

Formulation, Evaluation, and Characterization of Nitrofurantoin-Loaded Solid Lipid Nanoparticle

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Abstract: Nitrofurantoin is an established antibacterial drug widely used in the management of uncomplicated urinary tract infections. However, conventional formulations may provide limited control over the drug's release characteristics and formulation performance. In the present work, solid lipid nanoparticles (SLNs) were explored as a lipid-based carrier system for nitrofurantoin. SLNs consist of a solid lipid phase dispersed within an aqueous medium and stabilized using suitable surface-active agents. Incorporation of nitrofurantoin into this type of carrier may provide better control over drug distribution and release while offering a flexible platform for pharmaceutical formulation.

The study focuses on the formulation and evaluation of Nitrofurantoin-loaded SLNs using glyceryl monostearate (GMS) as the lipid and Poloxamer 188 as the stabilizing agent. Important formulation characteristics, including particle size, polydispersity, zeta potential, drug content, entrapment efficiency, surface morphology, and in-vitro drug release, were considered for evaluation. The influence of lipid solidification and formulation composition on the behavior and stability of the nanoparticles was also considered. Drug-release data were further examined using mathematical kinetic models to understand the probable release mechanism. The overall objective was to develop a stable nitrofurantoin-loaded SLN formulation with suitable physicochemical characteristics and controlled drug-release behaviour.

Keywords: Nitrofurantoin; Solid lipid nanoparticles ; encapsulation efficiency; characterization; stability; Polydispersity index ; evaluation; zeta potential.

1. Introduction

Nitrofurantoin is an established antibacterial agent used particularly for the treatment of uncomplicated urinary tract infections. Its continued clinical use has encouraged investigation into formulation approaches that may improve the handling and delivery characteristics of the drug. Conventional dosage forms generally provide limited opportunity to modify the drug environment and release pattern after administration. [1,2].

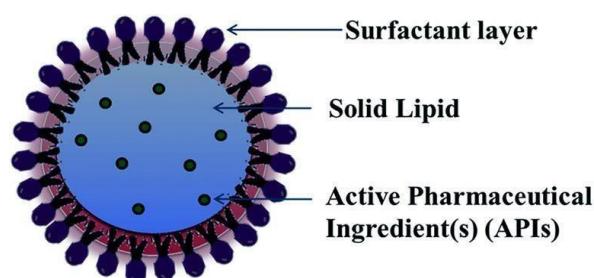


Figure 1: The general structure of solid lipid nanoparticles (SLN)

Nanotechnology-based delivery systems provide an alternative approach for modifying the physical presentation of pharmaceutical substances. Among

these systems, solid lipid nanoparticles (SLNs) have received considerable attention because their matrix is composed of a lipid that remains solid under normal storage and physiological conditions. The lipid phase is dispersed in an aqueous medium with the help of a suitable stabilizer. Different preparation techniques and characterization procedures have been developed for these systems, allowing their properties to be adjusted according to the intended application. [4–6,9–10]

For nitrofurantoin, incorporation into an SLN system may influence the distribution of the drug between the lipid and aqueous phases and may consequently affect its release from the formulation. The characteristics of the lipid matrix, concentration of the stabilizing agent, manufacturing conditions, and subsequent cooling process can all influence the final properties of the nanoparticles. [4–8,10]

An important consideration during SLN development is the physical state of the lipid matrix. Changes in the internal organization of the lipid during storage can modify the space available for the incorporated drug and may consequently affect drug retention and release. Therefore, successful formulation development requires a balance between particle-size reduction, physical stability, adequate drug incorporation, and maintenance of the desired release characteristics. [4–8,10]

The present study was undertaken to formulate and evaluate nitrofurantoin-loaded solid lipid nanoparticles using glyceryl monostearate as the lipid component and Poloxamer 188 as the stabilizing agent. The prepared formulation was examined for important physicochemical and performance-related characteristics to identify its suitability as a lipid-based delivery system.

2. Formulation-Relevant Properties of Nitrofurantoin

The performance of a nitrofurantoin-loaded SLN formulation depends not only on the properties of the drug but also on the interaction between the drug, lipid and stabilizing components. During preparation, the drug may distribute between the molten lipid phase and the surrounding aqueous

phase. The extent of this distribution can influence the amount of drug retained within the nanoparticles and, consequently, the entrapment efficiency and drug-loading capacity of the formulation. [4–10]

The physical structure of the lipid after cooling is another important factor. As the lipid changes from the molten to the solid state, its internal organization develops and may change further during storage. Such changes can influence the amount of drug that remains associated with the lipid matrix and can contribute to alterations in the release profile. [4–8,10]

The concentration of the surfactant also requires careful consideration. An adequate amount is necessary to maintain dispersion stability and prevent excessive aggregation of the particles. However, increasing the surfactant concentration may also modify the distribution of the drug between the lipid and aqueous phases. Therefore, the lipid-to-surfactant ratio must be optimized rather than selected solely on the basis of particle-size reduction. [4–6,9–10]

For the development of nitrofurantoin SLNs, the major formulation-related factors can therefore be summarized as follows:

Drug incorporation: The affinity of nitrofurantoin for the selected lipid influences the quantity of drug retained in the nanoparticle matrix.

Lipid solidification: The structural changes occurring during cooling and storage can affect drug retention and subsequent release.

Surfactant concentration: Poloxamer 188 contributes to stabilization of the dispersion, while its concentration may also influence drug distribution and particle characteristics.

Particle characteristics: Particle size, size distribution and surface charge provide useful information regarding the physical state and stability of the prepared dispersion. [4–10]

These factors should be considered together during formulation optimization because improvement in one characteristic may sometimes be accompanied by an undesirable change in another.

3. Solid Lipid Nanoparticles: Concept and System Behavior

Solid lipid nanoparticles are colloidal lipid-based carriers in which the drug is incorporated into or associated with a solid lipid matrix. The particles are maintained as a dispersion in an aqueous medium with the assistance of one or more stabilizing agents. The composition of the lipid phase, type and concentration of surfactant, processing conditions and cooling procedure collectively determine the properties of the final formulation. [4-10]

Unlike a conventional liquid emulsion, an SLN formulation undergoes solidification of its lipid phase after preparation. This change in physical state is important because the arrangement of lipid molecules within the particle can influence the location and mobility of the incorporated drug. During storage, further changes in lipid organization may occur, which can modify drug retention and release characteristics. [4-8]

3.1 Why SLNs behave differently from emulsions

In a conventional emulsion, the dispersed lipid remains in a liquid state. In contrast, the lipid phase of an SLN is converted into a solid-state during cooling. The resulting solid matrix provides a different environment for drug incorporation and movement.

The extent of lipid organization may vary according to the lipid composition and processing history. Consequently, the characteristics of an SLN formulation can change with time if the lipid matrix undergoes further structural rearrangement. Such changes are important during stability evaluation because they may influence particle properties, drug retention and release behaviour. [4-8]

For this reason, characterization of SLNs should not be limited to particle size alone. Parameters such as size distribution, zeta potential, drug content, entrapment efficiency, morphology, release behaviour and stability provide complementary information about the quality and performance of the formulation. [9-10]

4. Advantages and Disadvantages of Nitrofurantoin-Loaded SLNs

4.1 Advantages:

- The lipid matrix can provide a controlled environment for drug incorporation and may help modify the release rate of nitrofurantoin. [4,5]
- Incorporation of the drug into the lipid phase may reduce direct exposure of the drug to the surrounding aqueous environment. [4,5]
- SLNs can be prepared using physiologically acceptable lipid materials, depending on the intended route of administration. [5]
- The formulation can be adapted to different pharmaceutical dosage-form approaches according to the properties required for the final product. [5]
- Solid lipid matrices can provide useful physical characteristics for storage when the formulation is appropriately optimized. [4,5]
- The particle characteristics can be modified by changing formulation variables such as lipid concentration, surfactant concentration and processing conditions. [4,5]
- SLNs provide a platform in which drug release can be investigated and adjusted through changes in matrix composition and particle characteristics. [4,5]
- The system can be further investigated for incorporation into advanced drug-delivery formulations intended to improve formulation performance. [5]

4.2 Disadvantages

- Changes in the structure of the lipid matrix during storage may reduce the amount of drug that can remain incorporated in the particles. [4,5]
- Variation in raw materials or processing parameters can contribute to differences between individual formulation batches. [5]
- Structural changes within the lipid phase during storage may affect the long-term release and stability profile of the formulation. [4,5]

5. Preparation and Methodology

5.1 Probe ultrasonication method followed

by magnetic stirring

Composition:

- Nitrofurantoin
- GMS
- Poloxamer 188
- Distilled water q.s.
- Method: Probe ultrasonication

Step 1: Prepare lipid phase

- Take GMS in a beaker.
- Heat it to about 70-75°C until completely melted.
- Add Nitrofurantoin to the melted GMS.
- Stir gently until the drug is uniformly dispersed.

Step 2: Prepare aqueous phase

- Take about 80-90 mL distilled water in another beaker.
- Add Poloxamer 188.
- Stir until it dissolves completely.
- Heat the aqueous phase to approximately 70-75°C.

Step 3: Prepare pre-emulsion

- Slowly add the hot Poloxamer solution to the molten GMS/drug mixture.
- Keep the mixture on the magnetic stirrer at about 1500 rpm for 10 minutes.
- This produces a coarse pre-emulsion.

Step 4: Probe ultrasonication

- Transfer the pre-emulsion to a suitable sonication vessel.
- Immerse the probe into the dispersion without touching the bottom or sides.
- Sonicate for 5 minutes using the probe sonicator.

Figure 2: Probe sonication of the SLNs



- Use the amplitude recommended by your instrument/SOP; avoid excessive heating.
- If your instrument has pulse mode, use it to control temperature.

Keep the sample temperature controlled during sonication.

Step 5: SLN formulation

- After sonication, allow the dispersion to cool gradually to room temperature while gently stirring.
- As GMS cools and solidifies, the Nitrofurantoin-loaded SLN forms.
- Make the final volume up to 100 mL with distilled water if necessary.

Step 6: Storage

- Transfer the dispersion into a tightly closed vial/bottle.
- Store at approximately 4°C rather than in the freezer.

6. Evaluation of the optimized nitrofurantoin SLNs

6.1 Particle size and PDI

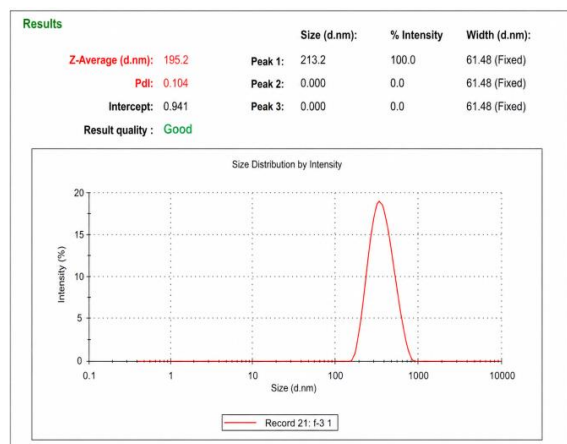


Figure 3: Particle size and PDI of optimized Nitrofurantoin SLNs.

6.2 Zeta potential

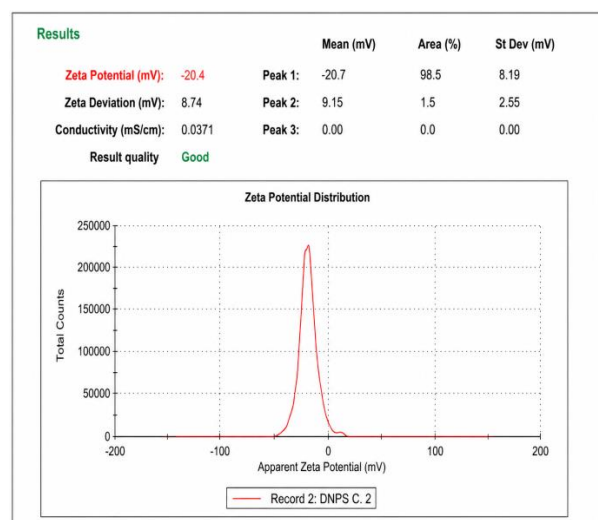


Figure 4: Zeta potential of optimized SLNs formulation.

6.3 Drug content

The result of the drug content of the optimized formulation is shown in **Table:1**

Evaluation parameters of Nitrofurantoin SLNs	Results
pH	7.2 ± 0.3
%Drug content	88±0.08

6.4 Surface Morphology by SEM

The SEM image of the optimized formulation is depicted.

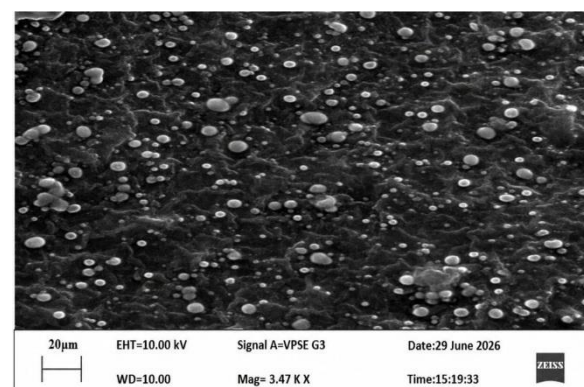


Figure5: SEM analysis of optimized Nitrofurantoin SLNs.

7. CHARACTERIZATION OF OPTIMIZED FORMULATION

Table2: Characterization of optimized formulation.

Parameters	Trail 1	Trail 2	Trail 3	Average
Particle size (nm)	195.1	195.3	195.2	195.2±0.17
Zeta potential (mV)	-20.2	-21.2	-20.1	-20.4±0.13

Drug content (%)	88.5	89	88.8	88.7±1.31
Entrapment efficiency (%)	87.8	89.6	88.8	88.73±0.73
CDR (%)	81.8	81.2	81.4	81.37±0.83

7.1 *In vitro* drug release study

The results of the *in vitro* drug release study of the optimized formulation are shown in Table 17, and the drug release profile is depicted in **Table :3**

Time(hr)	(%)CumulativeDrugRelease
0.5	1.77 ±0.27
1	2.74±0.42
2	9.04±0.24
3	15.78±0.17
4	28.40±0.48
5	37.78±0.35
6	43.05±0.16
7	63.98±0.20
8	72.48±0.34
9	81.37±0.52

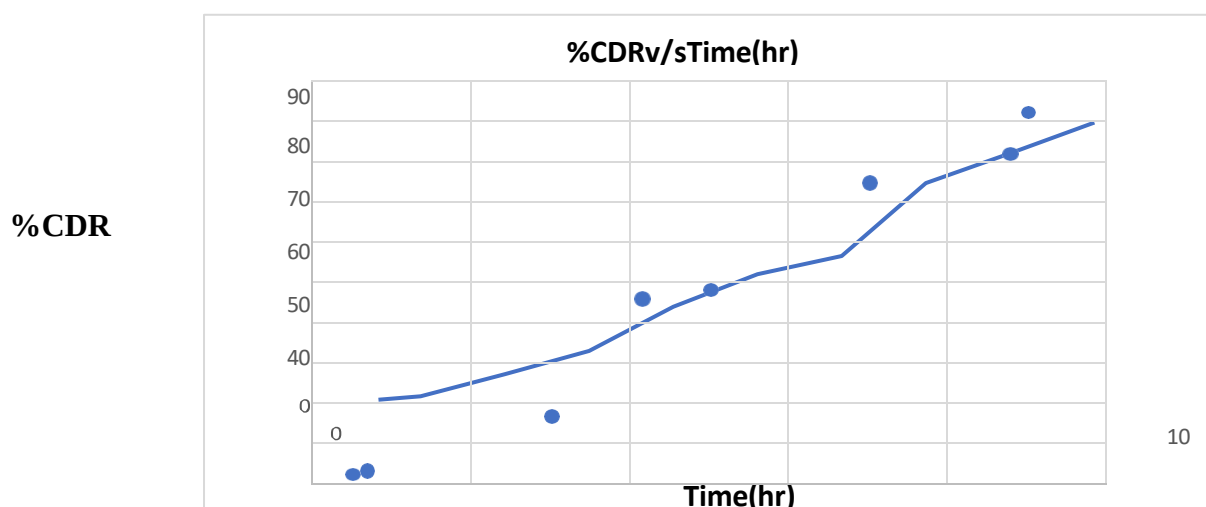


Figure 6: %CDRvsTIMEof optimized SLN

7.2 Drug release kinetics

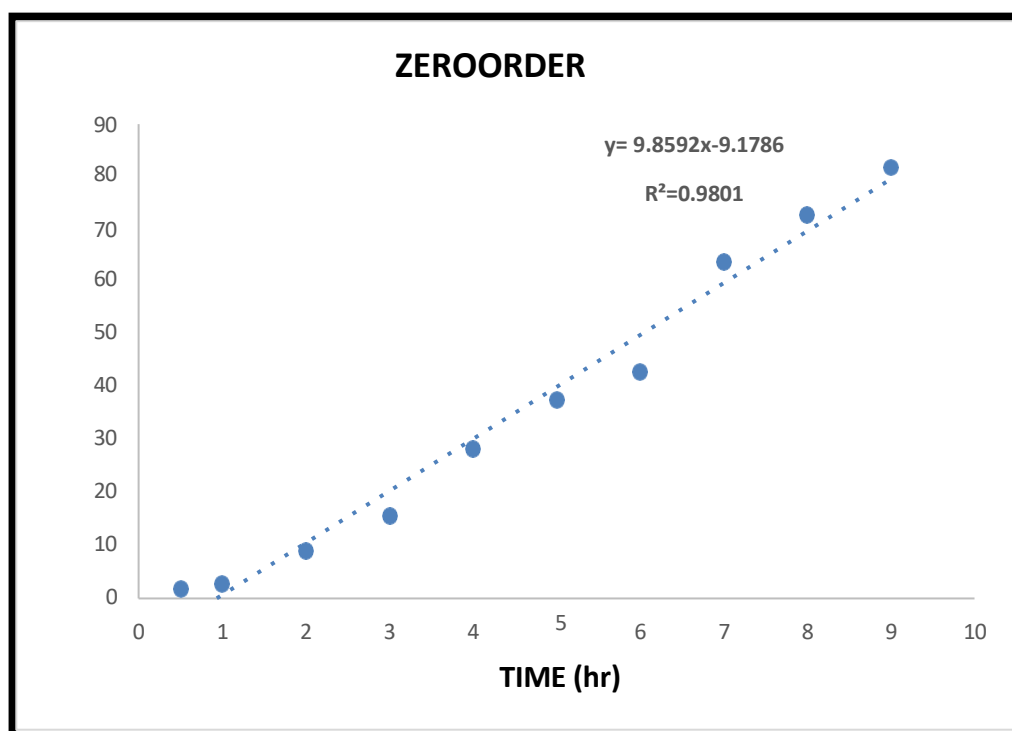


Figure7:Zero-orderkineticsplot ofSLNs.

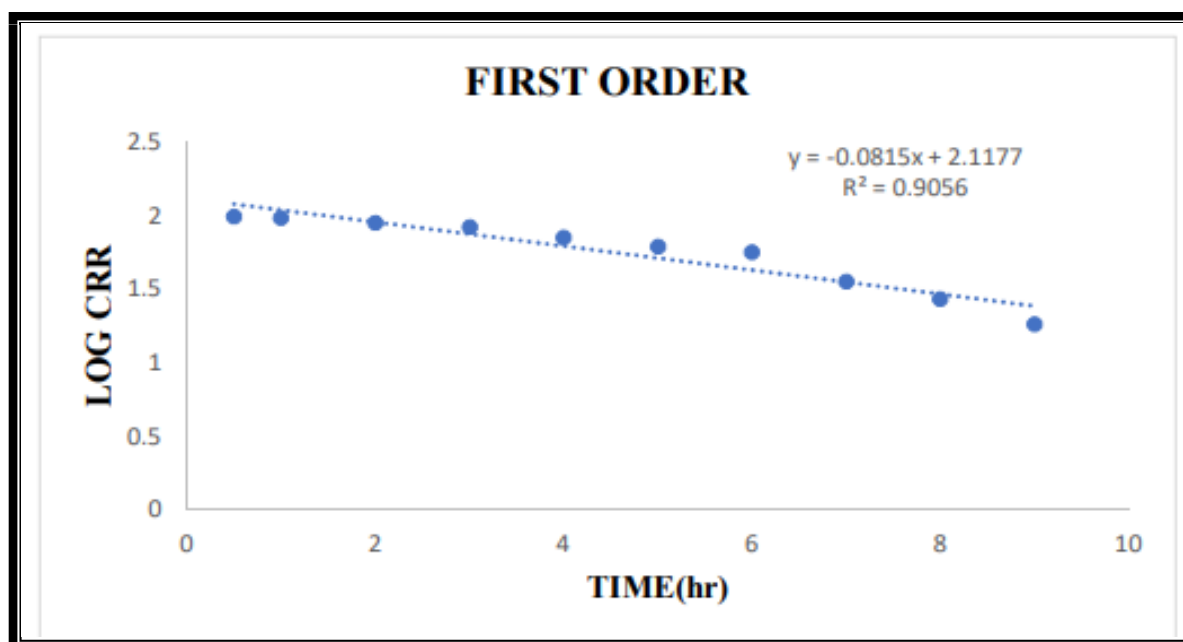


Figure8:First-orderkineticsplot of SLNs.

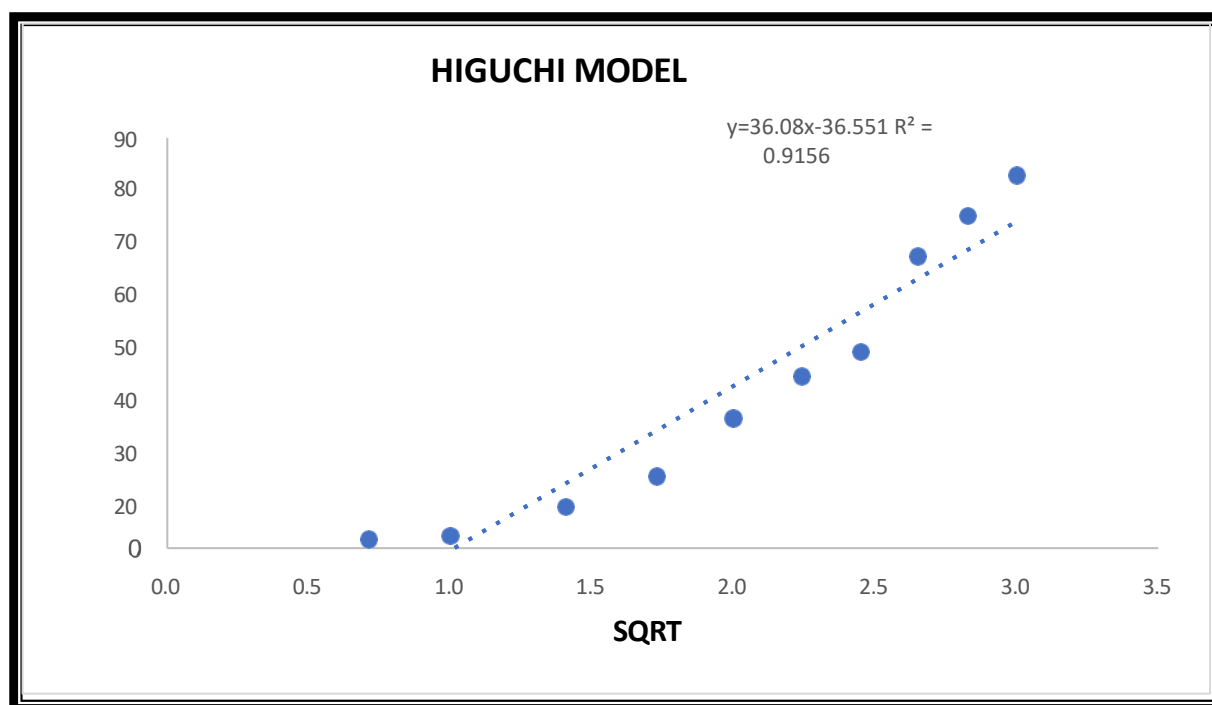


Figure9:Higuchi plotof SLNs.

FormulationCode	RegressionFactor			Korsmeyer-Peppas	
	Zero-order	First order	Higuchi model	R ²	N value
Optimized Formulation	0.9801	0.9938	0.9156	0.9883	1.4185

Table4:Results of release kinetic models for the optimized formulation

7.3 Stability Studies

After 60 days of storage at room temperature, the optimized SLN formulation was evaluated for various parameters. The results obtained after the stability period indicated that the formulation remained stable, with no significant changes observed in the evaluated parameters.

Table 5: Stability studies of different parameters of the optimized SLN formulation.

Parameter	Resultsobtained on 1 st Day	Resultobtained after 30 Days	Resultobtained after 60 Days
Particulatesize(nm)	195.2±0.17	196.7±0.12	197.7±0.18

Zetapote ntial (mV)	-20.4	-19.2	-19.6
PercentageD rug content (%)	88±0.56	88±0.49	89±0.46
Percentage Entrapment Efficiency(%)	87.64±0.73	87.56±0.38	88.86±0.83
Percentage Drug release at 9hr (%)	81.37±0.83	83.56±0.96	83.66±0.92

8.Result and Discussion

Solubility study:The drug is sparingly soluble in water & alcohol. It is completely Soluble in Dimethyl formamide.

Melting point : 270⁰C to 272⁰C

λmax of the Drug : 369nm

8.1 PRE-FORMULATION STUDIES

Pre-formulation studies are an essential initial step in the systematic development of a pharmaceutical dosage form. The physical and chemical characteristics of the drug, both alone and in combination with selected excipients, were investigated to obtain information necessary for developing a stable and effective formulation. The objectives of the pre-formulation studies were:

- To determine the important physicochemical properties of the drug substance.
- To assess the compatibility of the drug with selected excipients using FTIR spectroscopy.

8.2 Melting Point

The melting point of the drug was determined using a melting point apparatus (Thiele's tube method). The experimentally obtained value was compared with the reported literature value. The melting point of the drug was observed to be 273°C (270–275°C).

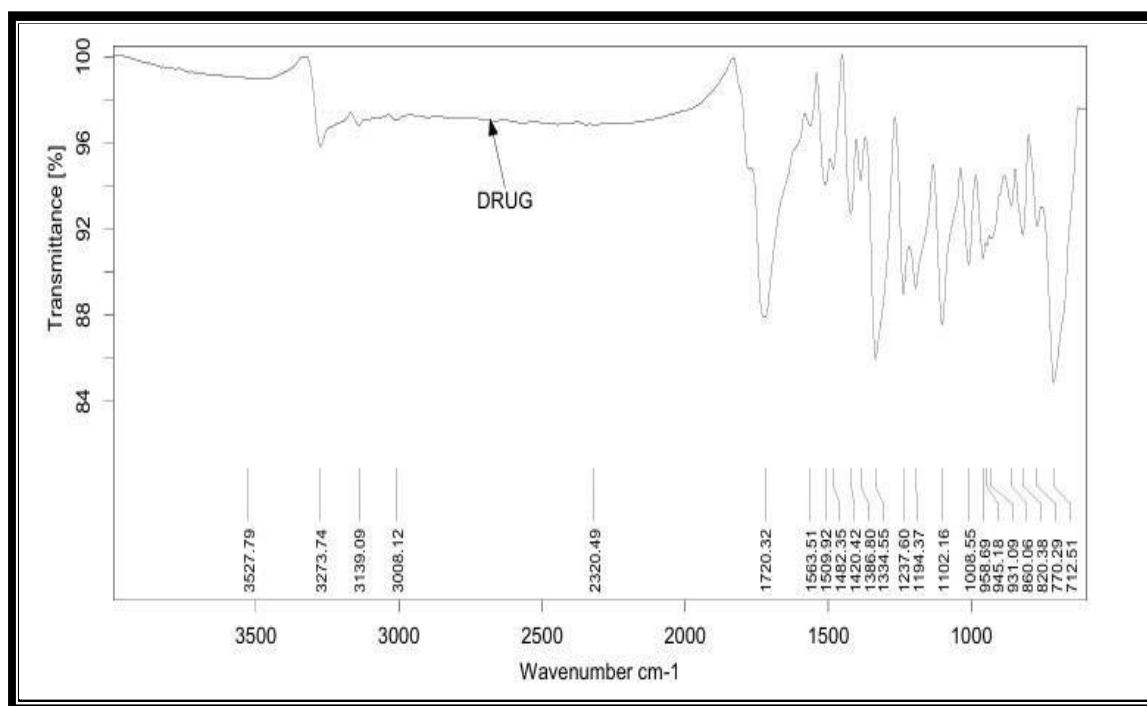


Figure10: The FT-IR spectrum of pure Nitrofurantoin

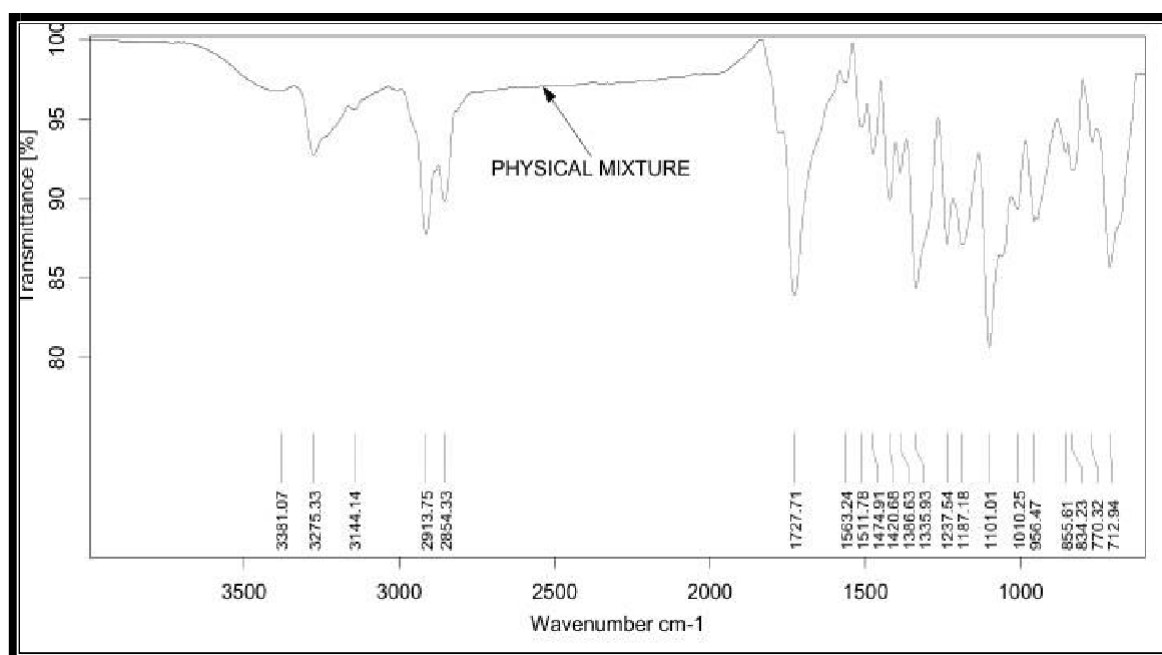


Figure11: The FT-IR spectrum of the physical mixture of Nitrofurantoin+GMS+Poloxamer188(1:1)

The FTIR spectrum corresponds to *nitrofurantoin*. The key functional groups identified in the spectrum, such as the amide group (C=O), nitro groups (-NO₂), hydroxyl (-OH), and aromatic structures, are all characteristic of nitrofurantoin. This confirms that the FTIR data represents the drug nitrofurantoin.

A perusal of the above FTIR spectra, the characteristic peaks of Nitrofurantoin pure spectrum were retained in the FTIR spectra of the physical mixture of drug with GMS and Poloxamer 188. Therefore, there was no drug-lipid interaction was found. Hence, these lipids were used for the preparation of SLN.

8.3 Formulation Design of Nitrofurantoin SLNs

Experimental Run

Table 6: experimental batches with results of particle size (nm) and entrapment efficiency (%)

	Factor1	Factor2	Response1	Response2
Runs	A:GMS (mg)	B:Poloxamer188 (mg)	Particle size (nm)	EE (%)
1	300	150	184	84.9
2	300	100	213	74.1
3	400	200	207	89.3
4	400	100	201	82.3
5	200	100	252	52.3
6	400	150	213	84.4
7	200	200	247	57.3
8	300	200	195	86.7
9	200	150	252	59.3

8.4 .Conclusion

The present study was an effort to design, formulate, and evaluate the nitrofurantoin-loaded SLN to achieve more solubility, stability, permeability, and enhanced antibiotic action of the drugs. Nitrofurantoin belongs to BCS class II, exhibiting low solubility and less stability. Hence it would be beneficial to improve the solubility and stability of the drugs which would in turn lead to probable improvement in the bioavailability of the drugs. Therefore, it was decided to formulate SLN of nitrofurantoin.

SLN were prepared by the ultrasonication method using GMS as a solid lipid, poloxamer 188 as a surfactant, and water as a solvent. The results of particle size and entrapment efficiency of the optimized formulation were within $\pm 5\%$ variation of predicted results. Preliminary compatibility studies FTIR indicated that there was no interaction between the drug and selected excipients. As there was no shift in the peaks, it was concluded that the drug had not undergone the process of degradation or complexation. The

optimized SLN formulation method showed 195.2nm and 201nm particle size, 0.104 and 0.134 PDI, 87.64% and 92% entrapment efficiency, and -20.4mV and -26.9mV zeta potential. Further, SEM results showed that the SLN revealed that there was no segregation and particles were spherical in shape. The optimized SLN *in vitro* release patterns show controlled release over the period of 9 hrs. The release of NFT from the optimized SLN followed first order and Higuchi release

kinetics. Both systems exhibited excellent stability in terms of Zeta potential, particle size, polydispersity index, and encapsulation efficiency following storage for eight weeks. The study concluded that nitrofurantoin--loaded SLNs can be an effective novel drug delivery approach for the treatment of UTI.

9. References

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