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RESEARCH ARTICLE OPEN ACCESS

FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF CANDESARTAN CILEXETIL

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ABSTRACT

The aim of the present study was to develop sustained release formulation of Candesartan cilexetilto maintain constant therapeutic levels of the drug for over 12 hrs. HPMC-K 100 M, Sodium Carboxy Methyl Cellulose, Grewia gum, Almond gum were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F9) showed better and desired drug release pattern i.e., 99.9% in 12 hours. It contains the HPMC-K 100 M 1:1as sustained release material. It followed Zero order release kinetics mechanism.

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INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2, 3]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained 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[4]. 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 levelof a drug often translates into better patient compliance, as well as enhanced clinical efficacyof the drug for its intended use[5, 6]. The first sustained 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. Sustained 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 sustained or sustained 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, sustained 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[7, 8]. Sustained 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 sustained 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 sustained 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 sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9]. 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 sustained 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[10,11]. 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. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The sustained 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[12].

METHODOLOGY

Analytical method development

Determination of absorption maxima: 100mg of Candesartan cilexetilpure 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 with100ml 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 10µg/ml using Double beam UV/VISspectrophotometer in the range of 200 – 400 nm.

Preparation calibration curve: 100mg of Candesartan cilexetilpure 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 1, 2, 3, 4, and 5ml of solution and make up to 10ml with 0.1N HCl to obtain 10, 20, 30, 40 and 50 µg/ml of Candesartan cilexetilsolution. The absorbance of the above dilutions was measured at 330nm 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, ATR FTIR facility using direct sample technique.

Formulation development of Sustained 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 Candesartan cilexetil.

Procedure: In the present work the Candesartan cilexetiltablets were prepared by direct compression method. The drug and the excipients were passed through 72# size mesh prior to the preparation of dosage form.

Table 1. Formulation of Captopril patches

INGREDIENTS	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Captopril	25	25	25	25	25	25	25	25	25
Eudragit-L100	40	80	120	-	-	-	-	-	-
Eudragit-S100	-	-	-	40	80	120	-	-	-
Eudragit RSPO	-	-	-	-	-	-	40	80	120
Dichloromethane	10	10	10	10	10	10	10	10	10
Methanol	10	10	10	10	10	10	10	10	10
Dibutylphthalate (in %w/v)	20	20	20	20	20	20	20	20	20
Dimethylsulphoxide (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

All the quantities were in mg

MATERIALS

Weighing Balance Sartourius, Tablet Compression Machine (Multistation) Lab Press Limited, India, Hardness tester Monsanto, Mumbai, India., Vernier calipers Mitutoyo, Japan, Roche Friabilator Labindia, Mumbai, India.

The entire ingredients were weighed separately and mixed thoroughly for 10 minutes in double cone blender to ensure uniform mixing in geometric ratio. The tablets were prepared by direct compression technique using 7mm punch.

RESULTS AND DISCUSSION

Analytical Method

Standard graph of Candesartan cilexetilin 0.1N HCl: The scanning of the 10µg/ml solution of Candesartan cilexetilin the

ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at λ_{max} as 330 nm.

Standard Curve of Candesartan cilexetilin Phosphate buffer pH 6.8 : The scanning of the 10µg/ml solution of Candesartan cilexetilin the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 330 nm.

The standard concentrations of Candesartan cilexetil (10-50µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.997, which suggests that it obeys the Beer-Lamberts law.

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

Table 2. Standard curve ofCandesartan cilexetilin 0.1N HCl

Concentration (µg/ ml)	Absorbance
0	0
10	0.229
20	0.421
30	0.632
40	0.828
50	0.931

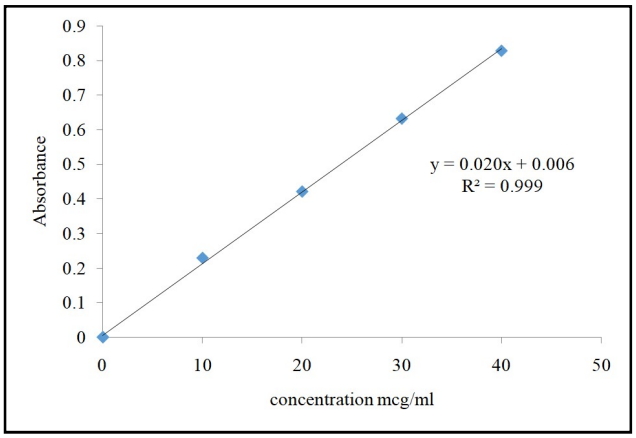

Fig. 1. Calibration curve of Candesartan cilexetilin 0.1 N HCl at 330nm

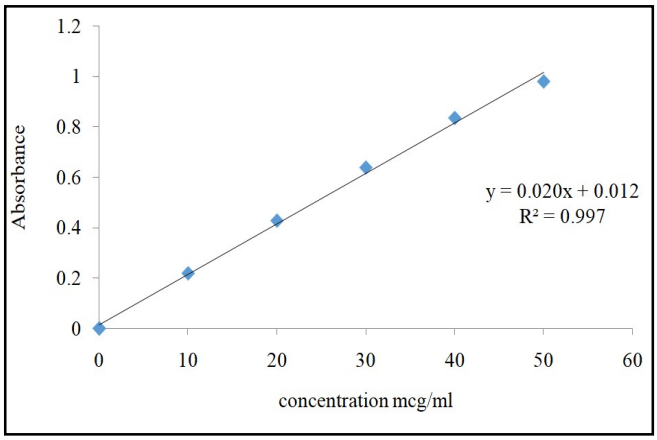

Fig. 2. Calibration of Candesartan cilexetilin Phosphate buffer pH 6.8

Table 3. Standard curve of Candesartan cilexetilin Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
10	0.219
20	0.428
30	0.639
40	0.836
50	0.981

Drug and Excipient Compatibility Studies

FTIR study

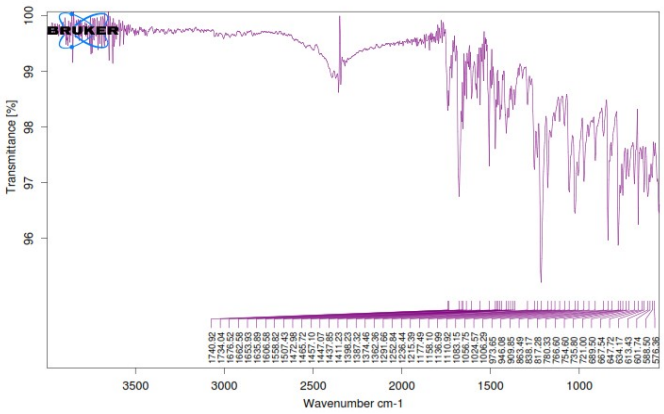

Fig. 3. Ftir graph of pure drug

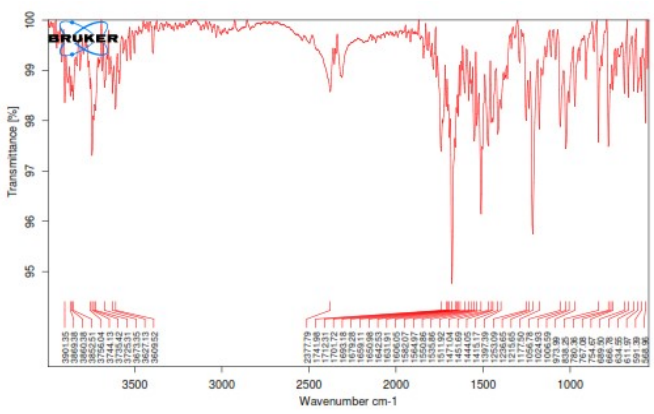

Fig. 4. Ftir graph of optimised formulation

Pre-compression parameters

Table 4. Pre-compression parameters of powder blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	39.90 ± 0.01	0.424 ± 0.001	0.517 ± 0.01	18.00 ± 0.01	1.21 ± 0.01
F2	40.13 ± 0.01	0.412 ±0.015	0.530 ±0.021	22.23 ± 0.01	1.29 ± 0.01
F3	19.98 ± 0.01	0.348 ±0.001	0.401 ± 0.001	13.22 ± 0.01	1.15 ± 0.01
F4	20.36 ± 0.015	0.523 ± 0.002	0.604 ± 0.017	13.41 ± 0.02	1.15 ± 0.01
F5	20.60 ± 0.015	0.382 ± 0.001	0.439 ± 0.002	12.98 ± 0.01	1.15 ± 0.01
F6	21.41 ± 0.01	0.421 ± 0.002	0.492 ± 0.002	14.43 ± 0.02	1.17 ± 0.02
F7	20.16 ± 0.015	0.465 ± 0.015	0.532 ± 0.001	12.59 ± 0.01	1.14 ± 0.01
F8	19.66 ± 0.02	0.332 ± 0.002	0.375 ± 0.015	11.46 ± 0.01	1.13 ± 0.01
F9	24.72 ± 0.01	0.345 ± 0.018	0.401 ± 0.012	13.97 ± 0.01	1.16 ± 0.02
F10	22.31 ± 0.015	0.386 ± 0.002	0.443 ± 0.015	12.87 ± 0.01	1.15 ± 0.01
F11	25.12 ± 0.015	0.373 ± 0.012	0.446 ± 0.03	16.67 ± 0.01	1.20 ± 0.01
F12	23.26 ± 0.001	0.409 ± 0.001	0.462 ± 0.001	11.47 ± 0.01	1.13 ± 0.01

Post Compression Parameters For tablets

Table 5. Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	198.15±0.25	4.8±0.04	0.51±0.04	3.6±0.03	102.3 ± 0.21
F2	197.53±0.34	4.5 ± 0.02	0.61±0.03	3.2 ±0.02	99.50 ± 0.22
F3	200.25±1.15	4.7±0.01	0.45±0.02	3.3 ±0.05	97.2 ± 0.19
F4	199.15±1.31	4.7±0.05	0.54±0.07	3.6±0.04	99.3 ± 0.13
F5	196.23±0.25	4.6±0.09	0.48±0.08	3.6 ±0.09	104.3 ± 012
F6	195.26±1.25	4.7±0.01	0.45±0.02	3.4±0.05	98.2 ± 0.19
F7	200.10±0.95	4.8±0.07	0.51±0.04	3.3 ±0.03	102.3 ± 0.28
F8	199.62±0.86	4.7±0.04	0.55±0.07	4.3 ±0.05	98.3 ± 0.20
F9	198.15±1.17	4.7±0.04	0.56±0.04	3.7±0.08	100.8 ± 0.17
F10	200.08±1.72	4.8±0.01	0.45±0.05	4.4 ±0.05	98.8 ± 0.14
F11	195.75±0.81	4.5±0.01	0.55±0.02	3.6±0.06	98.2 ± 0.15
F12	197.86±2.02	4.8±0.03	0.52±0.03	4.7±0.04	103.5 ± 0.14

Table 6. Dissolution Data of Candesartan cilexetil Tablets Prepared with (Drug: polymer) Ratios of polymers like HPMC-K 100 M (F1), Sodium Carboxy Methyl Cellulose (F2), Grewia gum (F3), Almond gum (F4)

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED			
	F1	F2	F3	F4
0	0	0	0	0
1	28.4	29.6	31.4	22.6
2	36.3	39.9	46.6	28.8
3	46.6	47.6	59.9	35.6
4	57.5	59.6	68.6	57.3
5	64.6	67.1	79.8	66.8
6	76.3	78.6	88.3	77.6
7	84.2	90.6	99.5	85.8
8	95.7	99.4		93.4
10	99.8			100.1
12				

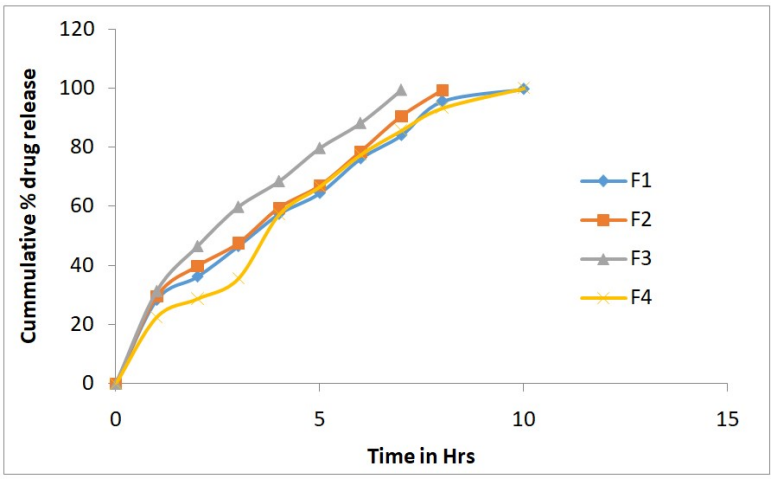

Fig. 5. Dissolution study of Candesartan cilexetil Sustained tablets (F1 to F4)

Table 7. Dissolution Data of Candesartan cilexetil Tablets Prepared with 1:0.75 (Drug: polymer) Ratios of polymers like HPMC-K 100 M (F5), Sodium Carboxy Methyl Cellulose (F6), Grewia gum (F7), Almond gum (F8).

TIME (hr)	Cumulative percent of drug released			
	F5	F6	F7	F8
0	0	0	0	0
1	19.7	24.2	27.9	16.8
2	29.2	33.3	41.6	22.7
3	42.1	42.6	48.2	30.5
4	53.4	54.3	60.4	49.1
5	61.9	61.8	66.8	61.7
6	70.6	72.6	78.6	68.8
7	76.8	81.8	87.3	73.4
8	81.6	94.2	98.7	81.1
10	97.3	99.1		98.2
12	100.2			

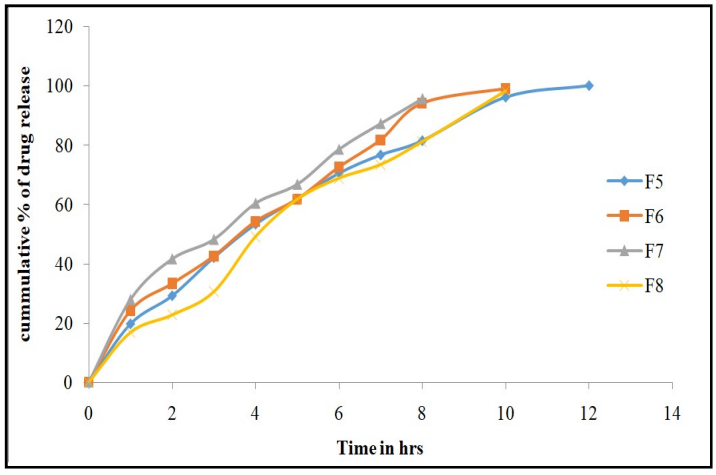

Fig. 6. Dissolution study of Candesartan cilexetil (F5 to F8)

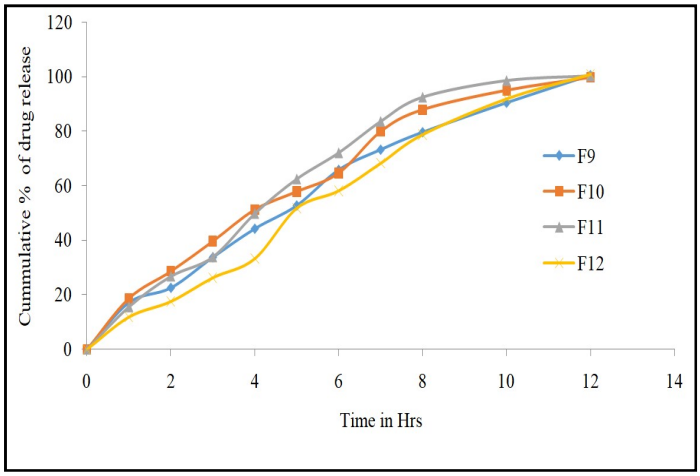

Fig. 7. Dissolution study of Candesartan cilexetil (F9 to F12)

Table 8. Dissolution Data of Candesartan cilexetilTablets Prepared with 1:1 (Drug: polymer) Ratios of polymers like HPMC-K 100 M (F9), Sodium Carboxy Methyl Cellulose (F10), Grewia gum(F11), Almond gum (F12).

TIME (hr)	**Cumulative percent of drug released**			
	F9	**F10**	**F11**	**F12**
0	0	0	0	0
1	17.2	18.7	15.6	11.9
2	22.6	28.6	26.8	17.6
3	33.8	39.6	33.9	26.3
4	44.3	51.2	49.8	33.3
5	52.8	57.8	62.5	51.8
6	65.9	64.6	72.1	58.2
7	73.3	79.8	83.6	68.3
8	79.7	89.8	92.5	78.8
10	90.5	96.9	98.6	91.9
12	99.9	100.1	100.3	98.9.

Table 9. Release kinetics data for optimized formulation (F9)

Time (t)	Cumulative (%) release q	root (t)	Log(%) release	log (t)	log (%) remain	release rate (cumulative % release / t)	% drug remaining
0	0	0			2.000		100
1	17.2	1.000	1.236	0.000	1.918	17.200	82.8
2	22.6	1.414	1.354	0.301	1.889	11.300	77.4
3	33.8	1.732	1.529	0.477	1.821	11.267	66.2
4	44.3	2.000	1.646	0.602	1.746	11.075	55.7
5	52.8	2.236	1.723	0.699	1.674	10.560	47.2
6	65.9	2.449	1.819	0.778	1.533	10.983	34.1
7	73.3	2.646	1.865	0.845	1.427	10.471	26.7
8	79.7	2.828	1.901	0.903	1.307	9.963	20.3
10	90.5	3.162	1.957	1.000	0.978	9.050	9.5
12	99.9	3.464	1.995	1.079	0.041	8.242	1.1

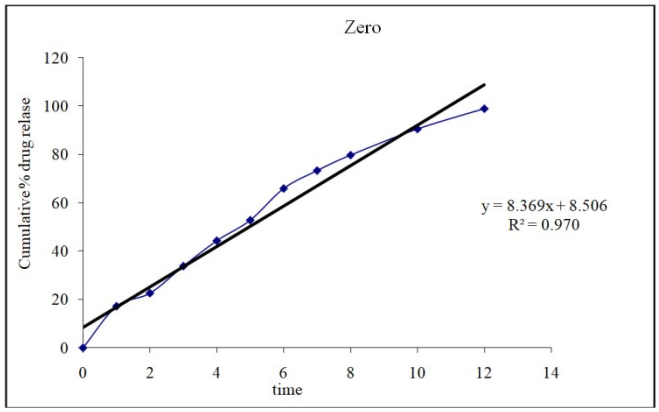

Fig. 8. Graph of zero order kinetics

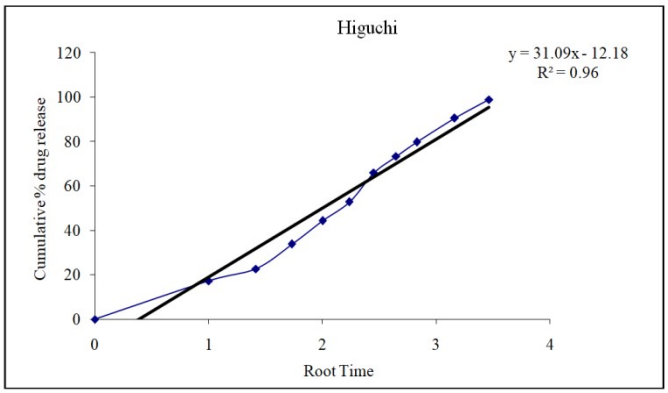

Fig. 9. Graph of higuchi release kinetics

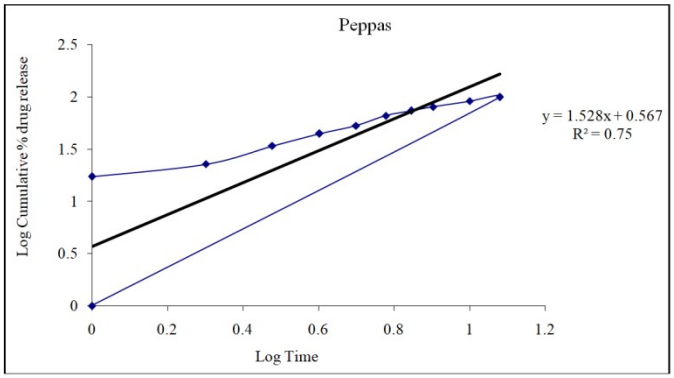

Fig. 10. Graph of peppas release kinetics

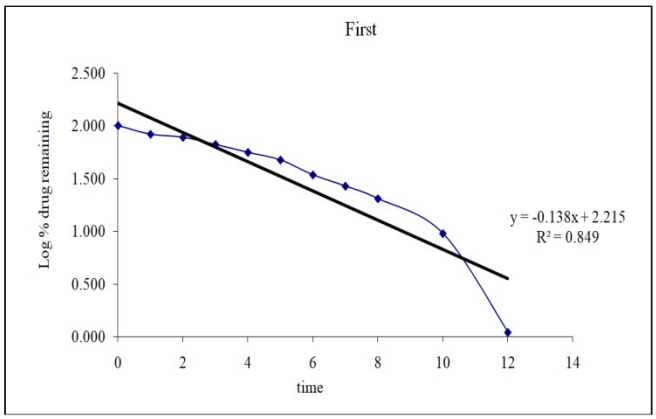

Fig. 11. Graph of first order release kinetics

CONCLUSION

Results of the present study demonstrated that SR matrix of Candesartan cilexetil prepared with polymers like synthetic polymer HPMC K100 M and Natural polymer Almond Gum could proved to control the drug release for 12hr. The formulations contain same concentration polymers like sodiumcarboxy methyl cellulose and Grewia Gum are not retard the drug release up to 12Hrs. The optimized formulation kinetic parameters were evaluated it follows the zero release kinetics.

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