

# Strategic Improvement of the Solubility and Permeability of Naftidrofuryl Through Novel Solid Lipid Nano Formulation Technology and Method Development and Validation Using the RP-HPLC Method

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## Abstract

Solid lipid nano formulation is an interesting approach to increase poorly soluble drugs bioavailability. Naftidrofuryl (class IV drug) is a serotonin antagonist that belongs to the class of vasodilators and has only 10% bioavailability due to its low solubility and permeability. The current work deals with the nano formulation of naftidrofuryl solid lipids by microemulsion method. The solid lipid nano formulation was characterized by particle size (PS), zeta potential (ZP), and transmission electron microscope (TEM) analysis. The results showed that the PS was 82.1 nm with a ZP of -56.6 mV, showing good stability. TEM analysis shows that the particles had spherical solid lipid morphology. The analytical method was developed and validated as per the '(Q2) R1 ICH' guidelines. All the results reported were in specified limits. Forced degradation studies of naftidrofuryl were conducted according to International Conference on Harmonization (ICH) (Q1A) R2 guidelines.

## Keywords

Solid lipid nanoparticles, Naftidrofuryl, Particle size, Transmission electron microscope, International conference on harmonization

## Introduction

Naftidrofuryl, a selective serotonin inhibitor used as a vasodilator, is known chemically as (RS)-2-(diethylamino)ethyl-3-(1-naphthyl)-2-(tetrahydrofuran-2-ylmethyl)propionate with a molecular weight of 383.524 g/mol. It belongs to the Biopharmaceutical Classification System (BCS)-IV class, characterized by low permeability and solubility [1].

Norio Taniguchi of Tokyo University of Science is credited with coining the term "nanotechnology" in 1974. It is described as the investigation and application of structures in the size range from 1 nm to 100 nm. Using advanced nanotechnology, some items on the market have been upgraded [2]. Oncology, immunology, ophthalmology, and other professions can all be affected by nanotechnology. The many reduction procedures used in pharmaceutical research led to different nanostructures with special physicochemical and biological characteristics. They help reduce toxicity, reduce patient-to-patient variation, and improve solubility and bioavailability.

Pharmaceutical nanoparticles are solid drug carriers of submicron size and may or may not be biodegradable [3]. The genesis of nanoparticles is highly dependent on the nanostructure. Compared to bulk metals, they have different physical and chemical characteristics [4]. Due to their slower dissolution rate, drugs with low water solubility have reduced bioavailability. According to the

BCS classification, drugs can be divided into 4 types according to their permeability and solubility in aqueous media.

The BCS was developed in the mid-1990s to classify medicinal compounds based on their membrane permeability and water solubility (Table 1) [5]. It was difficult to improve the requirements for BCS-IV drugs because BCS-II or BCS-IV drugs dissolve or dissolve in the intestinal fluid at low doses, but similar drugs do not at high doses. Table 2 summarizes solubility criteria [5] based on Indian, United States, and British Pharmacopoeias [6].

**Table 1:** Classification of drugs as BCS-I to BCS-IV.

S. No.	Drugs	Solubility	Permeability
1	Class I	High	High
2	Class II	Low	High
3	Class III	High	Low
4	Class IV	Low	Low

**Table 2:** Solubility criteria.

Description	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10000
Insoluble	More than 10000

Liposomes, emulsions, and polymeric micro- and nanoparticles are just a few examples of colloidal carriers that can be carried by solid lipid nanoparticles (SLNPs), which were first proposed in 1991 [7]. Due to their superior alternative particle carrier system, nanoparticles produced from solid lipids are used as novel colloidal drug carriers for intravenous applications. SLNPs are submicron physiological colloidal carriers with 50 to 1000 nm size that are released in water or an aqueous surfactant solution. Due to their, large surface area, small size, high drug load and phase interaction at the interface, SLNPs have special characteristics [8].

## Materials and Method

### Materials

We sourced naftidrofuryl (Figure 1), soy lecithin and stearic acid from Finar, India. The methanol was shipped from Rankem, Maharashtra, while the chitosan was purchased from Hi-Media in Mumbai. Acetonitrile was supplied from Sigma Aldrich of Maharashtra. The ultra-pure water is made using Milli-Q® refinement technology from Millipore Corporation-Bedford (MA, USA). Analytical grade chemicals and solvents were last.

### Methodology

#### Chromatographic conditions

The isocratic approach to elution was used in the

experiment. As bipartite mobile phase, a 60:40 v/v combination of acetonitrile and phosphate buffer (potassium di-hydrogen orthophosphate), adjusted to pH 3.0, was used. The acetic acid, which was used to adjust pH 3, was filtered using a vacuum filter. Approximately 20 L of material were injected in each cycle and the eluate was measured with ultraviolet detectors at wavelengths of 225 nm.

#### Solubility studies by a shake-flask method

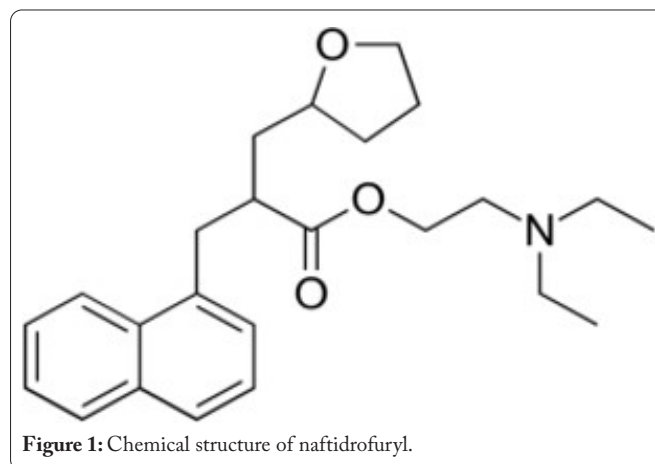
Studies have been conducted on the solubility of naftidrofuryl in various solvents, including water, methanol, acetonitrile, ethanol, and chloroform. A standard 25 ml bottle containing 50 mg naftidrofuryl and 10 ml solvent was kept at 25 - 30 degrees Celsius for 48 h in an isothermal shaker. Drug was added until steady-state saturation was reached. Samples were removed from the shaker and centrifuged at 4000 rpm for approximately 5 min. Whatman filter paper was used to separate the supernatant and solubility was measured by ultraviolet-visible spectroscopy at 225 nm [9].

#### Preparation of working standard solution and stock solution

Accurately measure 10 mg of naftidrofuryl using a working standard in a clean, dry 10 ml volumetric flask. To this was added 5 ml of methanol and left in a sonicator to completely dissolve. Methanol was then used to make up the remaining volume to create 1000 µg/ml concentrated solution. 1 ml of the stock solution was transferred into a 10 ml vial. Methanol was used to bring the final volume to the required level, giving a concentration of 100 g/ml. A separate standard 10 ml vial has been produced with different concentration ranges for secondary stock solution (g/ml), including 0.5, 1, 2.5, 5, 7.5, 10, 12.5, and 15 µg/ml. The finished solution was stored at -50 °C for future use.

#### Formation of SLNPs

On a magnetic stirrer, 100 mg of stearic acid was accurately weighed, added to a clean, dry beaker, and stirred at 2000 rpm at 60 °C. The solution was then given 30 mg of naftidrofuryl once the lipid had completely melted. A cleaned and dried beaker was kept in a magnetic stirrer at 60 °C while continuously stirring 20 ml of double distilled water. Then 10 mg of soybean lecithin was added, and the mixture was stirred until completely dissolved. Solution B was dosed into a 2 ml syringe and poured into "solution A" [10]. A beaker with 50 ml



**Figure 1:** Chemical structure of naftidrofuryl.

of cold water was filled and the beaker was placed on an ice-filled plate. Solution B was added dropwise to 50 ml of cold water. The reaction was carried out on a mechanical stirrer at 2000 rpm at 60 °C for about an hour and the resulting solution was sonicated [11].

### Characterizations of SLNPs

To control the ZP and PS of SLNPs, a dynamic laser light scattering technique was developed [12]. The SLNPs dispersion was centrifuged at 20000 rpm for 120 min at 10 °C in a chilled centrifuge to calculate entrapment efficiency (EE). The equation 1 was used to determine the percentage of EE (%EE).

$$\%EE = \frac{\text{Total quantity of drug} - \text{Quantity of drug present in supernatant}}{\text{Total quantity of drug}} \times 100 \quad (1)$$

The polydispersity index (PDI) is used to examine the degree of PS dispersion of produced SLNPs. An ideal PDI would be between 0 and 1. Using high-resolution TEM, PS, size distribution, morphological, topographical, compositional, and crystal information were examined. TEM was used to image pre-dried SLNPs [13].

### Cumulative drug release

Cumulative drug release (%CDR) was calculated using the dialysis bag approach. The membrane diffusion method (also known as the dialysis method) was used to perform drug release tests for the produced nano formulation. 50 ml of a selected buffer medium solution (6.2 pH of potassium di-hydrogen phosphate buffer) was collected and maintained on a magnetic stirrer at 4000 rpm at constant temperature for one hour in a cleaned and dried 100 ml beaker. A diffusion bag soaked overnight in buffer solution was removed. 5 ml of the prepared formulation was measured out, transferred to the other side of the dialysis bag and one end of the bag was tightly sealed. Assessed the formulation for leaks. The dialysis bag was then immersed in the beaker, which was filled with a buffer solution to help release the drug. Using a syringe, 2 ml sample was taken from the buffer medium at predetermined intervals, such as 0 s, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 24, 48, and 72 h, and the same amount of buffer solution was added to maintain the equilibrium volume of the solution [14].

At different time intervals, the proportion of drug delivery studies was estimated using equation 2.

$$\%CDR = \frac{C_t}{C_0} \times 100 \quad (2)$$

Where  $C_0$  is the quantity of SLNPs laden, and  $C_t$  is the amount of drug released at time t.

### Permeability study

We bought male White Leghorn chicks from the neighborhood market that weighed between 600 and 900 g. 6.3 g NaCl, 0.35 g KCl, 0.14 g CaCl<sub>2</sub>, 0.16 g KH<sub>2</sub>PO<sub>4</sub>, 0.15 g MgSO<sub>4</sub>·7H<sub>2</sub>O, 2.1 g NaHCO<sub>3</sub> and 5 g glucose were combined to form the Krebs-Ringer solution to create. The chicken was sacrificed, the abdomen underwent a midline incision, and the small intestine was exposed to isolate the out turned intestine. By gently washing the lumen with a pH 7.4 buffer solution

(Krebs-Ringer's solution), the mucus was gently removed. The first 6 cm of an intestinal segment was removed and placed in an oxygenated Krebs-Ringer solution. A warm Krebs-Ringer solution was used to clean it well and the fat layer next to the intestine was gently scraped away. The proximal end of the gut was turned upside down, examined for damage, and then ligated over a specially designed glass rod to create an inverted pouch [15]. The permeability of each pure drug and the permeability of the manufactured SLNPs were independently assessed. The SGF material, which had been oxygenated, was then poured into this pot. Six ships underwent permeability testing. 5 ml samples were taken at intervals of 0, 15, 30, 45, 60, 90, and 120 min. After each sampling, the same amount of SGF medium was added to the dissolution jar as shown in the. Optimized and tested RP-HPLC techniques were used to estimate the amount of permeable material released [16].

### Analytical method validation

#### Linearity

The linearity response was measured between 0.5 and 15 g/ml. The stock solution was appropriately diluted with mobile phase to create a range of concentrations. The data were evaluated using the linear regression equation. The peak area ratios of the reference substances were calculated relative to their concentrations.

#### Precision

Three different doses (0.5, 5, and 15 g/ml) were injected on the same day to assess intra-day precision. Relative standard deviation percentage (RSD%) has been calculated. This experiment was performed over several days to determine inter-day precision.

#### Accuracy

Accuracy was assessed using three independent point levels (0.5, 5, and 15 g/ml). The samples were made by mixing the standard formulation of naftidrofuryl with the SLNPs version. The chemically introduced drug was recovered.

#### Limit of detection (LOD) and limit of quantification (LOQ)

In accordance with ICH recommendations, equation 3 and equation 4 are used to determine LOD and LOQ [17].

$$LOD = 3.3 \times N/S \quad (3)$$

$$LOQ = 10 \times N/S \quad (4)$$

Where S is the slope of the associated calibration curve and N is the standard deviation of the compound's peak regions.

### Studies for stability of SLNPs

The strength of the prepared standard samples was assessed at room temperature (25 °C) after an 8-h interval analysis of the solution. Sample stability is ensured throughout the analysis by verifying that sample preparation and analysis time have not led to drug deterioration [18].

#### Ruggedness

The ruggedness of the approach was assessed by adjusting experimental parameters such as instruments, operators, solvents, reagent sources and columns of a similar

type. Retention time, asymmetry factor, capacity factor and selectivity factor were among the chromatographic features evaluated.

### Robustness

By injecting the standard solutions under optimized conditions - 1% methanol in the mobile phase, 0.1 ml flow rate, 5 changes in wavelength and 5 changes in pH - it was possible to investigate the robustness of the method. End results have been noticed and documented.

### Forced degradation studies

Standard naftidrofuryl samples were exposed to acidic, alkaline, oxidative, thermal, photostable, and neutral conditions as part of the degradation process.

Alkaline degradation was performed by refluxing the materials with 0.1 N NaOH for 30 min at 60 °C, while acidic degradation was performed by refluxing the samples with 0.1 N HCl. Then was added 30% v/v HClO<sub>4</sub> and the mixture was refluxed at 60 °C for 30 min to prevent oxidative damage. The material degraded in three different ways: thermal, photostable, and neutral. A sample was heated at 60 °C for about 72 h in an oven to measure thermal degradation; 200 Wh/m<sup>2</sup> in a photostability chamber to measure photodegradation; and refluxing water at 60 °C for 6 h to measure neutral degradation. Naftidrofuryl was synthesized at a final concentration of 1 mg/ml by sufficient dilution. By placing 10 µl of the samples in the system and viewing the chromatograms, sample stability can be assessed [19].

## Results and Discussion

### Formulation of SLNPs

SLNPs were made using the microemulsion approach. Based on the differences between the drug, stearic acid, and chitosan, the procedure was optimized. The smaller particle size in the F3 formulation is related to the lower fat content. The PS would increase as the fat content increases. This is due to the way the surface of the drug is coated with lipids. Table 3 shows the formulation.

### Characterization of naftidrofuryl SLNPs

#### ZP and PS

The PS of naftidrofuryl SLNPs ranged from 1200 nm to 82.1 nm and 2 nm. Optimized nanoparticles containing naftidrofuryl are included in the formulations. With an average diameter of 82.1 nm, stearic acid:chitosan showed the least PS (Figure 1). A remarkable change in PS resulted from the change in the mass ratio of chitosan and stearic acid. Lower fat content is related to smaller PS. The surface coating of lipids on the outer drug layer causes the PS to increase as

the lipid concentration increases. SLNPs have a ZP range of -56.6 mV. Negative ZP values show nanoparticle stability due to electrostatic attraction. The PDI ranged from 2.90 to 2.99. Consistent SLNPs distribution of molecular weights of polymer chains, uniform cross-linking, and the creation of networks with more organized organization are all indicators of PDI as shown in figure 2.

### 3.2.2. TEM of SLNPs

TEM images of SLNPs were found to be uniform in size and spherical as in figure 3. There was no evidence of nanoparticle agglomeration. However, there was good agreement between the TEM result and the calculated PS using the dynamic light scattering approach. From the TEM data, the fabricated SLNPs was determined to have a constant spherical shape.

### %EE

SLNPs shown the %EE of ranging from 34.62 to 52.67%. The percentage of drug entrapped in these systems can vary depending on the amount of solid lipids such as stearic acid, surfactant, and polymer, among others. Accordingly, the most appropriate combination of lipid drug and surfactant should be used to achieve the highest EE [20]. The concentrations of chitosan and stearic acid that were increased showed a decrease in the percentage of EE. When the stearic acid concentration was increased, the capture efficiency may have dropped due to aggregates formation. The results showed that maximum purification efficiency was achieved with the naftidrofuryl:stearicacid:chitosan ratio of 3:10:1.

### Chromatographic conditions

To create a simpler, more accurate, and more affordable

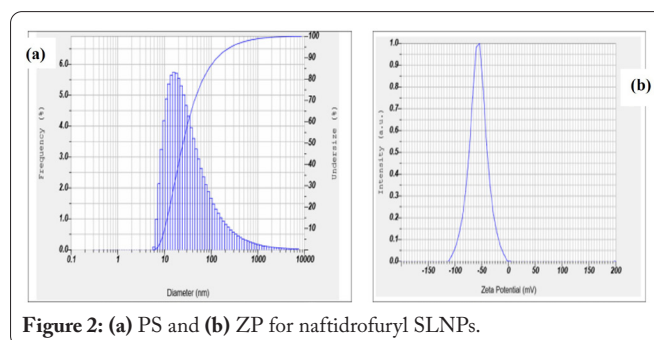


Figure 2: (a) PS and (b) ZP for naftidrofuryl SLNPs.

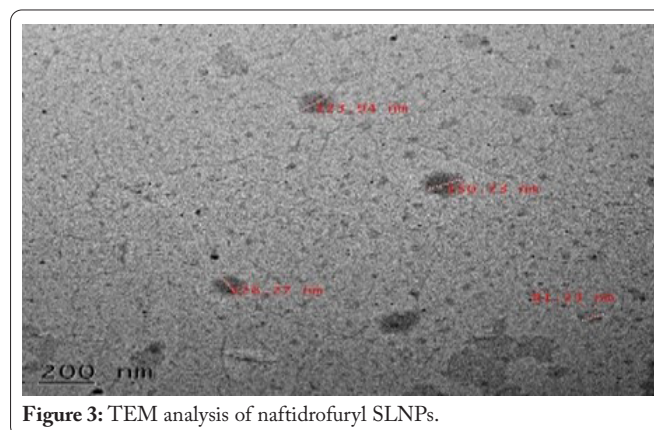


Figure 3: TEM analysis of naftidrofuryl SLNPs.

Table 3: Preparation of SLNPs of naftidrofuryl.

S.No.	Content	Drug (mg)	Stearic acid (mg)	Chitosan (mg)	Speed (rpm)	Time (min)
1	F1	10	100	20	2000	60
2	F2	30	100	20	2000	60
3	F3	30	100	10	2000	60

liquid chromatography method for separating and measuring the drug, preliminary work was done using the right combination of mobile phase, pH, erratic flow rate, elution type isocratic or gradient, column type and temperature with wavelength. In the initial stage, the pH was adjusted between 2.5 and 4 and the mixture of the mobile phase of acetonitrile and phosphate buffer (60:40 v/v) was used. As faster chromatographic separation is allowed with correct peak symmetry and reduced peak tailing, the mobile phase of acetonitrile in combination with phosphate buffer at pH 3 was chosen from the pilot study.

### Solubility studies

The solubility study of naftidrofuryl was performed by the shake flask method with various solvents such as chloroform, acetonitrile, ethanol, and methanol [21]. Solubility results showed that the maximum solubility was observed in acetonitrile with methanol 25 mg/ml and the lowest solubility in chloroform 15 mg/ml.

### Method development

The approach has been verified against several criteria, including precision, linearity, specificity, accuracy, stability, LOQ, LOD and robustness, in accordance with ICH (Q2R1) standards.

Retention time for naftidrofuryl was 2.2 min (Figure 4). The linearity of the method was evaluated with concentrations ranging from 0.5 µg/ml to 15 µg/ml. The standard curve was plotted using analyte concentration and response factor. This illustrates the linear relationship of concentration and peak area for selected analyte concentration range 0.5 to 15 µg/ml. The correlation coefficient, slope, and intercept values determined to be 0.9932.

Linearity was assessed by adding standard solutions to previously analyzed sample solutions at three different levels of LQC, MQC, and HQC (Figure 5). The developed approach yielded a high recovery rate of 93.79 - 95.67% of the examined samples, as shown in table 4.

To determine accuracy (Table 5), both intra-day (Table 6) and inter-day (Table 7) precision were considered. To assess intraday accuracy, six duplicates were generated at three different levels. The observed %RSD values are shown. The inter-day precision was determined by an inter-laboratory test. The RSD value is less than 2% found.

LOQ and LOD, which were calculated using the signal-to-noise ratio, were estimated to be 10 and 30 ng/ml, respectively. The determined relative standard deviation to be less than 2%. Since the %RSD was less than 2%, it was concluded that the method was reliable and sustainable. The solution appeared to remain constant during the investigation.

According to the ICH criteria, all measurements related to the suitability of the system are within permissible limits and have been found to be acceptable. A search was performed, and the validity of the method was checked against the ICH criteria (Q2R1).

The approach shows no conflicting peaks when blank and

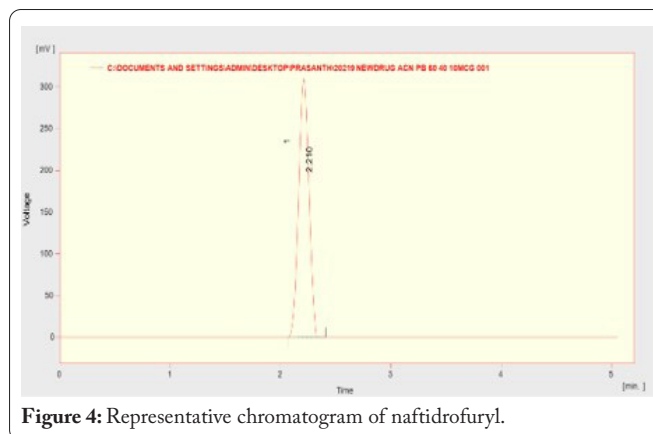


Figure 4: Representative chromatogram of naftidrofuryl.

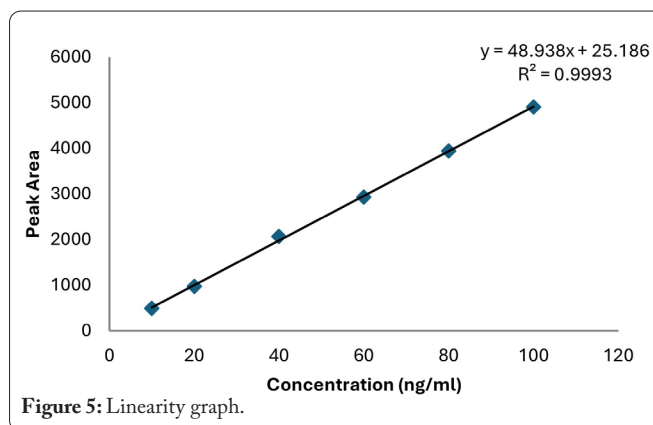


Figure 5: Linearity graph.

Table 4: Linearity studies for the naftidrofuryl.

S.No.	Concentration (µg/ml)	Peak area average	STDEV	%RSD
1	0.5	264.825	2.881	1.088
2	1	682.665	3.372	0.494
3	2.5	1268.925	6.783	0.534
4	5	2333.523	40.364	1.729
5	7.5	3053.481	74.865	2.451
6	10	3752.905	44.534	1.186
7	12.5	4569.257	30.635	0.670
8	15	5431.393	17.162	0.315

placebo injections are performed during the drug retention time as shown in figure 6 and figure 7, respectively.

### Force degradation studies

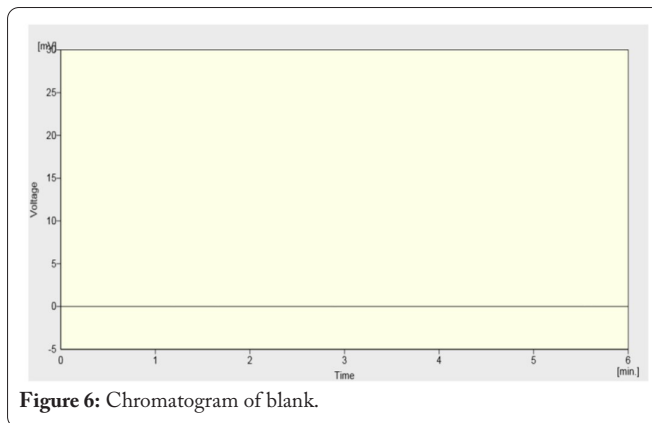
Under varying exposure conditions, naftidrofuryl has shown varying degrees of deterioration. The results are shown in table 8. Of all conditions tested, acid was found to have the highest rate of degradation (72.65% w/w), followed by oxidation (70.02% w/w), the thermal study (69.54% w/w), photolytic (67.16% w/w) and alkaline (60.17% w/w). Alkali, photolytic, thermal, oxidant, and acid were in this order of percent degradation, respectively.

### %CDR and release kinetics

Figure 8 shows the percentage of CDRs over a 72-h period ranging from 57.183 to 92.318%. After 72 h, the formulation of naftidrofuryl SLNPs3 showed a higher CDR (92.318%) compared to previous formulations. There were

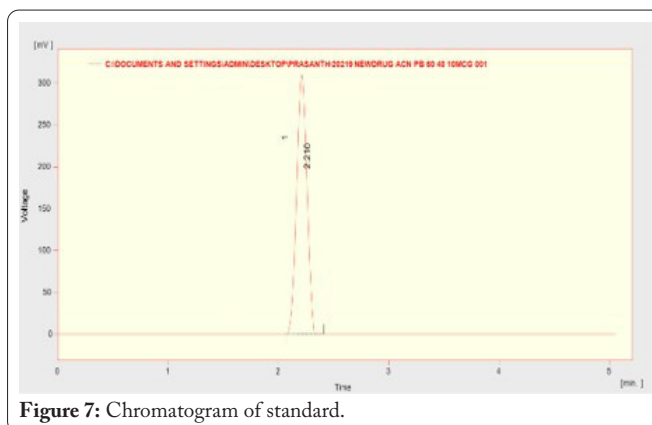
**Table 5:** Accuracy studies for the naftidrofuryl.

S. No.	Concentration (µg/ml)		Measured concentration (µg/ml)	% Nominal (%w/w)
	Actual concentration	Added concentration		
1	10	0.5	9.10	93.79
			9.25	
			9.64	
2	60	5	22.71	94.02
			22.83	
			23.97	
3	100	15	39.36	95.67
			34.51	
			34.84	



**Table 6:** Inter-day precision of naftidrofuryl.

Concentration (µg/ml)	Peak area			%RSD (%)
	1 <sup>st</sup> day	2 <sup>nd</sup> day	3 <sup>rd</sup> day	
0.5	483.710	483.361	489.728	0.062
5	3670.535	3690.066	3693.679	0.127
15	7021.364	7028.164	7066.201	0.205



**Table 7:** Intra-day precision of naftidrofuryl.

Concentration (µg/ml)	Peak area			%RSD (%)
	1 h	2 h	3 h	
0.5	481.937	487.078	489.287	1.248
5	3461.380	3542.010	3567.031	3.134
15	7024.818	7027.216	7031.562	1.170

surfactant matrix and that diffusion of the matrix caused the drug to be released (Table 9).

**Permeability study by everted chick intestinal sac method**

observable fluctuations in drug release with increasing drug concentration and a fixed stearic acid:chitosan release ratio of 10:1. As the stearic acid:chitosan ratio (SLNP1 to SLNP3) was changed, the amount of drug delivered was also changed. The results show that complex formation can temporarily delay drug release. The highest drug release was observed in the naftidrofuryl:stearic acid:chitosan (3:10:1) ratio, which can be attributed to the small particle size, large surface area and increased contact with the dissolving fluid. The release medium decomposed the naftidrofuryl into the nanoparticles. The larger nanoparticle size can provide more vacuum space, slowing down particle discharge. The CDR claimed that the drug was uniformly dispersed or dissolved in the lipid

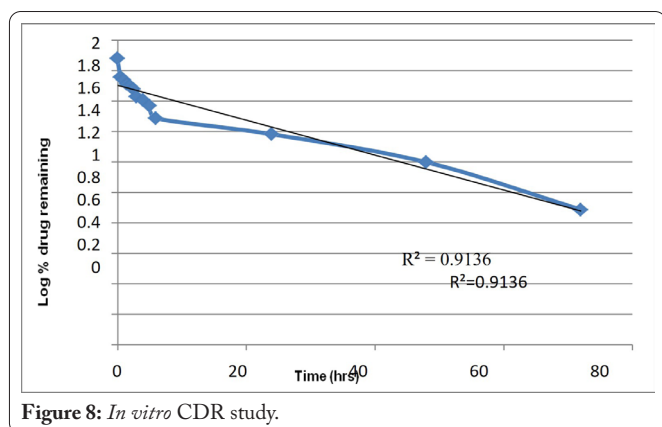
Drugs must have a certain degree of permeability to be bioavailable. An outward-facing digestive tract model was used to study permeability. This approach has several advantages, including reduced need for study samples, faster experiment times, and reduced first-pass metabolism [22]. According to the study, naftidrofuryl has a patency of 38.79%, while naftidrofuryl-SLNP3 has a patency of 86.93%. Compared to pure naftidrofuryl, naftidrofuryl-SLNP3 showed a 2.2-fold increase in permeability.

**Conclusion**

The biopharmaceutical categorization system places the water-soluble drug naftidrofuryl in class-IV (poor solubility

**Table 8:** Forced degradation studies for naftidrofuryl.

S. No.	Time (h)	Acid hydrolysis % degradation (%w/w)	Alkaline hydrolysis % degradation (%w/w)	Photolytic % degradation %w/w	Thermal % degradation (%w/w)	Oxidative % degradation (%w/w)
1	0	31.77	36.53	28.94	34.14	32.79
2	1	36.35	40.04	33.46	38.53	36.76
3	2	40.27	45.20	38.72	44.97	41.56
4	3	45.89	50.27	42.48	49.40	45.81
5	4	49.54	50.61	45.09	53.72	50.35
6	6	56.73	54.72	49.57	56.26	54.06
7	24	61.24	54.91	54.21	60.185	59.24
8	48	65.18	56.83	59.38	64.97	65.47
9	72	72.65	60.17	67.16	69.54	70.02



and low permeability). The current study focuses on physical modifications that boost solubility and permeability. SLNPs for naftidrofuryl can be generated using the successfully established technique. Naftidrofuryl SLNPs have demonstrated greater solubility and permeability than the tablet form of the drug. The analytical technique was made under ideal chromatographic conditions, verified to ICH (Q2R1) standards, and all validation parameter results reported were within acceptable ranges. Based on the reported results, it was determined that the SLNPs formulations created showed higher solubility and drug permeability.

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## Conflict of Interest

None.

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Table 9: Drug release kinetics.

Time (h)	F <sub>1</sub> % CDR	F <sub>2</sub> % CDR	F <sub>3</sub> % CDR
0	11.736	14.376	24.763
0.5	24.891	29.189	43.018
1	29.349	31.439	45.493
1.5	31.113	34.911	48.704
2	33.741	37.147	50.307
2.5	35.703	40.037	52.322
3	36.232	42.232	55.747
4	38.747	46.747	59.787
5	40.787	49.787	63.190
6	43.910	53.910	69.476
24	48.746	57.746	76.016
48	52.010	62.010	84.286
72	57.183	66.913	92.318

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