Formulation And Evaluation Of Zaltoprofen Nanovesicle Loaded Transdermal Patch

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ABSTRACT: Rheumatoid arthritis (RA) poses a significant global health burden, affecting millions worldwide. In India alone, an estimated 36 million individuals suffer from this debilitating condition. In this study, nine batches of niosomes (Z1-Z9) were formulated with varying compositions of cholesterol and surfactants, aiming to develop an effective transdermal delivery system for RA treatment. Evaluation parameters including polydispersity index (PDI), vesicle size, and entrapment efficiency were meticulously examined. Results indicated that formulations Z6 and Z8 exhibited superior performance compared to other batches.The optimized formulations (Z6 and Z8) demonstrated high entrapment efficiencies of 84.4±1.53% and 87.6±1.46%, with particle sizes of 356±54.71 nm and 253±37.01 nm, respectively, and acceptable PDI values. Utilizing PEG 400 and HPMC k-100M, niosomal transdermal patches were successfully developed from Z6&Z8 batch Characterization of (Z6 and Z8) patches revealed uniform thickness (0.332±0.001 mm and 0.328±0.001 mm), consistent weight (351.47±0.717 mg and 345.46±0.901 mg), and minimal moisture uptake (5.26±0.16 and 4.16±0.12), The Z8 batch patch emerged as an ideal candidate based on comprehensive evaluation parameters. affirming their suitability for RA treatment. Furthermore, the selected optimized transdermal patches exhibited drug release kinetics following zero order, Higuchi's kinetic, and Korsemeyer-Peppas models.
Keywords: Niosomal Transdermal patch, Zaltoprofen, RA, Non-ionic surfactant.

I.   INTRODUCTION:

Arthritis is a broad term that refers to inflammation of the joints. It is one of the most common long-term illnesses and a major contributor to disability. The word "arthritis" is used broadly to describe joint inflammation. The main causes of disability and significant health care costs are rheumatic diseases like arthritis.However, it may surprise you to learn that it encompasses more than 100 different conditions that affect the joints themselves and the bones and tissues around them[1].

Rheumatoid arthritis(RA), is an autoimmune and inflammatory disease, which means that your immune system attacks healthy cells in your body by mistake, causing inflammation (painful swelling) in the affected parts of the body[2]RA mainly attacks the joints, usually many joints at once .Its Impacts 25 million people around the globe, affecting nearly three times as many women as men.Although the symptoms of the various varieties of arthritis are generally similar, such as stiffness, edoema, and joint discomfort restricted range of motion, the illnesses are not the same and are treated differently.

According to the 2011 census, the population of India stands at 1,210,569,573. The reported prevalence of RA in India has varied from 0.3% to 0.75%. Assuming an average prevalence of 0.5% with the adult population of 60%, the projected burden of RA in India is 36 million patients[3]
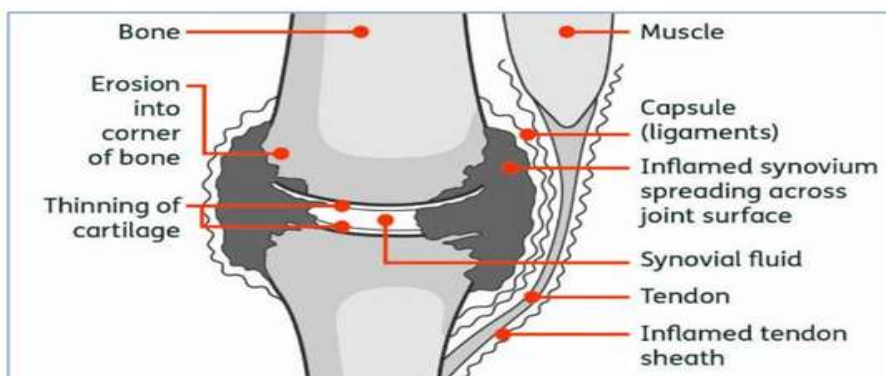
Figure:-1.1A joint badly affected by Rheumatoid Arthritis

1.2 Stages of Rheumatoid Arthritis:
Stage 1: - The body mistakenly attacks its own joint tissue.
Stage 2: - The body makes the antibodies and the joints start swelling up.
Stage 3:-The joints start becoming bent and deformed. The fingers become crooked. These misshapen joints can press on the nerves and can cause nerve pain as a well.
Stage 4 :- If not treated the disease will progress to the last stage in which there's no joint remaining at all & the joint is essential fused.

II.   NIOSOMES:
Pharmaceutical compounds can become more stable and soluble when they are delivered via niosomes, which are nonionic surfactant vesicles and are thought to be innovative drug delivery vehicles. They were founded to offer medicinal compounds targeted and regulated release[4]
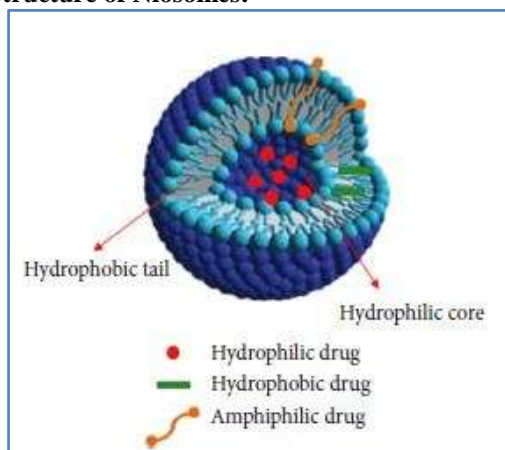
Structure of Niosomes:

Figure:- 2.1 niosomes

2.1. Advantages of Niosomes:
1**.** Niosomes have low toxicity, are non-immunogenic, biodegradable, biocompatible, and patient compliance[5]
2. Niosomes can increase the way that drugs penetrate the skin[6]
3.Niosomes can increase the medication's stability when it's encapsulated.
4.There is control over the vesicle formulation's properties, such as size, lamellarity, surface charge, concentration, and drug sting[7]

2.2. Limitation   of Niosomes Drug-Delivery System:-
1. A short shelf life for the niosomes aqueous solution may be necessary because of medicine combination, aggregation, permeability, and hydrolysis of the encapsulated drugs[8]

2.3. Preparation Methods of Niosomes:-
1. Transmembrane pH Gradient Method
2. Reversed-Phase Evaporation
3. Ether Injection
4. Bubbling of Nitrogen
5. Sonication
6. The Enzymatic Method
7. The Single-Pass Method
8. Microfluidization
9. Formation of niosomes from proniosomes

III.   TRANSDERMAL PATCH:-
Transdermal drug delivery systems, or "patches," are ways of dosing that are intended to distribute a medicinally successful dose of medication through the skin of a patient. Because transdermal delivery may avoid first pass metabolism and improve patient compliance, respectively, it presents a considerable benefit over oral and injectable approaches. Transdermal

delivery not only makes it possible to continuously distribute drugs with short biological half-lives, but it also keeps pulsed entry into systemic circulation from happening, which commonly leads to unwanted side effects[9]
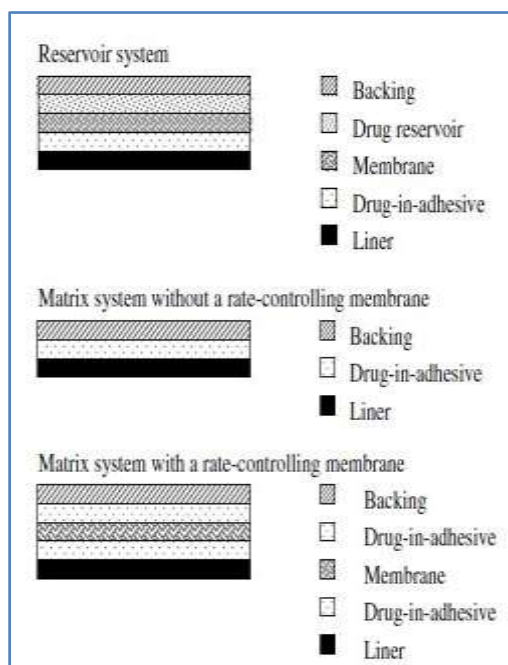

Figure:-3.1 TDDS Types

3.1 Anatomy of a TDDS:
1) Release liner
2) Backing
3) Overlay

4) Membrane
5) Excipients and enhancers:
6) Pressure sensitive adhesive

3.2 Advantages of TDDS:-[10-11]
1. Transdermal medicine provides a continuous, long-lasting infusion of a medicament. It is also possible to prevent side effects or treatment failures that are commonly linked to sporadic dosing.
2. It is feasible to self-administer And continuous, sustained release of drug
3. The transdermal patch can be removed at any moment to stop the medication input.
4. Dose delivery unaffected by vomiting or diarrhea

IV. METHOD & MATERIALS:-
Preparation for Zaltoprofen loaded Niosome:
Step 1: Dissolve Ingredients like drug, surfactant, and Cholesterol in selected organic solvent
Step 2: At room temperature, organic solvent was extracted using a vacuum rotary evaporator.
Step 3: Dry thin layer formation on the flask wall's surface
Step 4: The vesicles were formed by rehydrating the dry surfactant film with the help of rotary evaporator without vacuum with 15 ml phosphate buffer saline ph 6.8 which contained the drug and was kept at 60°C to eliminate any traces of organic solvent
Step 5: The finished niosomal suspension was kept in the refrigerator for further investigation.

V. TRAIL BATCHES OF NIOSOMES:

SR.NO.	RECORD NAME	SURFACTANT	MOLAR RATIO (SURFACTANT: CHOLESTEROL)	AMOUNT OF DRUG
1	ZL-1	Span 60	1:1	100
2	ZL-2	Tween 80	1:1	100
3	ZL-3	Tween 60	1:1	100

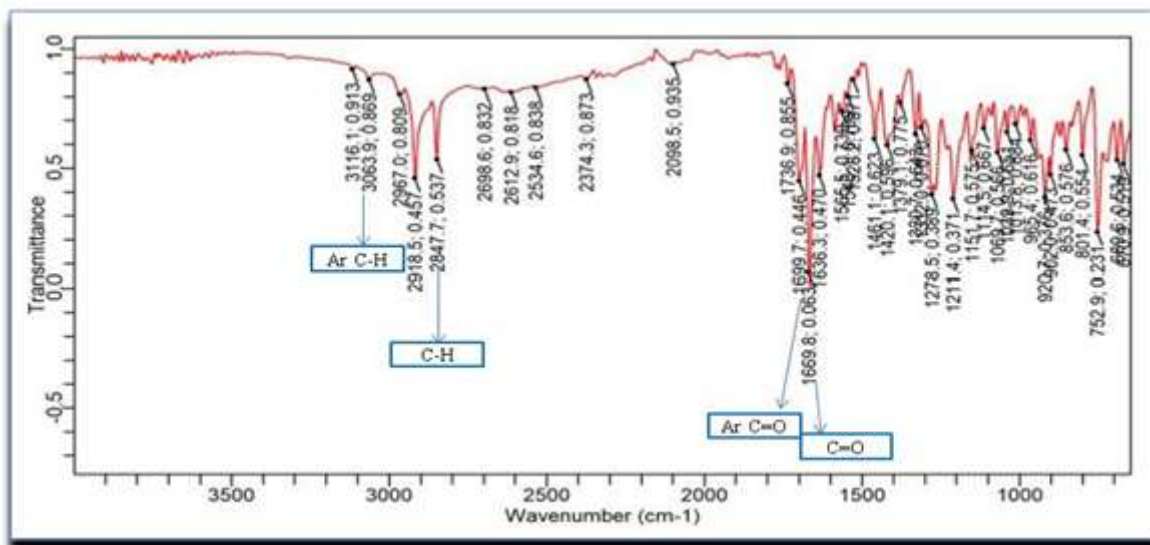## 5.2 DSC analysis of pure drug Zaltoprofen:-

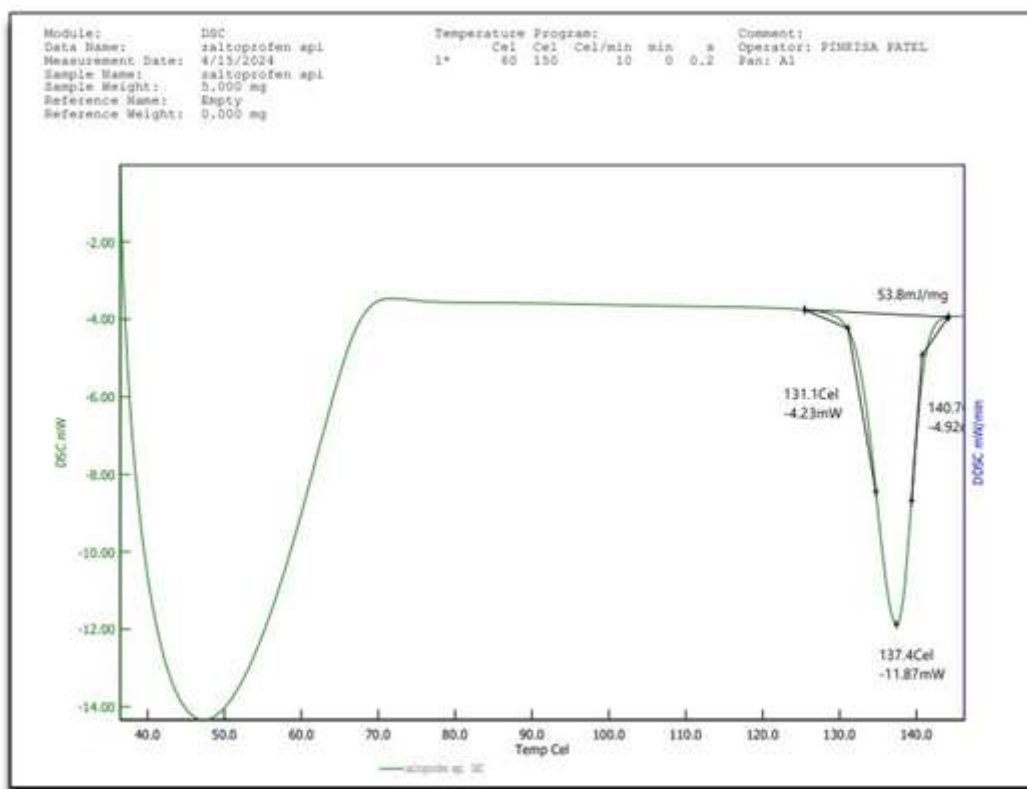Figure:- 5.1 Identification of drug by FT-IR study

Figure:5.2 DSC Thermal analysis results of Zaltoprofen

5.3 Preliminary study for screening of surfactant:-
In vesicle formation with a ratio of (1:1),(1:1.5),(1:2)surfactant: cholesterol with a total lipid concentration of 500 µM and a fixed amount of Zaltoprofen (100 mg), process-related factors, such as flask rotation speed and hydration time

evaporation, and the organic solvent are investigated using the approach of trial and error. With 9 different batches(Z1 and Z9) to different ratio with 3 different surfactant.The procedure was improved in the trial batches of formulation by changing various process-related factors at various levels to see how they affected the development of niosomal thin film.

5.4 Evaluation of Optimized batch Niosomes:
Drug loaded niosomes preparations (15ml) are spun at 10000 rpm for 15 minutes at 40C in a chilled centrifuge to separate niosomes from unentrapped medicines. The supernatant separated using a micropipette without affecting these diment layer. A UV spectrophotometer was used to measure the supernatant layer(free drug) at 234 nm after had been diluted in PBS pH 6.8. The ratio of drug entrapment niosomes is calculated using the below formula

Entrapment Efficiency = (Total Drug Amount - Unentrapped Drug/Total Amount Drug) x 100

Determination of Particle Size Analysis (PSA):-
Using a Malvern zeta-sizer, the niosomal solution was diluted and then put into a cuvette with a suitable blank to determine the niosomes' average vesicle size. at Maliba Sophisticated instrument center for Research And testing ,Bardoli was used to determine the size division of the niosomes. Water was used to dilute the sample, and 25°C was the constant temperature.

Zeta potential:-
Using the Malvern Zeta-sizer Nano ZS, the zeta potential index of the Z6 and Z8 niosomal formulation was evaluated.
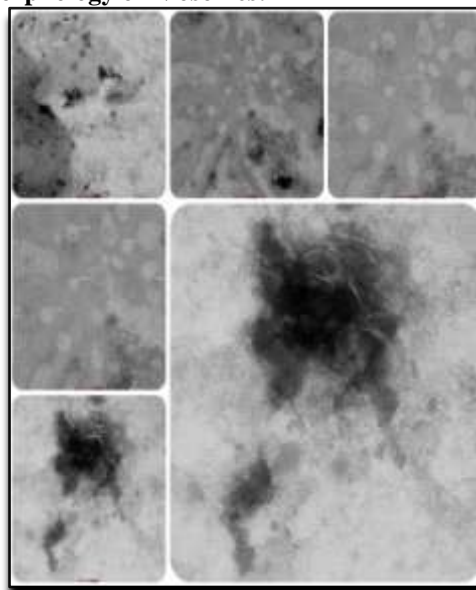
Morphology of Niosomes: -

Figure:-5.3 TEM of Niosomes

The morphological characteristics of a dispersed system can be examined using TEM analysis. As seen in the TEM images of the representative spherical shape in figure, the particle size was similar to the results of particle size analysis.

% Drug Release from Niosomes : -
Studies on the in vitro release of Niosome suspensions were conducted using phosphate buffer (pH 6.8). provide the release statistics for Zaltoprofen-loaded niosomes, correspondingly for Z6 & Z8.

Sr. no.	Time (hr)	% CDR (Z6)	% CDR (Z8)
1.	0	0	0
2.	1	15.90	11.56
3.	2	26.75	24.72
4.	4	32.58	30.45
5.	6	40.50	42.33
6.	8	53.02	47.91

7.	10	62.55	58.68
8.	12	76.65	62.63
9.	14	81.85	73.15
10.	16	87.56	84.45
11.	18	91.44	86.21
12.	20	93.56	92.29
13.	24	**98.80**	**99.60**

Initial drug concentration = Z6 15.90 % & Z8 11.56 %

5.5 Characterization of Zaltoprofen loaded Niosomes:

Sr.no	1	2
Formulation code	**Z6**	**Z8**
Entrapment Efficiencies%	84.4	87.6
particle size (nm)	356	253
Zeta potential	-20.6	-32.7
In-vitro % Drug Release 24hr	98.60	99.60

VI. DISCUSSION:-

From the above result,Tween 80(Z6) Span 60(Z8), was selected for further selected for preparation of niosomes as it produced a uniform vesicle shape.so it was selected for further studies. Tween 80 & Span 60 shows good entrapment efficiency,vesicle size. The batch Z6 & Z8 showed a better % entrapment efficiency of 84.4 & 87.6 %, 356.5 & 253 nm vesicle size, In vitro 98.60 &99.60

5.6 Preparation of Zaltoprofen loaded niosomal patches

Solvent casting evaporation was used to create Zaltoprofen-loaded niosomal patches (ZLT–NP), following the protocol outlined in. As a plasticizer, a 1:1 aqueous solution of PEG400 and HPMC K-100 M was developed. After being reconstituted in 2 milliliters of distilled water, the selected niosomal formulation was added to the combination of aqueous polymeric solution. After that, the mixture was thoroughly stirred with a magnetic stirrer to achieve consistency, and air bubbles were removed by sonicating it for 15 to 20 minutes. After that, the mixture was put into glass moulds and let to dry for 24 hours at room temperature. displays the percentage of PEG 400, HPMC K-100 M, and the niosomal formulation that was employed. demonstrates the ZLT-NP manufacturing process. Each created patch was examined visually for colour, homogeneity, flexibility, brittleness, and smoothness after being removed from the moulds.

5.7 Evaluation of Zaltoprofen transdermal patches:-

The prepared transdermal patches were assessed for in vitro research, moisture absorption, folding durability, homogeneity of medication content, and thickness uniformity.

Thickness
Using a micrometer, the thickness of the transdermal patches was measured three times, and the average values were computed[12]

Weight variation
Three patches from each batch were weighed separately to assess the weight fluctuation, and the average weight was computed[13].

Folding Endurance
For the prepared patches, folding endurance was measured by hand. The number of times the patch is folded in the same location is how it is expressed, either until visible cracks appear or the patch breaks. This is crucial to verify the sample's resistance to folding. Additionally, this indicates brittleness[14]

Moisture Uptake
A desiccator with room temperature was used to store weighed films for a full day. After that, they were removed and placed in a desiccator with a saturated potassium chloride solution at 65% relative humidity until a consistent weight was reached. The percentage of moisture uptake was computed as follows [15].
{(Final weight – Initial weight) / Initial weight}* 100 = % moisture uptakes

Sr. no.	Time (hr)	% CDR (Z6)	% CDR (Z8)
1.	0	0	0
2.	1	16.9	10.29
3.	2	25.99	25.64
4.	4	33.71	30.94
5.	6	41.55	41.54
6.	8	54.08	48.96
8.	10	61.27	59.68
9.	12	75.14	63.38
10.	14	82.67	74.11
11.	16	88.75	83.39
12.	18	92.23	85.21
13.	20	94.54	93.39
14.	24	**98.78**	**99.54**

Drug Content Uniformity
Using a UV/Visible spectrophotometer and the pharmaceutical standard, the content uniformity test was performed to ascertain the drug's uniform distribution in the patches. The transdermal patch measuring 3.14 cm2 was dissolved in 100 cc of phosphate buffer with a pH of 6.8. After being shaken for two hours in a

mechanical shaker to create a homogenous solution, this was filtered. An identically treated drug-free patch was used as a blank. Using a UV/visible spectrophotometer and appropriate dilution, the absorbance at 234.5 nm and 338 nm was measured to estimate the drug concentration in each formulation [16]

In Vitro Permeation Studies

The Franz cell setup was employed to investigate Zaltoprofen penetration from the niosomal patches. There were 1.767 cm2 of effective diffusion surface area and 12 mL of receiving chamber capacity. There was no soaking or hydration while using a Strat-membrane. The membrane held in place between the donor and receptor compartments of the vertical diffusion cells. Twelve millilitres of PBS solution with twenty percent isopropanol were added to the receptor compartment. The temperature of the receptor compartment was adjusted to 32 C, which is comparable to skin temperature[17-18].

5.7 Characterization of Niosomes loaded Transdermal patch:-

Sr.no	1	2
Formulation code	Z6	Z8
Thickness (mm)	0332±0.001	0.328±0.001
Weight variation (mg)	351.47±0.717	345.46±0.901
Folding Endurance	246	243
Moisture uptake (%)	5.26±0.16	84.5±0.26
Drug Content(%)	4.16±0.12	87.33±0.20

In-Vitro % Drug Release Study:-
Release kinetic studies:

The in-vitro drug release data of all formulations were analysed for determining kinetics of drug release. The obtained data follows Zero order, Higuchi's Kinetic, korsemeyerpeppas. After examining these parameters, it was concluded that niosomal Transdermal patch .The highest correlation coefficient ($r2$) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the examination of correlation coefficient ($r2$) indicated that the drug release.

Table :- kinetics release

Batch		Z6	Z8
Zero order	R^2	0.947	0.971
First order	R^2	0.833	0.891
Higuchi's Plots	R^2	0.981	0.984
Korsmeyer Peppas plots	R^2	0.996	0.977

Stability studies: -

Based on the results of in-vitro drug release two best formulations Z6 and Z8 were selected for one month stability studies at Refrigerator .The stability studies were conducted according to the method .The selected formulations were evaluated for Thickness, Weight variation, folding Endurance, moisture uptake, drug content and in-vitro drug release. The results showed that there was no significant change in Thickness, Weight variation, folding Endurance, moisture uptake, drug content and drug release profile throughout the study period. One months of stability studies revealed that; The Z8 batch patch emerged as an ideal candidate based on comprehensive evaluation parameters

VII. CONCLUSION:-

The development of Zaltoprofen-loaded niosomal transdermal patches represents a groundbreaking advancement in sustained drug delivery for rheumatoid arthritis (RA) management. Through meticulous optimization and rigorous evaluation, a highly efficient and stable drug delivery system has been achieved. The integration of optimized niosomes into transdermal patches yielded formulations with excellent drug release profiles and robust stability, as validated by ICH guidelines. This novel approach offers promising prospects for improved RA treatment modalities, emphasizing its potential for clinical translation and future research in transdermal drug delivery and RA management.

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