FORMULATION AND EVALUATION OF MODIFIED RELEASE MATRIX TABLET OF A MODEL ANTIBIOTIC

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ABSTRACT-The purpose of the investigation was Formulation and Evaluation of Modified release matrix tablet of Model antibiotic, for which Bioequivalence will be proved with reference product and a better bioavailability, may be expected than reference product. Drug polymer compatibility was studied by Physical observation and FTIR study. The drug and polymer in the optimized formulation was found to be compatible. Model tablet was prepared by Direct compression method.750mg of Model drug was taken in a single tablet of 1200mg.The evaluation parameter such as Weight variation, Thickness, Hardness, Friability, Drug content uniformity, In-vitro drug release studies in different dissolution medias i.e., 0.1 N HCL, 0.01 N HCL,4.5 AB,6.8 PB, stability testing of matrix tablets using ICH accelerated stability conditions were performed. The results were within the limit. From the release profile, F7 was selected to be the best formulation as it showed complete and most comparable release with respect to reference product. The order of release was zero order, mechanism of release was diffusion controlled and exponent of release was Non- fickian type diffusion controlled.

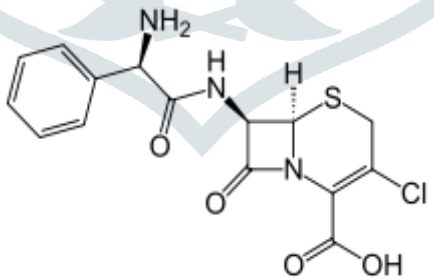
Key words **–Modified release, Matrix tablet, Antibiotic, Non-fickian**

INTRODUCTION

The present research work aims to develop a stable Modified Release Hydrophilic Matrix tablet of Model drug X, a second generation antibiotic, for which Bioequivalence will be proved with reference product and a better bioavailability may be expected than reference product. It focuses in development of patent non infringing Hydrophilic Matrix tablet. **S**ince the dawn of modern medicine, researchers have continually searched for new and improved ways to administer medicinal products. Although conventional oral formulations are still the most widely administered dosage forms, they are improved today by many different controlled-release technologies, including delayed-onset and extended/sustained-release formulations. No doubt many new different types of delivery systems entered to the market and created a large impact on patient's compliance and convenience.Still the Oral ingestion has been the most commonly employed route of drug delivery and a major area of research now a days.Over the years, greater attention has been focused on the development of modified release dosage forms.

Drug Profile

API Specification Model Drug is a Semi-synthetic, broad-spectrum second-generation cephalosporin antibiotic used to treat certain infections caused by bacteria such as pneumonia lung, skin, throat, and urinary tract infections.



(Chemical structure of Second Generation Cephalosporin)

Formulation Table

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Model Drug*	787.81	787.81	787.81	787.81	787.81	787.81	787.81	787.81
Lactose Monohydrate	50.19	50.19	50.19	50.19	50.19	50.19	50.19	50.19
HPMC K4M	20	20	20	15	15	15	12	12
HPC-M	50	40	35	35	30	25	25	25
HPMC E5	272	282	287	292	297	302	305	305
Magnesium Stearate	10	10	10	10	10	10	10	10
Talc	6	6	6	6	6	6	6	6
Aerosil 200	4	4	4	4	4	4	4	4
Total Weight	1200	1200	1200	1200	1200	1200	1200	1200

Table 1 (Formulation table)

METHODOLOGY

Drug polymer compatibility study

Physical Observation

FTIR study

Evaluation of precompression parameters

Bulk Density (B.D.) = Mass of Powder M (gms)/ Apparent Volume V_0 (ml)

Tap Density (T.D.) = Mass of Powder M (gms)/ Tapped Volume V_f (ml

Hausner's Ratio = Tap Density (T.D.) / Bulk Density (B.D.)

Angle of Repose $\theta = \tan^{-1}$ (H/R)

Analytical studies

Determination of λmax of drug X

Construction of calibration curve of drug X

Formulation design

Direct compression method, Dry granulation method, Wet granulation method

Evaluation of matrix tablets

Thickness, Weight Variation Test, Drug Content, Hardness, Friability

Data Analysis (Curve Fitting Analysis):

- To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:
- Cumulative percentage drug released Vs Time (In-Vitro drug release plots)
- Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
- Log cumulative percentage drug remaining Vs Time (First order plots)
- Log percentage drug released Vs Log time (Peppas plots)

Stability studies

In order to assess the stability of drug product, accelerated stability studies were conducted for the selected batch F_7. The development batch were packed in blister pack and kept for stability at 40°C ±2 °C/75% RH ±5% for 3 months.

Storage Condition	Duration
40°C ±2 °C/75% RH ±5%	1, 3, 6 Months
30°C ±2 °C/65% RH ±5%	1, 3, 6 Months
25°C ±2 °C/60% RH ±5%	1, 3, 6 Months

RESULT AND DISCUSSIONS

Evaluation of pre-compression parameter

Angle of repose tells about the flow ability of the blend. It is one of the important parameter in tablet manufacturing. In the present investigation angle of repose was found to be highest f or F_4 and lowest for F_6. F_7 has angle of repose 25.78 which indicates good flow.

Formulations	Angle of repose (θ)	Compressibility Index (%)	Bulk density	Tapped density
F_1	**24.30**	**25.48**	**0.54**	**0.72**
F_2	**26.77**	**26.10**	**0.52**	**0.71**
F_3	**25.28**	**23.98**	**0.53**	**0.73**
F_4	**28.31**	**24.38**	**0.55**	**0.73**
F_5	**24.51**	**25.65**	**0.54**	**0.72**
F_6	**23.89**	**27.14**	**0.51**	**0.70**
F_7	**25.78**	**24.66**	**0.55**	**0.73**

(Table 2.Evaluation of Pre compression parameter)

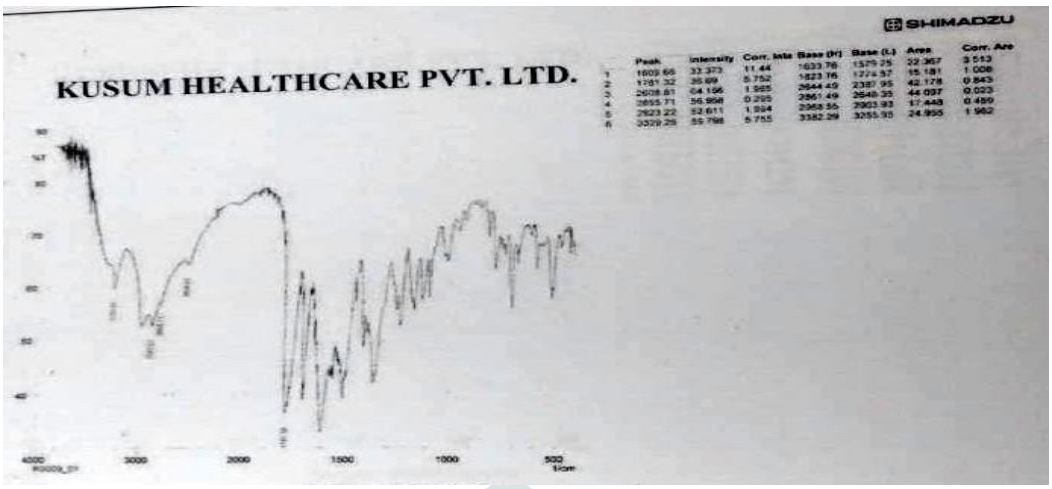
Physical Observation

Samples were observed for four weeks and any change with reference to the control sample was recorded. No appreciable changes were observed during the study. From this it was predicted that there was no physical interaction between drug, polymers and excipients.

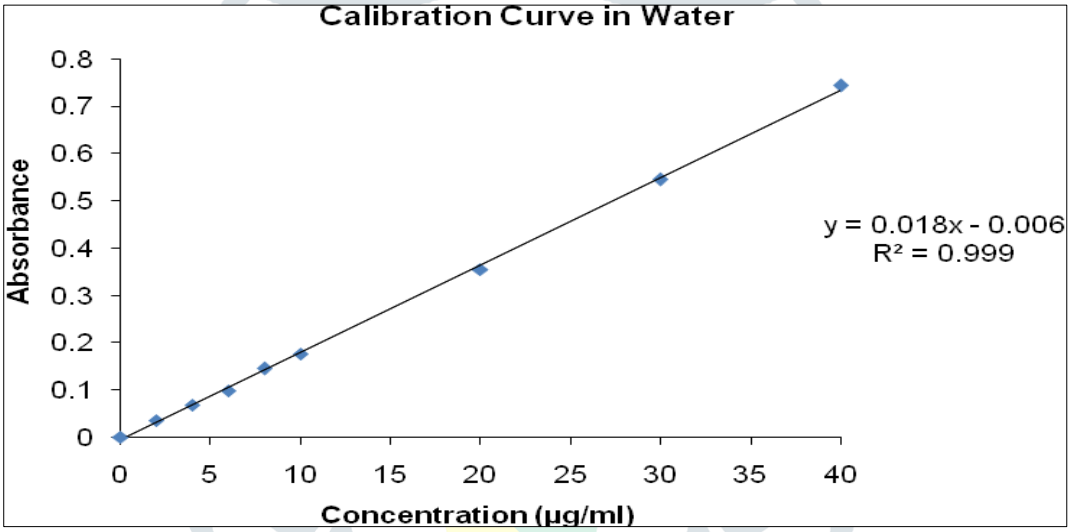
FTIR STUDY

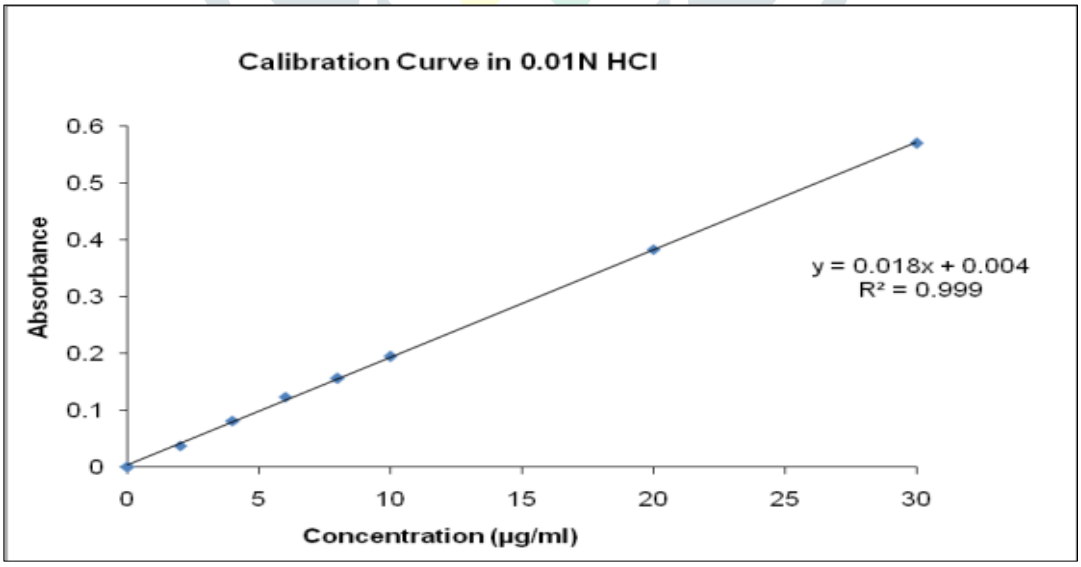
The Fourier transform infrared (FTIR) spectroscopy study of drug X, different polymers and the combination of drug – polymers was carried out with SHIMADZU 8400S FTIR spectrophotometer. The pure drug was dispersed with KBr in the ratio of approximately 1:100. It was then placed in the sample holder, scanned and FTIR spectra were obtained. Similarly the FTIR spectra

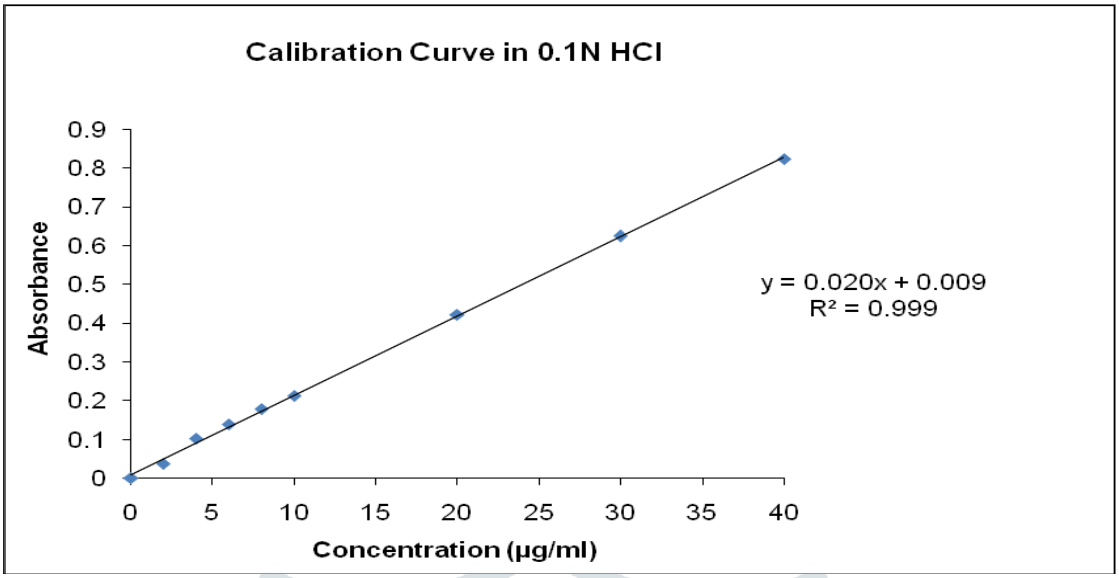
of polymer as well as the drug – polymer combinations were obtained. From the obtained FTIR spectra the drug polymer interaction was studied.

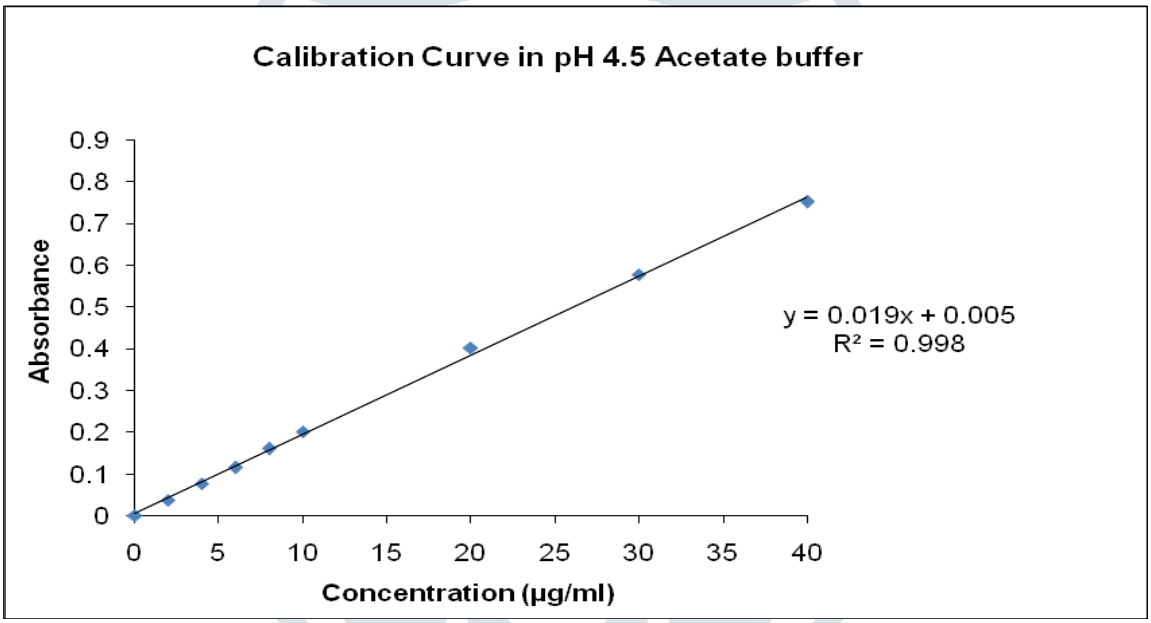


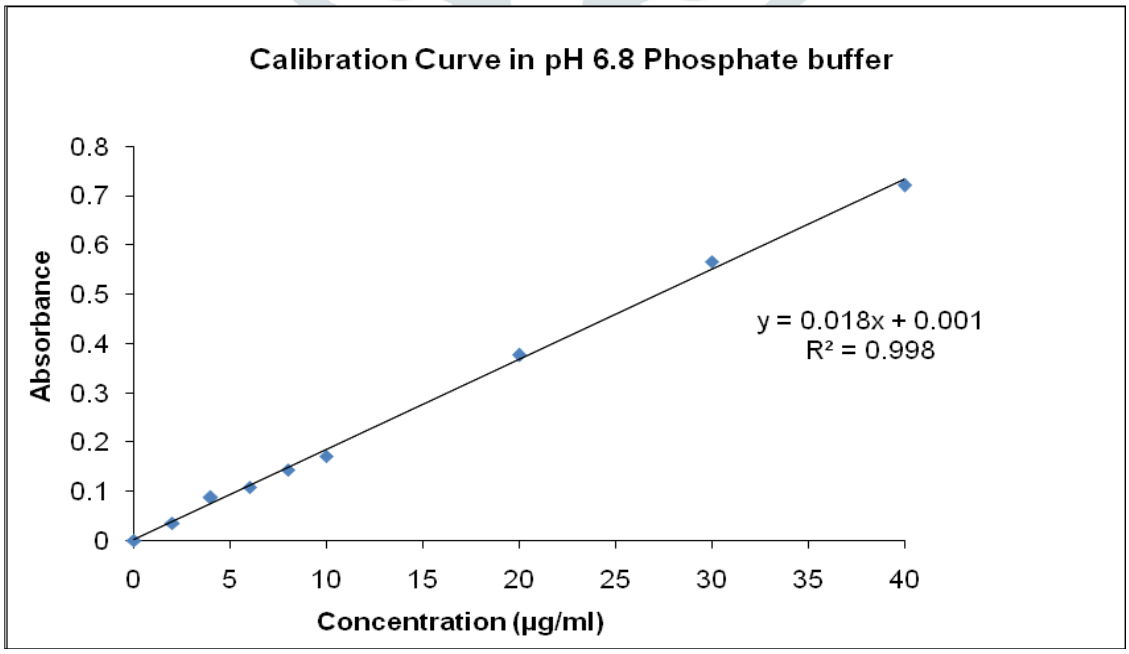
Standard Calibration Curve





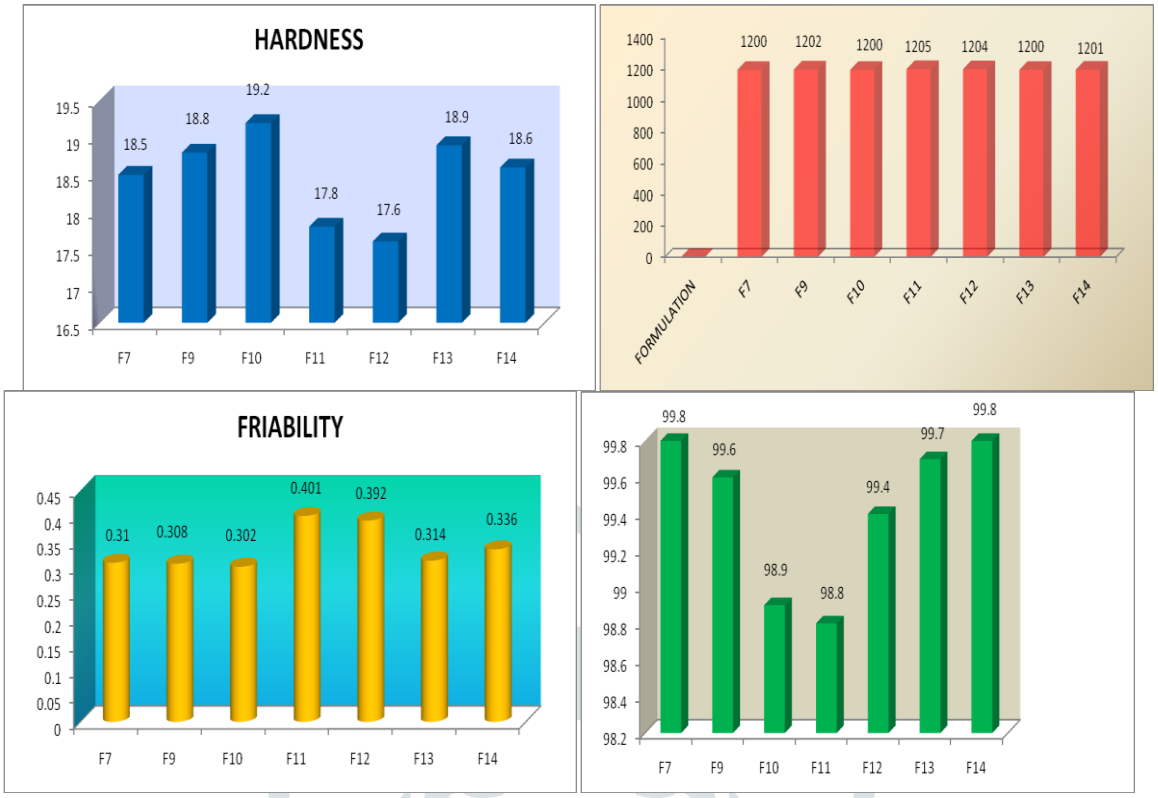






(Fig 1. Standard Calibration Curve)

Evaluation of Matrix Tablet

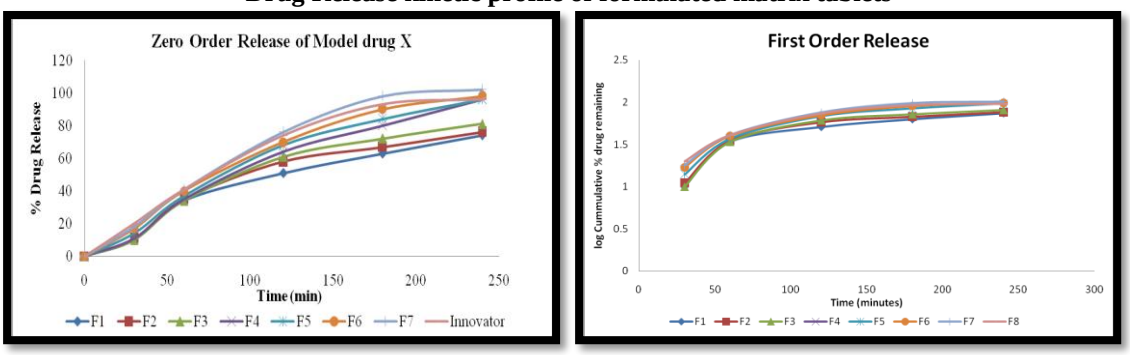


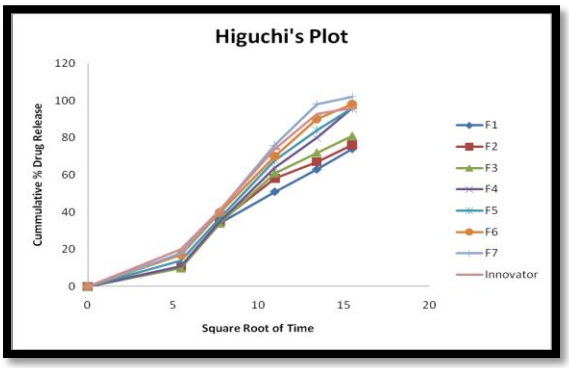
(Fig 2.Graphical analysis of Evaluation Parameters)

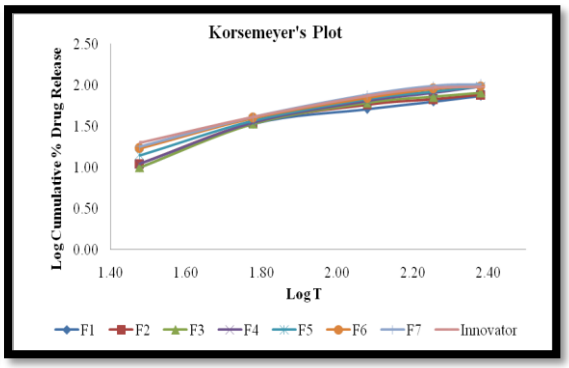
Formulations	Weight variation (mg)	Hardness (kg /cm^2)	Friability (%)	Drug content uniformity (%)
F_7	1200	18.5	0.310	99.8
F_9	1202	18.8	0.308	99.6
F_{10}	1200	19.2	0.302	98.9
F_{11}	1205	17.8	0.401	98.8
F_{12}	1204	17.6	0.392	99.4
F_{13}	1200	18.9	0.314	99.7
F_{14}	1201	18.6	0.336	99.8

(Table 3.Evaluation of Matrix Tablet)

Drug Release kinetic profile of formulated matrix tablets







Formulation	Order of Release		Higuchi	Release Exponent
	Zero order	First order		
F_1	0.941	0.658	0.958	0.916
F_2	0.920	0.646	0.954	0.895
F_3	0.931	0.669	0.947	0.978
F_4	0.967	0.661	0.948	1.012
F_5	0.954	0.656	0.956	0.916
F_6	0.947	0.631	0.963	0.854
F_7	0.935	0.629	0.955	0.853
Innovator	0.924	0.606	0.962	0.777

(Table 4. Drug release Kinetic)

STABILITY TESTING OF MATRIX TABLETS USING ICH ACCELERATED STABILITY CONDITIONS

Tests	Observation				
	40°C/75%RH				
	Initial		1 M	2 M	3 M
1. Description	Capsule shaped biconvex blue colored film coated tablet		No change observed	No change observed	No change observed
2. Assay (%)	793.46		759.2	752.5	739.8
3. Water by KF	4.622		4.844	5.22	5.356
4. Hardness(Kp)	17- 19		17- 19		
5. % Drug Release Dissolution Parameters: Water, 900mL, USP Apparatus 1, 100 rpm	Time (Min)	Initial	% Drug release		
	30	18	17	19	20
	60	41	39	40	44
	120	74	70	71	75
	180	87	84	87	88
	240	99	96	96	98

CONCLUSION

The purpose of the investigation was to develop and evaluate the modified release matrix tablets of model antibiotic to achieve better therapeutic effect. Drug polymer compatibility was studied by FTIR and visual study. The drug and polymer in the optimized formulation was found to be compatible. Modified release Matrix tablets were successfully prepared by direct compression method. The precompression parameters such as compressibility index, bulk and tapped density, angle of repose were calculated. Different tablet evaluations such as drug content, weight uniformity, hardness, thickness, and friability of the prepared matrix tablet were carried out. The results were found satisfactory. Formulation F_7 was selected to be the best formulation as it showed complete and most comparable release with respect to reference product. The order of release is found to be zero order and mechanism of release is found to be Non-Fickian diffusion. The selected batch was kept in accelerated stability showed satisfactory physical stability at 40 C and 75% RH respectively .No appreciable changes were found in any of the formulations. In vivo study is the future scope of this investigation.

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