



## Formulation and Evaluation of Floating Alginate Microbeads of Hydralazine Hydrochloride

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Received: 18-02-2021; Revised: 20-03-2021; Accepted: 27-03-2021; Published on: 20-04-2021.

### ABSTRACT

Hydralazine is a direct-acting vasodilator and has a short biological half-life (2-4 hours) due to significant first-pass metabolism with poor oral bioavailability. The aim of the current research is to reduce the frequency of dosing and enhance bioavailability to improve patient compliance by developing and systematically evaluating the sustained release of Floating alginate microbeads of Hydralazine hydrochloride. Using sodium alginate as the hydrophilic carrier in combination with different viscosity grades of HPMC such as HPMC K4M, HPMC K15M and HPMC K100M as drug release modifiers for the preparation of floating alginate microbeads of Hydralazine Hydrochloride by ionotropic gelation and cross-linking technique. Prepared beads were evaluated for percentage yield, particle size, micromeritic properties, drug entrapment efficiency, drug loading capacity, swelling ratio, *in-vitro* buoyancy studies, *in-vitro* release (in acidic buffer pH 1.2) and *in-vitro* release kinetic study. No significant drug-polymer interactions were observed from FT-IR studies. In fixed concentration of sodium alginate and calcium chloride and increases in the coating polymer concentration results increases in diameter of microbeads and also decrease the swelling ratio of beads. With the increase in coating polymer ratio, drug entrapment efficiency has been improved. All the formulations (F<sub>1</sub> to F<sub>9</sub>) floated immediately or with a very short lag time and remained floating up to 12 hours. From the result of *in-vitro* dissolution studies reveals that the formulation F<sub>9</sub> gave sustained release pattern of drug upto 12 hours (99.75%) and exhibited zero order kinetic followed by non-fickian diffusion transport of mechanism. Hence the formulated HPMC K100M coated sodium alginate beads can be used as an alternative and cheaper carrier for the oral controlled delivery of Hydralazine hydrochloride, especially for the treatment of congestive heart failure.

**Keywords:** Hydralazine hydrochloride, HPMC K4M, HPMC K15M, HPMC K100M, Ionotropic gelation method, Floating alginate microbeads.

QUICK RESPONSE CODE →

DOI:

10.47583/ijpsrr.2021.v67i02.015



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2021.v67i02.015>

### INTRODUCTION

The most desirable and recommended method of delivering therapeutic agents for their systemic effects is oral drug delivery, largely due to patient acceptance, convenience and cost-effective manufacturing processes.<sup>1</sup> The drug bioavailability of pharmaceutical dosage forms is influenced by numerous factors including gastric residence time (GRT) and gastric emptying time (GET). In general, the gastric emptying process lasts from a few minutes to a few hours from the stomach to the small intestine. This variability results in an unpredictable bioavailability of the dosage form given orally. Furthermore, the relatively short gastric emptying time may result in an incomplete release from the dosage form of the drug. Floating drug delivery system (FDDS) is one of gastroretentive dosage forms that could prolong GRT to obtain sufficient drug bioavailability. FDDS have a lower density than gastric fluids and thus remain buoyant

in the stomach without affecting the gastric emptying rate for a prolonged period of time.<sup>2</sup>

Microbeads are multi particulate drug delivery systems used for the sustained delivery of drugs with more uniform distribution of the drug in the gastrointestinal tract and to reduce local irritation. Microbeads are small, solid and free flowing particulate carriers containing dispersed drug particles either in solution or crystalline for that allow a sustained release or multiple release profiles of treatment with various active agents without major side effects.<sup>3</sup> It can be prepared by various methods with many natural and synthetic polymers were investigated for their use in drug delivery. Alginates, natural polymers found in brown algae, have been investigated for the controlled drug delivery. Alginate's safety is well-established and offers a further protective effect on the viability of mucous membranes of the gastrointestinal tract.<sup>4</sup>

Hydralazine is a directly acting vasodilator and widely prescribed in the treatment of congestive heart failure and hypertension. Following oral administration, it is readily absorbed and subjected to significant first-pass metabolism. It is reported for a short biological half-life of 2-4 hours. Therefore, to produce better patient compliance by reducing dosing frequencies and enhanced oral bioavailability sustained release gastroretentive dosage forms of Hydralazine might be beneficial.<sup>5</sup>



The main aim of the present study was to develop the sustained release oral product of floating alginate microbeads of Hydralazine hydrochloride using different viscosity grades of HPMC like HPMC K4M, HPMCK15M and HPMC K100M as drug release modifiers in various proportions to reduce the dosing frequency and thereby improve the patient compliance and also improve the bioavailability of the drug. The obtained beads were evaluated for percentage yield, particle size analysis, encapsulation efficiency, drug loading capacity, swelling ratio, *in-vitro* floating properties, *in-vitro* release behavior and stability study.

## MATERIALS AND METHODS

### Materials

Hydralazine hydrochloride was procured as gift from the Exeltis- Ordain Health Care Global Pvt Ltd (Chengalpattu). Polymers like Sodium alginate, HPMC K4M, HPMC K15M, HPMC K100M were used. Calcium carbonate, Calcium chloride and all other reagents used were analytical grade.

### Methods

#### Preformulation studies

#### Melting point

Melting point of the sample was determined by Capillary tube method.

#### Standard curve of Hydralazine hydrochloride

The drug solutions (2-10µg/ml) were taken in 0.1N Hcl in standard cuvette and scanned in the range of 200-400nm using UV spectrophotometer. The absorbance of each sample was measured at 234.8nm using 0.1N Hcl as a blank. The calibration curve was then plotted by using concentration at X-axis and absorbance at Y-axis.

### Fourier transform infrared (FTIR) spectral analysis

Pure drugs, polymers, excipients and drug-excipient mixture were subjected to FTIR studies to investigate the Drug- excipient interactions. The IR spectra of the test samples were obtained by Pressed Pellet Technique using Potassium bromide. The drug is mixed with KBr and pellet is formed. Each KBr disk was scanned at 4 mm/s at a resolution of 2 cm over a wave number region of 400 to 4,500 cm<sup>-1</sup>. The characteristic peaks were recorded.<sup>6-8</sup>

### Formulation of floating alginate microbeads

The microbeads were prepared by Ionotropic gelation technique in which sodium alginate (3%w/v) was accurately weighed and dissolved in slightly warmed distilled water. The sodium alginate solution was homogenized by stirring on magnetic stirrer for 45 min before formulation. HPMC K4M / HPMC K15M / HPMC K100M and calcium carbonate (gas forming agent) were dispersed in alginate solution under constant stirring for uniform mixing. Drug was accurately weighed and added or disperse in alginate solution during homogenization. After completing the homogenization process, solution was kept stand for 15 min without stirring and then sonicate for 10 min using bath sonicator to remove the air bubbles formed during homogenization. In another beaker 100 ml of water containing acetic acid (10%v/v) and calcium chloride (5%w/v) solution was prepared in which sodium alginate solution containing drug was dropped with the help of 29-gauge hypodermic needle fitted with 10ml syringe into previously prepared calcium chloride solution. 10 cm distance was maintained during dropping the alginate solution. Beads were incubated for 30 min and after complete incubation beads were separated by filtering the solution. Obtained beads were washed three times with distilled water and dried at 40°C. Prepared beads were stored in very tight container before further use in their characterization.<sup>9</sup>

**Table 1:** Formula for floating alginate microbeads of Hydralazine Hydrochloride

Formulations	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	F <sub>8</sub>	F <sub>9</sub>
Drug (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPMC K4M (g)	0.5	1.0	1.5	-	-	-	-	-	-
HPMC K15M (g)	-	-	-	0.5	1.0	1.5	-	-	-
HPMC K100M (g)	-	-	-	-	-	-	0.5	1.0	1.5
Sodium alginate (%w/v)	3	3	3	3	3	3	3	3	3
Calcium Carbonate (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium chloride (%w/v)	5	5	5	5	5	5	5	5	5
Acetic acid (% v/v)	10	10	10	10	10	10	10	10	10

### Evaluation of microbeads

#### Determination of percentage yield

The percentage yield of floating alginate microbeads was calculated by the following formula:

$$\text{Percentage yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$



### Particle size analysis

The particle sizes of drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out as triplicate.

### Determination of flow properties

Flow properties were determined by bulk density, tapped density and Angle of repose.

### Bulk Density and Tapped Density

A measured quantity of granules was transferred to a measuring cylinder measuring its initial volume [V<sub>0</sub>] and tapped manually either manually or using some tapping device till a constant volume [V<sub>f</sub>] and it includes the true volume of the granules and void space between them. The bulk density and tapped density was calculated by the following formulae.

Bulk density is the ratio between a mass of granules and its bulk volume [V<sub>0</sub>]. It is expressed by g/cm<sup>3</sup>

$$\text{Bulk density} = \frac{\text{Mass of the beads}}{\text{Bulk volume of beads [V}_0\text{]}}$$

Tapped density is the ratio between a mass of granules and volume of the granules after tapping [V<sub>f</sub>]. It is expressed by g/cm<sup>3</sup>

$$\text{Tapped density} = \frac{\text{Mass of the beads}}{\text{Tapped volume of beads [V}_f\text{]}}$$

### Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of a pile powder and the horizontal plane. The tangent of the angle is equal to the coefficient of friction between the particles. Microbeads were allowed to fall freely the funnel, which was fixed at 1 cm above the horizontal flat surface until the apex of pile just touches the tip of the funnel. The formation of sharp cone would mean poor flow property while a good spread would indicate a superior flow property. The angle of repose (Θ) was determined by formula,

$$\text{Angle of repose } (\Theta) = \tan^{-1} (h/r)$$

Where, **h** = height of pile; **r** = radius of pile

### Drug Loading and Entrapment Efficiency

An accurately weighed sample of beads (100mg) was crushed in a mortar. The crushed material was dissolved in 75ml of 0.1N HCl, then made up to 100ml. This mixture was filtered and analyzed by UV spectrophotometer at λ max 234 nm against 0.1N HCl as blank. The drug loading and entrapment efficiency percentage can be calculated by using the following equations.

$$\text{Drug Loading \%} = \left( \frac{\text{Actual drug content}}{\text{Weight of beads}} \right) \times 100$$

$$\text{Entrapment Efficiency \%} = \left( \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \right) \times 100$$

### Evaluation of Swelling ratio

Swelling ratio was studied by measuring the percentage water uptake by the beads. About 50 mg of beads were accurately weighed and placed in 100 ml of acid buffer (pH 1.2- 0.1N HCl). The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

$$\text{Swelling ratio} = \frac{\text{Weight of wet beads}}{\text{Weight of dried beads}}$$

### In-vitro floating properties

The floating alginate beads of Hydralazine Hcl were immersed in 900ml of 0.1N HCl (pH 1.2) in USP type II apparatus at 50 rpm maintained at 37 ± 0.5°C. The floating ability (buoyancy) of beads was measured by visual observation. The time taken to float at the surface of dissolution medium known as floating lag-time and duration of floating were noted.

### In-vitro dissolution studies

In-vitro dissolution studies were performed for all the formulations using USP type II apparatus. An accurately weighed floating alginate beads were taken into 900ml 0.1 N HCl buffer (pH 1.2). The temperature was maintained at 37 ± 0.5°C and stirred at a speed of 50 rpm. At specified time intervals 5 ml of sample was withdrawn, at the same time 5 ml of fresh dissolution media was added to maintain sink condition. The collected samples were filtered if necessary and analyzed at 234.8 nm using UV spectrophotometer against 0.1 N HCl buffer (pH 1.2) taken as blank.

### Release kinetic study

In order to understand the mechanism and kinetics of drug release, the drug release data of the in-vitro dissolution study was analyzed with various kinetic equations like zero-order, first order, Higuchi and Korsmeyer and pappas equation. Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the plots.<sup>10-15</sup>

## RESULTS AND DISCUSSION

### Preformulation studies

#### Melting point determination

Melting point of the crystalline Hydralazine hydrochloride found to be 172 ± 0.145°C

#### Standard curve for Hydralazine hydrochloride in acid buffer pH 1.2

The λmax of Hydralazine Hcl at 10µg/ml concentration was found to be 234.8 nm. In the 2-10 µg/ml range, the

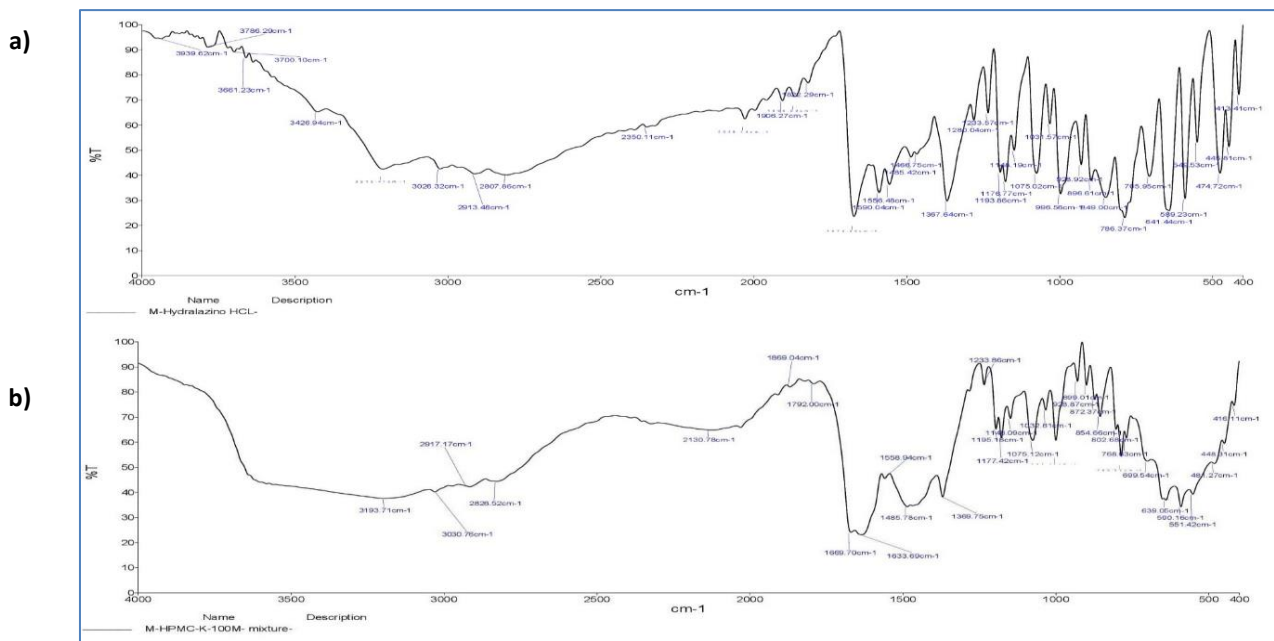


standard calibration curve was found to be linear ( $R^2=0.999$ ).

**Fourier transform infrared (FTIR) spectral analysis**

The interaction study between the drug and excipients in different formulations were performed using FTIR spectrophotometer. The pellets were performed on KBR press. The spectra were recorded over the wave number

range of 4000 to 400  $\text{cm}^{-1}$ . The drug shows different peaks at C-H stretching = 3026.32, C=C stretching = 1590.04, N-N stretching = 1367.64, C=N stretching = 1193.86, C-H out of plane = 996.56. FT-IR spectra of Hydralazine and its physical mixture excipients are exactly same and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.



**Figure 1: a)** IR spectra of Hydralazine hydrochloride **b)** IR spectra of Hydralazine Hydrochloride and HPMC K100M with other excipients

**Evaluation of Floating alginate microbeads**

**Determination of percent yield**

The percentage yield of all the formulations ( $F_1$  to  $F_9$ ) of microbeads were obtained in the range of 85.3 %w/w to 94.5 %w/w. The values of production yield are depicted in Table 2.

**Particle size analysis**

The mean particle size of the various formulations ( $F_1$  to  $F_9$ ) of microbeads were obtained in the range between  $1.33 \pm$

0.06 mm and  $1.45 \pm 0.03$  mm. In fixed concentration of sodium alginate and calcium chloride and increases in the coating polymer concentration results increases in diameter of microbeads ( $F_1$  to  $F_9$ ). Data is given in table 2.

**Drug entrapment efficiency**

In formulations  $F_1$  to  $F_9$ , the drug entrapment efficiency increased progressively with increasing concentration of coating polymers with different viscosity grades from 71.93 %w/v to 97.89 %w/v. The results are shown in Table 2.

**Table 2.** Characterization of formulations

Formulations	% Yield (w/w)	Mean diameter (mm)	Entrapment efficiency (%w/w)	Drug loading (%w/w)	Bulk density ( $\text{g}/\text{cm}^3$ )	Tapped density ( $\text{g}/\text{cm}^3$ )	Angle of Repose ( $^\circ$ )
$F_1$	85.3	$1.33 \pm 0.06$	$71.93 \pm 0.03$	$10.19 \pm 0.02$	$0.47 \pm 0.04$	$0.893 \pm 0.02$	$35.21 \pm 0.03$
$F_2$	89.1	$1.35 \pm 0.07$	$74.50 \pm 0.04$	$11.52 \pm 0.09$	$0.682 \pm 0.03$	$0.872 \pm 0.05$	$33.05 \pm 0.02$
$F_3$	91.7	$1.36 \pm 0.06$	$78.72 \pm 0.03$	$11.23 \pm 0.03$	$0.762 \pm 0.05$	$0.865 \pm 0.04$	$31.17 \pm 0.05$
$F_4$	87.3	$1.34 \pm 0.08$	$82.77 \pm 0.05$	$13.83 \pm 0.04$	$0.709 \pm 0.04$	$0.819 \pm 0.02$	$23.95 \pm 0.03$
$F_5$	90.8	$1.37 \pm 0.06$	$83.61 \pm 0.06$	$13.60 \pm 0.06$	$0.745 \pm 0.03$	$0.825 \pm 0.03$	$27.65 \pm 0.02$
$F_6$	92.3	$1.39 \pm 0.07$	$86.18 \pm 0.04$	$15.20 \pm 0.05$	$0.763 \pm 0.06$	$0.829 \pm 0.05$	$25.02 \pm 0.03$
$F_7$	89.3	$1.37 \pm 0.08$	$90.93 \pm 0.02$	$11.39 \pm 0.07$	$0.733 \pm 0.04$	$0.804 \pm 0.04$	$29.79 \pm 0.05$
$F_8$	93.7	$1.43 \pm 0.06$	$93.04 \pm 0.07$	$12.69 \pm 0.03$	$0.769 \pm 0.08$	$0.813 \pm 0.03$	$21.27 \pm 0.04$
$F_9$	94.5	$1.45 \pm 0.03$	$97.89 \pm 0.05$	$13.02 \pm 0.07$	$0.783 \pm 0.03$	$0.819 \pm 0.05$	$20.45 \pm 0.02$

Values are mean  $\pm$  SD, n=3



### Micromeritics study

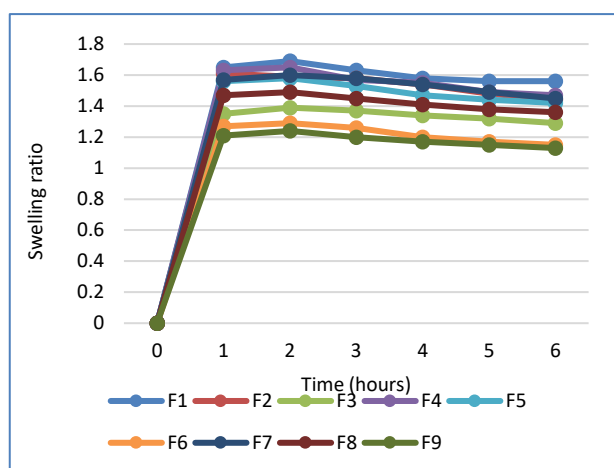
The bulk densities of all the formulations (F<sub>1</sub> to F<sub>9</sub>) were found to be within the range of 0.47-0.78 g/ml (i.e.) the density of all formulations obtained are less than the density of 0.1N HCl (1.004 g/ml). Therefore, the floating alginate microbeads are float in 0.1N HCl. Tapped density values were lies in between 0.804 to 0.893 g/cm<sup>3</sup> indicates good packing. The values of angle of repose are found to in the range of 20.45° to 35.21° indicated acceptable flow property and also good packing ability. The results are shown in Table 2.

### Swelling study

The release of the entrapped drug from the microbeads depends on the swelling behavior, because swelling is directly proportional to the drug release. The dynamic swelling study was carried out in 0.1N HCl of pH 1.2 and the results are depicted in Table 3. The polymer concentration has significant effect on swelling ratio of beads. As the amount of polymer was increased, the swelling ratio of beads was decreased.

**Table 3.** Swelling ratio of floating alginate microbeads

Time (hours)	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	F <sub>8</sub>	F <sub>9</sub>
1	1.65	1.61	1.35	1.63	1.56	1.27	1.57	1.47	1.21
2	1.69	1.59	1.39	1.65	1.58	1.29	1.60	1.49	1.24
3	1.63	1.58	1.37	1.57	1.53	1.26	1.58	1.45	1.20
4	1.58	1.54	1.34	1.55	1.47	1.20	1.54	1.41	1.17
5	1.56	1.48	1.32	1.49	1.44	1.17	1.49	1.38	1.15
6	1.56	1.44	1.29	1.47	1.42	1.15	1.45	1.36	1.13



**Figure 2:** Swelling ratio of floating alginate microbeads

### In-vitro floating properties

Beads of all formulations floated immediately with very short lag time and remained floating up to 12 hours.

### 7. In-vitro release study

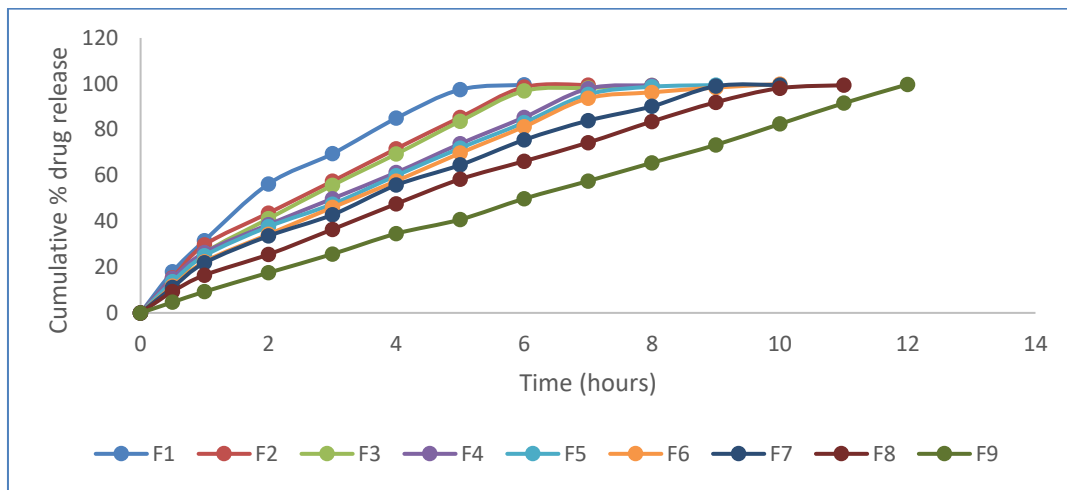
The cumulative percent drug release from various formulations was represented in table 4. From the figure. 3, it is evident that the polymer HPMC K100M (F<sub>9</sub>) has sustaining effect on the release of drug (99.75% at 12 hours) from the floating alginate microbeads. Formulations with HPMC K4M and HPMC K15M was unable to sustain the drug release for desired period of time.

**Table 4.** Cumulative % drug release of formulations (F<sub>1</sub> to F<sub>9</sub>)

Time (hours)	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>	F <sub>7</sub>	F <sub>8</sub>	F <sub>9</sub>
0	0	0	0	0	0	0	0	0	0
0.5	17.93 ±0.05	15.37 ±0.04	11.65 ±0.04	15.05 ±0.02	13.65 ±0.03	11.63 ±0.03	11.13 ±0.03	09.27 ±0.07	4.65 ±0.03
1	31.56 ±0.02	29.67 ±0.02	26.08 ±0.02	26.36 ±0.03	24.95 ±0.06	22.36 ±0.04	21.81 ±0.06	16.49 ±0.02	9.27 ±0.02
2	56.29 ±0.04	43.58 ±0.06	41.09 ±0.06	38.55 ±0.05	37.63 ±0.02	34.28 ±0.06	33.56 ±0.04	25.51 ±0.05	17.52 ±0.06
3	69.45 ±0.03	57.46 ±0.03	55.67 ±0.05	49.86 ±0.03	47.48 ±0.02	45.98 ±0.03	42.84 ±0.03	36.43 ±0.04	25.67 ±0.04
4	84.97 ±0.07	71.67 ±0.03	69.36 ±0.03	61.27 ±0.04	59.93 ±0.04	57.56 ±0.05	55.76 ±0.02	47.61 ±0.03	34.59 ±0.07
5	97.46 ±0.06	85.34 ±0.05	83.67 ±0.06	73.83 ±0.02	71.93 ±0.03	69.74 ±0.03	64.56 ±0.04	58.34 ±0.04	40.76 ±0.03
6	99.51 ±0.03	98.53 ±0.06	96.86 ±0.05	85.36 ±0.07	83.05 ±0.05	81.26 ±0.04	75.49 ±0.05	66.21 ±0.06	49.85 ±0.05
7	-	99.45 ±0.05	98.17 ±0.02	97.89 ±0.04	95.38 ±0.04	93.64 ±0.02	83.92 ±0.07	74.32 ±0.04	57.54 ±0.06
8	-	-	99.23 ±0.06	99.29 ±0.05	98.72 ±0.07	96.27 ±0.06	90.15 ±0.06	83.55 ±0.05	65.51 ±0.03
9	-	-	-	-	99.42 ±0.03	98.36 ±0.03	98.96 ±0.03	91.94 ±0.03	73.34 ±0.06
10	-	-	-	-	-	99.89 ±0.07	99.43 ±0.05	98.08 ±0.05	82.45 ±0.05
11	-	-	-	-	-	-	-	99.36 ±0.07	91.54 ±0.07
12	-	-	-	-	-	-	-	-	99.75 ±0.03

Values are mean ± SD, n=3



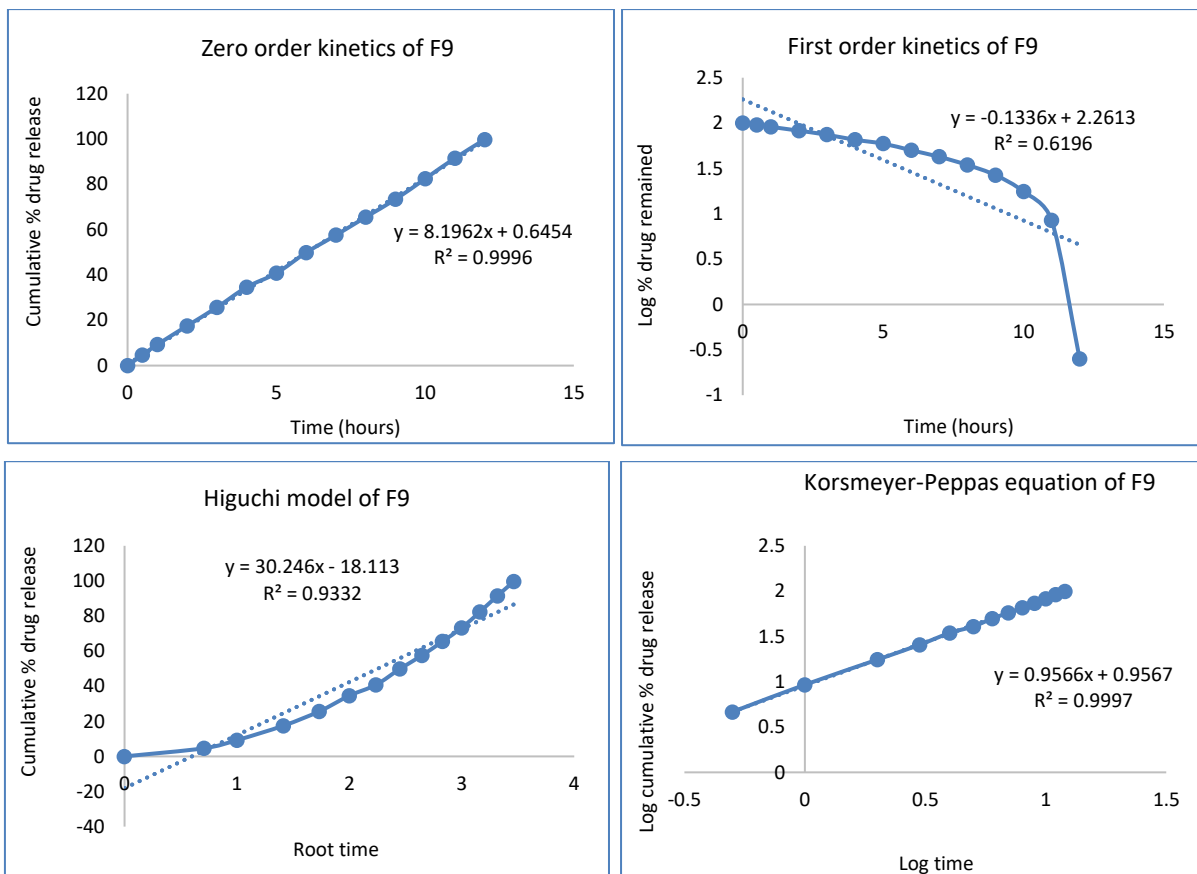


**Figure 3:** *In-vitro* drug release of formulations (F<sub>1</sub> to F<sub>9</sub>)

The difference in the drug release profiles of various formulations was due to the presence of different viscosity grades of polymers with different concentrations. Formulations F<sub>9</sub> was considered as best formulation

among all the nine formulations as it showed good buoyancy properties (very short floating lag time and floating time >12 hours) and sustained the drug release for desired period of time (12 hours).

***In-vitro* Release kinetic study**



**Figure 4:** *In-vitro* release kinetics of optimized formulation F<sub>9</sub>

The drug release data of optimized batch F<sub>9</sub> was subjected for mathematical treatment to check whether the release is following first order or zero order kinetics. The F<sub>9</sub> showed most satisfactory zero order release (R<sup>2</sup>= 0.9995) which is illustrated in Fig.4. which describes that the drug release rate is independent of its concentration whereas dependent on the composition of microbeads. The value

of ‘n’ gives an indication of the release mechanism; when n>0.5 for Fickian diffusion, 0.5 < n < 1.0, diffusion and non-Fickian transport and n=1 for case II transport, were implicated. Lastly, when n > 1.0 super case II transport is apparent. From the kinetic data value showed that, prepared microbeads exhibited zero order kinetics followed by non-fickian transport (n= 0.948).

## CONCLUSION

In the present study floating alginate microbeads of Hydralazine hydrochloride were formulated to achieve sustained release of the drug. From the preformulation studies like melting point, solubility and UV analysis were complied with standards. The FTIR spectra revealed that, there was no interactions between polymers and drug. The floating alginate microbeads was prepared by Ionotropic gelation method using different viscosity grades of polymers like HPMC K4M, HPMC K15M and HPMC K00M in different concentrations.

The obtained microbeads were found to be free flowing, discrete and the % yield was found to be 85.3 to 94.5%, drug entrapment efficiency was found to be 71.3 to 97.89% and swelling index of beads were satisfactory. The dissolution was performed up to 12 hours and the drug release was found to be 99.75% for formulation F<sub>9</sub>. Comparing different viscosity grades of HPMC provided better-sustained release characteristics with excellent *in-vitro* drug release. From the above results also indicated that at higher viscosity grades of polymer concentrations (F<sub>9</sub>) drug release was retarded greatly. The results of *in-vitro* release kinetics of F<sub>9</sub> indicated sustained release and exhibited zero order kinetics followed by non-fickian transport mechanism.

Therefore, the floating alginate microbeads of Hydralazine hydrochloride are promising pharmaceutical dosage forms by providing sustained release drug delivery systems and improving bioavailability of drug. The developed formulation shows an alternative to the conventional dosage form for the treatment of Congestive Heart Failure in patients.

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**Source of Support:** None declared.

**Conflict of Interest:** None declared.

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