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DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF NANOCRYSTALS OF NITROFURANTOIN

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Keywords:

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ABSTRACT: Nitrofurantoin is a broad-spectrum bactericidal antibiotic that affects both gram-negative and gram-positive bacteria. Nitrofurantoin exhibits bacteriostatic or bactericidal effects by inhibiting the synthesis of DNA, RNA, protein, and cell wall synthesis. Nanocrystals of NFT were prepared by a cold high-pressure homogenization technique. To improve the dissolution rate, the drug was formulated in a nanocrystal by using an emulsion diffusion method, high-pressure homogenization or sonication. NFT was dispersed in aqueous surfactant solution containing poloxamer 188, PVPK 30, and HPMC E3 under continuous stirring. Poloxamer 188 was used as a surfactant for the preparation of the NCs. Formulation NC9B3 has a mean particle size 231 ± 9 nm with polydispersity index 0.09 ± 0.02, which indicates a very narrow particle size distribution. % Entrapment efficiency was 98.3 ± 0.7 slow drug release profile indicates the homogeneous dispersion of NFT in the lipid matrix. NCs have crystalline nature with rough surfaces, which has been confirmed using SEM analysis. XRPD spectra show the reduction in the crystalline behavior of the drug and the lipid after the formation of the NCs. There was no significant change in the mean particle size and polydispersity index after 6-month storage at 25 °C / 60% RH.

INTRODUCTION: Nitrofurantoin is a drug of choice for UTIs [1]. Nitrofurantoin is active against common causes of urinary tract infection, including *E. coli* [2]. Sustained-release drug delivery systems offer advantages of attenuation of adverse effects, fewer fluctuations in plasma drug concentration, improved patient compliance, reduction in dosing frequency [3]. The bioavailability of the drug and its absorption from the gastrointestinal tract can be greatly improved by particle size reduction [4]. The total therapeutic effectiveness of nano-formulation depends not only on the action of the drug itself but also on other factors related to the delivery system [4, 5].

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Nitrofurantoin is a broad-spectrum bactericidal antibiotic affects both gram-negative and gram-positive bacteria [6]. The compound has no apparent adverse effects on the developing fetus and can be used in pregnant women [7]. In the proposed research work, we have to formulate, optimize and evaluate the nano-formulations of antibiotic drug (Nitrofurantoin) by improving the solubility and bioavailability nanocrystals, a carrier-free colloidal delivery system in nano sized range, is an interesting approach for poorly soluble drugs [8].

The research work shall emphasize on the design, development and characterization of the nano-formulations of nitrofurantoin (NFT) through the novel approach. The short biological half-life (0.3 to 1 h) and dosing frequency more than one per day make nitrofurantoin an ideal candidate for sustained release [5, 17]. Hence, there is a need of nitrofurantoin nano-formulations for bioavailability enhancement. Nanocrystals (NCs) have been recognized as an effective formulation and drug

delivery because of its advantages like higher bioavailability, better stability, high compatibility, low toxicity, ease of process scale up and large scale production [14].

Several methods had been utilized for the formulation of NCs like high pressure homogenization, solvent evaporation. High pressure homogenization and sonication are used widely as efficient and promising technique for NCs [16, 23, 24].

The present study was carried out to develop high pressure homogenization was utilized followed by ultrasonication for the preparation of NCs. The top down technologies are based on particle fragmentation to submicron units and high-pressure homogenization [14, 15].

Prepared NCs were characterized mean particle size, entrapment efficiency and assay as well as *in-vitro* release of the formulation. Nanocrystals enhance the solubility and bioavailability by decreasing the particle size of the drug and also to control the drug release profile by using polymers in different ratio and different type of stabilizers [8-10].

In the present research, also, SEM and XRPD evaluation were performed on the Initial and Stability samples of the optimized formulation batch [19-21].

MATERIALS: Nitrofurantoin was kindly supplied by Hetero Labs Limited, Andhra Pradesh, India as a gift sample. Glyceryl Monostearate and Glyceryl Behenate (Compritol 888 ATO) were obtained as a gift sample from Gattefosse, Mumbai, India. Poloxamer 188, PVPK 30, HPMC E3 obtained from Sun Pharma, Vadodara. All remaining reagents and chemicals were of analytical grade. Purified water used for all experiments was Milli-Q Plus, Millipore.

METHODS:

Analytical Method Development using HPLC-UV Technique: The HPLC system used consists of LC-10AD/20AD pumps coupled with an ultraviolet (UV) detector. The conditions on which these instruments run are as below.

Manufacturing Model: Perkin Elmer 200 series.
Pump: Series 200, Binary pump.
Detector: Variable single wavelength UV/VIS.
Sampling Method: Auto sampler.

Mobile Phase: Dissolve 6.8 g of monobasic potassium phosphate in 500 ml water adds about 30 ml 1.0 N NaOH sufficiently to adjust pH 7.0 and dilute with water to 1000 ml.

HPLC Column: L1

Wavelength: 254 nm

Injection Volume: 10 µl

The NFT stock solutions were prepared by dissolving appropriate quantities of NFT in dimethyl formamide + 50 ml internal standard solution (Internal standard: 1 mg/ml acetanilide in water) mobile phase, sonicated for 30 min for complete dissolution and makeup to the mark in the volumetric flask with mobile phase to yield a final concentration 1000 ppm. Further, 1 ml of the above solution was diluted to 10 ml with the mobile phase (100 ppm).

Physical Compatibility Study: Compatibility studies were carried out for an appropriate selection of excipients. Studies were carried out by mixing the drug with various excipients in the required proportion in glass vials. Vials were closed with a rubber stopper and kept at three conditions, namely 40 ºC / 75% RH; 25 ºC / 60% RH; and photo stability for 1 month. Physical observations of the blend were done during the study at regular intervals. The compatibility of NFT with selected excipients was confirmed by FTIR.

Formulation Development of NCs:

Optimization of the Composition and Process:

Composition for the Preparation of the Nanocrystals: On the basis of literature survey and drug excipients compatibility we have formulated batch NC1 which is a placebo and batch NC2 is with a drug by keeping the ratio of the organic phase, surfactant and polymer and stirring speed as well as homogenization pressure same to two cycles to check the feasibility. High-pressure homogenizations are used widely as an efficient and promising technique for SLNs preparation. An optimized and robust process of high-speed homogenization may help to achieve the desired LPV loaded SLNs.

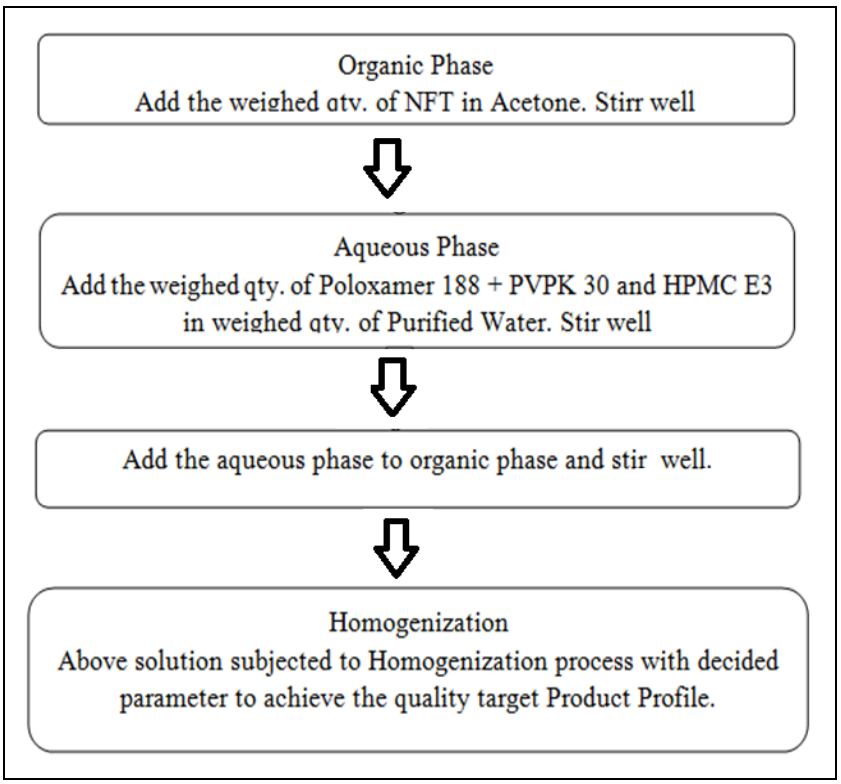


FIG. 1: MANUFACTURING FLOW CHART

TABLE 1: COMPOSITION AND PROCESS PARAMETER FOR PRELIMINARY DEVELOPMENT BATCHES

S. no.	Batch no.	NC1	NC2
	Ingredients	Quantity in gm	
1	NFT	NA	1.2
2	Acetone	60.0	60.0
3	Poloxamer 188 + PVPK 30 (1:5)	1.2	1.2
4	HPMC E3	1.2	1.2
5	Purified water @	Q.S	Q.S
S. no.	**Parameter**	**NC1**	**NC2**
1	Stirring using an overhead stirrer	3000 RPM for 5 min	3000 RPM for 5 min
2	Homogenization pressure (Bar)	1500	1500
3	Homogenization cycle	2	2

TABLE 2: FORMULATION OPTIMIZATION BY FORMULATION VARIABLES

S. no.	Ingredients	NC2	NC3	NC4
			Qty in gm	
1	NFT	1.2	1.2	1.2
2	Acetone	1.2 g of API in 60 g of organic solvent		
3	Poloxamer 188 + PVPK 30 (1:5)	1.2	0.6	0.6
4	HPMC E3	1.2	0.6	0.3
5	Purified water		Q.S	
S. no.	**Parameters**	**NC2**	**NC3**	**NC4**
1	Stirring using overhead stirrer	3000 RPM for 5 min	3000 RPM for 5 min	3000 RPM for 5 min
2	Homogenization pressure (Bar)	1500	1500	
3	Homogenization cycle	2	2	2

TABLE 3: FORMULATION OPTIMIZATION BY PROCESS VARIABLES

S. no.	Parameters	NC5	NC6	NC7	NC8	NC9
1	Stirring using overhead stirrer	3000 RPM for 5 min	3000 RPM for 5 min	3000 RPM for 5 min	3000 RPM for 5 min	3000 RPM for 5 min
2	Homogenization pressure (Bar)	500	750	1000	1250	1500
3	Homogenization cycle	2	2	2	2	1

Formulation Optimization by Formulation Variables: In the present study, the formulation was optimized by considering the formulation variables to achieve the defined quality target product parameter. The composition and process parameter is mentioned as per the following table.

Formulation Optimization by Process Variables: In the present study, the process was optimized by considering the process variables to achieve the defined quality target product parameter. Composition was the same as mentioned in Batch no. NC3 and process parameter change as per the following table in S. no. NC5 to NC9 to achieve desired mean particle size, PDI, zeta potential, and assay. Composition and process parameter of Batch no. NC9 was taken forward to optimize the % pearlitol 25C content as a cryoprotectant. Formulation and process parameters are as mentioned in the below table.

Composition and Process Parameter for Pearlitol 25C Optimization Batches: Pearlitol 25C levels were kept at 50, 100, and 150% of the API for the optimization purpose, and batch no. were assigned as mentioned in above table.

Optimization of Freeze Drying Process: The final NC solution of Batch no. NC9B was divided into Batch no. NC9B1, NC9B2, and NC9B3 equally. The vials were first kept on the condenser surface.

TABLE 4: COMPOSITION AND PROCESS PARAMETER FOR PEARLITOL 25C OPTIMIZATION BATCHES

S. no.	Freeze drying parameter	NC9 A	NC9 B	NC9 C
		Pearlitol 25C level 50% of the API	Pearlitol 25C level 100% of the API	Pearlitol 25C level 150% of the API
1	Temperature (Condenser)		-70 °C	
2	Vacuum (mTorr)		100	
3	Cycle time (H)		24	

TABLE 5: OPTIMIZATION OF FREEZE DRYING PROCESS

S. no.	Freeze drying parameter	NC9 B1	NC9 B2	NC9 B3
		Pearlitol 25C level 100% of the API		
1	Temp	-70 °C	-70 °C	70 °C
2	Vacuum (mTorr)	100	100	100
3	Cycle time (H)	12	18	24

RESULTS AND DISCUSSION: A suitable stability-indicating analytical method development is very critical. The standard curve was generated for the entire range from 0 to 100 µg/ml; the results of standard curve preparation are shown in **Fig. 2**.

Observation of Drug Excipients Compatibility Studies: Compatibility study of drugs with excipients were done at initial, after 2 weeks at 25 °C / 60% RH and 1 Month 25 °C / 60% RH. Changes in appearance and molecular structure were observed by FTIR.

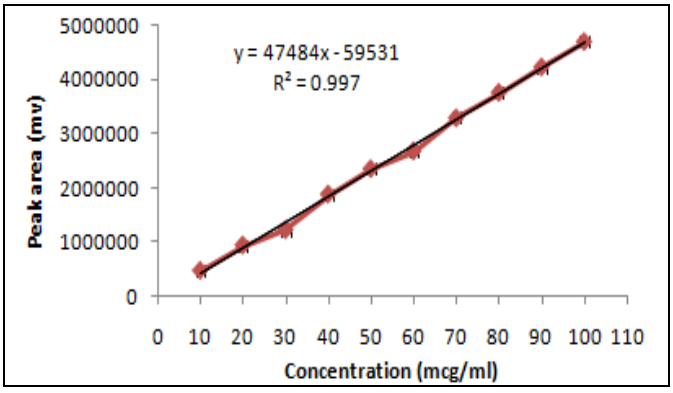


FIG. 2: LINEARITY CURVE OF NITROFURANTOIN

TABLE 6: OBSERVATION OF COMPATIBILITY STUDY OF DRUG AND EXCIPIENTS

S. no.	Sample name	Initial	2 Week 25 °C / 60% RH	1 Month 25 °C / 60% RH
1	Nitrofurantoin (NFT)	Yellow color powder	Yellow color powder	Yellow color powder
2	NFT + Poloxamer 188	Yellow color powder	Yellow color powder	Yellow color powder
3	NFT + PVPK 30	Yellow color powder	Yellow color powder	Yellow color powder
4	NFT + Poloxamer 407	Yellow color powder	Blackish yellow color powder	Blackish yellow color powder
5	NFT + HPMC E3	Yellow color powder	Yellow powder	Yellow color powder
6	NFT + HPMC E5	Yellow color powder	Yellow color powder slight sticky	Yellow color powder sticky behavior

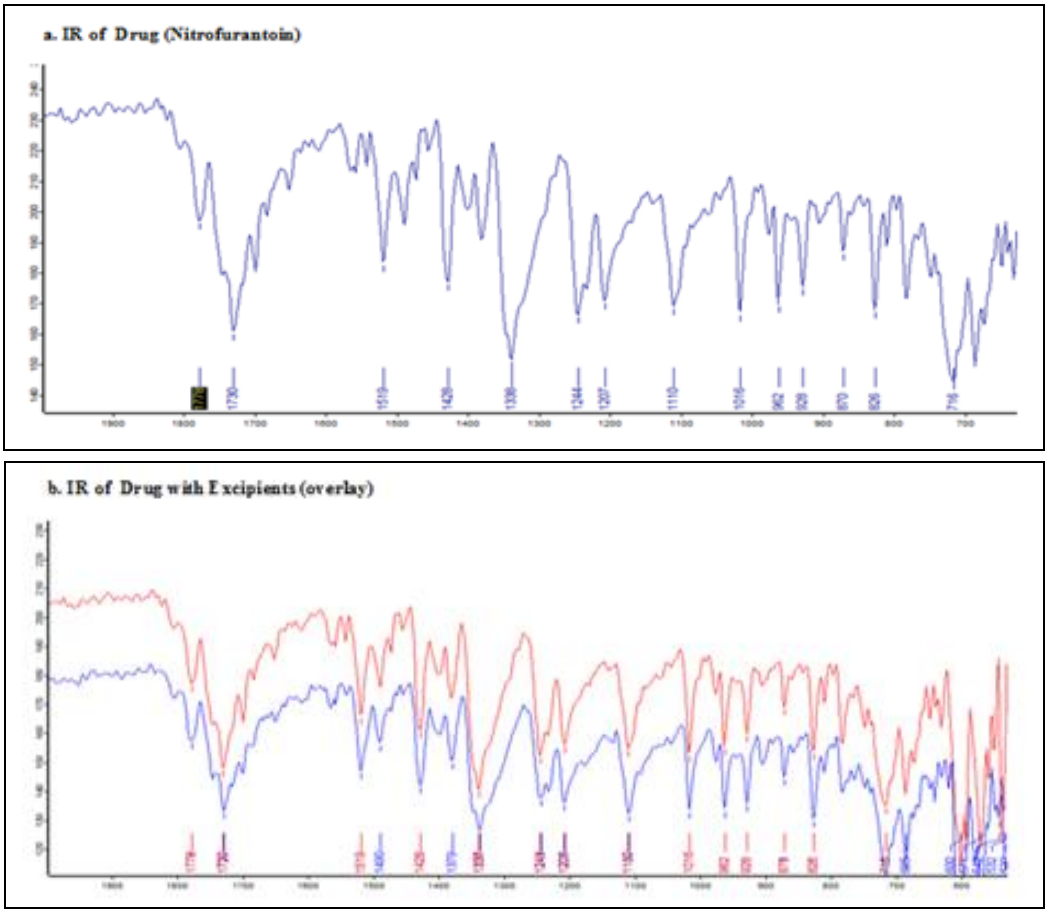
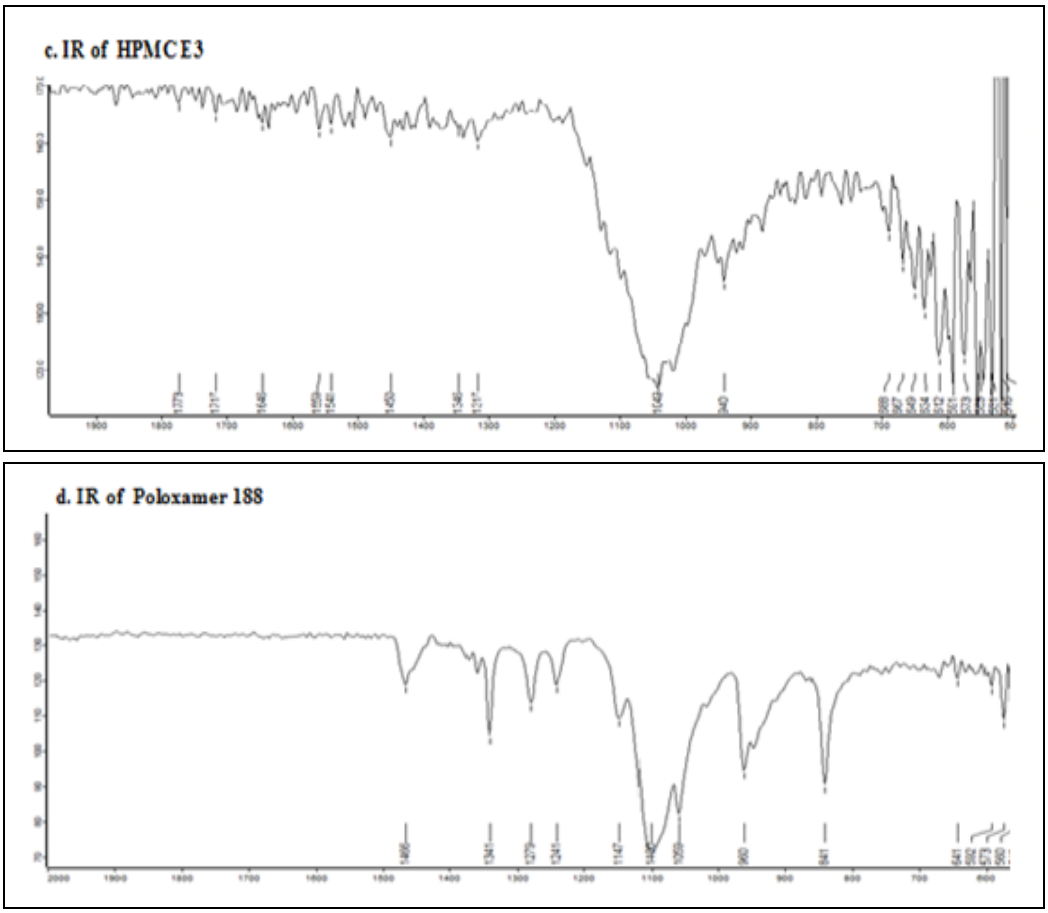


FIG. 3: IR GRAPH OF DRUG (NITROFURANTOIN) AND DRUG WITH EXCIPIENTS OVERLAY



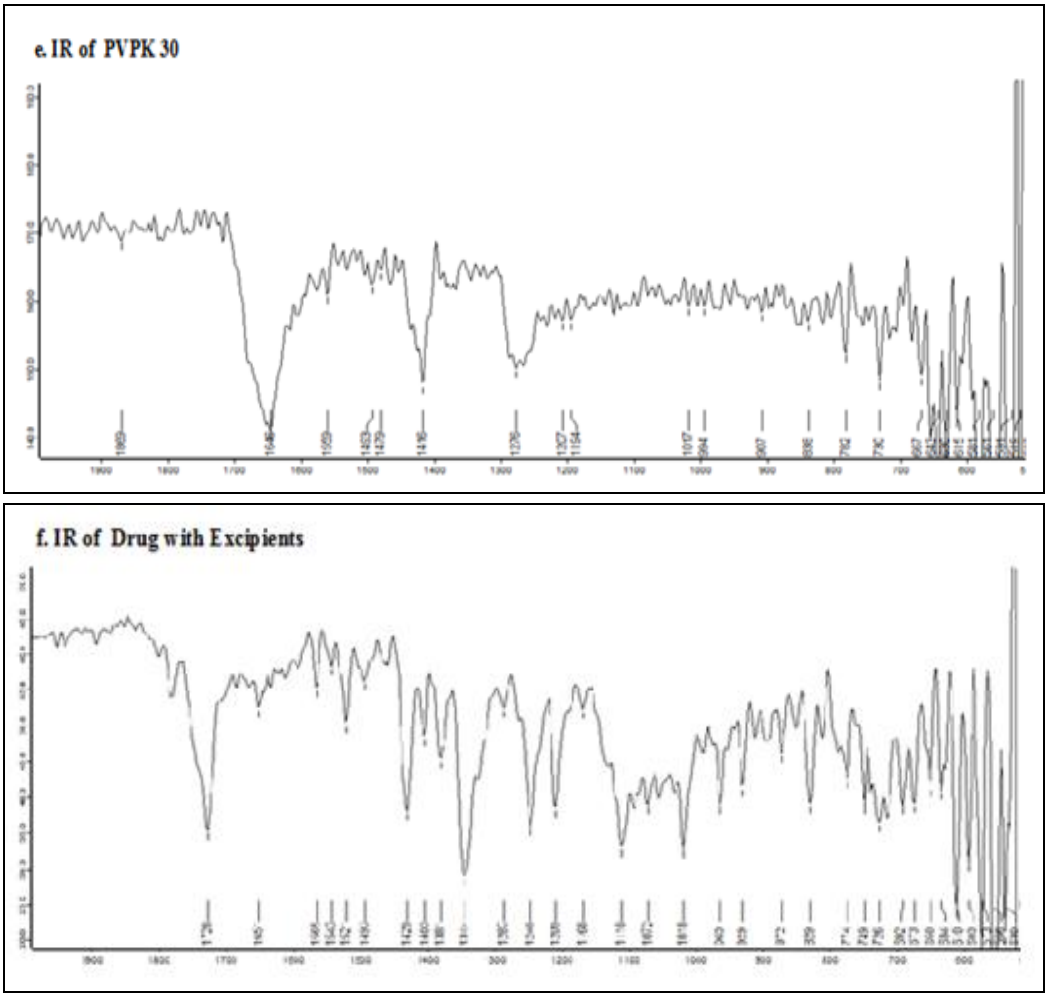


FIG. 4: IR GRAPH OF EXCIPIENTS AND DRUG WITH EXCIPIENTS

Evaluation and Characterization of NC:

Evaluation of the Preliminary Development Batches: Preliminary batches were manufactured as per the composition and process parameter mentioned in **Table 1**. The results are mentioned in the below table.

Evaluation of the Formulation Optimization Batches: Ideal NC has a small particle size with narrow particle size distribution (Polydispersity index < 1%). In the present study composition and process, parameter areas mentioned in **Table 2,** different ratio of drug: poloxamer 188 + PVPK 30: HPMC E3 was optimized. The results are as mentioned below the table.

TABLE 7: RESULTS OF THE PRELIMINARY DEVELOPMENT BATCHES

S. no.	Evaluation	NC2
1	Mean particle size (nm)	413 ± 49
2	Polydispersity index	0.39 ± 0.05
3	Zeta potential (-mv)	-29.3 ± 0.13
4	Assay	99.1 ± 1.5

TABLE 8: RESULTS OF THE FORMULATION OPTIMIZATION BATCHES

S. no.	Evaluation	NC2	NC3	NC4
1	Mean particle size (nm)	413 ± 49	198 ± 13	279 ± 38
2	Polydispersity index	0.39 ± 0.05	0.12 ± 0.03	0.22 ± 0.02
3	Zeta potential (-mv)	-29.3 ± 0.13	-38.1 ± 0.12	-22.3 ± 0.24
4	Assay	99.1 ± 1.5	100.0 ± 0.5	98.9 ± 1.1

TABLE 9: RESULTS OF THE PROCESS OPTIMIZATION BATCHES

S. no.	Evaluation	NC5	NC6	NC7	NC8	NC9
1	Mean particle size	829 ± 109	745 ± 69	332 ± 41	213 ± 17	238 ± 12
2	Polydispersity index	2.39 ± 0.29	2.11 ± 0.41	1.01 ± 0.33	0.14 ± 0.08	0.09 ± 0.06
3	Zeta potential (-mv)	----	---	---	- 35.4 ± 0.31	-36.1 ± 0.19
4	Assay	---	---	---	101.1 ± 0.7	99.8 ± 0.3

Evaluation of the Process Optimization Batches: Optimized and robust process of NC may help to achieve the desired quality target product profile. Compositions are the same as Batch no. NC3 and process parameters are as mentioned in **Table 3**. Batches are evaluated, as mentioned in below table.

TABLE 10: RESULTS OF THE PEARLITOL 25C OPTIMIZATION BATCHES

S. no.	Evaluation	NC9 A	NC9 B	NC9 C
1	Mean particle size (nm)	--	223 ± 8	241 ± 11
2	Polydispersity index	--	0.11 ± 0.03	0.12 ± 0.02
3	Zeta potential (-mv)	--	-41.1 ± 0.22	-43.4 ± 0.18
4	Assay	--	99.1± 0.5	98.8 ± 0.6
5	Water content	--	2.1 ± 0.2	1.8± 0.2
6	Residual solvent (PPM)	--	97 ± 3	83 ± 5
7	Appearance	Loose self supporting cake	Acceptable porous cake	Acceptable porous cake

It has been observed that physical appearance of the Batch no. NC9 A was not acceptable as loose self supporting cake was observed which is due to ineffective concentration of pearlitol 25C as a cryoprotectant or bulking agent.

Hence, pearlitol 25C concentration needs to be increased further, to get the desired target product profile. There is no significant difference between the target product parameters of Batch no. NC9 B and NC9 C.

They all are within the acceptable range, including the physical appearance and residual solvent content. Therefore, Batch no. NC9 B having the 100% pearlitol 25C of the API has been taken forward for the optimization of the freeze-drying process.

Evaluation of the Optimization Batches for Freeze Drying Process: Freeze drying is an essential process to enhance the stability of the formulation. Appearance and the Water content of the formulated cake are the key evaluation parameter.

The final NC dispersion of Batch no. NC9B was divided into Batch no. NC9B1, NC9 B2, and NC9 B3 equally. These were then subjected to lyophilization process in a virtis benchtop lyophilizer with the parameters as shown in **Table 12**. The results are as mentioned in the below table.

TABLE 11: RESULTS OF THE OPTIMIZATION BATCHES FOR FREEZE DRYING PROCESS

S. no.	Evaluation	NC9 B1	NC9 B2	NC9 B3
1	Mean particle size (nm)	--	327 ± 13	231 ± 9
2	Polydispersity index	--	0.21 ± 0.04	0.09 ± 0.02
3	Zeta potential (-mv)	--	-29.4 ± 0.12	-38.8 ± .15
4	Assay	--	97.9 ± 0.3	98.3± 0.7
5	Water content	--	4.3 ± 0.4	1.9 ± 0.3
7	Appearance	Loose self-supporting cake	Acceptable porous cake	Acceptable porous cake

Batch No. NC9 B2 and NC9 B3 seem to be satisfactory. There is no significant difference between Batch No. NC9 B2 and NC9 B3 By considering the lower value of residual solvent content, Batch no. NC9 B3 was taken further, for complete analysis and to be loaded in the stability study.

Evaluation of the Optimized Batch for Drug Release Profile: All batches NC2, NC3, NC4, NC8, NC9, NC9 B, NC9 C, NC9 B2, and NC9 B3 were packed in a capsule. *In-vitro* drug release study was performed in **Fig. 9** in the USP-II apparatus with sinker using 900 ml of Phosphate buffer (pH 7.2) at 50 RPM for 12 h.

Batch no. NC9B1 shows the loose self-supporting cake indicates the higher water content, which is due to the insufficient cycle time of 12 H.

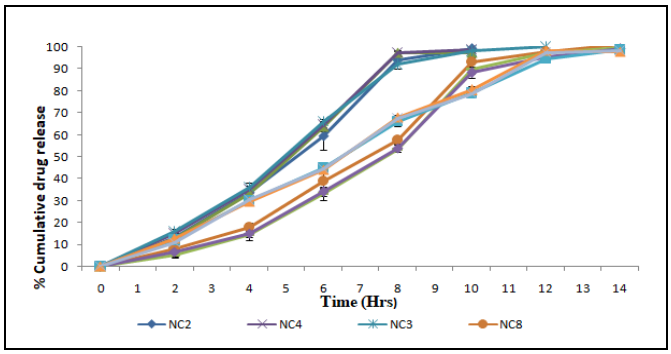


FIG. 5: DRUG RELEASE PROFILE OF OPTIMIZED BATCHES

Stability Study of Optimized Batch: NC9 B3 was chosen for the stability study. Selected formulae were packed in HDPE sealed glass bottles and stored at ambient room temperature in desiccators over anhydrous $CaCl_2$ and at 2-8 °C in the refrigerator. 25 ± 2 °C / 60% relative humidity (RH) or 40 ± 2 °C / 75% relative humidity for 6 months. The chosen formulae were evaluated for mean particle size (nm), polydispersity index, zeta potential, % assay, degradation product, related substances, microbial limit, and zone of inhibition.

TABLE 12: STABILITY DATA OF THE BATCH NO. NC9 B3 (CAPSULES CONTAINING NC IN HDPE BOTTLE)

Evaluation	25 °C / 60 RH condition				
	Initial	1 M	2 M	3 M	6 M
Mean particle size (nm)	231 ± 9	229 ± 5	241 ± 6	239 ± 7	251 ± 13
Polydispersity index	0.09 ± 0.02	0.11 ± 0.01	0.11 ± 0.02	0.09 ± 0.01	0.16 ± 0.01
Zeta potential (mV)	-38.8 ± 0.15	-35.8 ± .08	-38.1 ± .07	-40.4 ± 0.12	-41.1 ± 0.14
% Assay	98.3 ± 0.7	97.3 ± 0.9	98.2 ± 1.2	99.1 ± 2.3	97.8 ± 1.3

Inference: Batch no. NS9B3 is complied as per target specification at 2-8 °C and 25 °C / 60% RH up to 6 months.

Characterization of Nanocrystal:

In-vitro Characterization of the Optimized Batch (Batch No. NC9B3):

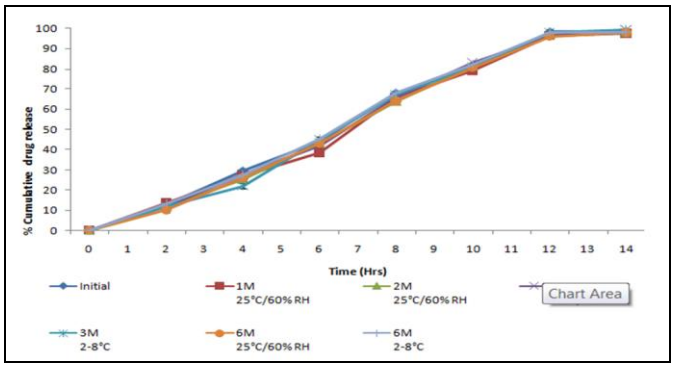


FIG. 6: *IN-VITRO* CHARACTERIZATION OF STABILITY BATCH NO. NC9B3

Characterization of NC using SEM and XRPD:

Characterization of NC using SEM:

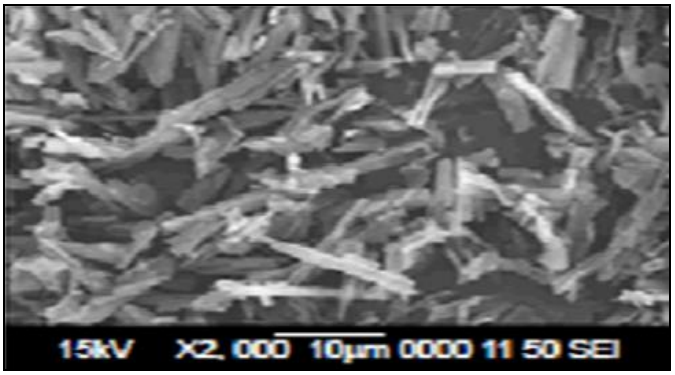
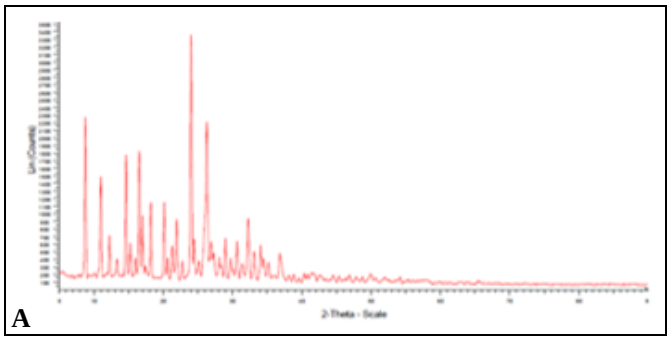
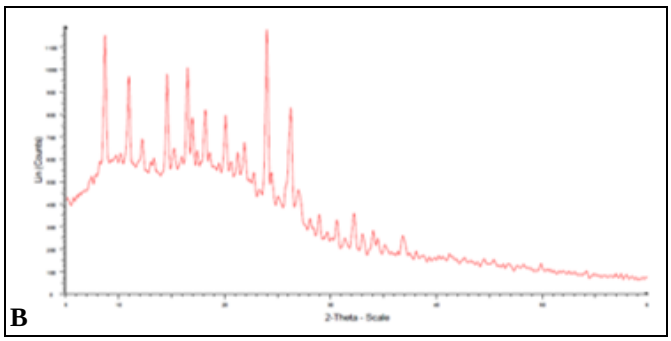


FIG. 7: SEM EVALUATION OF THE NC

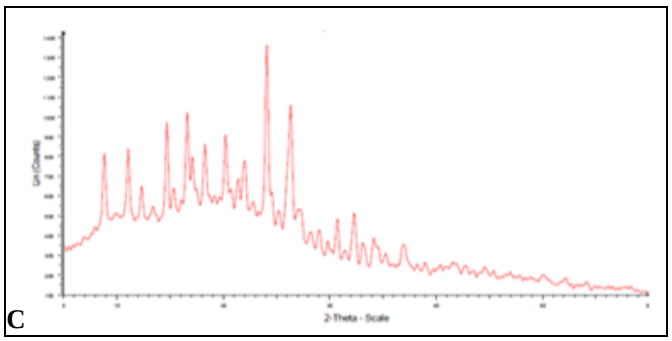
XRPD Spectra of Optimized Batch:



NFT



NFT + EXCIPIENT



NC

FIG. 8: XRD SPECTRA

CONCLUSION: In the present investigation, NCs of NFT were successfully manufactured using a cold high-pressure homogenization technique. The effect of the formulation composition and process parameter on the NCs were evaluated and optimized. Optimized formulation shows the desired quality target product profile. Bioavailability increment indicates higher GI uptake of nitrofurantoin nanocrystals in comparison to nitrofurantoin solution. Stability data shows that there is no significant difference in the optimized formulation after 6 months at 2-8 °C and 25 °C / 60% RH conditions. These storage conditions of NCs were found appropriate for drug delivery. The study opens the chances of manufacturing by competitive cost at a commercial level.

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CONFLICTS OF INTEREST: There are no conflicts of interest.

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