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Research Article

Complexation of poorly water soluble drug norfloxacin with cyclodextrin

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Abstract

The aim of the present study is to enhance the solubility and dissolution rate of poorly water soluble drug of Norfloxacin with Cyclodextrin by direct compression method. The adding a water-soluble polymer, like PVP and HPMC, with the aim to increase the aqueous solubility of both the complex and the drug itself. The prepared tablets were evaluated for all pre-compression parameters and post-compression parameters. The drug-excipients interaction was investigated by FTIR. All formulation showed compliances with Pharmacopoeial standards. The study reveals that formulations prepared by direct compression F5 exhibits highest dissolution using crospovidone showed faster drug release 98.33 % over the period of 60 minutes while disintegration time of the tablet was showed 2 minutes comparison to other formulations.

Keywords: Complexation, Cyclodextrin (CD), Inclusion, Norfloxacin, Solubility

1. Introduction

Cyclodextrins have been receiving increasing application in pharmaceutical formulations in recent years due to their approval by various regulatory agencies. However, the use of cyclodextrins in solid oral dosage forms is limited to low dose drugs with large stability constants due to the mass limitations of oral dosage units. Therefore, in cases where the low complexation efficiency would require a larger amount of CD than that acceptable for solid or liquid dosage forms, the enhancement of the complexation capacity of the chosen CD is of practical importance. The positive effect of the addition of small amount of a suitable water soluble polymer to a drug-CD system in improving both the complexing and solubilizing efficiencies of the CDs[1].There has been great interest in cyclodextrin inclusion compounds as a means of increasing the solubility and dissolution rate of poorly soluble drugs. β-cyclodextrin and its derivatives have been used in pharmaceutical formulations to enhance the solubility, dissolution rate, membrane permeability, stability and bioavailability of slightly soluble drugs. This is due to their ability to molecularly encapsulate a wide variety of drugs into their hydrophobic cavity which imparts changes in physicochemical properties, resulting in the enhancement of water solubility and drug-dissolution rate. Poorly water soluble drugs usually show low bioavailability as their absorption rate is dissolution-rate limited and is consequently low. Cyclodextrins are considered to be good candidates for dissolution-rate enhancement of drugs having poor water solubility[2]. Although CDs can increase the aqueous solubility of drugs, many applications need large amount of CDs. But for several reasons, such as production cost and toxicity, CD amount have to reduce in pharmaceutical use. To achieve this goal, several approaches can be considered. The first is the use of CDs, which present a higher solubility in water. The second method consists in adding a water-soluble polymer, like PVP, and HPMC, with the aim to increase the aqueous solubility of both the complex and the drug itself[3].

2. Experimental

2.1 Formulation

All the ingredients are accurately weighed according to the formula and were thoroughly blended. Then the mixture was compressed on a Cadmach single punch tablet machine.

Table No: 1 Formulation composition

Ingredients	F1	F2	F3	F4	F5
Pure Norfloxacin	100	100	100	100	100
Norfloxacin:β-CD(1:1) KM	100				
Norfloxacin:β-CD(1:2) KM		200			
Norfloxacin:β-CD(1:3) KM			300		
Norfloxacin:β-CD(1:4) KM				400	
Norfloxacin:β-CD(1:5) KM					500
MCC	480	380	280	180	80
Stearic acid	10	10	10	10	10
Magnesium stearate	5	5	5	5	5
Aerosil	5	5	5	5	5
Total wt. of tablet	700	700	700	700	700

All quantities are given in mg.

2.2 Phase solubility studies[4]

Phase solubility studies were carried out at room temperature 25^0c according to the method reported by Higuchi and Connors. Fixed amount of Norfloxacin was added to distilled water containing various concentrations of β-CD (3-15mM) in a series of stoppered conical flasks and shaken for 48 hrs on a rotary flask shaker. The suspensions were filtered through Whatman No.1 Filter paper and assayed for Norfloxacin using UV spectrophotometer at 277 nm against blanks prepared using same concentration of β-CD in distilled water.

The apparent stability constant (Kc) was calculated from the phase solubility diagram using the following equation:-

K1:1 = slope / S_o (1-slope)

S_o is the equilibrium solubility of Norfloxacin in water

The slope was obtained from the initial straight line portion of the plot of Norfloxacin concentration against β-CD.

2.3 Preparation of complexes

2.3.1 Kneading method

Inclusion complex of Norfloxacin and β-CD in 1:1 molar ratio was prepared by the CD, not by dissolving but kneaded like a paste with small amount of water to which the drug component has been added. Drug component can be dissolved in a small amount of methanol in which CD has been suspended. Several hours of grinding of paste in mortar result in evaporation of solvent and formation of powder like complex[5].

2.4 Evaluation of inclusion complexes[6]

2.4.1 Drug content estimation:-

The 50mg powder from inclusion complexes was taken in a 50ml volumetric flask. About 40ml of ethanol was added and mixed thoroughly. The contents were repeatedly warmed in a hot water bath while mixing to dissolve the drug in the solvent and then the solution was made upto volume with ethanol. The solution was then suitably diluted and assayed for the drug content at 277 nm by the UV spectrophotometer.

2.4.2 *In-vitro* dissolution study

Dissolution rate of Norfloxacin and inclusion complexes of Norfloxacin-β-CD was studied using lab India Disso 2000, an eight stage dissolution testing apparatus, with a paddle stirrer in 900 ml distilled water, Maintained at 37 ± 0.5 ◦c and at a speed of speed of 75 rpm. Five ml of samples were withdrawn at time intervals of 10, 20, 30, 45, 60 min. The solution was then suitably diluted and assayed for the drug content at 277 nm by the UV spectrophotometer.

2. 5 Preparation of Norfloxacin Tablet

2.5.1 Direct Compression Technique

In this method, tablets are compressed directly from the mixture of the drug and excipient without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level[7].

2.6 Preformulation Study of Norfloxacin[8]:

Table No. 2: Organoleptic properties

S. No.	Properties	Observation
1.	Colour	A white or pale yellow hygroscopic, photosensitive, crystalline powder.
2.	Odour	Odourless
3.	Taste	Bitter

2.7 Melting point determination

Melting point of the Norfloxacin was found to be 221^0C and it matched with literature value confirming the identity of sample.

3. Observation and Result

3.1 UV absorption Maxima

UV spectrum of Norfloxacin was interpreted absorption maxima using the UV-spectrophotometer and noted wavelength maxima in acidic buffer (pH 1.2), phosphate buffer (pH 7.4) and distilled water (Figure 1, 2 and 3)

Fig No. 1: UV absorption Maxima of Norfloxacin in acidic buffer (pH 1.2)

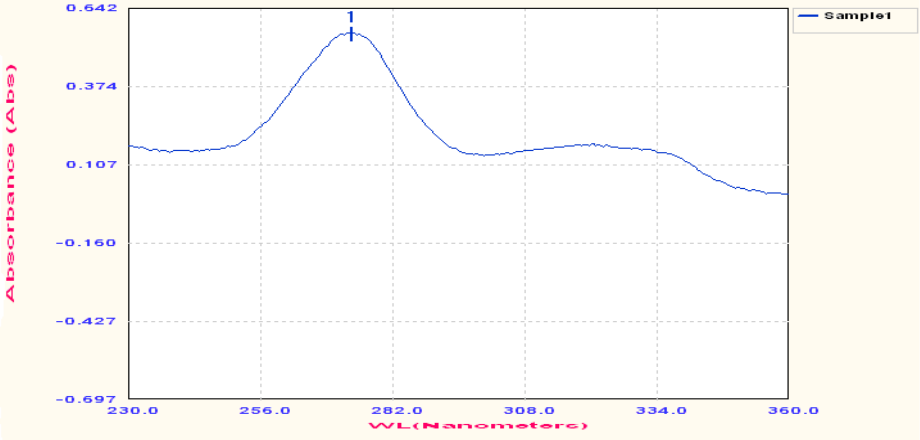


Fig No.2: UV absorption Maxima of Norfloxacin in distilled water

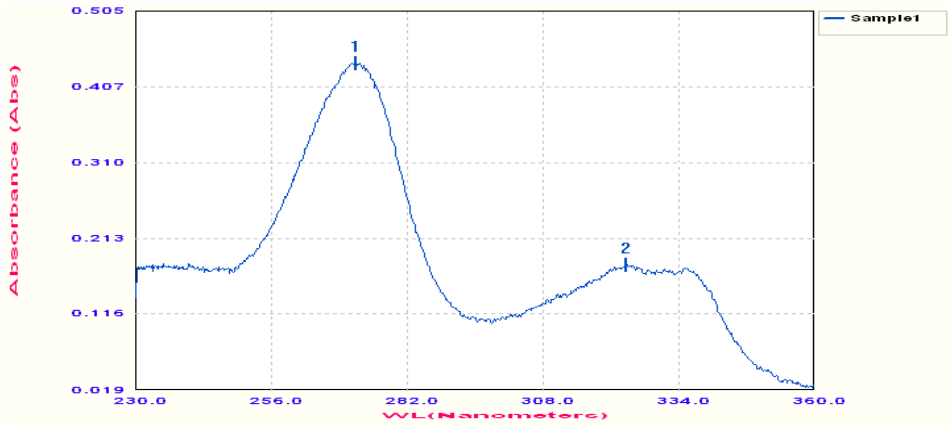
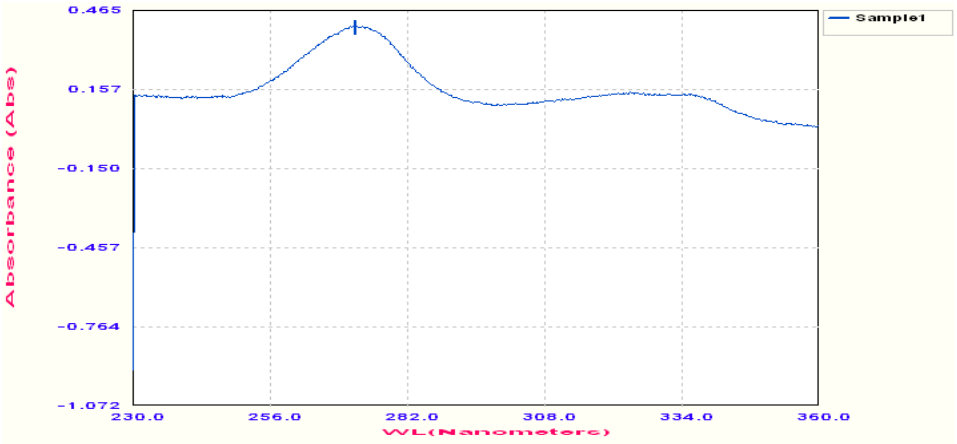


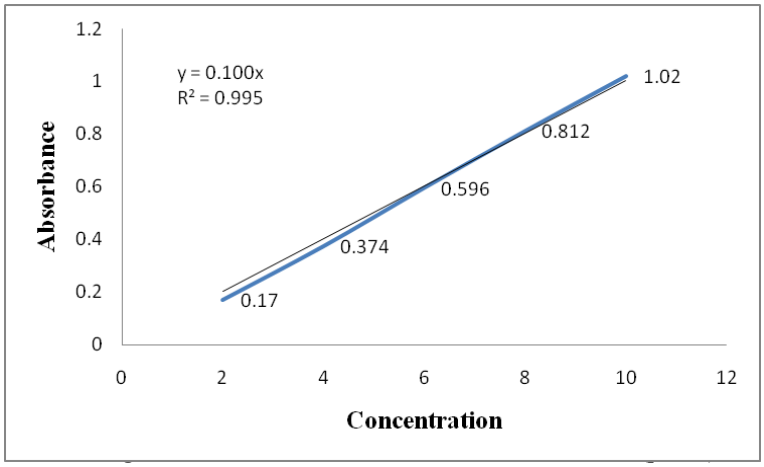
Fig No.3: UV absorption Maxima of Norfloxacin in phosphate buffer (pH 7.4)



3.2 Calibration curve of Norfloxacin in acidic buffer (pH 1.2)

The calibration curve for Norfloxacin in acidic buffer is in the concentration range of 2-10µg/ml. λmax is 277nm.

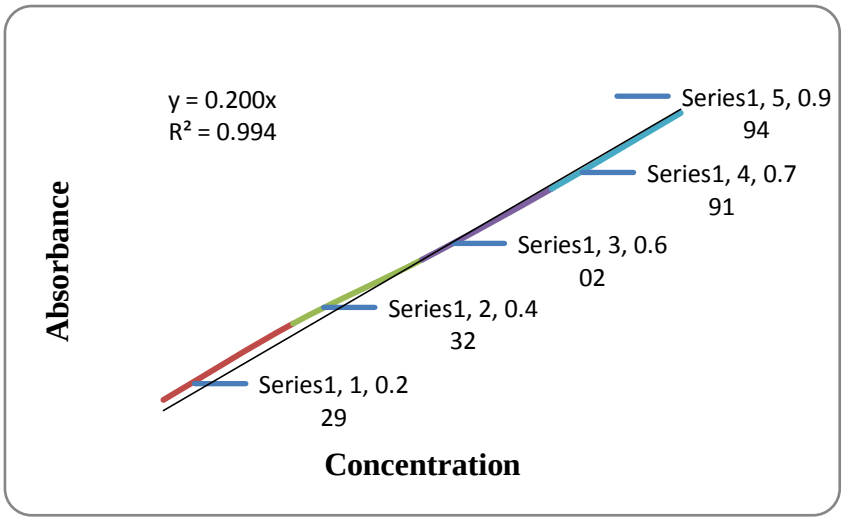
Fig 4: Calibration curve of Norfloxacin in acidic buffer



3.3 Calibration curve of Norfloxacin in distilled water

The calibration curve for Norfloxacin in distilled water is in the concentration range of 1-5µg/ml. λmax is 270.2 nm and 324 nm.

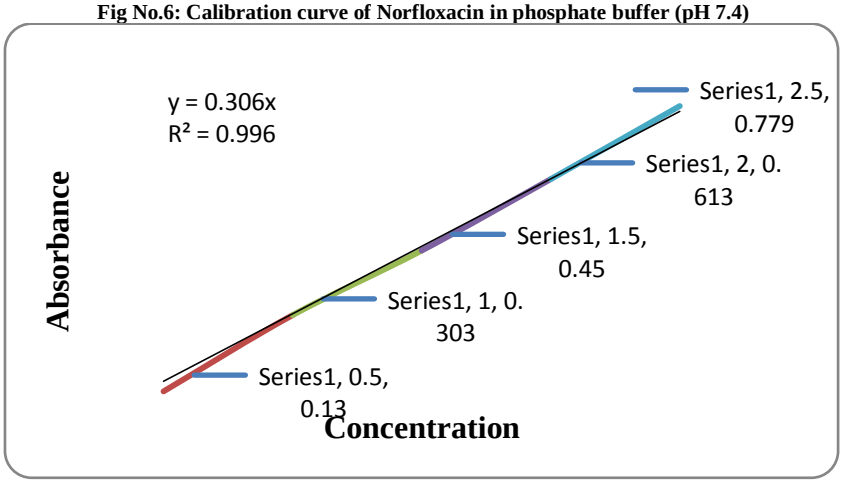
Fig No.5: Calibration curve of Norfloxacin in distilled water



3.4 Calibration curve of Norfloxacin in phosphate buffer (pH 7.4)

The calibration curve for Norfloxacin in phosphate buffer is in the concentration range of 1-5µg/ml. λmax is 270.2 nm and 324 nm.

Fig No.6: Calibration curve of Norfloxacin in phosphate buffer (pH 7.4)



3.5 FT-IR Spectra of Norfloxacin

The obtained IR spectrum was interpreted with the structure of Norfloxacin.

Fig No.7: IR Spectra of Norfloxacin (standard)

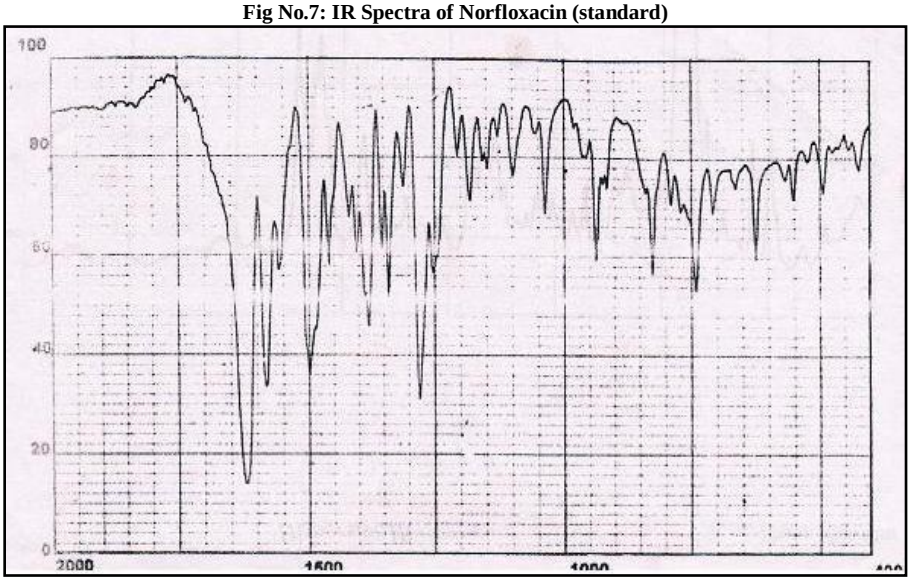
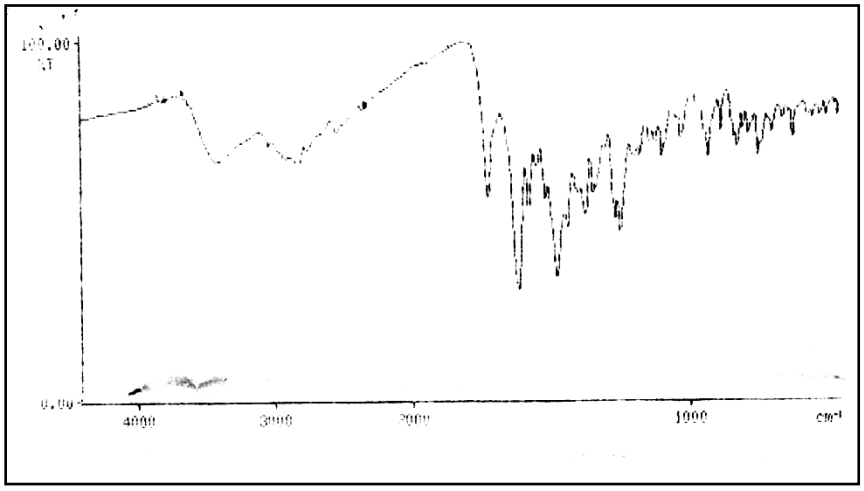


Fig No.8: FT-IR Spectra of Norfloxacin (sample)



3.6 Drug-Excipient compatibility study[9]:

Compatibility of the drug with excipients was determined by FTIR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

FTIR Spectra are shown in fig. 9, 10 and 11.

Fig No.9: FT-IR Spectra of Norfloxacin

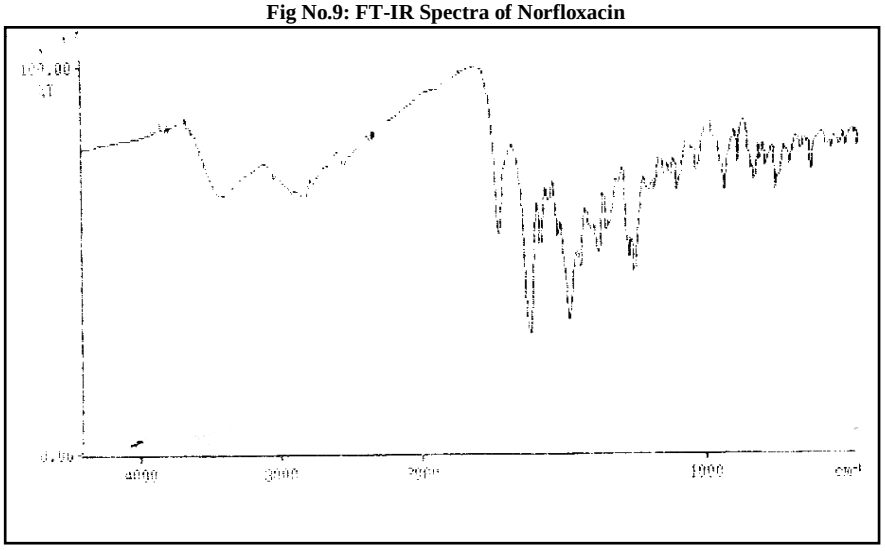


Fig No-10: FT-IR Spectra of β-Cyclodextrin

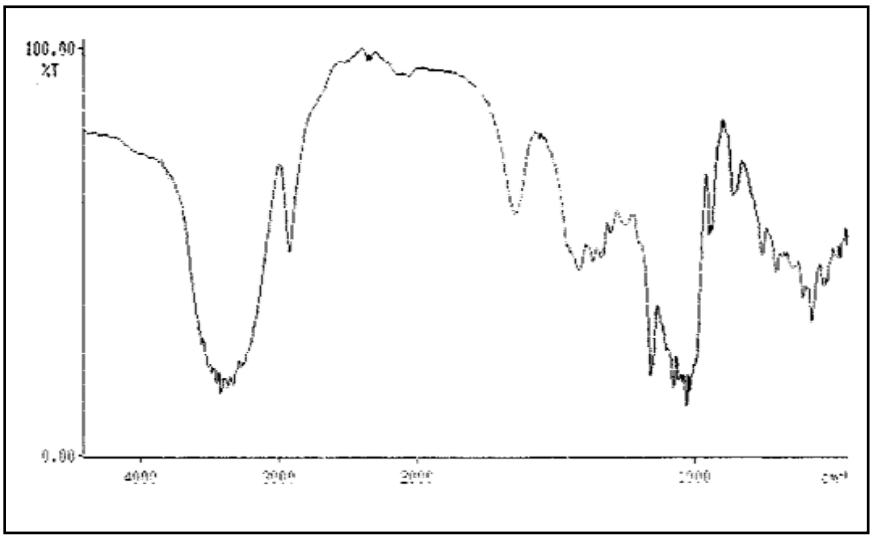
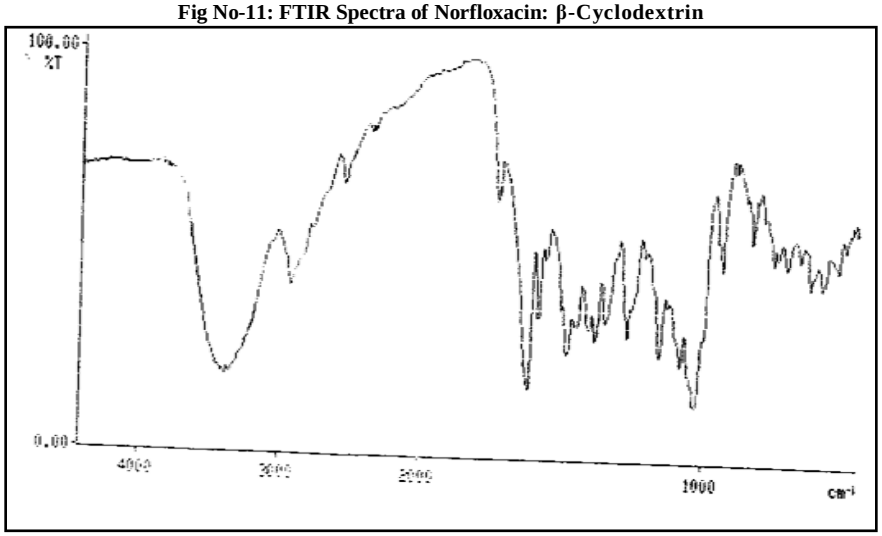


Fig No-11: FTIR Spectra of Norfloxacin: β-Cyclodextrin

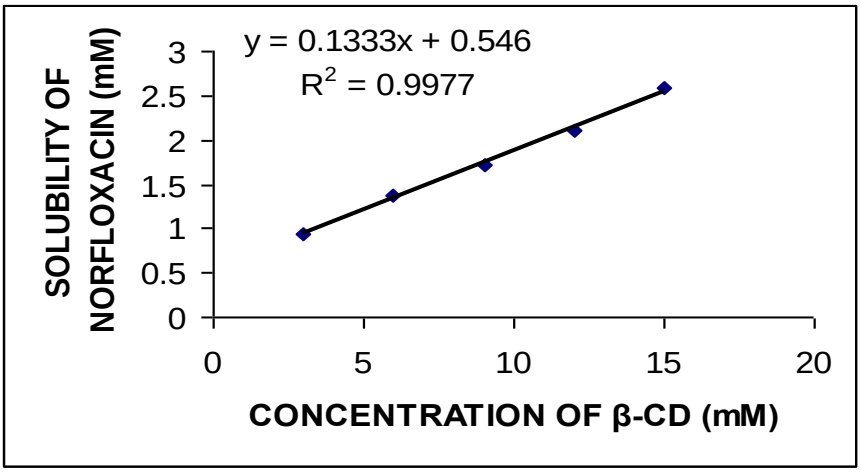


3.7 Phase solubility Studies:

Table No-3: Phase solubility diagram

S. No.	Concentration of β-CD (mM)	Solubility of Norfloxacin (mM)
1.	3	0.224
2.	6	0.432
3.	9	0.645
4.	12	0.823
5.	15	0.987

Fig No-12: Effect of β-CD on the solubility of Norfloxacin



The constant value was found to be 333 M^{-1}. The range within the 100 to 1000 M^{-1} considered ideal. K_c value in the range of 200-500 $^{m-1}$ indicated stronger interactions between the guest molecules (drug) and host molecules (β-CD) and greater stability of the complex formed. Thus the value of stability constants indicated that the complexes formed between drug-β-CD are stable**.**

A Smaller K1:1 value indicates too weak an interaction, whereas a larger value indicates the possibility of limited release of drug from the complex thereby interfering with drug absorption.

3.8 Evaluation of inclusion complexes[8, 9, 10].

3.8.1 Drug content estimation

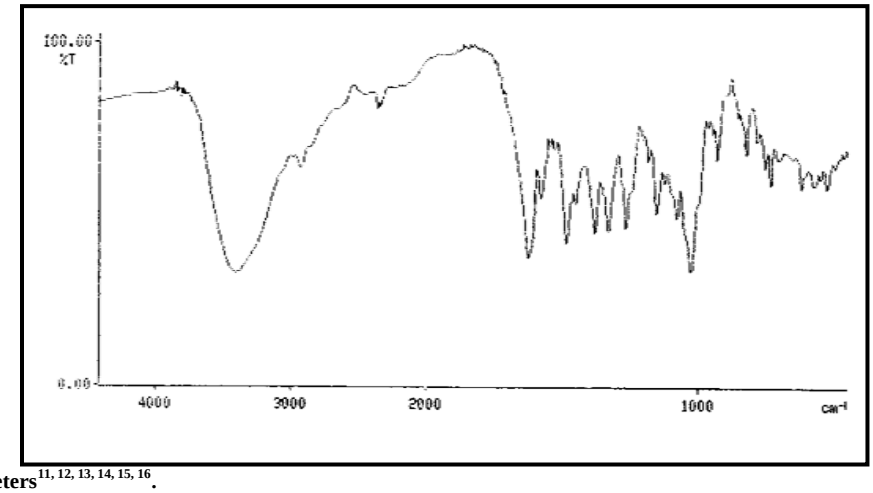
Table No-4: Drug content estimation

β-Cyclodextrin	% Norfloxacin content
	Kneading method
NORFLOX: β-CD (1:1)	92.89
NORFLOX: β-CD (1:2)	94.67
NORFLOX: β-CD (1:3)	96.34
NORFLOX: β-CD (1:4)	97.56
NORFLOX: β-CD (1:5)	98.76

3.8.2 Characterization of inclusion complexes:

By FT-IR

Fig No-13: FTIR Spectra of Inclusion complex of Norfloxacin: β-Cyclodextrin



3.9 Evaluation parameters[11, 12, 13, 14, 15, 16].

3.9.1 Evaluation of blend

The blend was evaluated for tapped density, bulk density, % compressibility and Hausner ratio.

Table No-5: Evaluation of blend

Batch code	Bulk density	Tapped density	Angle of repose	Carrs index	Hausners ratio
F1	0.46	0.54	25.28	14.81	1.17
F2	0.44	0.53	24.35	16.91	1.20
F3	0.47	0.56	26.18	16.07	1.19
F4	0.45	0.53	24.53	15.09	1.17
F5	0.43	0.50	23.73	14.00	1.16

3.9.2 Evaluation of Norfloxacin tablets[17, 18].

3.9.2.1 Weight variation

All the formulations were complying with weight variation test as per IP. The results are shown in table 6.

3.9.2.2 Hardness

Hardness of the tab. was determined using a Pfizer hardness tester. It is expressed in kg/cm^2. The results were shown in table 6.

3.9.2.3 Friability

The friability of the tablets was in the range of 0.2 to 0.48%. The results were shown in table in 6.

3.9.2.4 In vitro Disintegration test

The disintegration time obtained for formulation F1 to F5 is shown in table No. 6. The result of the disintegration test revealed that F5 has faster disintegration and it disintegrant within two minutes.

Table No-6: Evaluation of physical parameters of Norfloxacin tablets

Batch code	Weight variation	Thickness	Hardness	Friability	*In vitro* disintegration Time (min)
F1	**Pass**	2.93	2.2	0.21	35
F2	**Pass**	2.96	2.4	0.22	27
F3	**Pass**	2.91	2.3	0.24	25
F4	**Pass**	2.30	2.1	0.28	24
F5	**Pass**	2.98	2.2	0.30	21

3.9.2.5 Dissolution test[19]:

USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. Acidic buffer pH 1.2, 500ml was used as a dissolution medium. The dissolution medium was covered with black polythine to protect the solution from light. A sample (1ml) of the solution was withdrawn from the dissolution apparatus at 10, 20, 30, 45, 60 minutes. And withdrawn volume was replaced with fresh dissolution media. The withdrawn samples were diluted with dissolution medium. Determination of amount of drug dissolved from tablets was carried by UV Spectrophotometer at 277 nm. The results were shown in table 7 respectively and fig 14, 15, 16, 17, 18, and 19.

Table No-7: Dissolution studies in Acidic buffer (pH 1.2)

S. No.	Time (min)	% Drug Release					
		Pure drug	F1	F2	F3	F4	F5
1.	10	5.08	20.76	26.28	26.28	36.85	39.34
2.	20	12.56	56.76	58.34	60.23	63.45	65.29
3.	30	19.41	65.43	68.29	71.33	73.89	76.56
4.	45	26.77	77.95	79.39	82.78	84.78	88.23
5.	60	32.4	87.38	89.92	92.46	96.2	98.33

Fig No-14: % Cumulative drug release profile of batch F1

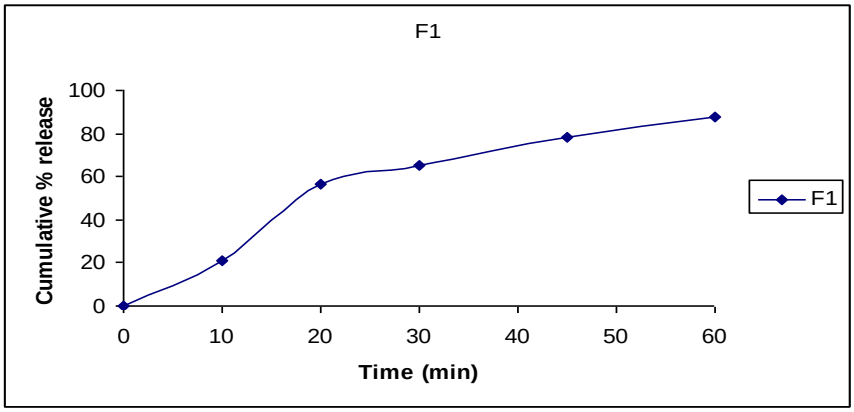


Fig No-15: % Cumulative drug release profile of batch F2

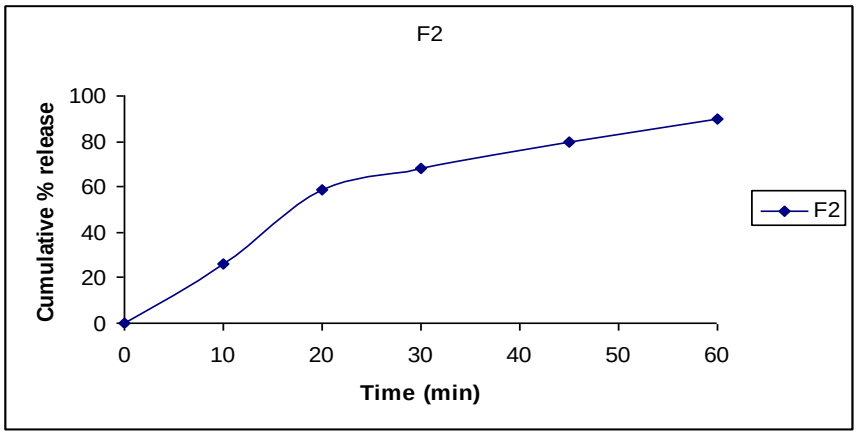


Fig No-16: % Cumulative drug release profile of batch F3

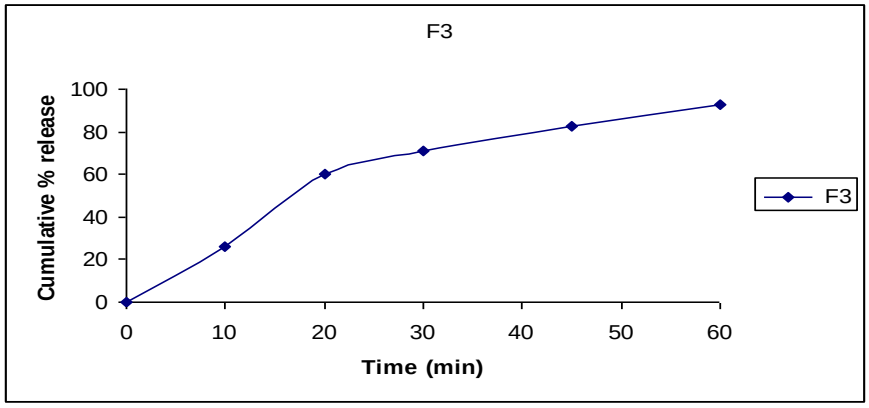


Fig No-17: % Cumulative drug release profile of batch F4

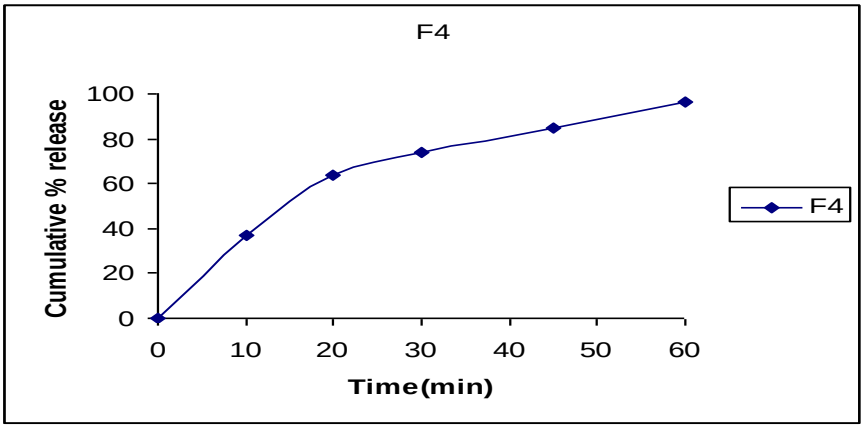


Fig No-18: % Cumulative drug release profile of batch F5

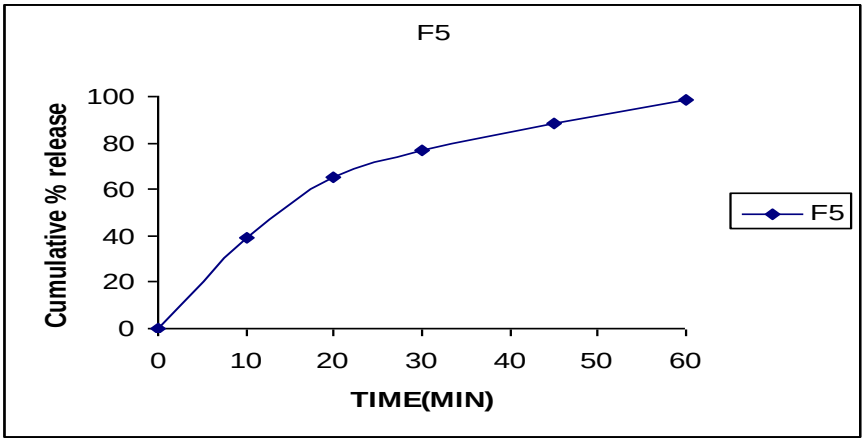
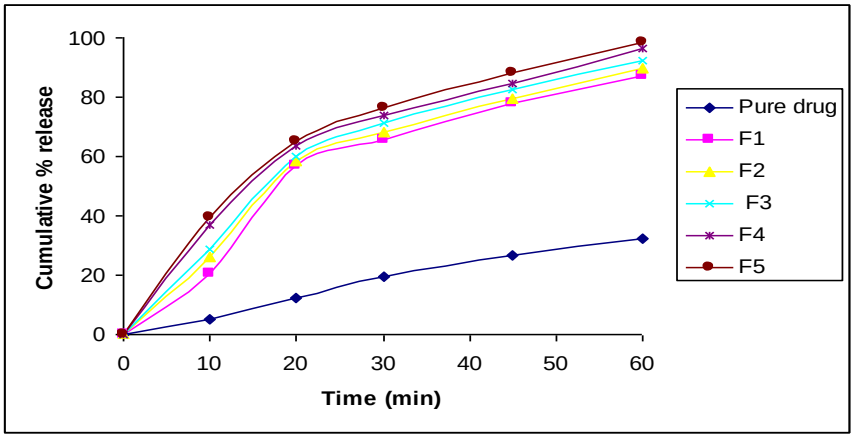


Fig No-19: % Cumulative drug release profile of batch F1-F5 and pure drug



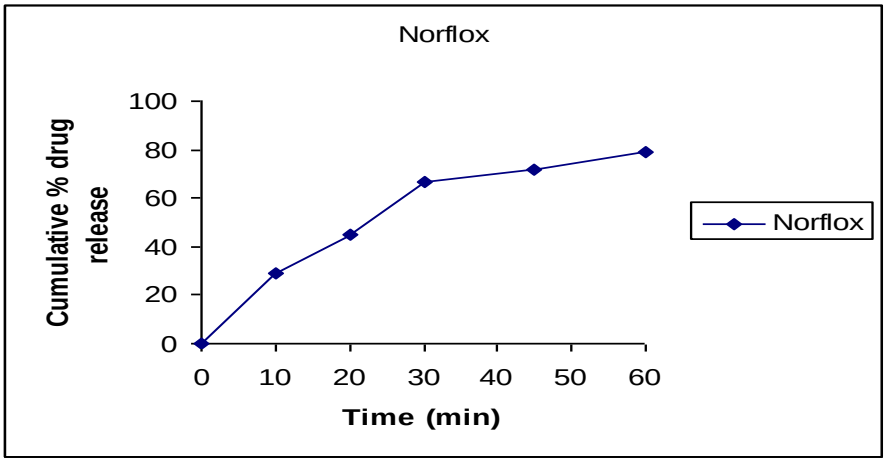
3.10 Comparison of Norfloxacin tablet with conventional marketed tablet:

The best formulation F5 was compared with marketed tablet (Norflox 100 mg) for *in vitro* dissolution study. The results were shown in table 8.

Table No-8: Percentage cumulative drug release profile of Marketed tablet and formulated tablet

Time	% Drug Release		
	F5	Time (min)	Norflox
10	39.34	10	29.19
20	65.29	20	45.25
30	76.56	30	66.82
45	88.23	45	71.54
60	98.33	60	78.67

Fig no-20: Percentage cumulative drug release profile of Marketed tablet.



4. Conclusion

The calibration curve of Norfloxacin was linear in the range of 2 to 10 µg/ml with R^2 value 0.9998 in pH 1.2 Acidic buffer, 0.9995 in phosphate buffer, and 0.9992 in water. The drug excipients compatibility studies using FT-IR indicated no interaction between the drug and polymers used. Phase solubility study revealed ideal affinity between drug and β-cyclodextrin in water. The constant value was found to be 333 M^{-1}. Thus the value of stability constants indicated that the complexes formed between drug-β-CD are stable[20].

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