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ACCELERATING NITRENDIPINE DELIVERY: NANOSUSPENSION FAST-DISSOLVING FILM FOR ORAL TRANSDERMAL USE

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Nitrendipine, Nanosuspension, Wet media milling, Fast dissolving film, Solvent casting method

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ABSTRACT: The present research work is aimed to formulate and evaluate Nitrendipine nanosuspension (NTD-NS) and nanosuspension loaded oral fast dissolving film (NS-OFDF) to improve its low solubility and bioavailability. Wet media milling technique was employed to prepare NTD-NS, which was optimized and evaluated for different parameters. Poloxamer 188, Poloxamer 407, HPC, HPMC E5, HPMC E15, HPMC E50, HPMC K4M, PVP K30 were used for preparing various nanosuspension formulations. HPMC E15 and SLS were used to formulate optimized nanosuspension. NTD-OFDF was prepared using the optimized nanosuspension by solvent casting method. PEG 400 is added during film formation as plasticizers and HPMC is added as film former polymer. The NTD-OFDF were prepared, optimized and evaluated for different parameters. Optimized NTD-NS depicted particle size of 455.2 nm with polydispersity index (PDI) of 24.9% and zeta potential of -24.2 mV. Optimized NTD-OFDF exhibited surface pH of 7.12±0.0251, folding endurance of321±4, thickness of 0.171±0.003, disintegration time of 28.133±0.493 sec which was in the standard limits. The drug release from NTD-NS loaded OFDFs increased significantly, reaching a maximum of 80.84±0.445 % in pH 7.4 buffer, the release data was fitted into first order model yielding the highest correlation coefficient (R^2) (R^2=0.925).

INTRODUCTION: Hypertension is the elevation of systolic BP, diastolic BP, or both above normal levels, is common in developed and developing countries and increases in prevalence with age increase. In recent years, hypertension has been defined as a BP of 140/90 mmHg or more [1]. Calcium channel blockers are thought to be a more effective antihypertensive medicine than the other antihypertensive drugs for lowering the cardiovascular disease associated with hypertension. Stroke prevention also involves the use of calcium channel blockers [2].

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Nitrendipine (NTD) is a dihydropyridine based second generation calcium channel blocker [3]. NTD works mainly by causing dilation of coronary and systemic arteries. Therefore, it increases the delivery of oxygen to the myocardial tissue which makes NTD a potent drug to treat angina pectoris and hypertension in patients. It is a BCS Class II drug which has low water solubility. NTD goes through ample first pass metabolism in the liver and presents poor oral bioavailability (10-20%) in humans [4].

Hence there is a need to develop a formulation to increase drug solubility and drug dissolution rate with minimum presystemic hepatic metabolism to handle poor bioavailability allied with NTD. The low solubility of an active pharmaceutical ingredient is a major concern for pharmacists during drug formulation development. Low solubility of active pharmaceutical ingredients

(API) decreases bioavailability of drugs. Unpredictable absorption and solubility behaviour are seen in new chemical entities (NCEs). Most of the NCEs emerges from drug discovery were found to have low aqueous solubility [5]. Such type of drugs came under the category of BCS Class II (low solubility and high permeability) or BCS Class IV (low solubility and low permeability) of Biopharmaceutical classification system (BCS) [6]. Several solubility enhancement techniques have been employed to enhance the solubility are polymer entrapment, solvates and hydrates, hydrotrophy, solid dispersions, polymorphs, surfactants, reduction in particle size by different techniques of micronization or nanonization [7].

Nanosuspensions in many cases have given good results in improving saturation solubility by increasing the surface area available for dissolution [8]. It has been reported that development of nanosuspensions with high drug loading, increased dissolution and better bioavailability [9]. Stability of nanosuspension is the major challenge associated with it. These are thermodynamically unstable and tend to show particle growth during storage [10]. In recent years, Attempts have been made to modify nanosuspension to different solid dosage forms such as powders, pellets, tablets, capsules, oral films. Oral films have many advantages than other oral dosage forms since it undergoes quick disintegration and dissolution in the oral cavity, rapidly delivers the drug across oral mucosa bypassing the hepatic metabolism and resulting enhancement of bioavailability [11]. The present research work is an attempt to formulate nanosuspension by wet media milling to improve aqueous solubility and bioavailability of NTD and to improve stability of NTD loaded nanosuspension by formulation of OFDF.

MATERIALS AND METHOD:

Materials: NTD was procured from Concept Pharmaceuticals Ltd., Mumbai. SLS was obtained from Central Drug House Pvt. Ltd., New Delhi. PEG 400 was obtained from Atulya Chemical Pvt. Ltd., Mumbai. Poloxamer 188, Poloxamer 407, polyvinyl pyrrolidone K-30 was obtained from BASF, SE, Germany. HPMC E5, HPMC E15, HPMC E50 were obtained from DuPont de Nemours, USA. HPMC K4M was obtained from Otto Chemie Pvt. Ltd., Mumbai. Hydroxy propyl cellulose (HPC) was obtained from Merk & Co., USA. All other reagents were of analytical grade and were used without further purification.

Formulation, Optimization and Preparation of Nitrendipine Nanosuspension by Wet Media Milling Technique [12-15]: By using glass beads as a milling agent in the formulation procedure, wet media milling is employed to produce nanosuspension. In a 15mL glass vial, a weighed quantity of glass beads (3g) and 3mL distilled water were added. After that, 30mg Nitrendipine and a predetermined amount of various polymers were added, and the mixture was stirred for 24 hours at 750 rpm on a magnetic stirrer. After milling, the resulting nanosuspension was decanted from the glass beads and washed with water. Formulated nanosuspensions are shown in **Table 1.**

NTD-NS were prepared by using different type of surfactant, different concentration of selective polymer in different concentration (30-150 mg) and optimized concentration as further analysis at different stirring speed (750-1500 rpm). All the parameter was analysed for solubility study & particle size. The method of preparation of Nanosuspension was found to be simple and reproducible.

TABLE 1: FORMULATION OF NANOSUSPENSION USING DIFFERENT POLYMERS

S. no.	Formulation code	Drug (mg)	Polymer concentration (30mg)
1	F0	30	No Polymer
2	F1	30	Poloxamer 188
3	F2	30	Poloxamer 407
4	F3	30	Sodium lauryl sulfate
5	F4	30	PVP K30
6	F5	30	HPC
7	F6	30	HPMC K4M
8	F7	30	HPMC E05
9	F8	30	HPMC E15
10	F9	30	HPMC E50

For optimization the concentration of the chosen polymer is doubled, stirring speed kept at 1000 rpm during formulation F10-F13 which is shown in **Table 2.**

TABLE 2: FORMULATION OF NANOSUSPENSION USING DIFFERENT SELECTED POLYMERS

S. no.	Formulation code	Drug (mg)	Polymer concentration (60mg)
1	F10	30	SLS
2	F11	30	PVP K30
3	F12	30	HPC
4	F13	30	HPMC E15

SLS and HPMC E15 were selected for further formulations in combined form with drug in formulation F14-F19 based on their good drug solubility results.

TABLE 3: FORMULATION OF NANOSUSPENSION USING DIFFERENT CONCENTRATIONS OF HPMC E15 AND SLS

S. no.	Formulation code	Drug (mg)	SLS concentration (mg)	HPMC E15 concentration (mg)
1	F14	30	30	30
2	F15	30	30	60
3	F16	30	60	30
4	F17	30	90	30
5	F18	30	120	30
6	F19	30	150	30

Formulation F18 was selected as optimized formulation and for stirring speed optimization formulation F20-22 were prepared on variable stirring speeds.

TABLE 4: FORMULATION OF NANOSUSPENSION CONTAINING SLS AND HPMC E15 USING DIFFERENT STIRRING SPEED

S. no.	Formulation code	Drug (mg)	SLS (mg)	HPMC E15 (mg)	Stirring speed (rpm)
1	F20	30	120	30	750
2	F18	30	120	30	1000
3	F21	30	120	30	1250
4	F22	30	120	30	1500

Evaluation of Nanosuspensions:

Visual Appearance: All the batches of nanosuspension were studied for colour and physical appearance.

Solubility Study: Saturation solubility was carried out for bulk drug and nanosuspensions. Pure Nitrendipine (30mg) were taken with 3 ml of water and stirred on magnetic stirrer for 24 hrs. Then dispersion is taken out and centrifuged at 10000 rpm and 4°C and then analysed against distilled water on UV Visible spectrophotometer.

For nanosuspensions, the nanosuspensions were taken and centrifuged at 10000 rpm and 4°C and then dispersion taken and diluted to 10 ml and analysed against distilled water on UV Visible spectrophotometer [16].

Drug Content: For determination of drug content the Nanosuspension was centrifuged for 5-10 minutes at 5000 rpm.

Then the supernatant 1 ml was removed and diluted up to 10 ml with water then filtered and absorbance checked at wavelength of 236 nm [17].

Characterization of NTD-NS: Based on the solubility studies the F18, F20, F21, F22 formulations were selected. Particle size studies were done on all formulations which are shown in **Table 8**. Then Zeta potential study was done for optimized formulation which is shown in **Fig. 2.**

Particle Size and Zeta Potential Determination: The particle size (PS) and zeta potential of the nanosuspension were determined by the method of photon correlation spectroscopy and electrophoretic mobility, respectively, using a particle size analyser. 1ml of prepared NS was taken and diluted to 10 ml, added into the sample cell, put into the sample holder unit for Zeta potential and particle size determination, respectively [18].

Transmission Electron Microscopy (TEM): Transmission electron microscopy (TEM) studies were performed for optimized formulation F21 using Transmission Electron Microscope.

The liquid nanosuspension optimized formulation F21 was dropped on copper–gold carbon grid and allowed to dry. This grid was then mounted in the instrument and photographs were taken at various magnifications shown in **Fig. 4(A)** and **Fig. 4(B)** [19].

Fourier-transform Infrared (FT-IR) Spectroscopy: FT-IR spectroscopy was used for the determination of drug interaction with excipients, an FT-IR spectrum (Bruker Alpha, Berlin, Germany) of NTD, drug plus excipients mixture, and NS formulation F21 was recorded. The samples were analysed with a sampling range of 4000–450 cm^{-1}. An IR spectrum was recorded after a sample of NTD, drug plus excipients mixture, and formulation F21 were filled into the die cavity of the sample holder [20]. The FTIR spectra are shown in **Fig. 5-9.**

Formulation of Nitrendipine Nanosuspension loaded Oral Fast Dissolving Films: Solvent casting method was used to make NTD-OFDF of an optimised NTD-NS formulation F21. HPMC E15 and PEG 400 were accurately weighed and added to the NTD-NS formulation and mixed for 30 minutes using a magnetic stirrer.

With the use of a doctor blade, the entire mixture was moulded on a glass petri dish. It was dried for 4 hours at 50° C in a hot air oven. After drying, the films were removed with a needle, cut into 1×1 cm cubes, wrapped with butter paper, and stored in a desiccator until further investigation [21]. Composition of OFDF formulations given in **Table 5.**

TABLE 5: FORMULATION OF OFDFs USING DIFFERENT CONCENTRATIONS OF PEG 400 AND HPMC E15

S. no.	Formulation code	Nanosuspension (ml)	HPMC E15 (mg)	PEG 400 (mg)
1	F23	10	0.05	0.010
2	F24	10	0.1	0.015
3	F25	10	0.15	0.020

Evaluation of Oral Fast Dissolving Films Loaded with Nitrendipine Nanosuspension:

Visual Appearance: Films were evaluated for visual appearance and noted down the findings.

Surface pH: Films were slightly moistened with water and the electrode of the digital pH meter was brought in contact with the surface of the films. The pH reading was noted in triplicate [21].

Folding Endurance: Folding endurance was determined by folding the 1×1 cm piece of film at the same place repeatedly till it broke. The number of folds which the film could withstand before it breaking indicates folding endurance. Measured the folding endurance in triplicate [22].

Thickness: The thickness of the film was measured using digital Vernier Calliper with a least count of 0.001 mm at different spots of the film. The thickness was measured for formulations at three different spots of the film and average was taken and standard deviation (SD) was calculated.

Weight Uniformity: Three different films of the individual batches were taken randomly and weighed to calculate the average weight. The individual weight of the film should not deviate from the average weight of the three films [23].

Content Uniformity: Prepared fast-dissolving film was dissolved in 100 ml of distilled water and filtered. After suitable dilutions with distilled water, the concentration of the drug was determined by measuring the absorbance at 236 nm against the distilled water as blank.

Characterization of Nitrendipine Loaded Oral Fast Dissolving Films: Based on physical evaluations i.e. appearance, surface pH, thickness, weight uniformity, content uniformity which were performed on all oral films.

Optimized film formulation F24 was selected. FT-IR study of pure drug and oral film was performed for study of any interactions after film formation from optimized nanosuspension formulation F21.

FT-IR Study: The FT-IR of pure drug and film of optimized polymer was measured using Fourier Transform Infra-Red Spectrophotometer. Pure drug and optimized film were separately placed on die

cavity and applied pressure by pressure gauge [24]. FT-IR spectrum was recorded over a range of 450 – 4000 cm^{-1}.

***In-vitro* Drug Release Study:** *In-vitro* drug release study of pure drug powder and optimized film formulation F24 was performed using Franz diffusion cell apparatus. A standardized Franz-type diffusion cell consists of two compartments donor compartment and receptor compartment.

Different concentrations of drug in phosphate buffer were taken in donor compartment. The membrane was mounted between the donor and receptor compartments. The phosphate buffer (7.4), as a medium, was taken in a receiver compartment to maintain the sink conditions. The medium was magnetically stirred at 300 rpm to maintain a temperature of 37°C. The amount of drug diffused was withdrawn periodically at 0, 1, 5, 10, 15, 20, 25, 30, 45, 60, 90, 120 min and estimated spectrophotometrically at 236 nm [25].

RESULTS AND DISCUSSION:

Evaluation of Nanosuspension Formulation:

Visual Appearance: Appearance of nano-suspension formulations was found to be translucent except F0 formulation which consist of pure drug and water only.

TABLE 6: VISUAL APPEARANCE OF NANOSUSPENSION

S. no.	Formulation code	Appearance
1	F0	Partial Dissolution
2	F1	Translucent
3	F2	Translucent
4	F3	Translucent
5	F4	Translucent
6	F5	Translucent
7	F6	Translucent
8	F7	Translucent
9	F8	Translucent
10	F9	Translucent
11	F10	Translucent
12	F11	Translucent
13	F12	Translucent
14	F13	Translucent
15	F14	Translucent
16	F15	Translucent
17	F16	Translucent
18	F17	Translucent
19	F18	Translucent
20	F19	Translucent
21	F20	Translucent
22	F21	Translucent
23	F22	Translucent

FIG. 1: OPTIMIZED NITRENDIPINE NANOSUSPENSION (F21)

Solubility Study: Formulation F18, F20, F21, F22 was found to have high and almost similar solubility which shows that there is negligible change on further increasing stirring speed above 1250 rpm during NS formulation.

TABLE 7: SOLUBILITY DATA OF NANO-SUSPENSION FORMULATIONS (F0-F22)

S. no.	Formulation code	Solubility (mg/ml) ±SD
1	F0	0.0024±0.0001
2	F1	0.0041±0.0001
3	F2	0.1061±0.0012
4	F3	0.6895±0.0018
5	F4	0.3312±0.0018
6	F5	0.3197±0.0018
7	F6	0.2059±0.0012
8	F7	0.2147±0.0018
9	F8	0.4061±0.0025
10	F9	0.2927±0.0031
11	F10	0.7953±0.0025
12	F11	0.3570±0.0024
13	F12	0.3359±0.0018
14	F13	0.4628±0.0024
15	F14	0.9673±0.0018
16	F15	0.9281±0.0018
17	F16	1.0922±0.0018
18	F17	1.7327±0.0024
19	F18	2.4136±0.0030
20	F19	2.0201±0.0025
21	F20	2.2151±0.0030
22	F21	2.5452±0.0025
23	F22	2.5444±0.0036

*Mean±SD, n=3

Particle Size: Particle size of each selected nanosuspension formulations F20, F18, F21, F22 was calculated by particle size analyser. From the study it was concluded that 120mg SLS at 1250 rpm shows higher solubility and smallest particle size. Then F21 formulation selected as optimized formulation. Readings are given in **Table 8.**

TABLE 8: PARTICLE SIZE OF SELECTED NITRENDIPINE NANOSUSPENSION FORMULATIONS

S. no.	Formulation code	Stirring speed (rpm)	Particle size (nm)±SD
1	F20	750	853.4±0.7
2	F18	1000	501.2±0.5
3	F21	1250	455.2±0.2
4	F22	1500	463.7±0.3

*Mean±SD, n=3

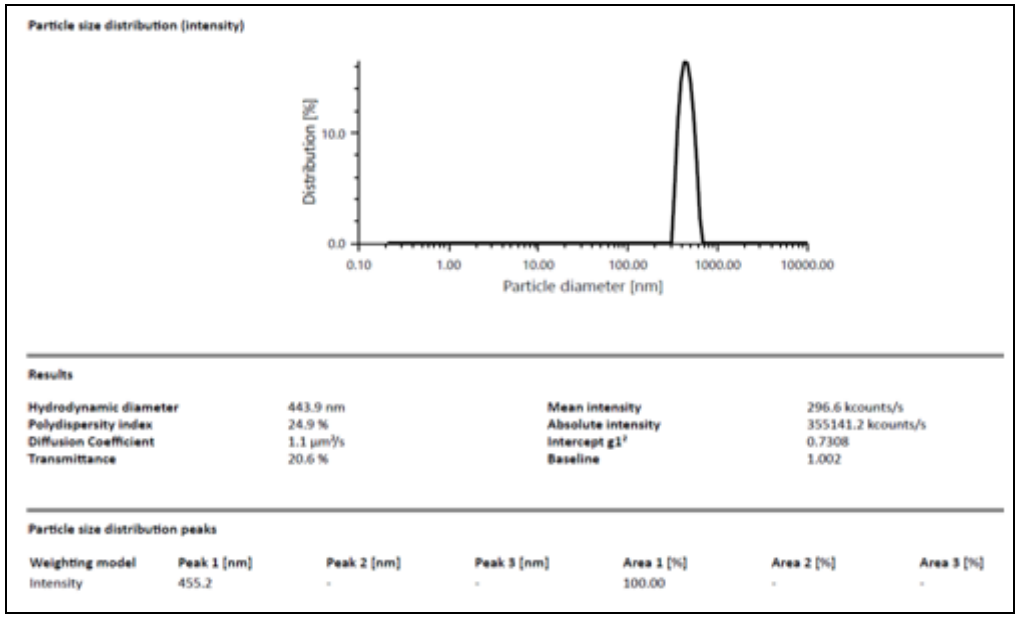

FIG. 2: PARTICLE SIZE OF NANOSUSPENSION FORMULATION (F21)

Zeta Potential: Zeta potential of optimized nanosuspension formulation F21 was found to be -24.2 mV±0.8mV which represents stability of formulation and shown in **Fig. 3.**

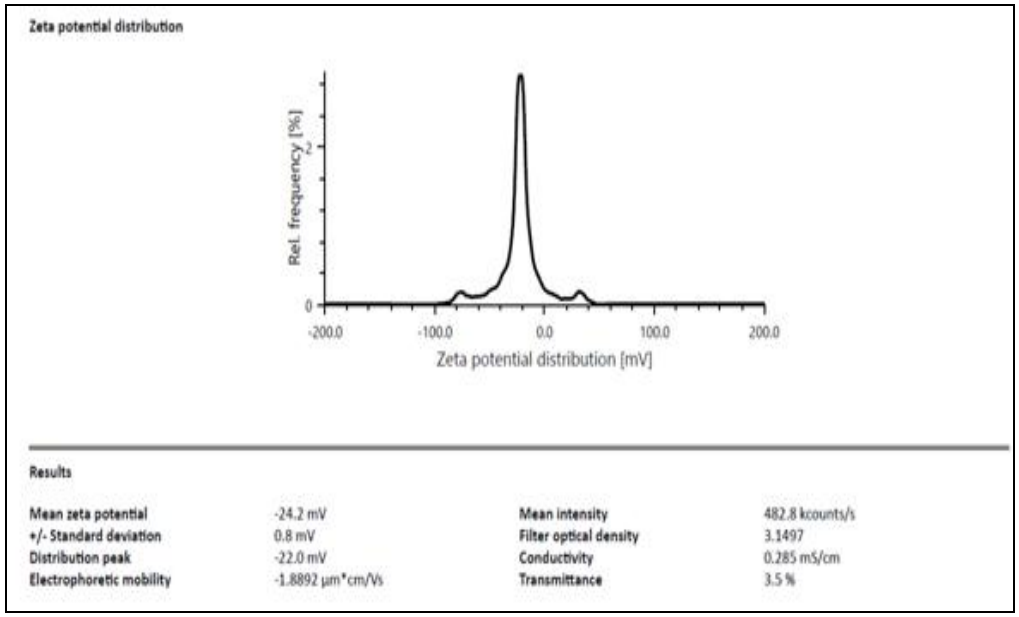

FIG. 3: ZETA POTENTIAL OF NTD NANOSUSPENSION FORMULATION (F21)

Transmission Electron Microscopy (TEM): The images of optimized nanosuspension formulation F21 obtained by transmission electron microscopy (TEM) shows no aggregation of the nanoparticles in **Fig. 4(A)** and **4(B).** The nanoparticles are approximately oval in shape not of uniform size as evident by the high value of polydispersity index (PDI).

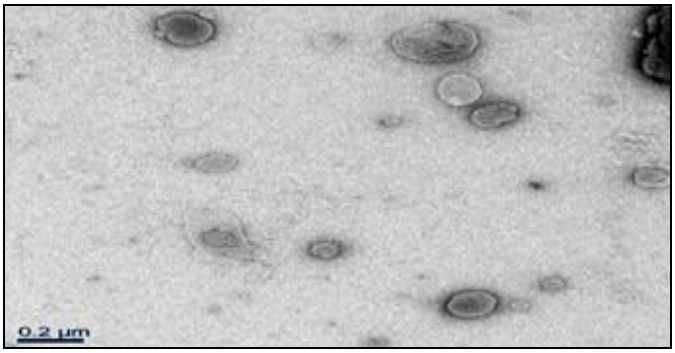

FIG. 4 (A): TEM OF OPTIMIZED NANOSUSPENSION FORMULATION F21

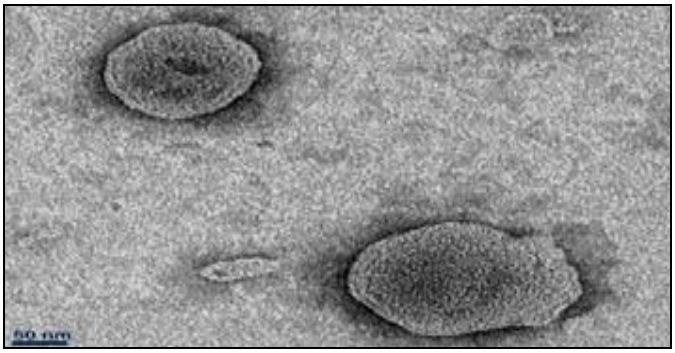

FIG. 4 (B): TEM OF OPTIMIZED NANOSUSPENSION FORMULATION F21

Fourier Transform Infrared Spectroscopy (FT-IR): The peaks of Nitrendipine, HPMC E15, SLS, PEG 400 was seen and results did not reveal any objectionable changes. There was no appearance or disappearance of characteristic peaks. There is no chemical interaction between NTD and polymers used. The FT-IR of NTD, HPMC E15, SLS, PEG 400 and Polymer mixture are shown in **Fig. 5-9** and interpretation is shown in **Table 9.**

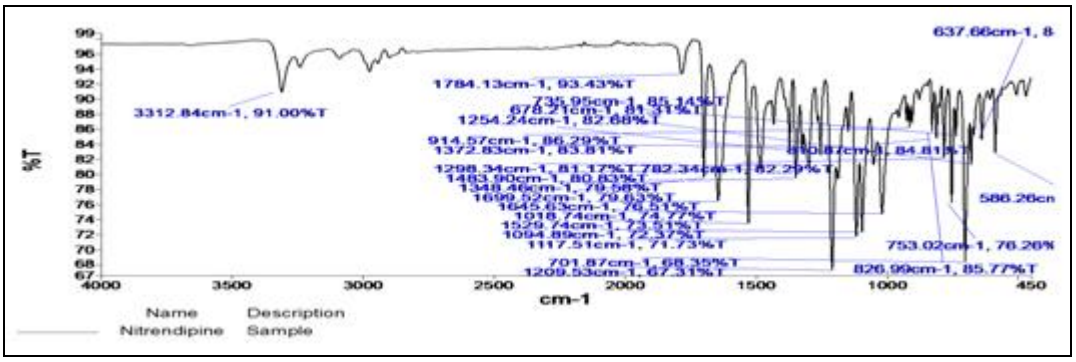

FIG. 5: FT-IR SPECTRUM OF NITRENDIPINE

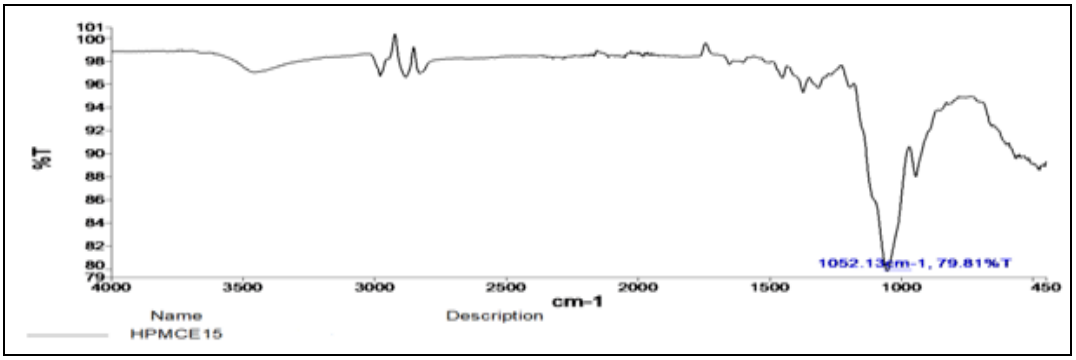

FIG. 6: FT-IR SPECTRUM OF HPMC E15

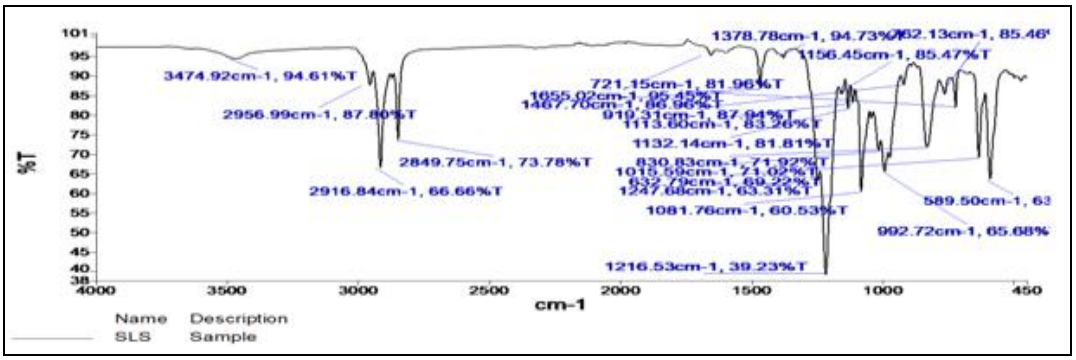

FIG. 7: FT-IR SPECTRUM OF SLS

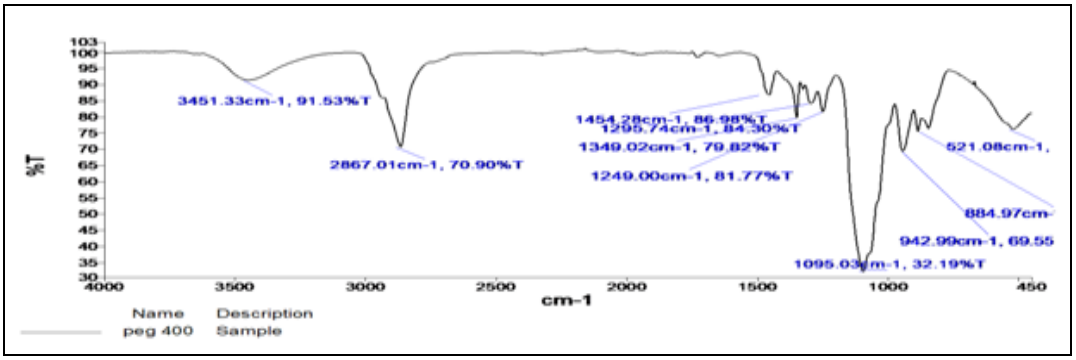

FIG. 8: FT-IR SPECTRUM OF PEG 400

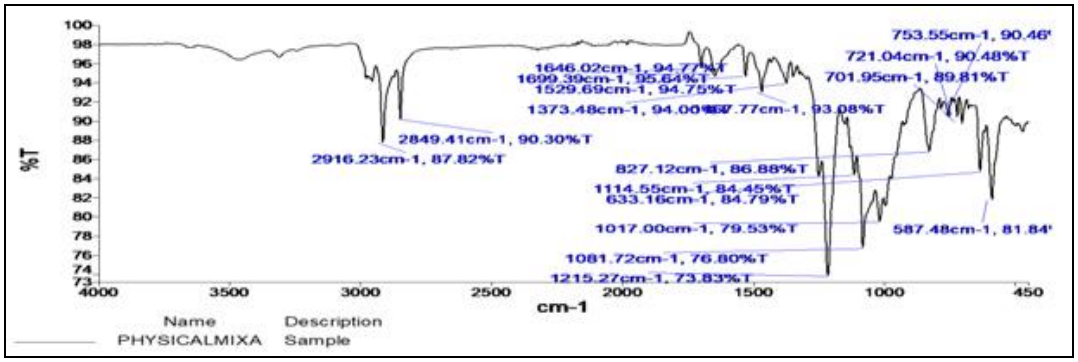

FIG. 9: FT-IR SPECTRUM OF NTD, HPMC E15, SLS PHYSICAL MIXTURE

TABLE 9: FT-IR INTERPRETATION OF NTD, HPMC E15, SLS, PEG 400 AND PHYSICAL MIXTURE

Sample	Infrared Peaks (cm^{-1})	Functional Groups
NTD	1529.74, 1699.52	NH bending for secondary amines
	1209.53	NH bending for esterified carbonyl groups
	753.02, 735.95, 701.87	Monosubstituted benzene
HPMC E15	1052.13	Stretching vibration of C-O-C group
SLS	3474.92	H-O-H stretching
	2956.99, 2916.84, 2849.75, 1467.70	CH2 Stretching and Bending
	1216.53	Skeletal vibration involving the bridge S-O stretch
	1081.76	C-C band stretching
	830.83 and 589.50	Asymmetric C-H bending of CH2 group
PEG 400	2867.01	CH2 Stretching
	1249	C-H Twisting
	1095.03	C-O-C Ether Stretching
	942.99	C-H Bending
NTD, HPMC E15,	1529.69, 1699.39	NH bending for secondary amines
SLS Mixture	1215.27	NH bending for esterified carbonyl groups
	753.55, 721.04, 701.95	Monosubstituted Benzene
	2916.23, 2849.41, 1467.77	CH2 Stretching and Bending
	1215.27	Skeletal vibration involving the bridge S-O stretch
	1081.72	C-C band stretching
	1017	Stretching vibration of C-O-C group
	827.12, 587.48	C-H bending of the CH2 group

Evaluation of Oral Fast Dissolving Films

Visual Appearance: All OFDFs were inspected visually and results are shown in **Table 10.**

TABLE 10: VISUAL APPEARANCE OF ORAL FAST DISSOLVING FILM

S. no.	Formulation Code	Appearance
1	F23	Non-Uniform
2	F24	Uniform
3	F25	Very Hard

FIG. 10: OPTIMIZED ORAL FAST DISSOLVING FILM (F24)

Surface pH: Surface pH of all OFDF was ranging from 6.79 - 7.64. Since the surface pH of the films was found to be around the neutral pH.

TABLE 11: SURFACE PH OF ORAL FAST DISSOLVING FILM FORMULATIONS

S. no.	Formulation code	Surface pH ±SD
1	F23	6.79±0.0225
2	F24	7.12±0.0251
3	F25	7.64±0.0211

*Mean±SD, n=3

Folding Endurance: Brittleness of the film was determined through the folding endurance. It measures the ability of the film to withstand rupture. Formulations F23 and F24 withstand high no of folds.

TABLE 12: FOLDING ENDURANCE OF ORAL FAST DISSOLVING FILM FORMULATIONS

S. no.	Formulation code	No of folds ±SD
1	F23	250±2
2	F24	321±4
3	F25	104±2

*Mean±SD, n=3

Thickness: Results showed that thickness of all formulations was varied from 0.153 ± 0.006 to 0.193 ± 0.002 mm. When the concentration of HPMC E15 is increased in F25, thickness of the strip increased.

TABLE 13: THICKNESS STUDIES OF ORAL FAST DISSOLVING FILM FORMULATIONS

S. no.	Formulation code	Thickness (mm) ±SD
1	F23	0.153±0.006
2	F24	0.171±0.003
3	F25	0.193±0.002

*Mean±SD, n=3

Disintegration Time: It was observed that *in-vitro* disintegration time varies from 26.567±0.321 to 35.500±0.360 sec for the three formulations as demonstrated in **Table 14** and **Fig. 17.** *In-vitro* disintegration time of NTD-OFDF containing HPMC E15 as polymer was affected by the thickness of the film, and as the amount of polymer increases, the disintegration time was increased significantly by increasing the concentration of the polymerin formulation F23, F24 and F25.

TABLE 14: DISINTEGRATION TIME OF ORAL FAST DISSOLVING FILMS

S. no.	Formulation code	Disintegration time (sec) ±SD
1	F23	26.567±0.321
2	F24	28.133±0.493
3	F25	35.500±0.360

*Mean±SD, n=3

Weight Uniformity: The variations of weights ranged between 0.279g ± 0.004 and 0.332g ± 0.004, which indicate that all the formulations with increasing amount of HPMC E15 and PEG 400 increases weight of film.

TABLE 15: WEIGHT UNIFORMITY OF ORAL FAST DISSOLVING FILMS

S. no.	Formulation code	Weight (g) ±SD
1	F23	0.279±0.004
2	F24	0.301±0.005
3	F25	0.332±0.004

*Mean±SD, n=3

Content Uniformity: All formulations were evaluated for percentage drug content. The drug content was found to be in acceptable range in all films but highest in formulation F24. The percentage drug content in optimised formulation F24 found to be 98.272 ±0.498 %. So, F24 was selected for further evaluations.

TABLE 16: CONTENT UNIFORMITY OF ORAL FAST DISSOLVING FILMS

S. no.	Formulation code	Drug content % ±SD
1	F23	78.984±0.517
2	F24	98.272±0.498
3	F25	86.616±0.549

*Mean±SD, n=3

FT-IR Study: The FT-IR spectra of optimized formulation (F24) indicate that characteristic peaks of drug is visible in the formulation and there is no objectionable interaction between drug and excipients. Peaks are shown in **Table 17** and **Fig. 11.**

TABLE 17: FTIR INTERPRETATION OF FTIR SPECTRA OF OPTIMIZED FORMULATION F24

Observed (cm^{-1})	Characteristics Peaks
1650.56	NH bending for secondary amines
1217.80	NH bending for esterified carbonyl groups
1056.95	Stretching vibration of C-O-C group
826.39 and 586.69	Asymmetric C-H bending of the CH2 group

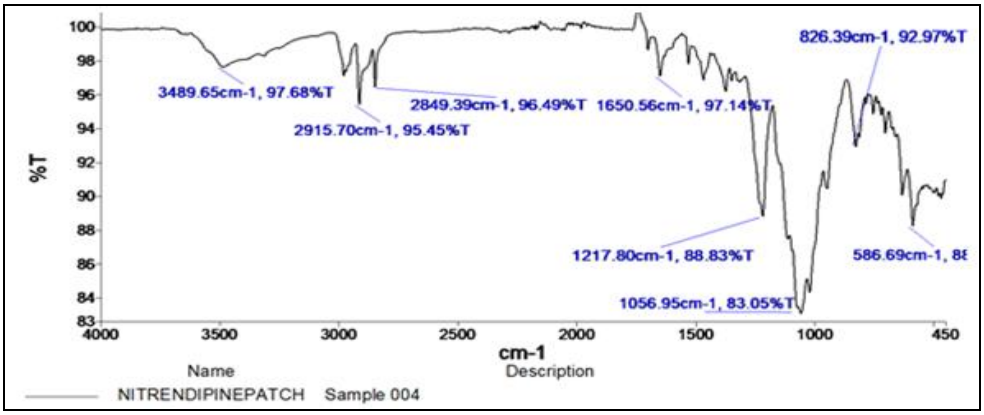

FIG. 11: FT-IR SPECTRA OF OPTIMIZED FILM FORMULATION (F24)

***In-vitro* Drug Release Study:** Drug release graphs for pure drug & NTD-OFDF shown in **Fig. 12** is significantly different from the profile of drug alone. In the pure drug solution, 24.46 ±0.187 % NTD was released within 30 min and followed by 35.73 ±0.154% in the 120 min, respectively. On the other hand, the release of NTD-OFDF was considerably increased with a maximum of 97.71 ±0.607 % release in the Phosphate buffer pH 7.4. The *in-vitro* drug release of optimized formulation F24 and Pure drug is shown in **Table 18.** To investigate the mechanism, the release data were fitted into various kinetics models, with the first order model yielding the highest correlation coefficient (R^2) (R^2=0.925), implying that the mechanism of NTD release from NTD-OFDFs was in an immediate manner.

TABLE 18: PERCENTAGE DRUG RELEASE OF FORMULATION F24 AND PURE DRUG

Dissolution Medium	Time (min.)	Drug Release of F24 Formulation (%)	Drug Release of Pure drug (%)
Phosphate Buffer pH 7.4	0	0.00±0.000	0.00±0.000
	1	28.13±0.445	4.01±0.154
	5	45.13±0.583	7.65±0.089
	10	62.72±0.734	9.90±0.175
	15	75.16±0.505	12.58±0.210
	20	77.98±0.607	19.66±0.121
	25	80.84±0.445	21.58±0.121
	30	87.41±0.292	24.46±0.187
	45	90.52±0.445	27.37±0.121
	60	93.82±0.292	30.21±0.147
	90	95.96±0.337	34.59±0.263
	120	97.71±0.607	35.73±0.154

*Mean±SD, n=3

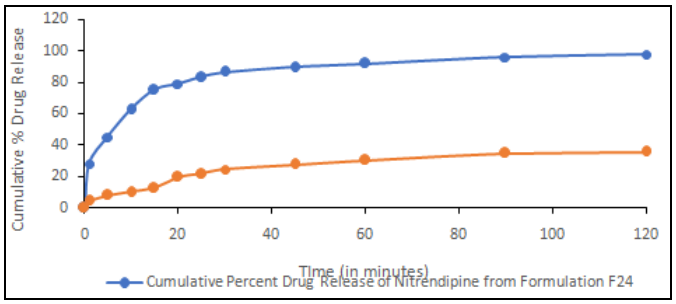

FIG. 12: PERCENTAGE DRUG RELEASE OF OPTIMIZED FORMULATION (F24) AND PURE DRUG

CONCLUSION: In this research work, NTD-NS by wet media milling technique was successfully formulated by using HPMC E15 and SLS as stabilizers. Optimized NS formulation (F21) showed enhanced solubility and dissolution with impressive nanocrystals range. NTD-NS loaded OFDFs were formulated by solvent casting method. Optimized NS loaded fast dissolving film formulation (F24) showed promising results in drug release, drug content, thickness, weight uniformity with rapid disintegration within 30 secs. Thus, formulated oral film increased solubility, dissolution, bioavailability of poorly soluble drug NTD with better patient compliance when compared to conventional tablets.

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CONFLICT OF INTEREST: Nil

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