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PREPARATION AND EVALUATION OF PERINDOPRIL CONTROLLED RELEASE MATRIX TABLETS USING DIFFERENT POLYMERS LIKE HPMCK100M AND PECTIN

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ABSTRACT

Perindopril is an angiotensin- converting enzyme (ACE) inhibitor, used to Hypertension (high blood pressure) and congestive heart failure (CHF). These inhibitors relax (arterioles) the muscles around small arteries. They expand the arterioles and allow to blood flow through more easily. This reduces blood pressure (B.P). Controlled release matrix tablets of perindopril were prepared by using three polymers, one of the hydrophilic polymer hydroxy propyl methyl cellulose K100M (HPMCK100M), pectin and carrageenan gum with four concentrations (drug: polymer ratios-1:1, 1:2, 1:3, 1:4),by wet granulation method. The granules were evaluated for bulk density, tapered density, bulkiness, angle of repose, Hausners ratio and compressibility index. In vitro release studies revealed that perindopril formulation with high proportion of HPMCK100M (1:1) was able to control the drug release for 12 hours (85.4±1.26). The in-vitro drug release data, curve-fitting kinetic analysis and all the formulations followed the mechanism of erosion and diffusion. All the formulations were subjected to stability analysis for stored at 45°±2℃, 75±5%RH up to 180 days.

KEYWORDS: Controlled Release, Perindopril, HPMCK100M, Guargum, Gum carrageenan, Wet Granulation.

INTRODUCTION

Controlled Release formulations of Perindopril can overcome some of these problems. Most of the matrix tablets can be prepared by wet granulation method. Among many polymers

(hydrophilic, lipophilic, natural gums, Hydrogels and Mucoadhesive polymers) in the formulation of matrix based controlled release drug delivery systems. Their flexibility to obtain a desirable drug release profile, broad regulatory acceptance and cost effectiveness are advantages of hydrophilic polymer matrix systems. The benefits providing hydroxypropyl methylcellulose (HPMCK100M) for formulation of hydrophilic matrix system like nonionic nature, Robust mechanism, consistent reproducible release profile, choice of viscosity grades, effectiveness of cost, and utilization of conventional methods and equipments. The following factors like drug dissolution, water penetration, polymer swelling, drug diffusion and matrix erosion are controlled by the hydration of HPMC, due to forms the gel barrier through which the drug diffuses.

The drug is release from these types of controlled release matrices occurs by dissolution or diffusion these are one type of controlled drug delivery systems, which deliver the drug in continuous manner by both diffusion and dissolution controlled mechanisms. To control the delivery of the drugs, which has various solubility properties, the drug is distributed in swellable hydrophilic (water soluble) substances, an insoluble matrix of non-swellable rigid hydrophobic (lipid soluble) materials or plastic polymers.

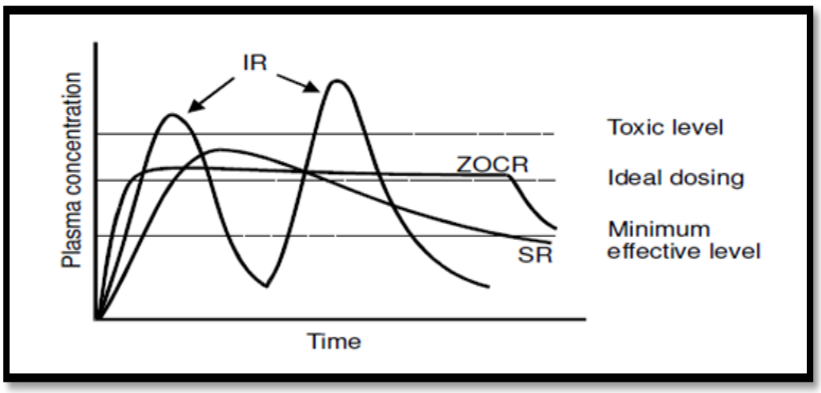


Fig 1: Drug release profile for different formulations(IR,SR,ZOCR).

MATERIALS AND METHODS

Materials

Perindopril was kind gift sample from Sun Pharmaceuticals private limited, Mumbai India. HPMCK100M, Talc, and Magnesium stearate were procured from KP labs, Hyderabad, India. Lactose, Karayagum, Isopropyl alcohol, Polyvinyl pyrrolidone were procured from S.d fine chemicals Pvt Ltd; Mumbai, India. All other chemicals and reagents were used of analytical grade.

Preparation of Ramipril controlled release tablets

Twelve formulations of controlled release tablets of Perindopril using HPMCK15M,Pectin and Gum carrageenan each with four formulations (1:1, 1:2, and 1:3, 1:4) were prepared by wet granulation method. The details of each formulation and with composition are shown to table-1.

Perindopril (drug) and polymers HPMCK100M, Pectin, Gumcarrageenan were mixed separately. Lactose and Pectin were added to the polymer-drug mixture and blended thoroughly for 5-6 minutes. A coherent mass is formed to dissolve the polyvinyl pyrrolidone (PVP) in sufficient quantity of isopropyl alcohol (IPA) and finally added to drug mixture. Then the coherent mass was passed through sieve number-16 to form granules and the collected granules were dried at $40\,℃ \pm 2\,°c$ for 2 hours. The dried granules were passed through the sieve number-22.The granules retained on sieve number-22 were evaluated for tapped density, bulk density, bulkiness, compressibility index, Hausners index and angle of repose(Table-IIA,IIB,IIC). Then the granules were mixed with talc, magnesium stearate and finally compressed in to tablets.[3] The same procedure was followed to prepare Perindopril tablets without polymers.

Table-1: Formulation batches of Perindopril CR Tablets (F-1 to F13) for Wet granulation method

Ingredients(mg)	Drug : Polymers												n
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13 #
Perindopril	4	4	4	4	4	4	4	4	4	4	4	4	4
HPMC K100M	4	8	12	16									
Pectin					4	8	12	16					
Gum carrageenan									4	8	12	16	
Lactose monohydrate	30	26	22	18	30	26	22	18	30	26	22	18	34
PVPK-300	6	6	6	6	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total(mg)	50	50	50	50	50	50	50	50	50	50	50	50	50

Note- # without polymers used

IR spectral analysis

The drug (Ramipril) and polymers like (HPMC K15M, PVPK-30, and Karayagum) must be compatible with one another to produce a stable product.[8] FTIR (Shimadzu, Japan, model-

8400s) using studied by interaction between drug and polymer as per the method described by Sharma. IR spectral analysis of pure Ramipril, Ramipril with HPMC K15M, and Ramipril with Karayagum were carried out. The peaks and patterns produced by the pure drug were compared with combination of polymers and pure drug.[10]

Evaluation of tablets

Hardness

The tablets to be tested by Monsanto hardness test apparatus[13] The test was performed by the tablet are held between a fixed and moving jaw of apparatus and the reading of the indicator is adjusted to zero (0). The screw knob was moved forward until the tablet breaks and noted the reading, force required to break the tablet.

Friability test

The Roche friabilator is used to performance of friability test.[14] The weighing ten (10) tablets and placed in the friabilator, which was then operated for 25 revolutions per minute (RPM). After 100 revolutions the tablets were dusted and reweighed. The formula used to determine the percentage of friability was

$$\text{Percentage friability} = \text{Initialweight-Finalweight/Initial weight} \times 100$$

Weight variation

For weight variation test, twenty (20) tablets were randomly selected and weighed individually. The individual weights were compared with average weight for determination of weight variation.[18]

Dissolution test studies

In-vitro dissolution release studies were performed using USP apparatus type-II at 50 rpm. The dissolution medium was 900 ml of phosphate buffer at PH7.4. The temperature was maintained at 37 ± 0.5 ℃. The drug release rate was evaluated by taking 10 ml sample, which was replaced with fresh medium every one one-hour interval up to 12 hours and suitable diluted with phosphate buffer (PH 7.4) and absorbance was measured at 208 nm using UV spectrophotometer[20]

Drug content

Ten tablets (10) were weighed and powdered. The powder equivalent to 100 mg of Ramipril was dissolved in 10 ml of 0.1 M Hcl, then make up to 100ml of phosphate buffer PH 7.4 in

100 ml standard flask. From this 10$\mu g/ml$, equivalent solution was prepared and analyzed at 208 nm using UV spectrophotometer.

Kinetic analysis

The mechanism of drug release rate kinetics of all the formulations to analyze the results of in-vitro release profiles were fitted in to zero order kinetic model, first order kinetic model, Higuchi model and korsmeyer Peppas model.[6] The results of in-vitro release profiles were plotted in models of data treatment as follows

Zero order kinetic model – Log cumulative percent drug released versus time

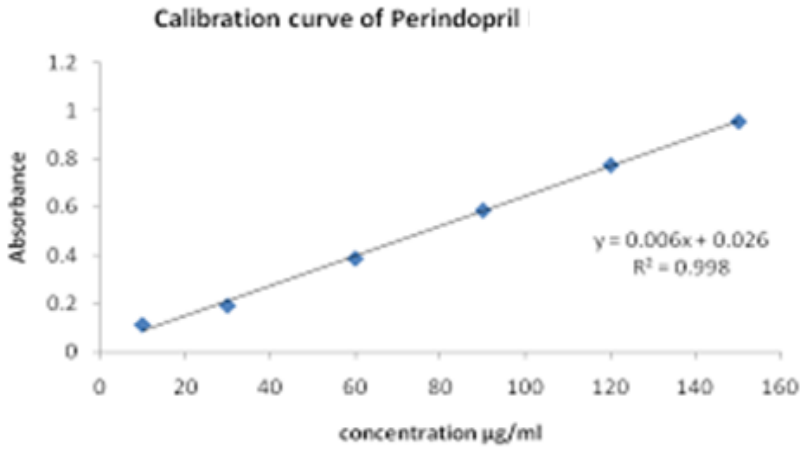
First order kinetic model – Log cumulative percent drug remaining versus time

Higuchi model – Cumulative percent drug release versus squire root of time

Korsmeyer model - Log cumulative percent drug released versus log time

Stability studies

Stability studies were analyzed to assess the stability of all controlled release formulations of Ramipril tablets. The prepared CR tablets were kept at 45 ℃ ± 2 ℃, 75± 5%RH for 180 days. At 15 days intervals the tablets were evaluated for all physical parameters. The perentage of Ramipril content and in-vitro drug release studies were also determined.



1.2 DRUG - EXCIPIENTS COMPATIBILITY STUDIES OF PERINDOPRIL

1.2.1 Fourier Transform Infra-Red Spectroscopy (FTIR)

FTIR spectra were recorded for 1:1 physical mixtures of Perindopril and polymers like HPMCK100M, Pectin and Gum carrageenan. Samples were prepared with KBr pellets (2 mg sample in 200 mg KBr) with a hydrostatic force of 5.2 N cm^{-2} for 3 minutes. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}

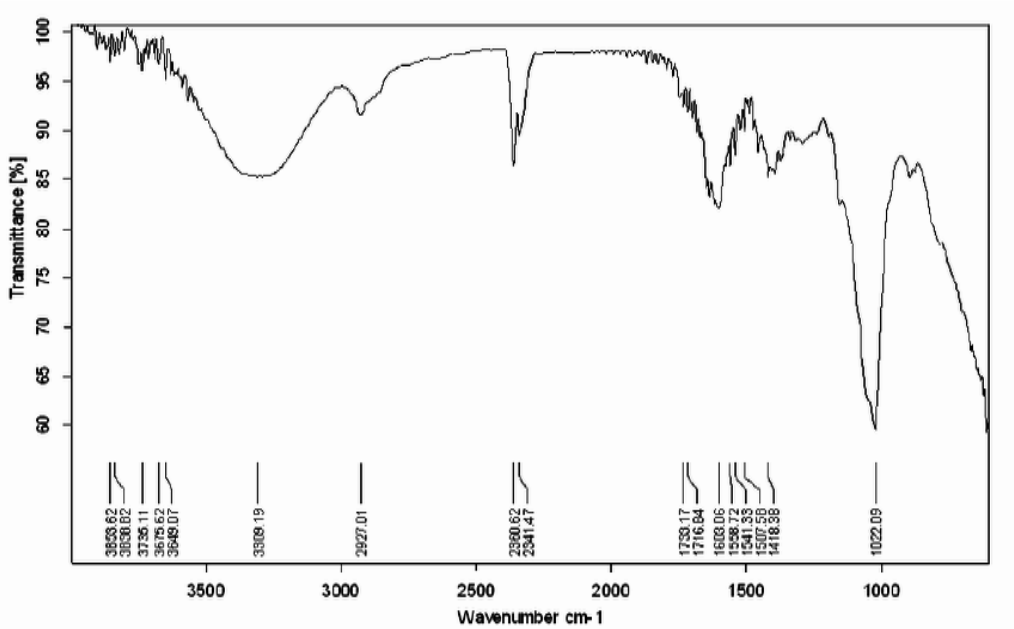


Fig-4 FTIR Spectra of Perindopril.

Table-4: Interpretation of FTIR results pure drug Perindopril.

S.no	Functional Group	Range(cm^{-1})	Observed Peak (cm^{-1})
1	N-H Stretching	3250-3400	3309.19
2	O-H Stretching	2800-3000	2927.01
3	O=C=O Stretching	2349-2400	2360.62
4	C=C Stretching	1600-1650	1603.06
5	O-H Bending	1395-1440	1418.38
6	C-O Stretching	1020-1075	1022.09

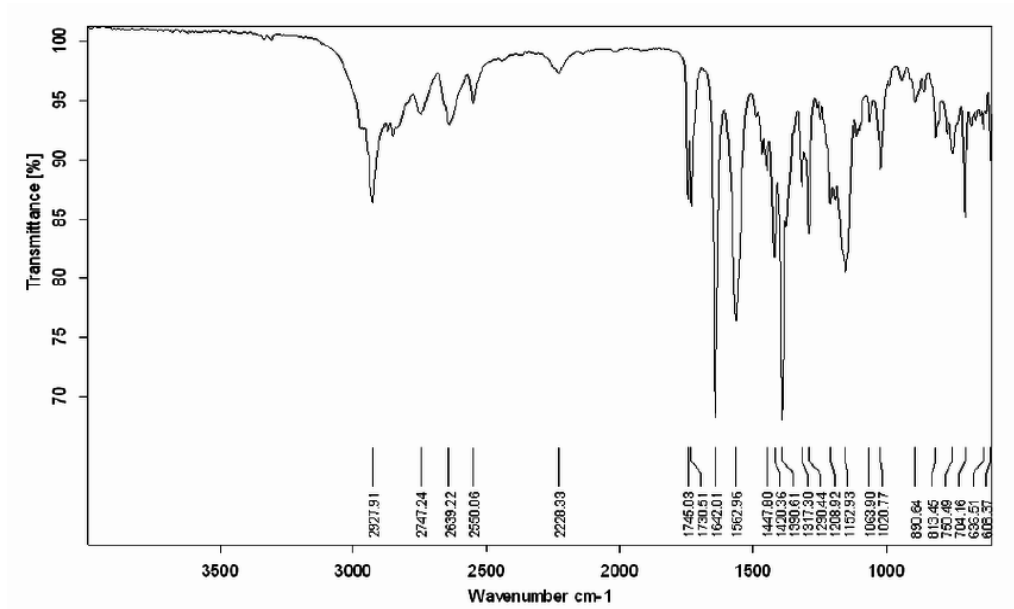


Fig-5 FTIR Spectra of Perindopril and mixture of polymers (HPMCK100M, Pectin, Gum carrageenan).

Table 5: Interpretation of FTIR results Perindopril and mixture of polymers (HPMCK100M, Pectin, Gum carrageenan).

S.no	Functional Group	Range(cm^{-1})	Observed Peak (cm^{-1})
1	N-H Stretching	2800-3000	2927.91
2	O-H Stretching	2500-3300	2639.22
3	C=O Stretching	1720-1755	1746.03
4	C=C Stretching	1626-1662	1642.01
5	N-O Stretching	1500-1600	1562.96
6	O-H Bending	1395-1440	1390.61
7	C-O Stretching	1085-1150	1150
8	C=C Bending	665-730	704.16

1.2.2 Differential Scanning Calorimetry (Dsc) Studies of Perindopril

Pure drug, excipients and their physical mixtures of pure drug and excipients (1:1) were sealed in aluminum pan and scanned between 25°C and 300°C with heating rate of 10°C per minute under an atmosphere of dry nitrogen. Any interaction can be observed to obtain the thermograms. **Differential Scanning Calorimeter (Shimadzu, Model no: DSC-60).**

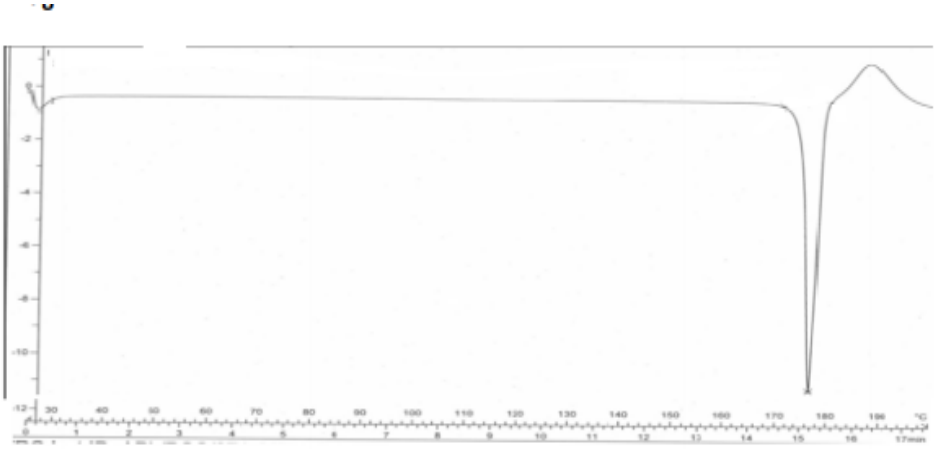


Fig-6 DSC Thermogram of Perindopril Pure drug.

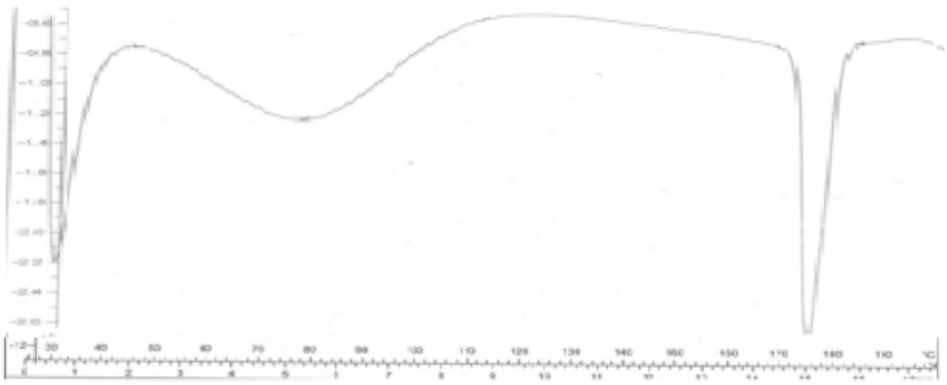
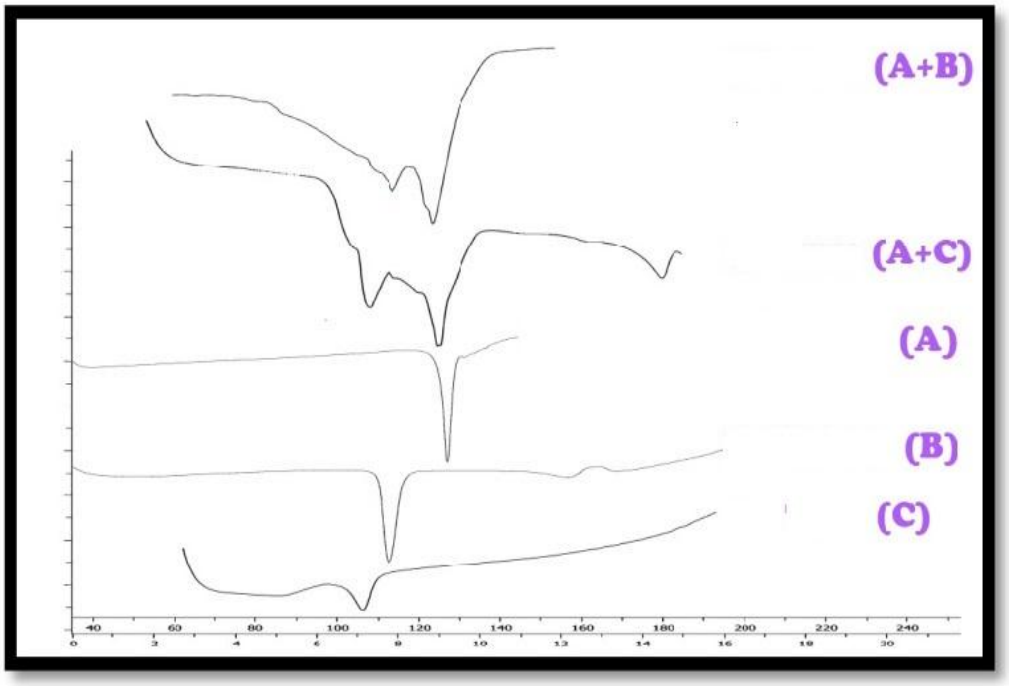


Table 7: DSC Thermogram of formulated Perindopril.

Table-6 Melting point of drug Perindopril and optimized formulation.

Name of the ingredient	Melting point
Perindopril pure drug	178^0C
Formulated Perindopril	175^0C

DSC was used to detect interaction between Perindopril and excipients. The thermogram of Perindopril exhibited a sharp endotherm melting point at 178^0C. The thermogram of Perindopril formulation exhibited a sharp endotherm melting point at 175^0C. There is no considerable change observed in melting endotherm of drug in optimized formulation. It indicates that there is no interaction between drug & excipients used in the formulation.



There were no any appreciable changes in peak value of drug in the DSC thermograms of drug-excipient mixtures from that of pure drug. While the DSC thermogram of Perindopril showed a sharp endothermic peak (T_{peak}) at 127.1°C in the thermograms of the drug-excipient mixtures, there were no appreciable changes in the drug T_{peak} values.

Though there was slight broadening or shifting towards the higher or lower temperatures, the melting endotherm of drug was well preserved. Quantity of material used in drug–excipient mixtures, resulted in less purity of individual component, has probably affected the shape of peak and enthalpy. Similar changes are reported. Hence, it may be concluded that the slight changes identify in melting endotherm of drug were likely due to presence of excipients and not due to any significant interactions between the polymers and drug under study.

1.2.4 X-Ray Powder Diffraction (X-RPD) Studies of Perindopril

XRD (Philips PW 1729, Netherlands) was employed for tracing the XRD patterns of Perindopril and SDs, using Nickel (Ni) filter, Cu K (α) radiation, a voltage of kV, a current of 20 Ma and receiving slit of 0.2 in. The sample were analyzed over 2θ range of 10° to 60°, with scan step size of 0.020 (2θ) and scan step time of 1 second. Intensity of the peak in perindopril drug was 1824.

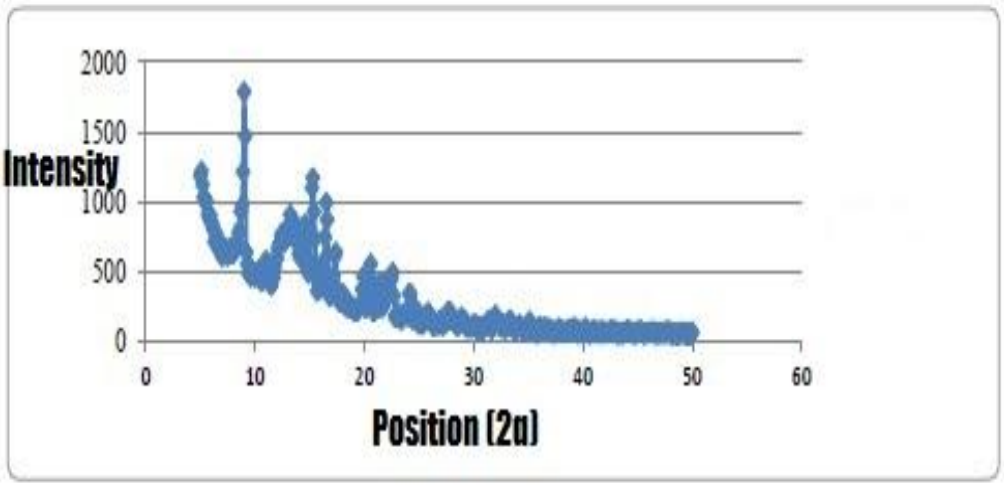


Fig-7 XRPD Studies of Perindopril Drug.

1.2.5 Pre-Compressed Properties Of The Powder Blend

Table 9: Pre-compression properties of Perindopril powder blend (F1-F4).

Parameters	Drug and polymer ratio (Perindopril: HPMCK100M)			
	F1	F2	F3	F4
Bulk density(gm/cc)*	0.36±0.14	0.39±0.12	0.31±0.53	0.33±0.16
Tapped density(gm/cc)*	0.37±0.91	0.32±0.41	0.40±0.11	0.32±0.36
Angle of repose *	19.24±0.94	18.22±0.81	19.19±0.25	19.03±0.12
Compressibility index (%)	10.50±0.26	10.24±0.22	11.65±0.91	10.11±0.51
Hausners ratio*	0.972	1.218	0.775	1.031

Table 10: Pre-compression properties of Perindopril powder blend (F5-F8).

Parameters	Drug and polymer ratio (Perindopril: Pectin)			
	F5	**F6**	**F7**	**F8**
Bulk density(gm/cc)*	0.34±0.18	0.30±0.14	037±0.36	0.32±0.16
Tapped density(gm/cc)*	0.31±0.21	0.36±0.81	0.36±0.14	0.29±0.38
Angle of repose *	20.04±0.94	18.11±0.82	19.92 ± 0.25	18.96±0.12
Compressibility index (%)	10.50±0.26	10.44±0.22	11.11±0.91	11.46±0.51
Hausners ratio*	1.096	0.833	1.027	1.103

Table 11: Pre-compression properties of Perindopril powder blend (F9-F13).

Parameters	Drug and polymer ratio (Perindopril : Gum carrageenan)				Control
	F9	F10	F11	F12	F13
Bulk density(gm/cc)*	0.32±0.22	0.34±0.16	0.38±0.50	0.29±0.72	0.39±0.44
Tapped density(gm/cc)*	0.35±0.24	0.36±0.57	0.38±0.16	0.36±0.32	0.36±0.66
Angle of repose *	18.21±0.94	18.23±0.82	19.21±0.22	18.76±0.12	19.80±0.25
Compressibility index (%)*	11.50±0.22	11.24±0.36	10.18±0.55	10.32±0.56	11.06±0.20
Hausners ratio*	0.914	0.944	1.000	0.805	1.083

DISCUSSION

- Bulk density were range between **0.290 - 0.390** gm/cc
- Tapped density were range between **0.290 - 0.400** gm/cc
- Compressibility index were range between **10.11-11.46 %**, indicates good flow properties of powder.
- Hausner's ratio were range between **0.805-1.213**
- Angle of repose was range between **18.11° - 20.04°**, which indicates good flow properties of powder.

1.2.6 Post-Compression Parameters of Perindopril Matrix Tablets

Table 12: Post-compression properties of Perindopril matrix tablets (F1-F4).

Parameters	Drug and polymer ratio (Perindopril : HPMC K100M)			
	F1	F2	F3	F4
Hardness (kg/cm2)	5.12±0.12	4.96±0.07	5.76±0.24	5.30±0.46
Friability (%)	0.42±0.04	0.53±0.07	0.29±0.03	0.41±0.02
Weight variation(mg)	49.6±0.7	49.1±0.4	49. 5 ± 0.7	49.4±0.2
Content uniformity (%)	48.16±0.33	47.6±0.10	50.8±0.20	46.4±0.16
Thickness(mm)	3.12±0.02	3.21±0.12	3.19±0.04	3.26±0.14
Diameter(mm)	7.12±0.31	7.50±0.15	7.18±0.08	7.24±0.02

Table 13: Post compression properties of Perindopril matrix tablets (F5-F8).

Parameters	Drug and polymer ratio (Perindopril : Pectin)			
	F5	F6	F7	F8
Hardness (kg/cm2)	5.87±0.18	5.10±0.07	5.22±0.45	5.19±0.12
Friability (%)	0.36±0.04	0.54±0.06	0.69±0.02	0.42±0.07
Weight variation(mg)	49.4±4.7	49.7±4.4	49.2±2.5	49.8±1.2
Content uniformity (%)	47.23±0.33	49.53±1.1	51.22±0.4	47.1±0.22
Thickness(mm)	3.22±0.02	3.26±0.12	3.11±0.04	3.16±0.14
Diameter(mm)	7.42±0.31	7.56±0.15	7.38±0.08	7.44±0.02

Table 14: Post-compression properties of Perindopril matrix tablets (F9-F13).

Parameters	Drug and polymer ratio (Perindopril : Gum carrageenan)				Control formulation
	F9	F10	F11	F12	F13
Hardness (kg/cm2)	5.14±0.12	5.36±0.09	5.45±0.10	5.12±0.14	5.33±0.12
Friability (%)	0.54±0.04	0.44 ± 0.04	0.39±0.01	0.47±0.01	0.25±0.04
Weight variation(mg)	49.9±4.7	48.9±4.2	49.1±5.5	49.2±1.2	49.0±1.2
Content uniformity (%)	48.26±0.33	49.61±1.10	52.2±0.20	50.4±0.22	48.4±0.02
Thickness(mm)	3.18±0.02	3.29±0.12	3.46±0.04	3.56±0.14	3.32±0.02
Diameter(mm)	7.02±0.31	7.16±0.15	7.28±0.08	7.14±0.02	7.10±0.06

Discussion

- Tablets hardness were range between **4.96 – 5.82 kg/cm^2**
- Tablets friability were range between **0.25 - 0.69 %**
- Tablets content uniformity range between **48.9 -49.9 mg**
- Tablets weight variation were range between **46.40-52.20 mg**
- Tablets thickness were ranges between **3.11-3.56 mm**
- Tablets diameter were ranges between **7.02-7.56 mm**

All formulation evaluation parameters are acceptable ranges, therefore tablets are physically good strength.

1.2.7 Dissolution Release Data Profile-Perindopril

In-vitro dissolution release studies were conducted to determine the % of drug delivery from perindopril tablet formulations with polymer, marketed tablet and perindopril tablet formulation without polymer (control formulation). Results of the in-vitro dissolution release studies of perindopril matrix tablet formulation with polymer are show in table-68.

The % drug release of all preparations after 24 hours using HPMC K100M as polymer was found to be 97.7% (F1), 97.6% (F2), 97.4 (F3) and 97.1(F4). It was found that the cumulative % drug delivery in the formulationF1 was more thanF2, F3 and F4. The cumulative % of drug delivery in the formulation F4 showed controlled release than F1, F2 andF3. A major role played in drug release was the polymer concentration. At higher polymer concentration, the drug delivery was extended than the lower concentration of the polymer. The graphical presentation data of the perindopril matrix tablet formulations with polymer is shown in (Figure – 41)

The % drug delivery of all formulations after 24 hours using pectin as polymer was found to be 98.4 (F5), 98.1% (F6), 97.8 (F7) and 97.5(F8). It was found that the cumulative % drug delivery in the formulation F5 was more thanF6, F7 and F8. The cumulative % of drug delivery in the formulation F8 showed controlled release than F5, F6 andF7.

The % drug delivery of all formulations after 24 hours using gum carrageenan as polymer was found to be 98.1% (F9), 97.9% (F10),97.6 (F11) and 97.5(F12). It was found that the cumulative % drug delivery in the formulationF9 was more thanF10, F11 and F12. The cumulative % of drug delivery in the formulation F12 showed controlled release than F9, F10 andF11

In overall twelve formulations HPMC K100M as polymer was found to be 97.1 % (F4). It was found that the cumulative % of drug delivery was very low compare to overall twelve formulations in different polymers, because of best formulation in controlled release.

In-vitro dissolution of best perindopril controlled release tablet formulation (control) was found to be 99.6 % in 7 hrs where as the perindopril release from marketed matrix tablet was 100 % in 22 hrs.

Table 15: Dissolution release profile of Perindopril CR Matrix Tablet Formulations F1 to F4.

Time (hrs)	Cumulative % of drug release			
	Ramipril:HPMC K15M			
	F1	F2	F3	F4
1	8.9±1.14	8.6±1.08	8.4±1.26	8.1±1.11
2	17.1±1.09	16.8±1.44	16.7±1.61	16.5±1.86
3	23.2±1.12	23.0±1.32	22.7±1.44	22.5±1.64
4	28.6±1.17	28.5±1.64	28.3±1.38	28.0±1.34
5	32.7±1.23	32.5±1.02	32.2±1.30	32.0±1.08
6	36.8±1.22	36.4±1,09	36.2±1.42	35.8±1.17
7	40.4±1.62	40.1±1.32	39.8±1.66	39.7±1.02
8	43.9±1.42	43.7±1.10	43.5±1.18	43.1±1.42
9	47.4±1.01	47.2±124	47.0±1.24	46.6±1.52
10	51.8±1.05	51.6±1.52	51.3±1.78	51.1±1.32
11	56.2±1.16	55.8±1.16	55.5±1.14	55.2±1.54
12	60.5±1.54	60.2±1.47	59.8±1.33	59.7±1.60
13	61.1±1.34	60.7±1.91	60.5±1.66	60.4±1.34
14	63.2±1.86	62.8±1.35	62.5±1.24	62.3±1.76
15	65.9±1.05	69.7±1.44	67.3±1.04	65.1±1.44
16	69.4±1.87	69.1±1.66	68.8±1.29	68.6±1.82
17	72.9±1.22	72.7±1.04	72.3±1.84	72.1±1.11
18	75.1±1.43	74.7±1.34	74.6±1.22	74.3±1.82
19	78.4±1.65	78.1±1.64	77.7±1.02	77.4±1.02
20	82.8±1.21	82.6±1.88	82.4±1.74	82.1±1.22
21	85.5±1.87	85.3±1.06	85.1±1.42	84.9±1.76
22	88.4±1.42	88.3±1.42	88.1±1.88	87.7±1.89
23	91.0±1.66	90.7±1.22	90.4±1.36	90.2±1.36
24	95.6±1.26	95.3±1.74	95.1±1.11	94.8±1.20

Table 16: Dissolution release profile of Perindopril CR Matrix Tablet Formulations F5 to F8.

Time (hrs)	Cumulative % of drug release			
	Perindopril : Pectin			
	F5	F6	F7	F8
1	13.7±1.21	13.5±1.15	13.4±1.06	13.1±1.86
2	20.9±1.64	20.6±1.05	20.4±1.98	20.1±1.61
3	25.6±1.07	25.3±1.73	25.1±1.25	24.9±1.11
4	28.6±1.14	28.5±1.54	28.3±1.32	28.1±1.17
5	33.8±1.09	33.5±1.45	33.2±1.16	33.0±1.24
6	39.9±1.18	39.7±1.27	39.5±1.65	39.1±1.42
7	43.6±1.12	43.4±1.07	43.1±1.44	42.8±1.31
8	48.8±1.17	48.5±1.03	48.3±1.59	48.2±1.82
9	54.2±1.28	54.1±1.37	53.8±1.17	53.6±1.44
10	59.6±1.73	59.4±1.09	59.1±1.04	58.8±1.29
11	63.8±1.57	63.5±1.66	63.2±1.09	63.0±1.41

12	68.0±1.96	67.8±1.14	67.5±1.29	67.2±1.51
13	71.4±1.46	71.2±1.08	71.1±1.00	70.8±1.66
14	73.0±1.90	72.9±1.09	72.6±1.13	72.3±1.07
15	75.2±1.64	75.0±1.11	74.9±1.27	74.7±1.02
16	76.6±1.08	76.3±1.92	76.1±1.19	75.7±1.12
17	78.5±1.00	78.3±1.88	78.0±1.04	77.7±1.48
18	80.4±1.64	80.1±1.46	79.8±1.62	79.6±1.30
19	84.4±1.24	84.1±1.82	83.8±1.77	83.5±1.72
20	87.6±1.07	87.3±1.66	87.1±1.34	86.9±1.22
21	90.5±1.32	90.2±1.27	90.0±1.09	89.7±1.17
22	94.8±1.52	94.5±1.31	94.3±1.02	94.1±1.85
23	96.4±1.41	96.2±1.00	96.1±1.54	95.9±1.14
24	98.4±1.06	98.1±1.64	97.8±1.52	97.4±1.22

Table 17: Dissolution release profile of Perindopril CR Matrix Tablet Formulations F9 to F13.

Time(hrs)	Cumulative % of drug release				
	Perindopril: gum carrageenan				#
	F9	F10	F11	F12	F13
1	14.6±1.76	14.5±1.04	14.3±1.26	13.8±1.10	18.9±1.22
2	21.7±1.64	21.4±1.64	21.3±1.14	21.1±1.26	31.2±1.82
3	27.2±1.55	26.9±1.28	26.7±1.64	26.4±1.61	44.4±1.26
4	31.3±1.42	31.1±1.01	30.8±1.44	30.5±1.22	58.1±1.42
5	34.5±1.07	34.3±1.66	34.2±1.06	34.0±1.42	73.3±1.20
6	40.4±1.12	40.1±1.34	39.8±1.91	39.7±1.84	87.6±1.72
7	44.6±1.42	44.4±1.09	44.1±1.62	43.9±1.42	99.6±1.04
8	49.2±1.85	48.9±1.61	48.6±1.18	48.5±1.21	-
9	55.7±1.63	55.4±1.23	55.2±1.25	55.1±1.90	-
10	60.6±1.49	60.3±1.29	60.2±1.13	60.0±1.64	-
11	64.9±1.23	64.7±1.16	64.4±1.22	64.1±1.42	-
12	69.1±1.08	68.7±1.10	68.5±1.30	68.3±1.50	-
13	71.9±1.02	71.7±1.25	71.5±1.86	71.2±1.25	-
14	74.2±1.17	74.1±1.54	73.9±1.60	73.7±1.76	-
15	75.7±1.21	75.5±1.33	75.3±1.16	75.0±1.66	-
16	77.5±1.17	77.3±1.77	77.1±1.07	76.8±1.31	-
17	79.2±1.39	79.0±1.02	78.7±1.04	78.6±1.22	-
18	81.8±1.46	81.6±1.19	81.3±1.11	81.1±1.09	-
19	83.3±1.22	83.1±1.44	82.8±1.16	82.5±1.72	-
20	88.6±1.44	88.4±1.00	88.1±1.14	87.9±1.94	-
21	91.7±1.81	91.4±1.26	91.1±1.46	89.9±1.01	-
22	94.2±1.08	93.9±1.14	93.6±1.34	93.5±1.54	-
23	96.5±1.11	96.3±1.62	96.0±1.31	95.7±1.06	-
24	98.1±1.92	97.9±1.60	97.6±1.72	97.5±1.33	-

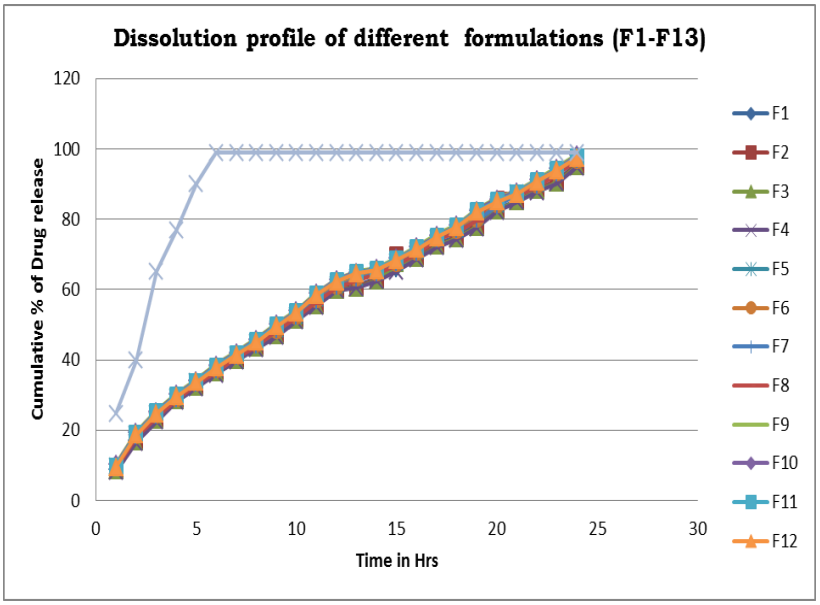


Fig 8: Graphical representation of Dissolution release profile of various Perindopril CR matrix formulations F-1 to F-13.

Table-18 Dissolution profile comparison of optimized formulation and marketed product (Coversyl).

Time (hrs)	Optimized formulations	Marketed product
1	12.1±1.00	16.5±1.34
2	18.6±1.09	21.8±1.05
3	23.3±1.36	25.6±1.56
4	26.5±1.41	28.9±1.82
5	31.7±1.04	34.1±1.24
6	37.5±1.22	40.1±1.02
7	41.8±1.83	45.7±1.84
8	47.3±1.17	49.0±1.90
9	51.8±1.01	53.2±1.52
10	58.1±1.61	56.4±1.21
11	61.5±1.77	62.7±1.23
12	66.2±1.00	67.4±1.41
13	68.4±1.71	72.5±1.98
14	71.0±1.69	76.9±1.07
15	72.6±1.05	80.4±1.42
16	74.2±1.18	84.2±1.54
17	76.6±1.12	87.1±1.23
18	78.5±1.16	89.8±1.51
19	82.9±1.00	93.2±1.59
20	86.1±1.01	95.5±1.62
21	88.2±1.23	98.1±1.82
22	90.5±1.26	100±1.04
23	93.5±1.07	
24	97.1±1.09	-

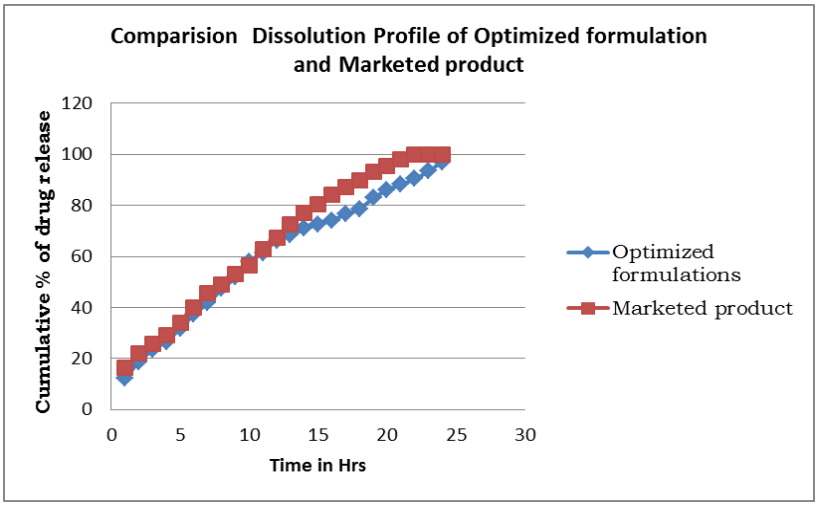


Fig 9: Graphical representation for Comparison of Perindopril optimized CR matrix Tablet Formulation with Marketed product. (Coversyl).

Table-19 Drug release kinetics various Perindopril CR matrix tablet formulations

1.2.8 KINETICS OF DRUG DELIVERY OF OPTIMIZED (F-4) FORMULATION

Formulation code	Regression co-efficient (R2)			Korsmeyer plot	
	Zero order plot	First order plot	Higuchi's plot	R2	Slope
F1	0.9826	0.9462	0.9564	0.7176	0.769
F2	0.9944	0.9582	0.9654	0.7024	0.734
F3	0.9969	0.9666	0.9642	0.7542	0.726
F4	0.9982	0.9632	0.9566	0.7264	0.818
F5	0.9888	0.9596	0.9612	0.6942	0.642
F6	0.9872	0.9586	0.9654	0.7164	0.729
F7	0.9912	09612	0.9464	0.7712	0.704
F8	0.9978	0.9684	0.9616	0.7244	0.794
F9	0.9864	0.9598	0.9489	0.7222	0.722
F10	0.9886	0.9684	0.9544	0.7342	0.689
F11	0.9978	0.9682	0.9224	0.7164	0.774
F12	0.9926	0.9616	0.9516	0.7787	0.706
F13	0.9856	0.9726	0.9742	0.7241	0.746

1.2.8.1 ZERO ORDER RELEASE

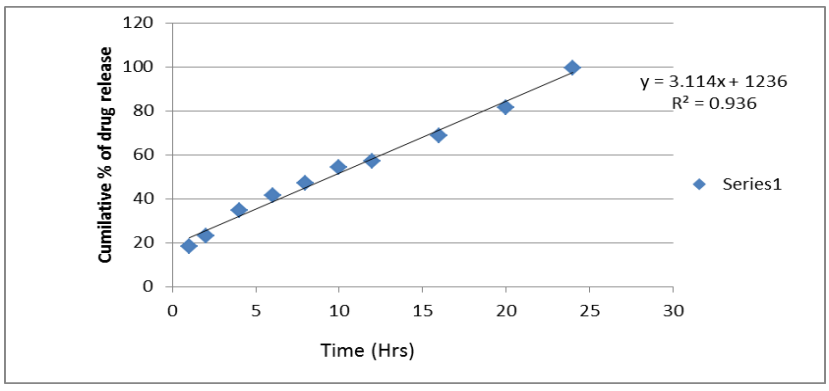


Fig-10 Zero order plot of perindopril optimized formulation (F4).

1.2.8.2 FIRST ORDER

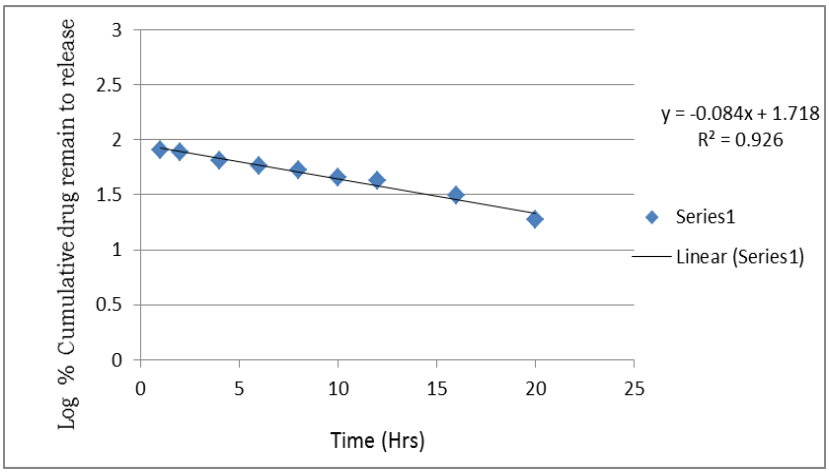


Fig-11 First order plot of Perindopril optimized formulation (F4).

1.2.8.3 HIGUCHI MODEL

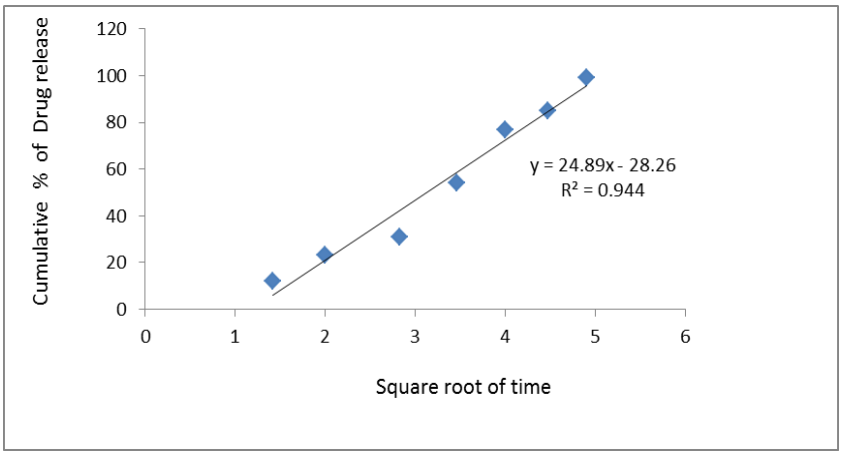


Fig-12 Higuchi plot of Perindopril optimized formulation (F4).

1.2.8.49.7.4 KORSMAYER-PEPPAS MODEL

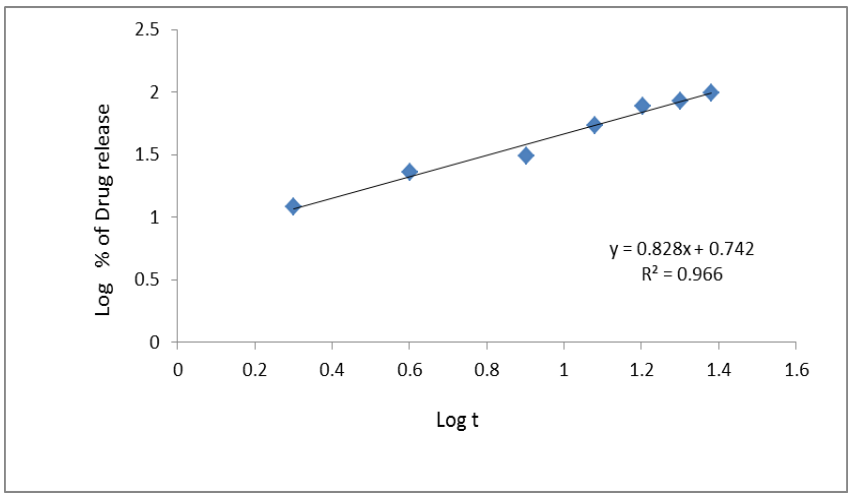


Fig-13 Korsmayer-peppas plot of Perindopril optimized formulation (F4).

Table-20 Drug Release Kinetics of Perindopril optimized CR matrix formulations F-4.

Formulation	Zero order (r^2)	First order (r^2)	Higuchi model (r^2)	Korsmayer-Peppas model		Best fit model
				r^2	"n" value	
F-4	**0.998**	0.967	0.951	0.749	0.828	Zero order

1.2.9 Stability Study

Table-21 ICH Summary of stability Parameters.

Study	Storage conditions	Minimum time period
General case	25^0C ($\pm2^0$C) at 60% RH(±5%RH)	12 months
Long term	30^0C ($\pm2^0$C) at 65% RH(±5%RH)	12 months
Intermediate	30^0C ($\pm2^0$C) at 65% RH(±5%RH)	6 months
Accelerated	40^0C ($\pm2^0$C) at 75% RH(±5%RH)	6 months

Table 22: Stability testing for Perindopril CR tablets (F4).

S.no	Stability Testing	Specifications	Intial	Time interval in months		
				1	3	6
1	Description	White crystalline powder	Complies	Complies	Complies	Complies
2	Thickness(mm)	3.2-3.6	3.26	3.26	3.26	3.26
3	Hardness(mm)	5.0-5.5	5.30	5.30	5.30	5.28
4	Friability %	0.1-0.8	0.41	0.41	0.41	0.41
5	Weight variation (mg)	47.5-52.5	49.4	49.4	49.4	49.3
6	Dissolution					
	2^{nd} hrs	B/W 10%-25%	18.6	18.6	18.6	18.8
	4^{th} hrs	B/W 20%-35%	26.5	26.5	26.5	26.8
	8^{th} hrs	B/W 30%-45%	47.3	47.3	47.3	47.5
	12^{th} hrs	B/W 50%-65%	64.2	64.2	64.2	64.3
	24^{th} hrs	NLT 80%	97.1	97.1	97.1	97.2

No significant difference was observed for a period of 6 months at 40^0C / 75 % RH condition for Perindopril controlled release tablets are maintained good stability.

CONCLUSION

The results of experimental studies of Perindopril matrix tablets proved that the granules of Perindopril showed good flow properties, evaluation tests of tablets are within the acceptable limits, Infra Red (IR) spectral analysis [16] proved that there was no polymer- drug interaction, all the formulations of kinetic studies were followed zero order drug release and stability analysis revealed that all formulations were found to be stable after storing at 45°± 2°C, 75±5% RH up to 180 days. The main drawbacks of the conventional dosage forms of Perindopril can be minimized by Perindopril controlled release (CR) tablets. Thus the results of the above study clearly indicated that Perindopril may be formulated as CR tablets using

HPMC K100M as polymer by wet granulation method which will be provide continuous release of drug at a predetermined rate and time.

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Abbreviations

HPMC = Hydroxy Propyl Methyl Cellulose, CR = Controlled Release, RH = Relative Humidity, UV = Ultra Violet.

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