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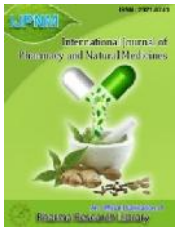

Research Article **Open Access**

Formulation and Evaluuation of Sustained Release Tablets of Perindopril

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A B S T R A C T

Prindopril sustained release tablets were formulated by using factorial design method. Eudragit EPO, Hydroxy ethyl cellulose and Ethocel were employed as polymers. Factorial design was employed in the development of formulations. The drug and excipient compatibility studies were carried out by using FTIR spectroscopy, from that it was evident that there were no interactions between drug and excipients.12 formulations were developed, the developed formulations were evaluated for various physicochemical parameters. The results were found to be within the limits. Invitro dissolution studies were carried out to optimize the concentration of polymer. From the invitro dissolution studies it was evident that the formulation (F6) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation. Stability studies were carried out for optimized formulation for about 2 months, there were no prominent changes in the dissolution values of formulation even after 2 months period of time.

Keywords: Perindopril, Synthetic polymers and sustained release tablets.

A R T I C L E I N F O

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1. Introduction

Perindopril is a long-acting ACE inhibitor used to treat high blood pressure, heart failure, or stable coronary artery disease in form of perindopril arginine (trade names include Coversyl, Coversum) or perindopril erbumine (Aceon). According to the Australian government's Pharmaceutical Benefits Scheme website, based on data provided to the Australian Department of Health and Aging by the manufacturer, perindopril arginine and perindopril erbumine are therapeutically equivalent and may be interchanged without differences in clinical effect. [2] However, the dose prescribed to achieve the same effect differs due to different molecular weights for the two forms. Perindopril shares the indications of ACE inhibitors as a class, including essential hypertension, stable coronary artery disease (reduction of risk of cardiac events in patients with a history of myocardial infarction / revascularization) and treatment of symptomatic heart disease or failure. In addition, the Perindopril Protection against Recurrent Stroke Study (Progress) found that perindopril reduces the risk of stroke in both hypertensive and nonhypertensive individuals with a history of stroke ortransient ischemic attack For perindopril as treatment for hypertension, the initial dose is 5 mg perindopril arginine (or 4 mg perindopril erbumine) once daily, then the dose may be increased to 10 mg perindopril arginine (or 8 mg perindopril erbumine) after one month of treatment to improve blood pressure control or in case of concomitant stable coronary artery disease.

Oral Drug Delivery

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized. Several types of modified-release drug products are recognized:

1. Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

2. Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. Targeted-release drug products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate /extended-release characteristics. Modified release drug products are designed for different routes of administration based on the physicochemical, pharmacologic and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form. Several different terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.

Oral Controlled Release Drug Delivery Systems

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

2. Materials and Methods

Perindopril (Aurabindo Pharma), HEC(Merck Specialities Pvt Ltd, Mumbai, India), eudragit (Merck Specialities Pvt Ltd, Mumbai, India), MCC, Mg. Stearate(Merck Specialities Pvt Ltd, Mumbai, India), talc(Merck Specialities Pvt Ltd, Mumbai, India).

Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve:

100mg of Perindopril HCl pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20,25,30,35 and 40µg/ml of Perindopril per ml of solution. The absorbance of the above dilutions was measured at 238 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:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit.

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release ofPerindopril . Total weight of the tablet was considered as 300mg.

Procedure:

1) Prindopril 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.

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage.

***In- vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl , p H 6.8 Phophate buffer
RPM -- 50
Sampling intervals (hrs) --0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c ± 0.5°c

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 238 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

3. Results and Discussion

The present study was aimed to developing Sustained release tablets of Perindopril using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Determination of lambda max and construction of Calibration curve:

In preformulation studies, it was found that the lambda max of Perindopril by spectroscopic method was 240nm and 242 with P^H 1.2 and P^H 6.8.

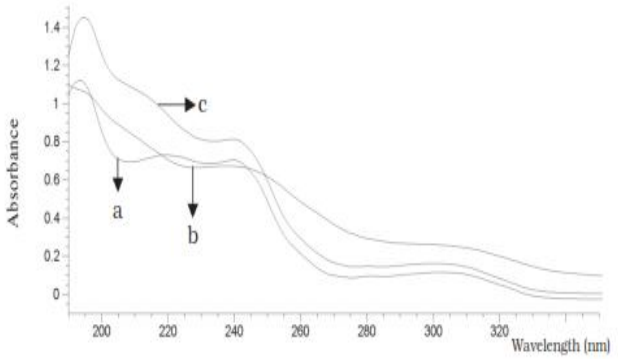

Figure 1: Determination of lambda max ofPerindopril with 0.1N HCl

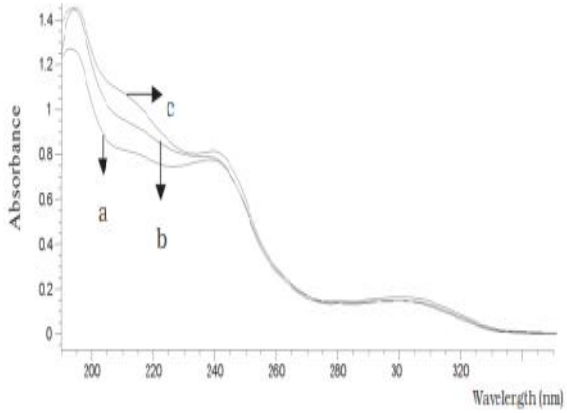

Figure 2: Determination lambda max of Perindopril in 6.8PH phosphate buffer

Table 1: construction of calibration curve of Perindopril with 0.1N Hydrochloric acid

S.No	Conc. (µg/ml)	abs
1	0	0
2	5	0.231
3	10	0.401
4	15	0.591
5	20	0.789
6	25	0.999

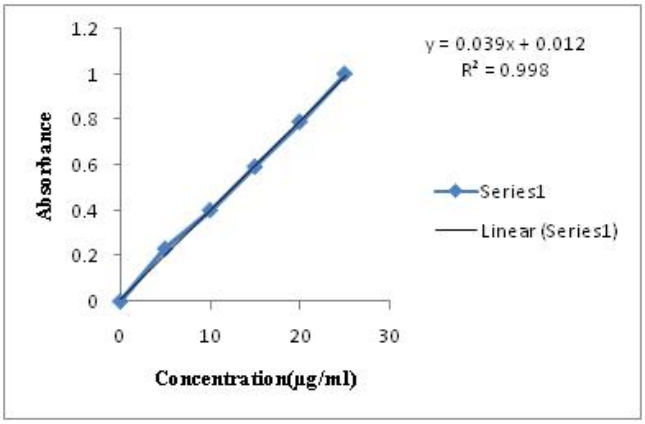

Figure 3: construction of calibration curve of Perindopril with 0.1N Hydrochloric acid

Table 2: Construction of Calibration Curve of Drug with Phosphate Buffer 6.8 P^H

S. No	Conc. (µg/ml)	abs
1	0	0
2	5	0.236
3	10	0.413
4	15	0.612
5	20	0.821
6	25	0.999

In this study at 240nm and 242nm in simulated gastric fluid (0.1N HCl) and phosphate buffer pH 6.8 respectively had good reproducibility in the concentration between 5-25µg/ml. Correlation between concentration and absorbance was found to be closer to 1 indicating that the method obeyed Beer Lamberts law.

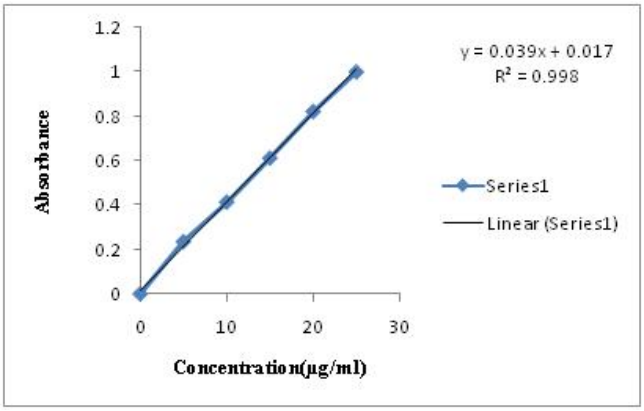

Figure 5: Construction of calibration curve of Perindopril with phosphate buffer 6.8P^{H}

In this study at 240nm and 242nm in simulated gastric fluid (0.1N HCl) and phosphate buffer pH 6.8 respectively had good reproducibility in the concentration between 5-25µg/ml Correlation between concentration and absorbance was found to be closer to 1 indicating that the method obeyed Beer Lamberts law.

Loose bulk density:

Bulk density of the formulation blend plays an important role in the compression of the powder. Bulk density was carried out and results were reported in the table 5.4. The bulk density of the formulation was found to be in the range of 0.67 g/cm3 to 0.71 g/cm3.

Tapped density:

Tapped density also plays an important role in knowing the compressibility of the formulation blend. It was found to be in the range of 0.78g/cm3 to 0.83 g/cm3. It was noted that the tapped density of all the formulation were greater than their respective bulk density thus indicating that all the powder formulation had a good compressibility.

Angle of repose:

The angle of repose for the formulation blend was carried out and the results were shown in the table 5.4. It can be concluded that the angle of repose for all formulations blend was obtained in the range of 25.11- 29.56 thus falling in the range official limits 25-30(good flow). Hence all the formulation blends possess good flow property.

Carr's consolidation index:

Carr's consolidation index was carried out and the results were shown in the table 5.4. The CCI was calculated based on LBD and TD. It was found to be in the range of 12.12-14.55 indicating that all the formulation blends possess good flow property for compression.

Hausner's ratio:

Hausner's ratio is the ratio between tapped bulk density and loose bulk density. Hausner's ratio was calculated for all formulation blends and reported in the table 5.4. All formulations having Hausner's ratio < 1.25.

The values of friability test were in the range from 0.61 to 0.79%. The per cent friability of all the formulation was less than 1% ensuring that the tablets were mechanically stable. The percentage of drug content for all formulations found to be in the range of 92.78-97.85%. It complies with official specifications.

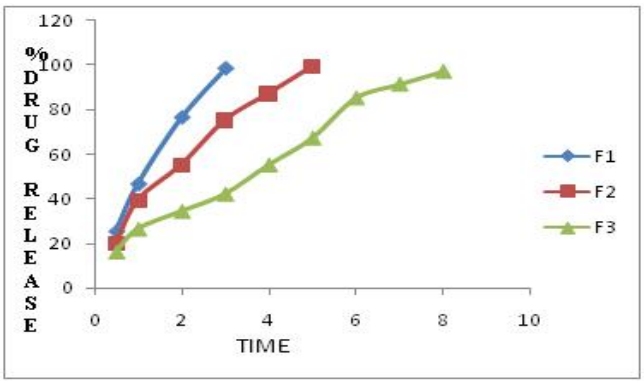

Figure 6: Dissolution profile of Perindopril (F1, F2, F3 formulations).

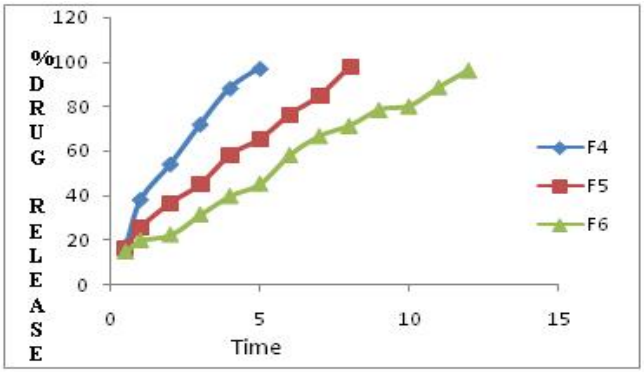

Figure 7: Dissolution profile of Perindopril (F4, F5, F6 formulations)

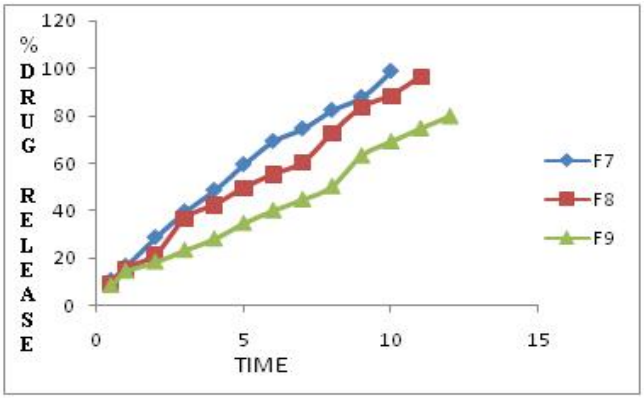

Figure 8: Dissolution profile of Perindopril (F7, F8, F9 formulations)

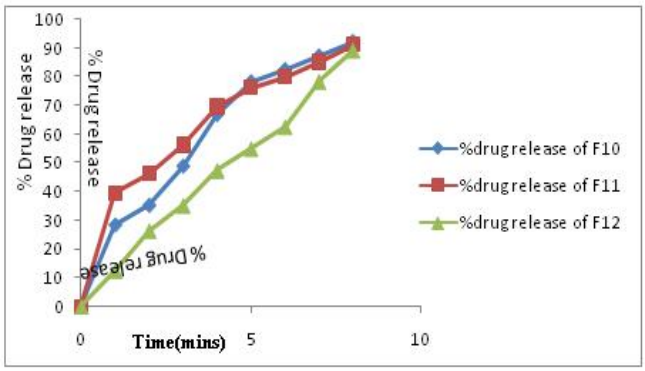

Figure 9: Dissolution profile o fPerindopril (F10, F11, F12 formulations)

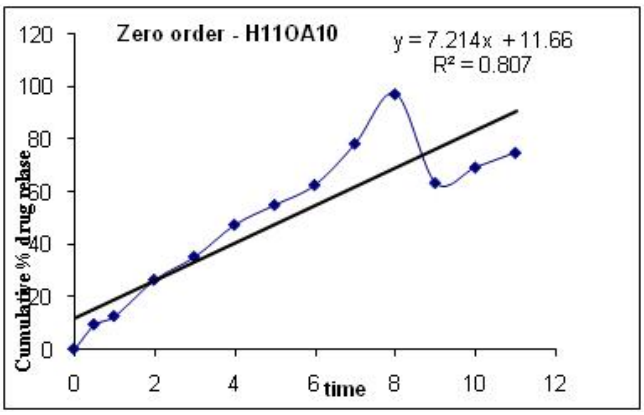

Figure 11: kinetics- zero order

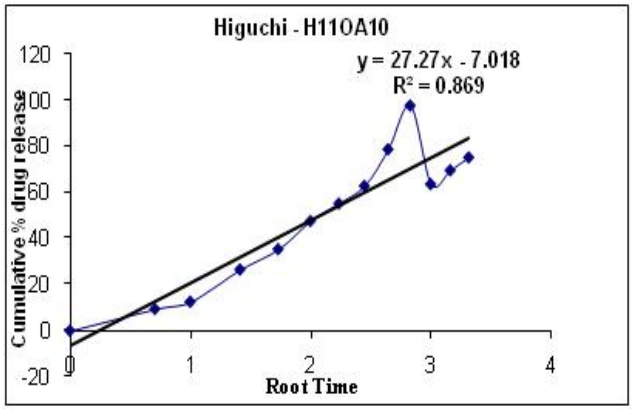

Figure 12: kinetics- Higuchi

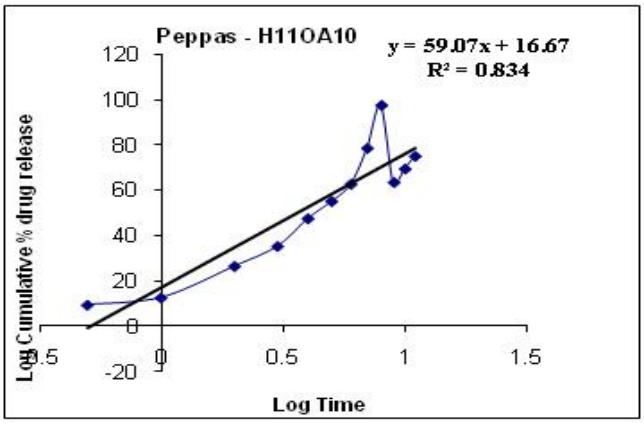

Fig 13: kinetics- peppas

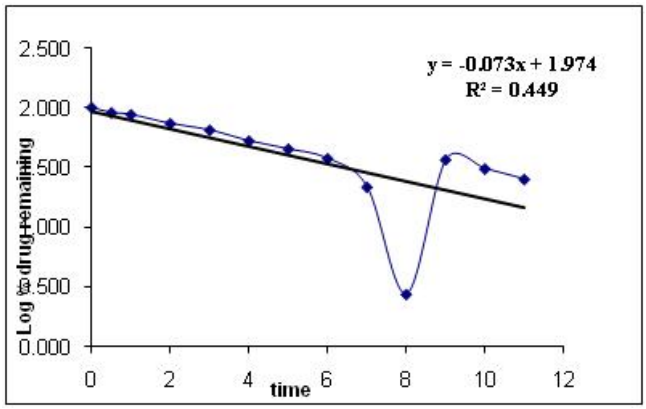

Fig 14: kinetics- first order

From the dissolution data it was evident that the formulations prepared with Eudragit EPO as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with HEC retarded the drug release in the concentration of 60 mg (F6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation. The formulations prepared with combination of polymer showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 3: Pre Formulation Studies

Formulation	Angle of repose	Bulk density	Tapped density	CCI	Hausner's ratio
F1	25.82	0.71	0.81	12.84	1.15
F2	27.35	0.70	0.80	12.50	1.14
F3	25.28	0.71	0.81	12.12	1.13
F4	25.11	0.69	0.79	12.73	1.15
F5	29.05	0.69	0.81	14.53	1.17
F6	26.76	0.70	0.82	14.55	1.17
F7	27.35	0.70	0.80	12.50	1.14
F8	25.28	0.71	0.81	12.12	1.13
F9	26.78	0.76	0.88	12.23	1.10
F10	25.76	0.71	0.80	13.55	1.11
F11	26.35	0.71	0.81	13.50	1.10
F12	26.28	0.74	0.84	13.12	1.14

4. Conclusion

The present research work was aimed to formulate and evaluate Perindopril sustained release tablets using various synthetic polymers. Eudragit EPO, Hydroxy ethyl cellusoe and Ethocel were employed as polymers. Factorial design was employed in the development of formulations. The drug and excipient compatibility studies were carried out by using FTIR spectroscopy, from that it was evident that there were no interactions between drug and excipients.12 formulations were developed , the developed formulations were evaluated for various physicochemical parameters. The results were found to be within the limits. Invitro dissolution studies were carried out to optimize the concentration of polymer. From the invitro dissolution studies it was evident that the formulation (F6) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation. Stability studies were carried out for optimized formulation for about 2 months, there were no prominent changes in the dissolution values of formulation even after 2 months period of time.

5. Acknowladgement

We sincerely thank **K.P labs (A Division of KDPL)** for their cooperation and support throughout the project.

Table 4: Formulation composition for tablets

Formulation No.	Prindopril	Eudragit EPO	HEC	Ethocel	Mag. Stearate	Talc	MCC pH 102
F1	10	30		30	3	3	QS
F2	10	60		30	3	3	QS
F3	10	90		30	3	3	QS
F4	10	120		30	3	3	QS
F5	10		30	30	3	3	QS
F6	10		60	30	3	3	QS
F7	10		90	30	3	3	QS
F8	10		120	30	3	3	QS
F9	10	60	60	30	3	3	QS
F10	10	75	15	30	3	3	QS
F11	10	15	75	30	3	3	QS
F12	10	45	45	30	3	3	QS

All the quantities were in mg

Table 5: Evaluation of uncoated tablets

Formulation	Thickness (mm) n=10	Hardness (Kg/cm^2) n=6	Wt variation (mg) n=20	Friability (%) n=10	Drug content (%) n=5
F1	2.69±0.157	3.58±0.34	200.11±0.405	0.63	94.46
F2	2.72±0.172	3.41±.67	200.86±0.963	0.65	95.53
F3	2.62±0.147	3.38±0.533	209.86±0.385	0.61	97.85
F4	2.65±0.150	3.45±0.563	209.02±0.523	0.67	93.86
F5	2.64±0.156	3.9±0.137	201.98±0.425	0.72	92.78
F6	2.68±0.164	3.84±0.193	200.86±0.910	0.79	96.16
F7	2.75±0.150	3.45±0.563	204.02±0.523	0.50	96.85
F8	2.74±0.156	3.9±0.137	203.98±0.425	0.60	97.86
F9	2.78±0.164	3.84±0.193	206.86±0.910	0.63	98.78
F10	2.22±0.167	3.23±.672	202.76±0.982	0.62	95.73
F11	2.52±0.151	3.43±0.551	204.82±0.364	0.64	97.65
F12	2.35±0.146	3.52±0.572	207.05±0.516	0.61	93.73

Table 6: Dissolution Data of Perindopril Tablets Prepared With Eudragit EPO in Different Concentrations

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	25.5	20.1	16.4	17.25	16.42	14.62	10.4	9.4	8.5	0	0	0
1	46.7	39.4	26.7	38.26	25.73	19.86	16.5	15.6	14.5	12.45	10.34	9.34
2	76.5	55.3	34.6	54.16	36.63	22.35	28.6	21.4	18.4	28.45	39.5	12.51
3	98.4	75.3	42.4	72.01	45.04	31.45	39.5	36.7	23.4	35.28	46.35	26.38
4		87.3	55.4	88.26	58.25	39.80	48.5	42.4	28.2	48.9	56.28	35.17
5		99.4	67.4	97.10	65.33	45.25	59.4	49.6	34.8	66.83	69.71	47.37
6			85.4		76.41	58.24	69.2	55.3	40.2	88.45	76.26	54.96
7			91.5		84.84	66.73	74.5	60.3	44.8	98.18	85.26	62.56
8			97.3		97.80	71.34	82.3	72.8	50.4		98.28	78.35
9						75.52	87.78	83.52	63.34			97.26
10						82.17	98.78	88.65	69.27			
11						87.10		96.56	74.86			
12						96.10			79.97			

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