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"Development and Evalaution Of Solid Nanoparticles Containing As ACITRITIN As Gel For Treatment Of Psoriasis".

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ABSTRACT

The goal of the research project was to create an NLCs Acitretin gel and carry out an in-vitro evaluation of several formulations. There was no interaction between the medication and the polymer or with thecorresponding surfactant, according to FTIR and DSC measurements. An updated NLC generation made of a lipid matrix with a unique nanostructure that has been created. These nanostructures enhance drug loading and securely bind the drug while it is being stored. The goal of this work was to create an Acitretin-loaded NLCs gel utilizing the Hot Homogenization technique that was efficient for topical Acitretin delivery. To stabilize NLCs dispersion, two types of surfactants, Tween 80 and Sodium Lauryl Sulphate (SLS), were combined with stearic acid as a solid lipid and oleic acid as a liquid lipid. NLC physiochemicalcharacteristics A lipid matrix-based new generation of NLCs has been created with a unique nanostructure. These nanostructures help with medication loading and effectively incorporate the medicine while it's being stored. The goal of this work was to create an Acitretin-loaded NLCs gel that could deliver Acitretin topically using the Hot Homogenization technique. NLCs dispersion was stabilised using a combination of two types of surfactants, Tween 80 and Sodium Lauryl Sulphate (SLS), as well as stearic acid as a solid lipid and oleic acid as a liquid lipid. NLC physiochemical properties.

KEYWORDS: NANO LIPID CARRIERS, HOMOGENIZATION,FTIR,SODIUM LAURYL SUPLAPHATE,TWEEN 80

I. INTRODUCTION

1.1PSORIASIS

- The research and development efforts that shape today's drug delivery systems are mostly focused on developing novel medicine formulations and novel drug administration techniques. Determining the mechanisms by which drugs are delivered to their intended targets within the body has recently seen an increase in development. As a result, more patients are following their treatment regimens. The main objective of the current study, which attempts to create an improvised drug delivery system for Act, is to increase the local bioavailability of the anti-psoriatic pharmaceutical acitretin (Act).
- Acitretin, also known as 13 cis-trans retinoic acid, is a psoriasis therapy druglicensedbytheUSFoodandDrugAdministration(June,1997)(WiegandandChou, 1998).
- The control of epithelial cell proliferation and differentiation, sebum production,and collagen synthesis are just a few of its favorable physiological effects thathave garnered a lot of attention. Currently, only oral capsules are manufacturedand sold.
- The two main objectives of research into novel drug delivery systems are improved therapeutic benefit from already existing medications and the safe and efficient distribution of new therapeutics to meet the body's spatial and temporal requirements. We refer to a colloidal drug delivery system (CDDS) as particle or vesicular dosing with a size range of 1 nm to 0.5 m. It facilitates medicine targeting, which increases bioavailability and lowers drug loss and breakdown. The percentage of drug accumulation at the therapeutic site increases, systemic side effects are greatly decreased, and harmful toxic effects are completely eliminated with this highly selective technique. Acitretin, a medicine that effectively treats both psoriasis and acne, has lately showed promise when used topically rather than orally (orally, in the digestive tract).Through this method, potentially fatal systemic adverseeffectsmay be mitigated.
- The safe and effective distribution of new treatments to satisfy the body's spatial and temporal requirements is one of the two main goals of research into novel drug delivery systems. The other is to increase the therapeutic benefit from currently available drugs. With a size range of 1 nm to 0.5 m,

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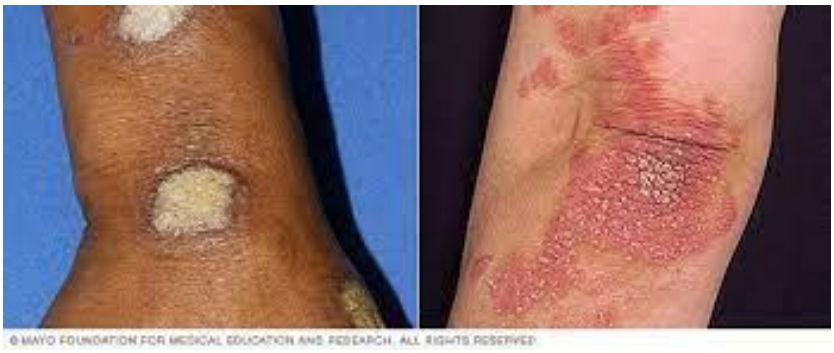
we refer to a colloidal drug delivery system (CDDS) as particle or vesicular dosing. It makes medication targeting easier, which raises bioavailability and reduces loss and breakdown of the drug. With this highly selective approach, the percentage of drug accumulation at the therapeutic site increases, systemic side effects are significantly reduced, and detrimental toxic effects are entirely eliminated. Recently, topical use of the medication acitretin, which effectively treats both psoriasis and acne, has shown promise in comparison to oral (orally, via the digestive system) use.

- Common psoriasis triggers include infections (such as streptococcus throat or skin infections), skin damage, stress, smoking, heavy drinking, a lack of vitamin D, and some medicines. Acne frequently appears on the shoulders, back, neck, chest, and upper arms. Acne arises when oil, dead skin cells, or bacteria clog skin pores. Acne outbreaks may be exacerbated by several medications, including testosterone and lithium, greasy cosmetics, hormonal changes, stress, and menstruation. Going the topical route has enormous advantages, including:
- Stayawayfromthebody'sfirst metabolicprocess
- the medicine can be applied and discontinued whenever necessary, patient compliance is increased.
- • Distributed without parenteral administration's risks.
- • Drug administration to a specific site while preventing systemic absorption



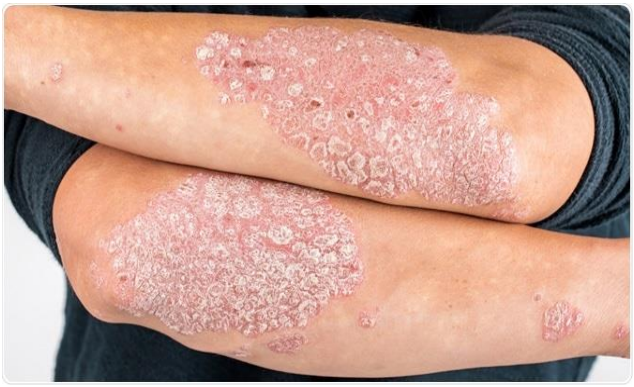


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Figure 1: Different Images showing Psoriasis

1.2 RESTRICTIONSOFPRESENTMARKETFORMULAS

- The FDA in the USA has issued a black box warning for acitretin (Katz et al., 1999). The black box warning, which is the very worst thing a medicine can contain for your health, is that. The medication comes with the following warnings (Katz et al., 1999):
- Teratogenicity: The teratogenic effects of retinoids are a defining feature of hypervitaminosis A. Hip deformity, meningomyelocele, meningoencephalocele, multiple synostoses, and craniofacial dysmorphisms including a high palate and anophthalmia are a few of the teratogenic consequences.
- Hepatotoxicity: Acitretin increases levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate transaminase (AST), and other liver serum enzymes.
- Ophtalmologic repercussions are adverse effects on the eyes, such as dryness and irritation. Some people might not be able to wear contact lenses while undergoing treatment due to these side effects.
- During acitretin medication, triglyceride levels increase in patients with pancreatitis. Patients with diabetes mellitus, obesity, strong alcohol use, or a family history of these illnesses are more likely to develop hypertriglyceridemia.

• Systemic retinoids like acitretin have infrequently been linked to benign intracranial hypertension, commonly known as pseudotumor cerebri, which can be managed with dietary changes and a lower acitretin dose. It is crucial to screen for papilledema as soon as the condition is detected.

1.3 DIFFERENT OTHER SIDE EFFECTSCANINCLUDE:

- Dry,crackedlips; peelingskinonthepalms,soles,andfingers
- Scratchy,flakyskinalloverthebody
- Thin nails
- Skinthatiseitherverystickyorextremelydelicate
- Signsinclude: astuffyordrynose,or nosebleeds
- Hairloss,itchyeyes,anddrylips
- Stiffness,soreness, andachingjoints and muscle
- CholesterolProblems

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1.4 REASONSWHYSOLID LIPIDNANOPARTICLES SHOULDBEUSED

- Since acitretin is a BCS class IV drug, its solubility profile is poor. Topical administration also causes decreased absorption through the skin. A diffusion barrier for the majority of substances is also provided by the stratum corneum, which is composed of corneocytes embedded in a lipid matrix. To enable skin penetration and the desired therapeutic impact, acitretin must be enclosed inside a lipid nanoparticle system.
- Solid lipid nanoparticles (SLNs), a novel kind of nanoparticulate carrier system, have garnered a lot of attention due to their enhanced drug delivery and stability. According to Muller et al. (2007), SLNs are composed of biocompatible lipids and are covered with an amphiphilic surfactant. According to Jain et al. (2014), they perform better than liposomes, polymeric nanoparticles, and fat emulsions. In terms of biocompatibility, good stability, drug release control, availability of scaling, and sterilising approach, SLN has advantages, according to Sala et al. (2018).
- By offering higher protection against chemical drug degradation, they circumvent the limitations of liposomes and other carriers (Soppimath et al., 2001; Garg et al., 2012; Jain et al., 2010). Other advantages of SLNs are their biocompatibility and possibility for scaling and sterilisation. These systems might also be suitable for manufacturing because they require no or very little organic solvents (Mühlen et al., 1998). The most desired characteristic of a topical formulation is possessed by SLNs since they do not cross the transdermal barrier and remain in the epidermis and dermis. (Jenning et al., 2000(b); Maia et al., 2002) provide evidence for this.

- In order to administer medication subcutaneously, lipid nanoparticles (SLNs) are used as the delivery system. The SLN-loaded gels are an appealing method of administering medication since they are straightforward to use and widely accepted. These gels are incredibly dependable and simple to use. Such systems may easily include pharmaceuticals, both hydrophilic and hydrophobic, increasing skin permeability and drug deposition. Gels like this one increase the stability of formulations by strengthening a rigid network. These gels also prevent the skin from drying out and peeling. These gels' thixotropy, greaselessness, ease of spreading, emollience, absence of discoloration, extended half-life, stability, and aesthetically pleasing appearance make them superior to others. The transparent gels of Carbopol 934P are what make it the best for gelling solid lipid.

1.5 DRUGSAVAILABLEFORPSORIASISTHERAPY(AdrianaRendonand KnutSchakel, 2019)

Table1: Different Drugs for Psoriasis Treatment

S.NO	DRUG	MECHANISM	APPLICATION
1	Methotrexate	Dihydrofolate reductase inhibition blocks purine biosynthesis; induction oflymphocyteapoptosis	S.C./Oral
2	Cyclosporin	Calcineurin inhibition leading toreducedIL-2	Oral
3	Acitretin	Normalisation of keratinocyte differentiation and proliferation via retinoid receptor binding	Oral
4	Fumarate	A transition from a pro-inflammatory Th1/Th17 response to an anti-inflammatory/regulatory Th2 response is encouraged by intracellular glutathione, regulation of Nrf2, NF-B, and HIF-1.	Oral
5	Apremilast	PDE4inhibitorincreasesinintracellular cAMPlevelsinimmuneandnon-immune cell types modulatinginflammation	Oral
6	Etanarcept	Dimeric humanfusion	S.C.

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		protein mimickingTNF-αR	

7	Infliximab	ChimericIgG1κmonoclonalantibodythat binds to soluble andtransmembraneformsofTNF-α	I.V.
8	Adalimumab	HumanmonoclonalantibodyagainstTNF-α	S.C.
9	Certolizumab	Fab portion of humanized monoclonalantibody against TNF-α conjugated topolyethyleneglycol	S.C.
10	Ustekinumab	IL-12/IL-23 p40 is a human IgG1k monoclonal antibody that binds specifically to the p40 protein component used by both IL-12 and IL-23 cytokines.	S.C.
11	Tildrakizumab	HumanizedIgG1κ,whichselectivelyblocks IL-23 by binding to its p19subunit	S.C.
12	Guselkumab	Human immunoglobulin G1 lambda (IgG1) monoclonal antibody that binds to IL-23's p19 component to specifically inhibit it	S.C.
13	Risankizumab	Humanized IgG1 monoclonal antibodythat inhibitsinterleukin-23 by specificallytargetingthep19subunit	S.C.
14	Secukinumab	HumanIgG1κmonoclonalantibodyagainstIL-17A	S.C.
15	Ixekizumab	Humanized, immunoglobulinG4κmonoclonal antibodyselectivelybindsandneutralizes IL-17A	S.C.
16	Brodalumab	Human monoclonalIgG2 antibody directedat theIL-17RA	S.C.

1.6 TOPICALDRUGDELIVERYSYSTEM

- Topical drug delivery devices are used to give medications directly to the skin. The drug is intended to permeate numerous skin layers. The largest organ in the body, the skin serves as a barrier to protect the body from the outside environment. The epidermis and dermis, the two outermost layers of skin, can both be reached by a medication when it is applied directly to the skin. Acitretin is a superb option for drug delivery through topical application because to its brief biological half-life, restricted oral bioavailability, and different dose-dependent adverse effects. In the usual formulations, only oral capsules are offered, and they have serious systemic side effects. Therefore, several drug delivery techniques are used to get around Topical drug delivery devices are used to give medications directly to the skin.
- The drug is intended to permeate numerous skin layers. The largest organ in the body, the skin serves as a barrier to protect the body from the outside environment. The epidermis and dermis, the two outermost layers of skin, can both be reached by a medication when it is applied directly to the skin. Acitretin is a superb option for drug delivery through topical application because to its brief biological half-life, restricted oral bioavailability, and different dose-dependent adverse effects. In the usual formulations, only oral capsules are offered, and they have serious systemic side effects.
- Therefore, several drug delivery techniques are used to get around limitations of traditional dosage forms.Nanoparticles(Shahetal.,2007),chitinnanogelsystems(Divyaetal.,2016),liposomes(Singhetal.,2009),niosomes(Hashimetal.,2018),ethosomes(Jainetal.,2007),nanoemulsions(Sarkar,2005),nanostructuredlipidcarriers(Agarwaletal(Benson,H.A,2005).Inthisageofregulatedandtargetedmedicationdelivery,acarrierbasedapproachfortopicaldrugadministrationisrapidlyevolving.Giventhat theyavoiddirect contactwiththeskin,thesecarrier-baseddeviceshaveagreatdealofpromiseasatargetingtool.
- Allofthesemethodshavethepotentialtoimpro

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vetheefficiencyofthemedicinebyincreasingitsskinpenetrationinavarietyofspeciesthathavebeen carefully characterized.

- Since acitretin is extremely lipophilic, it may be easily encapsulated in a lipid-based delivery system. The outcome will be increased systemic bioavailability andfeweradverse effects.

The following are some of the benefits that may be gained by using topical drugdelivery:

Since topical administration enables self-application of the medication, it improves patient compliance and prevents the active ingredient from being metabolised in the body's first metabolic step.

• The patient has the right to cease taking medication at any time.

• It improves the therapeutic effectiveness of the medication by preventing phenomena such as first-pass metabolism, gastrointestinal (GI) irritation, gastrointestinal (GI) breakdown, and insufficient absorption.

• Assist in reducing the pervasive issue of intra- and inter-patient variation in the administration of oral medications brought on by variations in renal clearance (Blum et al., 1982).

1.7 JUSTIFICATIONOFTOPICALDRUG ADMINISTRATION

In order to solve the biopharmaceutical issues, we may take one of two main steps.

- Helping or altering the skin's barrier function is the initial step. Topical antibioticsaid in repairing a compromised barrier and sunblocks strengthen the horny layer'sabilitytoshield vitaltissues fromdamagingUVrays.

• The second method bypasses the need for oral, systemic, and other medicines by penetrating the horny layer at the molecular level to deliver pharmaceuticals to healthy epidermal and dermal tissues. The epidermis might be difficult to reach when treating skin infections with a systemic approach. Moreover, the need for relatively large doses means that it might induce negative effects. However, the medicine is able to permeate into the living cutaneous tissue at therapeutic quantities when administered through the topical route, sparing the patient from any adverse pharmacological effects. Therefore, the skin serves as a necessary barrier, keeping harmful external compounds out while keeping vital endogenous ones in.

1.8 SOLIDLIPIDNANOPARTICLES ASATREATMENTFORPSORIASIS

To fill the gap between lipid (emulsion and liposome) and polymeric nanoparticle (NP) delivery technologies, SLNs were first introduced in 1991 (Sala et al., 2018). SLNs are highly sought-after as skin medicine carriers because of their lipid makeup. In fact, the lipid interactions between skin and SLNs may enhance the skin penetration of the encapsulated medications (Zhai and Zhai, 2014). The interfacial area increases with decreasing typical particle size of SLNs, which is between 40 to 1000 nm (Pardeike et al., 2009), increasing the possibility of drug penetration into deeper skin layers. Additionally, according to claims made by Porter et al. (2016), SLNs are the only ones that can target the epidermis, improving the benefit to risk ratio of topical treatment. The lipid matrix is made up of a solid lipid or a mixture of solid lipids dispersed in water at a rate of 0.1% (w/w) to 30% (w/w). According to Pardeike et al. (2009), a surfactant is often used at a concentration of 0.5% (w/w) to 5% (w/w) to maintain the stability of the system. The optimal carriers for topical treatments, according to a 2012 study by Mehnert and Mäder, are solid lipid nanoparticles.

Controlleddrugreleaseanddrugtargetingmaybepossible;

- drugstabilitymaybeimproved;drugpayload maybeincreased;
- both lipophilic and hydrophilic medicines may be included withoutcompromisingthe carrier's safety;
- thereneedbenobiotoxicitytothe drug;
- Organic solventsmaybe avoided.
- Noissueswithlarge-scalemanufacturingorsterilizing

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1.9 METHODSOFPREPARATIONOFSOLIDLIPIDNANOPARTICLES

- Solvent injectiontechnique
- Coldhomogenizationtechnique
- UltrasonicationorHigh-SpeedHomogenization
- Solventemulsification-evaporationtechnique
- Solventemulsification-diffusiontechnique
- Microemulsion-basedmethod
- Hothomogenizationtechnique

1.10 THEIMPORTANCEorNEEDOFONGOINGRESEARCHES

- The systemic medicine acitretin has received approval from the US Food and medicine Administration for the treatment of severe, drug-resistant psoriasis. Constrictive, red, denser plaques with underlying silver-white scales and repeated flare-ups of inflammation and hyperkeratosis are characteristics of the T-cell mediated skin condition psoriasis. Psoriasis' fundamental aetiology is unknown. Topical therapy, phototherapy, and systemic therapy are being used to treat the illness, although no one of these methods has been shown to be particularly successful at hastening recovery. The shoulders, back, neck, chest, and upper arms are common areas for acne to occur. Acne develops when bacteria, dead skin cells, or oil clog the skin's pores, according to Ravisankar et al. (2015)..
- Several factors, including increased sebum production, altered sebum lipid quality, androgen activity, interaction with NPs, pro- and anti-inflammatory properties, hyperkeratinization of the hair follicle, and Propionibacterium acnes growth within the follicle, are currently thought to contribute to acne (Georgel et al., 2005 and Zouboulis CC., 2004). Both disorders are typically treated initially with topical medications. Examples of side effects include dermatitis, irritation, and alterations in skin tone or colour. Oftentimes, phototherapy is recommended as a backup plan if topical treatments fail. According to Pradhan et al. (2013), phototherapy can cause skin cancer, hypertension, renal damage, hepatotoxicity, and hyperlipidemia among other side effects.
- Patients are less likely to take their medication as prescribedwhen it causes nausea and vomiting and has to be taken many times daily (often asmanyas fourtimes).

- One of the main reasons for inadequate treatment is the lack of a perfect anti-psoriatic and anti-acne drug carrier. Researchers are looking at the use of colloidal carriers such liposomes, ethosomes, transferosomes, nanostructured lipid carriers, microspheres, micelles, dendrimers, etc. to enhance therapeutic regimens. A topical carrier-based method that makes it easier for the medicine to enter the skin and stay there, preventing organ damage, will boost the effectiveness and appeal of acitretin as a treatment for psoriasis. There are several psoriasis carrier-based formulations on the market, such as Lipotar S Gel (coal tar liposomes).
- Acitretin'sstrongsystemicadverseeffects,including teratogenicity,hyperlipidemia,pancreatitis,ophthalmologicsymptoms,hyperostosis,andlivertoxicity, limit the drug's use in oral administration (Katz et al., 1999). Commonmucocutaneous side effects include cheilitis, hair loss, pyogenic granulomas, nailplateweakening,anddry,stickyskin.That'swhywecallthem"blackboxwarnings"onpharmaceuticals.Therefore,researchersareexploringothermedicationdeliverysystems.
- It is difficult to develop a topical formulation of acitretin due to the drug's physicochemical properties, such as its extremely low water solubility (0.0729 mg/ml), instability when exposed to light, air, and heat, and skin irritation episodes characterised by erythema, burning, and peeling of the treated area. Act must therefore be used topically as soon as possible to provide a more secure treatment strategy, as well as to increase local bioavailability of the medication at the action site and lessen the risk of systemic exposure.
- The stratum corneum serves as the main obstruction to topical therapy due to its barrier properties. The significantly thickened and inflamed stratum corneum, in particular for psoriasis and acne, may restrict the efficacy and anti-psoriatic activity ofthemedicationsgiven topicallyasstandarddoseforms(Hashimetal.,2018).
- Lipidcarriersystems,suchassolidlipidnanoparticles,areresponsiblefortransportingthemedicinedeeperintothedermis.

1.11 DRUGPROFILE

ACITRETIN

IUPACNAME:(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona2,4,6,8-tetraenoicacid (Porweletal., 2014).

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The FDA-approved systemic retinoid is (13-cis-trans retinoic acid). It is the first line of defence against psoriasis.Although the specific mechanism of action is uncertain, psoriasis is characterised by increased cell proliferation and keratinization, which are prevented by this medication.. As a result, it lessens scaling, plaque formation, and skin thickness. Additionally, nodulocystic acne appears to benefit from it (Andrew J. Scheman, 2002).

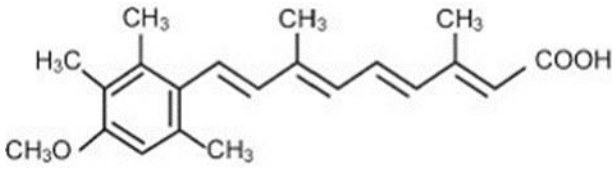

Figure 2:Structureofacitretin

Table 2: Drug parameter details

Parameter	**DrugSpecifications**
Brandname	Soriatane;Neotigason
ChemicalFormula	$C_{21}H_{26}O_3$
MolecularWeight	326.429g/mol
Solubility	0.0729mg/L
Metabolism	Hepatic
Meltingpoint	230˚C
Bioavailability	60%
ProteinBinding	>99.9%
Eliminationhalflife	49days
BCS Classification	II class (low solubility and high permeability)

Druginteractions: Thedrugswhichcaninteractwithacitretinthusaffectingitsactionare:(Katz*etal.*, 1998)

Table 3: Drug Interaction

S.No.	**Drug**	**Interaction**
1.	Tetracycline	Increasedphotosensitivity,Pseudotumorcerebri
2.	Minocycline	Pseudotumorcerebri
3.	Alcohol	Increasedconversiontoetretinate,hepatotoxicity
4.	OtherRetinoidsor VitaminA	Hypervitaminosis
5.	Corticosteroids	Hyperlipidemia
6.	Methotrexate	Increasedmethotrexatelevel,hepatotoxicity.
7.	Minipill	Interferewiththecontraceptiveeffect

Table 4: CommerciallyavailableformulationsofAcitretin

Name	**Strength/Capsule**	**Pharmaceuticalcompany**	**Route**	**Dosage**
Aceret25	25mg	ActavisSpecialty PharmaceuticalsCo	Oral	Capsule
Soriatane	25mg	TevaPharmaceuticalsUSA,Inc.	Oral	Capsule
Acitretin	17.5mg	ImpaxGenerics	Oral	Capsule
Acrotec25	25mg	SigmaPharmLaboratories,Llc	Oral	Capsule
Acetec10	10mg	MylanPharmaceuticalsInc.	Oral	Capsule

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3.1 Aimofwork

- Their development was intended to increase skin permeability. When water loss from the skin is stopped, the inter-corneocyte gaps widen and the corneocytes group closer together. Drugs have a higher likelihood of permeating the skin as a result (Desai et al., 2010; Zhai and Zhai, 2014). Due to higher occlusion and skin contact surface, smaller particle size for SLNs has been associated with improved skin penetration. Normally, particles have to be smaller than 260 nm (Adib et al., 2016).
- The study's findings suggest that the action is localised and does not penetrate the skin when there is an increase in SLN levels in the upper dermis (Jenning et al., 2000(b); Maia et al., 2002). NLCs with a lower liquid lipid content permeate the skin more thoroughly, according to research on skin permeation (Sala et al., 2018). This supports the notion that SLNs have greater skin permeability than NLCs (Teeranachaideekul et al., 2008).
- To overcome the aforementioned limitations of the conventional dose form, the main goal of the current work was to develop a safe and efficient targeted drug delivery method for topical administration. In the current study, an effort was made to develop a topical acitretin formulation based on a carrier.
- **Objective:**
- Pre-formulationstudies
- Preparationofstandardcurveof drug
- Drug-excipients compatibilitystudy
- Preparationandoptimizationoftheformulatio n
- Characterizationofformulation.
- *In-vitro*drugreleasestudy

3.2 RESEARCHENVISAGED

- Psoriasis is thought to be an immune system problem. Triggers include infections, stress and cold.
- The most common symptom is a rash on the skin, but sometimes the rash involves the nails or joints.
- Treatment aims to remove scales and stop skin cells from growing so quickly. Topical ointments, light therapy and medication can offer relief.

4.1PREFORMULATION STUDIES

A. Pre-formulationstudies

Identificationofdrug
Physicalappearance
Meltingpoint
I.R.spectroscopy
UVspectroscopy
Solubilitystudies
Preparationofstandardcurveof drug

B. Preparationandoptimizationoftheformulation

C. Characterizationofformulation.

Appearance
pH

D.In-vitrodrugreleasestudy

E. Results and Discussion

4.2 PREFORMULATIONSTUDIESOF ACITERTIN

Preformulation studies must be carried out to characterise the physicochemical, natural features of the drug that may affect the development of an

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effective dosage form prior to the synthesis and characterization of pharmaceutical dosage form containing therapeutic component. The physicochemical characteristics of the new compound that may have an impact on therapeutic performance and the creation of an effective dosage form should be the main focus of preformulation investigations. For the design of a delivery system to attain stability and maximal bioavailability qualities, preformulation data must be produced.

4.3 PREFORMULATIONSTUDIES

4.3. DRUGIDENTIFICATIONTESTS

4.3.2Physicalappearance

4.3.3Lightabsorptiontestfor ACITERTIN

4.3.4Meltingpoint

4.3.5 IRspectroscopicanalysis

4.3.6 DSCofACITERTIN

4.4 SOLUBILITYPROFILE

4.5 UVSPECTROSCOPICANALYSIS

4.5.1Determinationofabsorbancemaxima

4.5.2PreparationofstandardcurveofACITERTIN inphosphatebufferpH7.4

4.6 PARTITIONCOEFFICIENTSTUDIES

- **DRUGIDENTIFICATIONTESTS**

- **PHYSICALAPPEARANCE**

Green-yellow crystalline powder was discovered to be present in the medication ACITERTIN. photographic characteristics According to Makin et al. (1989), acitretin is a yellow to greenish-yellow powder with a maximal absorption at 352 nm (methanol) in the UV—visible spectrum. Acitretin can easily undergo photoisomerization processes when exposed to light, especially in solution, because of its conjugated tetraene structure. (PUBCHEM)

SOLUBILITY

Soluble in most organic solvents, fats and oils; low solubility in water probably similar to that of alltrans-retinoic acid, i.e. 0.21 jimol/L (Szuts & Harosi, 1991)

- **LIGHTABSORPTIONTESTFOR ACITRETIN**

In Phosphate Buffer 7.4, the visible and UV spectrums are equal at 352 nm (Makin et al., 1989).

- **MELTING/CRACKINGPOINT**

Table 5: MP of Acitretin determined through the MP apparatus was found to be 228-230 °C.

Properties	Observations	Standard(I.P.,2010)
Color	Yellow	Yellow
Odor	Slightlyethanolic	Slightlyethanolic
PhysicalAppearance	Crystallinepowder	Crystallinepowder
MeltingPoint	228-230°C	224C

Determination of UV Absorbance Maxima of Acitretin

- The standard solution of Acitretin (10µg/ml) was scanned in the range of 200-400 nm to record the spectra against pH 1.2 HCl buffer as a blank using UV Spectrophotometer. The wavelength maxima of acitretin were determined from the spectra recorded. The λ max of Acitretin was found to be 353 nm.

- Making a pH 1.2 HCl buffer standard calibration curve. setting up a stock solution
- Acitretin 10 mg, accurately weighed, is transferred to a volumetric flask of 100 ml. Then, methanol was used to create a volume of 100 ml and increase the drug concentration to 100 g/ml.
- The creation of a standard curve 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, and 1.6 ml of the stock solution were transferred to a 10 ml volumetric flask and diluted with pH 1.2 HCl buffer up to the mark in order to produce acitretin concentrations of 2, 4, 6, 8, 10, 12, and 16 g/ml, respectively. At 353 nm, the absorbance of each solution was measured using a UV-visible spectrophotometer. The absorbance v/s concentration (g/ml) graph was created in Microsoft Excel.

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Table 6: Standard curve data of ACITRETIN in phosphate buffer 7.4

S.NO	CONCENTERATION(µG/ML)	ABSORBANCE AT 352NM
1.	2	0.09
2.	4	0.241
3.	6	0.345
4.	8	0.401
5.	10	0.521
6.	12	0.621
7.	14	0.776
8.	16	0.816

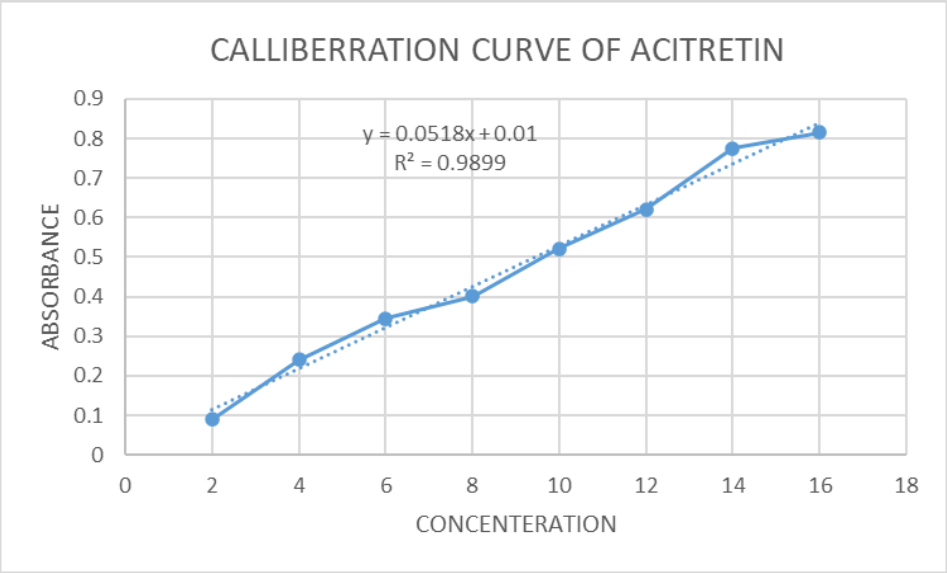

FIGURE 3: Calibration curve of ACITRETIN in Phosphate buffer 7.4

- **IR SPECTRA**

both C=O and C-O vibrations Ketones are expected to have a C=O stretch in the range of 1740–1660 cm-1, and carboxylic acids have a C=O stretch that is identical to this [20]. Due to its great intensity, the band is rather simple to identify.

In the current investigation, the band identified as the C=O vibration is seen at 1782 cm-1 in the FT-IR and 1767 cm-1 in the FT-Raman, and it agrees with the calculated value of 1791 cm -1 with an 80% PED contribution. Due to the high polarity of this multiple bonded group, it exhibits a strong infrared absorption band. The carbon and oxygen atoms in the C-O band both affect the carbonyl group's ability to absorb light. According to what we can see, the C-O vibration has been altered.However, these bands overlap with other bands that are caused by aromatic vibrations, making it impossible to definitively assign them.

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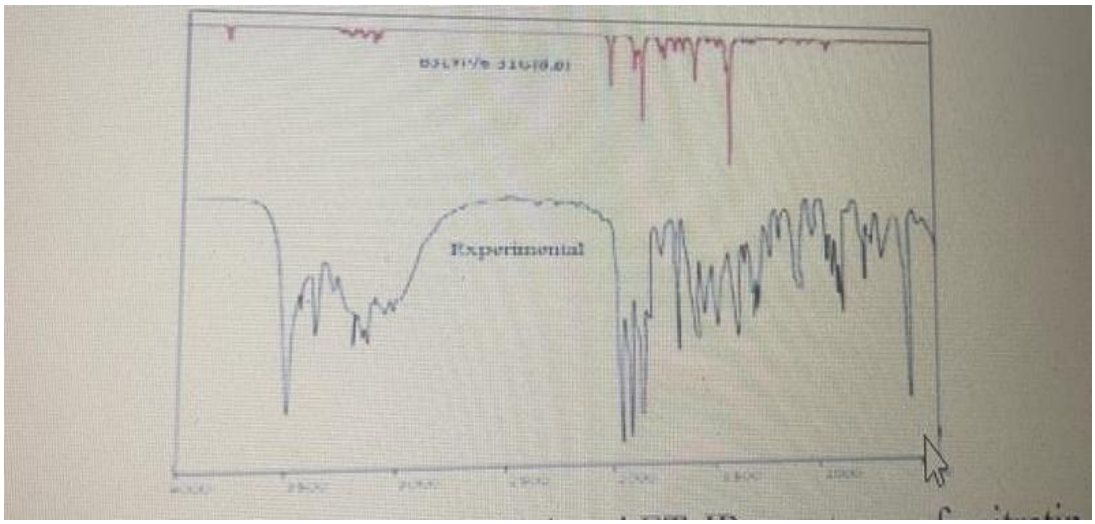

FIGURE 4: IR of Acitretin

- **DIFFERNTIAL SCANNING COLORIMETRY**
- DSC reveals all of the sample's physical characteristics, including its crystalline and amorphous nature, and illustrates potential interactions between drugs and polymers. Acitretin's DSC curve displayed a single endothermic peak at 225 oC. A low intensity peak at roughly 62 oC and an increase in the curve at 220 oC are visible in the optimise formulation's DSC profile. The decrease in crystallinity in a formulation is so established. Figure 5 depicts the physical mixing of the drug and polymers, as well as the thermal behaviour of Acitretin.

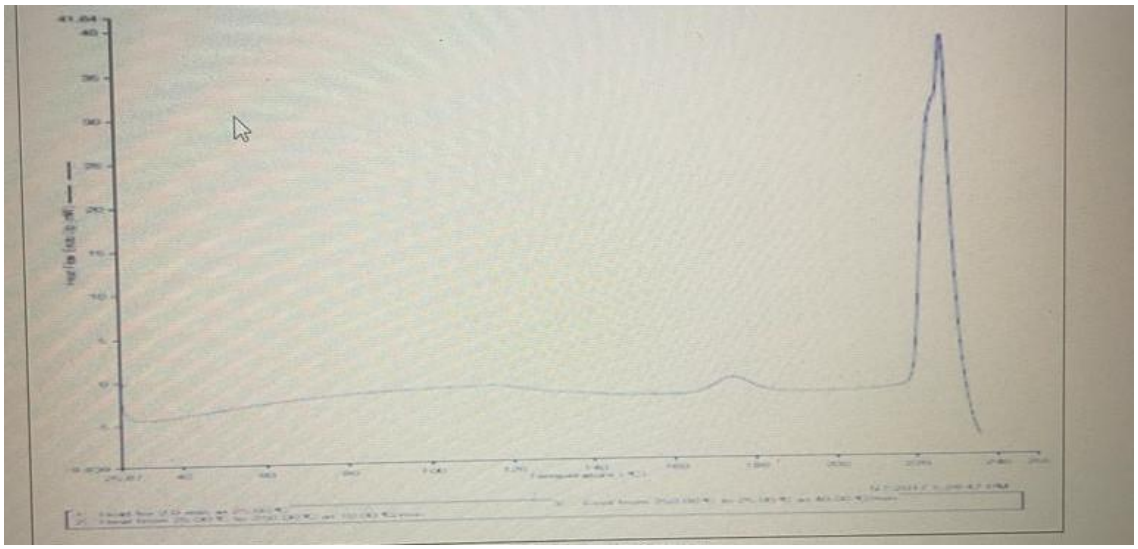

FIGURE 5: DSC of Acitretin

- **SOLUBILTY STUDIES**

Acitretin is sparingly soluble in aqueous buffers.For maximum solubility in aqueous buffers,acitretin need to be dissolved in DMF and then diluted with aqueous buffers.

Acitretin has solubility of 0.2 mg/ml in 1:4 solution of DMF: PBS(PH7.4).

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Table 7: Solubility of ACITRETIN

SOLVENTS	SOLUBILITY
DMF: PBS (pH 7.4)	++++ (VERY SOLUBLE)

- **PARTITION COEFFICIENT**

Partition coefficient (*P*) or distribution coefficient (*D*) is the ratio of concentrations of a compound in a mixture of two immiscible solvents at equilibrium
The log *P* value is a measure of lipophilicity or hydrophobicity
Partition of drugs from oil phase n- octanol and PBS.

Investigating the drug's partition behaviour in n-octanol:PBS (pH 7.4).By placing the drug (10 mg) in two different funnels, one of which contained 10 ml sections of n-octanol and the other of which contained 10 ml of PBS (pH 7.4), it was found. The separating funnel was shaken for 24 hours in a wrist motion shaker to equilibrate it. Following the division of the two phases, the drug concentration in the aqueous phase was evaluated at 352 NM.Utilising the following formula, it was calculated:

P O/W = [C ORGANIC / C AQUEOUS], equilibrium

Table 8: Partition Coefficientof ACITRETIN

Medium	Partition coefficient
n-octanol: PBS	0.64

III. METHODOLOGY

5.1 Method for Preparation of Nanostructured Lipid Carrier (NLC):

Acitretin-loaded NLCs are prepared using the hot homogenization method. Acitretin was dissolved in ethanol and combined with an acetone solution containing a mixture of stearic and oleic acid from the lipid phase. To stabilise NLC, a solution of tween 80 and sodium lauryl sulphate was added gently and dropwise to the mixture. Using a magnetic stirrer 8, the mixture was sonicated at 85 oC for 30 minutes at 1200 rpm. Using a hot homogenizer set at 15000 PSI, this main emulsion was transformed to the NLC system. The created emulsion was then cooled to room temperature while being stirred continuously, and the lipid was recrystallized to create a nanostructured lipid carrier (NLC). Lyophilization was done on the obtained NLC dispersions. Table 9 lists the formulas of various substances along with their makeup.

Table 9: Different Formulation of ACITRETIN

Sample	Drug(%w/v)	Ratio of oleic acid and stearic acid	Tween 80(%v/v)	SLS(%w/v)
F1	12 mg	8:2	2	2
F2	12 mg	8:2	2	3
F3	12 mg	8:2	2	4
F4	12 mg	8:2	3	2
F5	12 mg	8:2	3	3
F6	12 mg	8:2	3	4
F7	12 mg	8:2	4	2
F8	12 mg	8:2	4	3
F9	12 mg	8:2	4	4

5.2 Preparation of Acitretin Loaded NLCs Gel

NLC formulation is determined by the characterizations of the NLC dispersion (particle size, trapping effectiveness, and in-vitro release profile) described above. IJPSR, 2021; Vol. 12(6): 3381-3390; Kumari et al. P-ISSN: 2320-5148; E-ISSN: 0975-8232 The best physicochemical properties of International Journal of Pharmaceutical Sciences and Research 3383 were chosen 15. Continuous stirring was used to integrate the NLC dispersion into the HPMC gel. The dispersion was then homogenised using a homogenizer. To expel suffocated air, the gel was probe-sonicated for at least one hour before being left to stand overnight.

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Table 10: Formulation chart of methyl cellulose & Triethanolamine

Sample code	Methyl Cellulose(%w/v)	Neutralizing agent(%v/v) **Triethanolamine**.	pH
G1	1.5	6	5.2
G2	2.5	4	6.6
G3	3.5	2	8.5

"Neutralizing agent" is added to increase the pH and cause the dispersion to thicken and gel. Some neutralizing agents are **sodium hydroxide, potassium hydroxide, and triethanolamine**."

5.3 NLC Gel Evaluation: Homogeneity

After the generated gels were set in the container, they were all visually inspected to determine their homogeneity.They were tested for their appearance and presence of any aggregates.

5.4 Spreadability Study of NLC Gel

In order to test the spreadability of the gel formulations 24 hours after manufacturing, one gramme of gel was placed between two horizontal plates (20 20 cm2) and its diameter was determined after one minute. The normal weight of the upper plate was 220gm. The formula below was used to calculate spreadability. S = M × L/T S is for spreadability, M is for weight fastened to the upper slide, L is for the length of the glass slide, and t is for processing time.

5.5 Viscosity measurement

The DVE Digital Viscometer is a cost-effective and easy-to-use tool thanks to its direct torque% display, spindle and speed torque measurement accuracy, 1% whole range repeatability, and 0.2% complete range compatibility with all Brookfield accessory traceable viscosity standards. The speed for a wider speed range (0.3 to 100rpm).

Table11: Evaluation of Plain Methyl Cellulose gel

S.no	PERCENTAGE OF GEL (%)	Spreadibility (g×cm/sec)	Viscosity(cgs)
1	1.5	3.23	520
2	2.5	4.9	2341
3	3.5	10.2	8765

5.6 Determination of Entrapment Efficiency & Drug loading

To separate the lipids and aqueous phase, 2.0 ml of a drug-loaded sample was centrifuged at 2500 rpm for 90 min. With phosphate buffer pH 7.4 used as a blank, the supernatant solution was separated and examined using a UV spectrophotometer at 352 nm. The effectiveness of NLC's drug trapping was calculated as

Entrapment effectiveness (EE) = (WA-WS) * 100/WA

Drug loading (DL) equals WA-WS/WA-WS+WI*100

Where WA denotes the mass of acitretin added to the formulation, WS denotes the analysed weight of the drug in the supernatant, and Wl denotes the weight of added lipid. EE stands for entrapment efficiency.

Table 12: Drug loading & Entrapment Efficiency of Acitretin gel

S.NO	**FORMULATIONS**	**DRUG LOADING**	**ENTRAPMENT EFFICIENCY**
1.	F1	24	19
2.	F2	53	35
3.	F3	14	27
4.	F4	32	30
5.	F5	61	52
6.	F6	45	49
7.	F7	54	52
8.	F8	65	60
9.	F9	85	88

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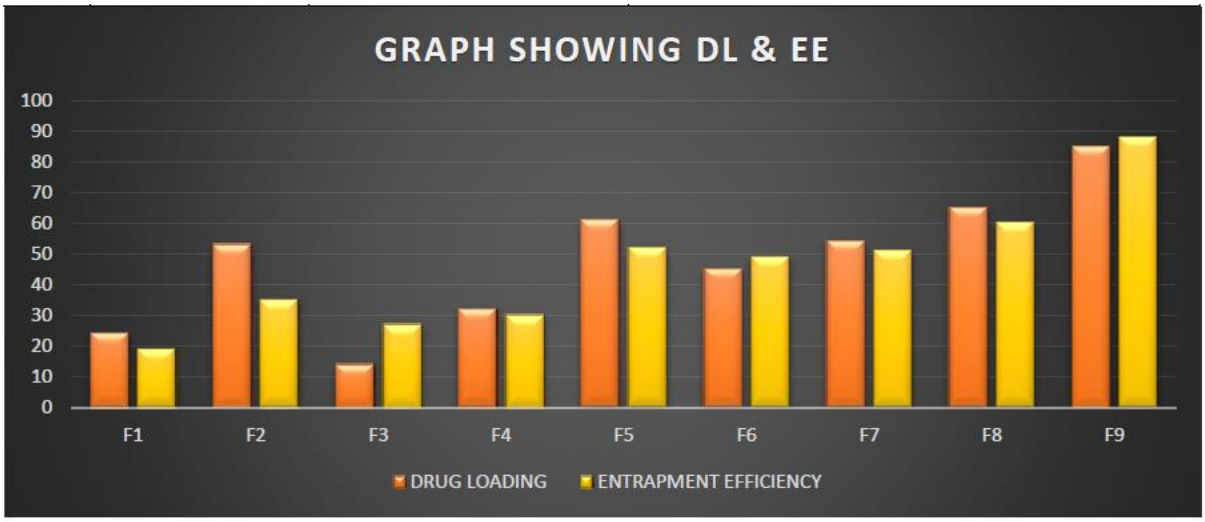

Figure 6: Graphical representation of Drug loading & Entrapment Efficiency

5.7 In-vitro Release Study of Nanostructured Lipid Carrier (NLC) of Gel

To evaluate the Acitretin release profile from each formulation, in-vitro drug release tests were performed using a modified Franz diffusion cell. The Franz diffusion cell was covered with a synthetic cellophane membrane. The receptor medium was around 45 ml of phosphate buffer with a pH of 7.4 and was swirled by the magnetic bar at 700 rpm in order to prevent differing concentrations within the acceptor medium and to reduce stationary layers. NLC gel dispersion (1 mg of medicine) was created and placed in the donor compartment. Throughout the experiments, the solution on the receptor side was maintained at 37 0.5 ·C. Three millilitres of the sample medium were removed from the receiver compartment through the side tube after a predetermined amount of time, and the same amounts of freshly prepared receptor media were then added. At 352 nm, a UV-Visible spectrophotometer was used to examine the materials.

Table 13: Formulations F8 showing % DR & % CDR

S.NO	FORMULATION	TIME	ABS.	CONC.	% D.R	%C.D.R
1.	F1	8	0.002	0.15	0.015	0.015
2.	F2	16	0.004	0.24	2.98	2.995
3.	F3	24	0.005	0.42	8.56	11.55
4.	F4	32	0.007	0.61	11.98	23.53
5.	F5	40	0.008	0.83	15.04	38.57
6.	F6	48	0.01	1.78	17.12	55.69
7.	F7	56	0.04	3.76	18.15	73.84
8.	F8	64	0.05	4.25	19.71	93.55

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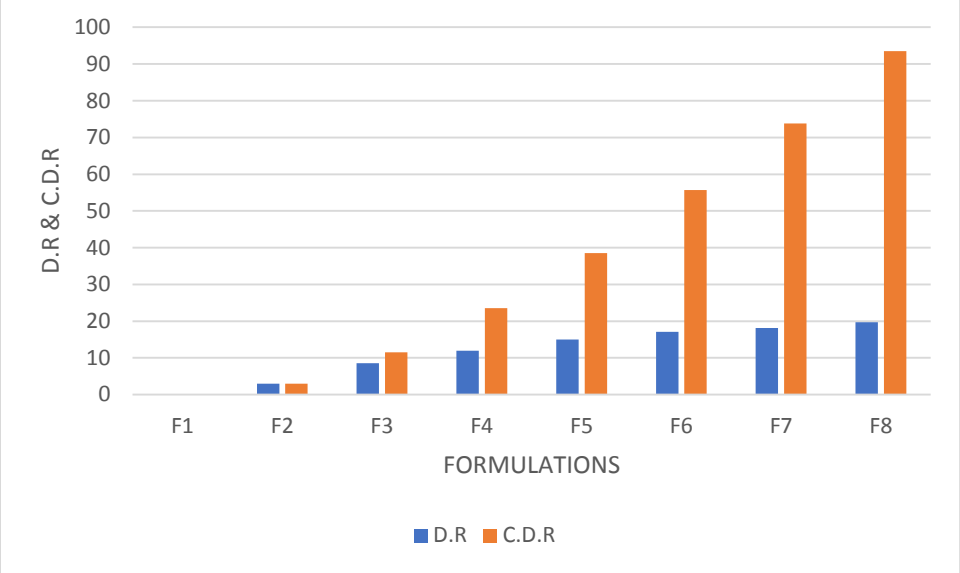

FIGURE 7: FORMULATIONS SHOWING D.R & C.D.R

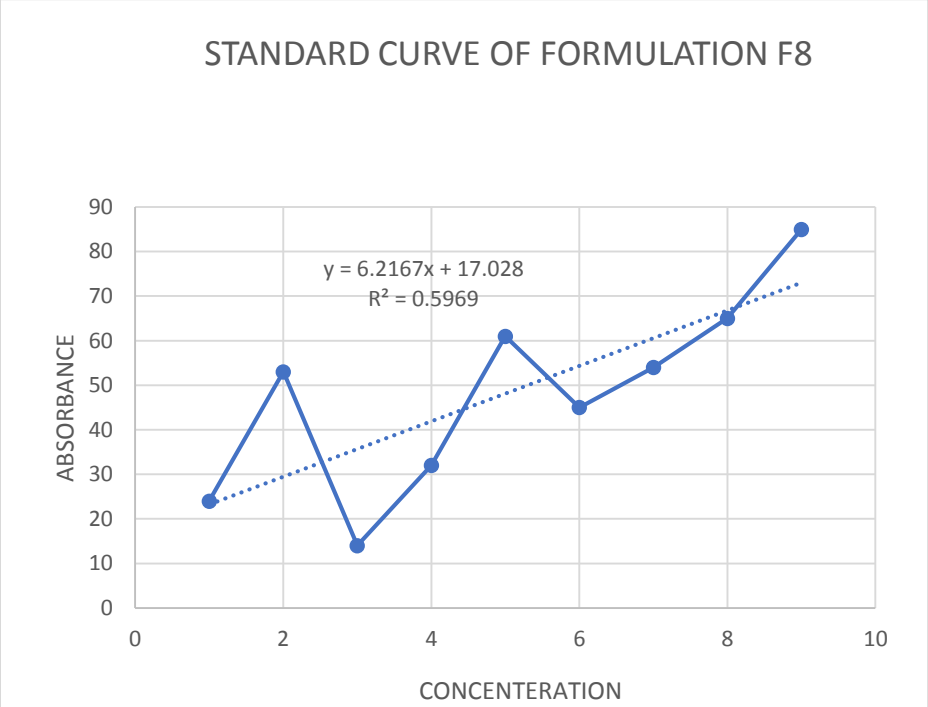

Figure 7: Standard Curve of Formulations F8

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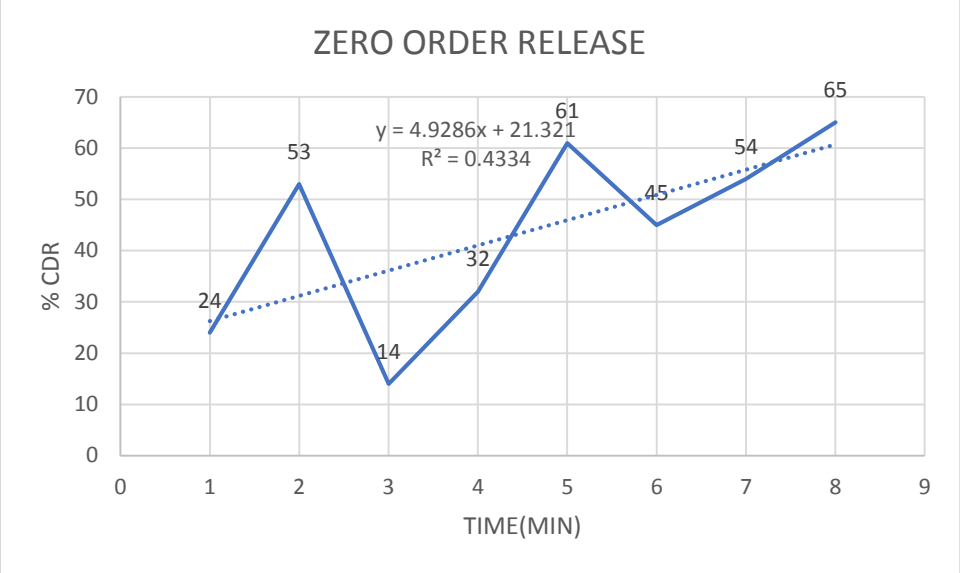

Figure 9: Standard curve of F8 showing zero order release

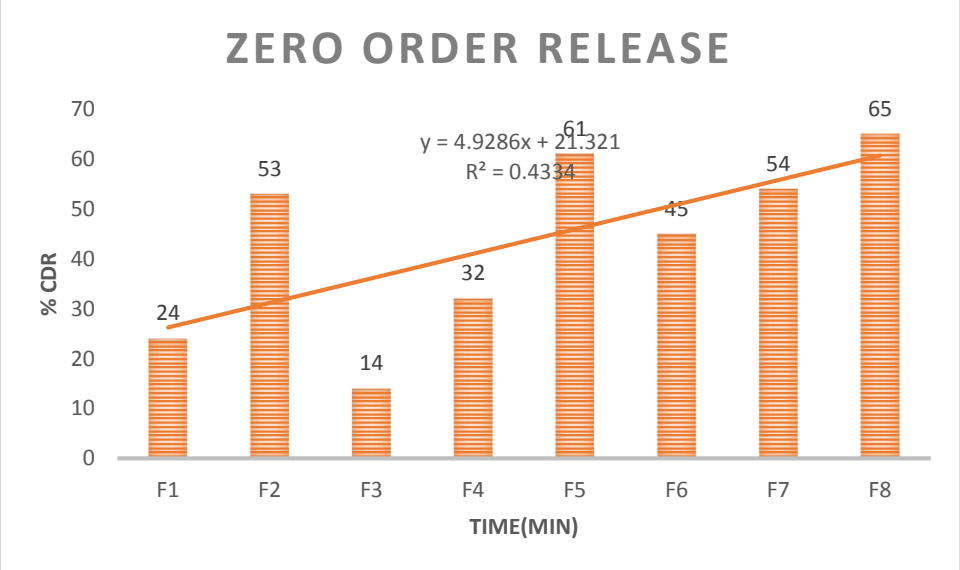

Figure 10: Graphical representation of F8 showing zero order release

5.8 Determination of TEM

Spherical droplets in the nanometer range may be seen in the NLC gel microscopy. Selected nanostructure lipid carrier formulations (1gm) were diluted with 500ml of phosphate buffer pH 7.4. On a film that was coated with a copper grid, a drop of the emulsion was placed, and any surplus droplets were rapidly wiped away with filter paper. After drying in the air at a predetermined air temperature, the grid was then placed into the microscope. To create the TEM images, the material that had been drying overnight was placed onto a copper grid inside the TEM's vacuum chamber. The results showed that the particles were spherical, and the particles in Fig. 11 did not appear to contain any drug crystals. The image shows the following because of the lipid makeup of the carriers:Different particle shapes exist.The picture shows some gathering of particles due to the lipid nature of carriers. Some particle shapes are different from spherical due to the drying process of sample treatment.

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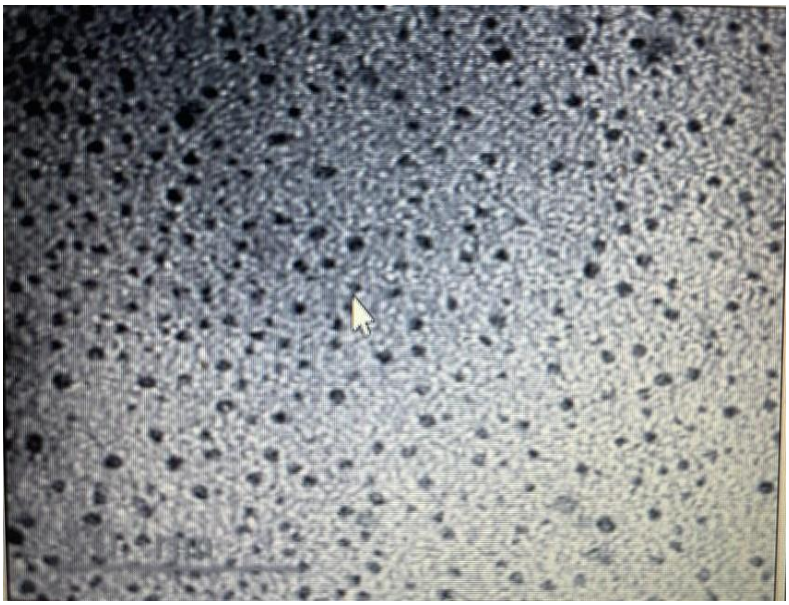

FIGURE 11:TEM IMAGE SHOWING SPHERICAL DROPLET IN Nano RANGE OF F8 FORMULATIONS.

VI. RESULT & DISCUSSION

Spherical droplets in the nanometer range may be seen in the NLC gel microscopy. Selected nanostructure lipid carrier formulations (1gm) were diluted with 500ml of phosphate buffer pH 7.4. On a film that was coated with a copper grid, a drop of the emulsion was placed, and any surplus droplets were rapidly wiped away with filter paper. After drying in the air at a predetermined air temperature, the grid was then placed into the microscope.

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The outcomes of the experiments demonstrated that the various surfactants had a significant impact on entrapment effectiveness. Poor entrapment efficiency was seen in formulations F1 to F7, which may be related to inadequate NLC formation. The formulations (F8 and F9) with the best entrapment efficiency were chosen. Evaluation of the HPMC plain gel at various concentrations led to the conclusion that 2.5% HPMC plain gel is compatible with the best-prepared NLCs and was utilised to make NLC gel.

The selection of these three formulations was made because when ionic and nonionic surfactants are combined, transparent dispersion with good stability is the result. It's possible that non-ionic surfactant (Tween 80) stabilises the stearic component of the NLC gel dispersion while ionic surfactant (SLS) stabilises the electrostatic component.

Using a Franz diffusion cell, the in-vitro release profile of the gel formulations of acitretin NLCs was tested for 48 hours. Due to the combination of surfactant in the highest proportion, the F9 formulation demonstrated greater drug release than other formulations. The Franz diffusion cell was used to conduct in-vitro permeation tests on the optimised NLCs gel (F8) utilising a cellophane membrane barrier. According to the figure, the release kinetics of selective F9 were assessed for zero-order. The NLCs gel system's release pattern and sustained release over an extended length of time were revealed by the in-vitro release research of the optimised formulation (F9).