acceptable skin pH range (5.5–6.4), and viscosity studies indicated satisfactory rheological behavior. Entrapment efficiency ranged from 76.89% to 90.25%, with formulation F6 showing the highest drug entrapment. In vitro drug release studies demonstrated sustained drug release behavior, and formulation F6 exhibited maximum cumulative drug release of 98.56% within 8 hours. Drug release kinetics revealed that the optimized formulation followed the Higuchi diffusion model with near zero-order release characteristics. Stability studies conducted according to ICH guidelines confirmed that the optimized formulation remained stable for three months under accelerated conditions. The results concluded that Tamoxifen spanlastic transdermal gel is a promising vesicular drug delivery system for targeted cancer therapy due to its enhanced entrapment efficiency, sustained drug release, improved stability, and potential to reduce systemic side effects associated with conventional therapy.

Keywords: *Tamoxifen, Spanlastics, FTIR Studies, Spread ability, In vitro drug release studies*

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INTRODUCTION:

Spanlastic vesicles are novel elastic nanovesicular systems developed to improve the delivery of pharmaceutical agents through biological membranes. They are composed mainly of non-ionic surfactants such as Span and an edge activator, which imparts elasticity and deformability to the vesicular membrane.[1] Due to their unique structural characteristics, spanlastics can easily penetrate through narrow pores and biological barriers, thereby enhancing drug permeation and therapeutic effectiveness. Breast cancer remains one of the most common and life-threatening malignancies affecting women worldwide.[2] Hormone-dependent breast cancer constitutes a major proportion of breast cancer cases, where selective estrogen receptor modulators such as Tamoxifen play a crucial role in treatment and prevention.[3] Tamoxifen is a non-steroidal anti-estrogen drug widely used for the management of estrogen receptor-positive breast cancer. It acts by competitively binding to estrogen receptors, thereby inhibiting the proliferation of cancer cells. Although Tamoxifen has demonstrated remarkable therapeutic efficacy, its clinical application is associated with several limitations including poor aqueous solubility, variable bioavailability, extensive first-pass metabolism, and adverse effects resulting from prolonged systemic exposure.[4] The incorporation of Tamoxifen into spanlastic vesicles may significantly improve its solubility, stability, and therapeutic performance. Spanlastic carriers can facilitate enhanced cellular uptake and localized drug accumulation at tumor sites, thereby reducing systemic toxicity and improving anticancer activity.[5] Furthermore, the nanosized vesicles may provide sustained drug release and improved pharmacokinetic behavior, contributing to better patient compliance and therapeutic outcomes. Therefore, the present study focuses on the development and characterization of Tamoxifen-loaded spanlastic vesicles for targeted cancer therapy.[6] The formulated spanlastics were evaluated for various physicochemical parameters including vesicle size, polydispersity index, zeta potential, entrapment efficiency, drug content, in vitro drug release, and stability studies. The study aims to establish an effective nanocarrier system capable of enhancing the delivery and therapeutic efficacy of Tamoxifen in cancer treatment.

MATERIALS AND METHODS:

MATERIALS

Tamoxifen was procured from Hetero Labs, HYD. Span 80, Tween 80 were obtained from Synpharma Research Lab, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METODOLOGY

FTIR Studies

Drug lipids interactions were studied by FT-IR spectroscopy. One to 2mg of drug, lipids and physical mixtures of samples were weighed and mixed properly to a uniform mixture. A small quantity of the powder was compressed into a thin semi-transparent pellet by applying pressure. The IR spectrum of the pellet from 400-4000cm^{1} was recorded taking air as the reference and compared to study any interference.[7]

FORMULATION DEVELOPMENT

Table-1: Formulation development of Spanlastics

Ingredients	F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:4)	F5 (1:5)	F6 (1:6)	F7 (1:7)	F8 (1:8)
Tamoxifen (mg)	10	10	10	10	10	10	10	10
Span 80 (% W/V)	50	100	150	200	250	300	350	400
Tween 80 (W/V)	10	20	30	40	50	60	70	80
Ethanol	10	10	10	10	10	10	10	10
7.4 Phosphate buffer	q.s	q.s	q. s	q.s	q.s	q.s	q.s	q.s

Preparation of Tamoxifen -Loaded Spanlastics by using *Ethanol injection method*[8]

1. **Organic phase:**
   - Dissolve the weighed amount of Span 80 and Tamoxifen in a measured volume of ethanol (usually 10 mL) at ~60 °C.
2. **Aqueous phase:**
   - Prepare aqueous Tween 80 solution in distilled water or phosphate buffer at the same temperature.
3. **Injection / Vesicle formation:**
   - Under continuous magnetic stirring (600–1000 rpm), inject the organic phase dropwise into the aqueous phase.
   - Vesicles form spontaneously as ethanol diffuses into water.
4. **Size reduction:**
   - Sonicate the suspension (probe sonicator) for 5–10 minutes to obtain nanosized, uniform vesicles.
5. **Maturation:**
   - Allow the dispersion to stand at room temperature for solvent evaporation and vesicle stabilization

Table-2: Formulation development of Spanlastics

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Spanlastics(mg)	10	10	10	10	10	10	10	10
Carbopol 934 (mg)	100	200	300	400	500	600	700	800
Methyl paraben (ml)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Glycerine (ml)	1	1	1	1	1	1	1	1
Water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s

Incorporation into Transdermal Gel[9]

1. **Gel base:**
   - Disperse Carbopol 934 in distilled water with gentle stirring and allow to hydrate for about 1 hour.
2. **Neutralization:**
   - Add triethanolamine dropwise until the gel forms and pH reaches 6.5–7.
3. **Addition of vesicles:**
   - Slowly fold the optimized spanlastic suspension into the Carbopol gel with gentle stirring to avoid vesicle rupture.
4. **Finishing:**
   - Add glycerin and methyl paraben adjust final weight with distilled water, and check pH and homogeneity.

CHARACTERIZATION

Particle Size

The particle size of the Spanlastic were determined using Particle Size Analyzer (PSA) with the dynamic light scattering (DLS) method. The measurements were performed using Horiba Scientific SZ-100, with the sample diluted 10 times in aqueous medium at room temperature.[10]

Zeta-potential:

The sample was diluted with distilled water (1:100 (V/V)) and zeta potential was determined using Malvern zetasizer (Nano ZS, Malvern Instruments, United Kingdom). Measurement was based on the electrophoretic mobility of the particles, which was converted to the zeta potential by inbuilt software based on the Helmholtz-Smoluchowski equation.[11]

SEM analysis

The shape, surface characteristics, and size of the Spanlastics were observed by scanning electron microscopy. Once again, 0.2 g of the Spanlastics in a glass tube was diluted with 10 ml of pH 7.4 phosphate buffer. The Spanlastics were mounted on an aluminium stub using double-sided adhesive carbon tape. Then the vesicles were sputter-coated with gold palladium (Au/Pd) using a vacuum evaporator (Edwards) and examined using a scanning electron microscope (Hitachi 3700N, Germany) equipped with a digital camera, at 10 kV accelerating voltage.[12]

EVALUATION PARAMETERS OF SPANLASTICS[13,14,15]

Physical evaluation:

The formulation was manually examined to check any variations in the color, odor, and texture

Measurement of pH:

PH of each formulation was determined by using pH meter. This was calibrated before with buffer solutions.

Determination of viscosity:

The viscosity measurement of Spanlastics transdermal gel was determined by using a Brookfield viscometer. 30gm of gel preparation was kept in 50ml beaker, set at room temperature and spindle at 5, 10, 20, 50, and 100rpm.

In vitro release studies:

Spanlastics sample (0.5g) was placed on the membrane and diffusion study was carried out at 37°C using 250ml phosphate buffer (pH 7.4) as receptor medium. 5ml of each sample was withdrawn periodically at 15, 30, 60, 120, and 240 minutes. Each sample was replaced with equal volume of fresh receptor medium. Samples were analyzed by UV- spectrophotometer for drug content using phosphate buffer.

Spread ability

Two sets of glass slides of standard dimensions were taken. The topical gel formulation was placed over one of the slides. The other slide was placed on the top of the gel, such that the gel was sandwiched between the two slides in an area occupied by a distance of 7.5 cm along the slides. Hundred g weight of gel was placed on the upper slides so that the gel was between the two slides was pressed uniformly to form a thin layer. The weight was removed and the excess of gel adhering to the slides was scrapped off. The two slides in position were fixed to a stand without slightest disturbance and in such a way that only upper slides to slip off freely by the force of weight tied on it. A 20 g weight was tied to the upper slide carefully. The time taken for the upper slide to travel the distance of 7.5 cm and separated away from the lower slide under the influence of the weight was noted. The experiment was repeated for three times and the mean time was taken for calculation.

Spread ability was calculated by using the following formula: $S = m \times l/t$

where,
S= spread ability, m-weight tied to upper slides (20 g),
l- Length of the glass slide (7.5 cm), t- time taken in sec.

Drug entrapment efficiency

Each formulation (1 g) was taken in a 50 mL volumetric flask and made up to volume with methanol and shaken well to dissolve the active constituents in methanol. The solution was filtered through Whatman filter paper and 0.1 mL of the filtrate was pipetted out and diluted to 10 mL with methanol. The content of active constituents was estimated Spectro photometrically by using standard curve plotted.

In vitro diffusion profile

In vitro release study of the formulated Spanlastics transdermal gel was carried out by using diffusion cell through membrane as a dialysis membrane. Diffusion cell with inner diameter 24mm was used for the study. 1 mL formulation was placed in donor compartment and freshly prepared 7.4 phosphate buffer was placed in receptor compartment. Dialysis membrane was mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that the membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1mL of sample was withdrawn from receiver compartment after 1, 2, 3, 4, 5, 6, 7 & 8 hrs. and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10mL in a volumetric flask with distilled water and analyzed by UV spectrophotometer.

Drug release kinetics

The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Koresmeyer Peppas model (equation 4).

i) Zero order kinetics:

$R = Ko\ t$ -- (1)

R=cumulative percent drug Ko=zero order rate constant

ii) First order kinetics

$\log C = \log Co - K_1 t / 2.303$ -- (2)

where C = cumulative percent drug K_1 = first order rate constant

iii) Higuchi model

$R = K_H\ t^{0.5}$ -- (3)

Where R = cumulative percent drug K_H = higuchi model rate constant

iv) Korsmeyer peppas model:

$M t / M \alpha = K_k t^n$

$\log M t / M \alpha = \log K_k + n \log t$ -- (4)

where K_k = Korsmeyer peppas rate constant 'M t / M α' is the fractional drug, n = diffusional exponent, which characterizes the mechanism of drug.

The obtained regression co-efficient (which neared 0.999) was used to understand the pattern of the drug from the Spanlastics transdermal gel.

Stability studies

The main objective of the stability testing is to provide evidence on how the quality of the drug product varies with time under the influence of temperature and humidity. The stability study for the Spanlastics transdermal gel formulation was done as per ICH guidelines in a stability chamber for a period of 3 months.

RESULTS AND DISCUSSION:

FTIR Studies

FTIR analysis was performed in order to study the compatibility of ingredients used in the preparation of Spanlastics using a Shimadzu FTIR spectrophotometer (Prestige21, Shimadzu Corporation, Kyoto, Japan). Tamoxifen and Excipients their mixture with ratio (1:1) was evaluated using FTIR spectrophotometer using potassium bromide disc technique where 1mg of the sample is mixed with 100 mg of dry powdered KBr, the mixture is pressed into a transparent disc and was inserted in the apparatus for IR scan.

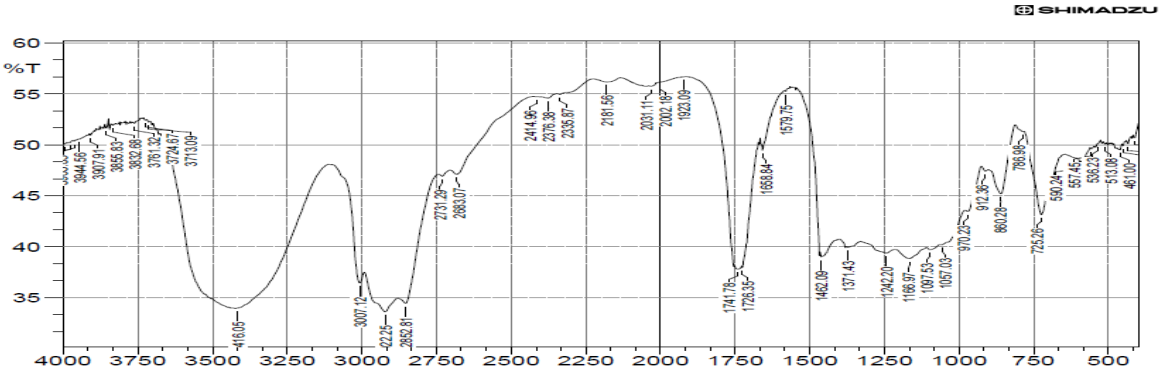

Fig-1: FTIR Studies of Tamoxifen

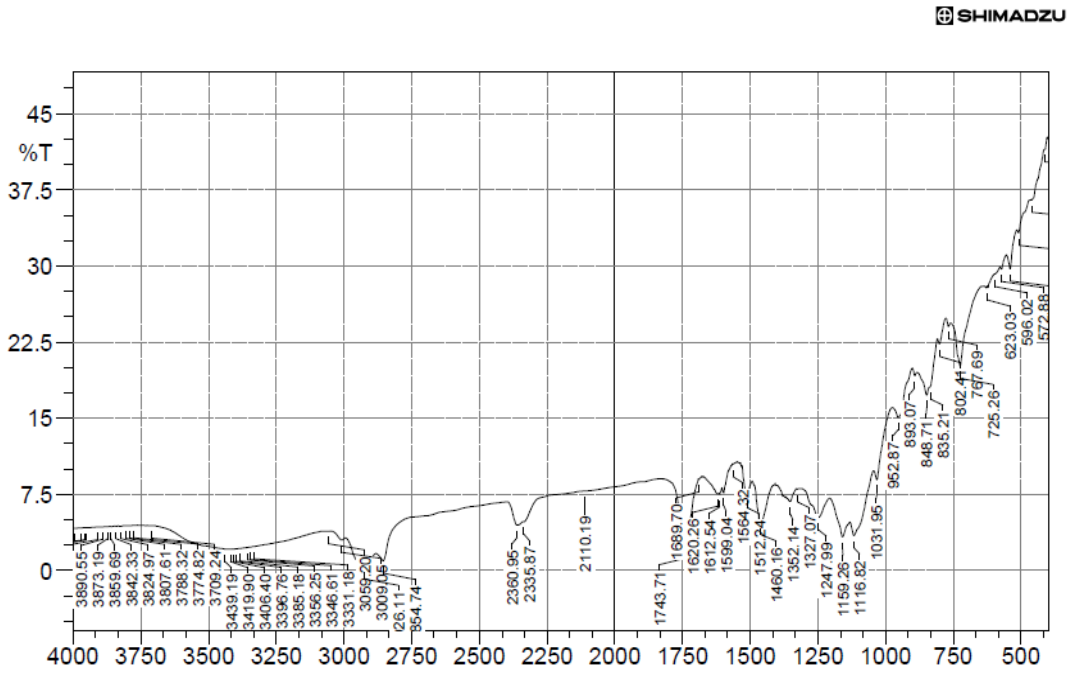

Fig-2: FTIR Studies of optimized formulation

Determination of Vesicle morphology and Size

The morphological characteristics of formulated Spanlastics were carried by using Scanning electron microscopy (SEM). A small drop of Spanlastics was placed between two rivets fixed on a gold-plated copper sample holder. The whole system was slushed under vacuum in liquid nitrogen. The sample was heated to - 85^{0}C for 30 min to sublime the surface moisture. Finally, the sample was coated with gold and allowed the SEM to capture the images at a temperature of - 120^{0}c and voltage of 5kV.

Particle size Analysis

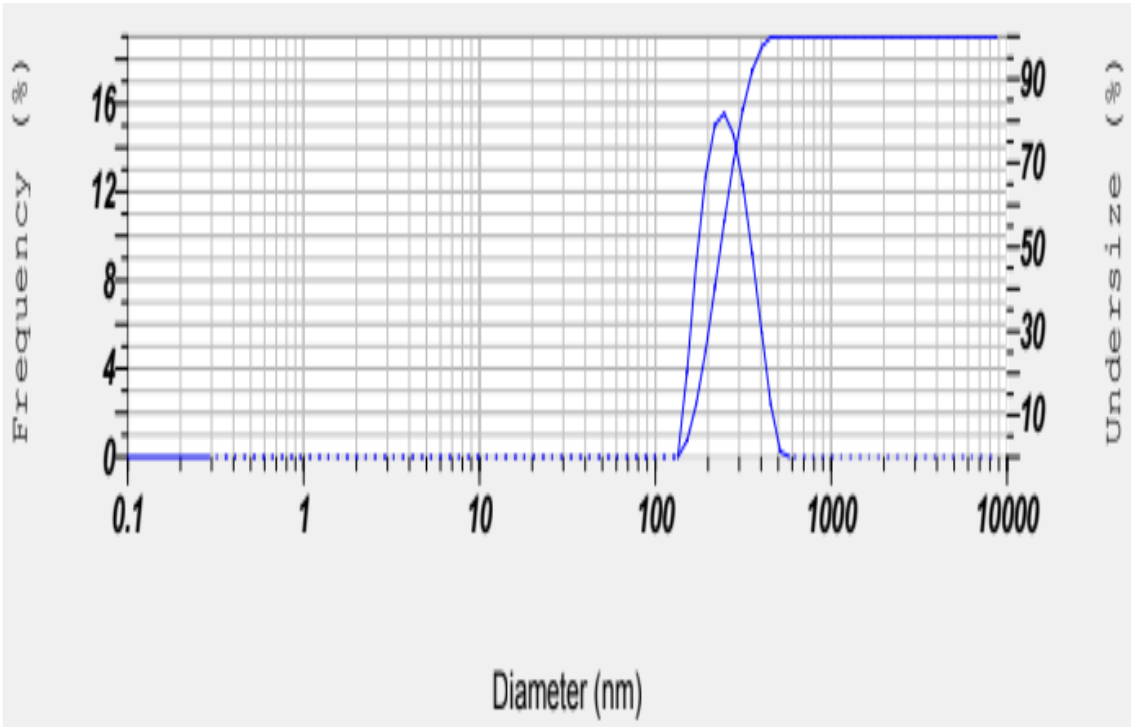

Fig-3: Particle size Analysis of Spanlastic

SEM Analysis

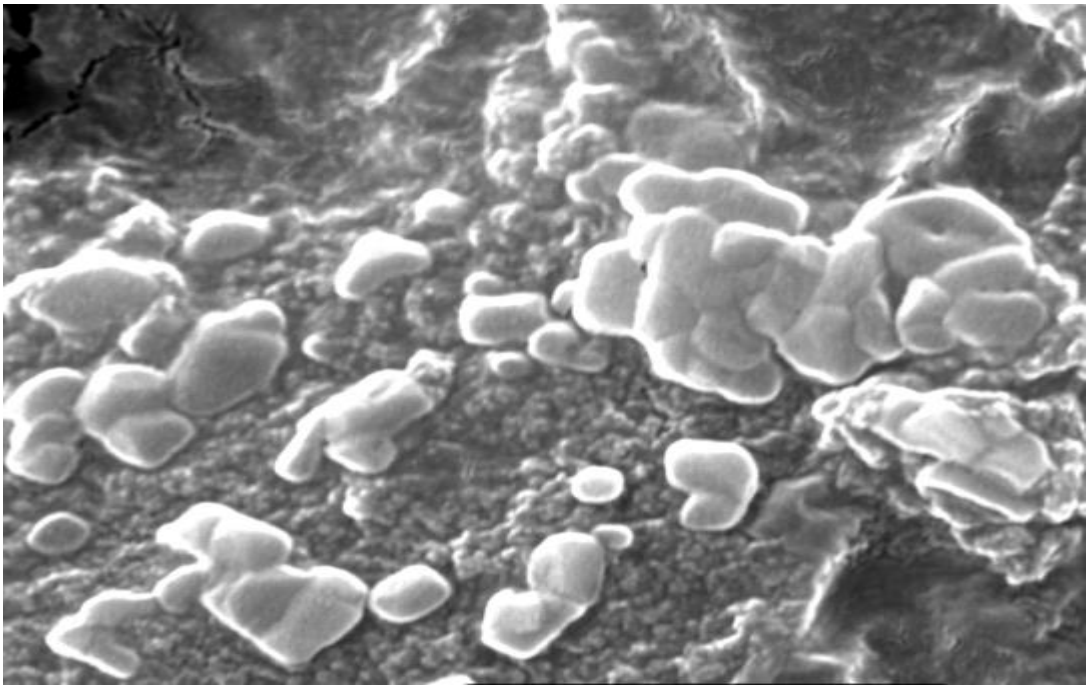

Fig-4: SEM analysis of Spanlastics

Zeta potential

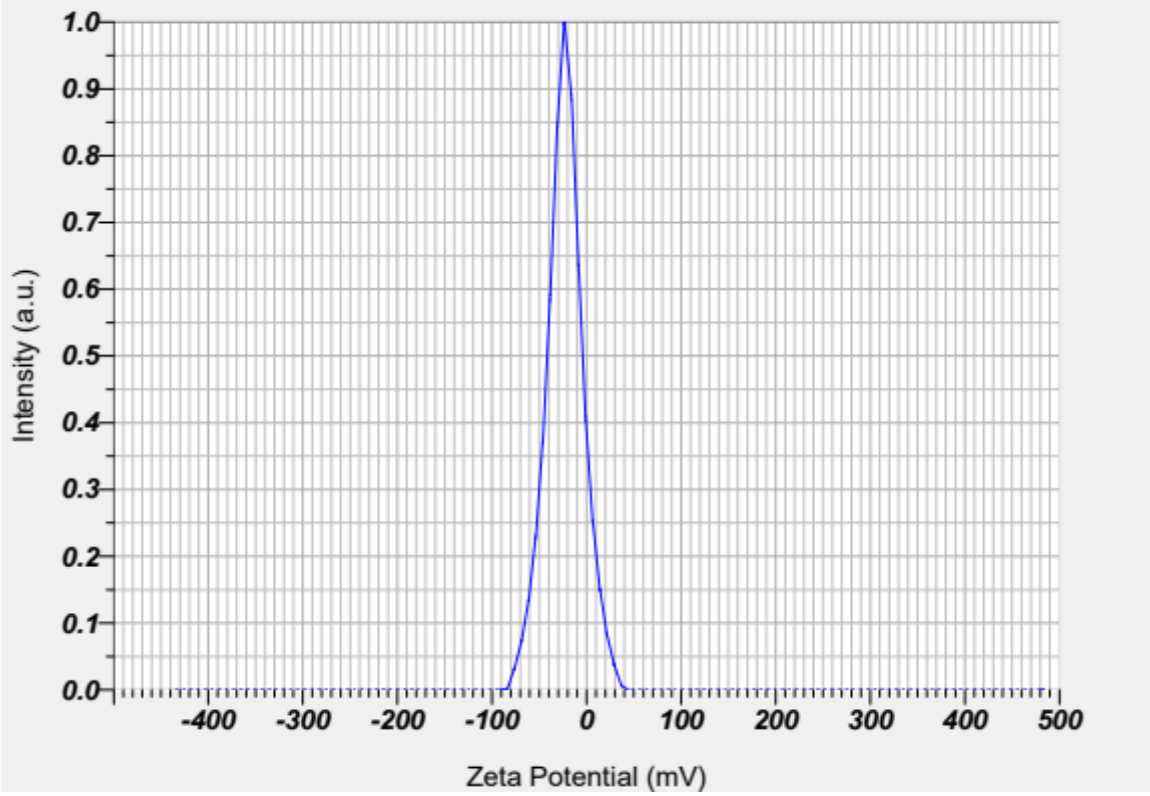

Fig-16: Zeta potential of Spanlastics

Table-3: Evaluation Studies of particle size and Zeta potential Spanlastics

F. No	Particle size (nm)	Zeta potential(mV)
F1	298	-28
F2	253	-26
F3	271	-24
F4	301	-31
F5	255	-25
F6	238	-21
F7	289	-23
F8	301	-29

Discussion

The particle size and zeta potential of the prepared Tamoxifen spanlastic formulations (F1–F8) were evaluated to determine vesicle stability, uniformity, and suitability for transdermal delivery. The obtained particle sizes ranged from 238 nm to 301 nm, indicating that all formulations were within the nanosize range suitable for enhanced skin permeation and targeted drug delivery. Among all formulations, F6 showed the smallest particle size of 238 nm, which may be attributed to the optimum concentration of surfactant and edge activator leading to better vesicle deformability and reduced aggregation. Smaller vesicle size is advantageous because it improves permeation through biological membranes and enhances drug accumulation at the target site.

The zeta potential values of all formulations ranged between −21 mV and −31 mV. Negative zeta potential values indicate good electrostatic stabilization of the vesicles and reduced chances of aggregation. Formulation F4 exhibited the highest zeta potential value (−31 mV), suggesting excellent stability, while F6 showed a zeta potential of −21 mV which was still sufficient to maintain stable vesicular dispersion.

EVALUATION PARAMETERS:

P^H and Viscosity

Table-4: PH and Viscosity values of all formulations

F.code	pH	Viscosity (cps)
F1	5.9	143
F2	6.2	139
F3	5.5	148
F4	5.7	143
F5	6.3	138
F6	6.1	153
F7	5.9	146
F8	6.4	147

Discussion: The pH of all Tamoxifen spanlastic gel formulations ranged from 5.5 to 6.4, which is close to the normal skin pH and indicates compatibility with topical application. The formulations are therefore less likely to produce skin irritation or discomfort upon application.

Among all formulations, F8 showed the highest pH value (6.4), whereas F3 exhibited the lowest pH value (5.5). The pH values remained within the acceptable range for transdermal preparations.

The viscosity values ranged from 138 cps to 153 cps. Adequate viscosity is essential for maintaining gel consistency, ease of application, and prolonged residence time on the skin surface. Formulation F6 exhibited the highest viscosity (153 cps), indicating good gel strength and stability, whereas F5 showed the lowest viscosity (138 cps).

The viscosity differences among formulations may be due to variations in polymer concentration and interaction between spanlastic vesicles and the gel matrix. The obtained viscosity values indicated satisfactory rheological properties suitable for topical administration.

Spread ability

Table-5: Spread ability values of all formulations

F. code	Spread ability (g.cm/sec)
F1	4.91
F2	5.20
F3	4.86
F4	5.23
F5	4.92
F6	4.83
F7	5.81
F8	5.65

Discussion: Spreadability is an important parameter for topical formulations because it determines ease of application and uniform distribution on the skin surface. The spreadability values of the prepared Tamoxifen spanlastic gels ranged from 4.83 to 5.81 g·cm/sec.

Formulation F7 exhibited the highest spreadability value (5.81 g·cm/sec), indicating superior spreading characteristics and ease of application. In contrast, F6 showed the lowest spreadability value (4.83 g·cm/sec), which may be due to its comparatively higher viscosity.

The results indicated that all formulations possessed acceptable spreadability properties, ensuring proper contact of the gel with the skin surface and improved drug permeation.

Entrapment Efficiency:

To determine the entrapment efficiency of a spanlastic transdermal gel, a weighed quantity of the gel equivalent to a known amount of drug is first dispersed in a suitable volume of phosphate buffer or other appropriate aqueous medium and vortexed to ensure complete release of the vesicles from the gel matrix. The dispersion is then subjected to ultracentrifugation at about 15,000–20,000 rpm for 30–60 minutes at 4 °C so that the spanlastic vesicles form a compact pellet while the unentrapped (free) drug remains in the supernatant. The clear supernatant is carefully separated and analyzed for drug content using a validated method such as UV-visible spectrophotometry

Table-6: Drug entrapment efficiency of all formulation

F.no	Drug entrapment efficiency
F1	76.89
F2	80.12
F3	78.81
F4	82.36
F5	84.56
F6	90.25
F7	87.83
F8	89.55

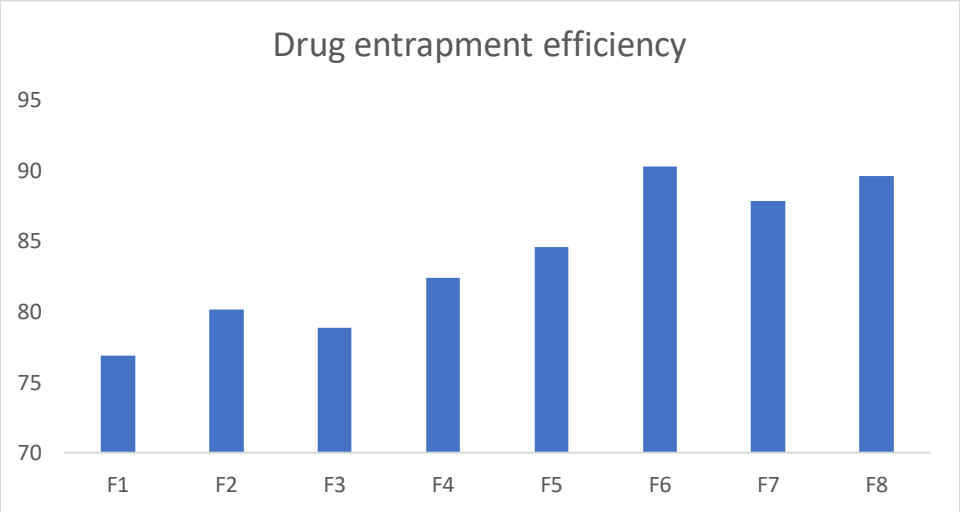

Fig-5: Drug entrapment efficiency of all formulation

Discussion: Entrapment efficiency is an important parameter that reflects the ability of spanlastic vesicles to incorporate and retain the drug within their bilayer structure. The entrapment efficiency of the formulations ranged from 76.89% to 90.25%. Among all formulations, F6 showed the highest entrapment efficiency of 90.25%, indicating maximum incorporation of Tamoxifen within the vesicles. The high entrapment efficiency may be due to the lipophilic nature of Tamoxifen, which has strong affinity toward the lipid bilayer of the spanlastic vesicles. Formulation F1 exhibited the lowest entrapment efficiency (76.89%). The increase in surfactant concentration and optimization of edge activator ratio may have contributed to enhanced vesicle flexibility and improved drug loading in optimized formulations. The results demonstrated that spanlastic vesicles are effective carriers for encapsulating Tamoxifen and can provide sustained drug release with improved therapeutic efficacy.

In vitro drug release studies:

Table-7: Results of Tamoxifen spanlastic Transdermal gel of all formulations

Time(hr.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	18.12	17.53	16.37	15.79	20.25	25.48	24.18	23.15
2	35.69	34.76	32.54	31.15	36.58	38.49	35.46	36.58
3	45.81	46.35	43.19	41.19	43.27	49.58	45.48	42.15
4	52.63	53.29	50.18	52.85	55.42	57.48	52.43	50.16
5	64.70	65.48	63.24	64.75	68.71	69.44	65.47	63.27
6	73.59	75.12	72.18	73.36	75.92	79.81	73.25	70.11
7	83.15	82.35	80.22	81.51	83.26	85.68	82.16	80.12
8	92.35	93.56	94.58	90.56	95.58	98.56	97.48	95.42

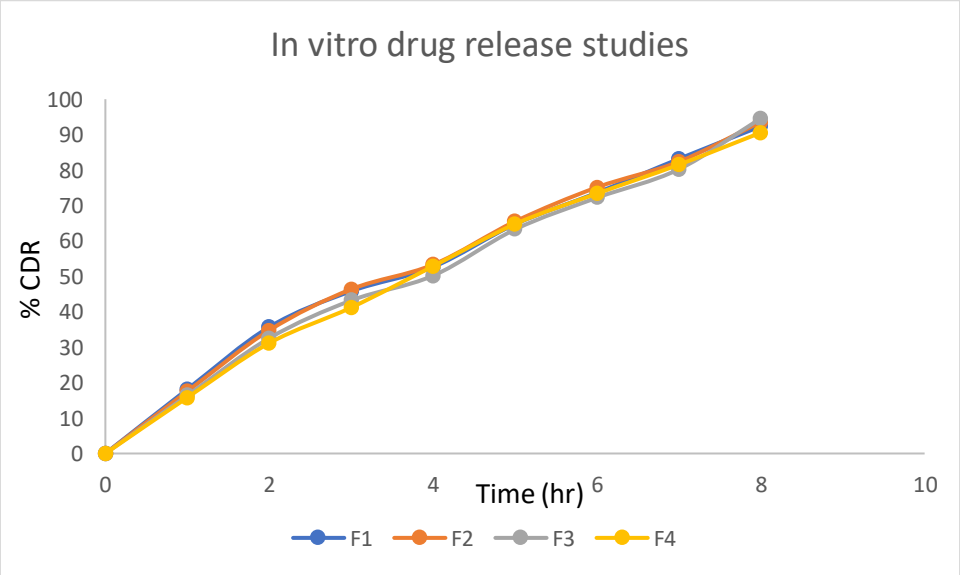

Fig-6: Drug release studies of (F1-F4) formulations

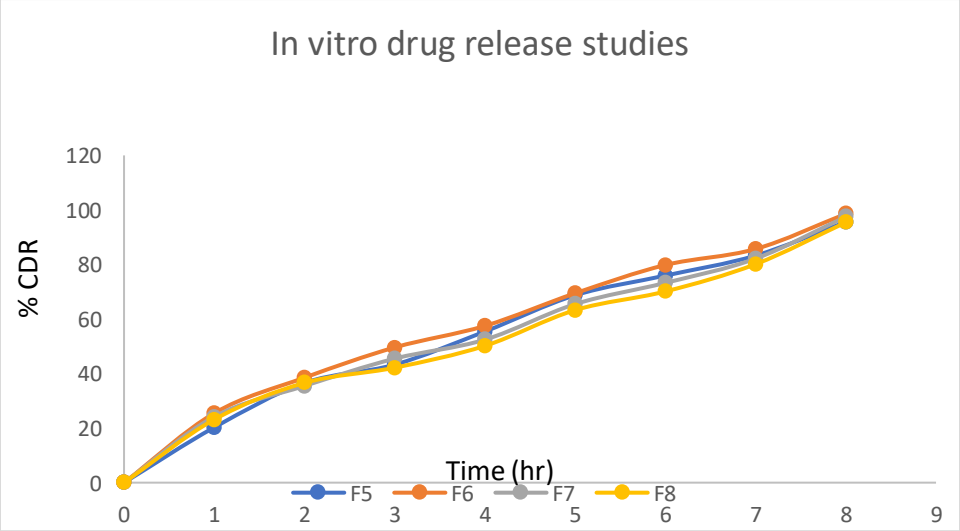

Fig-7: Drug release studies of (F5-F8) formulations

Discussion: The in vitro drug release study was performed to evaluate the release pattern of Tamoxifen from the prepared spanlastic transdermal gels. The cumulative drug release values increased gradually with time for all formulations, indicating controlled and sustained drug release behavior. Among all formulations, F6 exhibited the highest cumulative drug release of 98.56% at the end of 8 hours, suggesting efficient drug diffusion and optimized vesicle composition. The enhanced release from F6 may be attributed to smaller particle size, higher entrapment efficiency, and improved deformability of the spanlastic vesicles. Formulation F4 showed comparatively lower drug release (90.56%), possibly due to larger vesicle size and reduced permeability. The sustained release pattern observed in all formulations indicates that spanlastic vesicles can effectively control drug release and maintain therapeutic drug concentration over an extended period. Therefore, formulation F6 was considered the optimized formulation based on its superior release profile.

Kinetic modelling of drug release

Drug release kinetics help to understand how the drug is released from the formulation and to predict in vivo behavior. The common models used are: Zero-order, First-order, Higuchi, and Korsmeyer–Peppas.

Zero order kinetics

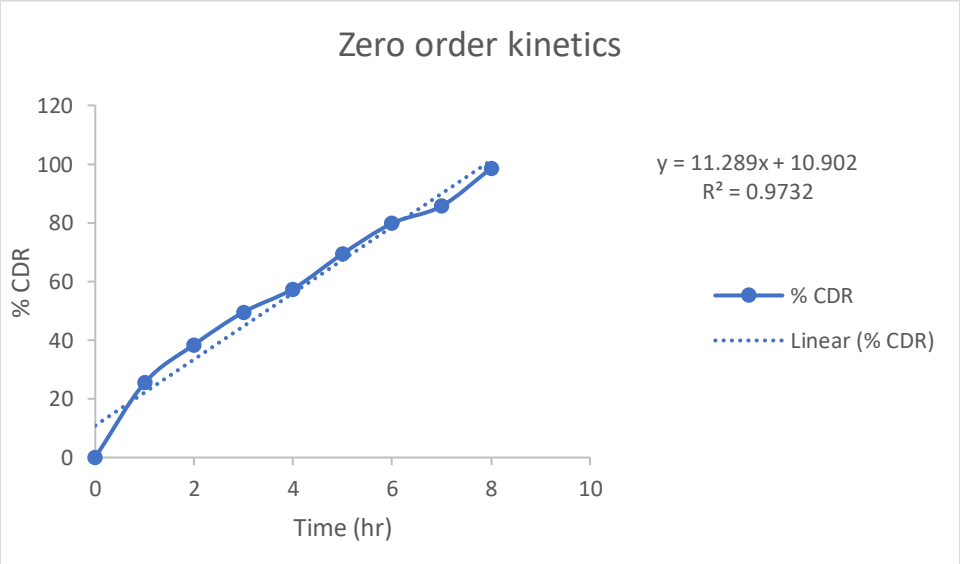

Fig-8: Zero order kinetics of optimized formulation

First order kinetics

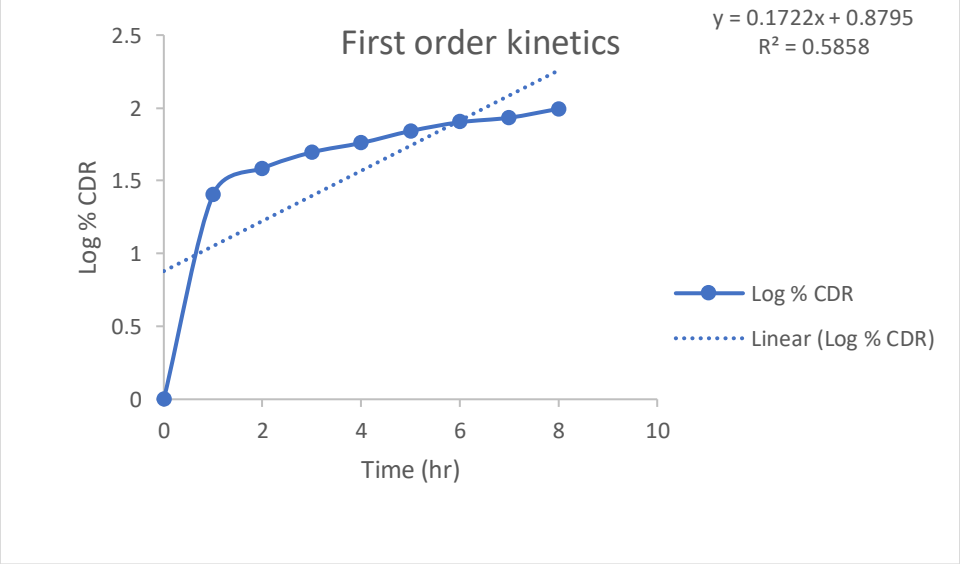

Fig-9: First order kinetics of optimized formulation

Higuchi model

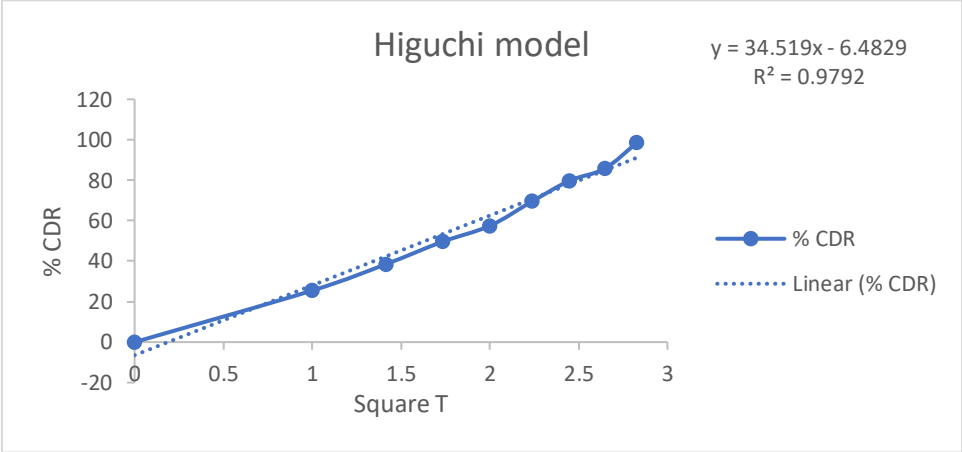

Fig-10: Higuchi model of optimized formulation

Korsmeyer peppas

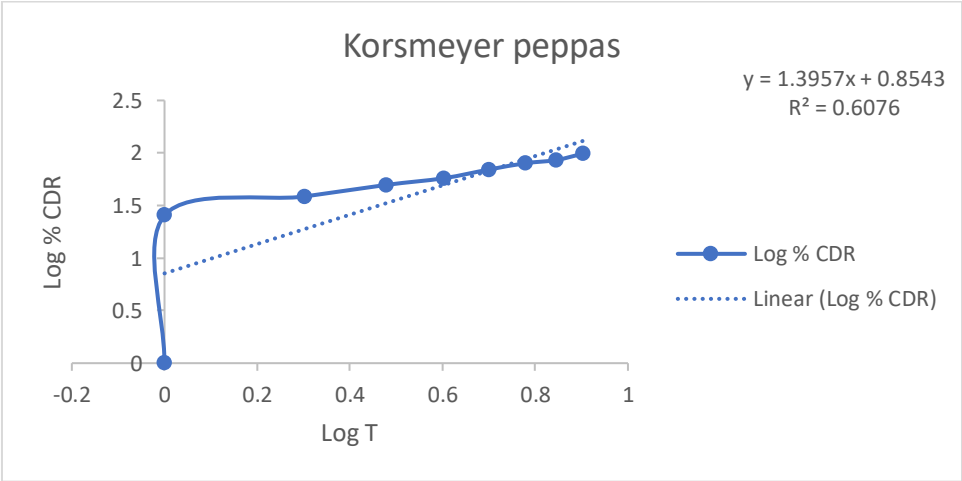

Fig-11: Korsmeyer peppas of optimized formulation

Discussion: Among these models, the Higuchi model showed the highest regression value (0.979), indicating that drug release predominantly followed diffusion-controlled release kinetics. The zero-order model also showed a high correlation (0.973), suggesting near constant drug release over time. The lower regression values obtained for first-order and Korsmeyer–Peppas models indicate that the release mechanism was mainly diffusion dependent rather than concentration dependent. Thus, the optimized formulation F6 demonstrated sustained and controlled release characteristics suitable for transdermal drug delivery applications.

Stability studies

Optimized formulations F6 was selected for accelerated stability studies as per ICH guidelines.

Table-8: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Formulation Code	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	98.56	97.35	96.84	95.78	Not less than 85 %
F-6	98.56	97.20	96.52	95.81	Not less than 85 %
F-6	98.56	97.26	96.43	95.56	Not less than 85 %

Discussion: Accelerated stability studies of the optimized formulation F6 were carried out at 40 ± 2°C and 75 ± 5% RH for a period of 3 months according to ICH guidelines. The formulation retained drug content above 95% throughout the study period, which was within the acceptable specification limit of not less than 85%. No significant changes in physical appearance, drug content, or consistency were observed during storage. The slight decrease in drug content over the storage period may be due to minimal degradation of the drug under accelerated conditions. However, the reduction was insignificant, confirming good stability of the formulation. The stability study results demonstrated that the optimized Tamoxifen spanlastic transdermal gel formulation possessed satisfactory physical and chemical stability and can be stored safely for prolonged periods without significant loss of therapeutic activity.

CONCLUSION:

The study successfully demonstrated the formulation and evaluation of Tamoxifen-loaded spanlastic transdermal gel as a novel vesicular drug delivery system for targeted cancer therapy. The prepared spanlastic vesicles showed nanosized particle distribution, good stability, high drug entrapment efficiency, and sustained drug release characteristics. Among all formulations, formulation F6 was identified as the optimized formulation based on its smallest particle size, highest entrapment efficiency, satisfactory viscosity, acceptable spread ability, and maximum in vitro drug release profile. The results suggest that spanlastic vesicles are effective carriers for enhancing the transdermal delivery of Tamoxifen by improving drug permeation, prolonging drug release, and potentially reducing systemic side effects associated with conventional oral therapy. Therefore, Tamoxifen spanlastic transdermal gel can be considered a promising and effective approach for targeted cancer therapy with improved therapeutic efficacy and patient compliance.

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