ISSN: 0976-7126
Jadhav et al., 11(12):7171-7197, 2020

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Development and In-vitro Evaluation of film coated tablet of Norfloxacin and Tinidazole

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Article info

Received: 08/11/2020

Revised: 30/11/2020

Accepted: 23/12/2020

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Abstract

In the present work, film coating technique successfully used for the taste masking of bitter tested drugs. Also the 2% film coating shows no any effect on the physical as well as performance parameters of the tablets. The formulation variable, i.e. different binders in different concentration used influence in vitro drug release profile, disintegration time and micromeritic properties of the prepared tablets. The excellent disintegration time offers the better immediate release profile of the tablets. The film coated technology employed, gives immediate release profile along with taste masking and smooth elegance. This results in burst release of drugs and successively rapid absorption through stomach to attain therapeutic plasma concentration. Stability studies show that drug content was within a range as per IP specifications. Also there was no change in colour seen during stability studies. Also the present work relates with two simple, accurate and reproducible spectrophotometric methods have been developed for the simultaneous estimation of Norfloxacin and Tinidazole which can be employed for the routine estimation of NF and TZ in both bulk and tablet dosage form.

Keywords: Formulation, Film coated, Norfloxacin and Tinidazole

Introduction

Norfloxacin

The 6-fluoroquinolones (also known as 4-quinolones or quinolones) are a series of synthetic antibacterial agents derived from, or related to, nalidixic acid and oxolinic acid. Position 1 is nitrogen in the bicyclical aromatic ring structure, with an alkyl group (ethyl or perhaps cyclopropyl) often attached there. Carboxylic acid at position 3 is required for antimicrobial activity, similarly like a keto group at position 4. Many improvements on these early quinolones carboxylic acids have been made based in systematic structure-activity studies. (*Wistrom J, Jertborn M, Ekwall E, et al*. 1992) A fluorine atom at position 6 on the quinolones carboxylic acid nucleus enhances the efficacy of these compounds against gram negative pathogens and broadens the spectrum of activity against gram-positive pathogens: a basic nitrogen-containing moiety enhances tissue penetration and reduces the central nervous system toxicity. Modifications of the basic structure at positions 2, 5 and 7 alter the pharmacokinetics of the compound. Over the last two decades, research on 4-quinolone-3-carboxylates has led to the discovery of a family of 6-fluoro-7-piperazinyl-4-quinolones. Norfloxacin was one of them.

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Tinidazole

Tinidazole, a synthetic imidazole derivative, has been used in the oral treatment of several protozoal infections - trichomoniasis, giardiasis and amoebiasis. Among the protozoal organisms inhibited by Tinidazole are trichomonas vaginalis, Trichomonas foetus, and Entamoeba histolytica. Tinidazole also has activity against some Gram-negative anaerobic bacilli, including Bacteroides spp. (*Dennis J. Cada, Danial E. Baker,2004*) Tinidazole is FDA approved for use in the treatment of trichomoniasis caused by *Trichomonas vaginalis* in female and male patients, giardiasis caused by *Giardia duodenalis (Giardia lamblia)* in adults and children older than 3 years of age, and intestinal amoebiasis and amoebic liver abscess caused by *Entamoeba histolytica* in adults and children older than 3 years of age.

Tinidazole is a prodrug and antiprotozoal agent. The nitro group of Tinidazole is reduced in *Trichomonas* by a ferredoxin-mediated electron transport system. The free nitro radical generated as a result of this reduction is believed to be responsible for the antiprotozoal activity. It is suggested that the toxic free radicals covalently bind to DNA, causing DNA damage and leading to cell death. The mechanism by which Tinidazole exhibits activity against *Giardia* and *Entamoeba* species is not known, though it is probably similar. (*www.drugbank.com*)

Need of Norfloxacin-Tinidazole combination

Most episodes of diarrhoea are acute, short duration and do not require antibiotics. Antibiotics are not even necessary for the most common bacterial infections that cause diarrhoea. Antibiotics, however, often are used when

(1) Patients have more severe and persistent diarrhoea.

(2) Patients have additional debilitating diseases such as heart failure, lung disease, and AIDS.

(3) Stool examination and testing discloses parasites, more serious bacterial infections (for example, *Shigella*), or *C. difficile*.

(4) Traveller's diarrhoea.

Materials and Methods

Formulation development and in vitro evaluation

Formulation of Core tablets

Starch paste with superdisintegrants

Procedure: (Starch paste 20%)

PART-A

Granulation:

1. Norfloxacin & MCC was sifted through mesh 40. They mixed geometrically in a polythene bag for 2-3 min. Then Tinidazole sifted through mesh 40.
2. Geometrically mixed all above ingredients for 2-3 min.
3. Preparation of binder solution: Required quantity starch dissolved in water to make slurry & then added to the boiling water. Heat the solution till translucent solution obtained. Solution so obtained was cooled & then required weight made up.
4. The blend obtained from step 2 was granulated with 20% w/v starch solution.
5. The granules obtained were then semidried at 60^0c for one hour & 45 min after which it was passed through mesh no 20 and finally drying of the granules done for One hour & 15 minutes.

PART-B

Blending & compression:

1. All the other ingredients were passed through mesh no. 40 separately.
2. The granule blend obtained from PART-A then blended with sodium starch glycolate, talc & magnesium stearate for 2-3 min.
3. The blend so obtained was then compressed into tablets using 21.2×8.9mm/CAPTAP punch in a single station tablet compression Machine. And the various parameters so produced were studied.

a. Gelatin with superdisintegrants

Procedure:

PART-A

Granulation:

1. Norfloxacin & MCC was sifted through mesh 40. They mixed geometrically in a polythene bag for 2-3 min. Then Tinidazole sifted through mesh 40.
2. Geometrically mixed all above ingredients for 2-3 min.
3. Preparation of binder solution: -Required quantity Methyl paraben & Propyl paraben were dissolved in hot water to which gelatin was added & dissolved by stirring. The solution so obtained was cooled & the required weight was made up.

4. The blend obtained from step 2 was granulated with Gelatin (20%w/v, 15%w/v, 5%w/v) solution.
5. The granules obtained were then semidried at 60^0C for one hour after which it was passed through mesh no. 20 and Final drying done for two hour.

PART-B

Blending & compression:

1. All the other ingredients were passed through mesh no. 40 separately.
2. The granule blend obtained from PART-A then blended with sodium starch glycolate, talc & magnesium stearate for 2-3 min.
3. The blend so obtained was then compressed into tablets using 21.2×8.9mm/CAPTAP punch in a single station tablet compression Machine. And the various parameters so produced were studied.

b. HPC with superdisintegrants :

Procedure: (HPC 12%)

PART-A

Granulation:

1. Norfloxacin & MCC was sifted through mesh 40. They mixed geometrically in a polythene bag for 2-3 min. Then Tinidazole sifted through mesh 40.
2. Geometrically mixed all above ingredients for 2-3 min.
3. Preparation of binder solution: - Required quantity Hydroxy propyl cellulose (SL) dissolved in IPA by stirring & then required weight made up.
4. The blend obtained from step 2 was granulated with HPC 12% w/v solution.
5. The granules obtained were then semidried at 60^0C for 30min. After which it was passed through mesh no 20.Final drying done for One hour & 30 min.

PART-B

Blending & compression:

1. All the other ingredients were passed through mesh no. 40 separately.
2. The granule blend obtained from PART-A then blended with sodium starch glycolate, talc & magnesium stearate for 2-3 min.
3. The blend so obtained was then compressed into tablets using 21.2×8.9mm/CAPTAP punch in a single station tablet compression Machine. And the various parameters so produced were studied.

c. HPMC with superdisintegrants :

Procedure: (HPMC 5%)

PART-A

Granulation:

1. Norfloxacin & lactose were sifted through mesh 40. They mixed geometrically in a polythene bag for 2-3 min. Then Tinidazole sifted through mesh 40.
2. Geometrically mixed all above ingredients for 2-3 min.
3. Preparation of binder solution: - Required quantity of hydroxypropyl methyl cellulose dissolved in water by stirring & then required weight made up.
4. The blend obtained from step 2 was granulated with HPMC (5%w/v) solution.
5. The granules obtained were then semidried at 60^0C for one hour after which it was passed through mesh no. 20. Final drying was done for two hour.

PART-B

Blending & compression:

1. All the other ingredients were passed through mesh no. 40 separately.
2. The granule blend obtained from PART-A then blended with sodium starch glycolate, talc & magnesium stearate for 2-3 min.
3. The blend so obtained was then compressed into tablets using 21.2×8.9mm/CAPTAP punch in a single station tablet compression Machine. And the various parameters so produced were studied.

Table 1: Formulation table of batches F-01 to F-07 of core tablets

Sr. No	Tablet ingredients (In mg.)	Formulation codes of prepared batches						
		F-01	**F-02**	**F-03**	**F-04**	**F-05**	**F-06**	**F-07**
1.	Tinidazole IP	603.60	603.60	603.60	603.60	603.60	603.60	603.60
2.	Norfloxacin IP	402	402	402	402	402	402	402
3.	Microcrystalline cellulose	91	91	116	116	152	143	144
4.	Sodium starch glycolate	-	-	-	10	10	10	10
5.	Binders	-	-	-	-	-	-	-
	a. STP (20%)	80.40	-	-	-	-	-	-
	b. Gelatin(20%)	-	80.40	-	-	-	-	-
	Gelatin (15%)	-	-	57.40	57.40	-	-	-
	Gelatin (5%)	-	-	-	-	20.4	-	-
	c. HPC (12%)	-	-	-	-	-	28.40	-
	d. HPMC (5%)	-	-	-	-	-	-	17.40
6.	Sodium starch glycolate	10	10	10	-	-	-	-
7.	Magnesium stearate	8	8	8	8	8	8	8
8.	Talc	5	5	5	5	5	5	5
	Total	1200	1200	1200	1200	1200	1200	1200

Evaluation of core tablets

a. Granule Evaluation

i)Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for granules of each formulation was determined by fixed funnel free standing cone method. The granules were allowed to flow out of the funnel orifice on a plane paper kept on horizontal surface. This forms a pile of angle of granules on the paper. The angle of repose was calculated by substituting the values of the base radius 'r' and pile height 'h' in the following equation (7.1).

$$\tan \theta = h / r$$

$$\text{Therefore } \theta = \tan^{-1} (h / r) \quad \text{eq. (7.1)}$$

ii) Moisture content and Loss on drying test

KF reagent test/Moisture content test

Suitable quantity of methanol was taken in titration flask of Karl Fischer titration and titrated with Karl Fischer reagent to end point. 0.5gm of the granules was weighed accurately and transferred quickly to the titration flask, dissolved by stirring and titrated with Karl Fischer reagent to end point.

Loss on drying test

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile

ISSN: 0976-7126
Jadhav et al., 11(12):7171-7197, 2020

matter of any kind that can be driven off under specified conditions. Weigh a glass-stoppered, shallow weighing bottle that has been dried. Transfer to the bottle the quantity of the sample specified in the individual monograph here 1gm of granules, cover it and accurately weigh the bottle and the contents. Distribute the sample as evenly as practicable by gentle sidewise shaking to a depth not exceeding 10mm. Dry the substance by placing the loaded bottle in the vacuum oven for 3 hrs. at 60ºC, remove the stopper and leave it also in the chamber. After getting cool glass bottle again weigh & calculate loss on drying.

iii) **Bulk density**

It is the ratio of mass and bulk volume. It is required to decide the appropriate packing of dosage forms. 10 gm granules were allowed to flow in a fine stream into a graduated cylinder and final volume was noted. The bulk density was obtained by dividing the weight of the sample in grams by final volume in cm^3 and it was determined by equation (7.2) given below,

$$\text{Bulk density} = \text{Mass/Bulk volume}$$

eq. (7.2)

iv) **Tapped density**

10 gm granules were allowed to flow in a fine stream into a graduated cylinder of a mechanical tapping device. The measuring cylinder was tapped until no change in volume and final tapped volume was noted. The tapped density was obtained by dividing the weight of the sample in grams by final tapped volume in cm^3 and it was calculated by using equation (7.3) given below,

$$\text{Tapped density} = \text{Bulk mass/ Tapped volume}$$

eq. (7.3)

v) Carr's Compressibility Index and Hausner's Ratio

Carr's index

It decides the flow properties of granules. It is an indirect method of measuring powder flow from bulk densities and was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation (7.4) given below-

$$Carr's\ index = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} X\ 100$$

eq. (7.4)

Hausner's ratio

It is essential to determine the compressibility strength of powders. It was determined by using equation (7.5),

Hausner's ratio = Tapped density/ Bulk density eq. (7.5)

Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

b. Core Tablet Evaluation:

Physical Properties of Tablets

The tablets were evaluated for various physical parameters like average weight, thickness, diameter, hardness and friability of the formulation.

i) Evaluation of appearance & dimensions

The overall appearance (thickness and diameter) of core tablet was noted especially to judge any defects in the tablets. For this, five tablets of each of the formulations type were used and the mean values were calculated

ii) Uniformity of Weight

Weigh individually 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage. In short, not more than two of the individual weights deviated from the overage weight by ±5% and none deviated by more than ±10% of average weight.

iii) Hardness testing

Tablet hardness was determined from the force required to fracture tablets by diametrical compression using a tablet hardness tester (Monsanto tester). Mean hardness of 6 tablets from each formulation was reported as tablet hardness. (Lachman, Liberman, 296-300).

iv) Friability testing

For tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weigh them accurately. The test is run only once unless the results are difficult to interpret or if the weight loss is greater than the targeted value, in this case, the test is repeated twice and the mean of the three tests is determined. A maximum loss of weight (from a

single test or from the mean of the three tests) not greater than 1.0 per cent is acceptable for most tablets. (IP-2010)

$$\%Loss = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial wt. of tablets}} x\ 100$$

eq. (7.6)

Test for performance evaluation

i. Test for uniformity of drug content

Test for uniformity of drug content was carried out using RP-HPLC method as follow,

- **Preparation of Mobile phase:**
  0.2% Triethylamine in water and Acetonitrile (80:20v/v) solution was used as mobile phase. For the preparation of mobile phase done in two steps, at first the 0.2% Triethylamine solution in water was prepared. For this according to density of triethylamine (0.726 gm/ml) add 2.7472 ml of triethylamine in 1000ml of dist. water to prepare 0.2% TEA. Then prepared suitable mixture of 0.2% Triethylamine in water and Acetonitrile (80:20v/v). Adjust the pH of mobile phase 2.6-2.8, with dil. Phosphoric acid. Solution passed through a filter having a 0.5µm or finer porosity & used as mobile phase.
- **Standard solution :**
  Weigh accurately about 20mg of NF working standard & 30mg of TZ into a 100.0 ml volumetric flask containing Mobile phase. Then sonicate the flask for 5-10 mins and to get properly dissolved. From this, transfer 5ml of solution into 50 ml volumetric flask and diluted with Mobile phase up to the mark and shake for 5 min. Then solution passed through a filter having a 0.5µm or finer porosity and used the filtrate as the standard solution.
- **Sample solution :**
  Grind about 20 tablets to fine powder in a dried mortar and weighed accurately the quantity of powder equivalent to 20mg of Norfloxacin and 30mg of Tinidazole into a 100 ml volumetric flask containing mobile phase. Then sonicate the flask for 5-10 mins and to get properly dissolved. Filter the solution through 0.45 µm filter. From this solution, transfer about 5 ml into 50ml of volumetric flask. Then solution used as the sample solution. Separately injected the standard preparation and the sample preparation into the liquid chromatography and recorded the area due to major peaks.

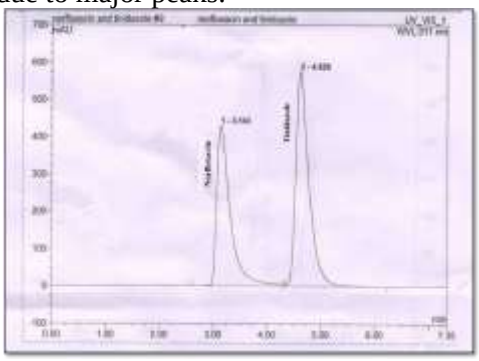

Figure 1: Chromatogram of standard solution of Norfloxacin-Tinidazole.

- **Chromatographic conditions:**
  By appropriate dilutions the samples were analyzed by HPLC. The column type, flow rate, wavelength, temperature, sample load, retention time of the both the drugs & run time parameters are depicted in the following

Table : Chromatographic conditions used in the HPLC analysis.

Parameter	Specifications
Column	C_{18}, 250x 3.9mm 5µ
Flow rate	1.0 ml/minute
Wavelength	311 nm
Temperature	Ambient
Load	20 µl
Retention time	3 min. for NF & 5 min. for TZ
Run time	About 10 minutes.

The contents of Norfloxacin & Tinidazole were estimated by using following formula.

$$\text{Drug content} = \frac{\text{Area of sample} \times \text{Wt.Of std.} \times \text{Purity of the drug} \times \text{Average wt.Of tablet}}{\text{Area of std.} \times \text{wt.Of sample} \times \text{Lable claim}}$$

The tablet passes the test if content uniformity falls within the range of 95.0 to 105.0% of label claim according to IP.

ii. Disintegration Test

The disintegration test apparatus consists of a basket-rack assembly containing six open-ended glass tubes held vertically on a 10-mesh (sieve opening of 2 mm) stainless-steel wire screen. Tablets are placed in each of the six tubes of the basket. During this testing, the wire screen is always maintained below the level of the immersion fluid. The temperature is maintained at

37°C±2°C unless specified otherwise in the individual monograph. Suspend the assembly in the beaker containing the 900 ml water and operate the apparatus for the 15 minutes. Remove the assembly from the liquid. The tablets pass the test if all of them have disintegrated. If 1 or 2 tablets fail to disintegrate, repeat the test on 12 additional tablets; not less than 16 of the total of 18 tablets tested disintegrate. If the tablets adhere to the disc and the preparation under examination fails to comply, repeat the test omitting the disc. The preparation complies with the test if all the tablets in the repeat test disintegrate.

iii. In Vitro Dissolution Study & Comparative Study

Prepared tablets were evaluated for their drug release in the physiological environment (Acetate buffer, pH-4). These studies were carried out using (Electro lab, India) USP apparatus type II. All other parameters as given in table 7.6,

Table 3: Dissolution parameters used in the dissolution testing

Parameters	Specifications
Apparatus	USP type-II Paddle.
Dissolution medium	Acetate buffer (pH-4)
Volume	900 ml
Speed	50 rpm
Volume of sample withdrawn	5 ml
Sample Interval	5min, 10min, 15min, 30min, 45 min
Temperature	37 °C±0.5 °C

Chromatographic conditions

After withdrawing samples from the dissolution apparatus, by appropriate dilutions the samples were analyzed by HPLC. The column type, flow rate, wavelength, temperature, sample load, retention time of the both the drugs & run time parameters are depicted in the Table 7.5.

Analysis:

Samples were taken at 5 min, 10min, 15min, 30min & 45min respective time points & Replaced with the fresh dissolution medium to maintain sink condition. Filtered the collected samples fill in small vials. 0.1 ml of the sample diluted up to 10ml by mobile phase. Then samples were injected to HPLC to analyze.

Formulation of Film coated tablets of Norfloxacin & Tinidazole

a. Selection of tablets for film coating

Plain tablets should possess adequate hardness allowing the tablets to withstand the stresses during the coating process without mechanical failure such as high friability, chipping, and capping. In addition, the plain tablets should possess the required disintegration characteristics so that the coated tablets will meet the final product disintegration requirements selected batches of the core tablets for the Film coating are selected on the basis of their Hardness & Disintegration time.

b. Preparation & Optimization of film coating formula:

The trials were conducted using various combinations of Hydroxy Propyl Methyl Cellulose 5cps and Hydroxy Propyl Methyl Cellulose 15cps as reported in results and discussion for batch size 1.0 L. The procedure and process parameters were as follows:

Procedure:

i) **Coating operations**

- The plain tablets are heated to 40~60 °C by applying hot air. Adjust the air pressure and the spraying speed of the spray gun to produce properly atomized coating liquid.
- Turn on the coating pan and change the rotation speed to 30~50 rpm. Spray the coating liquid onto the plain tablets until a uniform film coating is formed.
- Stop spraying and keep the coating pan running for an additional few minutes to avoid sticking between the coated tablets.
- Remove the coated tablets followed by drying at 60 °C.

ii) **Precautions**

- The plain tablets should be produced with adequate hardness and be resistant to abrasion. The plain tablets should be dedusted by sieving to remove any fine powder adhering on the tablet surface.
- During the coating process, the selection of the spraying rate of the coating liquid and the air blowing speed should be made with the aim not to over-wet the tablets and to prevent sticking. The temperature should not be too high or too low. If the temperature is too high, the coating film formed will not be uniform; on

the other hand, if the temperature is too low, drying will be very slow and the coated tablets may stick to each other.

- Air bubbles should be avoided during the coating process.
- The coating materials should be passed through a 100-mesh sieve. To prevent particle agglomeration coating solution should be 7 to 8 times homogenized by using a homogenizer.
- If the viscosity of the coating liquid is too high, it can be diluted with 60~70% alcohol before use (the solid concentration of the coating liquid is generally in the range of 3~8%).
- The coating liquid should be stirred throughout the coating process to avoid sedimentation.

c. Coating parameter Specification (*Shaikh. Shakeel A, 2011)*

During coating process the conditions maintained were as given in the table. Spraying conditions: Continuous, Spray gun: Bullows 630 with 0.8 mm nozzle, Speed of rotation of Pan 20 rpm, Inlet bed temperature below 60°C, Tablet bed temperature below 38 to 42°C, Spraying pressure: 5.82 to 7.0 kg/cm2 and Spray rate: 1000 ml in 45 minutes.

Table 4: Parameters specifications used during film coating

Coating Parameter	Specifications for organic coating
Coating pan	12 inch
Speed of rotation of Pan	20 rpm
Atomizing air pressure	6 to 7kg/cm2
Inlet air temperature	45^0 C
Outlet air temperature	35-40^0C
Temperature of tablets bed	30-35^0C
Pre drying in pan	10 min at 45^0C
Post drying in pan	10 min air drying
Spray rate	20ml per min.
Drying conditions	20 min at 40^0C
Relative humidity	40 ± 5%

Evaluation of Film coated tablets of Norfloxacin & Tinidazole

All formulations were evaluated by various physical and performance tests as follows.

Tests for physical evaluation:

a) Appearance & dimensions,
b) weight gain of 2% with Weight variation
c) Hardness
d) Friability
e) FTIR study
f) DSC study
g) Powder X-ray diffraction study

Tests for performance evaluation:

a) Assay of tablet
b) Disintegration test

The coated tablets were evaluated for various physical parameters like average weight, thickness, diameter, hardness, friability and total drug content of the formulation as well as for performance evaluation as per procedure described for core tablets.

Results and Discussion

The seven batches containing 400mg NF & 600mg TZ were prepared in duplicate by wet granulation as shown in table no 7.4. Norfloxacin were sifted through mesh 40. They mixed geometrically in a polythene bag for 2-3 min. Then Tinidazole sifted through mesh 40& geometrically mixed all above ingredients for 2-3 min. Then the blend obtained was granulated with 20% w/v starch solution (F1), Gelatin 20%, 15% and 5 % (F2, F3, F4). Also the HPC 5% w/v (F6) and HPMC 5% w/v (F7) were used as a binders to obtained the different batches. Sodium starch glycolate was used as superdisintegrants.The blend was compressed into tablets using the 21.2×8.9mm/CAPTAP punch in a single station tablet compression Machine (Erweka 400). Angle of repose is suited for particles >150µm. Values of angle of repose ≤30^0 generally indicate the free flowing material and angle ≥40^0 suggest a poor flowing material. The angle of repose for all batches was found to be in the range of 21º to 28º indicated good flowability of NTZ granules except batch F-06 which shows 40^0±1. The optimized batch F-07 shows 24.47º±0.84 which indicate the good flowability of the granules. Bulk density may influence compressibility; tablet porosity, dissolution and other properties depend on the particle size, shape and tendency of particles to adhere together. The bulk density and final tapped density were calculated and results are as in table 8.3. The bulk density & tap density of all the batches found in the range of 0.53±0.97 to 0.63±0.76gm/ml. The optimized batch (F-07) shows bulk density and tap density of about 0.59±0.71 and 0.68±0.61gm/ml respectively.

Carr's index evaluated interparticulate cohesive properties with angle of repose measurements and studied the effects of packing geometry of solids with bulk and tapped density. Bulk density and tapped density measurements found that density of granules depends on particle packing and that density changes as the granules consolidates. The degree of consolidation is unique to the granules and ratio of these densities is related to interparticulate friction. This ratio, percent compressibility, was used as an index of flow, adhesive/cohesive forces of particles as they relate to flow behaviour by examining normal and shear stresses on powder beds.Carr'scompressibility index (CCI) for NTZ granules was found to be in the range of 11-21% thus all the batches F-01 to F-07 of NTZ exhibited good to passable flowability. Besides F-06 all the batches shows the good flowability. The optimized batch (F-07) shows 11.94±0.55% of CCI, indicates HPMC as the good polymer as compared to other binders. The Hausner's ratio of NTZ granules was found to be in range of 1.13 to 1.26. The Hausner's ratio was found to be maximum for the batch F-06 & was minimum for Batch F-05. The Hausner's ratio of the optimized batch F-07 shows about 1.14±0.53. The moisture content& LOD of all batches NTZ granules were found (table 8.4) in the range of 4.77-5.95%. The moisture content and LOD of optimized batch F-07 was found to be 5.25±0.06% and 5.2±0.07%. This much of moisture content in the granules sufficient to form the tablets without picking and sticking. As observed in the experiment that there is no any such problem, hence it is optimized for NTZ tablets. According to the results (table 8.5) not more than twoof the individual weights deviated from theaverage weight by ±5% and none deviatedby more than ±10% of average weight. Indicates the uniformity in the granules prepared. Also as there was no much variation in thickness of tablets in each formulation, it shows that powder blends were consistent in particle size and uniform behaviour during compression process. Thickness and diameter of tablets of all batches were measured by using Mitutoyo DigimaticCaliper and there was no significant change in thickness and diameter of tablets.

All batches showed hardness in the range of 7-9 Kg/cm^2 and friability 0.1-0.55% (table 8.6). All the batches show optimum hardness and friability for film coating prerequisite. Tablet hardness reflects differences in tablet density and porosity. The optimized batch F-07 shows maximum hardness of about 9 Kg/cm^2 and the lowest friability 0.17±0.026%. Hence indicates to withstand maximum stress.

As the disintegration time directly relates to the dissolution of tablet, since it is the step in the dissolution of any formulation. Disintegration time should be minimum for the immediate release tablet formulation. Disintegration time for all the batches showed in table 8.6. The lowest disintegration time was found to be for batch F-07. Hence it is ideal for the film coating, as it will give faster release.

As the disintegration time results showed that the batch F-07 show lowest time to disintegrate, it will get release faster. This is supported by the results of dissolution study. The batch F-07 shows the 100% release in the 30 minutes.Hence said to be optimized batch. Also followed to F-07, the batch F-01 shows the 100% release in the 45 minutes. Hence both the batches selected for the film coating.

From this can be concluding that the polymer HPMC is suitable for NTZ tablet formulation and the 10mg SSG is sufficient for immediate release of the tablet.

Results indicate all the batches shows the drug content in range of the 98-100%. So according to IP tablet formulation contain the uniform drug content, as according to IPdrug content should be between 95-105%.

The hardness is very important for the tablets to film coat. The tablets should withstand the stress during the film coating in pan. Also the disintegration time important for faster release, hence based on these two parameters, tablets selected for the film coating. Batches of the core tablets for the film coating are selected were F-01 and F-07 as they shows the better results as compare to other batches.

The trials were conducted using various combinations of Hydroxy Propyl Methyl Cellulose 5cps and Hydroxy Propyl Methyl Cellulose 15cps as reported in (table8.11) for batch size 1.0 L.The coating trial 1 to 3 showed that break line remain covered. The coating trial 1 and 2 showed rough surface. The coating trial 4

showed the better results i.e. break line not covered, smooth surface with elegant color intensity. Hence the 20% HPMC-5cps and 10% HPMC-15cps were optimized for preparation of coating solution.

Thefilm coated tablets were evaluated for the standard evaluation test of the tablets. The weight variation test, dimensions, hardness, thickness and friability of the tablets were evaluated. The results shows there were no significant changes in hardness, thickness, and friability and disintegration time of the tablets. The objective of film coating hence said to be achieved, sinceafter the weight gain of 2% in the tablets during film coating tablet parameters were remain unaffected. Also the comparison with the marketed formulation (Norflox-TZ) showed the better results obtained in the optimized formulation F-07, as shown in the table 8.12.

Film coated tablet formulations compared with the marketed formulation (Norflox-TZ) for the in vitro drug release. The results indicate (Table 8.13& 8.14) that F-07 formulation showed 100% release in 30 min., while the marketed formulation require 45 min. for that. From this we can conclude that formulation F-07 was optimized formulation, as it can show better and rapid bioavailability i.e. action during the treatment of diarrhoea.

The frequency of vibrations of band depends on the masses of atoms and bond stiffness, and any factor that influence the stiffness will also alter frequency of vibration. Thus IR spectroscopy can be used as a tool to characterize complex formation.

FTIR spectra of pure Norfloxacin-Tinidazole combination& optimized tablet formulation (F7) illustrated in figure 8.12. As seen from the spectra there were no major changes in the FTIR spectra confirming absence of any chemical interaction between the components of tablet formulation. However, there were absence of peaks especially at 2500 cm-1 and 2750 cm-1 suggested that hydroxyl group of Norfloxacin showed a weak interaction with amine group of Tinidazole.

The slight decrease in melting endothermic point (129.7ºC &221.6ºC in TZ and NF respectively) and heat of enthalpy (100.3mJ/mg &87.7mJ/mg) in optimized formulation indicates the compatibility of formulation. Hence, decrease in the crystallinity of pure drug.

Crystallinity of Norfloxacin-Tinidazole and formulation was studied and diffractograms are shown in Tinidazole shows sharp peaks (table 8.16) at 10.5, 13.1, 13.3, 13.4, 22, 23.6, and $23.7^0 2\theta$. While Norfloxacin shows (table 8.17) at 10.1, 10.6, 16.4, 21.1, 25.2, and 25.3. In case of norfloxacin there is marked decrease in the peak sharpness and height. For Tinidazole peaks shows less decrease in peak height and sharpness. This was supported by the number of peaks observed in both diffractograms. Norfloxacin-Tinidazole showed more intense peaks which were reduced in diffractograms of F-07 (Figure 8.15) which indicated reduced crystallinity of Norfloxacin-Tinidazole.

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Cite this article as:
JadhavJ., Jain G. and Patel R.(2020). Development and In-vitro Evaluation of film coated tablet of Norfloxacin and Tinidazole, *Int. J. of Pharm. & Life Sci.*, 11(12): 7177-7197.
Source of Support: Nil
Conflict of Interest: Not declared
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Table 8.3: BulkDensity, tap density, angle of repose, CCI andHausner's ratio of NTZ granules

Batch code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (º)	CCI (%)	Hausner's ratio
F-01	0.63±0.23	0.71±0.12	23.83±0.76	12.6±0.74	1.13±0.49
F-02	0.59±0.017	0.67±0.45	21.67±0.58	11.94±0.47	1.14±0.24
F-03	0.59±0.45	0.67±0.73	23.83±0.76	11.94±0.22	1.14±0.51
F-04	0.59±0.82	0.71±0.93	27±1	16.90±0.28	1.20±0.36
F-05	0.63±0.76	0.71±0.24	26.96±1	12.6±0.43	1.13±0.42
F-06	0.53±0.97	0.67±0.51	40±1	20.9±0.37	1.26±0.72
F-07	0.59±0.71	0.68±0.61	24.47±0.84	11.94±0.55	1.14±0.53

Table 8.4: Moisture content and Loss on drying of Batch F-01 to F-07

Batch code	Moisture content (%)	LOD (%)
F-01	5.05±0.083	5.95±0.07
F-02	4.77±0.06	4.19±0.07
F-03	5.08±0.054	5±0.11
F-04	5.29±0.08	5.05±0.09
F-05	4.93±0.057	4.7±0.08
F-06	5.02±0.012	5.15±0.1
F-07	5.25±0.06	5.2±0.07

All readings are average ± SD (n=3).

Table 8.5: Weight variation test and dimensions of tablets

Sr. No.	Batch code	Weight variation (mg)	Thickness (mm)	Diameter (mm)
1.	F-01	1201±5.4	7.3±0.1	21.2×8.9
2.	F-02	1203.3±4.81	7.1±0.13	21.2×8.9
3.	F-03	1200±4.13	7±0.15	21.2×8.9

4.	F-04	1204±4.65	7±0.16	21.2×8.9
5.	F-05	1203±4.45	7.1±0.14	21.2×8.9
6.	F-06	1205±8.67	6.8±0.13	21.2×8.9
7.	F-07	1202±4.54	7.2±0.18	21.2×8.9

All readings are average ± SD (n=6)

Table 8.6: Hardness, friability and disintegration time of core tablets
All readings are average ± SD (n=6)

Sr. No.	Batch code	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (sec.)
1.	F-01	8	0.29±0.023	62.67±0.51
2.	F-02	8	0.35±0.02	1442.67±0.5
3.	F-03	7	0.47±0.02	1322±0.2
4.	F-04	7	0.49±0.03	1122.33±0.21
5.	F-05	7	0.55±0.02	721.3±0.16
6.	F-06	7	0.38±0.02	119.1±1.04
7.	F-07	9	0.17±0.026	27.33±2.08

Table 8.7: In vitro dissolution study of core tablets for Norfloxacin

Sr. No.	Time (min.)	% cumulative drug released in dissolution medium (NF)						
		F-01	F-02	F-03	F-04	F-05	F-06	F-07
1	0	0	0	0	0	0	0	0
2	5	20.18±0.35	10.60±0.47	12.01±0.05	10.26±0.42	12.42±0.13	15.14±0.05	25.42±0.54
3	10	45.25±0.29	20.1±0.54	23.47±0.28	23.18±0.62	26.12±0.24	35.28±0.25	52.45±0.12
4	15	76.48±0.34	34.12±0.14	30.38±0.41	32.17±0.54	38.45±0.12	45.1±0.5	81.14±0.31
5	30	97.25±0.65	54.78±0.30	52.78±0.4	59.10±0.5	62.4±0.02	64.74±0.05	100.40±0.42
6	45	100.53±0.15	65.58±0.35	68.64±0.21	72.18±0.3	75.8±0.1	80.18±0.15	100.8±0.8

All readings are average ± SD (n=3)

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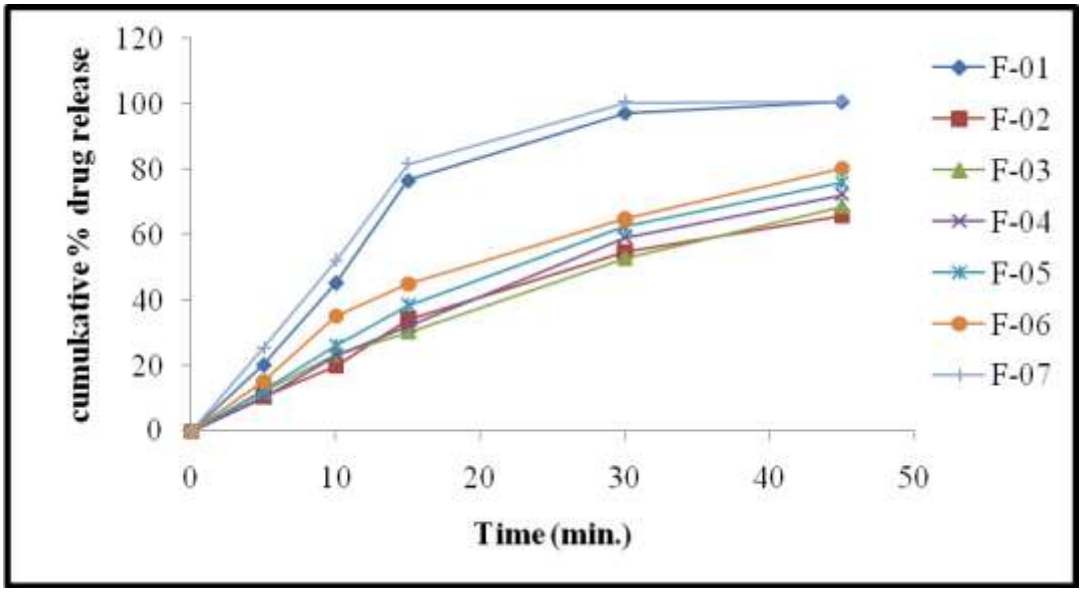

Figure 8.7: Plot of% cumulativedrug release of Norfloxacin versus time (min) showing drug release of NTZ core tablets

Table 8.8: - In vitro dissolution study of core tablets for Tinidazole

Sr. No.	Time (min.)	% cumulative drug released in dissolution medium (TZ)						
		F-01	F-02	F-03	F-04	F-05	F-06	F-07
1	0	0	0	0	0	0	0	0
2	5	21.18±0.35	12.60±0.42	12.01±0.05	11.47±0.2	14.2±0.37	15.4±0.75	27.42±0.1
3	10	47.25±0.29	21.1±0.14	23.47±0.28	23.8±0.1	26.4±0.2	38.5±0.1	50.1±0.3
4	15	63.78±0.34	37.12±0.23	30.38±0.41	35.5±0.2	39.7±0.2	44.8±0.1	62.3±0.7
5	30	85.25±0.05	55.8±0.1	50.7±0.1	58.20±0.5	62.4±0.72	68.74±0.3	98.95±0.01
6	45	99.1±0.5	68.58±0.5	70.1±0.11	73.7±0.1	77.1±0.3	81.8±0.57	101.4±0.27

All readings are average ± SD (n=3)

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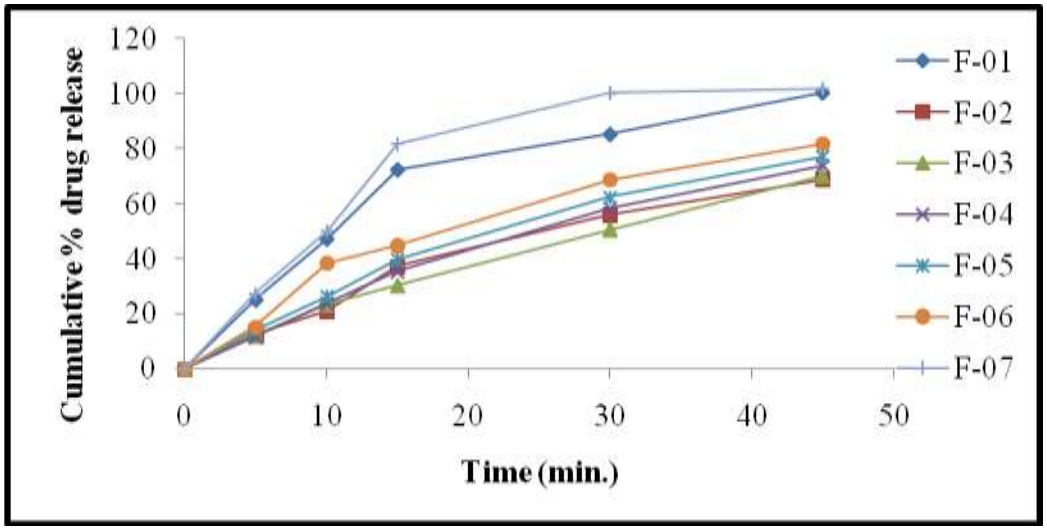

Figure 8.8: Plot of% cumulativedrug release of Tinidazole versus time (min) showing drug release of core NTZ tablets

Table 8.9: % drug content of the Norfloxacin and Tinidazole core tablets.

Sr. No.	Batch code	% Drug content	
		NF*	TZ*
1.	F-01	99.68±0.21	99.14±0.23
2.	F-02	99.28±0.08	98.53±0.14
3.	F-03	98.59±0.12	100.4±0.2
4.	F-04	98.15±0.04	99.13±0.08
5.	F-05	98.17±0.15	99.12±0.1
6.	F-06	97.41±0.12	99.7±18
7.	F-07	99.43±0.14	101.65±0.2

*All readings are average ± SD (n=3)

Table 8.10: Selected batches of the core tablets for the film coating

Sr. No.	Batch No.	Hardness (kg/cm^2)	Disintegration time (sec.)
1.	F-01	8	63±0.2
2.	F-07	9	27.33±0.18

Table 8.11: Optimization of Coating Formula

Parameters	Coating trial code			
	CT1	CT2	CT3	CT4
HPMC -5cps (%)	40	30	30	20
HPMC -15cps (%)	25	20	15	10
Titanium dioxide (%)	5	5	5	5
Talc (%)	4	4	4	4
Quinoline yellow ws(%)	2	2	2	2
PEG 200 (%)	4	4	4	4

Table 8.12: Physical evaluation parameters of film coated tablets

Sr. No.	Batch code	Avg. Wt. (mg.)	Dimensions (mm)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec.)
1.	F-01	1225±8	21.2×8.9	8	7.3±0.2	0.29±0.02	62.67±2.8
2.	F-07	1224±9	21.2×8.9	9	7.3±0.15	0.17±0.02	27.40±2.1
3.	MKT	1223.4±8.4	19.7×9.2	8	7.3	0.07±0.08	295.23±1.7

All readings are average ± SD (n=6)

Table 8.13: In vitro dissolution study of film coated tablets for Norfloxacin

Sr. No.	Time (min.)	% cumulative drug release in dissolution medium (NF)							
		F-01	F-02	F-03	F-04	F-05	F-06	F-07	MKT
1	0	0	0	0	0	0	0	0	0
2	5	20.8±0.5	10.60±0.7	12.01±0.45	10.26±0.72	12.42±0.17	15.14±0.25	28.42±0.15	22.28±0.15
3	10	45.2±0.27	20.1±0.57	23.47±0.08	23.18±0.62	26.12±0.29	35.28±0.27	51.45±0.11	40.21±0.7

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4	15	76.2±0.3	34.12±0.17	30.38±0.4	32.17±0.14	38.45±0.2	45.1±0.57	82.14±0.01	63.4±0.1
5	30	96.3±0.6	54.78±0.33	52.78±0.7	59.10±0.55	62.4±0.72	64.74±0.17	100.07±0.52	95.1±0.2
6	45	99.7±0.1	65.58±0.38	68.64±0.27	72.18±0.27	75.8±0.11	80.18±0.05	100.5±0.1	99.4±0.06

All readings are average ± SD (n=3)

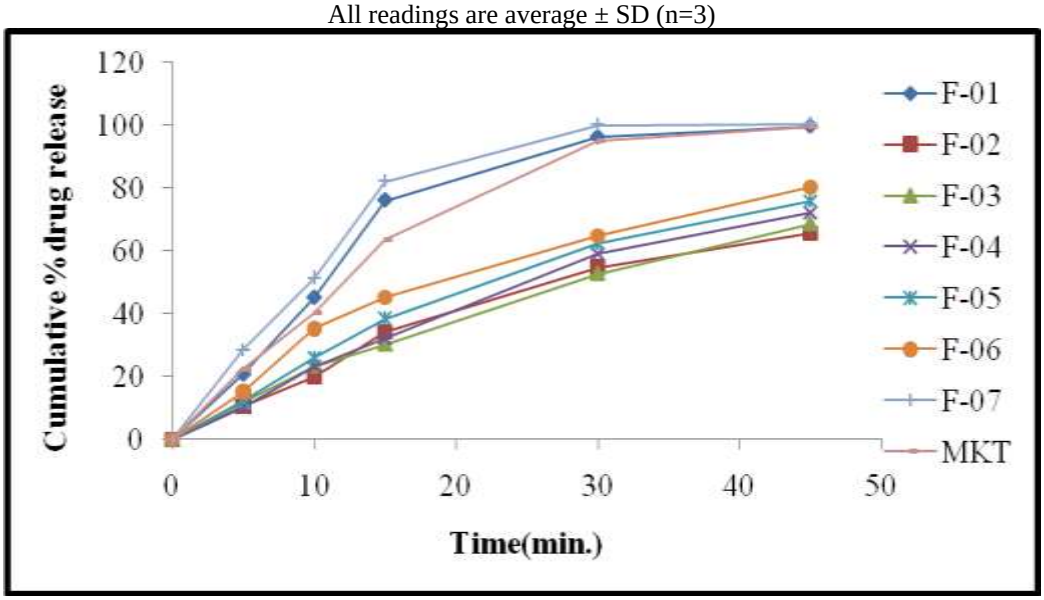

Figure 8.9: Plot of% cumulativedrug release of Norfloxacin versus time (min) showing drug release of NTZ coated tablets

Table 8.14: - In vitro dissolution study of film tablets for Tinidazole

Sr. No.	Time (min.)	% cumulative drug released in dissolution medium (TZ)							
		F-01	F-02	F-03	F-04	F-05	F-06	F-07	MKT
1	0	0	0	0	0	0	0	0	0
2	5	25.28±0.35	12.60±0.42	12.01±0.05	11.47±0.2	14.2±0.37	15.4±0.75	27.42±0.1	22.1±0.8
3	10	47.15±0.29	21.1±0.14	23.47±0.28	23.8±0.1	26.4±0.2	38.5±0.1	50.1±0.3	45.17±0.2
4	15	72.58±0.34	37.12±0.23	30.38±0.41	35.5±0.2	39.7±0.2	44.8±0.1	79.4±0.7	63.1±0.2
5	30	98.24±0.05	55.8±0.1	50.7±0.1	58.20±0.5	62.4±0.72	68.74±0.3	101.5±0.01	99.8±0.3
6	45	100.5±0.5	68.58±0.5	70.1±0.11	73.7±0.1	77.1±0.3	81.8±0.57	101.8±0.6	100.63±0.7

All readings are average ± SD (n=3)

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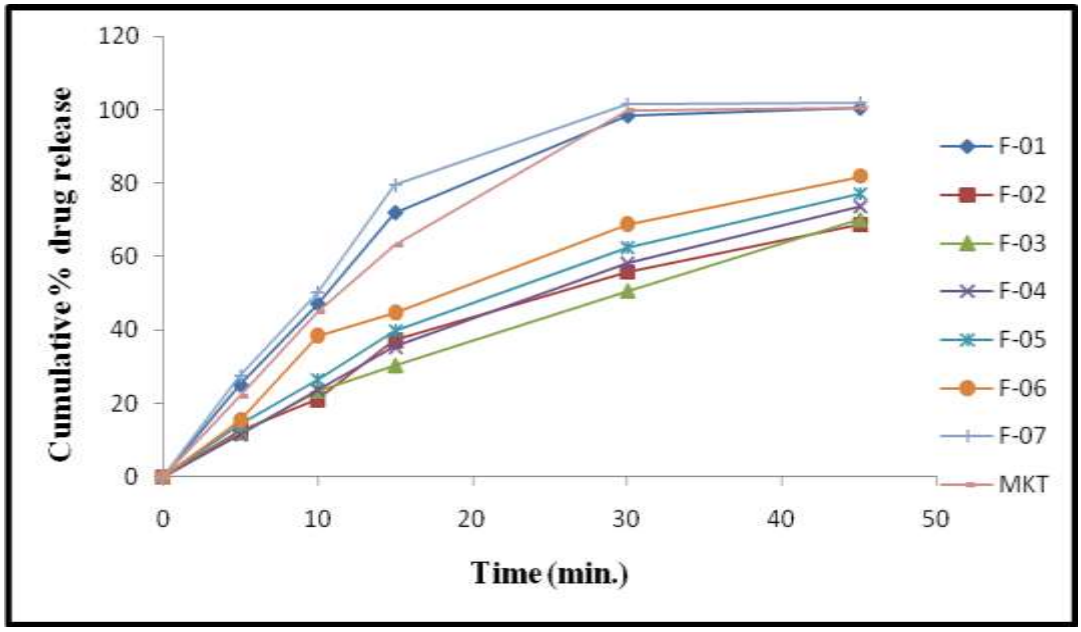
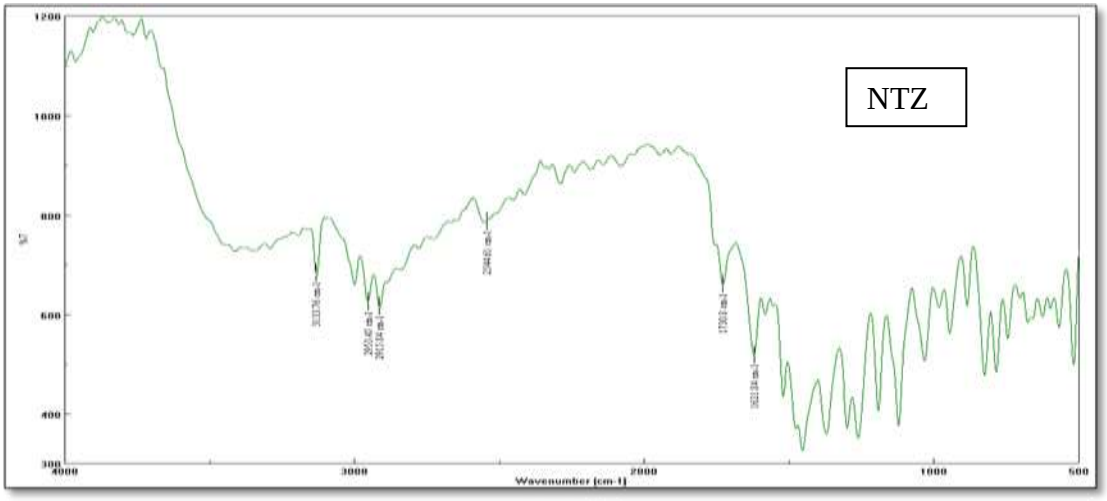


Figure 8.10: Plot of% cumulativedrug release of Tinidazole versus time (min) showing drug release of NTZ coated tablets

8.5.5 FTIR spectra



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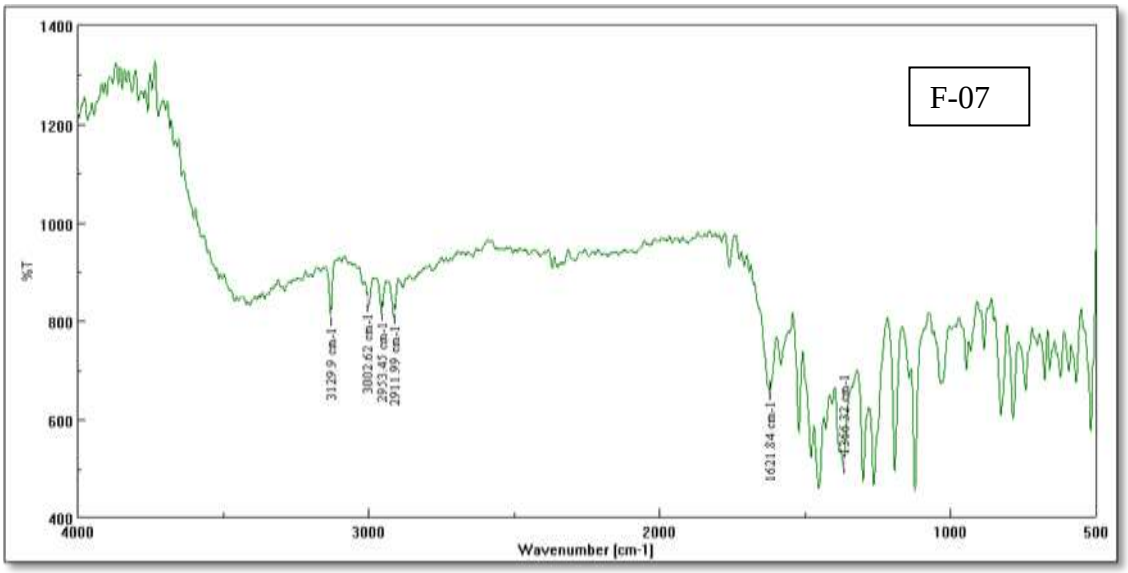

Figure 8.11: FT-IR of pure drug combination Norfloxacin-Tinidazole (NTZ) & tablet formulation (F_7)

Table 8.15: Ranges of functional groups of Norfloxacin & Tinidazole

Observed Peaks (cm^{-1})	Reported peaks (cm^{-1})	Norfloxacin Groups (Peak assignment)
3002.62	3000-2950	Aromatic, cyclic enes ν=CH &Ar-H
1730.94	1750-1700	Carbonyl of acids ν C=O Stretching vibration
1621.84	1650-1600	Quinolones (ν N-H Bending vibration)

Observed Peaks (cm^{-1})	Reported Peaks (cm^{-1})	Tinidazole Groups (Peak assignment)
3129.9	3119.98, 3000.69	aromatic C-H Stretching
2953.45, 2911.99	2956.34, 2913.91	Aliphatic C-H Stretching
1521.5, 1366.32	1521.56, 1367.28	N=O stretching
1040.25	1037.52	S=O stretch

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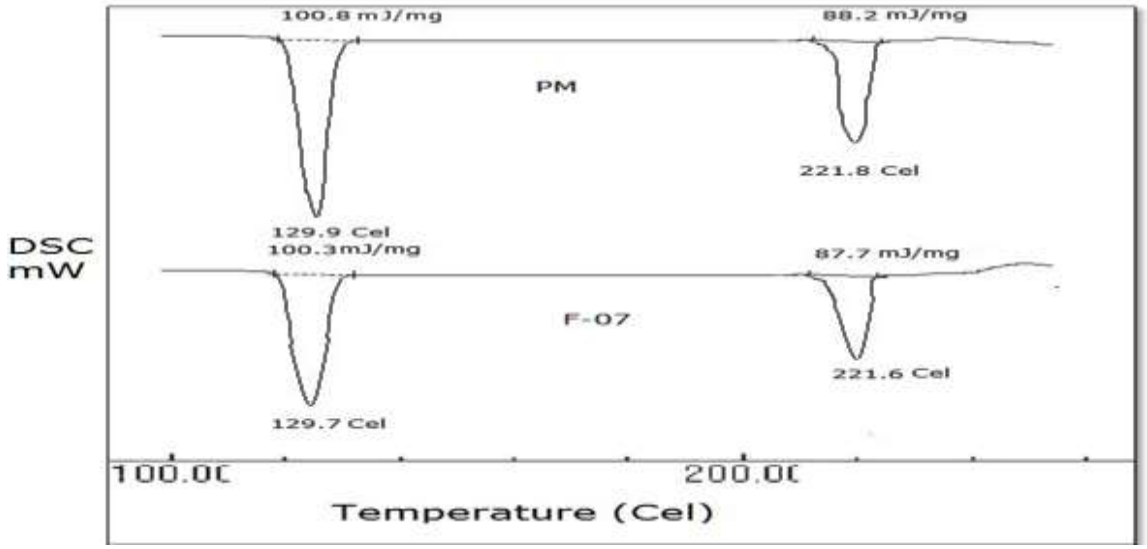

Figure 8.12: The overlainDSCspectra of physical mixture and optimized formulation (F-07)

8.5.7Powder X ray diffraction

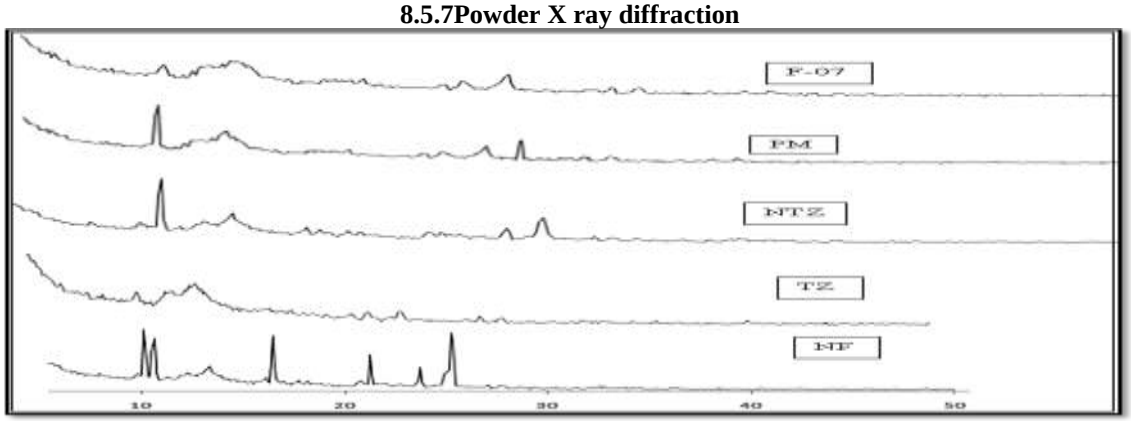

Figure 8.13: Overlain X-ray diffraction spectra of Norfloxacin, Tinidazole,Norfloxacin-Tinidazole combination, Physical mixture and optimized formulation.

Table 8.16: Peak intensities of Norfloxacin, physical mixture and optimized formulation

Sr. no.	$^{0}2\theta$	Peak Intensity		
		Norfloxacin	Physical mixture	Formulation (F-07)
1	10.1	1987	540	418
3	10.6	1699	891	640
4	16.4	1794	476	316
5	21.1	1176	246	227
6	25.2	223	216	148
7	25.3	1865	298	235

Table 8.17: Peak intensities of Tinidazole, physical mixture and optimized formulation

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Sr. no.	^{0}2θ	Peak Intensity		
		Tinidazole	Physical mixture	Formulation (F-07)
1	10.5	478	453	422
2	13.1	569	539	514
3	13.3	570	564	554
4	13.4	595	596	606
5	22	201	195	193
6	23.6	202	165	161
7	23.7	202	394	394