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SOLUBILITY ENHANCEMENT OF NITAZOXANIDE USING SOLID DISPERSION

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ABSTRACT

The objective of present study was to formulate directly compressible Oro-dispersible tablets of nitazoxanide with improved solubility by using solid dispersion technique. Nitazoxanide is a antiprotozoal agent; widely used in the treatment of giardiasis and crystopordiasis. Solid dispersion of nitazoxanide was prepared by Kneading method and physical mixture using polymer as a carrier and using three different drug:carrier ratios;1:0.5, 1:1 and 1:3.Saturation solubility of drug was determined in physical mixture and solid dispersion. Formulation batches of solid dispersion were characterized by drug content, FTIR Spectroscopy, DSC and *in-vitro* drug release. From the crystalline form of nitazoxanideis converted into amorphous state during formulation of solid dispersion Oro-dispersible tablet of nitazoxanide were designed using optimized solid dispersion and crospovidone as super disintegrant. Optimized oro-dispersible tablet shows disintegration time 54seconds and *in-vitro* drug release of 87.41±0.24%, whereas marketed dispersible tablet (--) shows disintegration time -- seconds and *in-vitro* drug release of 68.73±0.38% at the end of60minutes. Thus solid dispersion based oro-dispersible tablet of nitazoxanide shows increased solubility with patient compliance and convenience.

KEY WORDS: Nitazoxanide, Solid dispersion, Solubility, Oro-dispersible tablet, PEG 4000.

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INTRODUCTION

Nitazoxanide (NTZ) is a new Antiparasitic and antiprotozoal agent having broad spectrum of activity. It is a nitrothiazole derivative and its chemical name is 2-acetyloxyl-N-(5-nitro-2-thiazolyl) benzamide. It has anthelminthic activity against intestinal nematodes, cestodesand trematodes. It issued for treating both intestinal protozoal infection and helminthiasis. It is also used for treating diarrhea caused by Giardia lambila as well as for cryptosporidiosis in immune-compromised patient. The antiprotozoal activity of NTZ is believed to be due to interference with the pyruvate ferredoxin oxido reductase(PFOR) enzyme dependent electron transfer reaction which is essential for anaerobic energy metabolism. Nitazoxanide is a light yellow crystalline powder which is insoluble in water and poorly soluble in ethanol. It belongs to BCS class II drug in biopharmaceutical classification system i.e. low solubility and high permeability.

Solid dispersion (SD) in which compound are dispersed into water-soluble carriers, are generally used to improve the solubility and bioavailability of poorly water soluble drug**.** Much of research has been reported on solid dispersion technologies involves drug that are poorly water-soluble and highly permeable to biological membrane as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption will be concurrently accelerated with an increase in the rate of drug dissolution. In Biopharmaceutical classification system the drugs with low aqueous solubility and high membrane permeability are categorized as class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS class II drug.

Now a day's ODT's are being named as oro-dispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets. Oro-dispersible tablets are placed in the mouth where they dissolve or disperse fast before being swallowed and they are uncoated tablets. Oro-dispersible tablet are disintegrate within 180 seconds when the disintegration test has been conducted up to the test for disintegration of tablet. Orally disintegrating tablet are intended to disintegrate fast in the mouth to provide dispersion before being swallowed where the active ingredient is intended for gastrointestinal delivery and/or absorption.

MATERIALS &METHODS

MATERIALS-

NTZ was obtained from Ind-swift laboratories (J&K) as gift sample, Poloxamer 188&PEG 4000obtained from Glenmark pharma, Nashik. Crospovidone and Sodium starch glycolate from Research lab-fine chem. Industries, Mumbai. All other ingredients are of pharmaceutical and analytical grades.

METHODS -

1 Preparation of solid dispersion of nitazoxanide with PEG 4000:

1.1Preparationof physical mixture (PMs):

The physical mixture were prepared by mixing the required amount of nitazoxanide and PEG 4000 in the ratio of 1:0.5, 1:1, 1:3 for 15 minute in a mortar with pestle until homogeneous mixture obtained. This resulting mixture was sieved through a 40 mesh screen. The powder was stored in desiccator until further evaluation.

1.2 Preparation of solid dispersion by kneading method:

In this method, polymer was triturated in a mortar with ethanol:water (1:1) to get slurry like consistency. Later drug was incorporated into it by continuous trituration and it was carried out for about 1hr. Slurry was then air dried at 25^{o}c for 48 hrs. The product pulverized and passed through sieve number 80. The solid dispersion stored in a dessicator until further evaluation.

2 Characterization of solid dispersion

2.1Saturation solubility studies:

Excess quantity of pure nitazoxanide and its all prepared physical mixture and solid dispersion were added in 100ml of glass stoppered volumetric flask containing 25 ml of solvent (pH 7.5 buffer solution). The flask were sealed, placed on mechanical shaker and agitated for 24hrs at 37±0.5°C. After 24hrs, the samples were then filtered through whatman filter paper, diluted suitably and absorbance was measured at 416nm.

2.2 Drug content:

The drug content nitazoxanidein each physical mixture and solid dispersion was determined using by UV spectroscopy. Accurately weigh physical mixture or solid dispersion equivalent to 50mg of nitazoxanide was transferred to 100ml volumetric flask containing 10ml of DMF and dissolved and then further diluted to make 10 µg/ml. Concentrations were measured at 416nm by UV Visible spectrophotometer.

2.3 Infrared spectroscopy:

The FTIR spectra of pure drug nitazoxanide and optimized formulation were obtained by using FTIR spectrophotometer to study the interaction between drug and carrier in solid dispersion. The samples were prepared in KBr disc (2 mg sample in 200mg KBr) and the sampling range was 400-4000 cm-1. The FTIR spectra shown in figure 1-2

2.4 Differential scanning calorimetry:

Differential scanning calorimetry measurements were performed on nitazoxanide optimized formulation using differential scanning calorimeter. The samples were placed in a sealed aluminium crucible and evaluated with a heating rate of 20 º C/min at a temperature range of 25-250 ºC. The thermograms were recorded and were in the figure 3-4

2.5X-Ray Diffraction:

The XRD patterns of pure nitazoxanide, and optimized solid dispersion of were recorded using Bruker D8 advance X-ray diffractometer. Samples were irradiated with monochromatized Cu Ka radiation using nickel filter. a voltage of 45 kV, and a current of 40 mA.

2.6 *In-vitro* Dissolution studies:

The pure drug, physical mixture and solid dispersion equivalent to 100 mg of Nitazoxanide were subjected to the dissolution study using USP dissolution apparatus type II (Paddle) maintained at 37 ± 0.5°C and 75 rpm. Dissolution medium used is pH 7.5 phosphate buffer 900ml. Sample of 10ml were withdrawn at regular time interval. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 416 nm.

3 Formulation of tablet using solid dispersion of nitazoxanide:

The solid dispersion equivalent to 200mg of nitazoxanide were taken then mixed with directly compressible diluents(MCC-PH101)and super disintegrant (crospovidon). Magnesium stearate and colloidal silicon dioxide(Aerosil-200) passed through sieve number 60, mixed and blended with initial mixture pre-compression parameters were studied . Blend was compressed using rotary tablet press (Remi) using (punch size 10.5mm).The composition of nitazoxanide tablet formulation was mentioned in Table 1.

Table 1: Composition of Tablet formulation

Batch no. → Ingredients (mg) ↓	F1	F2	F3
nitazoxanide (Equivalent to 200mg)	300	300	300
crospovidone	9	13.5	18
MCC	122	117.5	113
Magnesium stearate	4	4	4
Colloidal silicone dioxide	5	5	5
Total	450	450	450

4 Evaluation-Tablet blend was evaluated by various pre-compression parameters like Angle of repose, Hausner's ratio, Carr's index, bulk density, tapped density.

4.1Angleof repose:
The flow characteristics of powder blend was measured by angle of repose (fixed funnel method)

$$\theta = \tan{-1}\ (h/r)$$

Where,
θ is the angle of repose
h is the height in cm
r is the radius in cm

The angle of repose was then calculated by measuring the height and radius of heap of the powder formed.

4.2Bulkdensity: It was measured by pouring the weighed powder into a measuring cylinder, and the volume was noted. It is expressed in g/ml and is given by,

$$D_b = M / V_0$$

Where, M is the mass of powder, $V_0$is the bulk volume of powder

4.3Tappeddensity: It is expressed in g/ml and is given by,

$$D_T = M / V_1$$

Where, M is the mass of powder, VT is the tapped volume of the powder

4.4Carr'sindex: It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

Carr's index = Tapped Density – Bulk Density / Tapped Density

4.5Hausner'sratio: Hausner's ratio is the ratio of tapped density to bulk density

Hausner's ratio = Tapped Density / Bulk Density

5 Evaluation of tablet: Compressed tablet of nitazoxanide were evaluated by various parameters like:

5.1Uniformity of weight: Weight variation test was done by weighing 20 tablets individually and calculating the average weight of tablet, and then comparing the individual tablet weight to the average weight.

Monograph	Average weight	Deviation
IP/BP	<80 mg	10
	Between 80 and 250 mg	7.5
	>250 mg	5
USP	<130 mg	10
	Between 130 and 325 mg	7.5
	>325 mg	5

Table 2: Weight variation specification as per IP/BP and USP

5.2Hardness: Tablet requires certain amount of strength to have a resistance from breakage, while transportation and handling before use. It was measured by Monsanto Hardness Tester. The test was performed on six tablets and the average was calculated.

5.3Friability: The friability of the tablet was determined using Roche friabilator. It is expressed in percentage (%). abrasion in plastic chamber Twenty tablets were initially weighed (W1) and transferred into the friabilator. The friabilator was operated at 25+_1rpm for a tablet with an average weight of 0.65gor less take sample of whole tablets corresponding to about 6.5g and for tablet with an average weight of more than 0.65g take a sample of 10 whole tablets. The tablet were de dusted and weighed again (W2). The % friability was then calculated by %.

$$\% \text{ Friability} = (W_1\text{-}W_2/W_1) \times 100$$

Where,
W1 =Weight of the tablet before test
W2 =Weight of the tablet after test (10)

5.4 Content uniformity of tablet:

Five tablets were weighed and powdered; a quantity of powder equivalent to 10 mg of drug was dissolved in 100ml Dimethyl Formamide (1000µg/ml). From this solution 1ml solutions were pipette and volume was made to 10ml using DMF to concentration 10 µg/ml. The drug content was determined by measuring the absorbance at 416nm. The drug content was calculated using the standard calibration curve. The mean percentage drug content was calculated as an average of three determinations.

5.5 Wetting time:

A piece of tissue paper (12cm X 10.75cm) folded twice was placed in a small Petri dish containing 6ml pH 7.5 phosphate buffer, a tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted.

5.6 Disintegration time:

The test was carried out on 6 tablet using the apparatus specified in I.P. 1996 Distilled water at 37^{o}C± 2^{o}C was used as a disintegration media and the time in the second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

5.7*In-vitro*Dissolution study:

In vitro dissolution of oro-dispersible tablet of nitazoxanide was studied using USP type-II dissolution apparatus (Electro lab) by employing a paddle stirrer at 75rpm 900ml of pH 7.5 phosphate buffer using as a dissolution medium. The temperature of dissolution medium was maintained at 37±0.5^{o}C throughout the experiment. One tablet was used in each test. Sample of dissolution medium (10ml) were withdrawn by means of syringe fitted with pre-filter at known interval of time and analyzed for drug release by measuring the absorbance at 416nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent drug released was calculated and plotted against time.

5.7 Stability studies:

Stability study was carried out as per ICH guideline (Q1A-Q1F) at 40°C ± °C/75 % ± 5% RH for the selected formulation (F3) for 1 month. After specified time intervals, parameters like hardness, drug content, disintegration time and in-vitro dissolution were evaluated according to the procedure described as above.

6 RESULTAND DISCUSSION-

By evaluating various parameters of solid dispersion and compressed tablets results were interpreted and discussed as follows.

6.1 Characterization of solid dispersion:

6.1.1 Saturation solubility studies Nitazoxanide PEG Solid dispersion:

Nitazoxanide PEG Solid dispersion was prepared by kneading method and fusion method by varying drug polymer ratio;(1:0.5,1:1,1:3)respectively were characterized by various parameters. Observations of Saturation solubility study was given in Table number3.From observed values; it can be concluded that formulation batch KPEG1 with drug:polymer ratio 1:0.5(prepared by kneading)exhibits maximum solubility of 3.4 mg/ml whereas formulation batch FPEG3with drug:polymer ratio 1:3(prepared by fusion)exhibits less solubility of 1.94 mg/ml.

Table2: Solubility and Drug content of various formulations

Sr.No	Formulation Code	Ratio	Method	Solubility (mg/ml)	% Drug Content
1	KPEG1	1:0.5	PEG 4000Kneading Method	3.4	98.05
2	KPEG2	1:1		2.9	95.73
3	KPEG3	1:3		2.1	91
4	FPEG1	1:0.5	PEG 4000Fusion Method	3.1	96.41
5	FPEG2	1:1		2.6	95
6	FPEG3	1:3		1.94	90

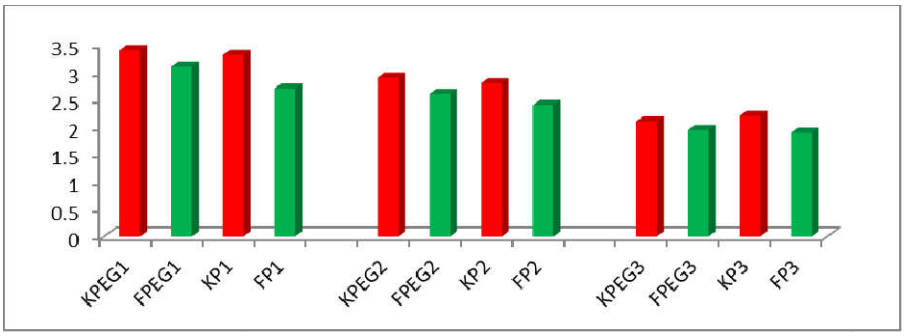
6.1.2 Saturation solubility studies Nitazoxanide Poloxamer Solid dispersion: Nitazoxanide ploxamer Solid dispersion prepared by kneading method and fusion method by varying drug polymer ratio;(1:0.5,1:1,1:3) respectively were characterized by various parameters. Observations of Saturation solubility study was given in Table number4. From observed values; it can be concluded that formulation batch KP1with drug:polymer ratio 1:0.5(prepared by kneading) exhibits maximum solubility of 3.31 mg/ml whereas formulation batch FP3with drug:polymer ratio 1:3(prepared by fusion)exhibits less solubility of 1.89 mg/ml.

Table 3: Solubility and percent Drug content of Nitazoxanide Poloxamer Solid dispersion

Sr. No	Formulation Code	Ratio	Method	Solubility (mg/ml)	% Drug Content
1	KP1	1:0.5	Poloxamer 188 Kneading Method	3.31	96.71
2	KP2	1:1		2.8	95.45
3	KP3	1:3		2.2	90
4	FP1	1:0.5	Poloxamer 188 Fusion Method	2.7	95.47
5	FP2	1:1		2.4	93.81
6	FP3	1:3		1.89	89

Graphical presentation for comparing the solubility differences observed in the poloxamer and PEG Solid dispersion of Nitazoxanide prepared by kneading and fusion method was given in Figure number 1.

Figure1: Graphical presentations of solubility study data



6.1.2 Analysis of drug content: The percent drug content of Physical mixture and solid dispersion shown in table4

Table 4: Percent drug content of Physical mixture and solid dispersion

Method	Ratio	Drug content
Physical mixture	1:0.5	97.16
	1:1	97
	1:3	94.3
Solid dispersion (Kneading method)	1:0.5	98.05
	1:1	95.73
	1:3	91

The drug content of nitazoxanide physical mixture and solid dispersion was found to be in range 91% to 98.05% and these values are within the acceptable range.

6.1.3 Fourier Transform InfraRed (FTIR) Spectroscopy:

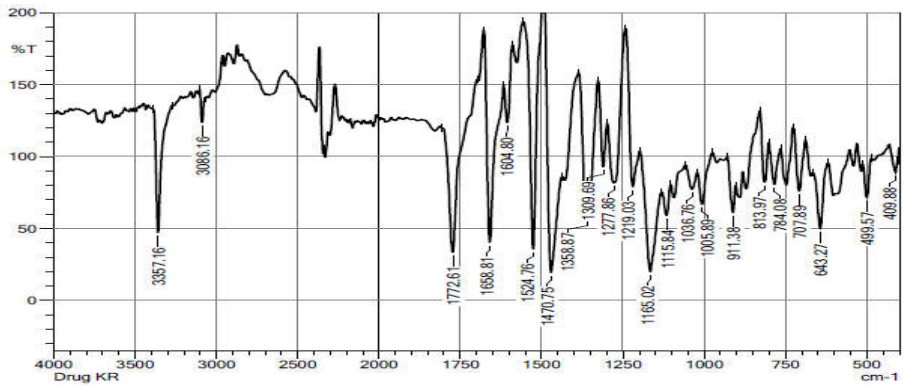


Figure2: FTIR spectrum of Nitazoxanide

N-H stretching at 3357.16 cm-1, aromatic C-H stretching at 3080.16cm-1, C=0 stretching at 1772.61cm-1, N=O nitro at 1524.76 cm^{-1}

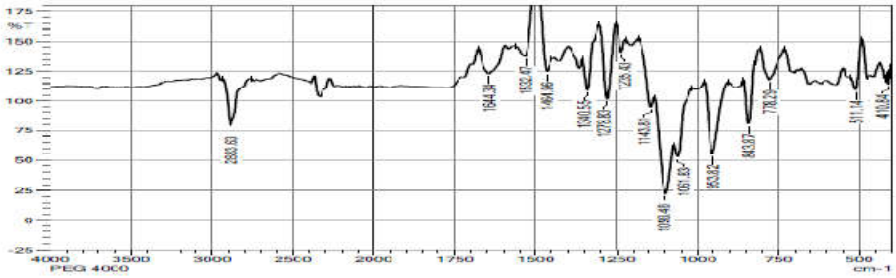


Figure 3: FTIR spectrum of PEG 4000

C-H stretching at2883.63 cm^{-1}, C-O stretching at 1098.48cm^{-1}.

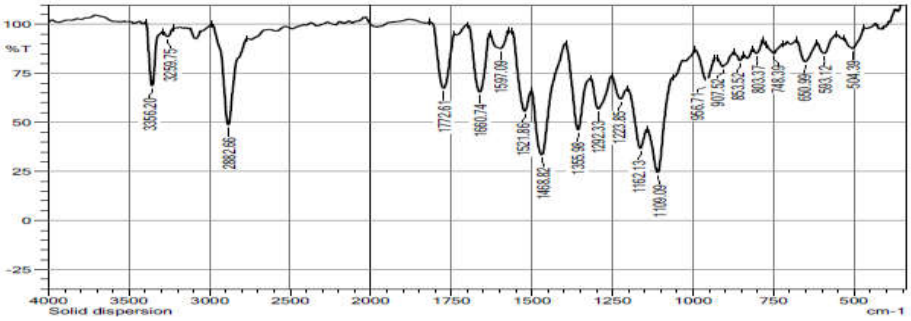


Figure 4: FTIR Spectrum of solid dispersion (1:0.5)

One additional peak at 1644.34cm-1 indicative of inter-molecular hydrogen bonding between (Nitazoxanide& PEG 4000)

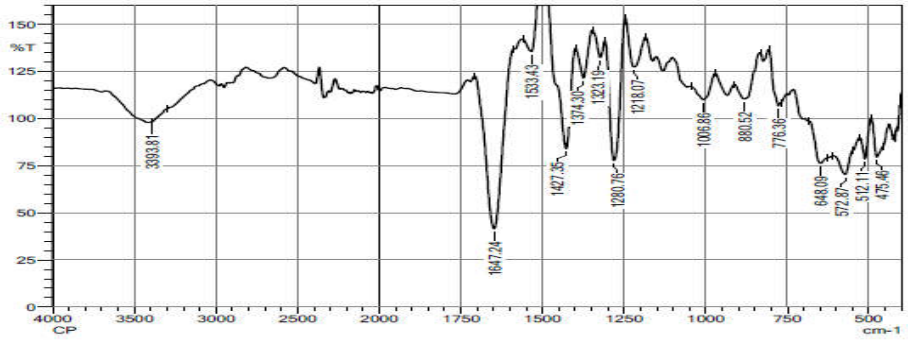


Figure 5: FTIR spectrum of Crospovidone

peak N-C=O amide stretch at 1647.24cm-1, and C-H bending at 1427.25cm^{-1}, C-N stretching at 1280.76 cm^{-1}

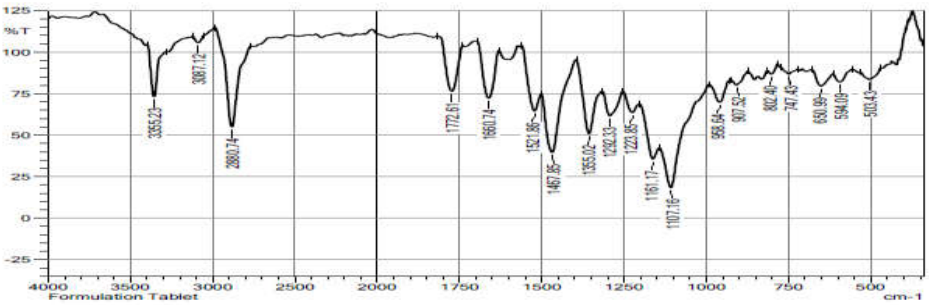


Figure 6: FTIR Spectrum of Orodispersibletablet (F3)

6.1.4 Differential scanning calorimetry study:

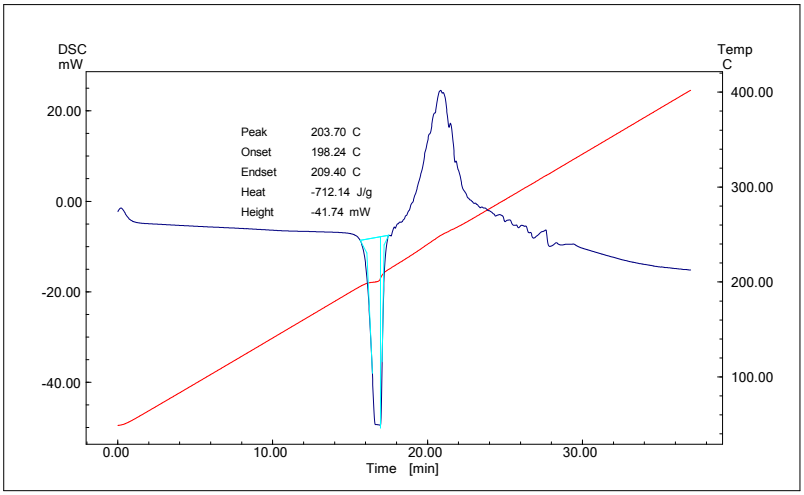


Figure 7: DSC Thermogramofnitazoxanide

Pure nitazoxanide showed sharp endothermic peak corresponding to melting point of nitazoxanideat 203.70°C, indicating crystalline nature

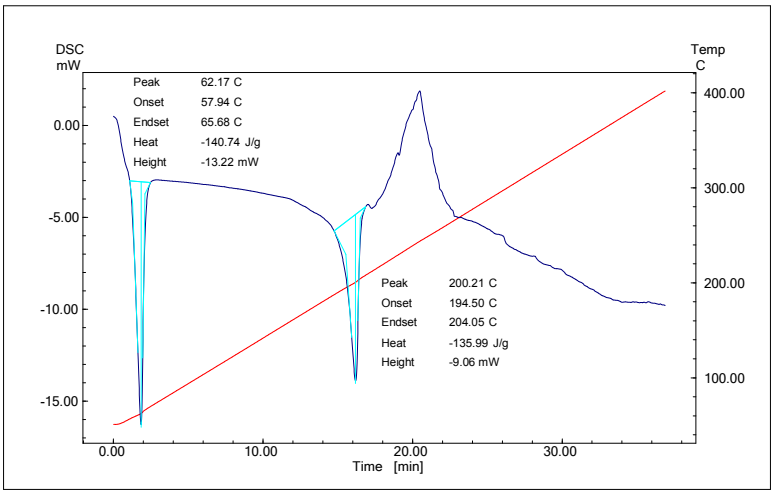


Figure 8: DSC Thermogramof Solid dispersion (1:0.5)

Optimized batch KPEG 1 observed at 200.21°C (Fig.7) it showed that the shifting of melting endotherm of Nitazoxanide & amorphous precipitation of the drug and better solubilization in carrier. Nitazoxanide losses crystalline nature and converts to amorphous nature.

6.1.5X-Ray Diffraction Study (XRD)

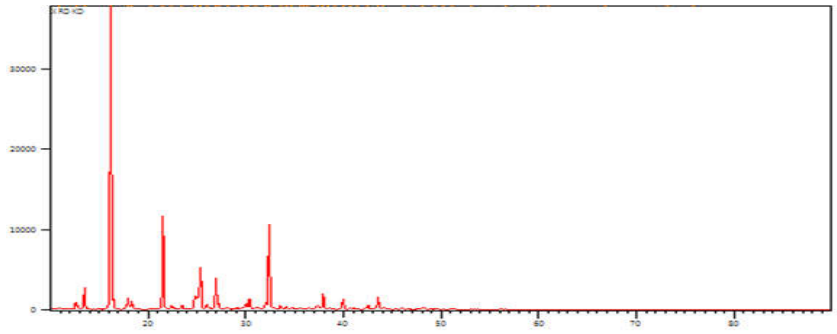


Figure9: XRD pattern of Nitazoxanide

Sharp numerous distinct peaks notably at 2θ angles, were 16.2°, 21.5°, 32.3°. series of sharp and intense diffraction peaks were emphasized crystalline state of pure nitazoxanide.

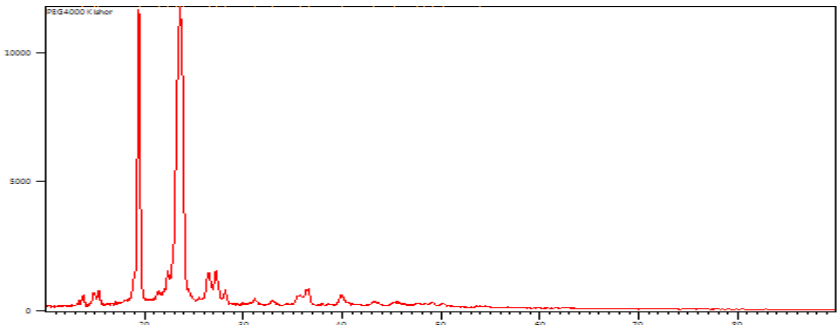


Figure10: XRD pattern of PEG 4000

Sharp numerous distinct peaks notably at 2θ angles, were 16.2°, 21.5°, 32.3°.

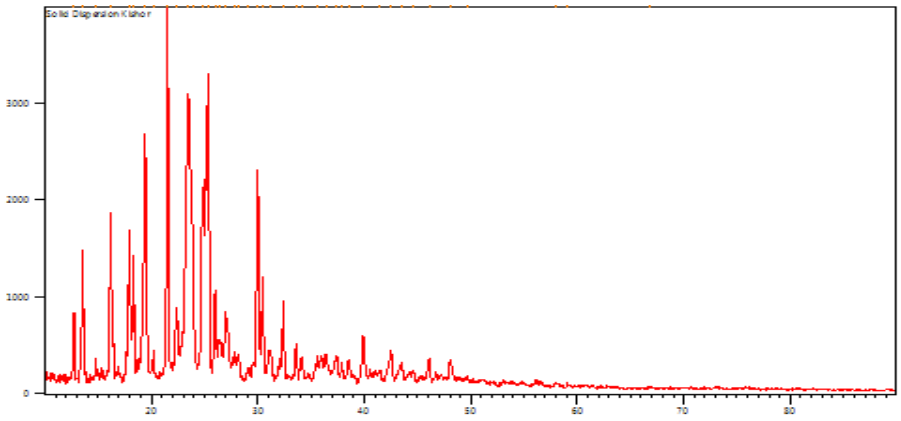


Figure11:XRD pattern of Solid Dispersion(nitazoxanide:PEG4000)

Showed all intense peaks , The crystallinity of drug in solid dispersion was less than that observed before preparation. But the pattern still showing the typical signals of Nitazoxanide but the intensity is weakened as shown in figure.

6.2 Evaluation of solid dispersion based Oro-dispersible tablet:

6.2.1 Pre-compression parameter of tablet blend:

Powder blend containing solid dispersion of nitazoxanide and various exipients were subjected for pre-compression parameter such as flow property, angle of repose, bulk density, tapped density, carr's index and hausner's ratio shown in table 5.

Table 5: Pre-compression parameter of solid dispersion based orodispersible tablet of nitazoxanide

Formulation Code	Angle of Repose (^{0})	Bulk Density (g/cm^2)	Tapped Density (g/cm^2)	Carr's Index (%)	Hausner's Ratio
F1	29.54	0.463	0.578	19.89	1.24
F2	31.78	0.489	0.594	17.67	1.21
F3	32.15	0.501	0.612	18.13	1.22

6.2.2 Post-compression parameter:

The tablet prepared by direct compression method subjected for evaluation according to various official specification and other parameters like shape and color, hardness, friability, weight variation, drug content, weighting time, in-vitro disintegration time and dissolution studies shown in table 6.

Table 6: Post-compression parameter of solid dispersion based Orodispersible tablet ofnitazoxanide

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content (%)	Wetting Time (sec)	Disintegration Time (sec)
F1	2.1±0.35	0.74±0.03	450±0.32	99.12±0.3	72.65±0.36	69±2
F2	2±0.24	0.82±0.05	449±0.14	98.34±0.04	68.02±0.41	61±4
F3	2.4±0.18	0.78±0.02	449±0.27	98.69±0.02	61.67±0.52	54±3

6.2.3*In-vitro*Dissolution study of formulated tablet:

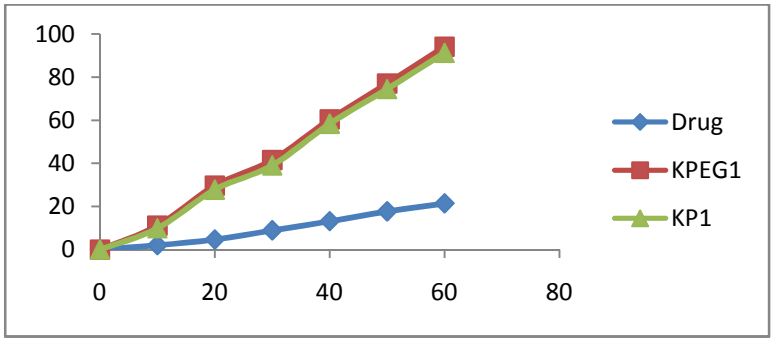


Figure11: In-Vitro Dissolution profiles of Nitazoxanide and optimized Solid dispersion of PEG 4000 & Poloxamer 188 prepared by kneading method.

In table 9, in-vitro dissolution profiles of Nitazoxanide& optimized solid dispersion were given. Pure Nitazoxanide& formulation batches KPEG1, KP at 60 minute shows % drug release 21.38± 0.191, 93.99±0.103, 91.19±0.106 respectively. Optimized batches shows marked increase dissolution rate than pure Nitazoxanide.

Comparison between Marketednitazoxanide tablet and formulated tablet (F3):

Table 10: Comparative result of marketed tablet and formulated tablet

Parameter	Marketed Tablet	Formulated Tablet (F3)
Hardness (Kg/cm^2)	2.3±0.39	2.4±0.18
Weight Variation	380±0.14	449±0.27
Friability (%)	0.81±0.06	0.78±0.02
Wetting Time (Sec)	59±0.34	61.67±0.52
Drug Content (%)	99.1±0.001	98.69±0.02
Disintegration Time (Sec)	51±2	54±3

Table 11: Percent cumulative drug release of marketed tablet and formulated tablet (F3)

Time (min)	Marketed Tablet	Formulated Tablet (F3)
0	0	0
5	6.41±0.23	35.39±0.14
10	14.35±0.35	54.8±0.27
15	22.54±0.2	73.31±0.10
30	37.59±0.14	80.30±0.06
45	50.70±0.08	84.82±0.19
60	68.73±0.38	87.41±0.24

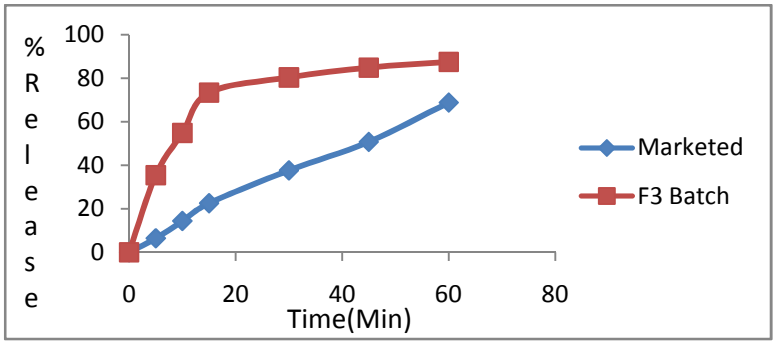


Figure 12: In-vitro dissolution profile of marketed tablet and formulated tablet (F3)

6.2.4 Stability study-

Table 12: Stability study of Oro-dispersible tablet (F3)

Parameters	Days				
	0	**7**	**14**	**21**	**28**
Appearance	Smooth	Smooth	Smooth	Smooth	Smooth
Hardness (kg/cm^2)	2.4±0.18	2.4±0.11	2.4±0.15	2.4±0.18	2.4±0.23
Friability (%)	0.78±0.02	0.78±0.12	0.76±0.09	0.76±0.39	0.78±0.22
DT (sec)	54±3	54±2	55±3	56±2	56±2
Drug content (%)	98.69±0.02	98.42±0.36	97.79±0.13	97.34±0.07	97.26±0.28

CONCLUSION-

The enhancement of the oral bioavailability is currently one of the greatest challenge in the development of poorly water soluble drugs. To increase the solubility and hence the bioavailability it is important to increase the dissolution of the poorly water soluble drugs. One of the possible ways to overcome this limitation is the use of solid dispersion technique. In order to overcome above problem, the present study was carried out to develop oro-dispersible tablets containing Nitazoxanide solid dispersion. Solid

dispersions of Nitazoxanide were prepared by using PEG 4000 in different ratios by physical mixture & kneading method. The drug and polymer ratio of 1:0.5, 1:1, 1:3 were used in order to enhance solubility and dissolution rate. After formulation completed Nitazoxanide, physical mixture & kneading method dispersions were proceeds for its evaluation study.

In order to investigate *in-vitro* release of pure drug, physical mixtures and solid dispersions with PEG 4000 were subjected to dissolution study in USP type II dissolution apparatus. PD, SD 1:0.5, SD 1:1 and 1:3 shows 21.38±0.191, 93.99±0.103, 89.31±0.103, 85.83±0.181 in 60 min respectively. It indicate that SD 1:0.5 shows higher drug release 93.99±0.103% within 60 min compared to PD and SD 1:1, 1:3. From the results of dissolution studies SD 1:0.5 is selected as best formulation for tablet formulation.

The results that are obtained for formulation F1-F3 shows good compression and flow property. The prepared tablets were subjected for post-compression parameters. The results for all formulations possessed good mechanical strength with sufficient hardness in the range of 2 to 2.4 kg/cm^2. The percent friability was found to be 0.74 to 0.82 which is less than 1% indicating tablets were mechanically stable. All formulations show 449±0.47 to 450±0.32 mg/tablet weight, which complies with pharmacopeias limit. Drug contents were found to be within pharmacopeias limit. The wetting time, dispersion time, disintegration time for all formulations was found to be in acceptable range. It is decreasing wetting, dispersion and disintegration time with increasing concentration of Super disintegrant.

The prepared oro-dispersible tablet of Nitazoxanide solid dispersion has shown better release and stability as compared to marketed formulation.

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