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Formulation and Evaluation of Floating Tablet of Cilnidipine as an Antihypertensive Agent

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ABSTRACT

The heart pumps blood to various parts of the body. As blood passes through the blood vessels or arteries it pushes against the walls of the arteries. This is called blood pressure. Sometimes, due to certain causes, this pressure remains high for a sustained period causing what is called hypertension or high blood pressure. Antihypertensive drugs comprise several classes of a compound with the therapeutic intention of preventing, controlling, or treating hypertension[1]. Cilnidipine is a dihydropyridine calcium channel blocker developed for the treatment of high blood pressure. Cilnidipine has a half-life of 30.4 minutes, the bioavailability of 13%. Thus it is decided to prolong the gastric residence time in terms of making a floating gastro retentive drug delivery system to increase drug absorption and hence bioavailability. In this study, Cilnidipine floating tablets were prepared by using different concentrations of polymers such as HPMC K15, HPMC K 100, Carbopol 934 as sustained-release polymer, MCC as the diluent, sodium bicarbonate as gas generating agent, citric acid as a swelling agent. The tablets prepared by direct compression technique were evaluated in terms of their pre-compression parameters and post-compression characteristics such as physical characteristics, drug content, total floating capacity, swelling index, and *in-vitro* release. The *in-vitro* release studies confirmed that the formulation (F4) of HPMC K-15 showed drug release 99.0% up to 12 hours. The best formulation showed no significant change in physical appearance, drug content, total floating capacity, swelling index, or *in-vitro* release after storage at 40˚C±2 ˚C /75%±5% RH for three months.

INTRODUCTION:

Floating systems or dynamically controlled systems are low-density systems that have sufficient buoyancy to flow over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. This result is increased gastric retention time and better control of the fluctuations in plasma drug concentration.

Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves the solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. The retention of oral dosage forms in the upper gastrointestinal tract causes prolonged contact time of drug with GI mucosa leading to higher bioavailability and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size, and thus improved patient compliance[2].

Cilnidipine is a dual blocker of L-type voltage-gated calcium channels in vascular smooth muscle and N-type calcium channels in sympathetic nerve terminals that supply blood vessels. The inhibition of N-type calcium channels may provide a new strategy for the treatment of cardiovascular diseases. L-type calcium channels are the main targets of the CCB. N-type calcium is distributed along the nerve and in the brain. Cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system. It inhibits the calcium influx in both in a vessel & the nerve. So causes vasodilation & inhibits the release of norepinephrine, which causes the vasodilation and decreases the heart rate & also decreases cardiac contraction in the heart. So, used in the treatment of hypertension. Cilnidipine comes under BCS class II i.e. low solubility high permeability. Cilnidipine has a half-life of 30.4 minutes, the bioavailability of 13%. Thus it is decided to prolong the gastric residence time in terms of making a floating gastro retentive drug delivery system to increase drug absorption and hence bioavailability[3,4].

MATERIALS AND METHODS:

MATERIALS:

Cilnidipine was purchased from Banglore Fine Chemicals, HPMC K-15, HPMC K-100 was obtained from Balaji Drugs. Carbopol 934, Microcrystalline cellulose, Sodium bicarbonate, Citric acid, Talc, and Magnesium Stearate were obtained from S.D Fine Chemicals.

METHODS:

Floating tablets containing Cilnidipine were prepared by direct compression technique using varying concentrations of release rate retardant polymers such as HPMC K15, HPMC K100, Carbopol 934 were used. Sodium bicarbonate used as a gas generating agent. All the powders were accurately weighed and passed through 40 mesh sieve. Except for Magnesium stearate and talc, all other ingredients were mixed thoroughly for 15 minutes. After sufficient mixing of drugs as well as other components, Magnesium stearate and Talc were added, as post lubricant, and the blend was further mixed for additional 2-3 minutes. The final blend was compressed into tablets having an average weight of 200mg using a tablet machine.

Table No. 1: Formulations of Cilnidipine floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cilnidipine	5	5	5	5	5	5	5	5	5	5	5	5
HPMC K15	30	60	90	120	-	-	-	-	-	-	-	-
HPMC K100	-	-	-	-	30	60	90	120	-	-	-	-
Carbopol 934	-	-	-	-	-	-	-	-	30	60	90	120
Sodium bicarbonate	50	50	50	50	50	50	50	50	50	50	50	50
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Mag. stearate	3	3	3	3	3	3	3	3	3	3	3	3

EVALUATION OF CILNIDIPINE FLOATING TABLETS

An evaluation was performed to access the pre-compression properties of the powder blend and post-compression properties of developed gastric floating tablet formulations.

Pre-compression Studies

Determination of angle of repose[5]

The angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontal plane.

$$\text{Tan } \theta = h/r$$

Where,

θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

Determination of Bulk Density and Tapped Density[6]

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-sec intervals. The tapping was continued until no further change, volume was noted. The bulk density, and tapped density were calculated using the following formula.

$$\text{Bulk density} = W / VO$$

$$\text{Tapped density} = W / VF$$

Where,

W = weight of the granules,

V_O= initial volume of the granules,

V_F= final volume of the granules.

Hausner's Ratio

It indicates the flow properties of the powder and the ratio of Tapped density to the Bulk density of the powder or granules.

Hausner's Ratio = Tapped density/Bulk density

Carr's Index[7]

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find Carr's index.

$$\textbf{Carr's Index (\%)} = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Post-compression Parameters

Hardness

The hardness of the tablet was determined by using the Pfizer hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed pointer rides along with a gauge in the barrel to indicate the force[8].

Thickness

The thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of three tablets of each formulation[9].

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drugs. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight, and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit[10].

Friability

Friability of the tablet was determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed[11].

The friability (F) is given by the formula:-

$$\textbf{\% friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Content uniformity

10 tablets were haphazardly selected and powdered. A measured amount of powder equivalent to the mass of one tablet i.e. 200 mg was accurately weighed and transferred into a 100 ml volumetric flask containing 0.1N HCL. The flask was shaken until complete dissolving. 1ml of the above solution was diluted with 0.1N HCL. The absorbance of the resulting solution was measured at 240 nm using UV- visible spetrophotometre[12].

***In-vitro* Dissolution Study**

900ml of 0.1N HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was used. The medium was allowed to equilibrate to a temp of 37±0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 12 hours at 50 rpm. A definite time intervals, 5 ml of the fluid was withdrawn, filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 240 nm.

Measurement of floating capacity

The floating behavior of the formulations was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as the floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT)[13].

Swelling Index (SI) Studies

The swelling studies of a dosage unit were measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37±0.5°C. After 1/2, 1,2,3,4, and 5h each dissolution basket containing the tablet was withdrawn, blotted with tissue paper to remove the excess water, and weighed on the analytical balance. The experiment was performed in triplicate for each time point. The swelling index was calculated by using the following formula[14].

Swelling index (SI) =

Wet weight of the tablet – Dry weight of the tablet/ Dry weight of the tablet.

RESULTS AND DISCUSSION:

Precompression evaluation parameter

The pre-compression parameters such as the angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were evaluated. The results of all the pre-compression parameters were found to comply with the specification of IP. The results are displayed in Table 2.

Table No. 2: Pre-Compression Parameter results of powder

Formulations	Angle of Repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's Ratio
F1	29.96±0.33	0.67±0.01	0.75±0.10	10.66±0.25	1.11±0.10
F2	27.14±0.26	0.64±0.26	0.73±0.09	12.32±0.14	1.14±0.08
F3	28.73±0.21	0.60±0.13	0.71±0.11	15.49±0.08	1.18±0.03
F4	27.43±0.31	0.65±0.08	0.74±0.14	12.16±0.07	1.13±0.09
F5	29.53±0.24	0.61±0.12	0.70±0.12	12.85±0.11	1.14±0.04
F6	28.78±0.22	0.63±0.18	0.72±0.15	12.5±0.012	1.14±0.05
F7	28.32±0.28	0.59±0.22	0.75±0.08	12.15±0.09	1.27±0.03
F8	27.96±0.36	0.65±0.18	0.74±0.13	12.16±0.18	1.13±0.11
F9	29.58±0.29	0.62±0.07	0.72±0.07	13.88±0.15	1.16±0.06
F10	26.23±0.27	0.69±0.03	0.81±0.05	14.81±0.06	1.17±0.13
F11	28.73±0.26	0.66±0.04	0.79±0.06	15.45±0.06	1.19±0.07
F12	29.50±0.23	0.68±0.11	0.77±0.12	11.68±0.21	1.13±0.10

All the values represent (Number of experiments n=3, mean ± SD)

Post compression evaluation parameter

All the formulations were subjected to post-compression evaluation such as thickness, hardness, friability, weight variation, and drug content. The results of these tests are shown in table 3.

Table No. 3: Post compression studies

Formulations/ Parameters	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	4.12±0.02	5.8± 0.04	0.78±0.18	198±1.45	90.2
F2	4.34±0.08	5.8±0.03	0.52±0.07	199±1.65	90.7
F3	4.42±0.07	5.8±0.03	0.73±0.53	194.5±1.14	93.7
F4	4.51±0.15	5.8±0.04	0.76±0.64	200.5±2.12	99.0
F5	4.42±0.05	5.9±0.06	0.56±0.08	197.5±1.38	91.7
F6	4.41±0.04	6.0±0.07	0.51±0.06	200.5±2.17	92.6
F7	4.22±0.03	6.0±0.06	0.78±0.78	198.5±1.61	93.4
F8	4.50±0.12	6.0±0.05	0.76±0.69	197.5±1.58	94.5
F9	4.41±0.11	6.0±0.05	0.79±0.89	194±1.32	95.6
F10	4.28±0.13	5.9±0.03	0.54±0.07	197.5±1.84	96.3
F11	4.54±0.17	6.0±0.05	0.72±0.15	198.5±2.11	95.9
F12	4.43±0.14	6.0±0.06	0.77±0.86	197.5±2.21	96.8

All the values represent (Number of experiments n=3, mean ± SD).

Swelling index

The swelling index of the prepared tablets from each formulation (F1 to F12) was evaluated. Formulations F1 and F2 show the swelling index of 290 & 310 % respectively up to 6 hours. Formulation F3 shows the swelling index of 325 % up to 11 hours. Formulations F4, F7, and F8 show the swelling index of 275, 315, and 320 % respectively up to 12 hours. Formulation F5 shows the swelling index of 245 % up to 7 hours. Formulations F6 & F9 shows the swelling index of 290 & 300 % up to 8 hours. Formulations F10 & F11 shows the swelling index of 290 & 325 % up to 9 hours. Formulation F12 shows the swelling index of 380 % up to 10 hours. The highest and lowest swelling was observed with the formulation of F12 and F5 respectively. The result of the swelling index is mentioned in Table No 4.

Table No 4: Swelling index

Formulation code	Swelling Index (%) at different time intervals											
	1 (hrs)	2 (hrs)	3 (hrs)	4 (hrs)	5 (hrs)	6 (hrs)	7 (hrs)	8 (hrs)	9 (hrs)	10 (hrs)	11 (hrs)	12 (hrs)
F1	70	120	165	205	250	290						
F2	80	130	180	225	265	310						
F3	65	95	135	170	195	215	235	250	275	295	325	
F4	50	85	105	145	175	190	210	220	235	245	260	275
F5	45	80	120	140	190	215	245					
F6	55	105	150	180	210	240	270	290				
F7	65	90	110	140	165	195	220	240	265	280	300	315
F8	75	100	125	145	170	205	220	245	270	290	310	320
F9	60	100	155	175	210	250	265	300				
F10	70	115	145	225	240	255	270	282	290			
F11	75	120	165	200	230	260	285	310	325			
F12	80	110	160	200	240	275	310	330	360	380		

Floating Capacity

The floating behavior of the tablets from each formulation F1 to F12 was evaluated. Formulation F1 floated up to 5 hours with a lag time of 3 seconds. Formulation F2 floated up to 6 hours with a lag time of 9 seconds. Formulations F3, F4, F7, and F8 floated up to 12 hours with a lag time of 16, 24, 21, and 25 seconds respectively. Formulation F5 floated up to 7 hours with a lag time of 6 seconds. Formulations F6 & F9 floated up to 8 hours with a lag time of 11 & 57 seconds. Formulations F10 & F11 floated up to 9 hours with a lag time of 127 & 70 seconds respectively. Formulation F12 floated up to 10 hours with a lag time of 120 seconds. The result of floating capacity is mentioned in Table no. 5.

Table No. 5: Floating capacity

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lag time (sec)	3	9	16	24	6	11	21	25	57	127	70	120
Log time (hrs)	5	6	12	12	7	8	12	12	8	9	9	10

***In-vitro* release studies**

The prepared tablets were evaluated for *in-vitro* release studies. Formulations F1 and F2 show drug release of 98.82 & 97.84 % at the end of 7 hours respectively. Formulation F3 shows the drug release of 97.44 % at 11 hours. Formulations F5, F6, and F12 show the drug release of 95.55, 92.79, and 98.55 % respectively at the end of 8 hours. Formulation F9 shows the drug release of 92.35 % at 9 hours. Formulations F10 and F11 show the drug release of 94.25 & 97.91 % respectively at the end of 10 hours. Formulations F4, F7 & F8 shows sustained release of drug up to 12 hours. A maximum amount of drug release (99%) was found in formulation F4 containing polymer HPMC K15 (120 mg).

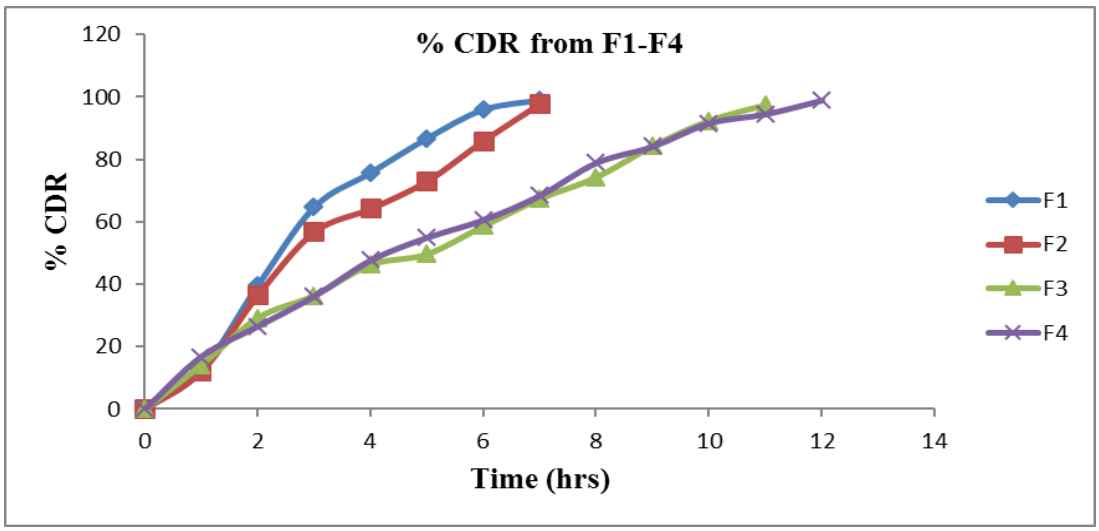

Figure No. 1: *In-vitro* release study of Cilnidipine from F1-F4

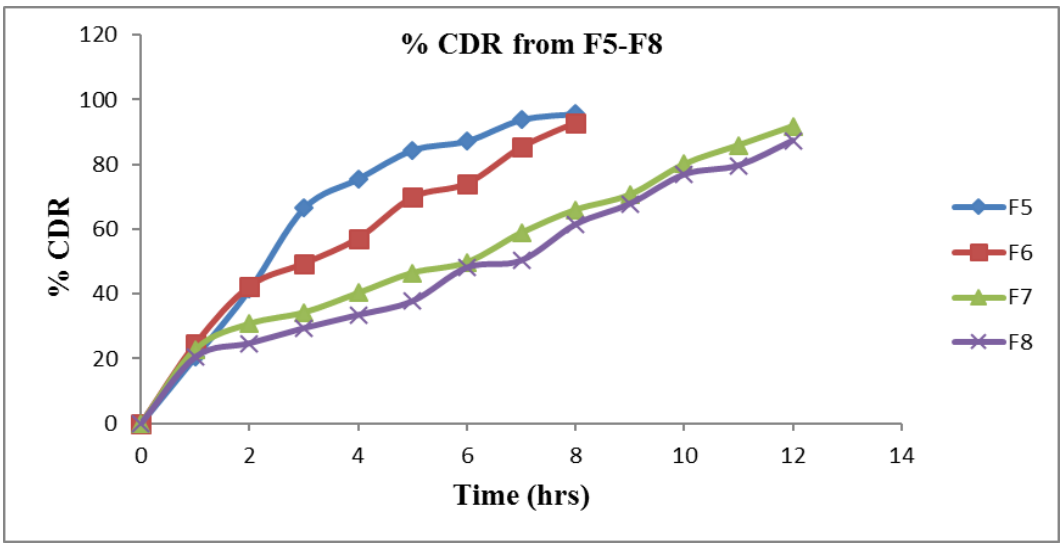

Figure No. 2: *In-vitro* release study of Cilnidipine from F5-F8

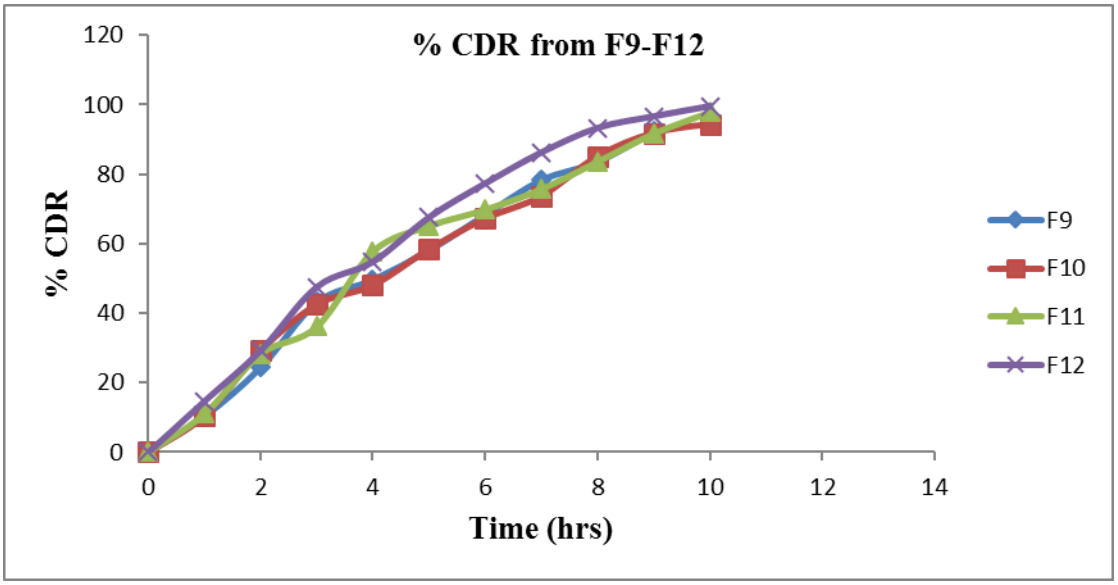

Figure No. 3: *In-vitro* release study of Cilnidipine from F9-F12

Kinetics modelling data

From the kinetics studies, where (r^2 = 0.99750) and ('n' value=0.7381), it can be concluded that the formulation follows Korsmeyer-Peppas model and Non-fickian diffusion. The kinetics of optimized formulation (F4) is shown in table no. 6.

Table No. 6: Kinetics modelling data

Formulations	Zero	First	Higuchi	Korsmeyer –peppas	
	r^2	r^2	r^2	r^2	'n'
F4	0.9778	0.843	0.9746	0.99750	0.7381

Stability studies results

The stability studies for best formulations were carried out as per procedure in the methodology part. There were not any significant changes in the drug after storage for about 3 months. The results of the stability are given in the following table no. 7.

Table No. 7: Accelerated stability study of formulation F4 at 40°C±2°C and 75%±5%RH

Months	Swelling index (%)	Floating capacity		Drug content (%)	Drug release (%)
		Lag time (sec)	Log time (hrs)		
1	270	23	12	98.99	98.90
2	270	23	12	99.89	98.90
3	275	24	12	99.0	99.0

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CONCLUSION:

The development of Gastroretentive floating drug delivery of Cilnidipine tablets is to provide the drug action for up to 12 hours. Gastroretentive floating tablets were prepared by direct compression technique using various polymers like HPMC K15, HPMC K100, Carbopol 934. The tablets were evaluated for different parameters such as drug excipient compatibility studies, hardness, weight variation, thickness, content uniformity, swelling index, floating capacity. In- vitro drug released studies performed in 0.1N HCL for 12 hrs and the formulation was subjected to zero order, first order, Higuchi release kinetics, and Korsmeyer peppas graph. The following conclusions could be drawn from the results of various experiments.

FTIR studies showed that there was no interaction between drug and excipients. The physicochemical properties of all the formulations with different concentrations of polymers were shown to be within limits. *In-vitro* drug release studies were carried out for all prepared formulations. F4 formulation was optimized based on the various physic-chemical evaluation parameter. Stability studies were carried out for formulation F4 for three months and the results show there is no significant difference in the drug content, floating behavior, swelling index, and drug release. The present study concludes that the gastroretentive floating drug delivery system of Cilnidipine may be a suitable formulation for the treatment of hypertension. Further, to confirm the suitability of the formulation future studies like in-vivo bioavailability studies is required.

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