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5 Fluorouracil Solid Lipid Nanoparticles (SLNs), Formulation and Evaluation for the treatment of Skin Disorders

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Abstract

The new generation submicron is SLNs (solid lipid nanoparticles). In which the lipid particles are in liquid lipid and solid lipid. These are safe, very much stable and it is biodegradable. These may have various topical applications and has an ability to deposit on skin. For the release of drugs, these reduce the local side effect and provide sustained release effect of drug. The current work is done for the formulation and evaluation of SLNs for the treatment of skin disorder. 5 Fluorouracil loaded SLNs are formed and were characterised by FTIR, DSC studies. Physiochemical and *In-vitro* study also investigated. The entrapment efficiency is range from 60±0.36% to 78±0.36%. Zeta potential ranges from-32±2.0 to -59±1.3. 5 Fluorouracil loaded SLNs have prolong release. This is followed zero order *in vitro* release kinetic.

Keywords: 5 Fluorouracil, SLNs, Characterisation, *In-vitro* study

INTRODUCTION

The largest organ of the body 'skin'. Skin provides protections against homeostasis. It also provides protection against UV light, physical and chemical pollutants, toxicity on skin can be manifested and it produces lots of skin disorders like actinic keratoses and melanogenesis. Now a day, actinic keratoses is the most serious illness.[1,2] Some physiological factors which may affect the diffusion of skin. It can influence the structure of skin. Environmental factors may affect the skin such as chemicals, solar radiations etc. some drugs may affect the skin such as aspirin, caffeine, nicotinates etc. as the skin is been aged the epidermis layer and corneocytes may be reduced and decreased. The melanocytes and Langerhans cells are been reduces in dermo epidermal interfaces. These layers may be vascular and cellular.[3,4,5]

Solid lipid nanoparticle are the nanoparticles which contain colloidal drug carrier and alike to Nano emulsion. SLNs may contain solid lipid whereas emulsion may contain liquid lipids. 0.5 to 5 % of surfactant is used in the stabilizer of solid lipid nanoparticles. SLNs are used as a carrier system for water dissolving and dynamic medication. The particle size is from 10 to 1000nm. These may be manufacture by the use of polymers.[6,7,8]

The new generation of nanoparticles are SLNs (Solid lipid nanoparticles). These are active vehicles. These may attract the colloidal drug carriers for topical use. SLN are range in submicron. It contains lipid components in solid state. SLNs are combined with polymeric, fat emulsion and liposomes.[9,10,11] These are biodegradable and biocompatible with controlled drug delivery and has a specific targeting. SLNs have no irritation on skin and it may protect the active compounds. SLNs drug easily administrated into the skin and reduces the irritation. These have better skin targeting effect.[12,13]

MATERIAL AND METHODS

5 Fluorouracil was supplied as gift sample from Unicure India Pvt Ltd, Noida, Uttar Pradesh, India. All excipients (Compritol 888ATO, Sodium taurocholate, Glyceryl Monostearate,

Glyceryl Trimyristate, Chitosan and Carbopol 934P etc.) were supplied by Sigma-Aldrich, New Delhi, India. All the other chemicals were used are analytical grade.

Identification of Drug

One of the major preliminary tests to be done for verification and assuring the purity of the drug sample prior to formulation creation is identification of the procured medication. As a Compendial test, an identification test is included to assist in establishing the identity of goods as purported. The appearance, solubility, and melting point of the drug sample were used to identify it in the current study, and this was confirmed by Fourier-transform infrared (FT-IR) spectroscopy assessment of distinct functional groups and DSC study.

Appearance

The procured drug sample was visually observed for its color and was compared with the reported appearance of the drug.

Solubility of drug

As a purity test, quantitative solubility tests are used. The drug's solubility in water and buffer solutions of various pH levels was tested. In a clean dry test tube, 10 mg of sample was placed, and buffer solution was gradually added in 1 ml aliquots with continuous shaking until it dissolved completely. The amount of solvent required to dissolve the medication powder was recorded, and the solubility was compared to previously published values.

Melting Point

The melting point is one of the methods for determining the purity of a medicine. As a result, the melting point apparatus was used to determine it for the sample using the capillary method (VMP-D, Veego). A small amount of the material was inserted in the melting point equipment in a capillary tube (closed at one end). The temperature at which the substance began to turn into a liquid and the temperature at which the solid vanished completely were both recorded.

FT-IR Analysis of Pure Drug

For the solid-state characterisation of pharmaceutical materials, Fourier Transform Infrared (FT-IR) is an important supplementary method. The substance was identified utilising an Alpha Bruker FTIR spectrophotometer and infrared spectroscopy. The disc method was used to prepare the sample. In a mortar-pestle, the medication was triturated with potassium bromide (about 5 mg sample with 100 mg dry potassium bromide) to obtain a fine and homogenous mixture. The pellets were made by compressing the powder with a potassium bromide press at 20 psi for 10 minutes. The sample disc was prepared and inserted in the sample compartment. In the range of 4000-400 cm-1, the sample was scanned in transmission mode. The acquired IR spectra were compared to a pure drug's standard spectrum.

DSC Study

For determination of Thermal behaviour of 5 Fluorouracil, differential Scanning Calorimetry (DSC) was performed. DSC Thermogram is been formed by the using of DSC instrument. In aluminium pans the sample is been placed and pressed it to seal. At nitrogen atmospheric condition aluminium pan and blank aluminium pan at 30°C to 300°C at a rate of 10°C/min. Indium is use for the calibration of instrument.

Method Validation

The developed analytical method was validated for various parameters like system suitability, Specificity, linearity, Precision, accuracy and LOD & LOQ as per ICH guidelines and data obtained were statistically analysed.

System Suitability

A system suitability test was performed for the validation of the analytical procedure. For SST selection some parameter was used like Percent relative standard deviation (% RSD) of the area, RSD of Retention Time (RT), USP tailing factor, theoretical plates, and resolution were used. For the determination of these parameters, standard solutions were pushed or injected by 6 times.

Specificity

This method is used for the determination and establishment of SLNs dispersion for lipids and surfactants. It did not interfere into the quantification of drugs. This method was evaluated by comparing the chromatograms of 5 Fluorouracil extracted from the SLNs and the blank nano-particle for the peak determination.

Linearity

For the determination of linearity, stock solution of 10 concentrations between 50 to 200µg/ml was injected in triplicate. Calibration curve of 5 Fluorouracil was plotted by peak area versus percentage of drug concentration. If the intercept is < 1% then the linearity was confirmed.

Precision

The analytical method's precision (repeatability) was determined by analysing six samples at 100% test concentration and calculating standard deviation (SD) and percent relative Standard deviation (RSD). The intra-day and inter-day precisions were calculated by analysing three samples at three different times on the same day and on three successive days, calculating SD and percent RSD, and analysing the results.

Accuracy

Accuracy was assessed at three concentration levels. Six replicates were analysed at 100% concentration level and three replicates each at 50% and 150% concentrations. Assessment Of accuracy was accomplished by evaluating the percent recovery of the analyst.

Limits of Detection and Lower Limit of Quantification

Limits of Detection and Lower Limit of Quantification is the lowest concentration of analyte and active ingredient in the sample. This is used for the determination of precision and accuracy. According to the ICH guidelines, this is based on the SD (standard deviation) and slope for the detection and quantitation limits. LOD and LOQ is been calculated by

LOD = 3.3 (SD/m)

LOQ = 10 (SD/m)

Formulation of SLNs

Selection of formulation Technique

High shear homogenization and solvent evaporation technique, microemulsion based SLN preparation technology, and others are some of the strategies for SLN formulation. The technique was chosen based on the particle size, PDI, and entrapment effectiveness of the nanoparticles achieved utilising the commonly used and reported to be dependable and powerful techniques with the trial batches.

Lyophilization

30ml of SLNs were placed into a 50ml of wide mouth fast–freeze flask. Then these tubes were placed into ultra-low temperature freezer at -20^{0}C for 12 to 15 hours. These frozen SLNs were lyophilized using freeze dryer at temperature -80^{0}C with 20 to 30 m Torr pressure for 24 to 25hours.

Evaluation of SLNs

For the determination of evaluation parameters like Particle Size, PDI, Zeta Potential, % Encapsulation Efficiency, % Drug Loading Capacity, Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) also performed for optimized formulation. In Vitro Drug Release and drug release kinetics were also studied.

Particle Size, PDI, Zeta Potential

Zetasizer Nanoseries Nano-ZS, Malvern Instruments, Malvern, UK, was used to assess the average particle size, PDI, and zeta potential of solid lipid nanoparticles. Particle size and zeta potential were determined using in-built dynamic light scattering, DLS, and Laser Doppler Electrophoresis. The materials were placed in 'folded capillary cells,' and the size, PDI, and zeta-potential values obtained were recorded. By using distilled water lyophilized SLNs were redispersed. These samples were taken into a cuvette and analysed at 90C.

% Entrapment Efficiency and % Drug Loading Capacity

% Entrapment efficiency was determined by determining the amount of free drug Spectrophotometrically at 265 nm in the supernatant after centrifugation of the known Amount of nanoparticulate dispersion at 10000 RPM using freeze centrifuge (BL – 135 R).

$$\% \text{ Entrapment efficiency} = \frac{\text{AAmount of entrapped drug}}{\text{AAmount of total drug}} \text{ X } 100$$

$$= \frac{\text{Weight of drug added in the formulation} - \text{Weight of free drug}}{\text{Weight of drug added in the formulation}} \text{ X } 100$$

$$= [(WT - WF)/WT] \text{ X } 100$$

$$\% \text{ Drug Loading Capacity} = \frac{W_{\text{total drug detected}}}{W_{\text{Total solid lipid added}}} \text{ X } 100$$

Percentage (%) Yield

The yield of the final solid lipid nanoparticle of all ratios was calculated by using the final weight of solid lipid nanoparticle after lyophilization and the initial weight of the drug and polymer used for the preparation of SLN[126].

Following formula is used for calculation of % yield:

$$\% \text{ Yields} = \frac{\text{Theoretical yield of SLN}}{\text{Practical yield of SLN}} \quad X\ 100$$

***In-vitro* Drug Diffusion Profiles**

This study was performed by bag diffusion method. This bag membrane should retain the nanoparticle and allow the free drugs to the dissolution media with a cut off of 15000 molecular weights. Double distilled water is been use for the soaking of this bag. It was remaining in this for 12 to 15 hours before use. 3ml of PBS with pH 6.8 were used for the dispersion of 200mg of Lyophilization SLNs. Then this solution was placed into the membrane bag with the two ends fixed by clips. Conical flask is use for the bag placed with the addition of 60ml of PBS pH 6.8. Then this conical flask was fixed on thermostatic magnetic stirrer with 38^0C at 100RPM. At a certain interval of time, 2 to 3 ml of media was taken out and it was replaced by fresh medium volumes. 0.22 µm is used for the filtration and it was injected by nylon syringe and assayed by HPLC method.

Scanning Electron Microscopy (SEM)

SEM (Scanning Electron Microscopy) is used for the morphology of SLNs. The samples for Scanning Electron Microscopy were prepared by light sprinkling nanoparticles on a double adhesive carbon tape, which was stuck to an aluminium stub. The stub was then coated with gold to a thickness of 200 to 500 Å under an argon atmosphere using gold sputter module in a high vacuum evaporator. The samples were then scanned and photomicrographs were taken at 27000x magnifications.

Transmission Electron Microscopy (TEM)

TEM (Transmission Electron Microscopy) are used for the morphology of SLNs. Distilled water with ratio of 1:10 was use for the dilution of SLNs. One drop of the diluted formulation was subsequently taken and placed onto a carbon-coated copper grid. The excess liquid was removed with filter paper and allowed to stand for 10 m. The grid was then stained with 1% phosphotungstic acid (PTA) and allowed to air dry for 5 m. The sample was then viewed under Transmission Electron Microscope (TEM) and photomicrographs were taken.

Drug Release Kinetics

In order to examine the release mechanism of 5 Fluorouracil SLNs, optimized Fluorouracil SLNs was performed. Determination of mechanism and kinetics of drug release were obtained by correlation coefficient (R2) values.

Zero Order Kinetics

% Cumulative drug released and time (h) graph was plotted for the Zero-Order Kinetic Model. Concentration is not depending on the release drug.

$$Q = K_0 t$$

Where, Q = Amount of drug release at time t,

K_0 = Zero order rate constant

t = Time (h).

The R^2 value obtained from the plot of the amount of medication released (Q) vs time (t) reveals zero order release, indicating that the release is concentration-independent.

First Order Kinetic Model

Log % cumulative drug released and time (h) graph was plotted for first order kinetic. Concentration plays most important role.

$$\ln (100-Q) = \ln Q_0 - K_1 t$$

Where, Q = Amount of drug release at time t,

K1= First order release constant

t = Time (h).

The regression coefficient (R2) value obtained from the log % ARR (Amount Remaining to Release) versus time, nearer to 1 indicates first order release signifying the release to be concentration-dependent.

Higuchi Square Release Equation

Fick's law is used for Higuchi model. This model describes the mechanism of drug release which is been followed by diffusion dosage form due to the presence of polymer matrix. % Cumulative drug released and the square root of time graph was plotted for Higuchi's kinetic.

$$Q = K_h t^{1/2}$$

Where, Q= Amount of drug release at time t,

K_h= Higuchi square root of time release constant

t = Time (h).

Higuchi's drug release model, which has a regression co-efficient of percentage drug release vs square root of time nearer to 1, implies Fickian diffusional release.

Korsmeyer and Peppas model

$$Qt / Q\infty = K \times t^{\lambda}$$

$$\text{Log } (Qt/Q\infty) = \text{Log } K + \Lambda \text{ Log } t$$

Where,

$Q\infty$ = Total drug released after infinite time t,

$Qt/Q\infty$ = Fractional drug released at time t

K = Kinetic constant incorporating structural and geometrical Characteristic of the drug/polymer system (devices).

Λ = Diffusion exponents that characterizes the mechanism of drug release.

t =Release time

A plot of log ($Qt/ Q\infty$) versus log t gives straight line of gradient λ and an intercept of log K.

Values of exponent Λ and the corresponding release mechanism. When the value n ≤ 0.45 reveals that Higuchi model or fickian diffusion the value 0.45 < n < 0.89. This value means the particular dosage form anomalous diffusion and non-fickian diffusion.

RESULTS AND DISCUSSIONS

Physical parameters of drug

Before moving forward with formulation development, it is necessary to identify the purchased drug sample and ensure its purity. Table 1 summarises the identification tests and inferences for the drug sample based on its appearance, solubility, and melting point determination.

Table 1: Identification Test for Drug

Parameters	Observations	Reported	Inferences
Appearance	White powder	White to almost white powder	Complies
Melting Point	280-285 ^{0}C	282 – 283 ^{0}C	Complies
Solubility	solubility of 5-Fluorouracil is 12.1 mg/ml in water	solubility of 5-Fluorouracil is 12.2 mg/ml in water	Complies

Drug Solubility Determination

The drug dissolution period was found to be 10 to 12 hours to reaches the equilibrium solubility. It did not generate excessive degradants. In short periods these may show insufficient dissolution and long period show unwanted degradants. For phase solubility studies the experimental optimum time is provided. Various pH is been determined by the saturation solubility of 5-Fluorouracil.

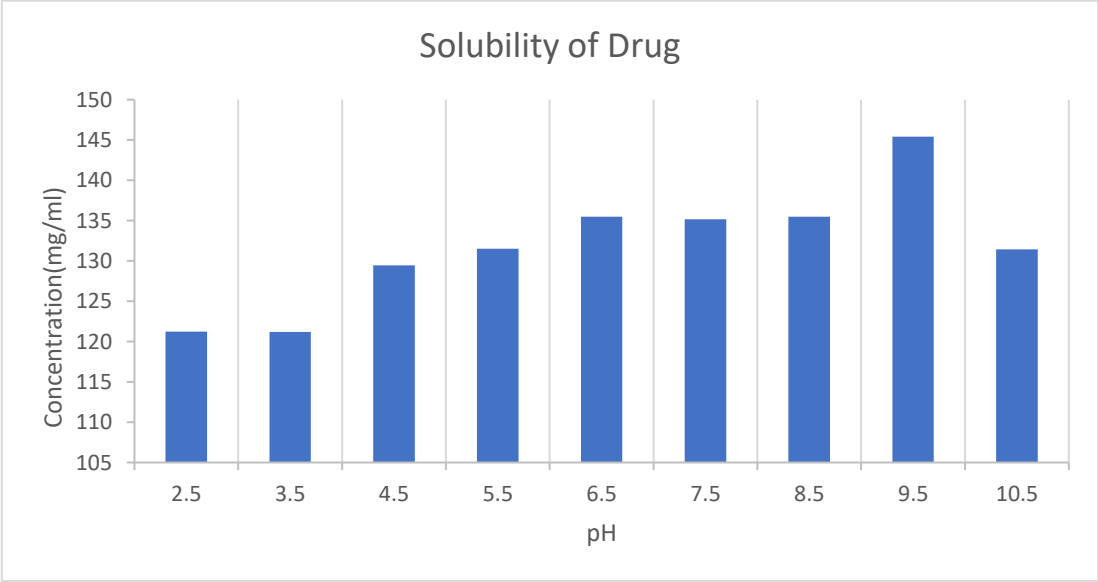

Figure 1: Solubility of 5 Fluorouracil in various buffer solutions

FTIR Study

The sample is confirmed to be of the medication 5 Fluorouracil based on the observations' conformance to the given criteria. Fourier-transform infrared (FT-IR) spectroscopy was used to determine the various functional groups present in the powder drug sample, which were then compared to the standard spectra of 5 Fluorouracil for confirmation. Figure 2 shows the observed and reported IR spectra of 5 Fluorouracil.

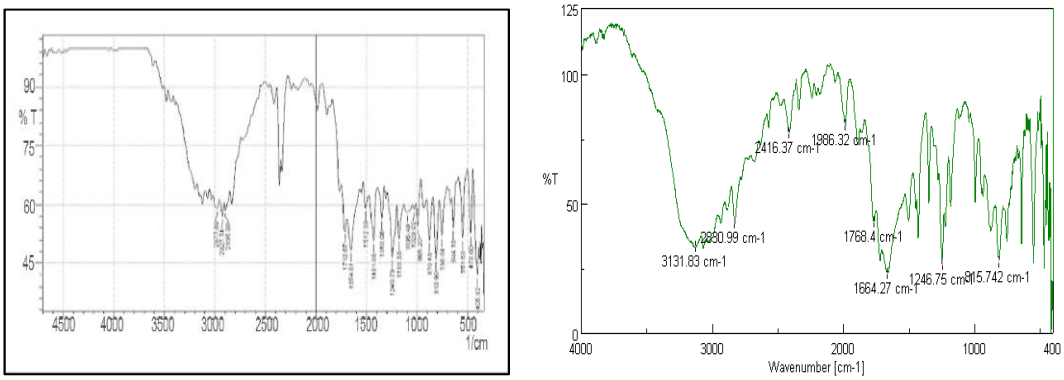

Figure 2: FTIR of 5 Fluorouracil (Pure Drug and Drug sample)

DSC Study

For determination of thermal behaviour of 5 Fluorouracil, Differential Scanning Calorimetry (DSC) was performed. It was done at a temperature of 30°C to 300°C. DSC Thermogram of 5 Fluorouracil shows peak at 283°C and confirm that Sample of drug is pure.

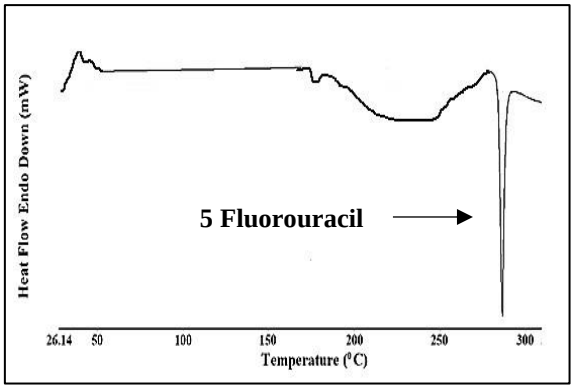

Figure 3: DSC Thermogram of 5 Fluorouracil

Method Validation

System Suitability

For optimisation of separation peak of 5 Fluorouracil at different pH buffer solution. This was detected at 265nm by different pH at flow rate of 1.5ml/min. By using injection of spiked drug profile is been estimated in API.

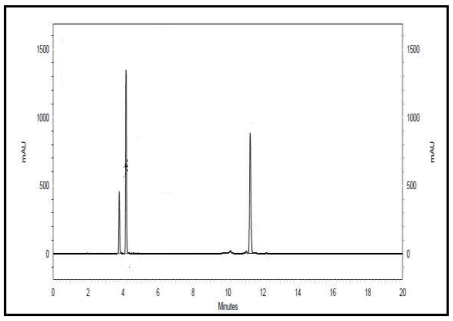

Figure 4: System Suitability Chromatogram of 5 Fluorouracil

Specificity

Specificity is the method to measure the potential impurities and degradation of the products. Another excipient is been absent. There were no other peaks. The specificity was verified by complete separation of 5 Fluorouracil and indicated that there was no interference in the quantitative determination of 5 Fluorouracil from SLNs components.

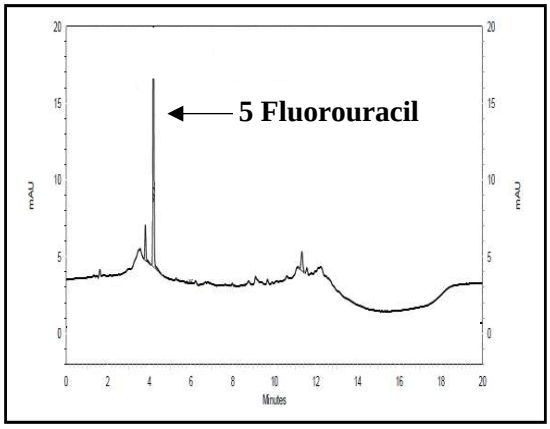

Figure 5: Analytical Profile of spiked SLNs without APIs and with API

Linearity

Linearity was observed in the concentration range of 55 to 135 for 5 Fluorouracil. Graph is been plotted for mean peak area versus drug concentration percentages. The result showed magnificent correlation coefficients ($R^2 \geq 0.998$).

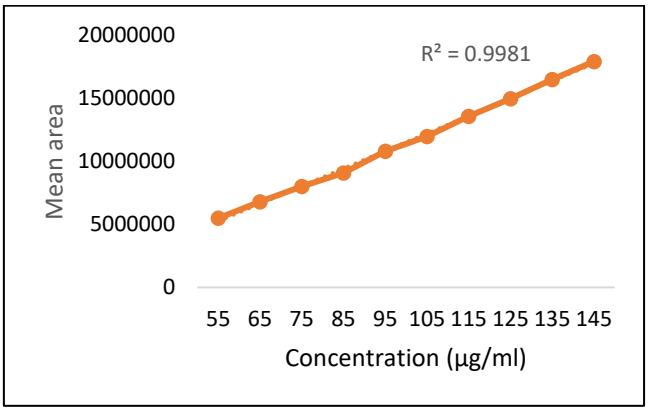

Figure 6. Calibration Curve of 5 Fluorouracil by HPLC method

Precision

From the experiment intra and inter day precision is been estimated. The RSD % of both them of 5 Fluorouracil was <0.05% and <0.98 %.

Table 2: Intra-day Precision and Accuracy of 5 Fluorouracil

% RSD	Amount (µg/ml)	Intra–days		
		Found (µg/ml)	Accuracy (%)	Precision (% RSD)
20%	9	8.50	99.48	0.05
50%	50	41.25	98.58	0.28
100%	90	82.48	99.74	0.56
150%	120	120.48	99.75	0.87
180%	160	189.48	98.73	0.98

Table 3: Inter-day Precision and Accuracy of 5 Fluorouracil

% RSD	Amount (µg/ml)	Inter–days		
		Found (µg/ml)	Accuracy (%)	Precision (% RSD)
20%	9	7.10	99.58	0.07
50%	50	45.75	98.75	0.29
100%	90	84.85	99.67	0.55
150%	120	130.58	99.89	0.88
180%	160	190.58	98.15	0.99

Limits of Detection and Limit of Quantitation

LOD and LOQ were estimated for the standard deviation and standard curve of slope. LOD and LOQ were calculated as 0.0053 and 0.0243 for 5 Fluorouracil.

Table 4: Results of LOD and LOQ

Drug	**SD**	**Slope**	**%RSD**	**LOD**	**LOQ**

5 Fluorouracil	44.587	23345	0.21	0.0053	0.0243

Recovery

2% data were recovered with the estimation of mean recovery data. Accurate method was obtained which was acceptable for ± 3% range.

Table 5: Recovery analysis of 5 Fluorouracil

Drug	Assay		Recovery		
	Found (µg/ml)	% RSD	Mean recovery (%)	± SD	% RSD
5 Fluorouracil	0.4578	0.47	120.124	840.15	7.12

Formulations of SLNs

Table 6: Formulation of Solid Lipid Nanoparticles

Formulation code	**5 Fluorouracil (% w/w)**	**Lipids (% w/w)**			
		Glycerol Monostearate	Glyceryl Behenate(Compritol 888ATO)	**Glyceryl Trimyristate**	**Dioleyl Trimethyl Ammonium Propane**
F1	1	3	1	--	--
F2	1	--	--	3	1
F3	1	1	3	--	--
F4	1	--	--	1	3
F5	1	3	1	--	--

F6	1	--	--	1	3
F7	1	2	4	--	--
F8	1	--	--	2	4
F9	1	4	2	--	--
F10	1	2	4	--	--
F11	1	--	--	2	4
F12	1	6	2	--	--
F13	1	--	--	6	2
F14	1	2	6	--	--
F15	1	--	--	2	6
F16	1	6	2	--	--
F17	1	--	--	6	3
F18	1	3	-	3	--
F19	1	--	3	--	3
F20	1	3	--	3	--

Surfactant: Poloxamer 188, Sodium Taurocholate Cryoprotectant: Mannitol

Evaluation of 5 Fluorouracil Loaded SLNs

Particle Size Analysis, Zeta Potential and PDI

Evaluation of Prepared formulation was performed for Particles Size, Zeta potential and PDI. The Particles size was formed normal ranges (209.6±4.57 to 625.3±3.3nm). These particles were acceptable nanometer range. PDI ratio for the mass of the given samples was found to be below 0.97 for all SLNs formulations. For pharmaceutical stability zeta potential has +ve and -ve value. For good stability, zeta potential has -14 to -52mV. Formulation F16 has close zeta potential (-50mV).

Encapsulation Efficiency, Loading Capacity and Percentage Yield

For the large scale of production, %EE, % Loading Capacity and % Yield was calculated. CCD (Central Composite Designed) was used for the evaluation of % EE, % Loading Capacity and % Yield.

Table 7: Evaluation of 5 Fluorouracil loaded SLNs Formulations

Formulation code	Mean Particle Size (nm) ± SD	Zeta Potential (mV) ± SD	PDI± SD	% Encapsulation Efficiency ± SD	Loading Capacity (%) ± SD	% yield ± SD
F1	209.6±4.57	-35±2.0	0.17±0.01	71±0.75	39±2.2	79±2.58
F2	321.4±7.48	-35±1.1	0.28±0.04	64±0.67	19±6.5	65±3.69
F3	245.1±8.45	-41±1.2	0.39±0.03	64±0.79	48±2.6	73±1.47
F4	421.6±7.85	-42±2.3	0.14±0.09	65±0.64	15±4.5	73±3.21
F5	301.8±6.48	-44±2.5	0.51±0.02	60±0.36	51±3.0	68±3.65
F6	502.1±8.9	-45±2.0	0.37±0.03	72±0.49	48±7.2	69±7.41
F7	315.2±7.5	-42±2.6	0.36±0.08	65±0.36	15±8.6	79±3.65
F8	215.9±5.6	-59±1.3	0.32±0.07	76±0.71	46±9.5	89±5.56
F9	317.2±2.4	-37±1.4	0.52±0.06	75±0.63	25±3.8	65±3.69
F10	458.3±9.5	-32±2.0	0.37±0.06	65±0.25	36±7.4	89±7.53
F11	501.2±4.9	-44±1.2	0.19±0.03	71±0.36	25±9.3	68±3.58
F12	625.3±3.3	-33±1.3	0.28±0.02	64±0.73	21±5.6	79±3.21
F13	458.9±4.7	-52±1.5	0.24±0.04	72±0.73	58±6.5	74±3.31
F14	459.7±10.8	-46±0.8	0.27±0.05	73±0.55	51±7.5	89±3.74

F15	357.19±9.7	-52±0.9	0.35±0.09	63±0.29	54±5.5	90±4.89
F16	328.14±2.5	-49±2.4	0.44±0.11	78±0.36	58±6.7	89±6.54
F17	457.18±6.8	-59±2.1	0.18±0.08	63±0.45	48±8.9	78±3.21
F18	369±11.5	-57±1.3	0.54±0.09	62±0.22	58±9.1	69±7.41
F19	478.8±2.8	-58±1.2	0.34±0.07	66±0.69	48±3.9	72±5.80
F20	391.5±4.5	-49±1.9	0.17±0.02	69±0.36	15±6.5	86±3.25

***In Vitro* Release Studies**

CCD (Central Composite Designed) of *In vitro* drug release of 5 Fluorouracil loaded SLNs evaluated by pH 6.9. This was done bag diffusion method. Studies show that there was no difference in drug solubility in buffer. % Cumulative drug release for Fluorouracil loaded SLNs formulations were range 80.48±3.6 to 98.18±75 after 24 hours. Due to possible degradation the lower percentage of encapsulated drugs in SLNs.

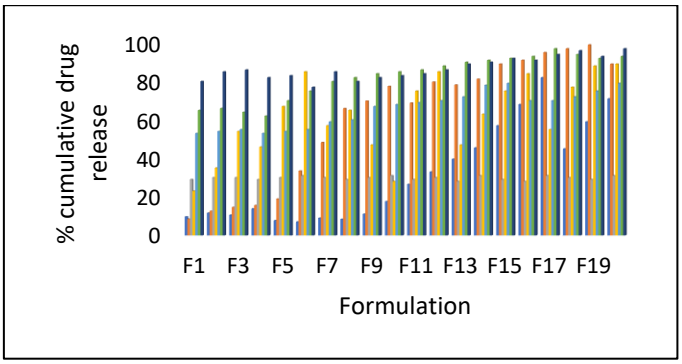

Figure 7. *In vitro* % CDR of Fluorouracil loaded SLNs Formulations

From all the above formulations, **F16** which contain 6% w/w Glycerol Monostearate and Glyceryl Behenate (Compritol 888ATO) as Lipid for SLNs preparation shows better results for Mean Particles Size (328.14±2.5), Zeta Potential (-49±2.4), PDI (0.44±0.11), % EE (78±0.36) and Loading Capacity (58±6.7). In vitro drug release study using Bag Diffusion method, F16 shows highest % cumulative drug release was 98.18±75 after 24 hours. From above all results data, F16 was selected as optimized formulation for further study.

***In Vitro* Drug Release Kinetics**

F16 were found to be very narrow in Particle Size and Zeta Potential. So that this was selected for *In Vitro* Drug Release Kinetics Studies. Different Types of Mathematical Models (Zero–Order, first–Order, Korsmeyer Peppas and Higuchi Models) were used for the *in vitro* drug release. R^2 squared correlation coefficient were determined by this model.

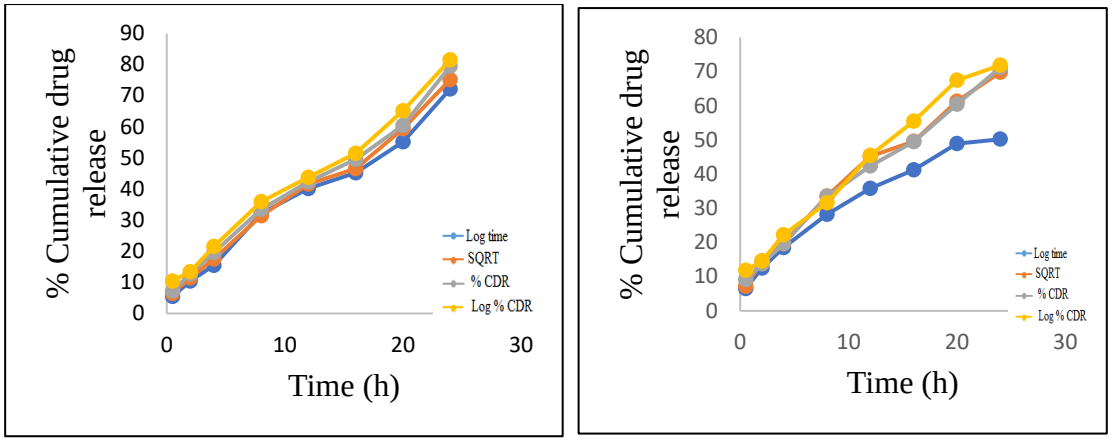

Figure 7. Zero and First Order Release Model of 5 Fluorouracil loaded SLNs (F16)

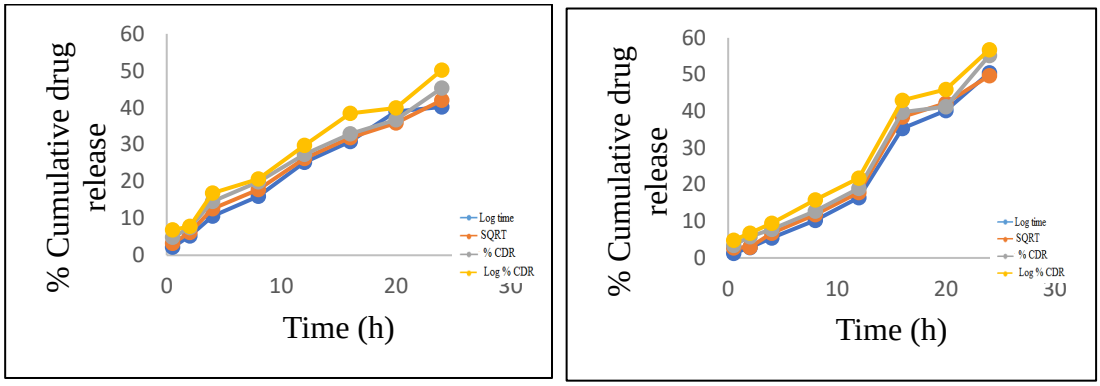

Figure 8. Korsmeyer Peppas Release Model and Higuchi Release Model of 5 Fluorouracil loaded SLNs (F16)

Scanning Electron Microscopy

SEM was use for the determination of 5 Fluorouracil loaded SLNs (F16). SLN belong soon to be discrete circular using a glossy appearance with none crevices. Image show that there is a complete removal of the solvent from the formulated SLN, and it also indicates particles size of 200nm that the formulation method was efficient.

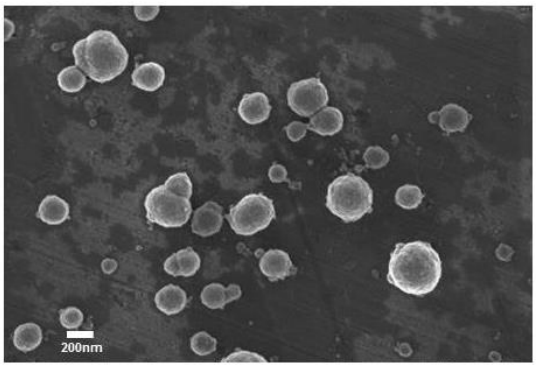

Figure 8: Scanning Electron Microscopy images of SLNs (F16)

Transmission Electron Microscopy

TEM is a plain study the particle morphology by examining the electrons that are grant during the variety. A picture is produced by interpreting alternation of startling atoms passed through the specimen, which is visualized via an estimate strategy or not precisely away a rare sensor record.

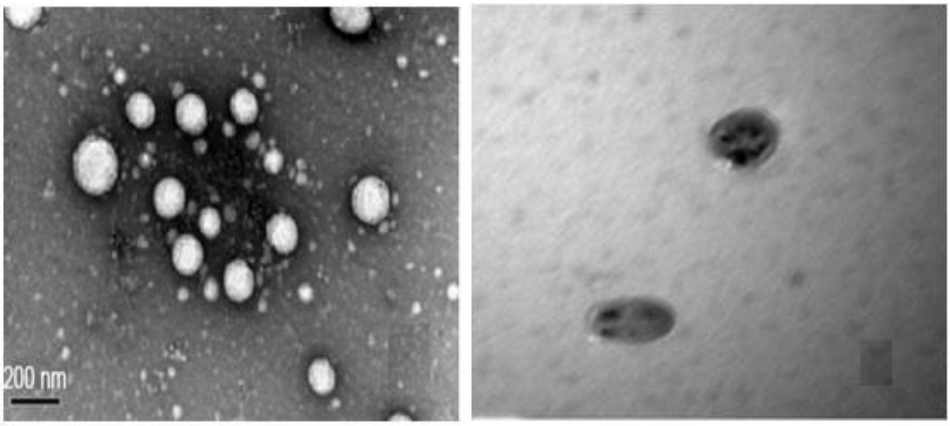

Figure 9: TEM images of SLNs (F16)

CONCLUSION

With the present investigations, it may be concluded that Solid Lipid Nanoparticles of a 5 Fluorouracil were successfully developed and optimized. Formulated SLNs may be converted in hydrogel for topical delivery of drug for skin disorder like actinic keratoses (AKs). Drug-excipient Compatibility studies of Drug, Lipid, Polymer, and their mixtures by FTIR and DSC conform that there is no chemical interaction between drug and excipients. Transmission Electron Microscopy (TEM) & Scanning Electron Microscopy (SEM) images revealed that the Nanoparticles in SLNs droplets were intact, non-aggregated and nearly spherical in shape. The release of drug from SLN incorporated formulations best fits in the Zero order release Kinetics (R2 = 0.9852), indicating concentration independent diffusion-controlled release. 5 Fluorouracil loaded SLNs has Particle Size 209 to 625 nm. This may help for the prolong the circulation time of SLNs in blood. PDI were found to be less than 0.6. Negative charge of zeta potential in SLNs formulation was show effective stability.

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