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FORMULATION DEVELOPMENT AND VALIDATION OF GESTRORETENTIVE SUSTAINED RELEASE TABLET OF CIPROFLOXACIN

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ABSTRACT

Tablets are often employed due of their many positive characteristics, including their simplicity, safety (in terms of dosing variation and stability), and convenience of production. The goal of validating an analytical technique is to prove that it is fit for that particular application. The process of creating and verifying the validity of an analytical technique is known as analytical method development and validation. It aids in boosting the data's consistency, correctness, and dependability in analyses. As a result of the improved patient convenience, enhanced efficacy, and reduced side effects possible with single component formulations, their prominence has grown. As time goes by, analytical chemists' labor gets more tiresome. These days, it's not enough to only think about the product's quality; you also need to analyze its contents without resorting to laborious and expensive extraction or separation operations beforehand. The creation of a standardized HPLC procedure for Ciprofloxacin 250 mg, 500 mg. The following chromatographic conditions were used in this liquid chromatographic method: In this study, the HPLC method for assay of ciprofloxacin in ciprofloxacin tablet 250mg and 500mg has been developed validated. Each step of the validation process is carried out in accordance with the most recent iteration of the ICH rules and their corresponding criteria. This study's findings show that the HPLC technique outlined in the protocol is valid for the determination of the assay of ciprofloxacin in ciprofloxacin tablet 250mg and 500mg, and that the procedure was simple to manufacture and use.Therefore, the approach is useful for the desired purpose.

Key words: Ciprofloxacin HPMC K4M HPMC, Xanthangum Dry granulation Matrix tablet.

INTRODUCTION

Among various types of process validations employed by formulation scientists, formulation validation is widely employed as it results in optimization of required dosage forms. Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. It is evident from the various literatures reports that the change in the various parameters during preparation of formulations like concentration of polymers, types of polymers, concentration of other additives and various manufacturing conditions affect the physicochemical and pharmacokinetic parameters of the product.

Hence, in the present work an attempt will be made to study the efficacy of two mucoadhesive hydrophilic polymers that is HPMC and Xanthangum on sustained release charecterstics of Acyclovir in order to validate the ideal formulation for preparing Sustained release tablets of Acyclovir. Thus prepared formulations will be evaluated for drug release pattern (up to 12 hrs) and the best formulation will be selected based on drug release data and will subjected to stability studies by ICH guidelines.

PROCESS VALIDATION

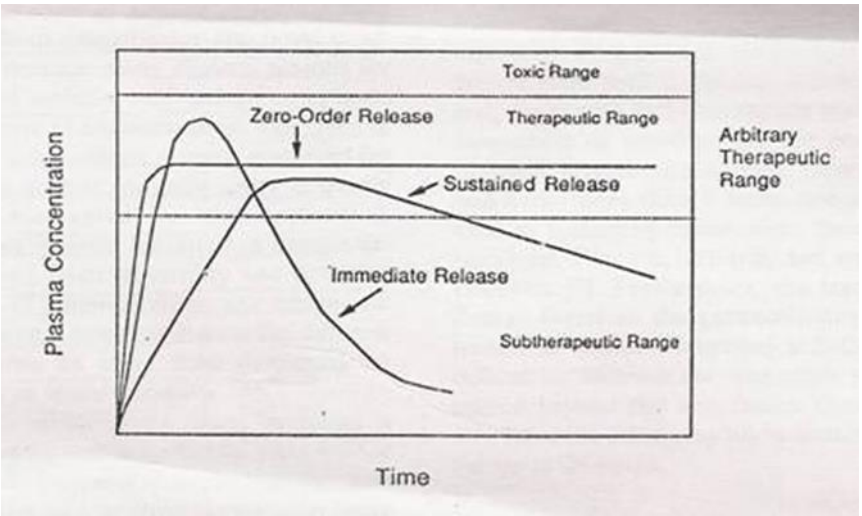
The U.S. FDA has proposed guidelines with the following definition for process validation; Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics.

According to the FDA, assurance of product quality is derived from careful and systemic attention to a number of important factors, including: selection of quality components and materials, adequate product and process design, and (statistical) control of the process through in-process and end-product testing. Thus, it is through careful design (qualification) and validation of both the process and its control systems that a high degree of confidence can be established that all individual manufactured units of a given batch or succession of batches that meet specifications will be acceptable.

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS: [3]

Controlled release drug delivery is one which delivers the drug at a predetermined rate locally or systemically for a specified period of time. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. Sustained release dosage form that provides medication over an extended period of time. Controlled release denotes that the system is able to provide some actual therapeutic control, whether this is of temporal nature, spatial nature or both. In other words, the system attempts to control drug concentrations in the target tissue. This correctly suggests that there are sustained release systems that cannot be considered as controlled-release systems.

Fig.1.1: Plasma drug concentration – profiles for conventional release formulation, a sustained release formulation and a zero – order controlled release formulation.



In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form that is independent of the amount of the drug in the delivery system (i.e., a constant release rate).

Advantages of controlled release drug delivery systems

1. Improved patient compliance.
2. Reduction in fluctuation in steady-state levels.
3. Increased safety margin of high potency drugs due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Better control of disease condition.
6. Reduced intensity of local or systemic side effects.

Disadvantages of controlled release drug delivery system

1. Decrease systemic availability in comparison to immediate release formulation or conventional dosage forms. This may be due to
   - Incomplete release
   - Increased first-pass metabolism
   - Increased instability,
   - Insufficient residence time for complete release
   - Site-specific absorption
   - pH dependent solubility
2. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
3. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
4. Higher cost of formulation.

An oral controlled-release system can be designed either as a continuous release system or as a pulsed release system.

1. Continuous release systems release drug continuously over an extended period of time.
2. Pulsatile release systems are characterized by a time period of no release followed by a rapid and complete or extended drug release.

Gastroretentive Delivery Systems

Many drugs which have poor absorption in GIT can be conveniently converted into Gastroretentive delivery systems. In Gastroretentive DDS, formulation changes will be made in such a way that the drug will remain in GIT for prolonged period of time.

Need For Gastro Retention

- ❖ Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- ❖ Drugs those are less soluble or degraded by the alkaline pH that encounters at the lower part of GIT.
- ❖ Drugs that are absorbed due to variable gastric emptying time.
- ❖ Local or sustained drug delivery to the stomach and proximal Small intestine to treat certain conditions.
- ❖ Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.
- ❖ Suitable drug candidates for gastro retention9:
- ❖ Drugs having Narrow absorption window in GIT, Example: Riboflavin and Levodopa.
- ❖ Drugs primarily absorbed from stomach and upper part of GIT, Example: Calcium supplements, Chlordizepoxide and Cinnarazine.
- ❖ Drugs that are locally in the stomach, Example: Antacids and Misoprostol.
- ❖ Drugs that degrade in the colon, Example: Ranitidine HCl and Metronidazole.
- ❖ Drugs that disturbs normal colonic bacteria, Example: Amoxicillin trihydrate.

Advantages of Gastroretentive Delivery Systems:

- ✓ Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose, Example: Furosemide.
- ✓ Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. Beta-lactam antibiotics (penicillin's and cephalosporin's)·
- ✓ Retention of drug delivery systems in the stomach prolongs overall.
- ✓ Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacin
- ✓ Disadvantages of Gastroretentive drug delivery system9:
- ✓ Floating system is not feasible for those drugs that have solubility or stability problems in G.I. track.
- ✓ These systems require a high level of fluid in stomach for drug delivery to float and work efficiently.

Formulation considerations for GRDDS:

- ✓ It must be effective retention in the stomach to suit for the clinical demand
- ✓ It must have sufficient drug loading capacity.
- ✓ It must control the drug release profile.

- ✓ It must have full degradation and evacuation of the system once the drug release is over.
- ✓ It should not have effect on gastric motility including emptying pattern.
- ✓ It should not have other local adverse effects.

Types of gastro retentive dosage forms

1. High density systems.
2. Floating systems.
    a) Effervescent floating dosage forms.
    b) Non effervescent dosage forms.
    c) Raft forming systems.
    d) Low density systems.
3. Expandable systems.
4. Superporous hydrogels.
5. Mucoadhesive/ bioadhesive systems.

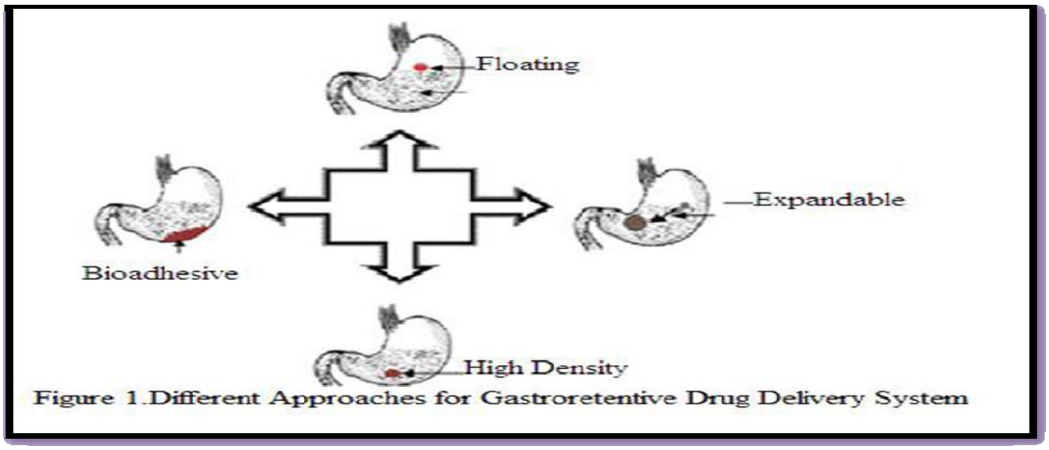


Figure: Different approaches for Gastroretentive drug delivery system Floating systems

Aim of research

The aim of the present study is to formulate gastro retentive matrix tablets using various grades of HPMC and in different concentrations. Hydrophilic polymer matrix systems are widely used in oral drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, hydroxypropyl methyl cellulose derivatives are frequently used because of their nontoxic nature, easy compression, swelling properties and accommodation to high levels of drug loading.

Additionally, HPMC is a pH independent material and hence drug release from hydroxypropyl methyl cellulose matrix formulations is generally independent of processing variables.44 Gastrointestinal resident time of the tablet vary from person to person about 8-12 hrs.45 Floating drug delivery system is retained in the stomach for prolonged period of time and also producing sustained effect. Hence floating technique is employed for the delivery of the BET hydrochloride.

Tab.: Formulation of Gastroretentive tablets

Ingredients	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX
Ciprofloxacin	100	100	100	100	100	100	100	100	100
HPMC K4M	120	150	180	-	-	-	30	60	90
HPMCK100M	-	-	-	120	150	180	90	90	90
Microcrystalline cellulose	85	55	25	85	55	25	85	55	25
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
PVP K30	15	15	15	15	15	15	15	15	15
Magnesium stearate	6	6	6	6	6	6	6	6	6
Isopropyl alcoho	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06

Average weight of one tablet = 376 mg

Tab. 8.5: % of polymers used in formulation of Ciprofloxacin gestroretentive tablets

Formulation	% of Polymer used	
	HPMC K4M	HPMC K100M
F-I	40	-
F-II	50	-
F-III	60	-
F-IV	-	40
F-V	-	50
F-VI	-	60
F-VII	10	30
F-VIII	20	30
F-IX	30	30

RESULTS AND DISCUSSION

Physical compatibility study:

The drug and the excipients were tested for their physical compatibility in order to obtain a safe and efficient dosage form. The results of the compatibility study are listed in Table 9.1

Tab.: Physical Compatibility study of drug and excipients

S.No	Drug and Excipients	Descriptions and conditions						
		Initial	Room temperature			40±2ºC		
			days					
			10	20	30	10	20	30
1.	Ciprofloxacin (CIP)	Off-white coloured powder	NC	NC	NC	NC	NC	NC
2.	HPMC	White coloured powder	NC	NC	NC	NC	NC	NC
3.	CIP+HPMC K4M	white coloured powder	NC	NC	NC	NC	NC	NC
4.	CIP+HPMC K100M	White coloured powder	NC	NC	NC	NC	NC	NC
5.	CIP + MCC	white coloured powder	NC	NC	NC	NC	NC	NC
6.	CIP + Sodium bicarbonate	White coloured powder	NC	NC	NC	NC	NC	NC
7.	CIP + PVP K 30	Pale yellow coloured powder	NC	NC	NC	NC	NC	NC
8.	+ Magnesium stearate	White coloured powder	NC	NC	NC	NC	NC	NC

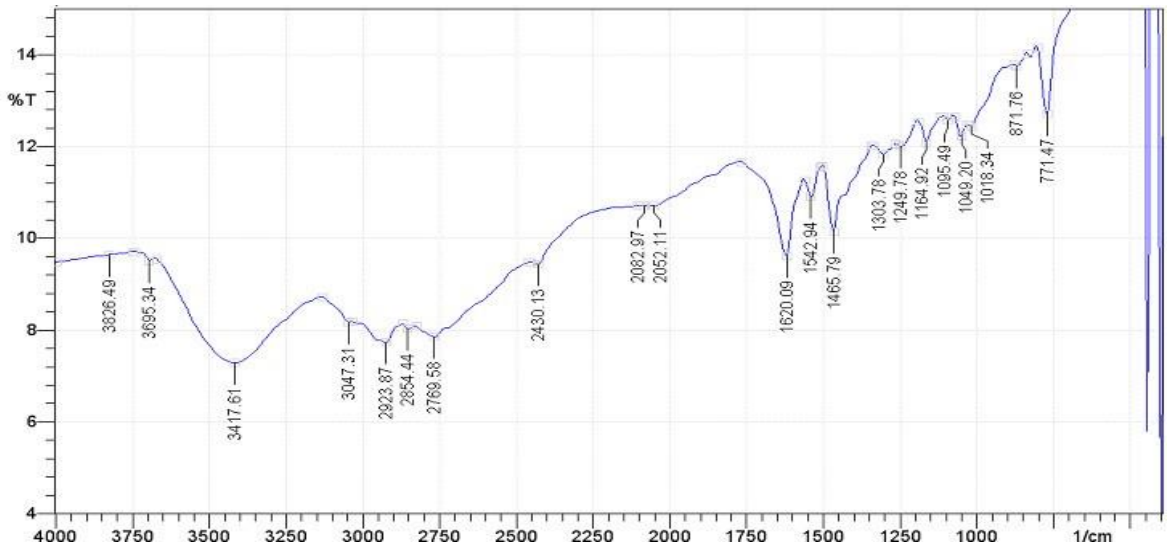
***NC:** NO CHANGE

The physical compatibility study was performed and the results showed that there was no sign of incompatibility. The drug and the excipients are physically compatible.

FTIR Study – Identification and Compatibility of Drug and Polymer:

The identification of drug and the compatibility between the drug and polymers was carried out using FTIR. The FTIR spectra of the pure drug, drug polymer mixtures and tablet powder are shown in Figures 9.1 to 9.7 and interpretation are shown in table 9.2 to 9.8

Fig.: FTIR Spectrum of CIPROFLOXACIN



Tab: FTIR Spectrum of Ciprofloxacin

Wave Number (cm^{-1})	Interpretation
3417	N-H Stretching
2923	C-H Stretching (aliphatic)
1620	C=C Stretching
1485	C-N Stretching

Fig.: FTIR Spectrum of Ciprofloxacin and HPMC K4M

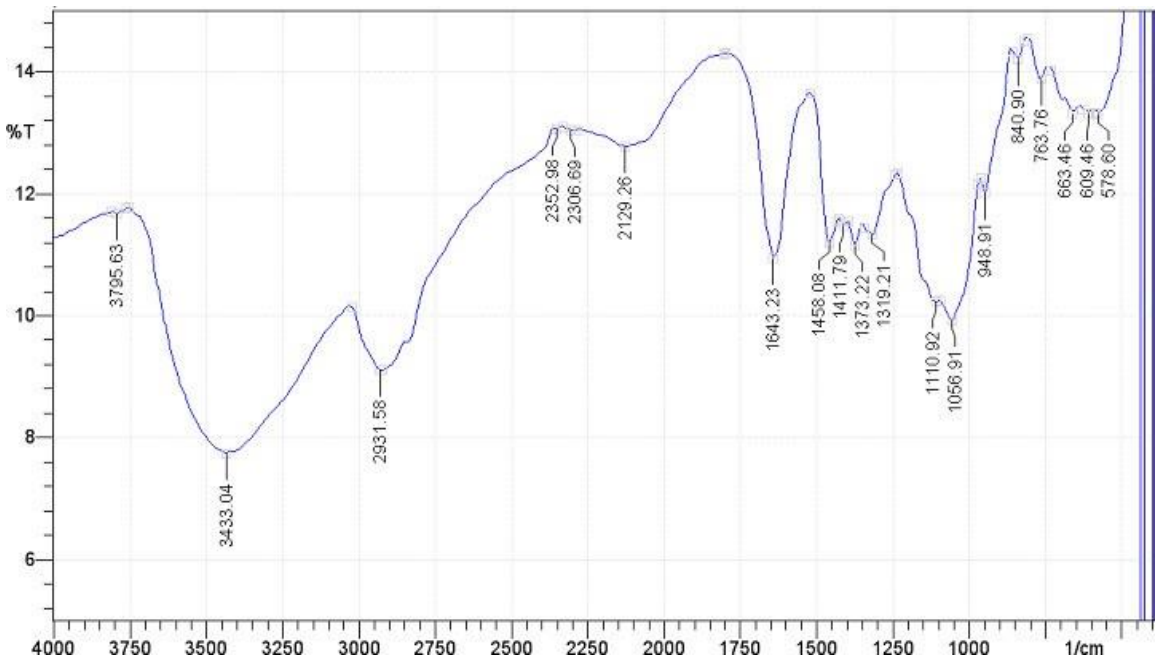
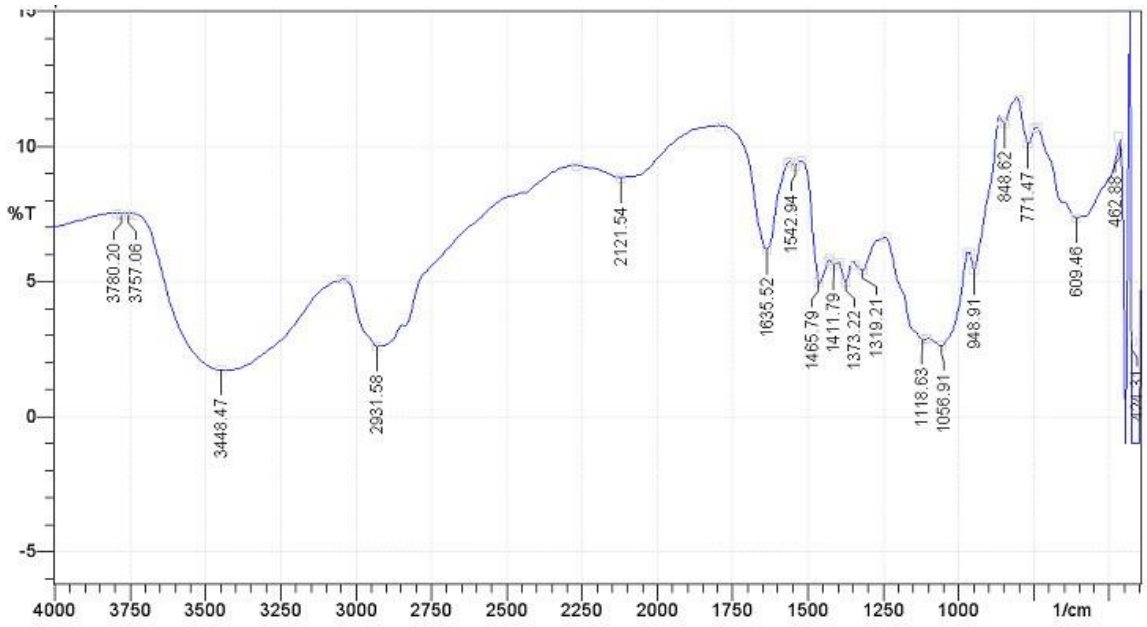


Table: FTIR Spectrum of CIPROFLOXACIN and HPMC K4M

Wave Number (cm^{-1})	Interpretation
3433	N-H Stretching
2931	C-H Stretching (aliphatic)
1643	C=C Stretching
1458	C-N Stretching

The peaks observed in the FTIR spectrum of CIPROFLOXACIN with HPMC K4M showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and HPMC K4M.

Fig.: FTIR Spectrum of CIPROFLOXACIN and HPMC K100M

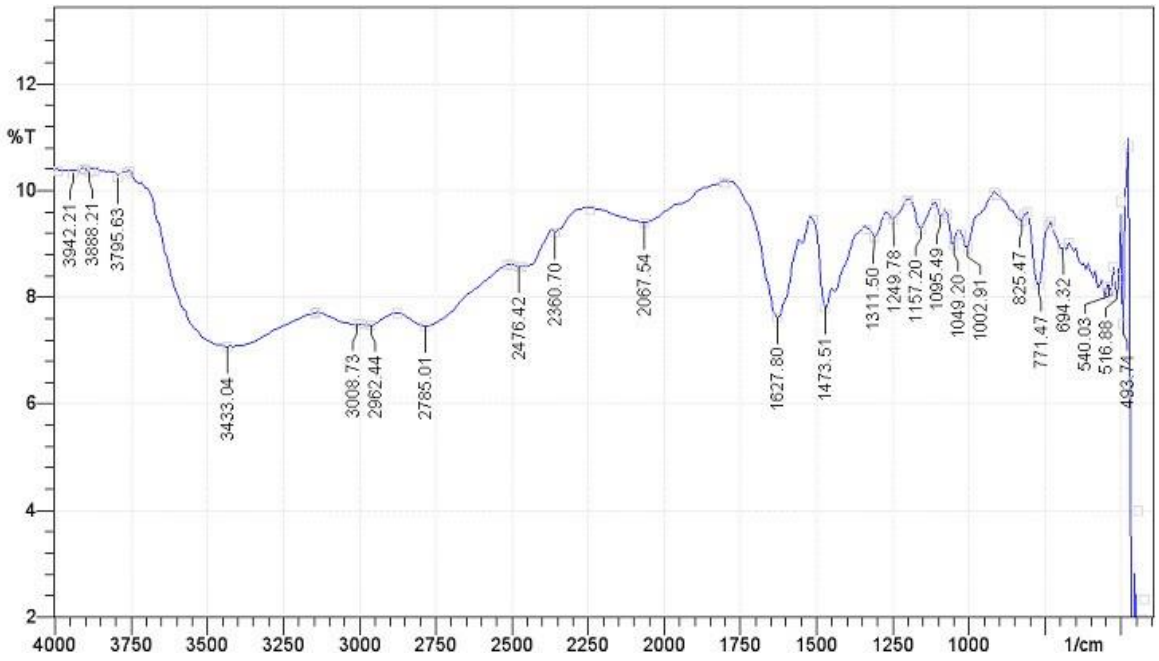


Tab.: FTIR Spectrum of CIPROFLOXACIN and HPMC K100M

Wave Number (cm^{-1})	Interpretation
3448	N-H Stretching
2931	C-H Stretching (aliphatic)
1635	C=C Stretching
1485	C-N Stretching

The peaks observed in the FTIR spectrum of CIPROFLOXACIN with HPMC K100M showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and HPMC K100M.

Fig.:FTIR Spectrum of CIP and Sodium bicarbonate

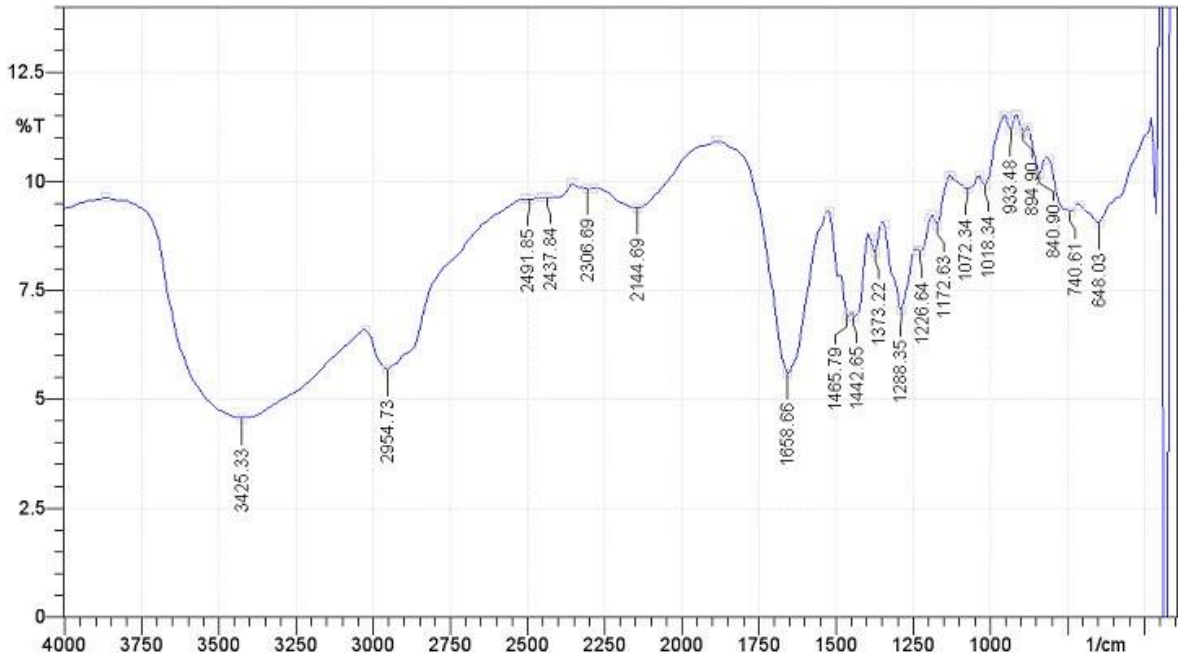


Tab.: FTIR Spectrum of Ciprofloxacin and Sodium bicarbonate

Wave Number (cm^{-1})	**Interpretation**
3433	N-H Stretching
3008	C-H Stretching (aliphatic)
1627	C=C Stretching
1473	C-N Stretching

The peaks observed in the FTIR spectrum of CIPROFLOXACIN with Sodium bicarbonate showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium bicarbonate.

Fig. : FTIR Spectrum of CIPROFLOXACIN and PVP K30

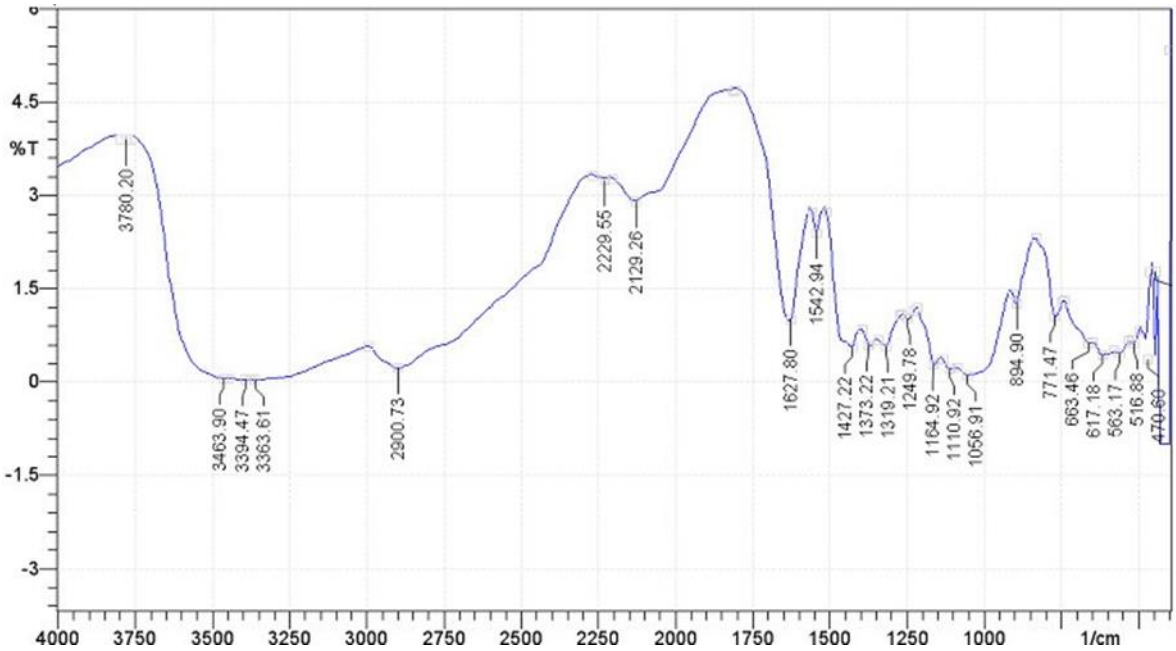


Tab: FTIR Spectrum of Ciprofloxacin and PVP K30

Wave Number (cm^{-1})	Interpretation
3425	N-H Stretching
2954	C-H Stretching (aliphatic)
1658	C=C Stretching
1485	C-N Stretching

The peaks observed in the FTIR spectrum of CIPROFLOXACIN with PVP K30 showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and PVP K30.

Fig: FTIR Spectrum of Ciprofloxacin and MCC

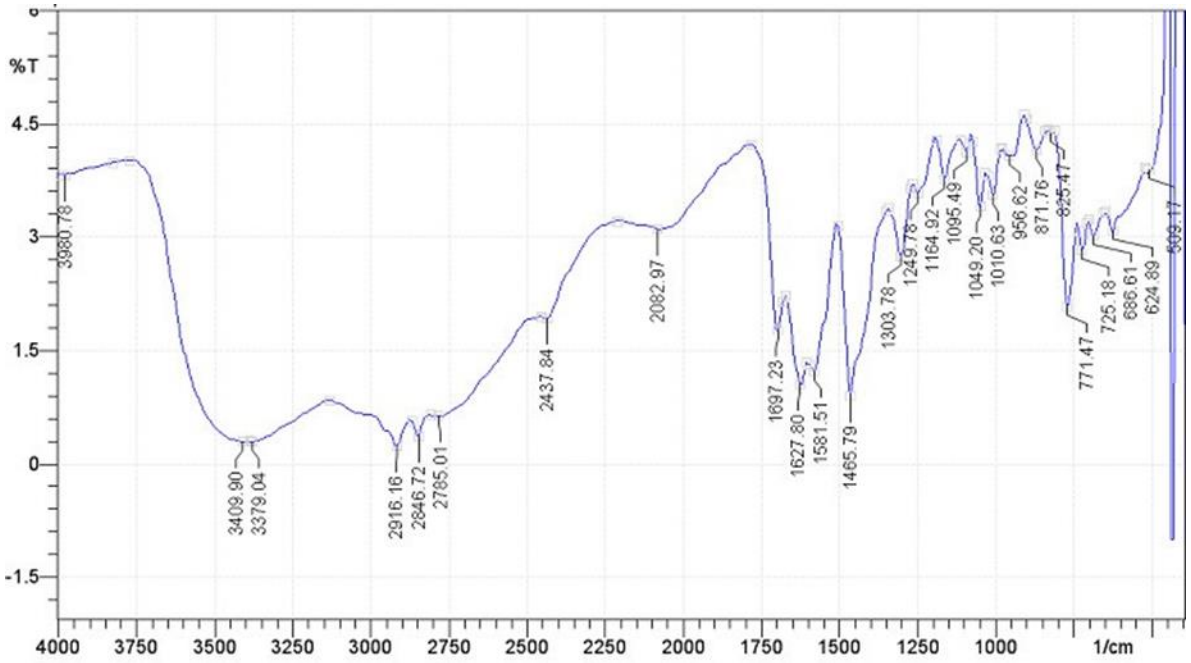


Tab.: FTIR Spectrum of CIPROFLOXACIN and MCC

Wave Number (cm^{-1})	Interpretation
3394	N-H Stretching
2900	C-H Stretching (aliphatic)
1627	C=C Stretching
1427	C-N Stretching

The peaks observed in the FTIR spectrum of CIPROFLOXACIN with MCC showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and MCC.

Fig: FTIR Spectrum of ciprofloxacin and Magnesium stearate



Tab.: FTIR Spectum of CIPROFLOXACIN and Magnesium stearate

Wave Number (cm^{-1})	**Interpretation**
3409	N-H Stretching
2916	C-H Stretching (aliphatic)
1697	C=C Stretching
1465	C-N Stretching

The peaks observed in the FTIR spectrum of CIPROFLOXACIN with Magnesium stearate showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Magnesium stearate.

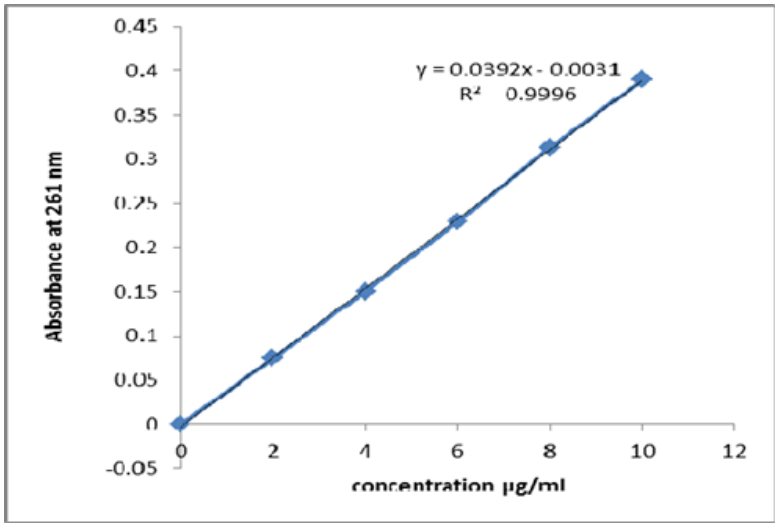
Standard Curve of Ciprofloxacin:

The absorbance of the drug in different concentrations in 0.1N Hydrochloric acid was measured at a wavelength of 309 nm. The results are given in Table 9.9. The standard curves plotted using the absorbance of various concentrations is shown in Figure 9.8

Tab. Data for Standard curve of CIPROFLOXACIN

S.No	Concentration (μg/ml)	Absorbance at 309 nm
1.	0	0
2.	2	0.075
3.	4	0.150
4.	6	0.229
5.	8	0.313
6.	10	0.390

Fig.: Standard Curve of Ciprofloxacin in 0.1N HCl



The standard curve is linear and starts from the origin. It obeys Beer – Lambert's law.

Precompression studies of the drug and powder blends:

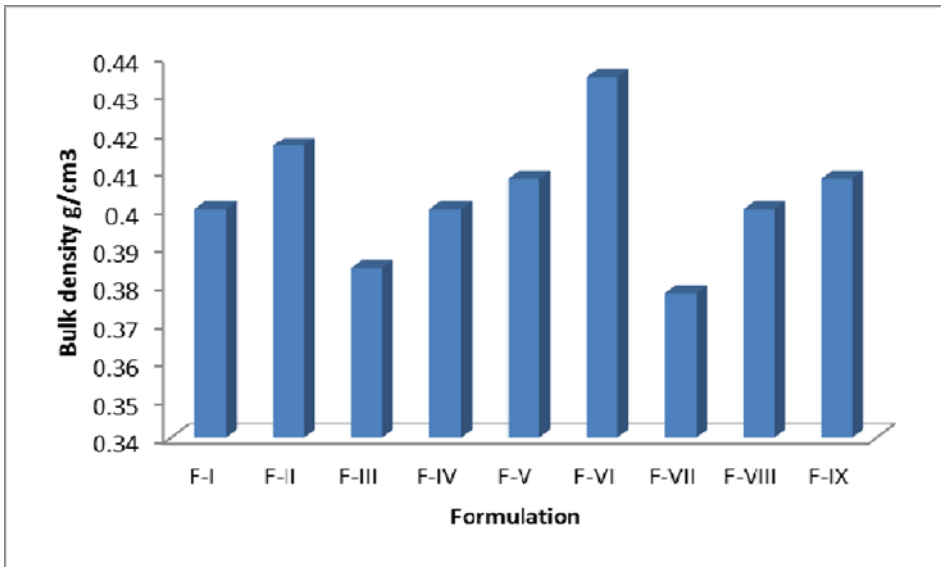
The results of the precompression study of the powder blends are given in Table .

.Tab.: Precompression study of powder blends

Drug/ Powder blends	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of Repose* (θ)
F-I	0.4000	0.5263	23.99	1.32	$30^0 03'$
F-II	0.4167	0.55562	25.00	1.33	$31^0 36'$
F-III	0.3846	0.5000	23.08	1.30	$32^0 69'$
F-IV	0.4000	0.5263	23.99	1.31	$31^0 98'$
F-V	0.4081	0.5128	20.41	1.25	$32^0 60'$
F-VI	0.4347	0.5556	21.76	1.27	$30^0 07'$
F-VII	0.3778	0.5000	24.44	1.32	$31^0 02'$
F-VIII	0.4000	0.5263	23.99	1.32	$31^0 08'$
F-IX	0.4081	0.5128	20.41	1.26	$32^0 21'$

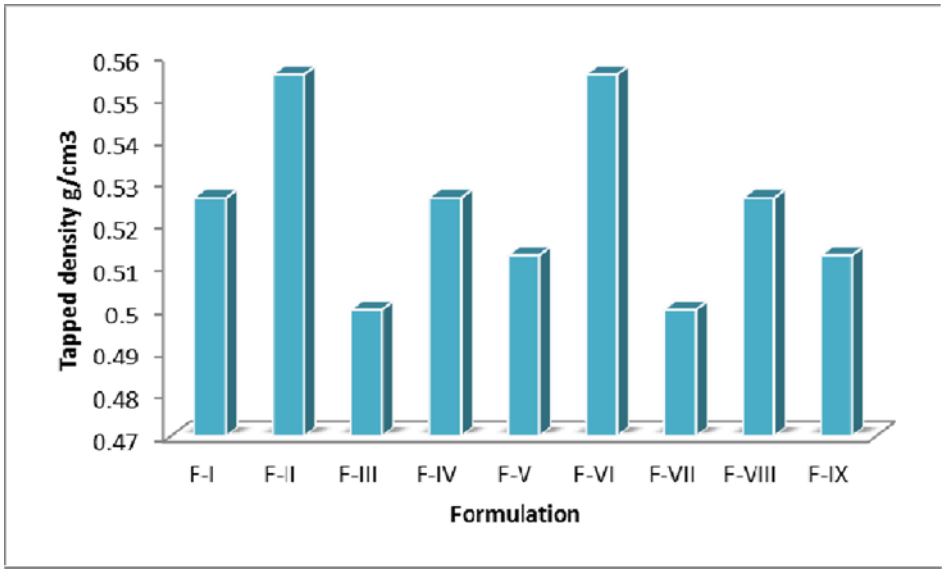
The drug blend has passable flow property. Hence, the tablets were prepared by wet granulation technique.

Fig.: Bulk density of powder blend



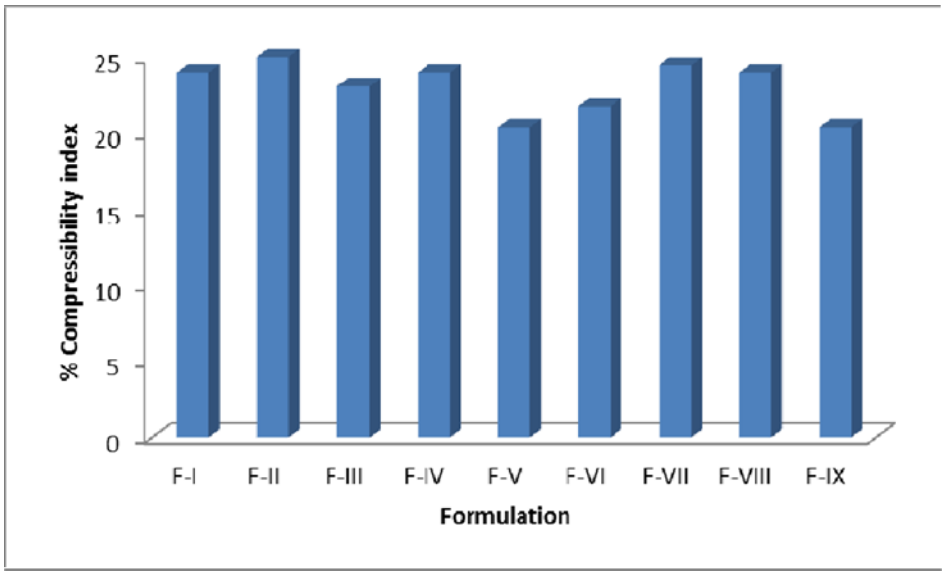
The bulk density of the powder blend of various formulations ranged from 0.3846 g/cm^3 to 0.4347 g/cm^3.

Fig.: Tapped density of powder blend



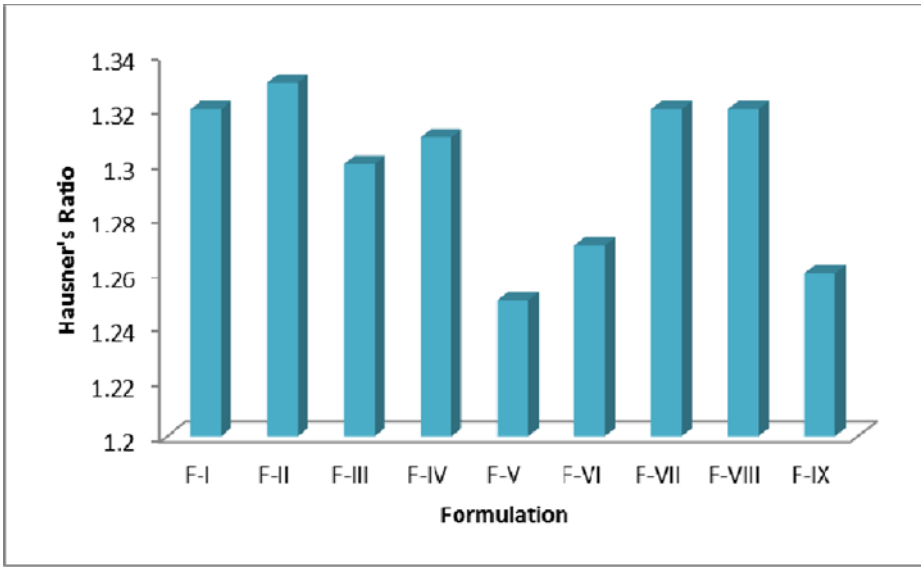
The tapped density of various formulations ranged from 0.5000 g/cm^3 to 0.5556 g/cm^3

Fig. : Compressibility Index of powder blend



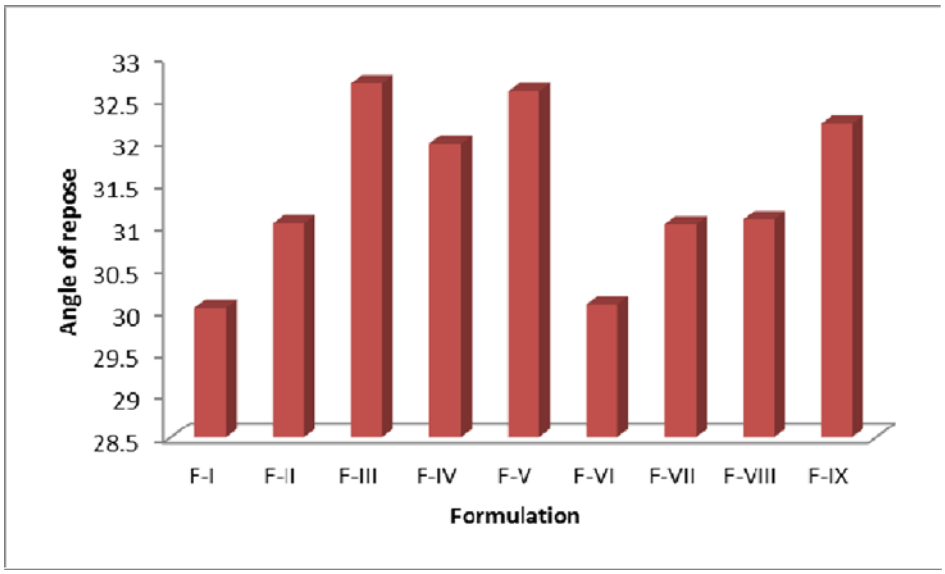
The compressibility index of various formulations ranged from 20.41% to 25.00% showing passable flow property. Hence wet granulation was used.

Fig.: Hausner's ratio of powder blend



The Hausner's ratio of various formulations ranged from 1.26 to 1.33 showing passable flow property.

Fig.: Angle of repose of powder blend



The angle of repose of various formulations ranged from 30º03' to 32º69' showing good flow property.

Evaluation of floating tablets:

1. **Description:**

The tablets were white coloured, round and flat faced with bevel – edged bisect.

2. **Uniformity of Weight:**

The tablets were tested for uniformity of weight and the results are given in Table 9.11

Tab.: Uniformity of Weight of floating tablets

Formulation	Average Weight* (g)
F-I	0.3023±0.0015
F-II	0.3024±0.0053
F-III	0.3022±0.0026
F-IV	0.3034±0.0032
F-V	0.3040±0.0021
F-VI	0.3025±0.0039
F-VII	0.3017±0.0044
F-VIII	0.2952±0.0037
F-IX	0.2995±0.0018

*Mean±SD (n=3)

The weight of the tablets ranged from 0.2952 g to 0.3040 g. The tablets (F-I to F-IX) comply with the uniformity of weight test.[56]

3. **Thickness:**

Thickness of various formulations is given in Table 9.12.

Tab.: Thickness of floating tablets

Formulation	Thickness* (mm)
F-I	4.0±0.012
F-II	4.0±0.015
F-III	4.0±0.014
F-IV	4.0±0.016
F-V	4.0±0.012
F-VI	4.0±0.017
F-VII	4.0±0.004
F-VIII	4.0±0.0181
F-IX	4.0±0.015

*Mean±SD (n=3)

The thickness of the tablets is 4.00 mm. The tablets (F-I to F-IX) have uniform thickness.

4. Diameter:

Diameter of various formulations is shown in Table 9.13.

Tab.: Diameter of floating tablets

Formulations	Diameter* (mm)
F-I	9.5±0.0
F-II	9.5±0.0
F-III	9.5±0.0
F-IV	9.5±0.0
F-V	9.5±0.0
F-VI	9.5±0.0
F-VII	9.5±0.0
F-VIII	9.5±0.0
F-IX	9.5±0.0

*Mean±SD (n=3)

The diameter of the tablets is 9.5 mm. The tablets (F-I to F-IX) have uniform diameter.

5. Hardness:

The hardness of the floating tablets is given in Table 9.14.

Tab. 9.14: Hardness of floating tablets

Formulations	Hardness* (kg/cm^2)
F-I	4.3±0.2236
F-II	4.2±0.2236
F-III	4.0±0.1095
F-IV	4.2±0.1414
F-V	4.1±0.0894
F-VI	4.3±0.2236
F-VII	4.3±0.3536
F-VIII	4.0±0.2739
F-IX	4.3±0.2608

*Mean±SD (n=3)

The hardness of the tablets ranged from 4.0 kg/cm^2 to 4.3 kg/cm^2. The tablets (F-I to F-IX) have sufficient hardness to withstand transport and handling.

6. Friability:

The friability of various formulations is given in Table 9.15.

Tab.: Friability of floating tablets

Formulations	%Friability*
F-I	0.6869±0.032
F-II	0.5500±0.025
F-III	0.5100±0.016
F-IV	0.4012±0.027
F-V	0.4213±0.014
F-VI	0.5001±0.035
F-VII	0.5224±0.022
F-VIII	0.4991±0.011
F-IX	0.6057±0.018

*Mean±SD (n=3)

The percentage friability of various formulations ranged from 0.4012% to 0.6869%. The percentage friability is within the limit.[58]

7. Drug content:

The content of active ingredient in various formulations is given in Table 9.16.

Tab.: Drug content of tablets

Formulations	Drug content* (%w/w)
F-I	97.6±2.3126
F-II	98.1±1.5185
F-III	98.3±1.3809
F-IV	98.7±1.0251
F-V	97.1±1.1638
F-VI	97.2±0.9515
F-VII	107.2±0.6368
F-VIII	96.5±0.3609
F-IX	95.8±0.8991

*Mean±SD (n=5)

The percentage of drug content ranged from 96.32%w/w to 99.22%w/w. All the formulations comply with the official standards.[60]

8. Swelling index

The swelling index of various formulations is given in Table 9.17

Formulations	Swelling index (%)
F-I	151
F-II	165
F-III	178
F-IV	167
F-V	176
F-VI	190
F-VII	175
F-VIII	183
F-IX	190

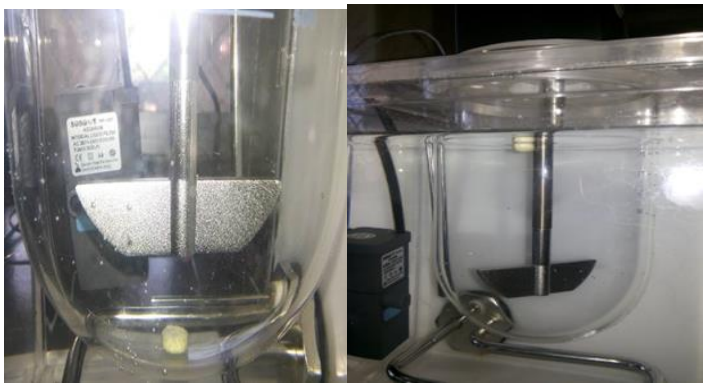


Fig.: floating lag time of tablets

a. At zero second **b. At 2 min 58 sec**

9. Buoyancy lag time and total floating time:

The buoyancy lag time and total floating time of various formulations are given in table

Tab.: Buoyancy lag time of floating tablets

Formulations	Buoyancy lag time (min)	Total floating time (hrs)
F-I	2 min 58 sec	>12
F-II	3 min 0 sec	>12
F-III	2 min 59 sec	>12
F-IV	2 min 51 sec	>12
F-V	2 min 45 sec	>12
F-VI	2 min 50 sec	>12
F-VII	2 min 54 sec	>12
F-VIII	2 min 38 sec	>12

F-IX	2 min 57 sec	>12

10. *In vitro* release study:

The results of *in vitro* release study are shown in Table and fig.

Tab.: *In vitro release study of tablets containing various concentrations of HPMC K4M*

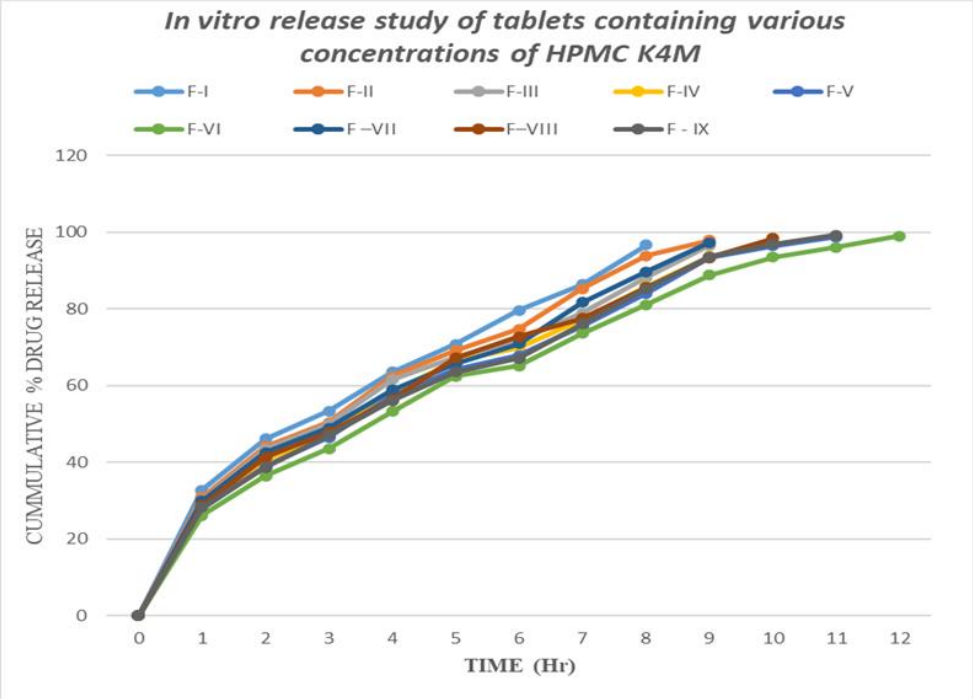
Time in hrs	**Cumulative % drug release**								
	F-I	**F-II**	**F-III**	**F-IV**	**F-V**	**F-VI**	**F –VII**	**F–VIII**	**F - IX**
0	0	0	0	0	0	0	0	0	0
1	32.8	30.9	30.2	28.9	28	26.2	29.9	28.7	28.2
2	46.1	44.2	43.4	40.7	38.9	36.4	42.6	41.3	38.6
3	53.4	50.4	49.9	47.0	46.5	43.5	48.9	47.9	47.1
4	63.6	62.4	61.6	58.3	57.3	53.2	58.9	56.4	56.1
5	70.8	69.2	67.4	66.4	64.3	62.4	65.8	67.2	63.6
6	79.6	74.7	71.9	69.9	67.9	65.2	70.9	72.7	67.1
7	86.4	85.2	78.9	77.3	75.5	73.6	81.7	77.5	76.1
8	96.7	93.8	88.2	85.9	84	81.1	89.7	85.6	85.2
9		97.9	96.5	93.7	93.3	88.8	97.3	93.3	93.6
				97.4	96.4	93.5		98.4	96.9
					98.8	96.1			99.2
						99.0			

Formulation F-I showed 96.7% drug release at the end of 8 hrs. The formulation F-II showed 97.9% drug release at the end of 9 hrs and the formulation F-III showed 96.5% drug release at the end of 9 hrs.

Formulation F-IV showed 97.4% drug release at the end of 10 hrs. The formulation F-V showed 98.8% drug release at the end of 11 hrs and the formulation F-VI showed 99.0% drug release at the end of 12 hrs.

Formulation F-VII showed 97.3% drug release at the end of 9 hrs. The formulation F-VIII showed 98.4% drug release at the end of 10 hrs and the formulation F-IX showed 99.2% drug release at the end of 11 hrs.

Fig.: Cumulative percentage drug release of formulation F-I to F-IX



Tab. 9.22: Release kinetics of the optimized formulation

Time in hrs	% cumulative drug release	%cumulative drug remaining	log %cumulative drug release	Square root of time	Log time	log %cum drug remaining	cube root of %drug remaining
0	0	100	0	0	0	2	4.6415
1	26.2	73.8	1.4183	1	0	1.8680	4.1945
2	36.4	63.6	1.5611	1.4142	0.3010	1.8034	3.9916
3	43.5	56.5	1.6384	1.73205	0.4771	1.7520	3.8372
4	53.2	46.8	1.7259	2	0.6020	1.6702	3.6036
5	62.4	37.6	1.7951	2.2360	0.6989	1.5751	3.3501
6	65.2	34.8	1.8142	2.4494	0.7781	1.5415	3.2648
7	73.6	26.4	1.8668	2.6457	0.8450	1.4216	2.9776
8	81.1	18.9	1.9090	2.8284	0.9030	1.2764	2.6637
9	88.8	11.2	1.9484	3	0.9542	1.0492	2.2373
10	93.5	6.5	1.9708	3.1622	1	0.8129	1.8662
11	96.1	3.9	1.9827	3.3166	1.0413	0.5910	1.574
12	99	1	1.9956	3.4641	1.0791	0	1

Fig: Plot of Zero Order Release Kinetics

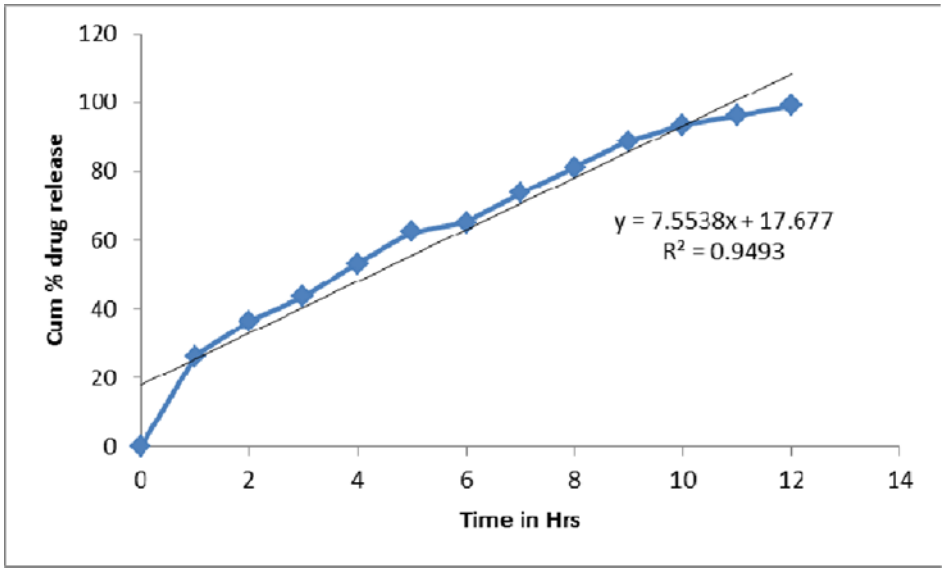


Fig.: Plot of First Order Release Kinetics

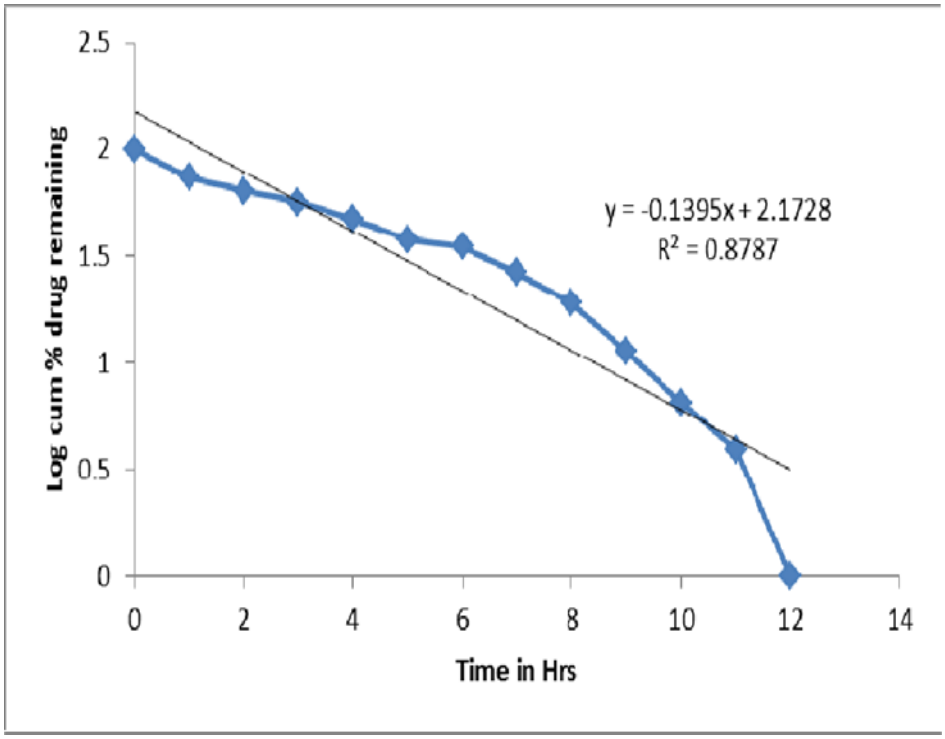


Fig: Plot of Higuchi Kinetics

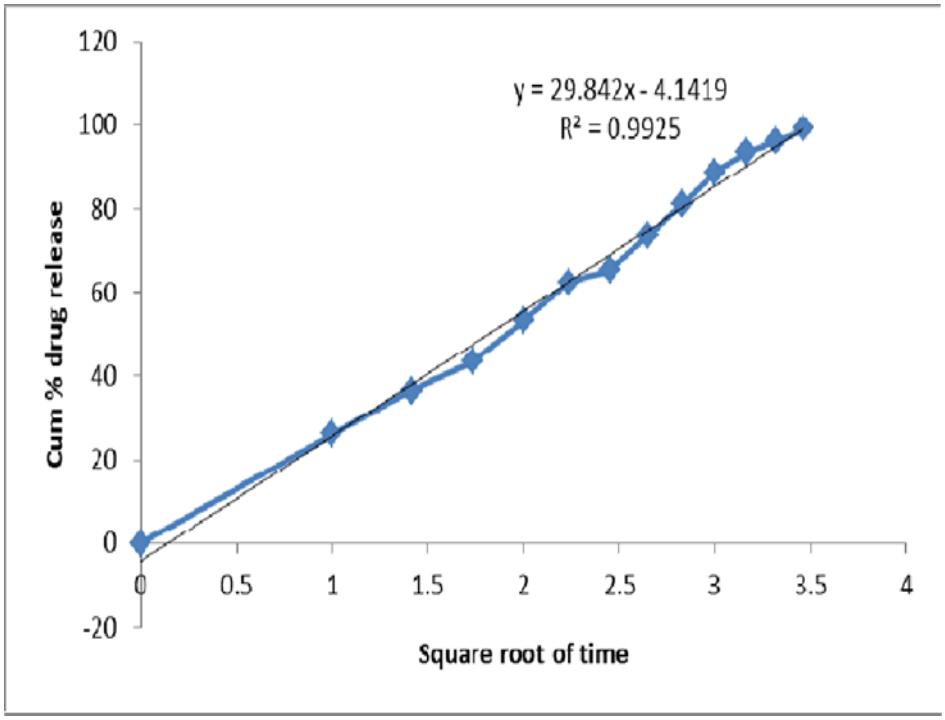


Fig: Plot of Korsemeyer Peppas Kinetics

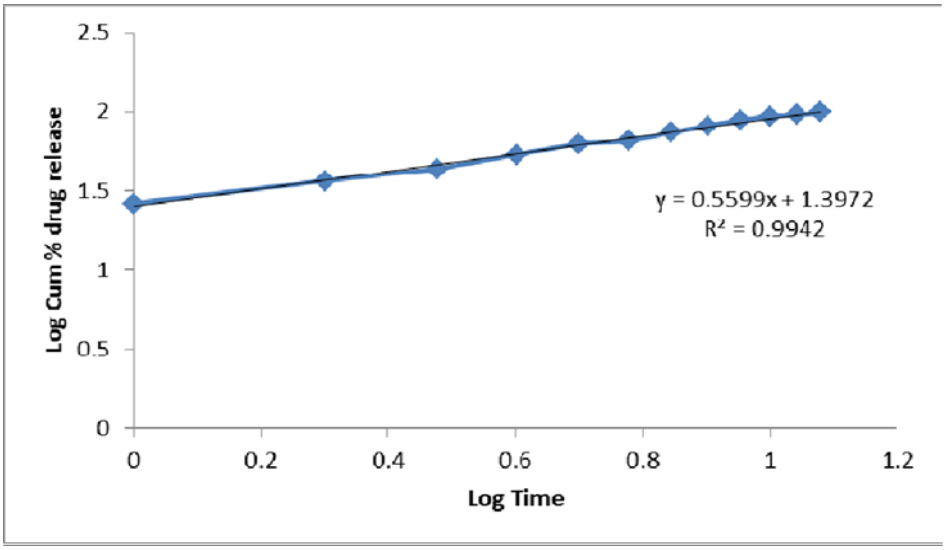
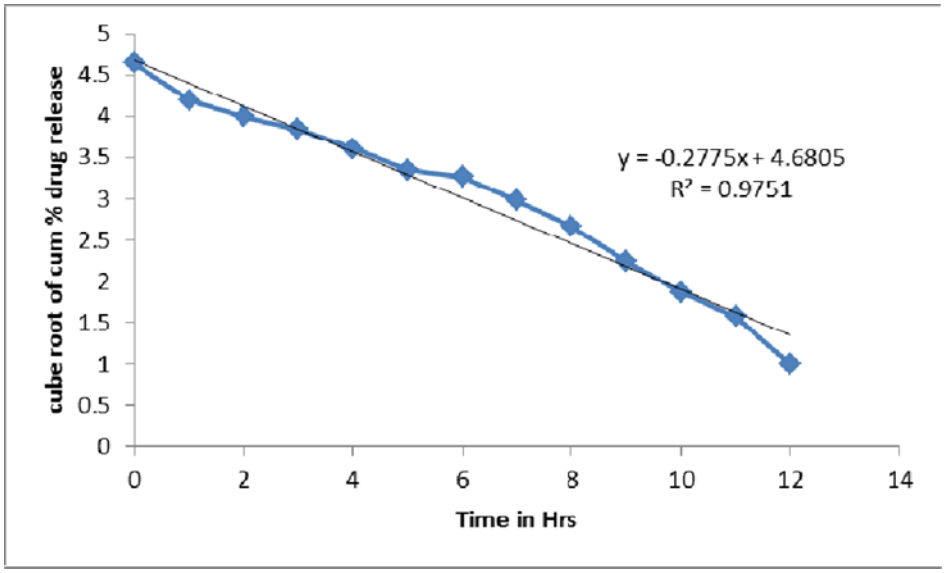


Fig.: Plot of Hixson – Crowell Kinetics



The plot of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2 values of various kinetic models are given in Table 9.23.

Table: R^2 values of various kinetic models

Kinetic model	Coefficient of determination (R^2)
Zero order	0.9493
First order	0.8787
Higuchi	0.9925
Korsmeyer and Peppas	0.9942
Hixson – Crowell	0.9751

Among the various plots, it was clear that Zero order equation showed good linearity (R^2 =0.9493). Therefore in the present study, the *in vitro* release profiles of CIPahistine were best described by Zero order release model followed by Korsemeyer – Peppas kinetics. The diffusion exponent of the solute n is 0.5599. Hence, the mechanism of drug release was found to be Anomalous non fickian transport.

STABILITY STUDIES

The stability study results of optimized formulation is given in table

Tab.: Stability of optimized formulation (F-VI)

S.No	Temperature 40±2ºC and RH 75±5%			
	Parameter	Month 1	Month 2	Month 3
1	Uniformity of weight (g)	0.3025±0.0047	0.3021±0.0024	0.3019±0.0056
2	Thickness (mm)	4.0±0.017	4.0±0.0151	4.0±0.0251
3	Diameter (mm)	9.5±0.0	9.5±0.0000	9.5±0.0000
4	Hardness (kg/cm^2)	4.3±0.2236	4.2±0.1256	4.4±0.2546
5	% friability	0.5001±0.035	0.4985±0.015	0.5142±0.1256

6	Floating lag time	2 min 50 sec	2 min 45 sec	2 min 58 sec
7	Total floating time	>12 hrs	>12 hrs	>12 hrs
8	Drug content (% w/w)	97.2±0.9515	97.4±0.8568	97.0±0.5623
9	*In vitro* drug release at the end of 12 hrs (% w/w)	98.0 ± 0.4622	97.9±0.5642	98.4±0.2315

From the above results, it is observed that the optimized formulation maintains the stability for 3 months.

SUMMARY AND CONCLUSION

The Ciprofloxacin was successfully formulated into controlled release floating tablets using various grades of matrix-forming polymer such as HPMC K4M, HPMC K100M and its combination by wet granulation method.

➢ Preformulation studies were performed for powder blends.

➢ Physical compatibility study showed that the drug and excipients are physically compatible with each other.

➢ Chemical compatibility study was performed using FTIR spectroscopy and FTIR studies revealed that there was no change in major peaks thus confirming no interaction between the drug and excipients.

➢ Ciprofloxacin powder blend had passable flow property which was substantiated by bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. Hence, the floating tablets of Ciprofloxacin were prepared by wet granulation method.

➢ The post compression parameters of tablets were evaluated and the results were found to comply within limit.

➢ The buoyancy lag time of all formulations were less than 3 min.

➢ The total floating time of all formulations were more than 12 hrs.

➢ The in vitro release studies were performed for all the formulations. Formulation F-VI containing 60% of HPMC K 100 M released 99.0% at the end of 12 hrs. Therefore, F- VI was chosen as the optimized formulation.

➢ The dissolution data of the optimized formulation were fitted to various kinetic models and the formulation F-VI fitted best to Zero order release kinetics. The mechanism of drug release was found to be diffusion, dissolution and swelling.

From the overall results, it is clear that the formulation F-VI containing 60% of HPMC K 100 M is the optimal formulation among the other formulations, as it produced controlled drug release than other formulations.

CONCLUSION

➢ The floating tablets of Ciprofloxacin may be useful over conventional system for effective treatment of vertigo in Meniere's disease.

➢ The floating tablets of Ciprofloxacin may be administered twice daily instead of four times a day.

FUTURE SCOPE

- Long term Stability studies for the optimized formulation as per the current ICH guidelines.
- Pharmacokinetic and toxicity study.
- Scale up studies for the optimized formulation. of ciprofloxacin sustained release dosage form.

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CONFLICT OF INTEREST: NIL

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