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Research Article

PREPARATION AND EVALUATION OF SOLID LIPID NANOPARTICLES FOR TOPICAL DELIVERY

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ABSTRACT

Solid lipid nanoparticles are the novel approach of drug delivery system. For topical delivery, their solid matrix provides the controlling drug release profile and also protects the API against chemical degradation. Their small particle size produced the adhesive properties leading to film formation on the skin. The aim of the study to prepare Solid lipid nanoparticles for topical delivery by the o/w solvent evaporation method and incorporated into an Aloe Vera hydrogel. An evaluation was done SEM (Scanning Electron microscopy), Zeta potential FT-IR and entrapment efficiency. Than SLNs were incorporated into the Aloe gel and evaluating by pH, Viscosity and drug release pattern. A result confirmed as the solid lipid nanoparticles formulated were found to be in the Submicron range (160nm-200nm).The entrapment efficiency was found to be near 37%. The release study shows the prolonged release pattern in the Solid lipid nanoparticles formulation in comparison to the plain Capsaicin . The gel formulated by the incorporation of capsaicin loaded gel shown further retardation of drug release. So, in conclusion the SLN formulated in a promising approach for the topical delivery of capsaicin. Therefore, SLNs represent an easy to manufacture, stable, physiologically compatible system with prolonged drug release and reduced irritancy.

KEYWORD: *CAPS, SLN , SEM, SA.*

INTRODUCTION

Topical drug delivery has a benefit to deliver drug at skin such as skin surface. Solid lipid nanoparticles are submicron size range colloidal carries (50-1000nm), which are composed of physiological lipids, dispersed in water or in an aqueous surfactant solution [1, 3, 4]. SLN are composed of well tolerated excipients and due to their small particle size they posses' similar adhesive properties leading to film formation on the skin. SLNs is more suitable for topical application because of its advantageous features like they are composed of physiological and biodegradable lipids, which show low toxicity, nanoparticle size provides more effective surface area, which results in close contact to the stratum corneum and can enhance drug penetration [2, 7]. Occlusive properties of lipid nanoparticles give increased skin hydration [2, 4]. In addition, lipid nanoparticles are able to enhance the photo stability, protection against oxidation and hydrolysis.

SLN as a Potential Carrier for Topical delivery:

SLN constitute as a lipid derivatives carrier system alternative for the topical drug delivery. SLN have a several advantages including:-

- Drug targeting (site specific) & possibility of controlled drug release,
- Improved the drug stability
- Improved the drug loading, incorporation of lipophilic & hydrophilic drugs,
- High affinity to the stratum corneum & enhancement the bioavailability of encapsulated materials [10].

Capsaicin is an alkaloid extracted, lipid soluble compound. It belongs to the family of Capsicum. Capsaicin is less employed because of its adverse effects as stinging, burning and erthyema at the application site. Incorporation of Capsaicin in SLNs retard the drug release and thus, the reduced the irritancy and other adverse effects [20-22].

MATERIALS AND METHODS

Materials:

Stearic acid, Glyceryl monostearate, polyvinyl alcohol, TWEEN 80, Capasaicin (DRUG), White soft paraffin, Aloe vera, Carbopol 940, Methyl parabene, Chloroform.

Methods:

Preformulation Studies:

Preformulation studies were performed to characterize the physicochemical properties of the drug that could affect the

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development of solid lipid nanoparticle and to identify the drug to confirm its authenticity.
The preformulation studies were done for drugs as follows:

A) Physical appearance of drug:

Odor - pungent
Color - off-white, ceramic color

B) Identification of drug profile:

I) Melting point study (by using Capillary tube method): Small amount of powdered drugs were filled inside the thin capillary tube and sealed, then capillary was placed into a melting point apparatus and thermometer was placed in the apparatus. The knob of apparatus was rotated in order to increase the temperature. The temperature at which the drug melted was recorded.

ii) Solubility of CAPS in solid lipid and solvent:

a) Here, we used the modified method (Kumar a Shah et al, 2007) to identify the capacity of a drug in the solid lipid. The solid lipids (GMS and SA) were separately heated above their melting point. Then, the molten lipid was gradually added in CAPS with continuous stirring .the required the amount of the CAPS was noted visually. The end point of the solubility study was the formation of aggregates and yellowish solution.

b) Solubility in a chloroform and methanol, tween 80.

c) Infra-red study (FT-IR): Fourier Transform Infra-Red Spectrometer (FTIR) of Thermo-Scientific (Nicole 6700). The solids in the powdered form through making pellet by mixing the same with the KBr under a hydraulic press. FT-IR helps to confirm the identity of the drug. FT-IR spectral measurement for pure capsaicin drug taken at ambient temperature. Drug and drug mixture with lipids were mixed with KBr by trituration in a mortar and the mixture was compressed into a pellet at 10 ton/cm^2 in a pellet maker. The sample was scanned at 400cm^{-1} - 4000cm^{-1} the results were compared with standard.

UV absorption spectra:

Scanning for λ-max of CAPS in methanol (30% v/v) and Methanolic Phosphate buffer solution pH-7.5 (70:30) in the range of 200-400nm.

Analytical method of Capsaicin:

Preparation of Stock solution and calibration solution:

- A standard stock solution was prepared by dissolving 10 mg of drug in a 10mL of PBS: M (70: 30 v/v) solution.
- From the stock solution, taken 1 mL and diluted with a 10 mL of PBS: M solution (concentration of the solution was 100 ug /mL).Further, pipette out the 1 mL from the above solution and diluted into PBS: M solution (concentration was 10 ug/mL).The resulting solution was scanned spectrophotometrically between 200 nm to 400 nm. The λ_{max} of the solution was found at 280 nm.

Preparation of a standard curve in Methanolic PBSpH-7.5 (70: 30v/v):

By UV Spectrophotometric (Shimadzu UV- 1601 UV-vis double beam, version 2.04) method, a standard stock solution of CAPS (1 mg/ mL) was prepared in PBS: M solution and dilution of the standard stock solution was prepared. The working standard solution concentration 1-10 ug/ml and the absorbance of the diluted working standard solution were recorded at 280 nm.

Formulation of solid lipid nanoparticles (by o/w nanoemulsion solvent evaporation method):

Using the method of "**one variable at one time**". In this method, the lipids were melted on a hot plate. The drug was dissolved in a solvent and added in a melted lipid. Lipids solution containing the drug was added drop wise into the aqueous solution then added a small portion of PVA solution under magnetic stirring for 1 hour. After that sonicated the o/w emulsion for 15 minutes and lastly, lyophilized and dry [2, 9].

SLN Characterization:

Determination of particle size and scanning electron microscopy:

The morphology of the particles was analyzed by using SEM model JSM 6490. Samples were prepared by coating with gold in a coating apparatus and observed the morphological characters on the screen of a computer attached to SEM apparatus.

Determination of Zeta potential:

The average particle size and PDI of nanoparticles were evaluated by photon correlation spectroscopy zeta sizer nano plus-3 (Japan). All the samples were suitably diluted in tween 80 (0.1%).

Entrapment efficiency:

The known amount of SLN was prepared in a methanol and kept aside for 1hr. after that filtered the solution then taken 1mL from the above Solution and diluted in 10mL of PBS: M (70:30%v/v). The diluted solution was analyzed at 280nm by using UV spectroscopy.

The entrapment efficiency was calculated by the following equation:

$$\% EE = [M_{inital\ drug} - M_{free\ drug} / M_{initial\ drug}] \times 100$$

Where $M_{initial\ drug}$ is the mass of initial drug used for analysis and the $M_{free\ drug}$ is the mass of free drug. [Kumar Shah et al]

Drug Release:

In 100ml of a beaker, filled with PBS: M (70:30v/v) solution and magnetic bar were used for continuous stirring along with maintaining the temperature at 37C. A known amount of SLN put into the beaker, sampling was done at 5min, 30min, 1hr,2hr,3hr,4hr,5hr …… 12hr. At the each sampling, 10mL withdrawn from the beaker and replaced the amount with the PBS: M solution. The drug concentration analyzed by using UV spectrophotometer at 280nm.

Development of secondary topical vehicle (formulation of Aloe Vera gel):

Aloe Vera gel was prepared from the aloe juice, the central parenchymatous pulp was scooped out with a spatula from the aloe leaves. The pulp was washed repeatedly with water. The pulp was blended, to obtain a juice. The obtained juice was filtered using a cotton bed to remove the rind Particles. Carbopol 934 was added and dispersed in a liquid, it is used as gelling agent. 0.5%w/w methyl paraben was added to the liquid. A solution of 0.5N NaOH solution was added drop wise until a gel was formed. Aloe Vera gel was stored in air tight container.

Characterization of Aloe Vera gel loaded SLN:

Determination of pH, Spreadability, and viscosity:

The pH of the gel was determined using Digital pH meter, standardized using pH4.0, pH7.0, and pH10.0. The

spreadability of a gel was determined using the technique: 0.5g gel was placed within the circle 1cm diameter pre-marked on a glass plate over which a second glass plate was placed. A weight of 500g was allowed to rest on the upper glass plate for 5min. the increase in the diameter due to spreading of the gels was noted.A sample (30g) was placed in a beaker and was allowed to equilibrate for a min. Using spindle no 4, at rpm 60. All reading was taken in triplicates.

Determination of drug content:

Drug content of solid lipid nanoparticles based gel was determined by dispersing a predetermined amount of gel in methanol. Absorbance was measured at 280nm.

In vitro release:

The release of drug from the solid lipid nanoparticles based gel was studied in pH 7.5 phosphate buffer using self-fabricated modified diffusion cell.

An appropriate amount (0.500 g) of a gel was placed in a double cut tube whose one end was tied with pretreated cellophane membrane. This acted as a donor compartment.

The tube was dipped in a beaker filled with 100ml of phosphate buffer of pH 7.5, this acted as a receptor compartment. The tube was mounted above beaker of phosphate buffer in such a way that the surface of the membrane was remaining in contact with the receptor compartment.

The whole assembly was placed on a magnetic stirrer with constant agitation speed and temperature maintained at 37˚C ± 2˚C.

RESULTS AND DISCUSSION

Pre-Formulation study: The physical appearance as observed was as following:

Physical appearance of drug:

- ***Color*** ***:*** white to light yellowish
- ***Odor*** ***:*** pungent
- ***Texture*** ***:*** crystalline powder

Identification of drug:

Melting point study: Melting point of CAPS is 69.0 ˚C -69.3˚C

Solubility of CAPS in Solid lipids: Solubility studies indicated that GMS and Stearic acid both have the effective solubility for CAPS. Stearic acid and GMS have favorable potential as a solid lipid for the present study.

Table No. 1: Solubility of CAPS in different solvent

S. No.	Solvent	Solubility
01	Chloroform	Soluble
02	Methanol	Soluble
03	Tween 80 (0.1%)	Soluble
04	Distilled water	Insoluble
05	Phosphate buffer pH - 7.5	Soluble

Infra-red study (FT-IR):

FT IR spectra of 'pure drug' and 'excipient' were compared to study the incompatibility of a drug with excipients. FT-IR studies were done to confirm the identity of the drug and to detect the interaction of the drug with carrier or excipients. FT-IR spectral measurement for pure CAPS drug and stearic acid polymer and the formulations were taken at ambient temperature. The results depict that drug and lipid did not show any incompatibility. The IR spectra of CAPS showed peaks at 2928.42(-OH) cm^{-1}, 2850.91cm^{-1}, 3314(-NH) cm^{-1}, 1623 (-C=O) cm^{-1}.

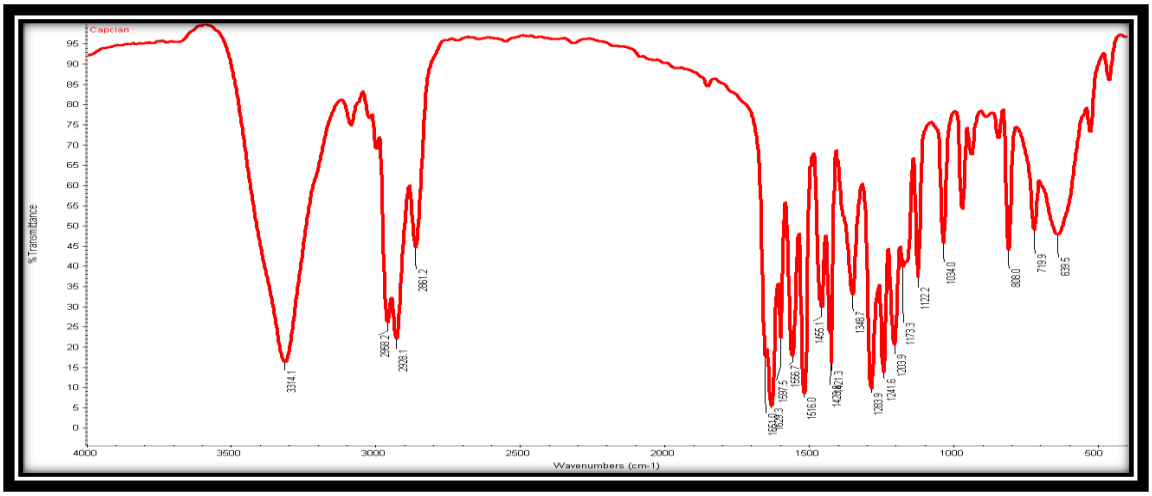

Fig. 1: IR spectra of capsaicin

IR spectra of Drug-lipid physical mixture: IR (KBr, cm^{-1}): 1703(-C=O) cm^{-1}, 2918(-O-H) cm^{-1}, 2849(-OCH_3) cm^{-1}.

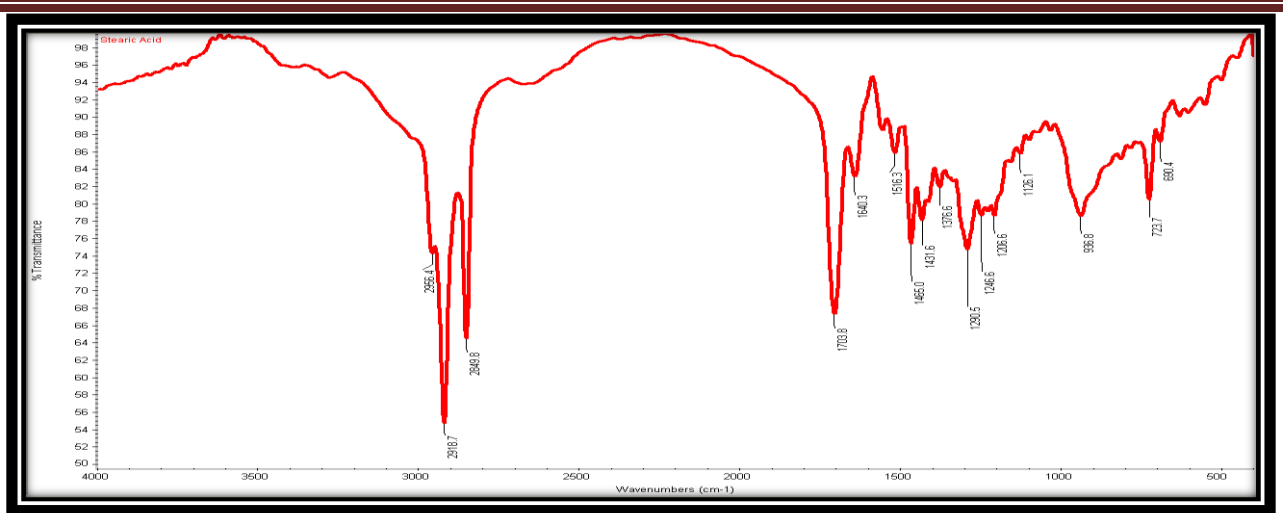

Fig. 2: IR spectra of drug – lipid

Scanning of CAPS in PBS: M (70: 30%v/v) [analysis of λ-max]:

U.V. estimation of the CAPS was done by U.V. Spectrophotometric method using U.V. and visible spectrophotometer-1601 (Shimadzu Japan). The UV spectrum of CAPS in PBS: M was scanned from 200nm-400nm. The λ-max was found to be 279.5nm.

Construction of calibration curve:

Calibration curve of CAPS in PBS: M: By using the UV –vis double beam spectrophotometer (Shimadzu, Japan), the absorbance of the solution (concentration range 1-10µg/mL) was recorded at 280nm (regression coefficient R2– 0.999). This indicated good linearity. The calibration curve of drug obeyed Beer Lambert's law in the concentration range studied. The results are shown in figure no. 3

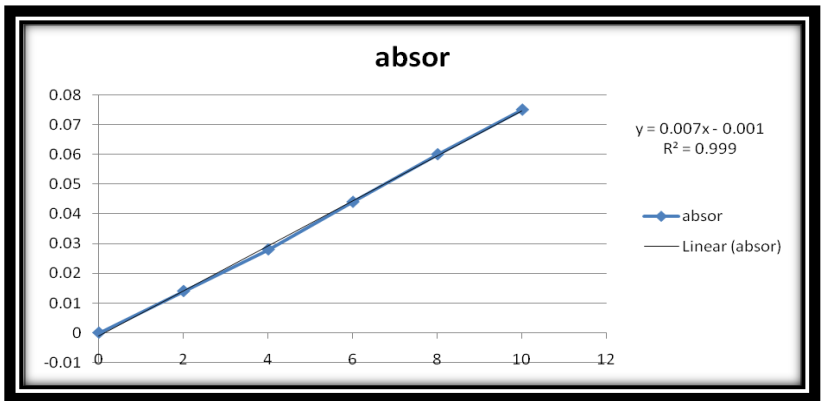

Fig. 3: Calibration curve

Development of SLN by o/w nanoemulsion solvent evaporation method:

The method of preparation of solid lipid nanoparticles is based on the method that reported Benita, Siekmann and Muller, Kumar A Shah. Hence, Stearic acid was selected for the preparation of SLN and chloroform used as the solvent.

Morphology and particle size determination: SEM images reveled that the Particle size of SLNs was in nano size range and the particles had the spherical morphology. The particle size data of SLN depicted that the increase the amount of SA content, increases the size of the particles. The reason behind this hypothesis is could be that the increase in lipid content in primary emulsion but the concentration of the stabilizer was constant. However, the same concentration of the stabilizer, there is increase in the particle size of the primary emulsion.

Table No. 2: Particle size of CAPS loaded SLN. Particles size expressed as mean± std deviation

Formulation	Surfactant	Size(nm)	Entrappment Efficiency%
F1	Tween 80	160 ± 0.00	37.237 ± 1.824
F2	Tween 80	178.26 ±1.626	25.553 ± 0.514
F3	Tween 80	201.32 ± 1.161	14.153 ± 0.346

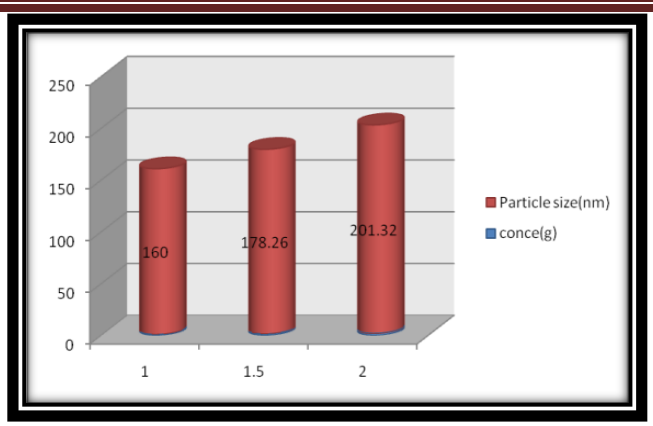

Fig. 4: Particle size of CAPS loaded SLN. Particles size expressed as mean± std deviation

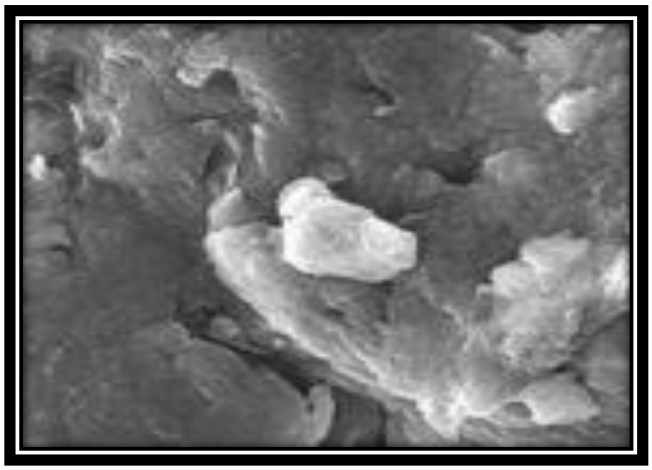

Fig. 5: SEM of formulation Capsaicin Loaded SLN

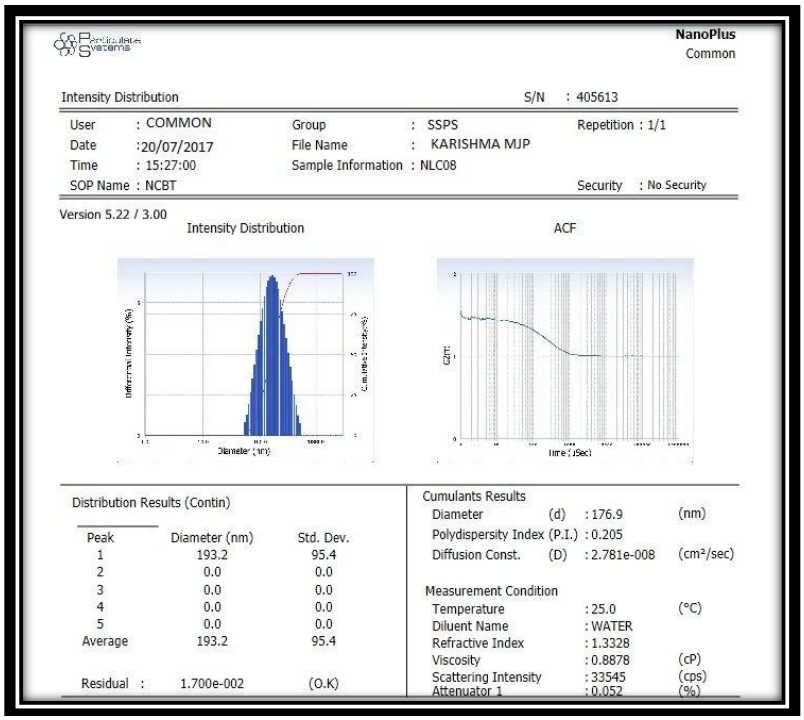

Fig. 6: Graph showing particle size of F1 formulation of CAPS Solid lipid nanoparticles

Solid lipid nanoparticles (1ml) were diluted up to 10ml with distilled water and average particle size and polydispersity index measured by zeta sizer. The results of Capsaicin loaded solid lipid nanoparticles are shown in fig no -6 and poly dispersibility index is 0.205.

Drug release study from SLN:

The release profile of the CAPS loaded SLN is presented in fig no-7 in this study, the SLNs showed the burst release at the initial stage (the first 30 min) followed by controlled release pattern. One of the favorable explanations for the burst release behavior in the early stage could be the diffusion of the encapsulated drug on the surface of the SLN and the other hypothesis that, CAPS was homogeneously distrusted in the nanoparticles.

The F1 formulation showed the slower drug release pattern then the F2 and F3. The release pattern depicted that the increasing the content of Stearic acid, increased the amount of the drug from the SLN carrier.

Table No. 3: In-Vitro % cumulative drug release study of Solid lipid nanoparticles F1, F2 & F3

S. No.	Time (min)	Drug release % F1	Drug release %F2	Drug release % F3
01	30	24.03	30.44	32.64
02	60	30.44	35.89	37.78
03	120	37.40	40.84	44.75
04	180	45.63	49.55	52.33
05	240	62.70	69.98	72.11
06	300	70.44	74.36	80.29

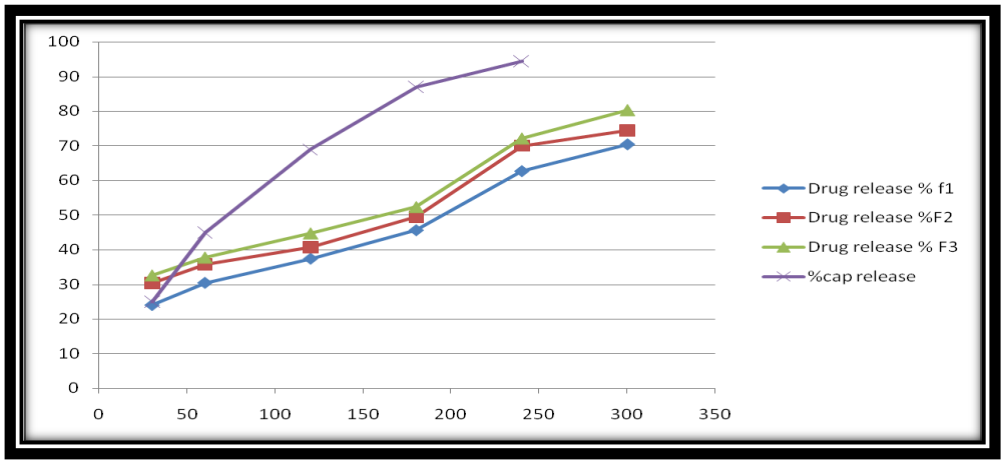

Fig. 7: Comparison of %cumulative drug release of F1, F2, F3 & Plain capsaicin solution

{Note –on graphical representation, % cumulative drug release vs time (min) respectively on Y-axis and X-axis}

Formulation of SLN based gel:

Aloe Vera gel is used as a base for the development of the secondary base for CAPS loaded SLN. Carpool 934, at the concentration 1%w/w was able to gel the SLN dispersion yielding gel with the desired characteristics .Therefore Carbopol 934 1g, was added to the 100mL of Aloe vera gel with the continuous stirring. A few drops of NaOH (0.5N) used to form a thick gel and slightly heated the gel to of a thick consistence of the gel

Characterization of SLN based CAPS- ALOE GEL:

Evaluation of pH, Spreadibilty and Viscosity of gel:

The pH was found to be 6.8 that are in acceptable limits. Spreadibilty is also an important property of the topical formulation. The diameter was found to be 6.8 cm, which indicates the good spredibility of the SLN based gel.

Viscosity: The viscosity of gel was found to be 1340±4.950cps at 60 rpm at room temperature.

Table No. 4: Evaluation of pH, Spreadibilty and Viscosity of gel

Evaluation parameter	Result
pH	6.8
Spreadibilty	6.8cm
Viscosity	1340±4.950cps

Drug release from SLN loaded gel:

The drug release from formulation of SLN loaded gel was studied up to 360 minutes (6 hours), about 69.59 % of drug released.

Drug release from Aloe gel:

In-vitro release of gel presented in fig no-16, which showed the slower release of drug as compared to the capsaicin plain gel. Drug release from Aloe Vera gel of SLN was found 69.59±1.21% at 360 min.

Table No. 5: Cumulative drug release of SLSs from Aloe Gel

S. No.	Time (min)	% Drug release from Aloe gel
01	5	14.85±2.21
02	30	25.09±1.51
03	60	39.266±0.55
04	120	46.66±3.34
05	180	53.35±1.53
06	240	64.30±4.21
07	300	69.59±1.21

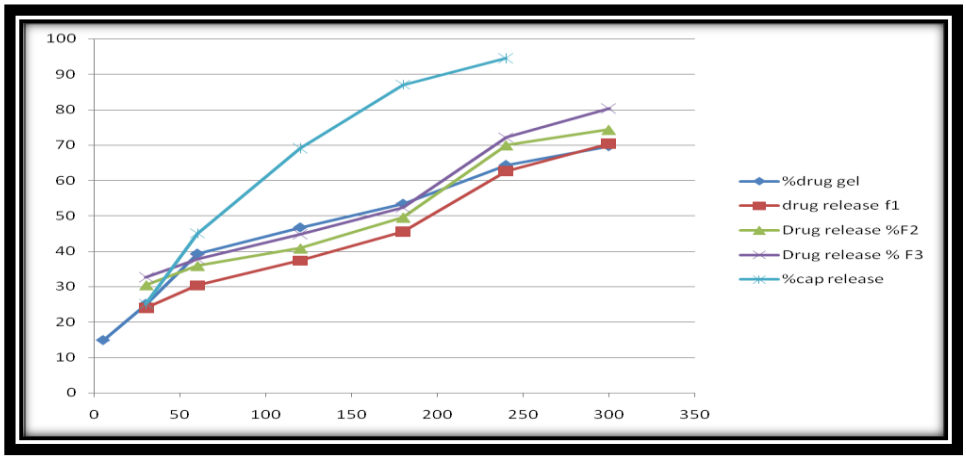

Fig. 8: Comparison graph of all formulation
(F1/F2/F3/ Capsaicin plain solution and Aloe Gel)[In-vitro cumulative drug release]
{Note –on graphical representation, %, cumulative drug release vs. time (min) respectively on Y-axis and X-axis}

CONCLUSION

As the solid lipid nanoparticles formulated were found to be in the Submicron range (160nm-200nm). The entrapment efficiency was found to be near 37%. The release study shows the prolonged release pattern in the Solid lipid nanoparticles formulation in comparison to the plain Capsaicin. The gel formulated by the incorporation of capsaicin loaded gel shown further retardation of drug release. So, in conclusion the SLN formulated in a promising approach for the topical delivery of capsaicin. Therefore, SLNs represent an easy to manufacture, stable, physiologically compatible system with prolonged drug release and reduced irritancy.

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