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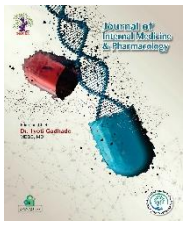

Research Article

Optimizing Norfloxacin Bioavailability: Formulation and Evaluation of Cyclodextrin-Based Tablets

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ARTICLEINFO

ABSTRACT

The present study focuses on the formulation of norfloxacin tablets using β-cyclodextrin and evaluates the tablets to enhance their bioavailability. Initially, compatibility studies, including FTIR analysis of norfloxacin and norfloxacin-excipient mixtures, were conducted to ensure the stability of the formulation components. The complexation of norfloxacin with β-cyclodextrin was carried out to improve the drug's solubility and, consequently, its bioavailability. Norfloxacin tablets were then prepared using the direct compression technique, a method known for its simplicity and effectiveness in tablet production. The formulated tablets were subjected to various evaluation parameters, including weight variation, hardness, friability, drug content, disintegration time, and drug dissolution profile. Among the formulations tested, the F5 formulation emerged as the optimized formulation, demonstrating superior performance in comparison to the marketed product. The study concludes that the norfloxacin-β-cyclodextrin complex significantly enhanced the bioavailability of norfloxacin, with the F5 formulation showing the most promising results.

Keywords: Norfloxacin; β-cyclodextrin; Dissolution; Bioavailability; Tablet

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1. Introduction

Norfloxacin (Fig. 1) is leading drug molecule is used as a antibiotic. It was approved by USFDA in 1986 and mostly prescribed for the treatment of diarrhea and sentry. How ever its pharmacokinetics is unpredictable for its oral dosage form. This could be due to the low permeability and low solubility. It is belonging to the class IV and have low oral bioavailability i.e. 30-40% and protein binding 14% due to the rapid first pass metabolism that disappointing the in vivo results. Therefore, it is necessity to develop a tablet dosage for having complex with CD that can be improved solubility and bioavailability.

Cyclodextrins are cyclic torus-shaped molecules with a hydrophilic outer surface and a lipophilic central cavity, which can accommodate a variety of lipophilic drugs. Because of the inclusion process, many physicochemical properties such as solubility, dissolution rate, stability and bioavailability can be favorably modulated. 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 (M. Narender R. et. al, 2005).

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 (K. P. R. Chowdary et.al, 2003). 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 good candidates for dissolution-rate enhancement of drugs having poor water solubility. (Deelip V et.al). Although CDs can increase the aqueous solubility of drugs, many applications need large number of CDs. But for several reasons, such as production cost and toxicity, CD amount must 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.

Thus, in the present study, we prepared tablet formulation having norfloxacin with CDs complex that enhance the solubility and bioavailability.

2. Materials and methods

2.1. Materials

Norfloxacin (purity 99.0 %) was obtained as a gift sample from Peekay scientific center (Bhopal, India). β-Cyclodextrin, HCL, KCL, and Potassium dihydrogen phosphate was obtained from Peekay scientific center (Bhopal, India). A distilled water obtained from Milli-Q Water Purification System (Millipore, USA) was used throughout the study. All other chemicals were received as pharmaceutical and analytical reagent (AR) grade and used in experiments.

2.2. Preformulation studies

2.2. FT-IR spectra of Norfloxacin and Drug-Excipient compatibility study

The drug sample was scanned on IR Spectrophotometer at $4000cm^{-1}$-$400cm^{-1}$ using KBR disc. The obtained IR spectrum was interpreted with the structure of Norfloxacin.

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

2.3. Preparation of complexes

Inclusion complex of Norfloxacin and β-CD in 1:1 molar ratio was prepared by the CD, not by dissolving but using kneading method by preparing 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.

2.4. Drug content estimation

The 50 mg powder from inclusion complexes was taken in a 50ml volumetric flask. About 40 mL 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.

2.5. Preparation of Norfloxacin Tablet using 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.

2.6. Preparation of mixed blend of drug and excipients

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. The formulation composition are shown in Table 1.

2.7. Evaluation of granules

Lubricated blend of all formulation was examined and determined angle of repose, bulk density, tapped density, cars index, Hassner's ratio. All observations are given in results and discussion section.

2.8. Evaluation of tablets

To design tablets and latter monitor the tablets is essential for production quality, quantitative evaluation, and assessments of tablets. Chemical, physical and bioavailability properties must be made to produce quality tablets.

Weight variation

20 tablets are selected and weighed individually to check for weight variation. Weight variation specification as per I.P.

Tablet hardness

Tablets require certain amount of strength, or hardness and resistant to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping, thus mechanical stability

before use depends on its hardness. The hardness of tablet of each formulation was measured in terms of kg/cm^2 by using Monsanto hardness tester.

Friability

Tablet hardness is not an absolute indicator of strength, since some formulation compressed in to very hard tablet tends to cap on attrition losing their crown portion, therefore another measure of tablets strength its friability is often measured. Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm, dropping the tablets through six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined by using formula.

$$\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablet}} \times 100$$

Uniformity of weight

Designed tablets contain specific amount of drug in specific amount of tablet formula. The weight of tablet being made is routinely measured to help ensure that tablet contains the proper amount of drug. 20 tablets were weighed and average weight was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage.

Drug content

Twenty tablets were weighed and powdered. The powder equivalent to 40 mg was taken and dissolved in to 100ml 0.1N HCl. This stock solution was shaken for 20 min on a sonicater. From stock solution 0.1 ml was taken and diluted with 0.1N HCl to achieve concentration up to 10 µg /ml. and the absorbance measured at the 277 nm. Drug content was determined by using calibration curve (y = mx + c) method.

Disintegration test

A generally accepted maxima is that for a drug to be readily available to the body, it must be solution. For most of the tablets the first important step towards solution is breakdown of the tablet in to smaller particles or granules, a process known as disintegration. The assembly was suspended in the liquid medium in the suitable vessel, preferably in 1000ml beaker. The volume of liquid such that the wire mesh at its highest point is at least 25 mm below the surface of the liquid and at its lower point is at least 25 mm above the bottom of beaker. A thermostatic arrangement was made for heating the liquid and maintain the temperature at 37 ± 2 ^{0}C. Assembly was suspend in the beaker containing the 1000 ml of 0.1N HCl and operated the apparatus for specified time. Remove the assembly from the liquid. The tablet passes the test if all of them have disintegrated. If 1 or 2 tablets fail to disintegrate repeat the test 12 additional tablets; not less than 16 of the total of 18 tablet tested disintegrate, finally observe the disintegration time of the tablets.

In vitro dissolution test

The most direct assessment of drug release from various tablet formulations or product is accomplished through in vivo bioavailability measurement. In vitro dissolution test has been extensively studied, developed and used as an indirect measurement of drug availability. USP XXIII type II apparatus was employed with a dissolution test apparatus The dissolution medium was 900 ml of 0.1 N HCl (simulated gastric fluid) at 37 ± 0.5 °C and the rotating speed was 50 rpm.

At appropriate time intervals, 1 ml of the solution was withdrawn, filtered, and assayed by a UV spectrophotometer (Elico BL 198) at 277 nm.

3.Result and discussion

3*.1. Preformulation study of norfloxacin*

3.1.1. FT-IR Spectra of Norfloxacin

The obtained IR spectrum was interpreted with the structure of Norfloxacin. The assignment for the character eristic band in the IR spectrum listed in Table 2.

3.1.2. Drug-Excipient compatibility study

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 such as norfloxacin, β-cyclodextrin, and blend of norfloxacin and β-cyclodextrin were taken for FT-IR study.

3.1.3. Phase solubility Studies

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.

3.1.4. Evaluation of inclusion complexes

Drug content estimation

Evaluation of blend

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

Evaluation of Norfloxacin tablets

All the formulations were complying with weight variation test as per IP. Hardness of the tab. was determined using a Pfizer hardness tester. It is expressed in kg/cm^2. The friability of the tablets was in the range of 0.2 to 0.48%. The disintegration time obtained for formulation F1 to F5. The result of the disintegration test revealed that F5 has faster disintegration, and it disintegrant within two minutes. All the results of weight variation, hardness, friability, and disintegration test are shown in table 6.

Dissolution test

USP 2 Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. Acidic buffer pH 1.2, 500 ml 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 mints. 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. 9, 10, 11, 12, 13, and 14.

Comparison of Norfloxacin tablet with conventional marketed tablet:

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

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.

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Table 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.

Table 2. IR spectral characteristics of Norfloxacin

S. No.	Peaks (cm^{-1})	Observed peaks (cm^{-1})	Groups
1.	1715 cm^{-1}	1690-1720 cm^{-1}	C=O
2.	2400-3400 cm^{-1}	2380-3410 cm^{-1}	OH
3	1700-1730 cm^{-1}	1690-1740 cm^{-1}	C=O
4.	1320-1210 cm^{-1}	1310-1220 cm^{-1}	C-O
5.	1100-1250 cm^{-1}	1090-1280 cm^{-1}	C-F

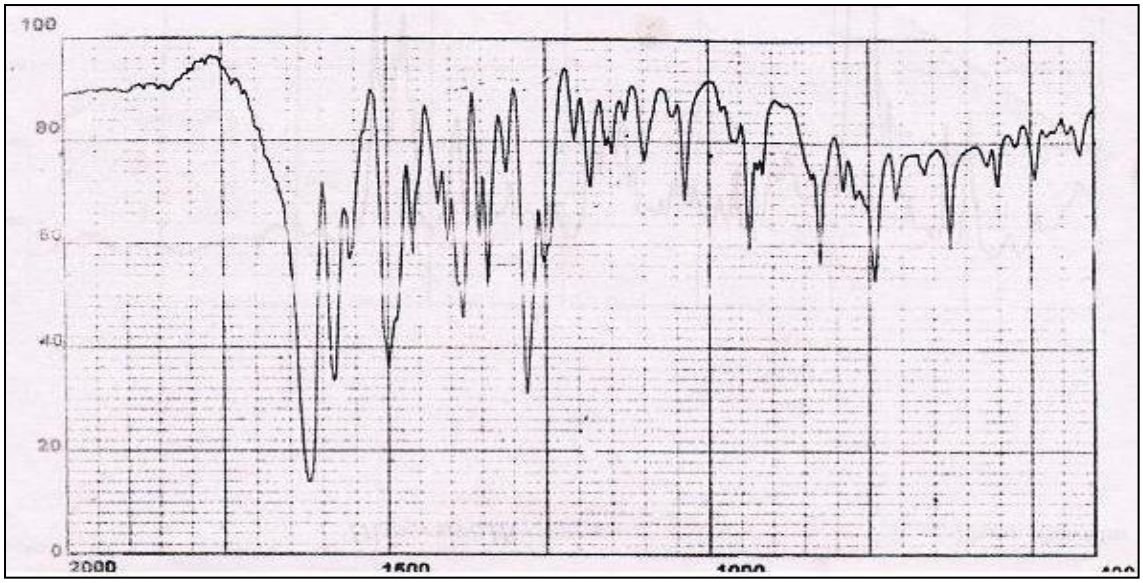

Fig 1: IR Spectra of Norfloxacin (standard)

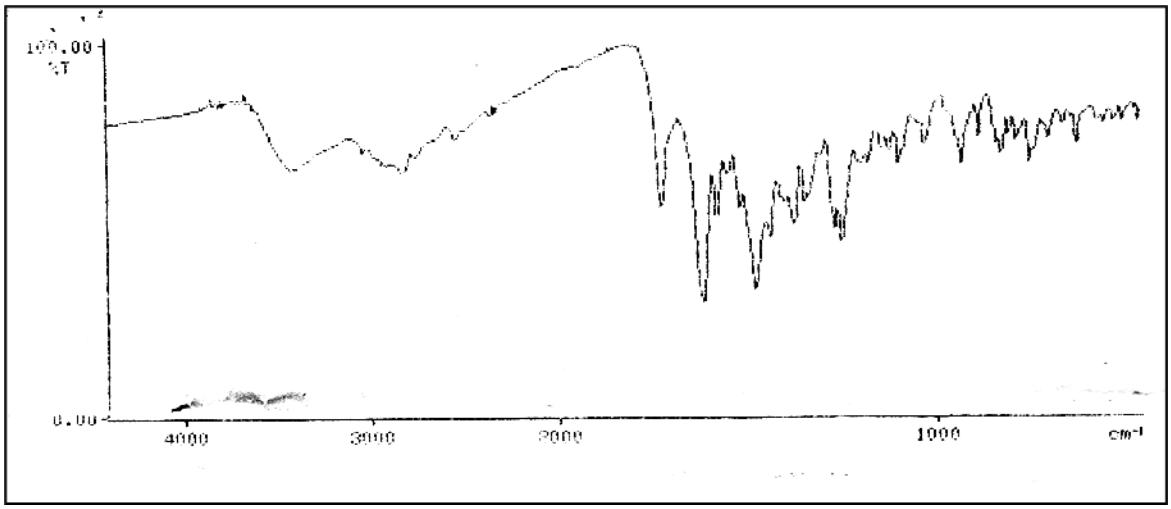

Fig 2: FTIR Spectra of Norfloxacin (sample)

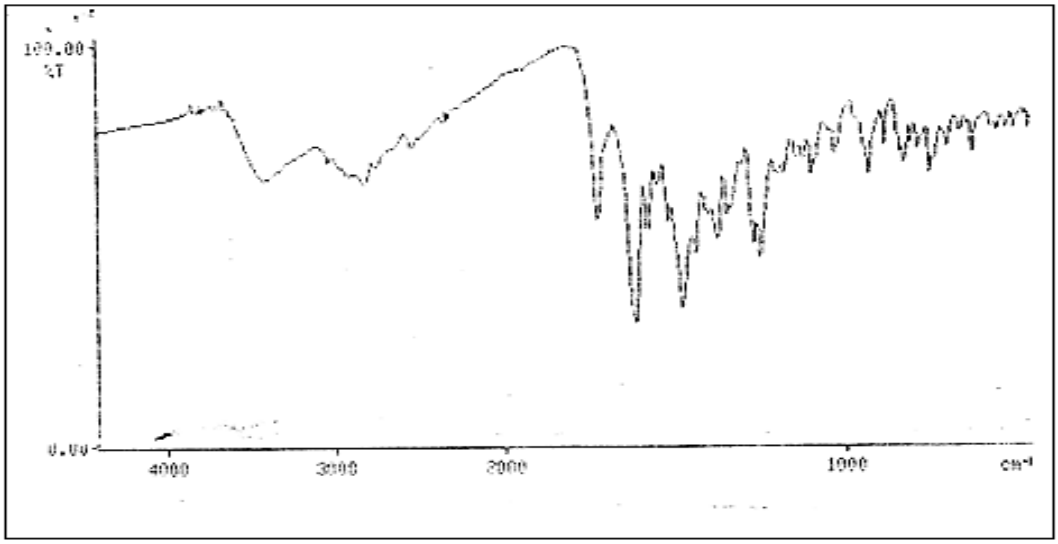

Fig 3: FT-IR Spectra of Norfloxacin

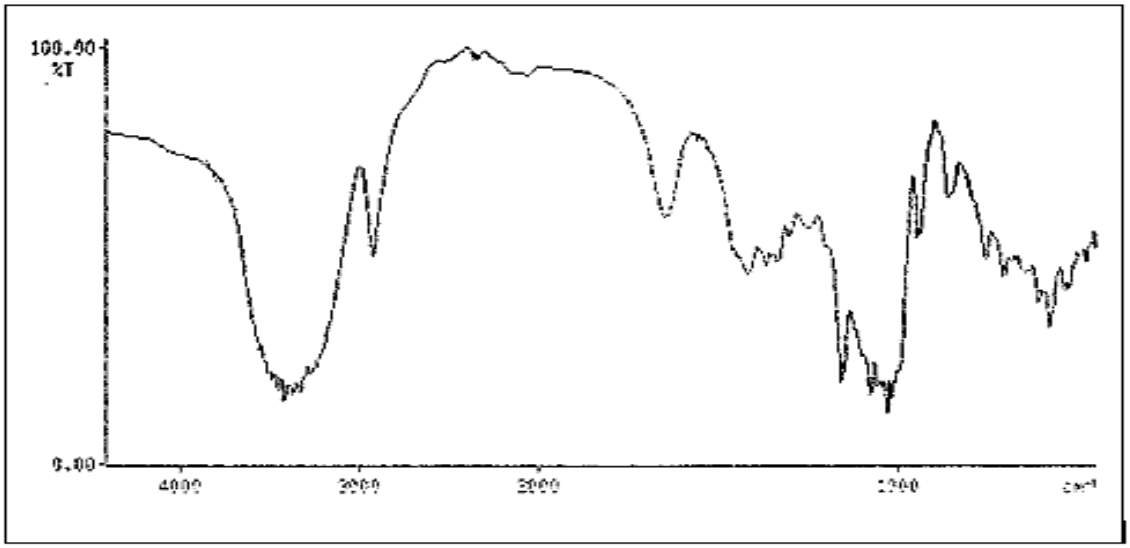

Fig 4: FT-IR Spectra of β-Cyclodextrin

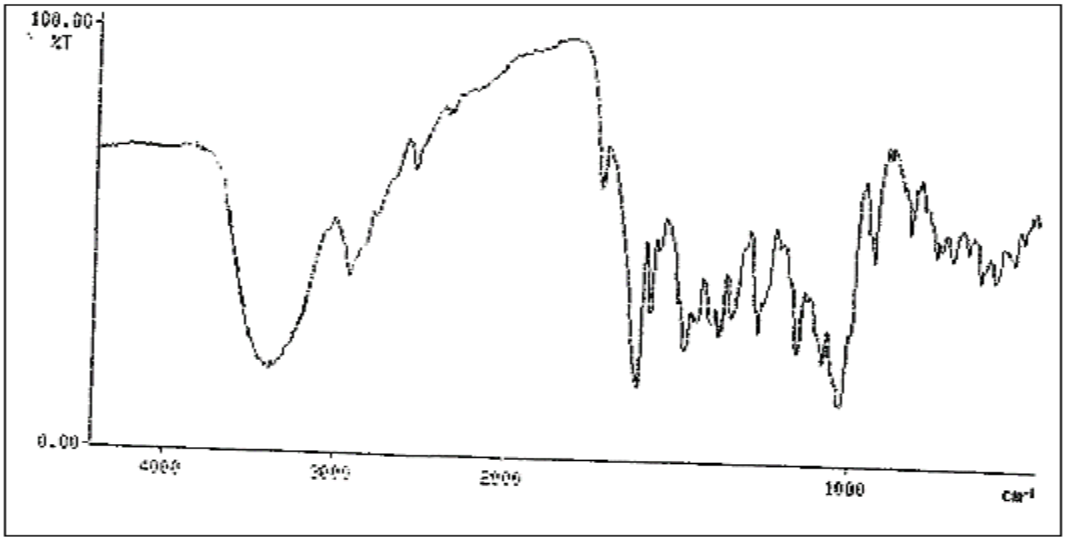

Fig 5: FTIR Spectra of Norfloxacin and β-Cyclodextrin:

Table 3: Phase solubility diagram

Sr.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

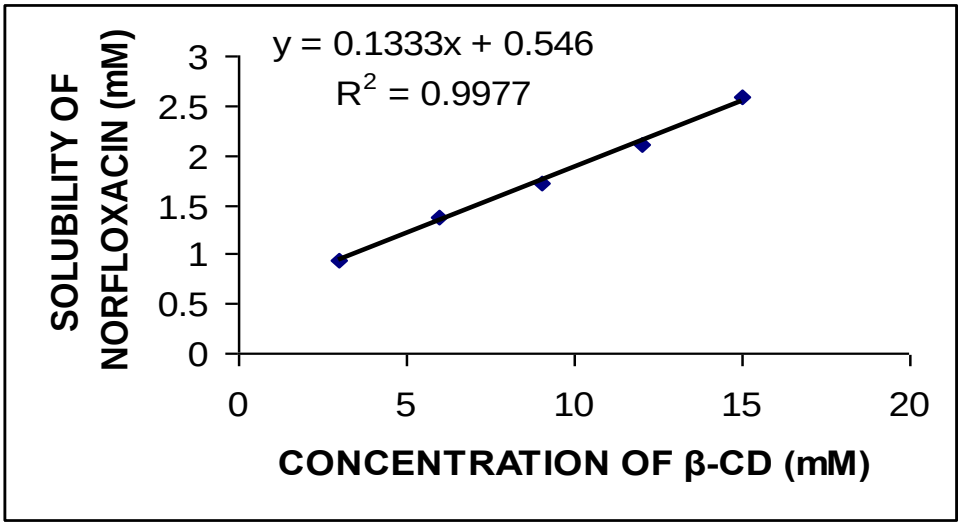

Fig 7: Effect of β-CD on the solubility of Norfloxacin

Table 4 Drug content estimation

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

Table 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

Table 6: Evaluation of physical parameters of Norfloxacin tablets

Batch code	Weight variation	Thickness	Hardness	Friability	In vitro disint. 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

Table 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

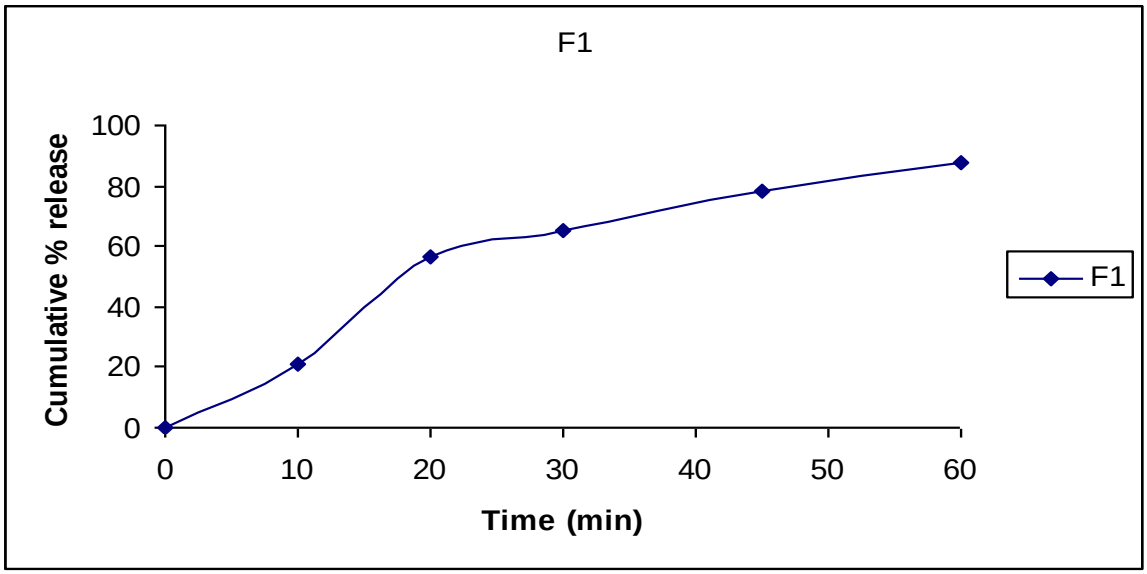

Fig. 9: % Cumulative drug release profile of batch F1

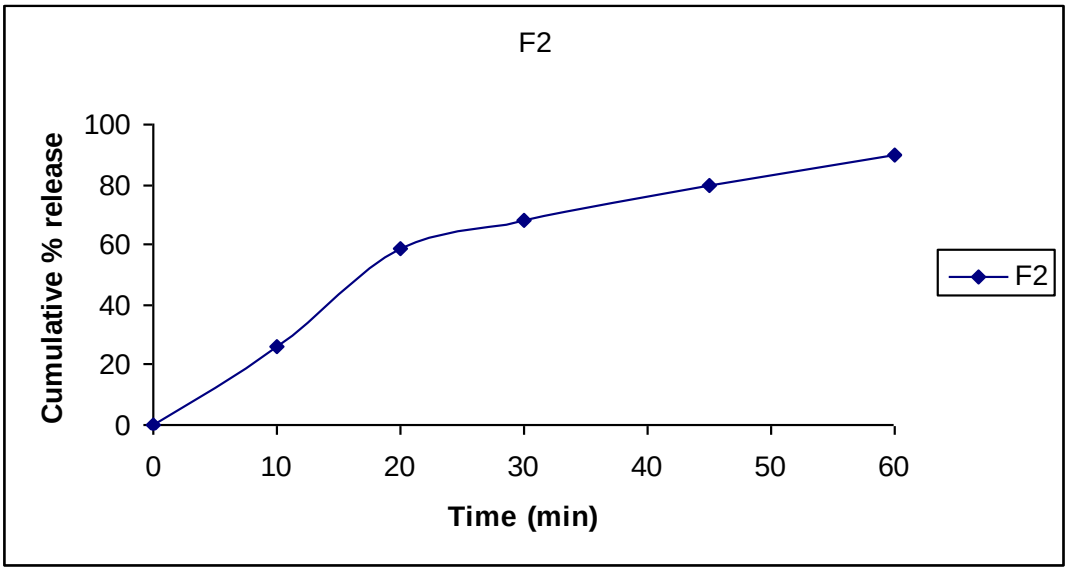

Fig. 10: % Cumulative drug release profile of batch F2

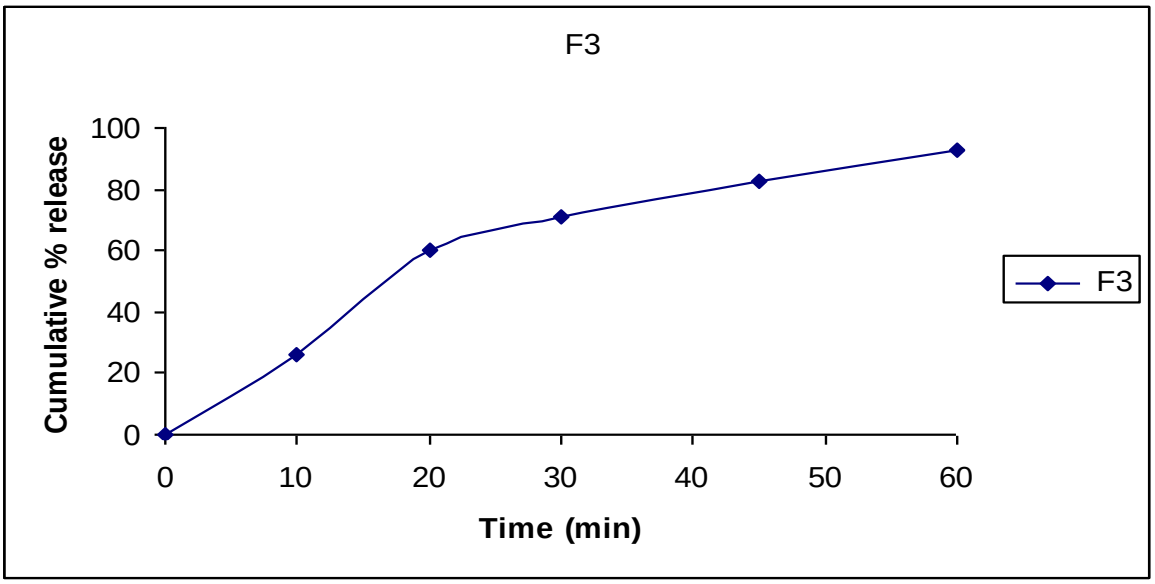

Fig. 11: % Cumulative drug release profile of batch F3

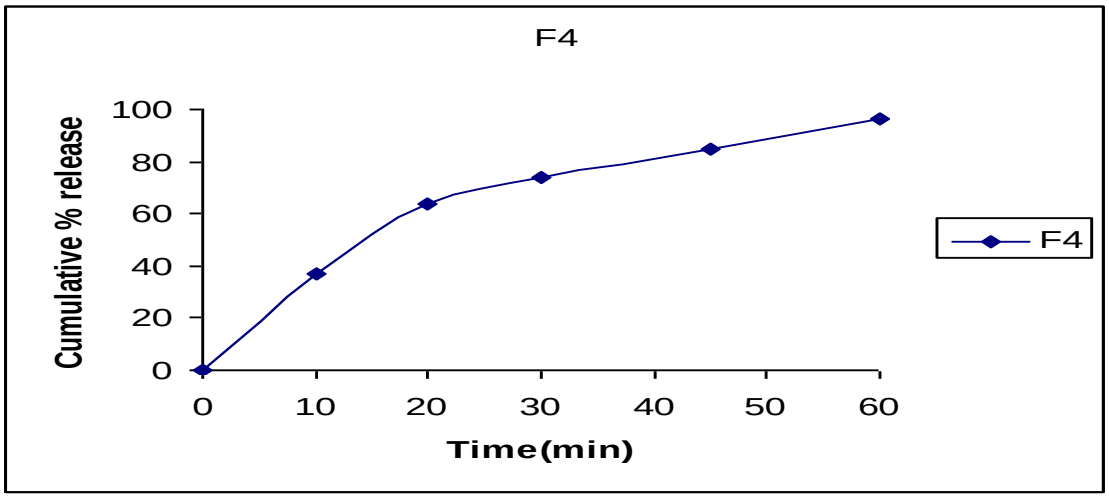

Fig. 12: % Cumulative drug release profile of batch F4

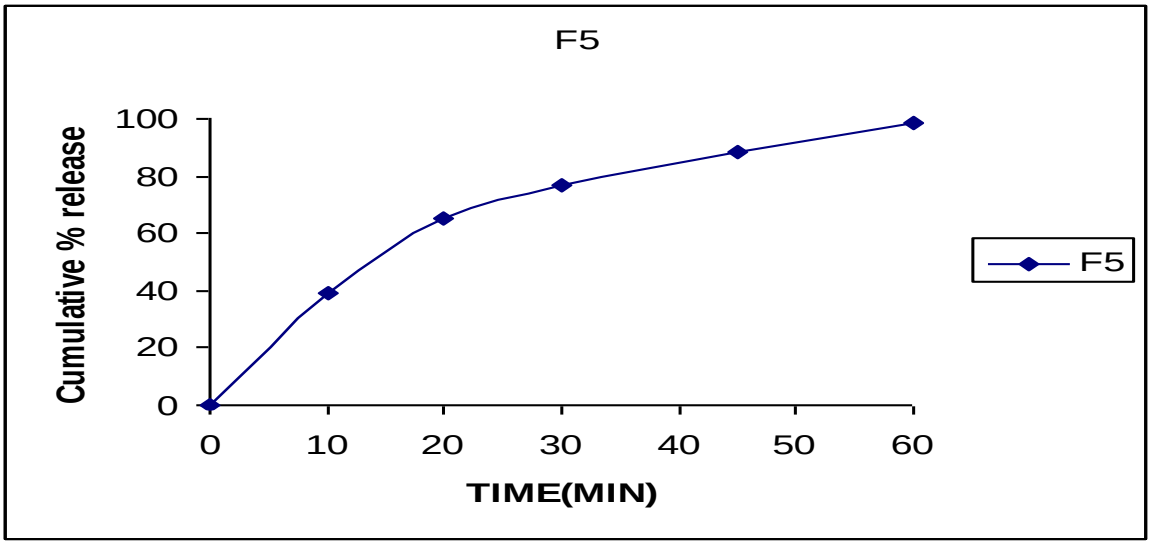

Fig. 13: % Cumulative drug release profile of batch F5

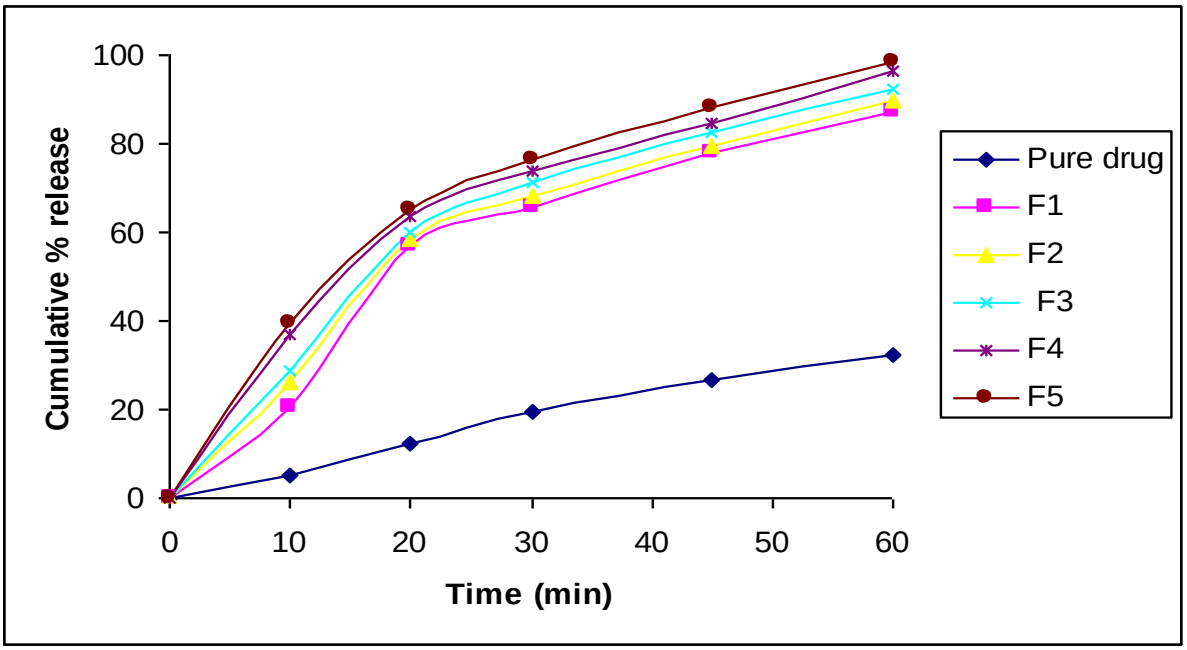

Fig. 14: % Cumulative drug release profile of batch F1-F5 and pure drug

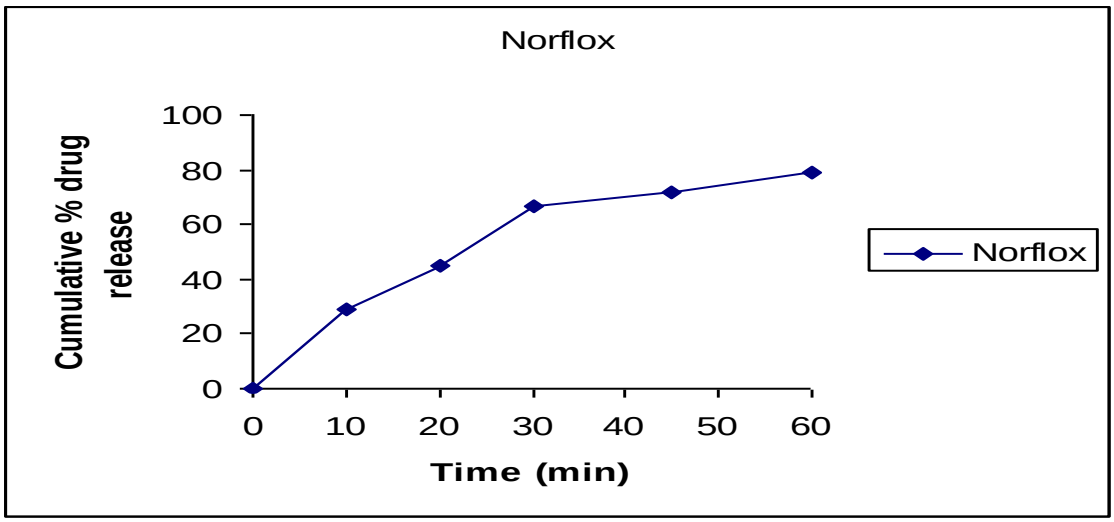

Fig. 15: Percentage cumulative drug release profile of Marketed tablet

Table 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