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RESEARCH ON TOPICAL GEL CONTAINING SOLID LIPID NANOPARTICLES LOADED WITH ACYCLOVIR

VIPUL SAINI*[1], RITU SAINI[1], JITENDRA KUMAR[2]
1. SMT. TARAWATI INSTITUTE OF BIOMEDICAL & ALLIED SCINCES, ROORKEE, UTTARAKHAND,INDIA
2. IBMERDOP MANGALAYATAN UNIVERSITY, ALIGARH, UTTAR PRADESH, INDIA

ABSTRACT
For extended therapeutic effect in the treatment of viral infections, new topical pharmacological alternatives are urgently required. In order to produce an efficient topical Acyclovir solid lipid nanoparticles (SLN) gel formulation with long-term therapeutic potential against tropical viral infections, bioavailability hurdles of Acyclovir were overcome. Acyclovir is a topical antiviral medication used to treat viral infections. Stearic acid and poloxamer 188 were used in the solvent diffusion approach to create the SLN for acyclovir. For the leading moiety's veracity, preformulation investigations were carried out. The generated SLN and gel formulations were then put through physicochemical testing, in-vitro drug release profiles, and kinetics studies. Following that, successful FTIR spectroscopy and scanning electron microscopy of the improved formulation were performed. The findings suggest that SLN F6 has a strong entrapment efficacy, with the greatest entrapment of 92.13%0.975. In terms of particle size, size distribution, and zeta potential, SLN show a mean particle diameter of about 344.3 nm, a unimodal size distribution, a polydispersity index of 0.168, an intercept value of 0.98 with 92% peak intensity, and a zeta potential of around 18.8 mV. Moreover, compared to other formulations, G3 gel exhibits a greater entrapment efficacy of 91.39%0.187. The G3 gel with 1.5% carbopol 934 w/v exhibits a sustained drug release profile with 79.57%0.213 of the drug release even after 24 hours. It is concluded that the Acyclovir loaded SLN based gel formulation containing carbopol 934 1.5% w/v is suitable for topical application and may show a much better result of anti-viralactivity.
KEYWORDS: Solid lipid nanoparticles loaded Gel, Drug Content, pH of the Gel, In-vitrodrug release study

INTRODUCTION
Solid lipid nanoparticles (SLNs) are a cutting-edge, revolutionary drug delivery technology in the pharmaceutical industry today (NDDS). Typical colloidal carriers including polymeric and micro, liposome emulsions, and nanoparticles are represented by the SLN, which was first identified in 1991. The contemporary SLN technique is linked to improved drug penetration, a robust release profile, and targeted drug administration with great physical stability and low degradability, among other things. 58, 60 The benefits of nanoparticles with diameters ranging from 10 to 1000 nm on improving medication bioavailability seem encouraging. In the era of colloidal drug carrier systems, which produces an alternative particle in the field of NDDS, formulation hyphenated with SLN is a crucial consideration.

Solid Lipid Nanoparticles
Solid lipid nanoparticles (SLNs) range in size from 50 to 1000 nm and are colloidal drug carrier systems composed of solid lipid diffuse in aqueous surface active solution.
Due to qualities including good tolerance, physical stability, biodegradability, high bioavailability, protection of relevant pharmaceuticals from decay, ease of preparation, and low toxicity, [21] SLN offer a better alternative to polymeric systems, colloidal systems, and other NDDS. [38, 43, 67] Furthermore, the production process can be changed to release the required drug, prevent drug deterioration, and stay away from organic solvents. This broad adaptability can be crucial for the marketing of new items. A carrier method for enhanced drug delivery, SLN is an intriguing quality. [1]

Structure of solid lipid nanoparticles

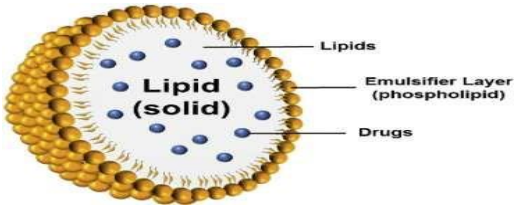


Figure 1: Structure of solid lipid nanoparticles. [36]

Advantages of SLNs

1. Increase the medications' stability.
2. Outstanding biocompatibility.
3. Steer clear of organic solvents. [74]
4. Long-term stability, #[4].
5. Increase trapped bioactive chemicals' bioavailability.
6. Sterilization and scaling up are very simple.
7. Manage and plan drug release. [21]
8. Minimal toxin.
9. Biocompatible and biodegradable

Disadvantages of SLNs

1. Poor drug loading capacity. [68]
2. Less compatibility for hydrophilic drugs
3. Unsure gelation tendency.

Gels

A "semisolid system where the liquid phase is blocked in a polymer matrix that causes a high degree of physical and chemical cross-linking" is what is meant by a gel.

Properties of gels:

1. . Gelling agents are employed in cosmetic and medicinal formulations.
2. . It should be secure, inert, and free from interactions with other formulation elements.
3. . The addition of a gelling agent to the formulation will provide a logical solid-like consistency during storage that can easily be broken down when shear forces are produced by squeezing the container, vortexing the bottle, or applying the formulation topically.
4. . Using anti-microbials should make it possible to prevent microbial strike.
5. . To avoid sloppiness.

It must to be sterile, much as ophthalmic gel

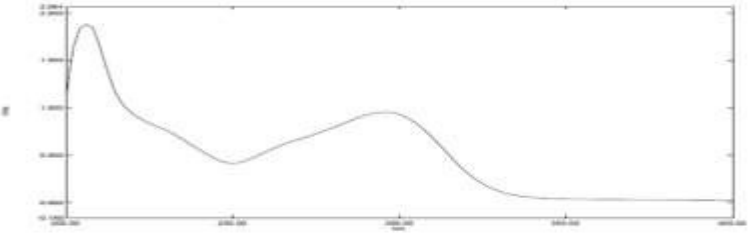
Preformulation study of drug

Melting Point:*(IP., 2007)* Melting point of Acyclovir was found to be 256.6 ±1.15^{0}C with decomposition.

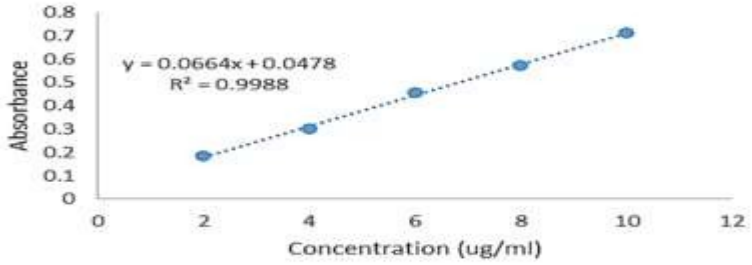
Determination of the absorption maximum of Acyclovir inethanol

The potential drug absorption was determined according to protocol using the highest amount of acyclovir that could be absorbed at 299 nm against a concentration of 2–10 g/ml. It was discovered that the regression

equation and coefficient were 0.0664x - 0.0478 and 0.998, respectively. Acyclovir absorption maximum determination and technique validation are related goals for qualitative and quantitative analysis.[48]



Absorption maxima of Acyclovir in methenol



Regression coefficient of Acyclovir against concentration

Figure 3: Absorption maxima of Acyclovir and regression coefficient against thedifferent concentration of Acyclovir (µg/ml)

Acyclovir's physicochemical studies were carried out to assess the drug's physicochemical characteristics. studies to assess the compatibility of acyclovir with hydrophilic and lipophilic compounds. The results demonstrate that Acyclovir has a low solubility potential in water, where it was found to be 0.00585 0.293 mg/ml, and in stearic acid, prectrol, and dynasan 114, where it was found to be 23.754 0.47, 18.314 0.85, and 22.875 0.32 mg/ml, respectively. Moreover, Acyclovir's non-aqueous solubility in n-octanol was 17.984 0.52 mg/ml. Acyclovir's log10P value in stearic acid, prectrol, dynasan 114, and n-octanol was simultaneously 3.98, 3.30, 3.87, and 3.65.

For a better compatibility examination of the leading moiety before and after formulation, acyclovir and stearic acid underwent FTIR analysis. Figure 4 and Table 1 show the FTIR spectra of acyclovir. Major IR absorption peaks of Acyclovir were observed at 2979.43 cm-1 (C-H stretch), 2198.82 cm-1 (C-N stretch), 1554.35 cm-1 (C-H aromatics stretch), 1471.35 cm-1 (C=C-C aromatic ring stretch), 820.41 cm-1 (para C-H distribution), and 759.46 cm-1 (C-Cl stretch). The main peaks that were discovered proved the Acyclovir's legitimacy and purity as being similar to the report that was used as a reference. [52]

Table 1: FTIR interpretation of Acyclovir

S.No.	Wave number (cm^{-}	Inference
1	3441.02	N-H stretching
2	3308.74	O-H stretching
3	3099.14	C-H stretching
4	1717.21	C=O stretching
5	1541.50	C=C and C=N stretching
6	1308.75	-CH_2 Wagging and twisting
7	1216.74	Aryl alkyl ether
8	1105.79	C-O stretching
9	1083.93	C-O-C stretching

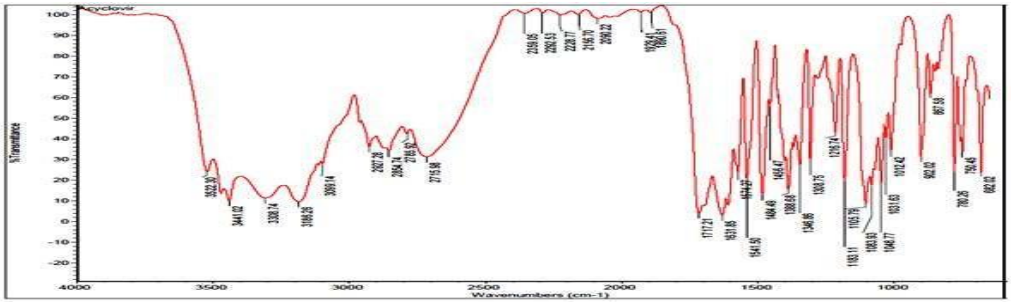


Figure 4 FTIR spectrum of Acyclovir

Development of the method for Acyclovir loaded solid lipidnanoparticles (SLN)

The technique involves a variety of modified nano-precipitation techniques, such as cooling sonication probe and nano-precipitation, for optimising SLN in relation to EE of acyclovir. 4°C and 25°C are the segmental temperature controls. A 4°C aqueous phase is instantly added to, and the resultant hyphenation with an organic phase causes a rapid precipitate. To achieve homogeneity, the temperature was adjusted throughout the early stages of nano-precipitation. By reducing bigger crystal size and aggregation of milled beads, high-pressure homogenization helps to achieve uniform homogeneity.[87] Moreover, stearic acid and poloxomer 188 (w/v) concentrations were alternately changed from 0.5 to 2% while the technique was being optimised for SLN. Following the successful coding of all produced groups of SLN, the percentage of the active moiety that was captured was measured spectrophotometrically at 299 nm. Statistics were used to analyse the collected data. Acyclovir-high SLN are selected as the best SLN and are put through additional testing.

Table 2: Preparation of different Acyclovir solid lipid nanoparticles

Different concentration of leading reagentsfor the formation of SLN			
SLN code	**Acyclovir %(w/v)**	**Stearic acid % (w/v)**	**Poloxomer 188 %(w/v)**
F1	1	0.5	1
F2	1	0.7	1
F3	1	1	1
F4	1	2	1
F5	1	1	0.5
F6	1	1	0.7
F7	1	1	1.5
F8	1	1	2

EVALUATION OF SLN

Evaluation of entrapment efficiency of SLN

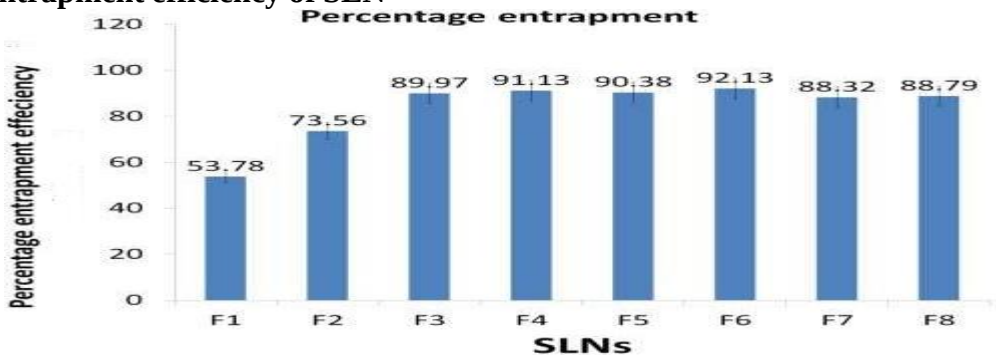


Figure 5: Percentage entrapment efficiency of Acyclovir in SLN

Acyclovir was initially evaluated spectroscopically and physicochemically in pre-formulation research. Percentage EE of Acyclovir was established following the successful production of various batches of nanoparticles. EE assessed spectrophotometrically at 299 nm as a percentage. The subsequent results show that SLN F6 and SLN F1 have the highest and lowest percentages of EE of Acyclovir loaded SLN, respectively, by 92.13%0.975 and 53.78%1.052 w/w. A study quoted by Ige et al. revealed the maximum% EE was between 90 and 95% w/w. 39 As a result, SLN F6 was chosen as an optimal SLN based on the percentage of drug entrapment, and evaluations of its physicochemical characteristics and gel formation followed. Graphical representations of the percentage of all SLN groups that were drug-entrapped.

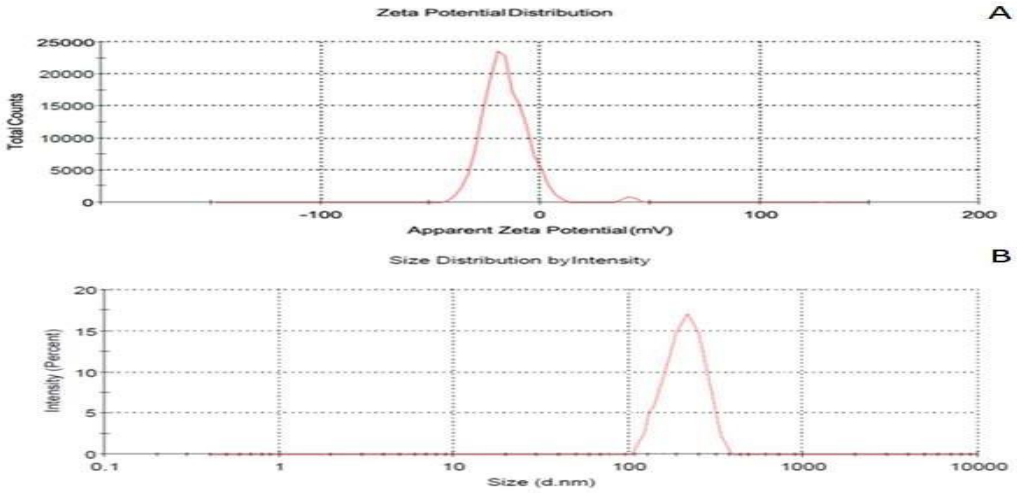
Physicochemical property

Based on their physicochemical properties, including colour, odour, pH stability, and water solubility, the SLN F6 were assessed. Physical and chemical analyses show that SLN is sufficiently more soluble in water than Acyclovir, having a white translucent colour, homogenous and uniform texture, fragrant flavour, and greater stability at pH.

Zeta potential and particle size and size distribution identification

Acyclovir SLN's zeta potential and particle size were successfully measured using the nano ZS90 zetasizer device. One of the key variables used to predict the physical stability of nanoparticles is zeta potential. A high zeta potential value is necessary for the stability of a nanoparticle system and indicates that a nanosystem will be more stable since it will be able to produce a dissuasive force between the nanoparticles. According to Fig. 6, SLN has a high zeta potential of 18.8 mV and indicates a highly stable nanosystem. SLN revealed a mean particle diameter of 344.3 nm, a unimodal size distribution, a polydispersity index (PDI) of 0.168, an intercept value of 0.98, and a peak intensity of 92%. When the PDI value is less than 0.5, it shows the dispersion factor with little nanoparticle agglomeration. [88]

Figure 6 zeta potential, particle size and size distribution of Acyclovir SLN F6



Optical microscopy

Optical microscopy of the improved preparation, SLN F6, characterised with a digital light optical microscope at a 100x magnification, and observation reveal that Acyclovir SLN is successfully localised with homogeneous and uniform texture inside SLN dispersion. It claims that the only particles that could be seen clearly against the microscope resolution power were those whose mean diameter was larger than 2.5 m. Furthermore, no self-assembled structures have been seen in SLN preparation. When using optical microscopy, micellar structures were not seen. Figure 7 displays optical microscopy pictures of SLN F6 with Acyclovir put on it.

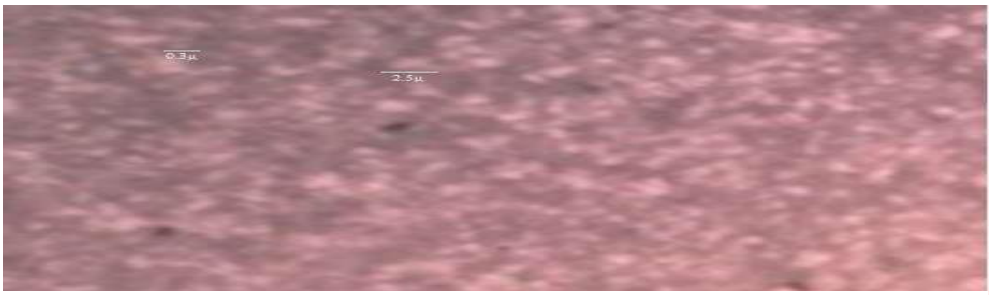


Figure 8 Drug-excipient comparability study by FTIR

To ascertain any potential interactions between the medicine and drug additives, FTIR analysis of SLN F6 was conducted. The main absorption peaks of acyclovir, according to spectral data, are at 2955.75 cm-1 for C-H stretching, 2523 and 2647 cm-1 for S-H stretching, 2201.52 cm-1 for CN stretching, 1556.90 cm-1 for C=N stretching, 1471.88 cm-1 for C=C aromatic ring stretching, and 720.33 and 1101.29 cm-1 for C-Cl stretching. Although the main stearic acid absorption peaks were discovered at 2914.97 cm-1 and 2848.05 cm-1 in the high-frequency range, attributed to the asymmetric and symmetric stretching vibrations of the -CH2- band, respectively, and at 1698.03 cm-1 for the -COOH stretching in the low-frequency zone. After the successful construction of the SLN, there have been no further alterations to Acyclovir, according to a spectral analysis of the optimised SLN. The reported referenced values are strongly supported by spectral data. [52]

Table 2: FTIR interpretation of SLN F6

Characteristics Peaks	**Reported (cm^{-1})**	**Observed(cm^{-1})**
-C = O stretch	1650 - 1850	1717.21
-COOH Stretch	1600 – 1900	1771.95
-NH amine stretch	3150 – 3300	3441.02
OH hydroxy stretch	3150 – 3650	3308.74
C-Cl stretch	550 – 850	609.29

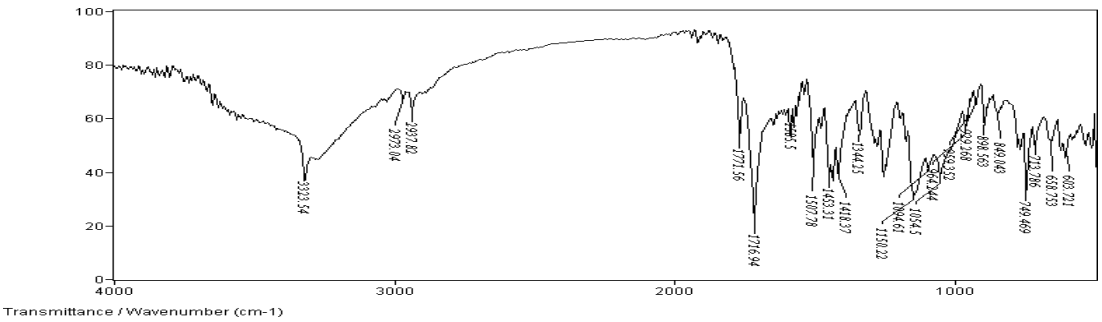


Figure 9: FTIR spectra of SLN F6

Optimization and evaluation of SLN gel

The preparation of the topical gel containing SLN loaded with Acyclovir was accomplished utilising the stirring method and carbopol 934 as the gelling agent. Unpretentious and reliable preparation methods for several SLN gels were discovered. First, the effectiveness of the four different SLN gel preparations, designated as G1, G2, G3, and G4, was assessed in order to measure the percentage of Acyclovir that was entrapped using spectrophotometry at 299 nm. The data obtained reveals that SLN G3 with 1.5% carbopol w/w has the highest drug entrapment percentage (91.39% 0.187). After that, the improved formulation is further assessed for physiochemical characteristics like spreadability, viscosity, pH, and appearance. Results show that the G3 gel's viscosity was determined to be 369cP, which is comparable to the gel viscosity reported by Jana et al. Additionally, the pH of the gel was determined to be 6.120.255.41 In the spreadability

evaluation, the spreadability factor of the prepared SLN gel was determined to be 4.5, and it is stated that the prepared gel produces excellent spreadability as an ideal topical formulation. From the perspective of patient compliance, spreadability is one of any topical formulation's crucial physical qualities. [18]

Figure 10: visual appearance of SLN G3 gel

In vitro drug release and kinetics study

It is routine practise to compare release profiles and predict release mechanisms using statistical models. Drug in-vitro release profile was carried out in a buffer system utilising the dialysis bag method for 24 hours. As shown in Figure 15 and Table 10, the percentages of Acyclovir that desolvate from SLN rise proportionately with time. A developed SLN is capable of releasing drugs in a controlled manner, according to evidence from release profiles. Most SLN forms use homogenous drug trapping throughout systems to explain the leading moiety's slow release.[62] According to Ekambaram et al., a regulated drug desolvation profile can be achieved when the drug is evenly distributed throughout the lipid matrix. Due to its larger HLB value than Cremophor RH 40, Poloxamer 407 has more efficacy against the rate of drug release from SLN.20 Furthermore, Poloxamer 407 has a high external spreadability, which lessens the impacts of the interfacial tension between SLN and the dissolution medium. Moreover, it speeds up drug disintegration and decreases the buildup of drug particles. Moreover, the lipid mass in SLN can improve the potency of the drug's desolvation and govern the size of nanoparticles. Drug release is delayed due to a lengthened effect due to the thickness of the lipid around the nanoparticle.[17]

Table 3: Percentage drug release profile of G3 and control gel.

Sr. no.	Time in hours	Percentage drug release of G3	Percentage drug releaseof control gel
1	0	0	0
2	0.25	7.375±0.153	1.923± 0.011
3	0.5	14.002±0.185	2.052± 0.155
4	1	22.064±0.102	3.042± 0.158
5	2	32.289±0.173	3.182± 0.162
6	3	40.622±0.165	5.094± 0.122
7	4	47.048±0.151	7.815± 0.205
8	6	55.582±0.163	8.706± 0.215
9	8	62.309±0.134	9.387± 0.118
10	12	69.939±0.115	9.035± 0.205
11	24	79.578±0.213	9.773± 0.158

%age Drug Release

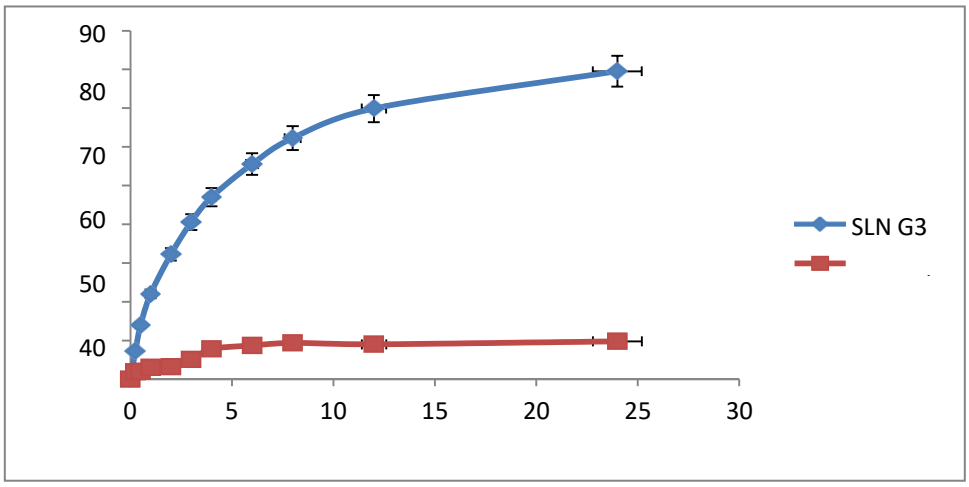


Figure 11: In-vitro drug release profile of SLN gel and control gel

Also, a medication release profile for optimal formulation applies to several kinetic models in vitro (zero-order, first-order, Higuchi, and KrosmayerPeppas model). The collected data were statistically examined in connection to the highest correlation and rate constant to state the kinetics profiling of drug release. Except for the zero-order equation, every model contained the best-fit line. The statistics show how drugs are distributed in homogeneous matrix systems in a regulated or regular manner, and they explain why drugs spread more slowly. According to observations, SLN G3 is a considerably more effective possible topical formulation for prolonged drug delivery. As evidenced by earlier bits of information, this conclusion is virtually identical to the virtuous covenant. Figure 16 shows a graphic representation of the SLN G3 gel's kinetics order.[84]

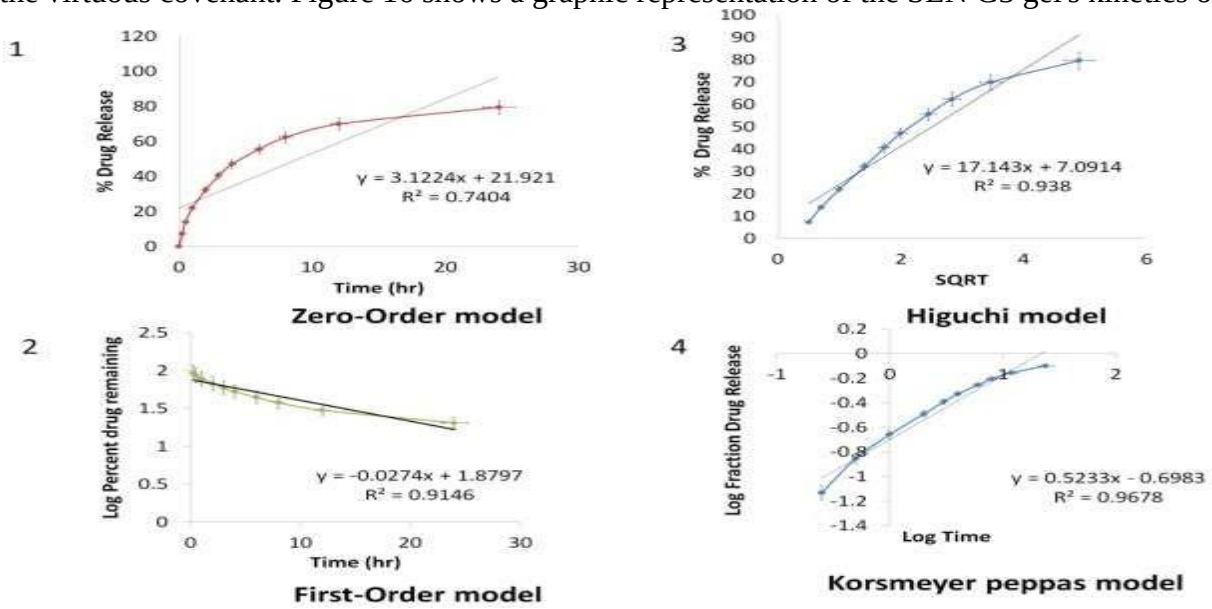


Figure12: kinetics order of SLN G3 gel

FTIR spectral analysis of SLN G3 gel

The successful FTIR study of SLN gel G3 produced spectrum data that matched those of acyclovir and stearic acid, indicating that there may be interactions between drugs and drug additives. According to spectral analysis results, the primary absorption peaks for N-H stretching are at 3331.36 cm-1, C-H stretching is at 2961.88 cm-1, C-N stretching is at 2193.49 cm-1, and C-Cl stretching is at 609.26 & 1044.56 cm-1 for

acyclovir. Although the primary absorption peaks of stearic acid have been assigned at 2932.49 cm-1 and 2863.16 cm-1 in the high-frequency area, which are attributed to asymmetric and symmetric stretching vibrations of the -CH2- band, and 1639.31 cm-1 for -COOH stretching in the low-frequency zone. Even after the consecutive creation of topical gel, spectral analysis of the improved formulation G3 demonstrates that no further drug-drug additive interactions are feasible. So, it may be argued that spectra demonstrate the SLN G3 gel's validity and purity.

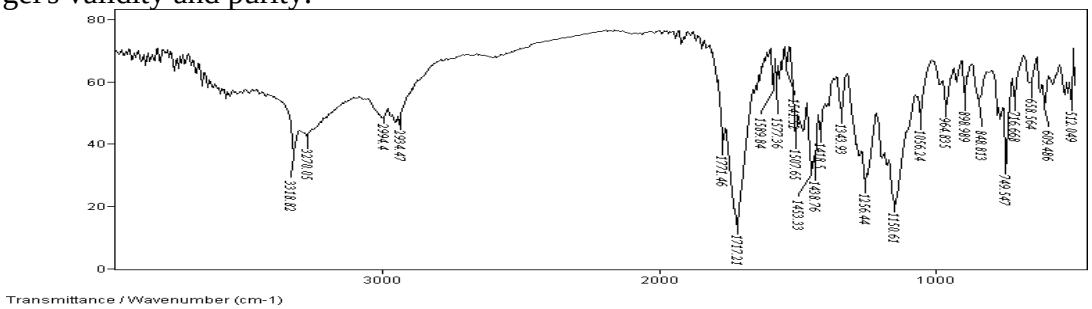


Figure13: FTIR spectra of SLN gel G3

Table 4: FTIR interpretation of SLN G3 gel.

Characteristics Peaks	Reported (cm^{-1})	Observed(cm^{-1})
N-H stretch	3300 – 2400	3331.36
C=C stretch	1638 – 1648	1639.31
CO - O – CO stretch	1040 – 1050	1044. 56
C – Cl stretch	550 – 850	609. 26

Scanning electron microscopy

Figure 18 illustrates the increased formulation's shape after SEM analysis. The majority of vesicles are well-defined, discrete, spherical, and have extensive internal aqueous spaces. SEM examination reveals low density of nanoparticles, which may be caused by the dilution of nanosuspension prior to taking SEM images. Acyclovir-loaded SLN in gel had a spherical shape and a smooth surface, according to SEM examinations.

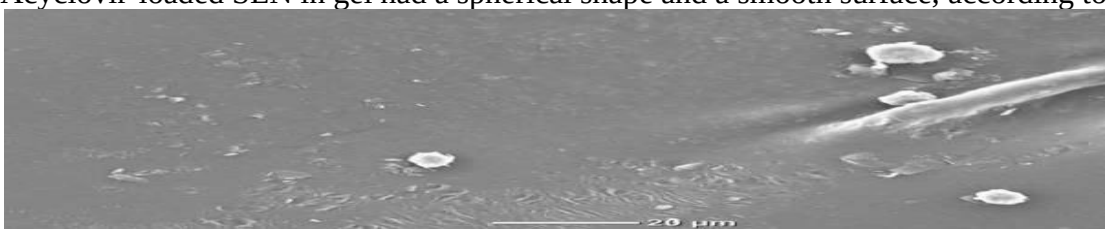
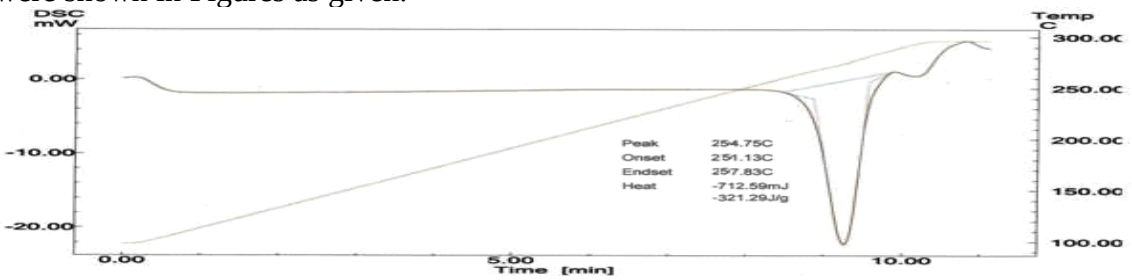


Figure 14: SEM analysis of SLN G3 gel

a) Differential Scanning Calorimetry (DSC)

The compatibility and interactions between drugs and polymer were checked using DSC,results obtained were shown in Figures as given.



.**Figure 15:** DSC Curve of pure Acyclovir

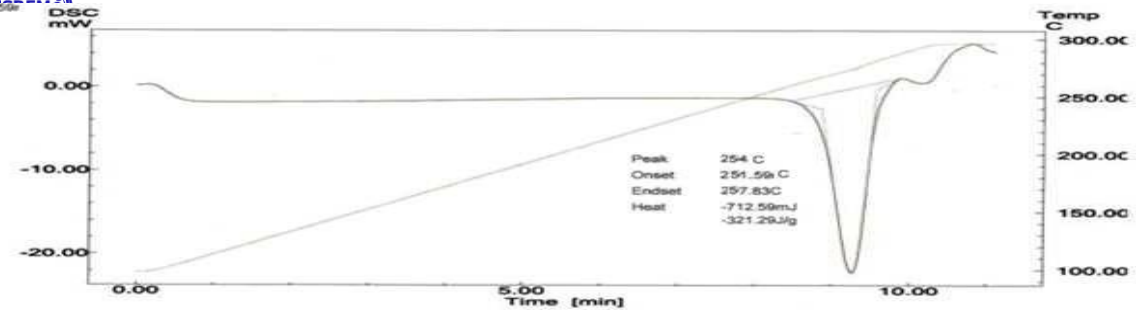


Figure 16: DSC Curve of Acyclovir with stearic acid

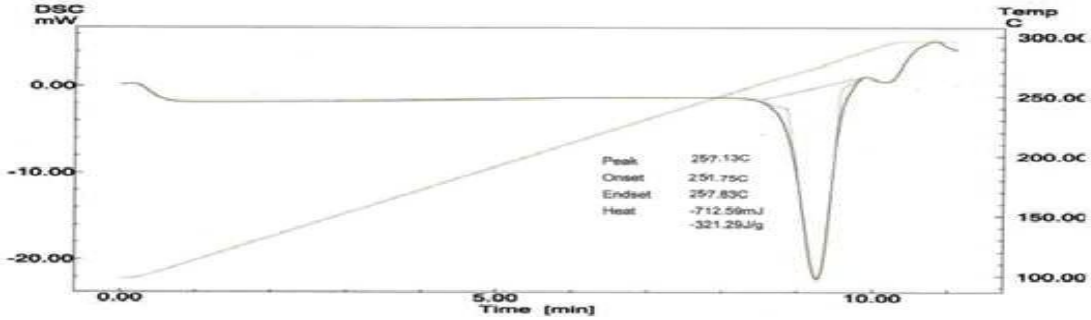


Figure 17 DSC Curve of F6

CONCLUSION

The goal of a topical drug delivery system is to deliver a therapeutic dose of medication to the appropriate location in the body, produce the intended effect, and maintain it for a period of time. To improve skin permeability and controlled drug release at the targeted site in the current study, we created solid lipid nanoparticles (SLN) that are loaded with acyclovir and added them to a topical gel of carbopol 934 that has good skin retention time. Physical and chemical characteristics of the manufactured gel were assessed in accordance with standards protocol to ensure patient compliance. There is no chemical interaction between Acyclovir and excipients, not even according to spectroscopic studies. The gel was examined under a microscope using optical and scanning electron microscopy, which revealed that SLN was distributed uniformly across the gel and that the kinetics of drug release were in good order. So, it can be said that SLN gel offers controlled drug release, and these systems can be effective as drug carriers for lipophilic pharmaceuticals, bioavailability enhancers for poorly water-soluble compounds using nanoparticles, and drug delivery systems.

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