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Research Article

Development and *In Vitro* Evaluation of Gastroretentive Floating Matrix Tablets of Hydralazine

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Abstract

The purpose of the present study was to develop an optimized gastric floating drug delivery system (GFDDS) containing Hydralazine as a model drug by using various proportions of polymers such as Sodium CMC, Carbopol p934 and HPMC K4M. This was employed to enhance the bioavailability and therapeutic efficacy of the drug. The sustained release formulations of Hydralazine using hydrophobic and hydrophilic polymers were prepared by direct compression method. Optimization of formulation was done by studying effect of drug to polymer ratio on drug release. FT-IR studies indicated absence of any interaction between Hydralazine, polymer (Sodium CMC, Carbopol P 934 and HPMC K4M) and excipients. Nine formulations were prepared and formulation F2 possessed good floating property with total floating time between 8-12 hours. The tablets were also evaluated for its hardness, friability, and *in-vitro* evaluation test. All parameters complied with IP limits. Results of this study indicated that the combinations of hydrophilic polymers with hydrophobic polymers are suitable to optimize sustained release formulation of Hydralazine.

Keywords: Hydralazine, Sodium CMC, Carbopol P934 and HPMC K4M, Floating Tablets.

INTRODUCTION

Despite tremendous advancement in drug delivery, oral drug delivery systems[1,2] has received the more attention and success because the gastrointestinal physiology offers more flexibility and better patient compliances[3,4]than other routes. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile.

Conventional oral dosage forms[5] such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Many attempts have been made to develop sustained release preparations with extended clinical effects and reduced dosing frequency [6,7]. A problem frequently encountered with conventional sustained release dosage forms is the inability to increase their residence time in stomach and no control over drug delivery, leading to fluctuations in plasma drug level.

Gastroretentive systems 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 solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proxima lsmall intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system(FDDS)

A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine[8,9]

Mechanism of floating systems: Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate[10,11] for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT.

METHODOLOGY

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-1}.

7.3. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. The various characteristics of blends tested as per Pharmacopoeia are:

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. 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. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ θ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Bulk density:

Bulk density is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo,was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

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. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

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. Compressibility Index is calculated using the following formula:

$$\text{Carr's Index} = [(tap - b) / tap] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Procedure for direct compression method:

1) Drug 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 by using 6 mm punch.

Evaluation of post compression parameters for prepared Tablets

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. 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. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 7.5: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

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 Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measure of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed 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, and loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W1] \times 100$$

Where, W1 = Initial weight of tablets

W2 = Weight of the tablets after testing

Determination of drug content:

Ten tablets were finely powdered ,quantities of the powder equivalent to one tablet weight of clopidogrel were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* Buoyancy studies:**

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described *by Rosa et al*) 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 floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* drug release studies**

Dissolution parameters:

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

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

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 12 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 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 media and analyzed by spectrophotometrically at 264 nm using UV-spectrophotometer.

7.5: 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.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$\text{Log } (100-F) = kt$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$F = k\, t1/2$ Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K\, t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

FORMULATION OF TABLETS:

Table 7.4: Formulation composition for Floating tablets

Ingredients	Formulation chart								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hydralazine	20	20	20	20	20	20	20	20	20
Sodium CMC	5	10	15	-	-	-	-	-	-
Carbopol p934	-	-	-	5	10	15	-	-	-
HPMC K4M	-	-	-	-	-	-	5	10	15
NaHCO3	15	15	15	15	15	15	15	15	15
Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Total weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULTS AND DISCUSSION

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

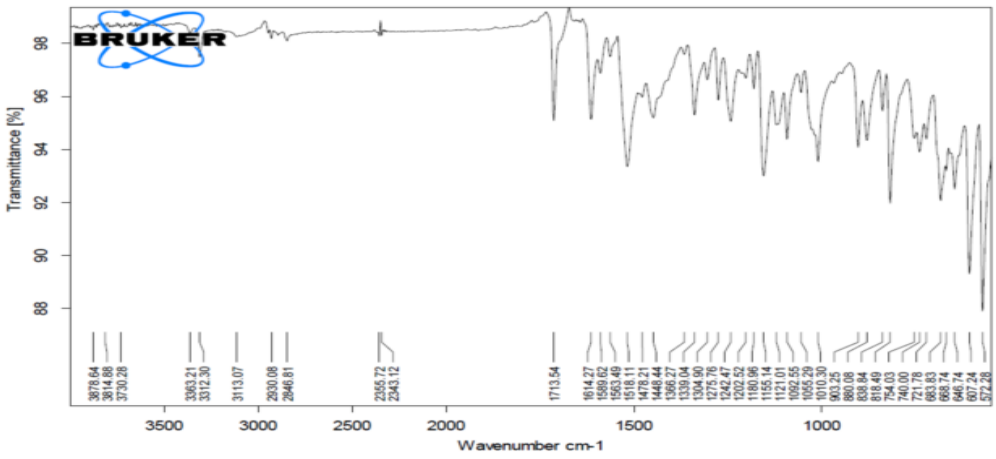
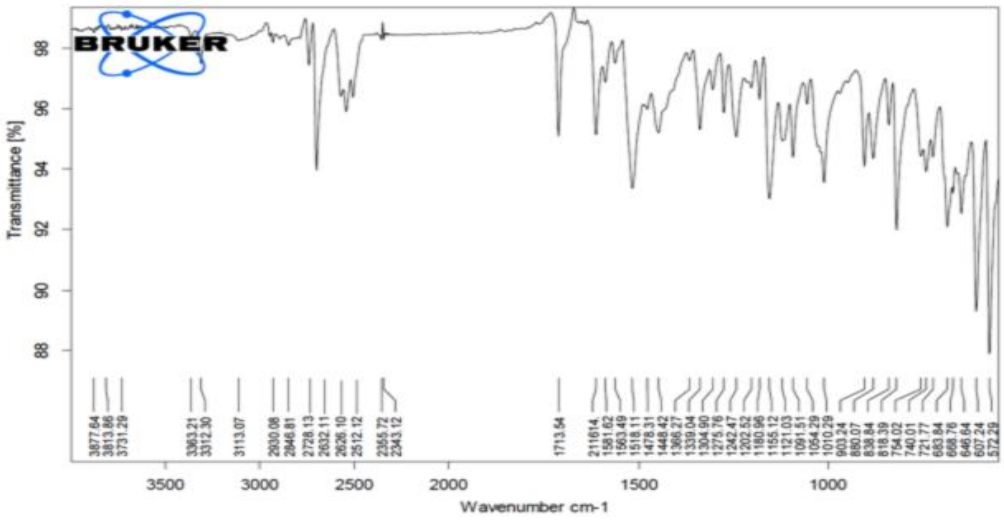


Figure 8.9: FTIR Spectrum of pure drug



FTIR Spectrum of optimised formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions. Hydralazine are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

Pre-formulation parameters of blend

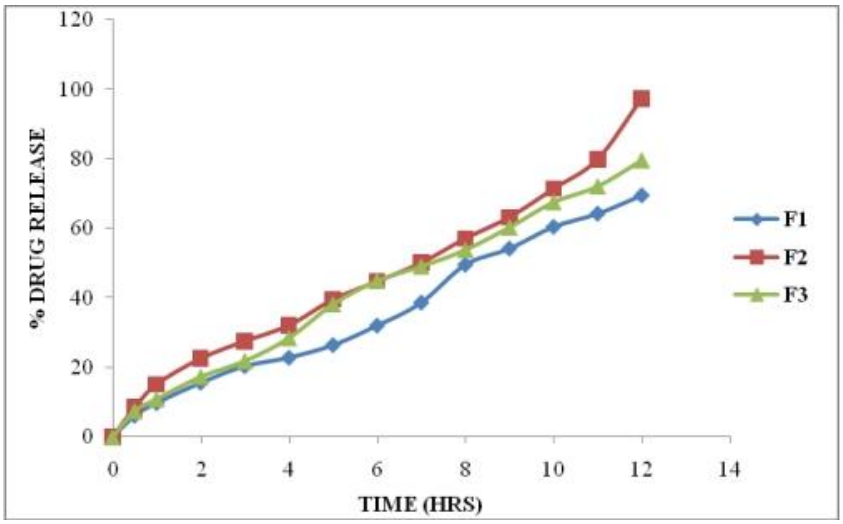
Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	28.36	0.46	0.54	14.81	1.19
F2	25.64	0.42	0.63	30.15	1.50
F3	27.02	0.44	0.54	18.05	1.22
F4	24.22	0.52	0.57	8.77	1.09
F5	31.38	0.57	0.63	9.52	1.10
F6	24.22	0.46	0.57	19.29	1.23
F7	30.11	0.42	0.52	19.23	1.23
F8	22.29	0.52	0.60	13.33	1.15
F9	27.02	0.48	0.57	18.75	1.08

***In vitro* quality control parameters**

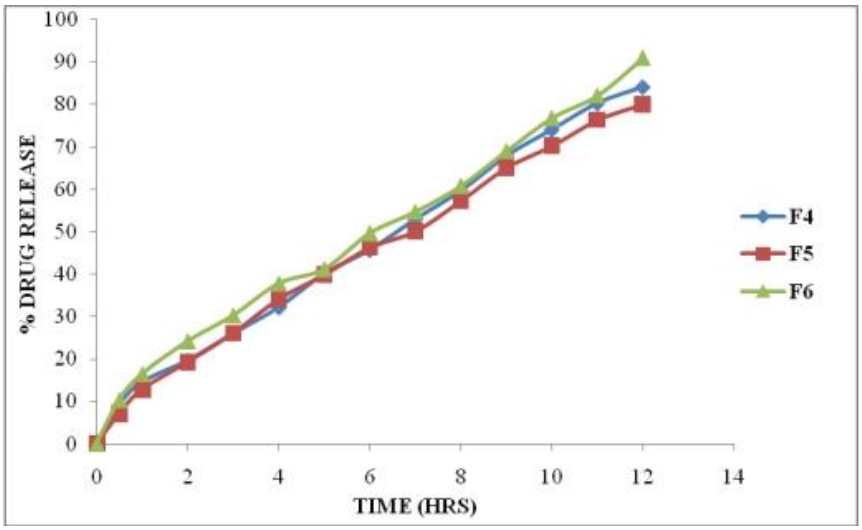
Formulation codes	Average Weight (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag time (sec)	Total Floating Time (Hrs)
F1	98.58	6.2	0.25	3.1	99.61	60	10
F2	99.69	6.8	0.36	3.8	98.65	68	9
F3	96.92	6.9	0.55	3.6	97.32	78	8
F4	98.63	6.1	0.61	3.1	95.69	90	7
F5	100.12	6.0	0.48	3.9	97.88	45	10
F6	99.5	6.5	0.63	3.7	98.59	86	9
F7	97.58	6.3	0.51	3.8	98.66	70	11
F8	98.85	6.8	0.35	3.6	97.26	78	9.5
F9	99.25	6.1	0.42	3.1	100.61	82	12.1

Dissolution data of Floating Tablets

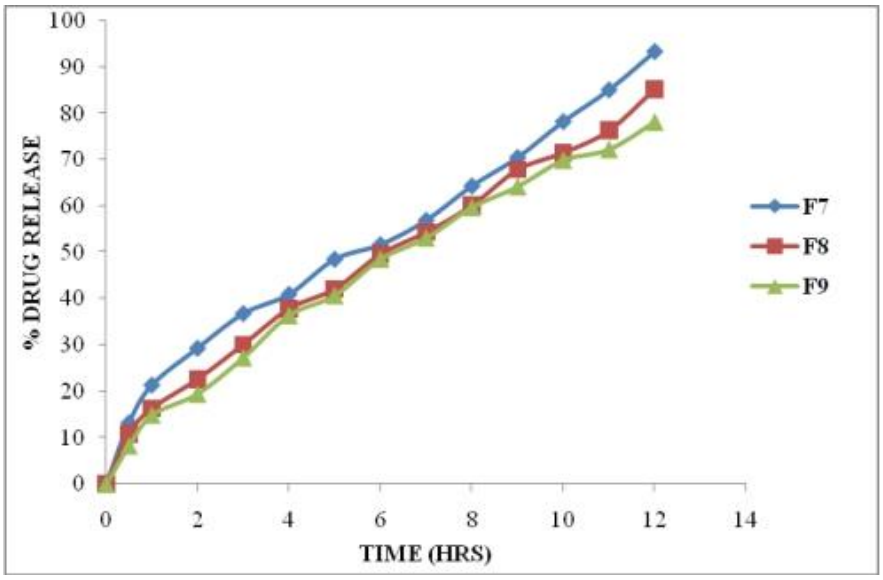
Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	6.21	8.59	7.52	9.15	7.10	10.34	13.26	10.90	8.29
1	9.86	15.20	10.96	14.55	12.83	16.46	21.42	16.35	14.92
2	15.68	22.65	17.38	19.64	19.28	24.18	29.37	22.68	19.48
3	20.45	27.60	21.91	25.98	26.12	30.27	36.84	30.14	27.31
4	22.89	32.16	28.54	32.17	34.10	37.81	40.99	37.86	36.42
5	26.51	39.58	38.23	40.11	39.87	41.20	48.56	42.11	40.70
6	32.10	44.78	44.98	45.69	46.28	49.66	51.71	49.63	48.57
7	38.72	50.15	49.14	52.92	50.12	54.69	56.97	54.33	53.12
8	49.61	57.11	53.88	59.66	57.33	60.78	64.38	60.11	59.72
9	54.26	63.23	60.36	67.86	65.12	68.99	70.52	67.82	64.20
10	60.52	71.41	67.59	74.10	70.29	76.80	78.28	71.49	69.90
11	64.30	79.89	72.14	80.31	76.43	82.10	85.12	76.25	72.21
12	69.55	97.31	79.64	84.15	80.11	90.97	93.39	85.20	78.11



Dissolution data of Hydralazine Floating tablets containing Sodium CMC



Dissolution data of Hydralazine Floating tablets containing Carbopol p934

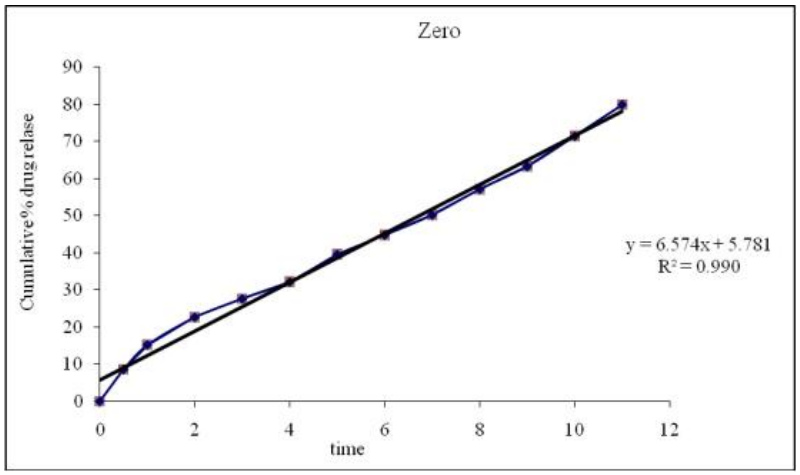


Dissolution data of Hydralazine Floating tablets containing HPMC K4M

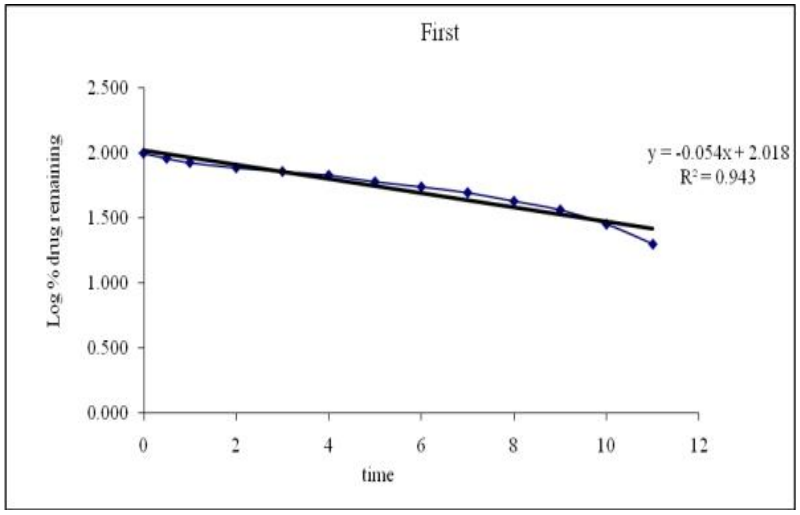
Hence from the above dissolution data it was concluded that F2 formulation was considered as optimised formulation because good drug release (97.31%) in 12 hour

Application kinetics for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE /	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	**0**	0			2.000				100	4.642	4.642	0.000
8.59	**0.5**	0.707	0.934	-0.301	1.961	17.180	0.1164	-1.066	91.41	4.642	4.505	0.137
15.2	**1**	1.000	1.182	0.000	1.928	15.200	0.0658	-0.818	84.8	4.642	4.393	0.248
22.65	**2**	1.414	1.355	0.301	1.888	11.325	0.0442	-0.645	77.35	4.642	4.261	0.381
27.6	**3**	1.732	1.441	0.477	1.860	9.200	0.0362	-0.559	72.4	4.642	4.168	0.474
32.16	**4**	2.000	1.507	0.602	1.831	8.040	0.0311	-0.493	67.84	4.642	4.078	0.563
39.58	**5**	2.236	1.597	0.699	1.781	7.916	0.0253	-0.403	60.42	4.642	3.924	0.718
44.78	**6**	2.449	1.651	0.778	1.742	7.463	0.0223	-0.349	55.22	4.642	3.808	0.834
50.15	**7**	2.646	1.700	0.845	1.698	7.164	0.0199	-0.300	49.85	4.642	3.680	0.961
57.11	**8**	2.828	1.757	0.903	1.632	7.139	0.0175	-0.243	42.89	4.642	3.500	1.141
63.23	**9**	3.000	1.801	0.954	1.565	7.026	0.0158	-0.199	36.77	4.642	3.325	1.316
71.41	**10**	3.162	1.854	1.000	1.456	7.141	0.0140	-0.146	28.59	4.642	3.058	1.584
79.89	**11**	3.317	1.902	1.041	1.303	7.263	0.0125	-0.098	20.11	4.642	2.719	1.922
97.31	**12**	3.464	1.988	1.079	0.430	8.109	0.0103	-0.012	2.69	4.642	1.391	3.251



Zero order release kinetics



First order release kinetics

Optimised formulation F2 was kept for release kinetic studies. From the above graphs it was evident that the formulation F2 was followed Zero order release mechanism.

CONCLUSION

The research was undertaken with the aim to formulate and evaluate the sustained release floating tablets of Hydralazine using Sodium CMC, Carbopol p934 and HPMC K4M as polymers. From results obtained, it was concluded that the formulation of sustained release tablet of Hydralazine containing a combination of polymers (Sodium CMC) was taken as ideal or optimized formulation for 12 hours release as it fulfills all the requirement of sustained release dosage form.

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