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Development and Evaluation of Nano Particles Based Loaded Topical Gel for the Treatment of Psoriasis and Other Skin Conditions

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ABSTRACT

Tacrolimus (NLCs) Nanostructured Lipid Carriers based gels have been papered as a promising Transdermal gels system for treatment of psoriasis. Tacrolimus drug having the first pass effect and to improve its bioavailability with reduction in dosing frequency and improve the drug loading capacity and drug release properties and dose related side effects. Three formulas were developed with different polymer ratios using a modified emulsification and low temperature solidification method. The gels were tested for clarity, homogeneity, Spreadability, Extrudability, viscosity, surface pH, drug content, uniformity, in vivo drug diffusion study using exvivo permeation study using rat abdominal skin, FTIR studies showed no evidence on interactions between drugs ,polymers and excipients. Tacrolimus- NLCs was successfully demonstrated by this method. Characterized for appearance, morphology, particle size, sentrapment efficiency, zeta potential and *in vitro* release, and then they were incorporated in a carbopol hydro gel to determine the influence on the *in vitro* drug transdermal delivery. In this study NLCs of Tacrolimus with the particle size 123.8 nm was formulated, which showed entrapment efficiency of 91.3±12 and zeta potential -31.1 Mv. The results revealed that there is increased solubility and bioavailability of the NLCs as compared to the drug commercial tacrolimus ointment. Excised full thickness of the rat skins were mounted on Franz diffusion cells and the formulations were applied for 48 h. Greater skin permeation of Tacrolimus was detected from the NLCs hydro gel than from the commercial ointment. Also higher retention was detected in the skin following NLCs hydro gel application Tacrolimus 0.5%gel containing Lipid nanoparticles are carriers with good prospects of successful marketing.

Key words: Psoriasis, Tacrolimus, Nano lipid particles, entrapment efficiency, skin permeation.

INTRODUCTION

Now days Novel Nano structured medicines (such as polymeric nanoparticles, liposomes, etc.) have shown they are having potential in improvement and more therapeutic benefits of present in antipsoriatic drugs by decreasing toxicity levels and improving their therapeutic efficacy with low toxicity [1]. Nano drug mainly targeting of psoriasis disease having different route of drug administration the drugs mainly promoting high Safety, high efficiency of Nanomedicines in the treatment of psoriasis. Nanotechnology mainly provides the growth of research and its applications in the area of Nanomedicine [2]. Since last decade, Different techniques have been used to formulate Nanopartic-ulate carrier systems like (NLCs& SLNs) are two varieties of nanocarrier systems are used[3].Nanomedicines having so many advantages and less toxic effects because they having natural origin lipid. In this research work nanostructured lipid carriers (NLCs) having many advantages for dermal applications and they provide controlled release of drug [4]. The preparation of NLCs using physiologically and biodegradable lipids been generally they having safe and low irritant potential for skin as well as cytotoxicity for normal human keratinocyte is low [5].

NLCs are small size they close contact with the stratum corneumand also increase absorbed drug by skin layers and they having chemical stability [6]. The development of nanocarrier system is an approach to overcoming such problems NLCs are

a new generation of SLNs. NLCs mainly suitable for Poorly water soluble drug as Dermally applied those drugs resulting in more efficient and deeper drug penetration [7].

Psoriasis is T-cell-mediated autoimmune inflammatory skin disease recognized by skin surface inflammation, epidermal proliferation, hyperkeratosis, and angiogenesis keratinization [8]. More notably, psoriasis is considered as an important risk factor for many critical diseases such as diabetes (type-IIDM) and cardio vascular diseases, including hypertension and hypercholesterolemia [9]. Moreover, other comorbidities that commonly associated with psoriasis are arthritis, depression, insomnia and obstructive pulmonary disease. Although the worldwide incidence and prevalence of psoriasis is poorly understood, yet it has been predicted that the global epidemiology of psoriasis account for 2 -- 4% of the world's population [10]. Psoriasis appears in a variety of forms, namely erythroderma psoriasis, guttate psoriasis, and plaque psoriasis, inverse psoriasis, [11]. Relapsing and pustular psoriasis spontaneous remission is a major problem associated with psoriasis, and the etiology is still evidence of clinical data pertaining to their safety and regulatory challenges [12]. The present research article provides a detail account on diverse targeted Nanomedicines available for effective treatment of psoriasis. [13].Topical permeation enhancement along with Nanomedicines as newer approaches in psoriatic therapy are also covered [14].

In case of dermatological diseases such as psoriasis, whose triggers are situated beneath the skin, it is preferable to manage drugs topically rather than systemically due to more efficient direct action with improvement of the local access for optimum amount of drug [15]. Topical administration also reduces the systemic burden and toxic effects of the drugs and it is considered the first line of treatment used in moderate psoriasis as it is considered safe and well accepted by the patients [16]. The successful implementation of these systems for drug delivery entirely depends on their ability to go through numerous anatomical barriers, sustained release of their content and stability in the nanometer size [17]. Various particulate lipid based colloidal carriers have also found application in anti-psoriatic drug delivery, in particular SLNs and NLCs [18].
Lipid based drug delivery systems are now days popular because of their potential to increase solubility and bioavailability of Poorly water soluble drugs [19]. This becomes an important tool, when it is necessary to supply the drug over a prolonged period of time, and to reduce systemic absorption, when the drug is irritating in high concentrations [20]. NLCs have the potential to adjust the drug release over an extended period with a reduced rate of systemic absorption. The lipid film formation above the skin and the succeeding occlusion effect was described for lipid nanoparticles with reduction of transepidermal water loss caused by this effect, leads to an augment in skin hydration after dermal application of SLNs or NLCs [21]. NLCs systems are a promising carrier for the topical delivery of antipsoriatic drugs as revealed by improved skin permeation and reduce irritation, narrow size distribution, better bioavailability and the compatibility of the drugs [22].
Tacrolimus BCS Class II drug has solubility problems and having poor bioavailability being insoluble in aqueous media as well as most of the commonly used vehicle (or) carrier excipients [23]. Tacrolimus is an immunosuppressant of macrolides with the same mechanism of action as cyclosporine [24]. However, the relative molecular weight of Tacrolimus is smaller, which allows it to penetrate the skin more easily [25]. Tacrolimus was incorporated into an ointment to treat skin diseases. It acted primarily on T cells in affected skin; blocking T cell activation by inhibiting the activity of the enzyme calcineurin [26].Tacrolimus could affect other immune cells, such as mast cells, eosinophils and basophils, by preventing cytokine production and release in from these cells [27]. Tacrolimus does not have corticosteroids-like side effects, which is significant; its formulation is considered to be safe. Even so, the currently available commercial tacrolimus ointment is not ideal, which has attracted public attention to the issues of latent systemic exposure and the safety of long-term usage about which the carcinogenic potential of tacrolimus 0.1% ointment was once reported [28].
In this study, Tacrolimus-NLCs were prepared by a solidification method emulsification and low temperature is used [29].The influence of experimental factors on entrapment efficiency and particle size was investigated to optimize the formulation [30].Therefore; it is required to improve the bioavailability of the drug by alternate approach. Hence, in the current research work, different nanoparticles were prepared by using various polymers (polymeric nanoparticles) and phospholipids (Nano Lipid carriers system) and a comparative study was conducted for testing the effect of polymeric/lipid nanocarrier type on skin permeation[31].The developed NLCs were characterized for appearance, morphology, particle size, entrapment efficiency, zeta potential and *in vitro* release [32]. Tacrolimus- NLCs were then incorporated in a carbopol hydro gel to study the skin penetration (*in vitro)* using Franz diffusion cells [33].
MATERIALS AND METHODS

Materials: Tacrolimus was obtained as a kind gift sample from Yarrowchem products Pvt. Ltd, Mumbai Stearic acid and oleic acid was obtained from Carbanio Chemicals, Pvt. Ltd, Mumbai. Tween 80, Poloxamer 188 and Mannitol were obtained from Carbanio chemicals Pvt. Ltd, Mumbai. All other polymers used were of a Yarrowchem products (Narsee Monjee Institute of Management Studies (NMIMS) Navy Mumbai) l grade.

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Method of Preparation of Tacrolimus-NLCs gel: The NLCs are prepared by using hot homogenization technique. Solid lipid is a Stearic acid is used; liquid lipid is a oleic acid is used, as and Poloxamer a co-surfactant / emulsifier.[9] the lipid oleic acid was melted at 10-15^{0}C above the melting point, the drug (0.5 mg) and Poloxamer was dispersed in the lipid is melted and the dispersion was kept at temperature is same. Preparation of An aqueous phase was by dissolving Tween 80 (1.4%w/w of total weight of SLN particles dispersion) as a surfactant/ stabilizer was dissolved in double distilled water and heated to temperature is same as that of melted lipid phase. The pre-heated aqueous phase was added to melted lipid phase and homogenized by hot high pressure homogenizer (12,000 psi Niro, Soavi,2017).[10] The formulation was cooled down in an ice bath and diluted with deionised water up to 100 ml. The prepared dispersion was lyophilized by using lyophilizer (Lark penguin classic plus) to obtain the off white cake of the drug which has the enhanced solubility and stability. Mannitol (5% w/v) was added as cryoprotectant.[11]

Preparation of Tacrolimus-NLC nanogel: The Tacrolimus gels were prepared by dispersing 0.5% w/w Carbopol 974P in the NLC formulation and subsequently neutralizing the carbopol dispersion using Triethanolamine. The final concentration of drug Tacrolimus in the gels is maintained as 0.5% w/w and named as Tacrolimus-NLC GEL.[12] the composition of Tacrolimus loaded NLCs based nanogel is showed in the table 1.

Table 1: The composition of Tacrolimus -NLC nanogel

Ingredients	Tacrolimus -NLC-1	TacrolimusNLC-2	Tacrolimus-NLC-3
Tacrolimus (Drug)(%w/w)	0.5	0.5	0.5
Carbopol 974P (%w/w)	0.50	0.75	1
Propylene glycol (%w/w)	5	5	5
Triethanolamine(ml)	0.8	0.8	0.8
Methyl paraben	0.05	0.05	0.05
oleic acid	1	0.75	0.50
Poloxamer 188	0.5	0.5	0.5
Tween 80	0.25	0.50	0.75
Stearic acid	0.1	0.2	0.3
Mannitol	1	1	1
Water (ml)	Q.s	Q.s	Q.s

Characterization of Tacrolimus NLCs particles size and zeta potential: The Determination particle size is important parameter in quality assurance& process control its involving mainly physical stability and dispersion of vesicle depends on particle size [(39)]. Zeta potential is very useful parameter for the assessment of the colloidal dispersions mainly physical stability of gels. Dyanamic light scattering (ZetaSizer Nano-ZS: Malvern Instruments Ltd, United Kingdom) was used to measure the partilcle size, polydispersity index and zeta potential of the NLCs [(27)]. NLCs were double distilled water suspended in for sample preparation for the test [(40)].

Differential Scanning Calorimetry (DSC): The crystallintity rate is depends on using DSC is estimated of melting enthalpy/g by comparison of the of the bulk material with the melting enthalpy/g of the dispersion [(41)]. The DSC thermo grams of the drug estimating by using instrument (Diamond DSC, Perkin) and lyophilized SLNs was recorded at heating rate

temperature is 10°C/min from temperature 0-250°C under N_2 flow.

X-ray Diffraction Studies (XRD): XRD study of drug Tacrolimus and NLCs, Tacrolimus were carried out to detect the crystallintity changes in the drug [(42)]. XRD recorded by using patterns were (Bruker, D8) with Cu-kα radiation. The scanning angle ranged from 10° to 50° of 2θ.

(SEM): Scanning electron microscopy The Tacrolimus NLCs surface and shape characteristics of were determined by using gold sputter technique in SEM NLCs drugs were loaded with fixed on subtitling double-sided tape [(43)]. The gels containing the sample were coated with gold using JEOL fine coat (JFC-1100F ion sputtering device).

***IN VITRO* DISSOLUTION STUDIES**

Tacrolimus NLCs *In vitro* dissolution studies of were carried out by USP type XXIV rotating basket type dissolution apparatus (Electro lab, Mumbai). Tacrolimus NLCs Optimization of prepared formulation batches was measured on the basis of % drug release (cumulative percentage) with respect to time. Perform the dissolution mainly using two different media prepared by using water (distilled and phosphate buffer saline) pH 6.8 each of 900 ml. prepared Tacrolimus NLCs were placed in each vessel with prepared medium was allowed to maintain at 50 rpm at 37^0C± 0.5^0C. Samples of 5 ml at different time intervals withdrawn up to 24 hr and maintained sink condition after that absorbance of the sample was measured by a UV double beam spectrophotometer (Eli co SL 159) at 294 nm and calculates cumulative percentage drug present in Tacrolimus NLCs.

Evaluation of Tacrolimus NLCs loaded nanogel drug release *in vitro studies*: Tacrolimus –NLCs nanogel *In vitro*, drug release studies were performed using dialysis bag technique [(44)]. The experiments were conducting by using mainly under sink conditions. 0.5 g of each formulation i.e. Tacrolimus -NLCs-1, Tacrolimus -NLCs-2, Tacrolimus -NLCs-3 gel, compared with marketed formulation (Protopic gel).Tacrolimus NLCs was loaded into a dialysis bag (molecular weight is 13-14 kg) dipped in to the 100 ml of 6.8 (pH) phosphate buffer solution magnetically stirred at tem 32^0c and pH is 6.8. Samples (5ml) were taken at predetermined intervals of 0 minus, 30 min, 45min, 2, 4, 6, 8, 10, 12 hrs from the NLCs solution, and replaced with equal volumes of fresh buffer solution and after that samples are tested spectrophotometrically calculated for drug concentration at λ_{max} 294 nm. The calculated cumulative drug release in nanogel.

After that triplicate drug release studies were performed by using A graph of % cumulative release at different time (in hrs) intervals and calculate the kinetics of drug release from the nanogel, described in mathematical models such as first order, zero-order, and Higuchi were used.

Skin irritation study: study was followed by procedures mainly involving for the SOP (standard operating procedures) at Preclinical Research & Development Organization and the Committee for the Purpose of Control and Supervision of Experimental guidelines set by the (Reg. No. No. 1736/CO/Re/S/14/CPCSEA dated 27/04/2018Vikas pharmacy College 8y) Vissannapeta, Krishna, India CPCSEA, Institutional Animal Ethics Committee approval of (IAEC).

The irritation potential ofTacrolimus-NLC NG1 was (0.5%w/w) mainly evaluated by the Draize patch test on rat (Westar rat) both male and female rat with age of 9-10 weeks carrying rats selected for the test. Three groups Animals were divided into as Group 1: No application (Control); Group 2: Tacrolimus-NLC (0.5% w/w); Group 3: Market Tacrolimus gel. Rat hair was removed from the around trunk between flank and shoulders exposing an area equivalent to approximately 10% of the total body surface. An amount of 0.5 w/w of the formulation was applied to the hair-free skin of rats by uniform spreading within hair free exposed area. The skin was observed for any visible change such as Erythema (redness) at 24, 48 and 72 hrs after the application of the formulations. The mean scores were recorded (ranging from 0 to 4) Erythema depending on the degree of Erythema i.e., No Erythema = 0, slight Erythema (barely perceptible – light pink) = 1,

moderate Erythema (dark pink) = 2, moderate to severe Erythema (light red) = 3, severe Erythema (extreme redness) = 4.

Anti-inflammatory activity: To perform the *in vivo* studies, approval is taken from (Reg. No. 1736/CO/Re/S/14/CPCSEA dated 27/04/2018Vikas pharmacy College 8y) Vissannapeta, Krishna, India CPCSEA, after approval of Institutional Animal Ethics Committee (IAEC) [45].nd their guidelines must follow in the complete study. For that carrageen an- induced hind paw edema, the method should be used which is developed by Western rat. Three groups of animals were taken, in each group, 3 animals were included. Young male Wistar of 180-250 gm weight was taken for study. These polypropylene used for housed in cages animals using, with free standard diet feed and water is provide under standard laboratory conditions of temperature; 23±2^{0}C with relative humidity[46]: 53±5%.

1% homogeneous suspension of carrageen an in saline used for induced in the Paw edema was by injecting 0.9 ml of suspension [47]. A total of three group, that is group 1 treated with carrageen an only which is as a control group, group 2 is treated with carrageen a topically applied Tacrolimus-NLC based nanogel and Group 3 any marketed formulation taken as standard[46]. The volume of the paw is measured with a digital plethysmometer [48].

Edema rate can be calculated by formula,

Edema Rate (E) = V_t -Vo / Vo

RESULTS AND DISCUSSION

Zeta potential &Particle size: Zeta potential of the optimized Tacrolimus -NLC-1is found 14.7 which showed the greater stability of the drug. The optimized NLCs were in the nanometric size range (161.2 nm) with having low polydispersity index 0.234(Fig.1 &2).Surfactant greatly influences by the particle size of formulation by causing increasing stabilization. The size of \nano particles may be the reason of drug having enhanced solubility.

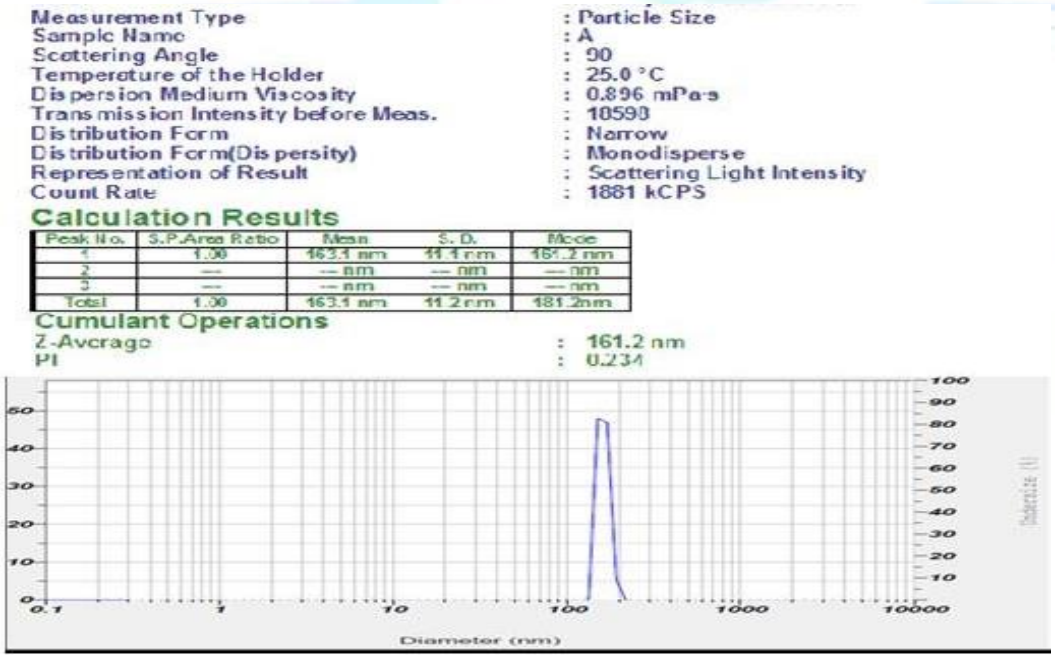
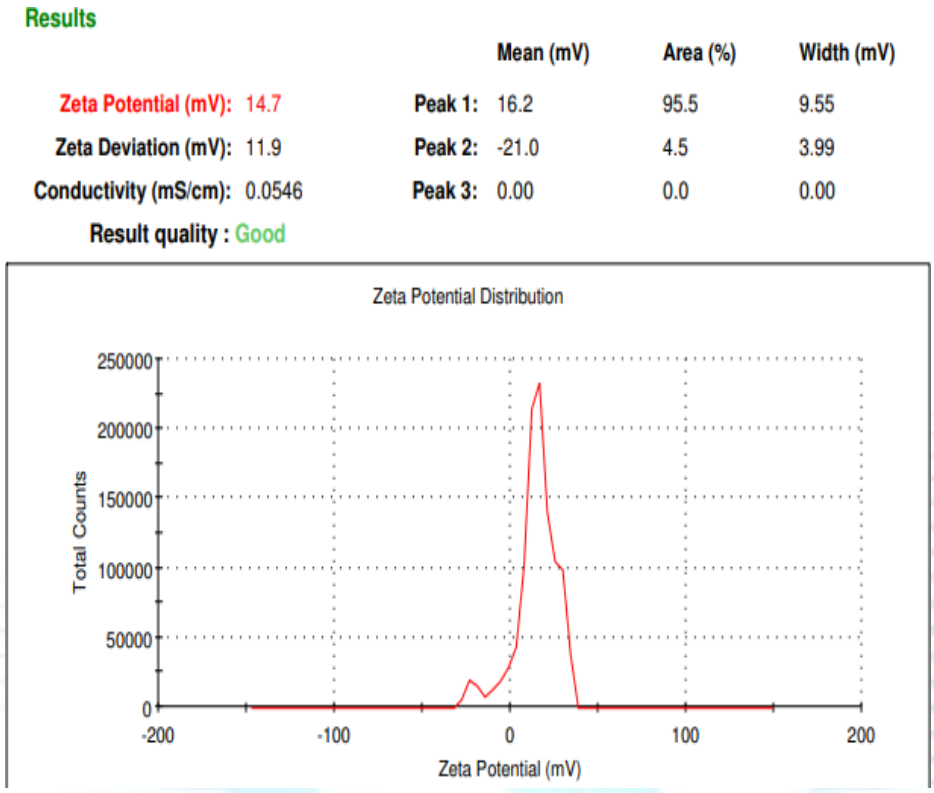


Figure 1: Particle size of the NLC.

Figure 2: Zeta potential of the optimized FK506 -NLC-1



DSC study: information usually is Differential Scanning Calorimetry employed for the about both the chemical & physical and the properties of formulated compounds. DSC Measurement mainly loss on heat or gain of heat it result of changes within physical or chemical as a function of the temperature. Curve of Differential Scanning Calorimetry pure drug showed peak at 196.54^{0}C mainly involving to the melting point of the drug. Graph of DSC is optimized formulation Tacrolimus-NLC-1 peaks showed two sharp peak at 163.54^{0}C endothermic of drug in the formulation of nanogel. And another one of melting endothermic peak of drug at 274.31^{0}C with the disappearance (**Fig 3**), indicating drug was encapsulated into the lipid with amorphous state. Peak was seen A shift in the (**Fig. 3**) this effect is produced due to the chemical interaction of the matrix containing lipids present in the drug

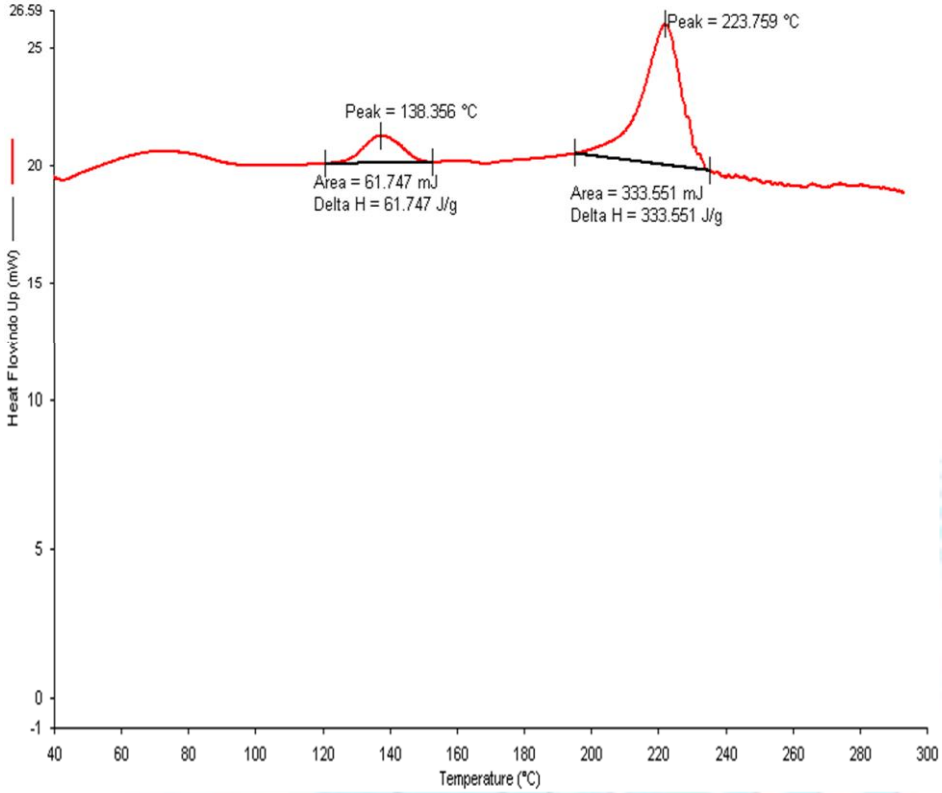


Figure.3: DSC Thermogam of drug and optimized NLC

XRD study: The powder of Tacrolimus was high crystalline nature it gave peaks at the 2θ value is sharp at the scan of X-ray (**Fig. 4**). XRD is also shows the patterns of Tacrolimus loaded NLC freeze-dried showing that peak intensity and reduced reduction in crystallintity of NLCs Formulation. The absence of these peaks indicating optimized NLCs the drug total stability depend upon of the phase of lipid matrix by demonstration of NLCs formulation.

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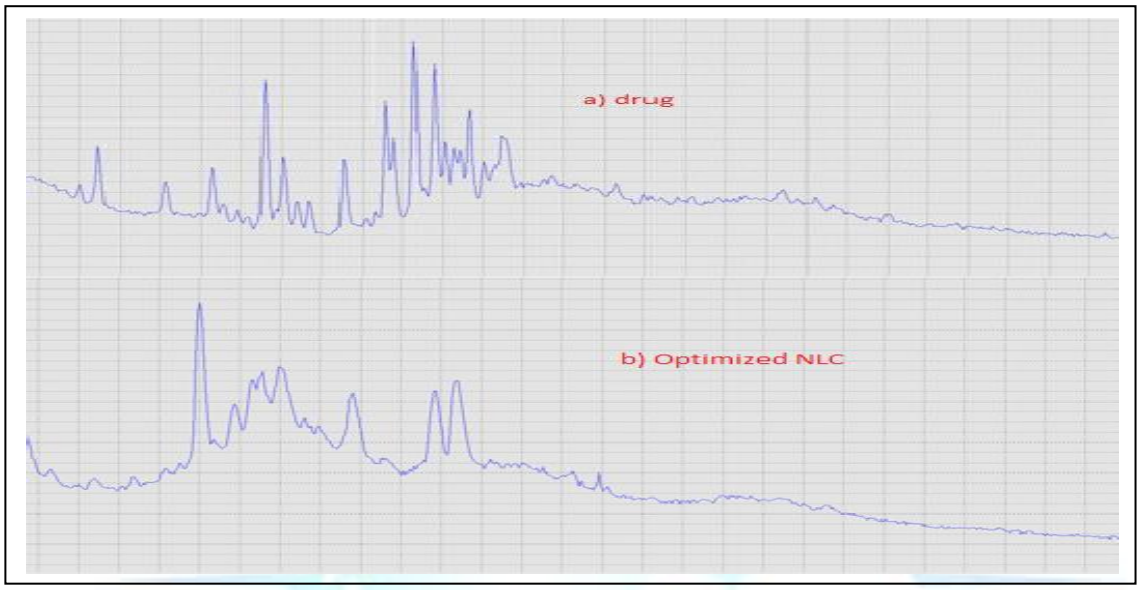
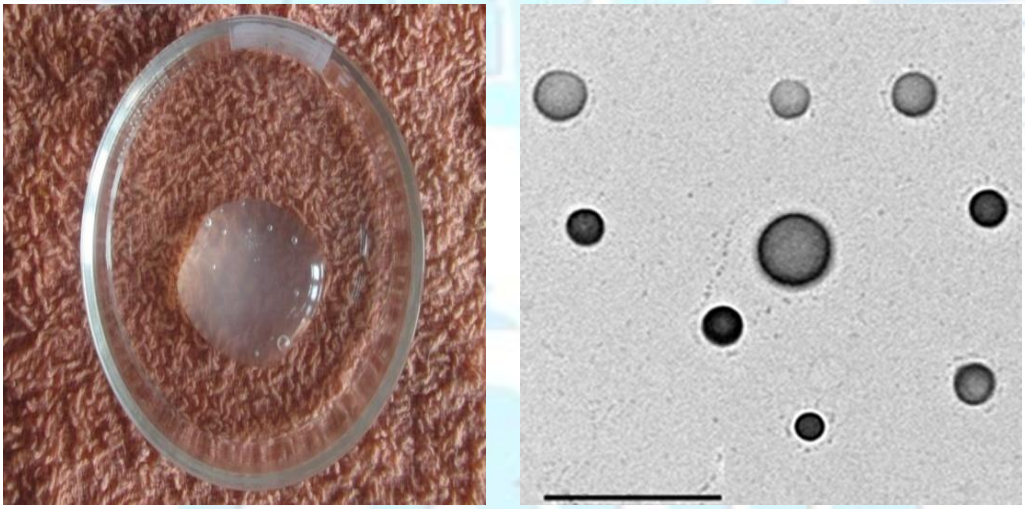


Figure 4: XRD study of the drug (a) and optimized NLC (b).

SEM (**Scanning electron microscopy):** The images of SEM optimized NLC are shown in **figure 5**. It showed the particles having circular shapes. Which is indicating the drug encapsulation into the lipid matrix into the circular manner.



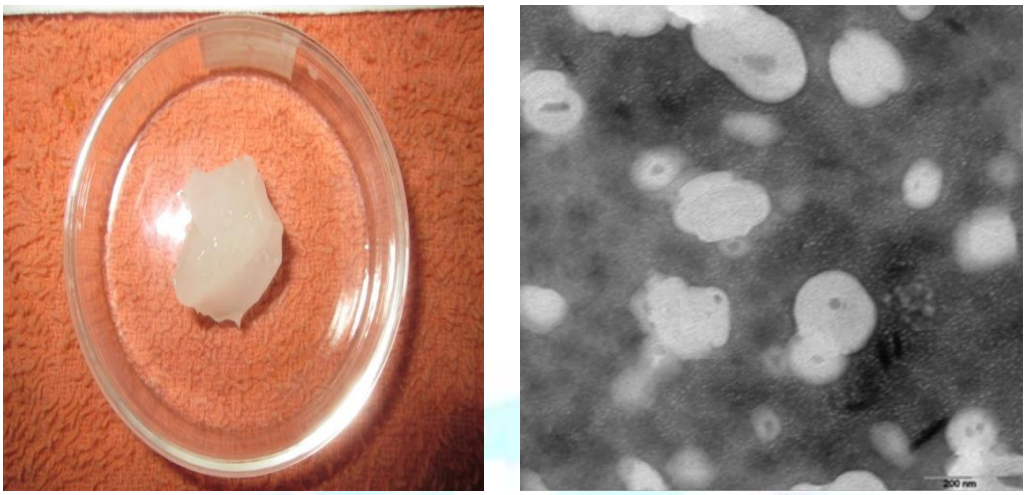


Figure 5 TEM images of prepare Tacrolimus gel transmission electron microscopy (circular shapes of the particles encapsulation of the drug into the lipid matrix into the circular manner).

Study ofTacrolimus-NLC Gel drug release by using dialysis bag diffusion membrane: studies of tacrolimus drug release diffusion results showed that 58.81±0.47% of the released drug within 8 hrs from the prepared Tacrolimus NLCs formulations. 0.50g of drug it was greater than different NLCs gel formulation (Tacrolimus -NLC-1) (Fig 6). Hence, Tacrolimus-NLC-1 Gel was optimized for the further evaluations. While comparing with marketed gel the Tacrolimus -NLC-1 gel showed greater and faster drug release (34.46±0.32%). The release data from FK506 -NLC-1 gel were tested for the \various models using for measurement of The r^2 value was found to be (r^2=0.927) model in Higuchi. Highest value indicated that the test formulation followed release kinetics based matrix diffusion method

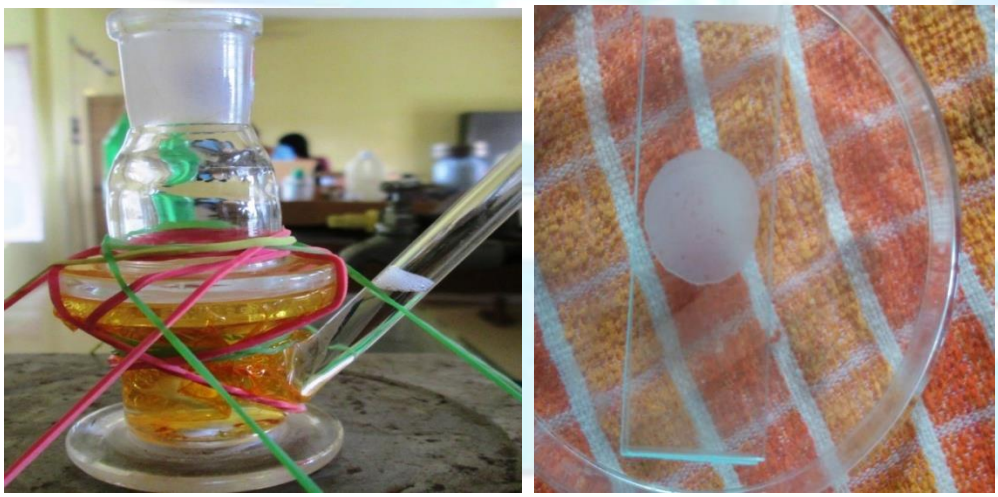


Figure 6: Diffusion study FK506 of drug and optimized NLC & spread ability of optimized NLC

TABLE 2: TACROLIMUS NLCS NANO GEL % DRUG RELEASE AND MARKETED GEL.

Time (hr)	FK506-NLC-1 CR)	(%FK506 NLC1 (% CR)	FK506 -NLC-3 (% CR)	Protopic gel (% CR) (Marketed gel)
0.5	0.97±0.01	0.94±0.05	1±0.05	0.92±0.05
1	3.57±0.27	1.99±0.20	2.22±0.50	2.33±0.18
2	7.71±0.55	4.81±0.031	5.20±0.80	4.95±0.85

3	13.36±0.24	8.91±0.42	9.43±0.85	7.77±0.50
4	20.40±1.29	14.56±0.78	15.33±0.75	11.37±1.60
5	28.90±1.05	21.80±0.37	22.65±0.40	15.81±0.35
6	38.80±2.02	31.86±0.95	31.25±0.20	20.65±0.30
7	49.10±2.20	43.20±0.17	41.30±0.95	26.10±0.15
8	61.11±0.28	55.60±0.22	52.45±0.05	31.95±0.10

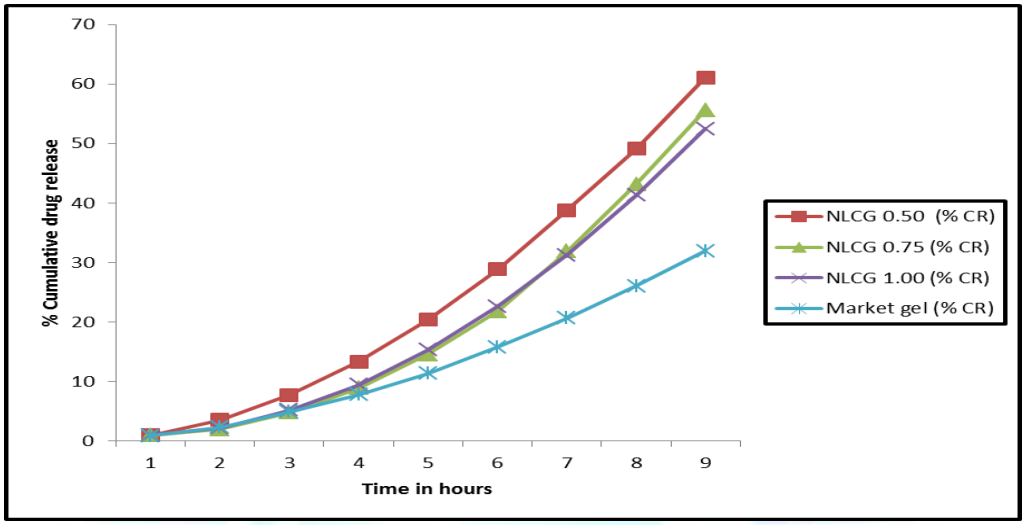


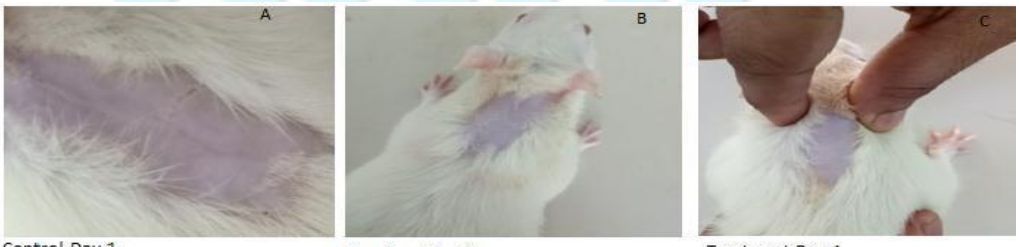
Figure 7: *In vitro* drug release of FK506 -NLCs-1, 2, 3 NLC gels and Marketed gel.

Skin irritation study: No abnormal changes were observed in clinical signs and no skin reaction for formation of Erythema and oedma were seen in any animal from control, marketed or treatment group animals. Based on the present study, it showed that NLC1-gel sample when applied daily to Westar rats dermal for a period of 3 days, was well tolerated with no evidence of irritation potential in rats.

Table 3: Skin irritation index Primary values at the end of 24, 48 and 72 hrs

Formulation	score of skin Irritation test		
	Time of skin application		
	24 hr	48 hr	72 hr
CONTROL	A	A	A
MARKETED GEL	A	A	A
FK506-NLC GEL	A	A	A

No reaction-A, Slight Erythema- B, Moderate Erythema-C, Severe Erythema-D



Control-Day 1
Normal skin of the animal

Standard-Day 1
Normal skin of the animal
No sign of irritation seen

Treatment-Day 1
Normal skin of the animal
No sign of irritation seen

Figure 9: Photographs of skin irritation study carried out on Westar rat, [A] Control (no application) [B] Marketed gel Tacrolimus NLCs

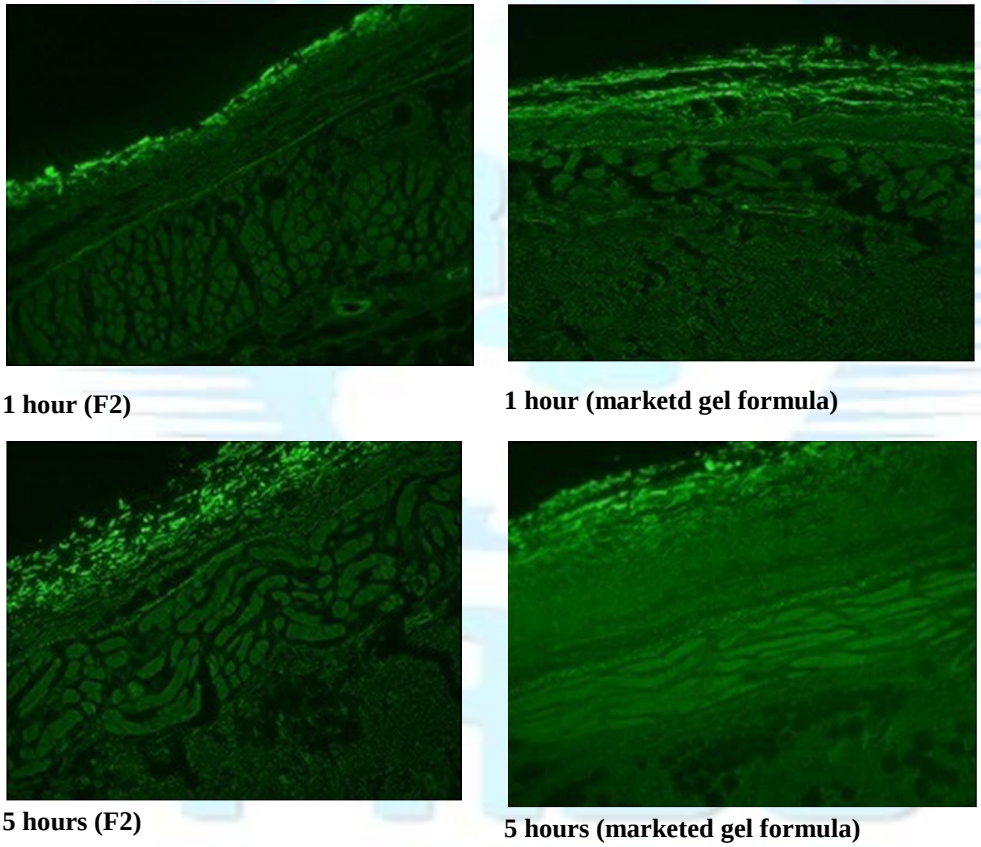


Figure 10: Fluorescence microscope images for rat skin layers for rhodamine florescence labeled transdermal delivery of FK506 gel formula (F2) and Marketed gel formula (magnification 400×).

***In vivo* study of anti-inflammatory:** *In vivo study of* anti-inflammatory activity of the Tacrolimus by using carrageen edema method by using an-induced rat paw. From the result, it showed that FK506 has an anti-inflammatory activity.[39] the activity of FK506 was enhanced due to the increased permeation through the skin due to the nanometer size range**.**

Table 4: Effect of Tacrolimus-NLC (0.5%w/w) edema on paw induced by carrageen in rats.

Treatment	Dose	Inflammation volume in ml					
		30 min	60 mints	120 mints	180 mints	240 mints	300 mints
Positive control	Carrageenan 1 % (0.1 ml)	0.26	0.39	0.70	0.81	0.73	0.66
FG506-NLC Nanogel		0.25	0.34	0.61	0.59	0.57	0.60
Standard gel(0.1)		0.22	0.25	0.34	0.36	0.35	0.32

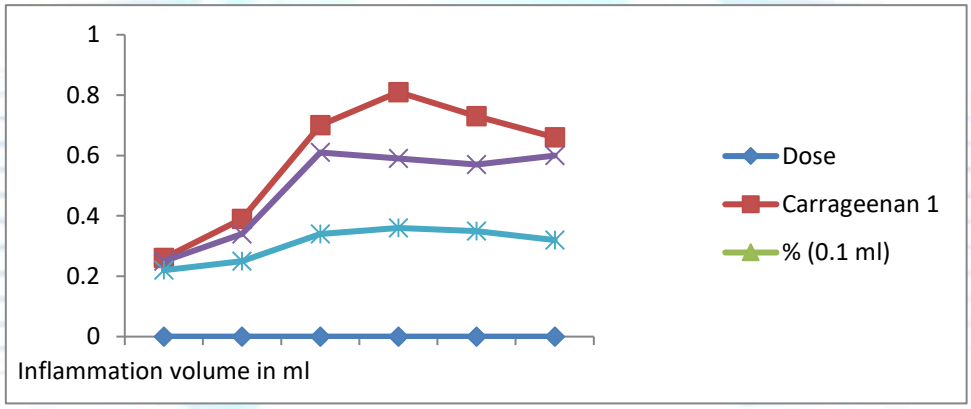


Figure 10: Inhibition of edema due to Tacrolimus-NLC nano gel.

CONCLUSIONS

In the present study, NLCs formulation loaded with tacrolimus was prepared by modified emulsification and low-temperature solidification method. The prepared NLCs were exhibited high entrapment efficiency with nanogel release of the drug up to 48 hr. The formulation showed improved drug loading capacity and a good ability to reduce the drug expulsion on storage. For an optimized batch of tacrolimus-NLC particle size was found to be 123.8 nm. The entrapment efficiency and zeta potential was found to be 91.3±12%, and-31.1 mV respectively. The percent (%) cumulative release of optimized batch tacrolimus NLC-1 was found to be 8.34 % and 61.11±0.28% at 1 h and 48 h, respectively. Further, DSC and XRD studies confirmed the nanogel of the drug into amorphous which is essential in the enhancement of the absorption rate followed by bioavailability. SEM study confirmed a nano-sized discrete spherical shape with a smooth surface area. Optimized formulation at room condition showed extremely stable for one month that supports the fact that dried lyophilized nano-carriers may remain stable for a longer period. It was concluded that the development of NLCs formulation could potentially exploit as a carrier with improved drug loading capacity and drug release properties. Thus, tacrolimus loaded NLCs formulation can be beneficial in the treatment of psoriasis.

Acknowledgement: We would like to thank Yarrowchem chemicals, Bangalore, for providing the gift sample of Tacrolimus. We are also thankful to the Principal, College of Pharmaceutical Sciences, for providing facilities to carryout spectral analysis and differential scanning calorimeter studies in Acharya Nagarjuna University, Guntur.

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