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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF GESTRORETENTIVE FLOATING TABLET OF PERINDOPRIL

Sanju Singh[1], Abhishek Dwivedi[1], Shubendu Mishra[2], Avalani Gunjan[3]

1. **Department of Pharmaceutics, RKDF University, Bhopal, M.P.**
2. **Department of Pharmaceutics, Radharaman College of Pharmacy, Bhopal, M.P.**
3. **Department of Quality, Bajaj Health Care, Baroda. Gujarat**

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***Correspondence for Author:**
Sanju Singh

Department of Pharmaceutics, RKDF University, Bhopal, M.P

Email: sekhar.subhendu@gmail.com

Abstract:

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. Gastro retentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance. Perindopril Eribumineis an angiotensin converting enzyme inhibitor and is used in the treatment of hypertensive and congestive cardiac failure. The bioavailability of Perindopril following oral administration is very low. Perindopril is absorbed rapidly on oral administration. When administered orally, frequent dosing is needed due to its short biological half life (0.8-1hr).Secondly drug undergoes high hepatic first pass metabolism. The present study focus on the development of floating tablets of perindopril hydrochloride using different polymer grades to achieve a sustained release for 24 hrs.

Keywords: Gastro retention, Angiotensin System, Gastroretnial tract system

INTRODUCTION:

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site specific delivery, oral dosage forms have really progressed. Gastro retentive dosage forms significantly extend the period of time, over which drug may be released and thus prolong dosing intervals and increase patient compliance.[1] Such retention systems are important for those drug that are degraded in the 0intestine like antacids or certain antibiotics, enzymes that act locally in the stomach. This system can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract, thus ensuring optimal bioavailability. [2,3] Various gastro retentive techniques were used, including floating, swelling, high density, and bioadhesive system, have been explored to increase the gastro retention of dosage forms. [4,5] Floating systems having low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach without affecting the gastric emptying rate for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastric retentive time and reduces fluctuation in plasma drug concentration. [6,7] Perindopril Eribumine[8-11] is an angiotensin converting enzyme inhibitor and is used in the treatment of hypertensive and congestive cardiac failure. The bioavailability of Perindopril following oral administration is very low. Perindopril is absorbed rapidly on oral administration. When administered orally, frequent dosing is needed due to its short biological half life (0.8-1hr).Secondly drug undergoes high hepatic first pass metabolism. The present study focus on the development of floating tablets of perindopril hydrochloride using different polymer grades to achieve a sustained release for 24 hrs.

Materials:

Perindopril was obtained as gift sample from Glenmark Pvt. Ltd., Mumbai. HPMC K14M was obtained from Suvidhanath Lab. Baroda. Carbopol was obtained from High Purity Chemicals Lab., Mumbai, Sodium Carbonate, Lactose, Talc and Magnesium stearate were obtained from S.D. Fine Chemicals. Pvt Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade.

Experimental:

Characterization of Perindopril:

Description: The sample of Perindipril was analyzed for its nature, color and taste.

Table 1. Physical Evaliuyation

Sr. No.	Property	Observation
1.	Colour	White
2.	Odour	Odourless
3.	State	Solid
4.	Nature	Amorphous

Melting Point: The melting point was taken by open capillary method.

Table 2. Melting Point-Determination

Sr. No.	Drug	Temperature
1.	Perindopril	150^0c
2.	Perindopril	152^0c
3.	Perindopril	150^0c
Mean		**150.6^0c**

Standard Curve of Perindopril: Perindipril has been quantitatively analyzed by various techniques. In present studies, Perindipril was estimated by UV Spectrophotometry method.

Table 3. Observation of Drug by UV

Sr. No.	Concentration	Wavelength	Absorbence
1.	10ppm	211.2	0.170

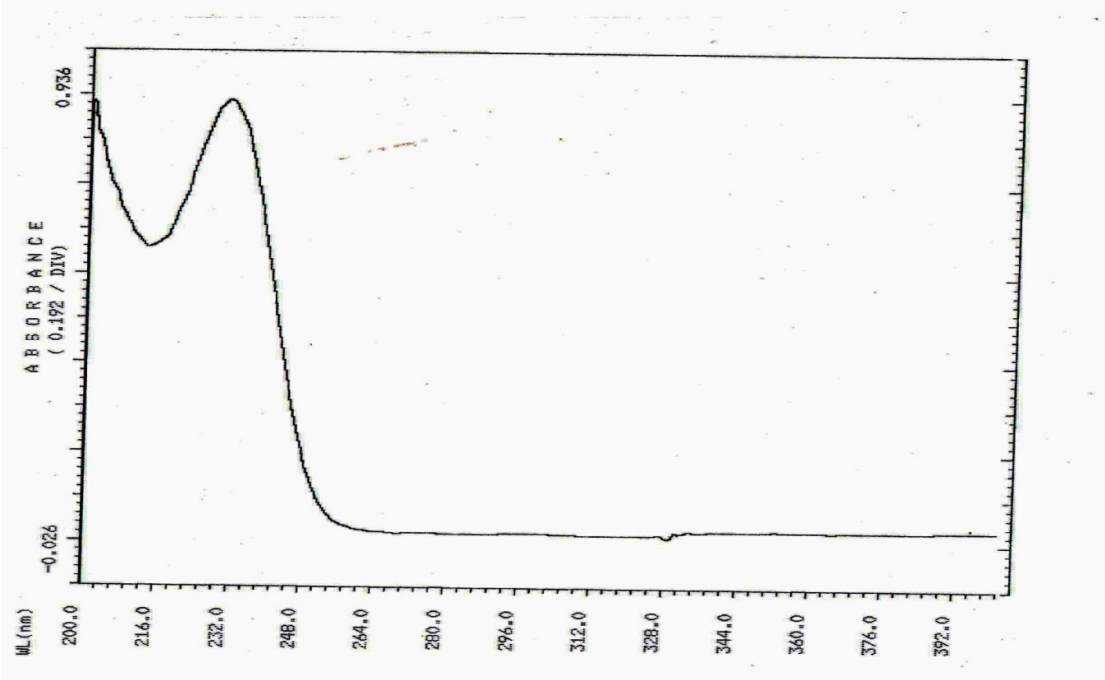


Figure 1. Plotted in UV of Perindopril

Table 4.Standard Calibration Curve of Perindopril

Sr. No.	Concentration (µg/ml)	Absorbance	Equation of line-
1.	2	0.038	**y** = 0.016x + 0.006
2.	4	0.073	
3.	6	0.108	**R^2** = 0.998
4.	8	0.137	
5.	10	0.170	

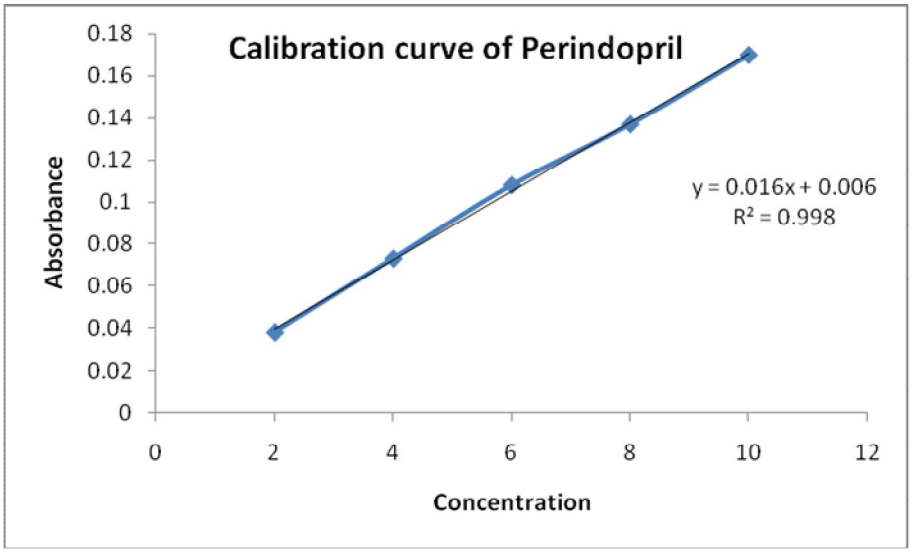
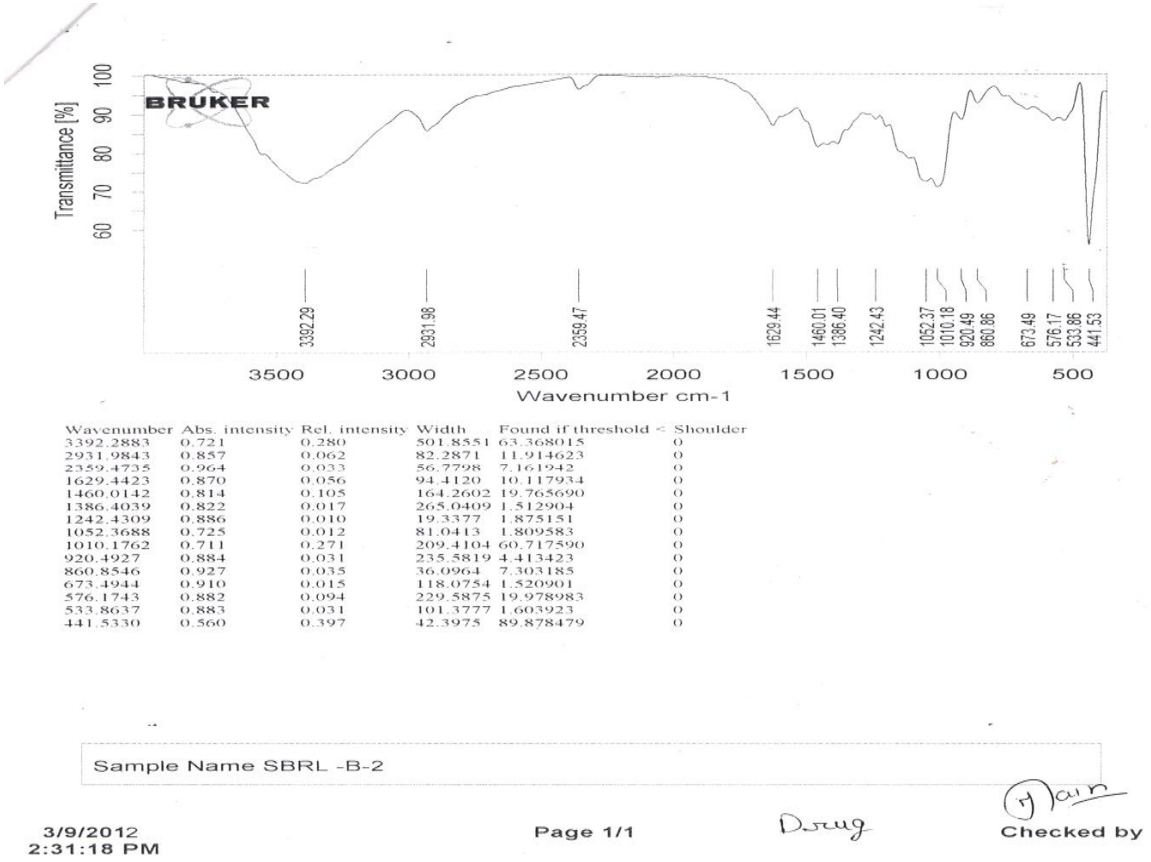


Fig-2. Calibration Curve of Perindopril

Infrared spectra analysis: Infrared spectrum of Perindipril was determined on Fourier Transform Infrared Spectrophotometer (FTIR-4100s) using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run.



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
3392.2883	0.721	0.280	501.8551	63.368015	0
2931.9843	0.857	0.062	82.2871	11.914623	0
2359.4735	0.964	0.033	56.7798	7.161942	0
1629.4423	0.870	0.056	94.4120	10.117934	0
1460.0142	0.814	0.105	164.2602	19.765690	0
1386.4039	0.822	0.017	265.0409	1.512904	0
1242.4309	0.886	0.010	19.3377	1.875151	0
1052.3688	0.725	0.012	81.0413	1.809583	0
1010.1762	0.711	0.271	209.4104	60.717590	0
920.4927	0.884	0.031	235.5819	4.413423	0
860.8546	0.927	0.035	36.0964	7.303185	0
673.4944	0.910	0.015	118.0754	1.520901	0
576.1743	0.882	0.094	229.5875	19.978983	0
533.8637	0.883	0.031	101.3777	1.603923	0
441.5330	0.560	0.397	42.3975	89.878479	0

Sample Name SBRL -B-2

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Drug

Checked by

Figure 3. drug interaction study of Perindopril

Preparation of Floating Tablet of Perindopril :

Each floating tablets containing Perindipril were prepared by a conventional wet granulation method, employing sodium bicarbonate, citric acid as gas generating agent and water-soluble polymer (HPMC K15M) as hydrophilic matrix in each formulation.**(Table No.1)** The concentration of gas generating agent (sodium bicarbonate) was developed as optimal concentration under experimental formulae and condition of preparation. All the ingredients were mixed thoroughly except magnesium stearate and talc. Granules were prepared manually with a solution of the Polyvinyl pyrrolidone (PVP K30) in sufficient isopropyl alcohol as binder. The wet mass was passed through a 16 mesh sieve no. and the wet granules produced were dried in hot air oven for 30 min at 50°C. The dried granules mixed with magnesium stearate as lubricant, talc as glidant and compressed into tablet on single punch machine (Khera made). Prior to compression, granules were evaluated for their flow and compressibility

characteristics.[12-15]

Table 5. Formulation of tablet

Fomulation Code	Perindopril (mg)	HPMC K15M (mg)	Sodium Bicarbonate (mg)	Sodium CMC (mg)	MCC (mg)	Citric acid (mg)	Sodium alginate (mg)	Magnesium Stearate (mg)
F1	4	15	15	6	40	8	2	10
F2	4	20	15	6	35	8	2	10
F3	4	25	15	5	30	8	2	10
F4	4	30	15	5	25	8	2	10
F5	4	35	15	5	20	8	2	10
F6	4	40	15	5	15	8	2	10

Evaluations of Granules Properties:

The flow properties of granules were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated.

Evaluation of Tablet Properties:

Weight variation test: 10 tablets were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight.

Weight uniformity test[16] :

If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test.[20] Tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average.

Hardness uniformity studies[16] :

The hardness of prepared formulation was measured by using Pfizer hardness tester. Five floating tablets were used for hardness uniformity studies. The hardness data used to calculate mean and standard deviation.

Thickness uniformity studies:

The thickness uniformity studies were carried out by using Vernier callipers. Five tablets were used for thickness uniformity studies and denoted in millimeter. The data obtained was used to calculate mean and standard deviation.

Drug estimation: 10 tablets were powdered and the blend equivalent to 25 mg of drug was weighed and dissolved in suitable quantity of methanoil. The solution was filtered, diluted and the drug content was analyzed spectrophotometrically at 243nm.[17]

Percentage of drug content is calculated by Y/X* 100

Where Y = Actual drug content (mg)

X = Labeled amount of drug (mg)

Friability: Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in plastic chamber revolving at 25 rpm and dropping the tablets at height of 6 inches in each revolution. Preweighed sample of tablets. was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.The friability (f) is given by the formula:

$$F = (W_0 / W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablet after the test. (Liberman HA *et al,*1989)

Disintegration: The time required for the tablets to disintegrate in mouth cavity was determined by holding the tablets in mouth. The tablet should disintegrate with in one minute when examine by the disintegration test for fast dissolving tablet by using artificial saliva or water by disintegration test apparatus.

Table 6. Evaluation of Tablet:

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)	Total floating duration

						(h)
F1	3.73±0.05	5.5	150.19± 0.24	0.98 ± 0.10	97.33± 0.92	8.23 ±0.03
F2	3.84± 0.08	5.4	150.18 ± 0.20	0.96 ± 0.08	98.20 ± 0.34	8.75±0.05
F3	3.96± 0.05	5.5	140.33 ± 0.28	0.99 ± 0.12	98.60 ± 1.39	9.05±0.06
F4	3.95± 0.05	5.7	160.10 ± 0.45	0.83 ± 0.04	98.14 ± 1.69	8.35±0.01
F5	3.93± 0.10	5.4	150.13 ± 0.83	0.87 ± 0.07	99.21 ± 1.07	6.40±0.06
F6	4.03± 0.06	5.8	156.16 ± 0.33	0.98 ± 0.05	98.50± 1.81	6.30±0.02
F7	4.05± 0.05	5.8	150.18 ± 0.11	0.99 ± 0.08	98.34 ± 0.37	6.40±0.05
F8	3.98± 0.05	5.5	140.04 ± 0.56	0.96 ± 0.12	98.31± 0.91	8.19±0.02

Dissolution rate study:

In vitro dissolution studies for all the fabricated tablets and the pure drug was carried out USP paddle method at 50 rpm in 900 ml of Phosphate Buffer pH 5.8, maintained at 37 $\pm$ 0.5 °C. 5 ml of aliquots withdrawn at specified intervals filtered through whatmann filter paper and analyzed at 243 nm using UV- Visible spectrophotometer. The dissolution media was then replaced by 5 ml of each fresh dissolution fluid to maintain a constant volume .(Jwuagwuma *et al*, 2002).

Table 7. Dissolution Profile of Perindopril Foating tablet

Time	**Cumulative % of Drug Release**							
(hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**

0.5	02.94	02.95	03.24	02.84	02.52	03.05	02.36	03.83
1	03.32	03.04	04.63	04.05	03.45	04.83	03.68	04.37
2	18.75	15.15	18.36	17.76	12.34	15.33	17.28	19.43
3	40.12	36.25	42.28	38.43	34.59	38.32	38.73	42.37
4	52.18	49.06	56.25	54.71	48.18	47.02	53.28	53.36
6	61.45	59.03	62.38	65.34	56.69	58.73	60.53	63.53
8	72.65	68.77	73.15	72.35	60.86	71.13	74.53	75.38
10	79.25	76.25	78.29	81.02	71.04	76.57	82.67	82.39
12	83.03	80.96	84.92	84.36	78.24	85.17	88.52	87.34

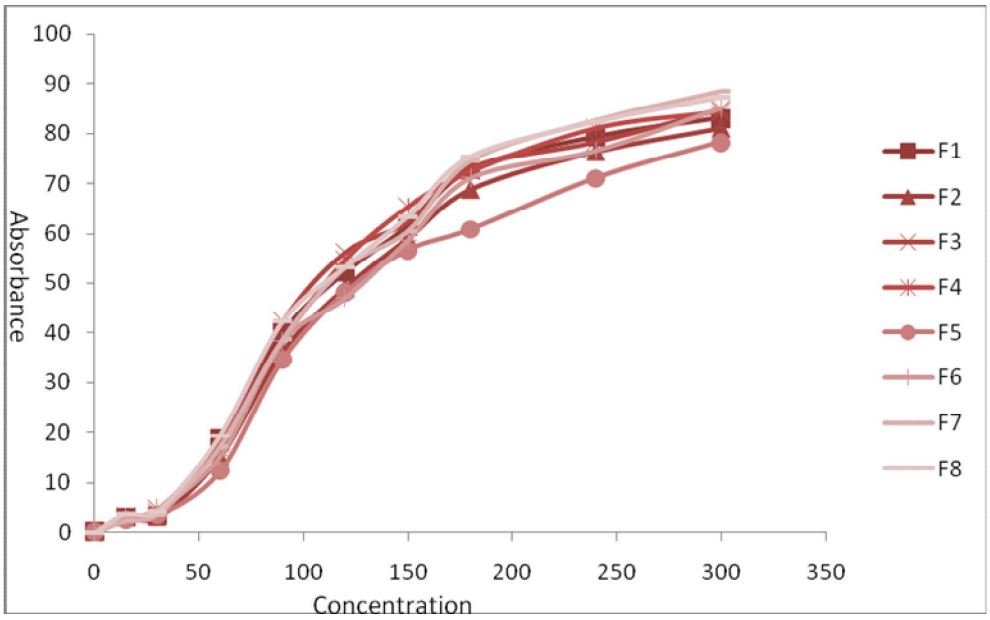

Figure 4. Dissolution curve of Perindopril Foating tablet

CONCLUSION:

Perindopril, can be successfully formulated as sustained release floating tablets which has the advantage to retain the dosage form in the effective site of absorption for long period of time and release the drug in sustained manner, ultimately achieving desired steady state concentration level and increased bioavailability of the drug. The current investigation proved that a

hydrophobic drug can be designed as modified release dosage form with desired qualities, using a hydrophilic polymer HPMC K15M and calcium carbonate as a buoyancy initiator. Additionally, ease of manufacturing process by direct compression implies that it ensures the capability of commercial utility by large scale production with satisfactory industrial feasibility.

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