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Development of nano structured lipid carrier based hydrogel for the treatment of psoriasis

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ABSTRACT

The present work aimed to develop Nanostructured Lipid Carrier Based Hydrogel for the treatment of psoriasis, delivered as a topical application on to the skin. Nanostructured Lipid carrier based Hydrogel loaded with methotrexate is a new technique for topical administration for psoriasis. Methotrexate loaded NLC's were prepared by a hot homogenization method using high-pressure homogenizer. Stearic acid and oleic acid were selected as the solid lipid and liquid lipid, respectively. Tween 80 used as a surfactant. The developed lipid formulations were incorporated in 1% Carbopol 934 gel medium to maintain the topical application consistency. Fourier-Transform Infrared Spectroscopy was employed to identify their functional groups. The particle size, zeta potential, polydispersity index for the MTX-NLC were found to be 239.12±3.65nm, -24.61mV and 0.245 to 0.517. Scanning electronic microscopy studies will reveal the surface morphology of the nanoparticles. The pH of the drug-loaded formulation was in the range of 4.93 to 5.83. Spreadability was in the range of 3.01±0.59cm to 8.13±0.34cm. Viscosity at 25±2°C was 67325 cps. In vitro studies suggest that initial release rate was observed within first 4 hrs and amount of drug release was 35 to 47± 3.61%, fast and sustained release rate reached by 24th hr and release rate of the drug was 72%. The stability studies reported that the formulation was stable for 30 days after the incorporation of the drug, and there was no drug degradation or decomposition and no change in physical appearance. Hence, results indicate the sustain release activity of MTX-NLC Hydrogels, which could help in preventing the cell division and proliferation of cell acting as a major barrier in the topical application of psoriasis.

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INTRODUCTION

Psoriasis is a proliferative disorder of the skin with repeating events of hyperkeratosis and inflammation with the worldwide manifestation around 2-5% (Mabuchi *et al.*, 2012; Tsuruta, 2009; Krueger and Bowcock, 2005). It is characterized by periodic recycling of red and sharp scaly skin plaques. Psoriasis is classified into chronic, plaque, guttate, pustular and erythroderma. Among all the above types, plaque psoriasis is the major one (Galimova *et al.*, 2008; Campalani and Barker, 2005).

The aetiology of this disease is multi-factorial that is the union of both environmental, as well as a genetic factor triggering the immune histological changes noticed in the skin (Kelly *et al.*, 2015). However, the cause of psoriasis is still unknown. In recent days, patients suffering from psoriasis shall often express their feeling of consciousness, anger, helplessness, embarrassment, and frustration (Armstrong *et al.*, 2012) which eventually is followed by low confidence, the absence of self-assurance, poor self-visualize and tremendous little feeling of prosperity (Kimball *et al.*, 2010) Psoriasis is associated with diseases like diabetes, cardiovascular diseases, hypertension, and hypercholesterolemia (Azfar *et al.*, 2012; Wu *et al.*, 2008).

Nanostructured Lipid carriers are the lipid nanoparticle, which is using very frequently these days to incorporate and to deliver lipophilic drugs (Kumar and Randhawa, 2013).NLC is the 2^{nd} generation of solid lipid Nanoparticles. Lipid Nanoparticles consists of lipids and surfactants, and they mentioned as generally regarded as safe (GRAS). Lipids used in NLC's are low toxic & biodegradable lipids, which exhibit in the nanosize large surface area having very close contact to the stratum corneum, which increases the more penetration of the drug into the skin (Xia *et al.*, 2007). NLC's are having more advantages than SLN like easy to scale up, low production cost, low toxicity. NLC'sare having more drug loading capacity and during the storage, it has very less drug expulsion than SLN (Fang *et al.*, 2013).

Methotrexate is an anti-metabolite; it acts as a folic acid antagonist, which is widely used to treat psoriasis (Nast *et al.*, 2015). Methotrexate can selectively work on the proliferation of cells, preventing cell division and proliferation of immune mother cells. Methotrexate with a suitable vehicle will produce a direct effect on the epidermis, which is useful for topical psoriasis. Penetration of methotrexate can be enhanced by chemical enhancer, which gives effective local inhibition of epidermal DNA synthesis (Shalom *et al.*, 2015). This becomes an essential tool in reducing the systemic irritation and reduces the irritation produced by the drug, and there is a lack of research regarding the topical application of methotrexate in preventing the cell division and proliferation of cells, which acts as major barriers in treating psoriasis. The active site of topical methotrexate is stratum spinosum and stratum germinativum, hence topical administration of methotrexate would be advantageous for patients to avoid its side effects.

Here in current research work focuses on delivering methotrexate by the colloidal carrier, i.e. Nanostructure lipid carriers in the form of hydrogel to overcome the above, mentioned barriers in the treatment of psoriasis.

MATERIALS AND METHODS

Methotrexate was purchased from Strides Arcolab's Ltd. Bangalore, India. Stearic acid, Polysorbate 80/ Tween 80, was purchased from Loba Chemie Pvt. Ltd. Mumbai, India. UV-Visible spectrophotometer was purchased from Shimadzu-1800, Japan, FT-IR spectrophotometer was purchased from Shimadzu-8400 S, Japan, Differential Scanning Calorimeter (DSC) was purchased from Shimadzu DSC-60, Japan.

Characterization of the pure active ingredient

UV visible (Ultraviolet- visible) spectrophotometer

l_{max} of the drug was conducted in phosphate buffer.

Fourier-Transform Infrared Spectroscopy (FTIR)

FT-IR range of the spectrum of active ingredient were utilizing FT-IR spectrophotometer Shimadzu 8400S (Tokyo, Japan) by KBR pellet method. In the range of 4000 to 400 cm^{-1}, the spectrum was recorded.

Differential Scanning Calorimetry

These studies were carried out utilizing Shimadzu DSC-60. The samples are closed in an airtight container and heat of a temperature range from 40 to 300^{o}C at a rate of 20^o C/min. At the flow rate of 40mL/min, nitrogen flow will be supplied to the inert atmosphere.

Compatibility studies

FT-IR and DSC will be employed to know the chemical compatibility between the drug and excipients.

FT-IR analysis

FT-IR analysis is used to determine the compatibility between the drug and total lipids, physical mixture and for the pure drug. A Physical combination of a lipid with or without the drug is mixed in the ratio of (1:4) along with (KBr) anhydrous potassium bromide. 0.1g of the mixture is mixed properly by using pestle and mortar with the help of KBr press a pellet shall undergo 15 tons of pressure which leads in the formation of compressed transparent KBr pellet. Individually anhydrous potassium bromide pellets will undergo scanning over a wavelength ranging from 400cm^{-1} to 4000. To examine any change in the shift, disappearance or appearance of the peak, the compatibility test will be investigated by measuring the IR spectra of the API, Physical mixture, and lipid.

DSC analysis

Differential Scanning Calorimeter performs a thermal study. DSC will be employed to confirm the thermal compatibility behaviour between pure drug, physical mixture and lipids. Around 5mg of the sample was exactly weighed and taken a well-closed airtight container and sealed with crimped and aluminium pans. Samples will be heated from 0^oC to 350^oC at a rate of 10^oC/min. Nitrogen will be purged without any interruption at a flow rate of 40ml/min.

NLC Formulation

Hot homogenization technique, along with high-pressure homogenizer, was employed to develop Nanostructured Lipid Carrier's. The molten lipid phase was prepared by mixing the lipids, (solid lipid + liquid lipid) it was heated at 5^oC more than the melting point of their solid lipid and liquid lipid. The aqueous phase was prepared by taking the surfactants and co-surfactants in the respective ratio, and the mixture was heated to 70^oC with constant stirring to dissolve the surfactant completely. The molten lipid phase consists of lipids were added to the aqueous phase slowly. This combined mixture was immediately homogenized at 10,000rpm for 20mins. Subsequently, obtained dispersion is followed by ultrasonication for 10 mins to decrease the size of the particle to Nano-size. The formulations are cooled at normal temp and placed in light resistance well-closed container at 5^oC. The obtained dispersion was centrifuged using filtration tubes at 4000rpm for 40mins at 25^o C, and then the nanoparticles were washed with distilled water repeatedly, frozen about -20^oC and samples were lyophilized for 48h.

Characterization and Evaluation of NLC's

Particle size and Zeta potential analysis

The particle size, Polydispersity index (PDI) and zeta potential was determined by using particle size analyser (i.e. Zeta sizer). To determine the particle size, the obtained NLC's was diluted with distilled water.

Determination of entrapment efficiency (EE)

The amount of the drug entrapped in Nano structured lipid Carrier formulation was investigated by centrifugation at 10,000 rpm, which leads in splitting the solid lipid and free drug. The developed nanostructured lipid carriers were added to the volumetric tube-containing methanol + water in the ratio of (1:1) and heating the solid lipid to their individually melting point and for 20 mins centrifuged at 10,000 rpm. With the help of UV-spectrophotometer, drug content will be investigated after the sample is being diluted.

Scanning Electronic microscope (SEM)

Scanning electron microscope was employed to investigate the surface morphology of the prepared NLCs. It is performed at 5 kV having different magnifications using Hitachi Noran system 7 manufactured by Thermo Fisher Scientific.

Preparation of NLC based Hydrogel

The hydrogel was prepared using a different concentration of poly (acrylic acid). The desired amount of poly acrylic acid was dispersed in water, and 5% of glycerol was added as a hydrating agent. The mixture was resulted for stirring for 10mins at 1000 rpm. Freshly prepared MTX-NLC's were incorporated in polyacrylic acid hydrogels using stirrer for 1000 rpm for 3mins to obtain the MTX-NLC based Hydrogel.

Characterization and evaluation studies of NLC based Hydrogel

Determination of pH

The measurement of accurate pH was done by using probe pH meter. Value is recognized by a meter after submerging the probe into the liquid.

Spread ability test

This test is performed using a parallel plate method. 0.1g of the gel is placed within a circle of 1cm premarked diameter on a glass plate, over which second glass plate was placed. On the upper side of the glass plate, a 200g of the sample will be kept for 5mins. The diameter will be increased based on the spreadability of the gel, and finally, the value is noted.

Viscosity studies

Viscosity of hydrogel was analyzed using a Brookfield Rheocalc Rheometer (Brookfield, USA) model with spindle using cone and plate geometry.

Drug content

Drug content was performed by taking 1ml of MTX-NLCs hydrogel from pH 7.4-phosphate buffer, further diluted to 100ml. It was investigated by UV spectrophotometer.

***In vitro* Drug diffusion study**

In vitro study release is determined by Franz-diffusion method. Here Release medium is selected as a 0.1M of Phosphate buffer saline, (Acceptor medium). 1gm of the sample will be placed on a cellulose nitrate membrane, which shall act as a diffusing barrier (Donor compartment). The assembly is water jacketed to maintain 32 ± 0.5^oC. Samples were ejected at different intervals of time for a period of 48 h and were detected using the UV spectrophotometer.

Stability studies

The hydrogel was filled in glassware and incubated at temperature 25±2°C/60±5% RH for 30 days. The initial formulation of these studies examined for visually appearance colour and Phase separation (Guideline 2003).

RESULTS AND DISCUSSION

Characterization of the pure active ingredient

UV visible (Ultraviolet- visible) spectrophotometer

Wavelength of absorbance maximum (λ_{max}) of methotrexate in phosphate buffer is depicted in Table 1 & Figure 1.

Table 1: Absorption maxima (λ_{max}) of Methotrexate

Solvent	Observed (nm)	Reported (nm)
Phosphate buffer pH 7.4	302.85	302

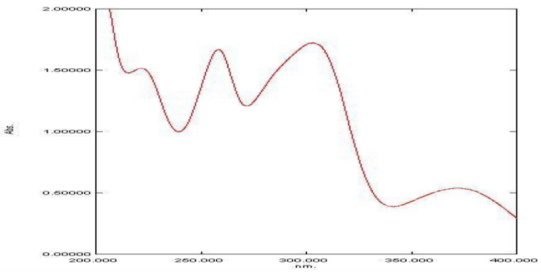

Figure 1: UV spectrum of Methotrexate

The Calibration curve graph of methotrexate was made in 7.4 pH, which is depicted in Table 2 & Figure 2. Coefficient regression is 0.9988 along a value of slope 0.0697 & value of Y-interception 0.0069. It indicates a straight line relationship between absorbance and concentration.

Table 2: Absorbance maxima at diff Conc of MTX in 7.4 pH buffer

Sl.no	Conc of MTX (μg/ml)	Absorbance
1	0	0
2	2	0.145±0.031
3	4	0.293±0.012
4	6	0.431±0.052
5	8	0.561±0.019
6	10	0.698±0.041
7	12	0.821±0.061

Conc-Concentration

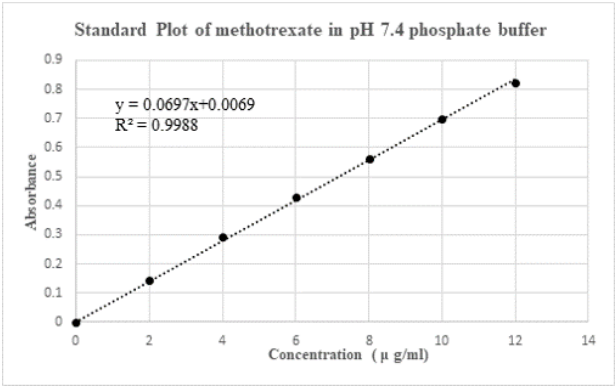

Figure 2: Calibration curve of Methotrexate

Fourier-Transform Infrared

This study indicates the pure drug which is showing the respective IR peaks along with the presence of Functional grp of MTX. (Figure 3 &Table 4)

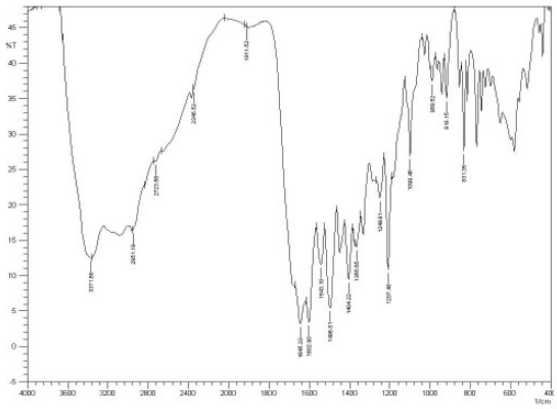

Figure 3: Calibration curve of Methotrexate

DSC study

DSC is performed for pure methotrexate represented in Figure 4. The endothermic peak appeared at 161.96°C representing the melting point of methotrexate.

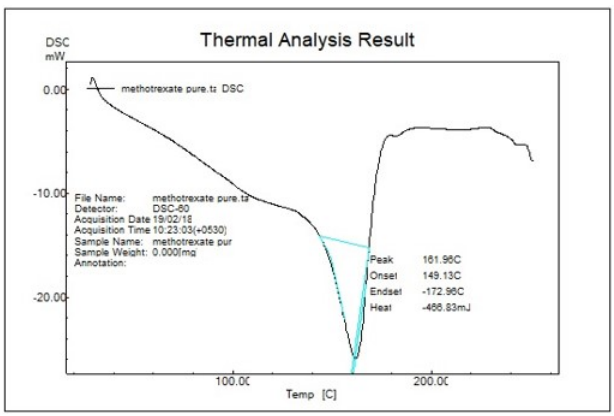

Figure 4: Thermogram of Methotrexate

Compatibility studies

FT-IR and DSC analysis are employed for investigating the API, Physical mixture and total lipids to check the compatibility between lipid and drug.

FT-IR analysis

The FT-IR of methotrexate, total lipid, the physical mixture was determined. The functional groups of pure drug, physical mixture, and total lipids were found to be correlative. FT-IR of the physical mixture and MTX, as shown in Figure 5Figure 6Figure 7 and Table 7. From the obtained result, there were no interactions between methotrexate and lipids. Hence, MTX and selected lipids were compatible with each other.

Table 3: Peaks of API, total mixture & lipids, Functional grp & corresponding peaks

Functional Groups	MTX	MTX+ total lipids
N-H stretching	3367.05	3368.21
C=O stretch	1632.75	1637.15
C-H deformation (CH3)	1438.33	1451.01
C-H deformation (aromatic)	829.11	838.91

MTX- Methotrexate

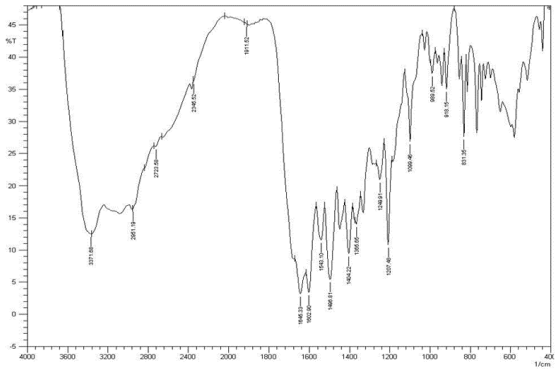

Figure 5: Methotrexate FT-IR

Differential Scanning Calorimetry

DSC graphs of methotrexate, total lipids & the physical mixture is shown in Figure 8Figure 9Figure 10. Endotherm peak of methotrexate DSC graph showed at 161.96^{o}C, and total lipid showed a single peak at 120.78^{o}C. The endothermic peak of physical mixture indicates there was no interaction between the drug and excipient. Hence, DSC analysis indicates there is no interaction between the drug and the selected lipids and physical mixture.

NLC Formulation

In the development of NLC, there are 2 major steps.

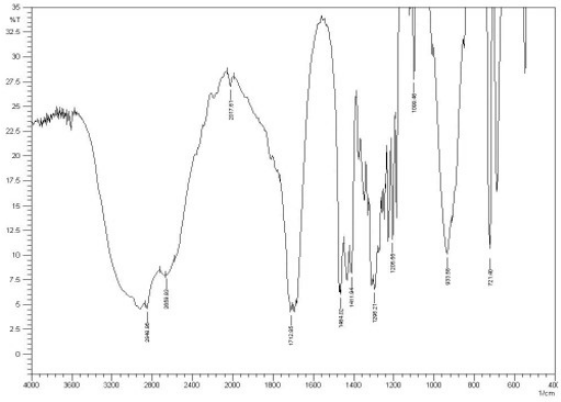

Figure 6: Total lipids FT-IR

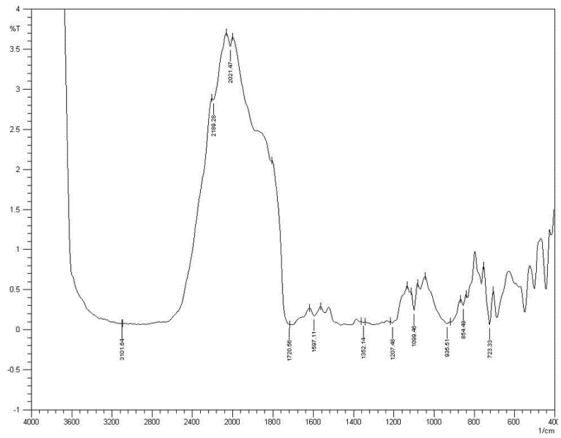

Figure 7: Physical Mixture FT-IR

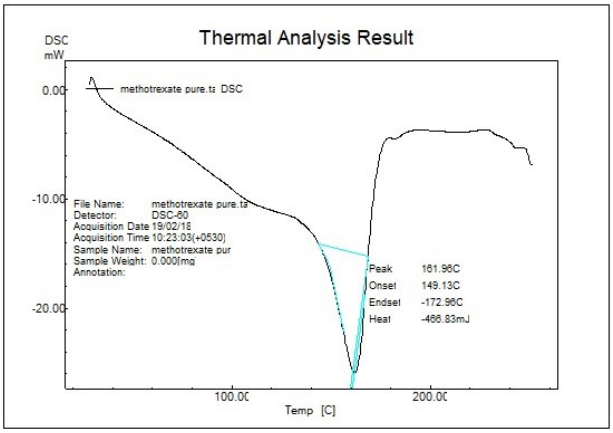

Figure 8: DSC thermograms of Methotrexate

I) Preparing the constant diffusion of API in an appropriate vehicle, II) Reducing the size. Composition of the oil phase content is stearic acid and oleic acid in the ratio 2:1 and tween 80 and PVA in the ratio of 2:1, acts as Co-surfactant and surfactant. In the preparation of nanostructured lipid carriers, the ratio of liquid lipid and solid lipid plays a very crucial role. Increase in solid lipid leads to decrease in entrapment efficiency, increase the liquid lipid facilitates in increase entrapment efficiency. In this ratio

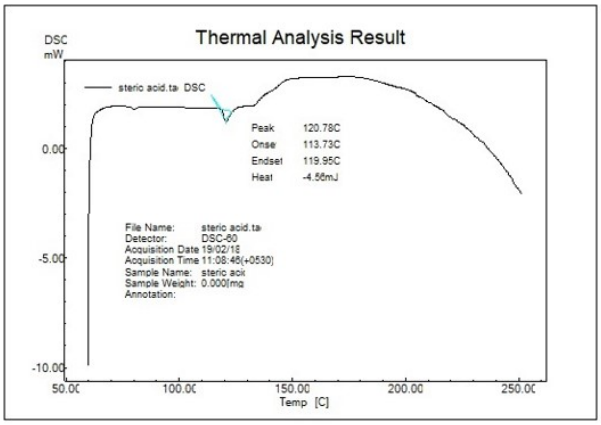

Figure 9: DSC thermograms of Total lipids

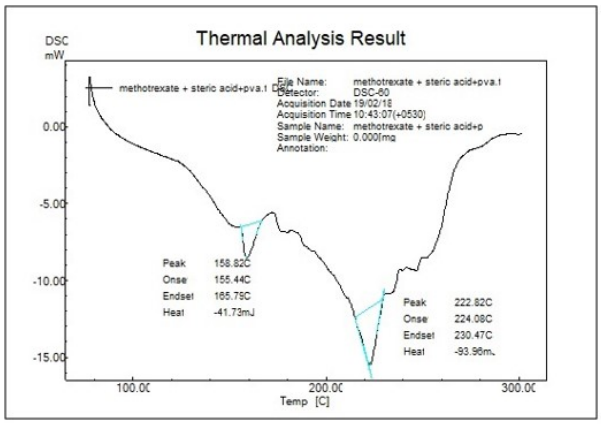

Figure 10: DSC thermograms of Physical Mixture

also impacts on prolong release profile of NLC. By taking all the facts, trial and error of experiment as well as a literature support the lipids and surfactant were selected in the given ratio.

Nanostructured lipid carriers formulation was developed by hot homogenization technique using high-pressure homogenizer. The molten lipid phase was prepared by mixing the lipids, (solid lipid + liquid lipid) it was heated at 5^{o}C more than the melting point of their solid lipid and liquid lipid. The aqueous phase was prepared by taking the surfactants and co-surfactants in the respective ratio, and the mixture was heated to 70^{o}C with constant stirring to dissolve the surfactant completely. The molten lipid phase consists of lipids were added to the aqueous phase slowly. This combined mixture was immediately homogenized at 10000 rpm for 20 mins. Subsequently, obtained dispersion shall be followed by ultrasonication around 10 minutes, to decrease the size of the particle to Nano-size.

Evaluation of NLC's

Zeta potential and Particle size analysis

In the evaluation of nanostructured lipid carriers particle size plays a very crucial factor because it will affect the amount of drug absorption & drug release. If the particle size is small, large will be the interfacial area for drug diffusion. MTX-NLC's of zeta potential and particle size of was -24.61mV and 239.12±3, 65nm. The surfactant concentration was increased to 2% the particle size was decreased. Similarly, *Liu et al,* during the preparation of isotretinoin-loaded SLNs results reported as the concentration of surfactant are increased, correspondingly the particle size also decreased. This is attributed to the concentration of lipid was increased, covers the surface of the lipid phase, which results in reducing the particle size.

PDI measures the size distribution of the nanoparticle in a sample. It results as monodispersed samples with a uniform particle size distribution will be having the PDI range between 0.1 to 0.7 and samples having broad size distribution have the PDI range >0.7. In this study, the PDI values of all MTX-NLC's formulation were ranging from 0.245 to 0.517, hence having a uniform particle size distribution. In the literature results reported as the Nano dispersion with <-60mV of zeta potential having great stability and physical stability having minimum < -30mV. All the developed MTX-NLC is showing the zeta potential value between the ranges of -21.45 to -26.61. It is observed that the concentration of the lipids and concentration of surfactants increases the particle size will decreases.

Determination of entrapment efficiency

Entrapment efficiency studies are performed to check the amount of methotrexate entrapped in NLC. Many factors, like types of lipids and concentration of surfactant, affect the entrapment efficiency of NLC's. It was seen that sufficient amount concentration of lipids increases in the entrapment efficiency. Higher the lipid concentration will prevent the escape of the drug by successfully bounding to the surfactant. This could be the main reason behind the increase in entrapment efficiency. Due to the presence of a sufficient amount concentration of surfactant, there was an increase in entrapment efficient and helps in solubilize the drug and stabilizing the entrapped drug molecule within the lipid matrix.

Scanning Electronic microscope

From the SEM photographs of MTX-NLC's samples, which is depicted in Figure 11. The MTX-NLC's is having a spherical shape and diameter of the particle was reported as good. The diameter of NLC's observed within 250nm.

Characterization and evaluation studies of NLC

Table 4: Formulation composition for the preparation of MTX-NLC

Formulation code	Drug (%w/w)	Lipids (%w/w)		Surfactant & Co-surfactant (%w/w)	
		SA	OA	Tween 80	PVA
MTX-F1	2	0.2	0.1	1.5	1
MTX-F2	2	0.28	0.15	2	1
MTX-F3	2	0.3	0.2	1.5	1
MTX-F4	2	0.38	0.25	2	1
MTX-F5	2	0.4	0.3	1.5	1
MTX-F6	2	0.48	0.35	2	1
PLACEBOMTX-F7	-	0.28	0.15	2	1

Table 5: Particle size and zeta potential of MTX-NLC's

Formulation code	Average particle size (nm)	PDI	ZP (mV)	EE %
MTX-F1	212.39±6.14	0.412	-21.45	51.36
MTX-F2	239.12±3.65	0.245	-26.61	64.63
MTX-F3	256.42±9.15	0.331	-22.36	61.19
MTX-F4	241.21±2.89	0.517	-24.12	58.64
MTX-F5	235.51±6.58	0.269	-25.96	56.87
MTX-F6	225.41±9.15	0.457	-23.98	59.37

PDI-Polydispersity index, ZP- Zetapotenital, EE-Entrapment Efficiency

Table 6: Physiochemical characteristics of MTX-NLC Hydrogel

Sl.no	Formulation Code	Carbopol 934	pH	Spreadability (cm)	Drug Content (%)
1	MTX-F2	0.5	4.93	3.01±0.59cm	96.15%±2.35
2	MTX-F2	1.0	5.43	6.61±0.43cm	98.26%±1.41
3	MTX-F2	1.5	5.83	8.13±0.34cm	97.34%±1.97

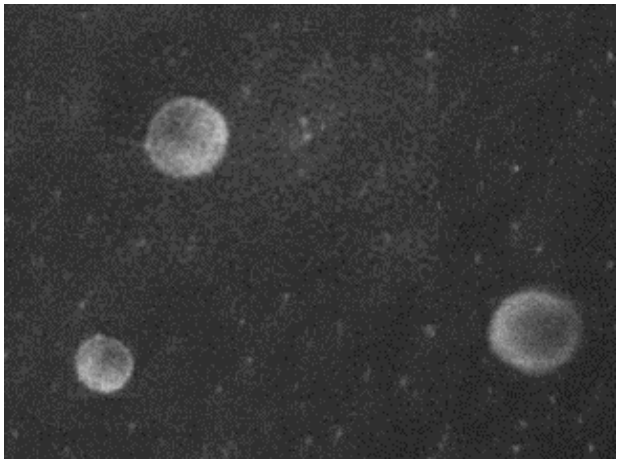

Figure 11: SEM photographs of MTX-NLC

based Hydrogel

Physiochemical characteristics of MTX-NLC Hydrogel

The Physiochemical Characteristics like pH, Spreadability, Drug content of MTX-NLC was being investigated for different concentrations of carbopol-934 like 0.5%, 1%, and 1.5% and results are reported inTable 7. According to the results, a 1% concentration of carbopol-934 was selected and incorporated in the formulation of MTX-NLC's. The pH of MTX-F2 based Hydrogel formulation was found to be 5.73±0.16 show inTable 7. The pH of MTX-F2 formulation was within the acceptable range for topical applications. Spreadability in topical formulation plays a vital role in patient compliance and which helps in consistence application of gel on the skin. The spreadability values of different concentration of carbopol-934 (0.5%, 1%, 1.5%) are represented in Table 7. It will be very, much comfortable. The application has been spread easily over the inflamed or diseased skin. The therapeutic activity of topical formulation would be based on spreadability values. The spreadability values of 1% gel loaded with MTX-F2 was found to be 6.61±0.43cm.

Drug content

Amount of drug content in MTX-F2 was 97.26%±1.41. The value of drug content is understood that the drug was considerably carried

in the Hydrogel.

Viscosity study

Viscosity of the methotrexate-F2 formulation was observed 25±2^{o}C. Viscosity was increased in normal 25±2^{o}C. The viscosity was found to be 67325 cps at 25±2^{o}C

In vitro Drug diffusion study

The *in-vitro* response of MTX- NLC based hydrogel behaviour is showed as a cumulative release percentage of MTX-NLC, depicted in Figure 12. MTX-NLC based hydrogel initially showed burst release followed by sustained release of Methotrexate. NLC loaded MTX hydrogel formulation F2, F3, F4 were showing the percentage drug release around 40% within first 4hr depicted in Figure 12. The MTX-NLC based hydrogel was almost showed released activity in 2h. Formulation F2 initial release had seen at the first 4h and the rate of release reached to 35± 2.91% within two hours and 47± 3.61% by 4h. The release phase was fast because of the higher the area of surface the nanoparticles along with the outer shell precipitation or enrichment of drug particles leads in, adequate small distance diffusion. Hence, releasing the drug will be faster. From the therapeutic point of view, a fast releasing profile as surveyed as an advantage of an adequate amount of drug and increase in improve drug penetration. Followed by a quick release rate, it was sustain released, and total release rate reached to 68.01± 2.25% by 12h. Finally, the release rate was reached 72.13± 1.96% by 24h.

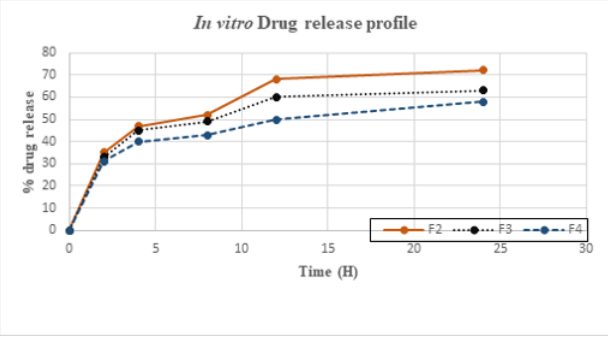

Figure 12: In vitro profile of F2, F3, F4 MTX-NLC's Hydrogel

Stability study

It is performed at a temperature of 25±2^{o}C/60±5% RH for 30 days. In some Formulations at 25±2^{o}C phase separation and precipitation was seen. During the period of the investigation, some formulation was stable, and it was confirmed via no phase separation or no precipitation formation and also no change in the pH as well.

Table 7: Particle size and zeta potential of MTX-NLC's

Days	Formulation	Physical appearance
0 days	MTX-F1	No precipitation
	MTX-F2	No precipitation
	MTX-F3	No precipitation
	MTX-F4	No precipitation
	MTX-F5	No precipitation
	MTX-F6	No precipitation
15 days	MTX-F1	No precipitation
	MTX-F2	No precipitation
	MTX-F3	No precipitation
	MTX-F4	No precipitation
	MTX-F5	Precipitation
	MTX-F6	No precipitation
30 days	MTX-F1	Precipitation
	MTX-F2	No precipitation
	MTX-F3	No precipitation
	MTX-F4	No precipitation
	MTX-F5	Precipitation
	MTX-F6	Precipitation

CONCLUSION

Here in this current research work, we developed the Nano drug delivery system as acceptable Topical administration carriers of psoriasis with Methotrexate as a pure API. This MTX-NLC was incorporated into Hydrogel, improving the treatment by increasing the MTX efficiency, meanwhile preventing its side effect associated along with it. Patient compliance will be more because topical administration of these Hydrogel is less greasy, transparent and comfortably applied on the skin. This study shows that the formulation of NLC Based Hydrogel have sustain release activity on the treatment of psoriasis and may be useful in solving the limitations of current drug delivery system.

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