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FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF AZILSARTAN USING DIFFERENT POLYMERS

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Abstract:

The objective of the present work was to Formulate and evaluate of extended release tablets of Azilsartan by using different polymers like HPMC K100M ,Ethyl cellulose and Xanthan gum with different ratios by using direct compression method. Azilsartan is used alone or together with other medicines to treat high blood pressure (hypertension). The tablets were formulated to reduce the frequency of dose admimistration and to improve the patient compliance. The FTIR studies indicates there is no interaction between drug and polymer for optimized formulation. The pre compression and post compression parameters are with in the IP limits. The in vitro dissolution study was done for 12hrs Among all the formulations A6 formulation was shows good drug release of 99.87%. The optimized formulation were fitted to zero order, First order, higuchi release model and korsmeyer –peppas model based on the regression coefficient.

Keywords: *Azilsartan, HPMC K100M ,Ethyl cellulose and Xanthan Extended release tablets.*

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INTRODUCTION:

Extended release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.

The first Extended release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida.

Extended release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

The goal in designing Extended or Extended delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, Extended release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.

Extended release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is Extended on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as Extended release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of Extended release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of Extended release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the Extended release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

RATIONALE FOR EXTENDED RELEASE DOSAGE FORMS:

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose . However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional

forms that may have to be taken three or four times daily to achieve the same therapeutic effect.

The Extended plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

Drawbacks of Conventional Dosage Forms:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

TERMINOLOGY:

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release
B) Extended release
- ✓ Controlled release
- ✓ Extended release

C) Site specific targeting
D) Receptor targeting

A) Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Extended release:

During the last two decades there has been remarkable increase in interest in Extended release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of Extended release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

1. Controlled Release:

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

2. Extended Release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

C) Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be Extended drug delivery systems.

MATERIALS AND METHODS:

AZILSARTAN Procured from Qualitek pharma., Provided by SURA LABS, Dilsukhnagar, HPMC K100M from Merck Specialities Pvt Ltd, Mumbai, India, Ethyl cellulose Merck Specialities Pvt Ltd, Mumbai, India, Xanthan gum Merck Specialities Pvt Ltd, Mumbai, India, PVP Merck Specialities Pvt Ltd, Mumbai, India, Talc Merck Specialities Pvt Ltd, Mumbai, India, Magnesium stearate Merck Specialities Pvt Ltd, Mumbai, India, MCC Merck Specialities Pvt Ltd, Mumbai, India.

Analytical method development:

a) Determination of absorption maxima:

100mg of Azilsartan pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100 ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Azilsartan pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 0.2, 0.4, 0.6, 0.8and 1 ml of solution and make up to 10ml with 0.1N Hcl to obtain 2, 4, 6, 8and 10µg/ml of Azilsartan per ml of solution. The absorbance of the

above dilutions was measured at 247 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a bruker FTIR facility.

Formulation development of Extended release Tablets:

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Azilsartan.

Procedure:

1) Azilsartan and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table: Formulation of Extended release tablets

RESULT AND DISCUSSION

INGREDIANTS	A1	A2	A3	A4	A5	A6	A7	A8	A9
Azilsartan	40	40	40	40	40	40	40	40	40
HPMC K100M	20	40	60	-	-	-	-	-	-
Ethyl cellulose	-	-	-	20	40	60	-	-	-
Xanthan gum	-	-	-	-	-	-	20	40	60
PVP	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
MCC	70	50	30	70	50	30	70	50	30
Total weight	150	150	150	150	150	150	150	150	150

The present work was designed to developing Sustained tablets of Azilsartan using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Azilsartan in 0.1N HCl:

The scanning of the 10µg/ml solution of Azilsartan in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 247nm. The standard concentrations of Azilsartan (2-10µg/mL) prepared in 0.1N HCl showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table: Standard curve of Azilsartan in 0.1N HCl

Concentration (µg/ mL)	Absorbance
0	0
2	0.109
4	0.232
6	0.351
8	0.478
10	0.613

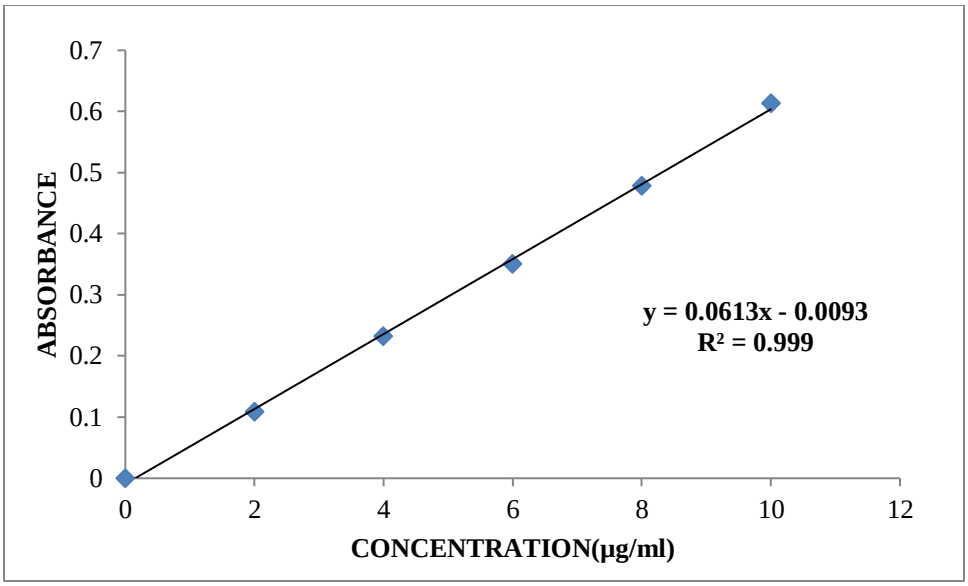

Fig: Calibration curve of Azilsartan in 0.1 N HCl at 247 nm

Standard Curve of Azilsartan in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Azilsartan in the ultraviolet range (200-400nm) against 6.8 pH phosphate buffer as blank gave the λ_{max} as 247nm. The standard concentrations of Azilsartan (2-10µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table : Standard curve of Azilsartan in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
2	0.157
4	0.302
6	0.452
8	0.601
10	0.745

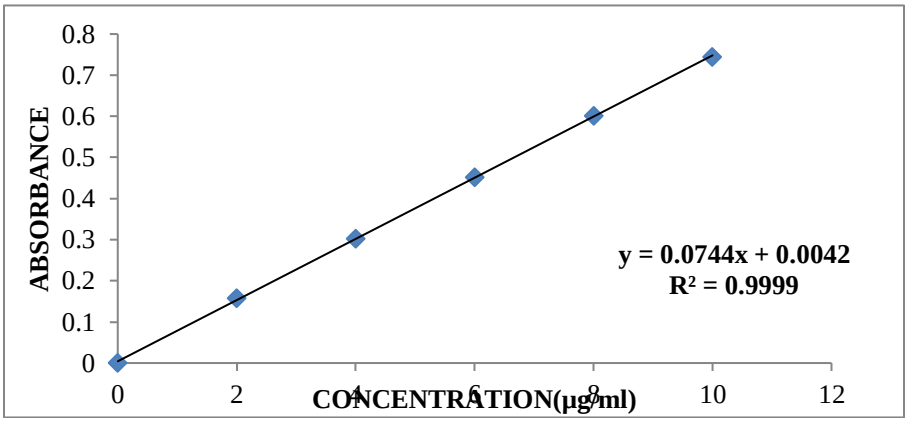

Fig: Calibration of Azilsartan in Phosphate buffer pH 6.8

Preformulation parameters of powder blend

Table : Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)	Hausner's Ratio
A1	25.25 ±0.52	0.43 ±0.022	0.61 ±0.033	11.20 ±0.03	1.10 ±0.06
A2	26.43 ±0.62	0.55± 0.08	0.64 ± 0.022	10.21 ± 0.12	1.12 ± 0.056
A3	28.38 ± 0.56	0.47 ± 0.08	0.54 ± 0.01	12.96 ± 0.42	1.14 ± 0.031
A4	27.26 ± 0.56	0.52 ± 0.055	0.59 ± 0.08	11.86 ± 0.57	1.13 ± 0.026
A5	25.46 ± 0.57	0.55 ± 0.08	0.62 ± 0.011	11.29 ± 0.57	1.12 ± 0.015
A6	27.61 ± 0.63	0.53 ± 0.09	0.61 ± 0.071	13.1 ± 0.15	1.15 ± 0.021
A7	24.15 ± 0.58	0.49 ± 0.01	0.56 ± 0.08	12.5 ± 0.21	1.14 ± 0.012
A8	26.08 ± 0.51	0.55 ± 0.011	0.62 ± 0.06	11.29 ± 0.35	1.12 ± 0.023
A9	25.41 ±0.65	0.52 ±0.091	0.59 ±0.064	14.33 ±0.21	1.19 ±0.022

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 24.15 ± 0.58 to 28.38 ± 0.56; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43 ±0.022 to 0.55 ± 0.011gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 ± 0.01 to 0.64 ± 0.022 the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 10.21 ± 0.12 to 14.33 ±0.21which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Post Compression Parameters For tablets

Table: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
A1	151.81	2.84	0.56	1.72	99.36
A2	149.37	2.63	0.43	1.98	98.85
A3	148.92	2.88	0.51	1.63	97.47
A4	149.34	2.72	0.48	1.77	99.69
A5	148.27	2.61	0.38	1.83	98.37
A6	150.48	2.73	0.44	1.56	99.22
A7	152.68	2.91	0.52	1.67	98.31
A8	149.84	2.56	0.38	1.93	98.12
A9	150.32	2.66	0.49	1.88	97.08

***In Vitro* Drug Release Studies**

The formulations prepared with different natural polymers by wet granulation method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table: Dissolution Data of Azilsartan Tablets Prepared With HPMC K100M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	A1	A2	A3
0	0	0	0
0.5	9.14	11.57	14.94
1	13.15	17.39	23.67
2	17.84	23.12	37.28
3	20.65	29.82	42.31
4	23.58	37.65	49.57
5	25.87	43.55	53.64
6	28.67	49.87	59.32
7	31.95	59.31	64.12
8	36.87	62.99	73.45
9	47.88	69.39	76.38
10	52.45	75.84	80.87
11	58.22	80.55	88.39
12	75.57	85.88	91.14

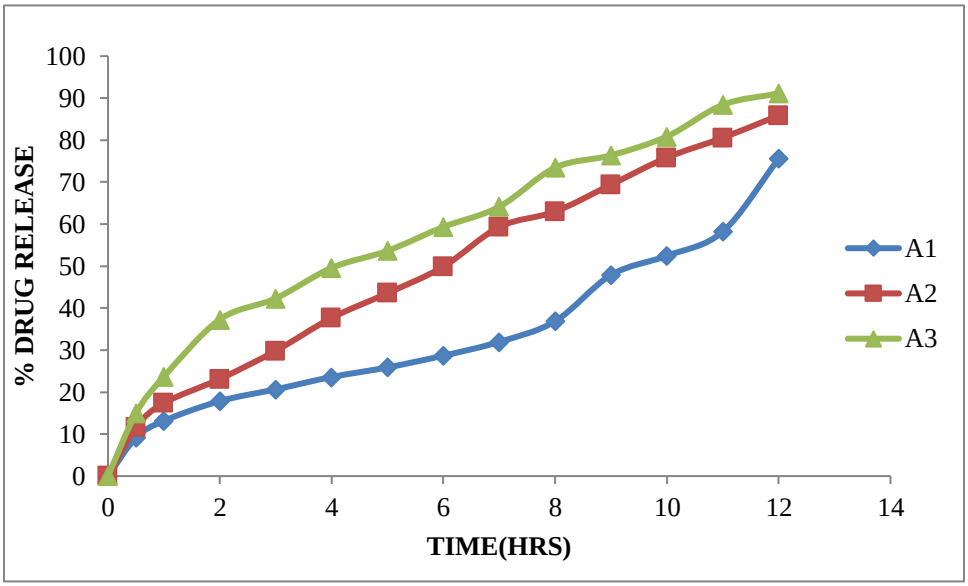

Figure : Dissolution study of Azilsartan Extended tablets (A1 to A3)

Table: Dissolution Data of Azilsartan Tablets Prepared With Ethyl cellulose in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	A4	A5	A6
0	0	0	0
0.5	16.65	22.15	19.61
1	25.85	28.91	27.74
2	36.55	38.87	36.51
3	46.14	47.91	45.35
4	55.48	55.14	52.47
5	68.62	64.56	59.84
6	74.32	63.11	63.61
7	78.21	68.38	69.87
8	79.92	72.87	74.11
9	85.10	80.54	85.80
10	98.26	85.64	89.39
11	92.36	90.39	95.68
12	94.61	93.49	99.87

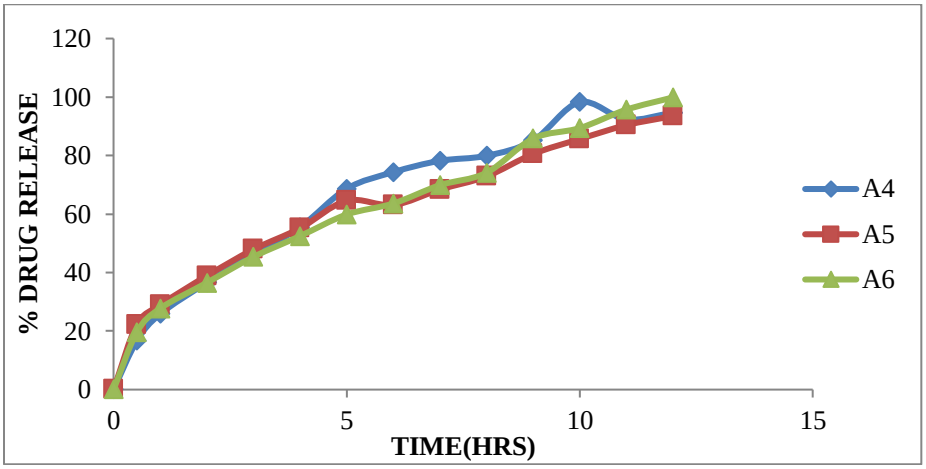

Figure : Dissolution study of Azilsartan tablets (A4 to A6)

Table: Dissolution Data of Azilsartan Tablets Prepared With Xanthan gum in Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	A7	A8	A9
0	0	0	0
0.5	16.59	15.41	12.34
1	25.11	20.22	15.69
2	33.65	26.69	22.78
3	42.54	34.95	28.34
4	45.16	41.32	35.22
5	51.39	47.29	44.95
6	55.16	55.64	51.78
7	61.31	60.65	57.61
8	66.87	65.96	62.28
9	78.91	71.58	68.32
10	81.74	75.32	71.62
11	86.12	81.99	83.83
12	89.58	84.15	87.25

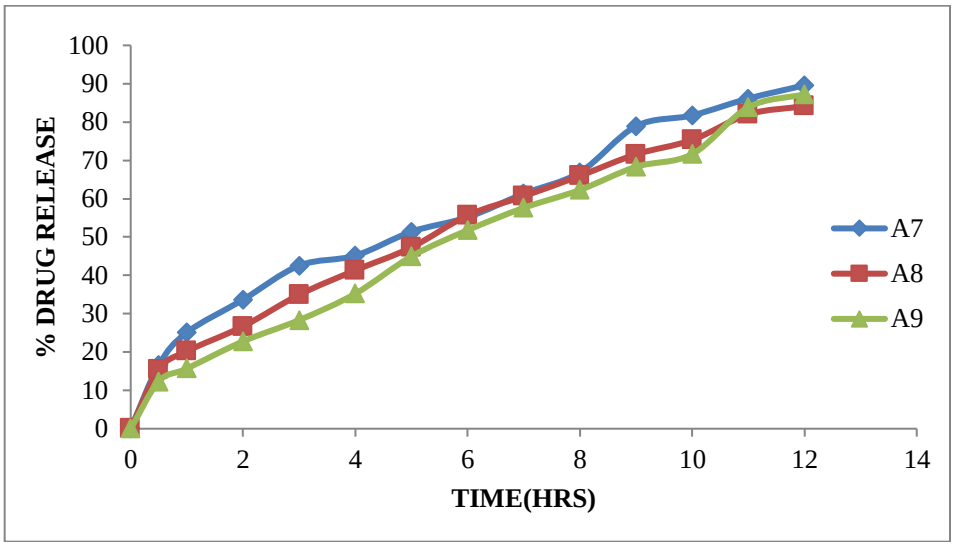

Figure : Dissolution study of Azilsartan tablets (A7 to A9)

From the dissolution data it was evident that the formulations prepared with HPMC K100M as polymer were retarded the drug release for12 hours.

Whereas the formulations prepared with higher concentration of Ethyl cellulose retarded the drug release up to 12 hours in the concentration 60mg. In lower concentrations the polymer was unable to retard the drug release.

The formulations prepared with Xanthan gum showed very less retardation capacity hence they were not considered.

Hence from the above dissolution data it was concluded that A6formulation was considered as optimized formulation because good drug release (99.87%) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Azilsartan release from Extended tablets. The data was fitted into various kinetic models such as Zero, First order kinetics; Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table

Table : Release kinetics data for optimized formulation (A6)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.61	0.5	0.707	1.292	-0.301	1.905	39.220	0.0510	-0.708	80.39	4.642	4.316	0.326
27.74	1	1.000	1.443	0.000	1.859	27.740	0.0360	-0.557	72.26	4.642	4.165	0.476
36.51	2	1.414	1.562	0.301	1.803	18.255	0.0274	-0.438	63.49	4.642	3.989	0.652
45.35	3	1.732	1.657	0.477	1.738	15.117	0.0221	-0.343	54.65	4.642	3.795	0.847
52.47	4	2.000	1.720	0.602	1.677	13.118	0.0191	-0.280	47.53	4.642	3.622	1.019
59.84	5	2.236	1.777	0.699	1.604	11.968	0.0167	-0.223	40.16	4.642	3.425	1.217
63.61	6	2.449	1.804	0.778	1.561	10.602	0.0157	-0.196	36.39	4.642	3.314	1.328
69.87	7	2.646	1.844	0.845	1.479	9.981	0.0143	-0.156	30.13	4.642	3.112	1.530
74.11	8	2.828	1.870	0.903	1.413	9.264	0.0135	-0.130	25.89	4.642	2.958	1.683
85.8	9	3.000	1.933	0.954	1.152	9.533	0.0117	-0.067	14.2	4.642	2.422	2.220
89.39	10	3.162	1.951	1.000	1.026	8.939	0.0112	-0.049	10.61	4.642	2.197	2.444
95.68	11	3.317	1.981	1.041	0.635	8.698	0.0105	-0.019	4.32	4.642	1.629	3.013
99.87	12	3.464	1.999	1.079	-0.886	8.323	0.0100	-0.001	0.13	4.642	0.507	4.135

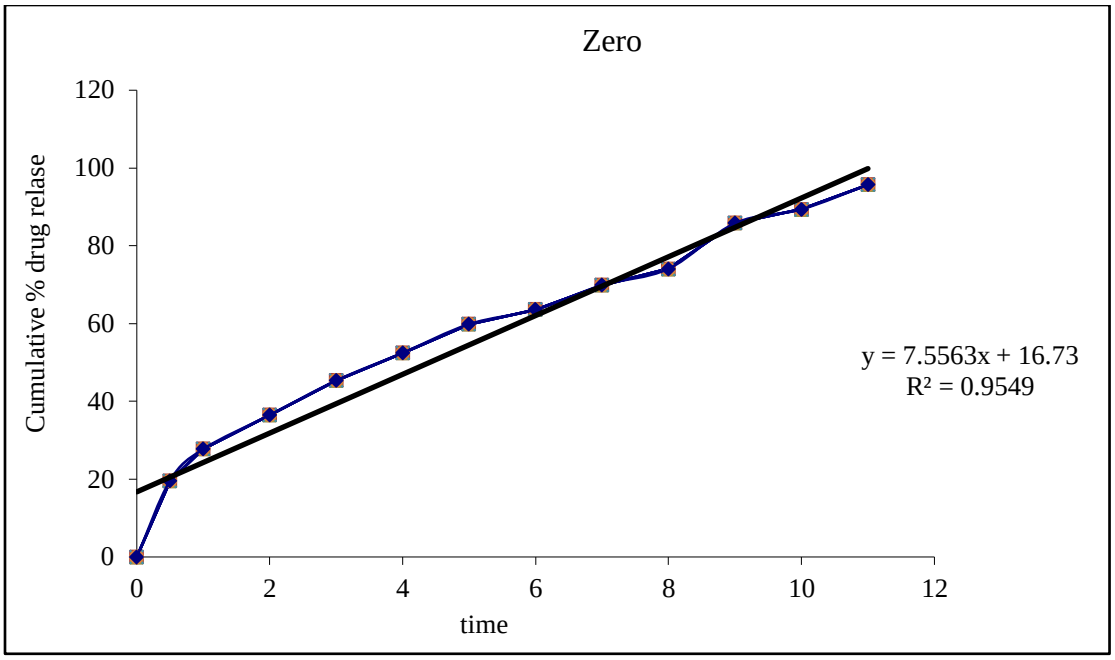

Figure : Graph of zero order kinetics

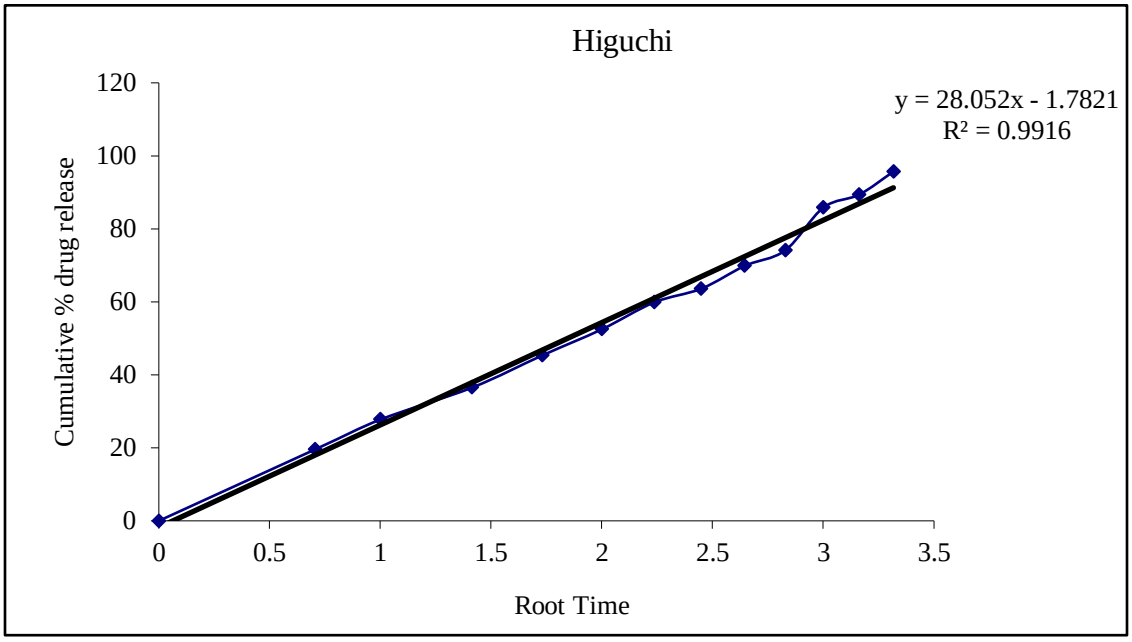

Figure : Graph of Higuchi release kinetics

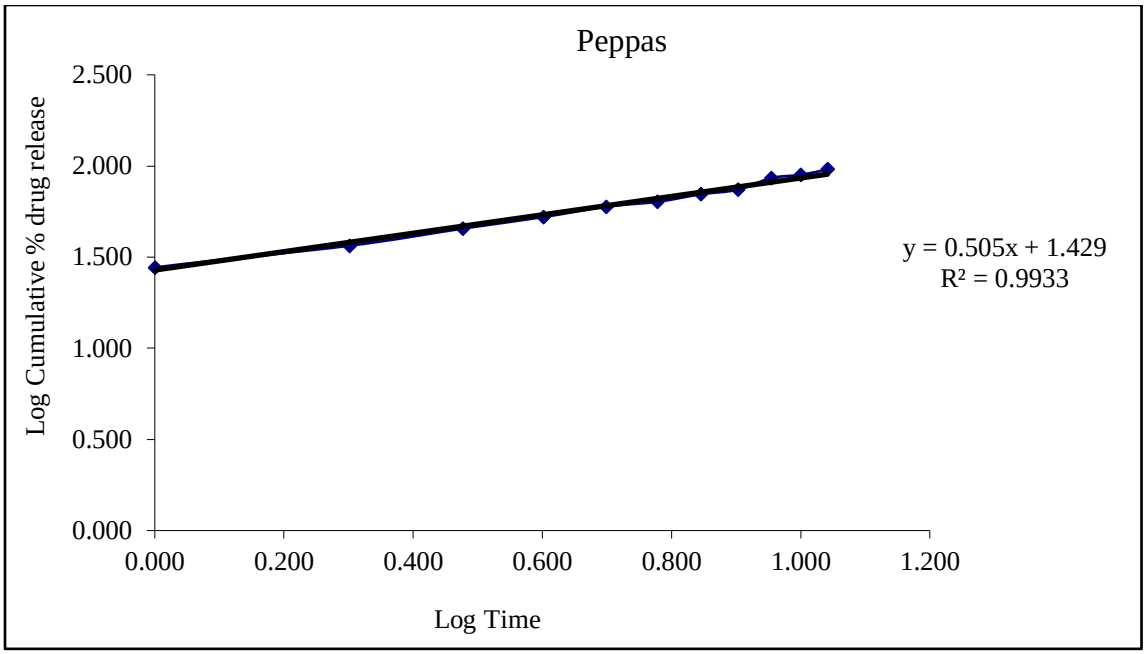

Figure : Graph of peppas release kinetics

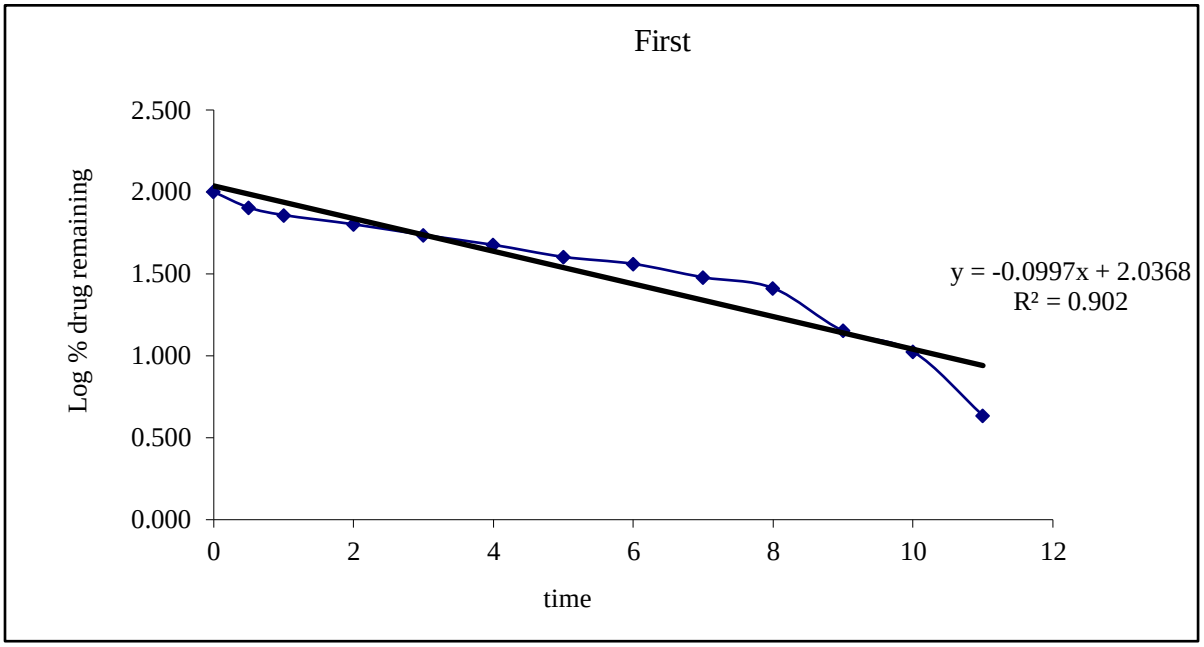

Figure: Graph of first order release kinetics

Optimised formulation A6was kept for release kinetic studies. From the above graphs it was evident that the formulation A6was followed Zero order release mechanism.

Drug and Excipient Compatability Studies

FTIR study

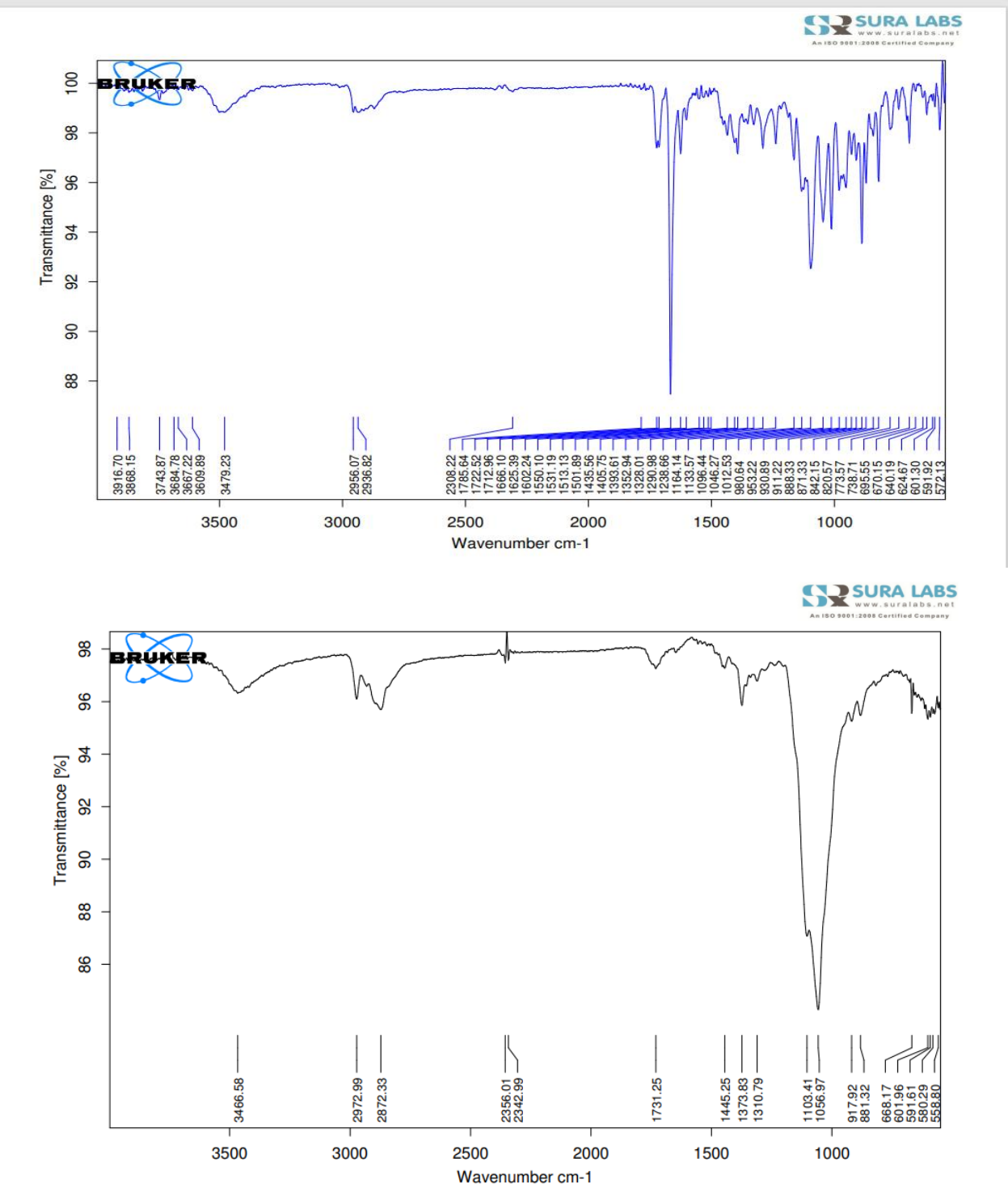

Fig : Ftir Graph Of Pure Drug Of Azilsartan Optimized Graph

There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimized formulation.

CONCLUSION:

- They are cost effective and exhibit predictable release behavior. So the ultimate aim of the present study was to prepare once daily extended release tablets of Azilsartan for improved patient compliance better therapeutic efficacy less side effects and reduce dosage with less toxicity for treatment of hypertension.
- The extended release tablets of Azilsartan was formulated and evaluated by using different polymers like HPMC K100M , Ethyl cellulose and Xanthan gum with different ratios.
- The pre compression and Post compression parameters like Weight variation, Friability, Hardness , thickness , Drug content and Dissolution drug release are in with IP limits.
- FTIR studies were done there is no interaction between drug and excipients
- Among all the 9formulations A6 formulation has showed good drug release with 99.87% for 12hrs.

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