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Research Article

## Formulation Development and Evaluation of Floating Wax Beads of Olopatadine Hydrochloride

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### ABSTRACT

In this study, a multiple-unit gastroretentive sustain release drug delivery system of Olopatadine hydrochloride was developed from a completely aqueous environment, avoiding the use of any organic solvent, thus releasing the drug for a prolonged duration of time. Emulsion gelation technique was used to prepare beads. The beads with edible oil were prepared by mixing and homogenizing olive oil and water containing pectin and molten wax which was then extruded in to calcium chloride solution. The effects of carnauba wax on drug entrapment efficiency, floating lag time and morphology and drug release was studied. It was found that carnauba wax was sufficient to sustain the drug release at gastric pH. The results show that these beads can entrap drug in sufficient amount and also can successfully deliver the drug in stomach for a prolonged duration of time avoiding the use of any organic solvent.

**Keywords:** Gastroretentive, Floating Wax Beads, Olopatadine

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### INTRODUCTION

Oral route of administration is one of the oldest and most extensively used routes for the administration of drug providing convenient method of effectively achieving both local and systemic effect. Various approaches are made in designing the formulations, which will overcome the disadvantages of conventional dosage forms, which include sustained/controlled release drug delivery system.<sup>1</sup> Multiple-unit floating systems may be an attractive option since they have been shown to lesser inter- and intra- subject availabilities in drug absorption as well as to lower the chances of dose dumping.<sup>2</sup> different approaches of floating drug delivery system like air compartment multi-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method,<sup>3</sup> microparticles based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of a longer lasting and more reliable release of drugs. The floating wax beads were prepared by the emulsion gelation method. The formation of beads occurs by the cross-linking of the calcium ions with pectin to form calcium pectinate. The morphology, floating properties, swelling studies, drug content, drug entrapment efficiency and drug release study was carried out. The purpose of the present study was to investigate the effect of incorporated wax, which prepared by the emulsion gelation method on the drug release profile.

### MATERIALS AND METHODS

#### Materials

Olopatadine hydrochloride was received as generous gift from Aurobindo Pharma LTD. Research Center (A Division of Aurobindo Pharma), Hyderabad. Pectin, Olive oil, Carnauba wax, Calcium chloride used were of laboratory grade and available at institute.

#### Preparation of floating wax beads

The emulsion of pectin, olive oil and Olopatadine hydrochloride was prepared in distilled water using a high speed homogenizer (IKA T25) at 3000 rpm. The weighed amount of the wax was melted on the water bath at the temperature of more than 50°C of melting point of the wax. The molten wax was dispersed in the previously heated homogenized emulsion of pectin, olive oil and Olopatadine hydrochloride and mixed until the homogeneous mixture was obtained. The hot melted mixture was extruded in the 2% w/v Calcium chloride solution through 22G syringe. The beads formed were allowed to remain in the calcium chloride solution for 10 – 20 mins for the hardening of the beads. The beads formed were then filtered and washed thoroughly with water to remove the excess of calcium from the surface of the beads.<sup>4</sup>

## Composition of formulation

**Table 1: Composition of formulation:**

Formulation Code	Drug	Pectin	Olive oil	Carnauba wax	Water Q.S.
	(mg)	(gm)	(ml)	(gm)	(ml)
F1	500	4	30	1	100
F2	500	4	30	4	100
F3	500	4	30	12	100
F4	500	4	30	16	100

### Micromeritic properties

All the prepared formulations of floating beads were evaluated for bulk density, tapped density, Carr's index and Hausner's ratio.<sup>5,6</sup>

### Percentage yield

All the prepared formulations of floating beads were evaluated for the percentage yield by using following formula.<sup>5,7</sup>

$$\text{Bulk Density} = \frac{\text{Mass of formulation}}{\text{Total volume of formulation}}$$

$$\text{Tapped Density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of powder}}$$

$$\text{Hausners ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

### Determination of drug content and drug entrapment efficiency

50 mg of beads were weighed and crushed in a pastel mortar and the crushed material was dissolved in 25 ml of 0.1 N Hydrochloric acid. The solution was kept for 24 hrs. Volume of this solution was made up to 50 ml with washings of mortar. Then it was filtered. The filtrate was assayed by spectrophotometrically using a UV spectrophotometer (Schimadzu, UV, 1800). The drug content and the entrapment efficiency were determined.<sup>8</sup>

### Floating lag time and floating time

The formulated bead sample (n=20) were placed in a beaker filled with 0.1N HCl (pH 1.2) solution. Temperature was maintained at 37 °C. The floating time of beads were observed for 12 hrs. The preparation was thought of to possess buoyancy in the test solution only when all the beads floated in it. The time the formulation took emerge on the surface of the medium (floating lag time) and the time for which the formulation remains floating on the surface of the medium (floating time) were noted.<sup>9</sup>

### Swelling studies

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug

loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus I. The basket containing beads put in a beaker containing 100 ml of 0.1N HCl (pH 1.2) maintained at 37 °C. The beads were periodically removed at predetermined intervals and weighed. Then swelling ratio was calculated as per the following formula.<sup>10</sup>

$$\text{Swelling index} = \frac{W_s - W_o}{W_o} \times 100$$

Where,  $W_s$  = weight of swollen beads,

$W_o$  = weight of dried beads

### Particle size determination

The particle size of beads was determined by the dry state using optical microscopy method. The stage micrometer and eyepiece micrometer were used for the measurement of the particle size. The size of the beads present in the 1cm<sup>3</sup> area of the slide was counted.<sup>11</sup>

### Surface characterization

Surface characterization of beads were examined with a scanning Electron Microscopy (Diya labs, airoli, Mumbai) beads were mounted on metal grids using double-sided tape and coated with gold under vacuum.<sup>12</sup>

### Differential Scanning Calorimetry (DSC)

The DSC measurements were performed on a DSC 60, Shimadzu, Japan differential scanning calorimeter with thermal analyzer. All accurately weighed samples were placed in a sealed aluminium pans, before heating under nitrogen flow (10 ml/min) at a scanning rate of 10°C per min from 25 to 300°C. An empty aluminium pan was used as reference.<sup>13</sup>

### Fourier Transform Infrared Spectroscopy (FTIR)

The compatibility study was carried out by using Fourier transform infrared spectrophotometer (BRUKER). FTIR study was carried on pure drug and physical mixture of drug and polymer. Physical mixtures were prepared and samples were kept for 1 month at room temperature. Infrared absorption spectrum of Olopatadine hydrochloride was recorded over the wave number 4000 to 400 cm<sup>-1</sup> using Fourier Transform spectrophotometer.<sup>13,14</sup>

### In- vitro drug release study

The release of Olopatadine hydrochloride from sustained release floating wax bead was determined using USP dissolution apparatus I at 50 rpm. The dissolution medium used 900ml of 0.1N HCl (pH1.2) and temperature was maintained at 37 °C. A sample (5ml) was withdrawn from the dissolution apparatus at 0 min., 1hr, 2hr, 4hr, 6hr, 8hr, 10hr, 12hr. The samples were filtered through Whatman filter paper and analysed using UV method. Cumulative % drug release was calculated and observed. The dissolution

of the formulation was compared with the 250mg of the capsule containing 5mg of the drug.<sup>4</sup>

### Best fit kinetic model for optimized formulation

The data obtained from study of diffusion kinetics of the optimized formulation was studied to obtain the best fit model. The best fitted model is the one which gives the highest R<sup>2</sup> value and least slope value.

### Stability study

Stability study of the formulation which gave maximum dissolution rate was carried out to point out any visual physical or chemical change made in the formulation after storing it at elevated temperature and humidity conditions. The optimized formulation was store in ambient colour bottle and stored at 40° C ± 2°C and 75% ± 5% Relative humidity for three months. Floating wax beads was analysed for the drug content.<sup>15</sup>

### Statistical Analysis

Results of ex-vivo experiments are reported as SEM analysis. The classical zero order release curve was found to be linear. The curves plotted according to Higuchi model were also found to be linear. The drug release occurs probably by diffusion and erosion and dissolution. From the above tables it was seen that the best fit model for formulation was Zero order kinetic, such type of model was applicable when sustained release dissolution mechanism are seen.

## RESULTS AND DISCUSSION

### Micromeritics properties

From the study of the micromeritics properties of the formulation it was found that the bulk density of the formulation lied within range of 0.3604 - 0.4804 g/cm<sup>3</sup>, tapped density within range of 0.5563- 0.4569. The Carr's index lies within range of 6.76 - 11.70 and Hausner's ratio within range of 1.2658 - 1.1277 which indicates that the prepared formulation have good flow property (Table 2).

**Table 2: Micromeritics properties of the formulation**

Batch Code	Bulk density (gm/ml) ± SD	Tapped density (gm/ml) ± SD	Carr's index ± SD	Hausner's ratio ± SD
F1	0.4804 ± 0.0045	0.5563 ± 0.0049	6.76 ± 0.0357	1.1277 ± 0.0010
F2	0.3920 ± 0.0013	0.4693 ± 0.0021	11.70 ± 0.0578	1.1904 ± 0.0085
F3	0.4312 ± 0.0020	0.5182 ± 0.0016	9.22 ± 0.0441	1.1834 ± 0.0058
F4	0.3604 ± 0.0011	0.4569 ± 0.0025	8.10 ± 0.0482	1.2658 ± 0.0011

(n=3)

### Percentage yield

All formulations F1 - F4 found percentage yield 97.14 - 95.20% which lied in the normal range in (Table 3).

**Table 3: Percentage yield of the formulations**

Sr. No.	Batch Code	Percentage Yield (%)
1	F1	97.14
2	F2	96.84
3	F3	95.65
4	F4	95.20

the range of 90.28% - 92.62%. Therefore entrapment efficiency was found to be less due to the diffusion of the drug into the calcium chloride solution during the formation of the microspheres (Table 4).

**Table 4: Drug content of the formulation**

Sr. No.	Batch Code	Contents(%) ± SD
1	F1	96.87 ± 0.2743
2	F2	96.84 ± 0.8369
3	F3	96.22 ± 0.7968
4	F4	95.21 ± 0.5750

(n=3)

### Drug content and drug entrapment efficiency

The percentage drug content of all prepared formulations was found to be in the range of 92.56 - 98.77%. Therefore uniformity of drug content was maintained in all formulations (Table 2). The percentage drug entrapment efficiency of all prepared formulations was found to be in

### Floating lag time and floating time

Floating lag time in the range of 1.21 - 1.76 min. and floating time >12hr for all formulations F1-F4. This is due the increase in the concentration of the carnauba wax. (Table 5).

**Table 5: Floating lag time and floating time of formulations**

Sr. No.	Batch	Floating lag time (min.)	Floating time ( hrs.)
1	F1	1.76 ± 0.04630	> 12
2	F2	1.35 ± 0.09391	> 11
3	F3	1.21 ± 0.00707	> 12
4	F4	1.25 ± 0.04221	> 12

(n=3)

### Swelling studies

For all prepared batches (F1-F4), percent swelling ratio was found to be in the range of 10 - 20.66 %. The F1 batch showed the maximum swelling index. This is because of the lipophilic nature of the carnauba wax which affected the swelling of the beads. (Table 6).

**Table 6: Swelling Index of formulations**

Sr. No.	Batch Code	Swelling $\pm$ SD
1	F1	20.66 $\pm$ 0.02471
2	F2	15.3 $\pm$ 0.05241
3	F3	14.66 $\pm$ 0.0254
4	F4	10 $\pm$ 0.01679

(n=3)

### Particle size determination

For F1-F4 batches average particle size was found to be in the range of 1.21 - 1.52 mm (Table 7).

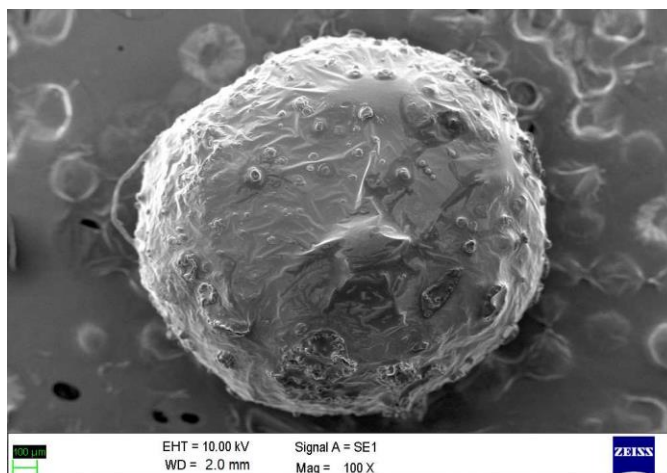
**Table 7: Particle size determination of formulation**

Sr. No.	Batch Code	Particle size (mm) $\pm$ SD
1	F1	1.51 $\pm$ 0.0251
2	F2	2.00 $\pm$ 0.0163
3	F3	1.46 $\pm$ 0.0258
4	F4	1.27 $\pm$ 0.0355

(n=3)

### Surface characterization

The SEM result showed that the particle size of formulation was found to have regular and spherical shape with rough and uneven surface (Figure 1).

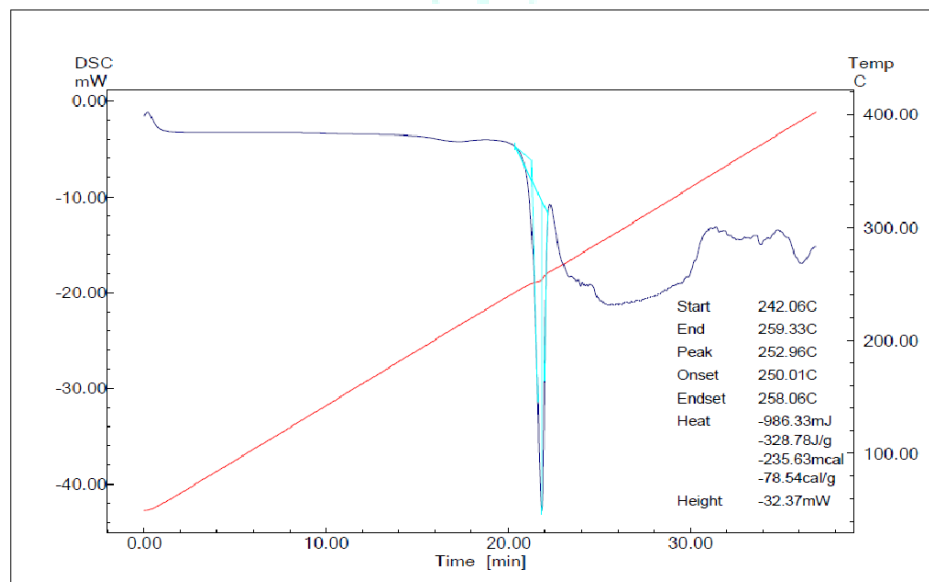


**Figure No. 1: Surface morphology of the formulation**

### Differential scanning calorimetric studies

Olopatadine Hydrochloride was compatible with polymer. There is slightly peak broadening in physical mixture of polymer to pure Olopatadine Hydrochloride (Figure 2).

Fourier transform infrared spectroscopy FTIR spectrum of the physical mixture shows that there is no interaction between drug and polymer (Figure 3).



**Figure No. 2: DSC thermogram of Olopatadine hydrochloride**

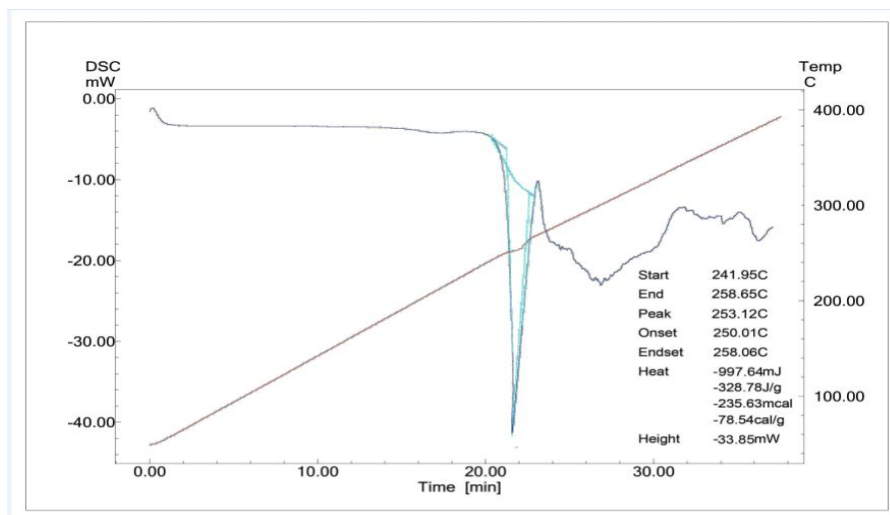


Figure No.3: DSC thermogram of formulation

**In vitro drug release**

The In vitro drug release study of different formulation maximum drug release 96.65% was shown by F1 batch. The data also suggested that floating beads formulation were capable to produce linear drug release for longer period of

time. Drug release profile of formulation F1 to F4 shown in (Figure No. 4) and dissolution profile F1 to F4 signified sustained drug release. Out of four formulations maximum release after 12 hr was found for F1 formulation. (Table 8 and figure 4)

Table 8: In-vitro drug release of different batches of the formulation

Time (hr)	F1	F2	F3	F4
0	0	0	0	0
1	11.04 ± 0.030	9.39 ± 0.025	6.73 ± 0.015	6.36 ± 0.020
2	19.81 ± 0.050	20.36 ± 0.088	10.49 ± 0.040	11.81 ± 0.020
4	36.55 ± 0.086	45.03 ± 0.030	19.26 ± 0.020	22.58 ± 0.030
6	58.52 ± 0.020	55.06 ± 0.051	23.10 ± 0.023	28.86 ± 0.030
8	71.71 ± 0.025	74.04 ± 0.061	31.36 ± 0.026	42.57 ± 0.010
10	86.16 ± 0.040	91.65 ± 0.047	34.06 ± 0.021	44.22 ± 0.030
12	96.65 ± 0.050	95.5 ± 0.015	58.74 ± 0.040	45.04 ± 0.020

(n=3)

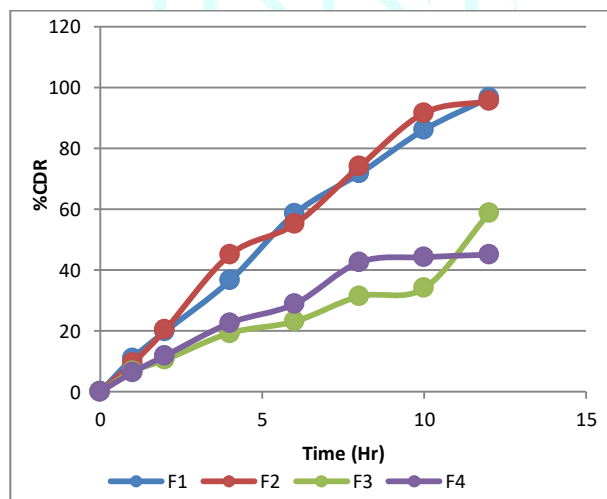


Figure No.4: Drug release profile of formulations F1-F4

From the comparative study of the formulation with capsule containing the dose of 5 mg of Olopatadine hydrochloride, it was found that the capsule containing drug showed the 98.51% drug release within 60 mins. and marketed

formulation showed the 98.50% drug release within 50 min. while the prepared formulation (F1 Batch) showed maximum drug release up to 96.65 % within 12 hrs. (Table 9 and figure 5 (A),(B))

Comparative dissolution profile of the formulation with marketed formulation

Table 9: Comparative dissolution profile of the formulation with marketed formulation

TIME (MIN)	% CDR		
	CAP(PLANE DRUG)	CAP(FORMULATION)	MKT. FORMULATION
0	0	0	0
10	36.80	1.17	39.54
20	47.77	3.36	61.48
30	61.45	4.19	72.45
40	80.68	6.38	86.16
50	98.37	8.02	98.50
60	98.51	11.04	
120		19.81	
240		36.56	
360		58.58	
480		71.72	
600		86.16	
720		96.65	

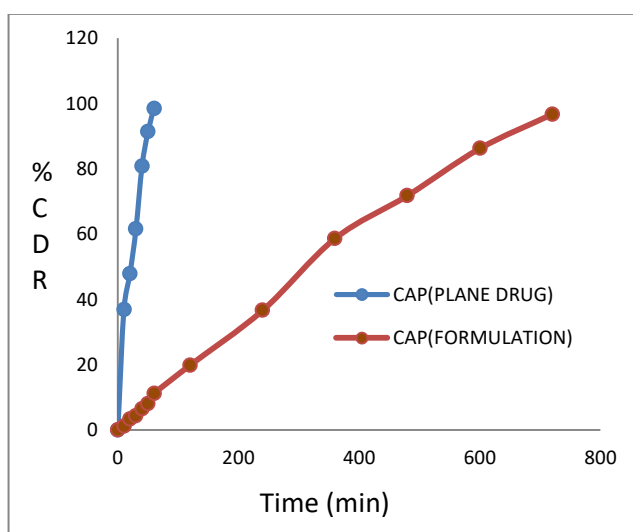


Figure No. 5(A): Comparative dissolution profile of formulation with capsule filled with drug.

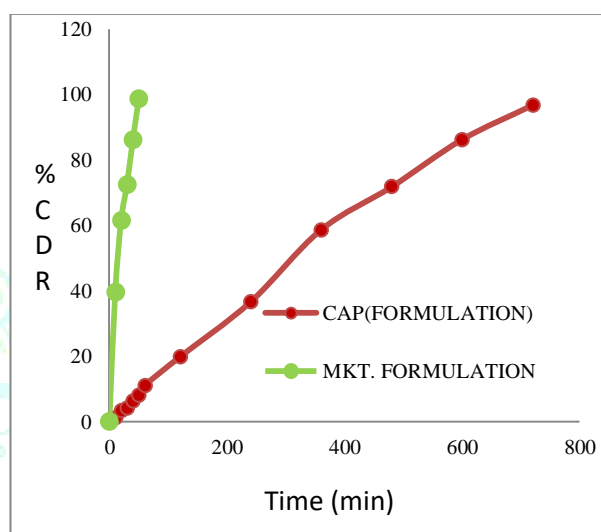


Figure No. 5(B): Comparative dissolution profile of formulation with marketed formulation.

Kinetic model for F1 batch

In order to investigate the mode of release from floating beads data were analysed with following mathematical model.

- A. Zero order kinetic
- B. First order kinetic
- C. Higuchi equation
- D. Korsmeyer-peppas equation

The classical zero order release curve was found to be linear. The curves plotted according Higuchi model were also found

to be linear. Korsmeyer-Peppas release curves  $R^2$  was found to be  $\geq 0.965$  for all 4 formulations. The drug release occurs probably by diffusion and erosion and dissolution. After comparing the coefficient of regression ( $r^2$ ) values of different kinetic models, drug release kinetics for optimized floating beads best fitted in Zero order kinetic release followed by Higuchi such type of model was applicable when sustained release dissolution mechanism are seen (Table 10 & Figure 6: (A), (B), (C) and (D)).

Drug release by using different models by F1 batch

Table 10: Drug release by using different models by F1 batch

Batch	Kinetic Model			
	Zero Order	First Order	Higuchi Model	Korsmeyer-peppas
F1	$R^2$	$R^2$	$R^2$	$R^2$
	0.991	0.893	0.991	0.986

**A. Zero order kinetic**

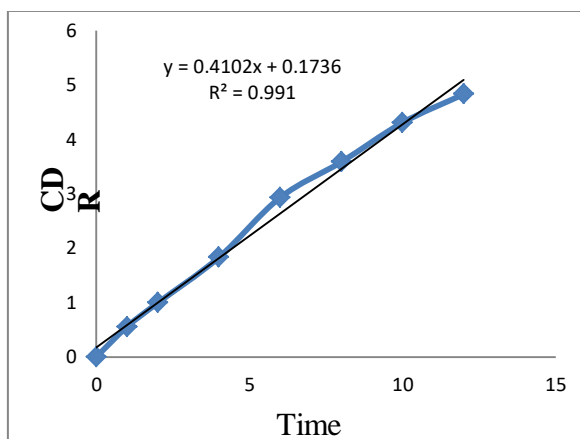


Figure No. 6(A): Zero order kinetic study

**C. Higuchi equation**

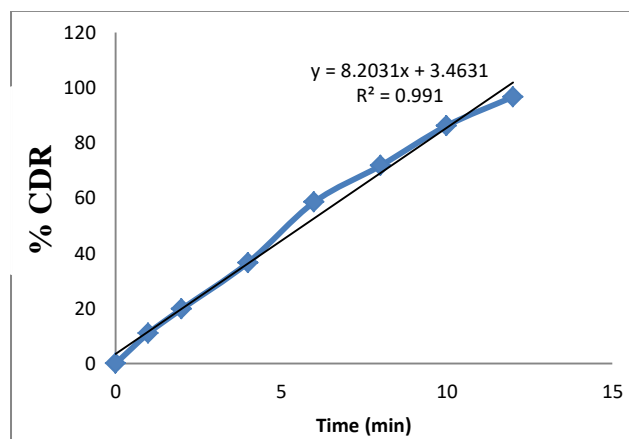


Figure No. 6(C): Higuchi plot

**B. First order**

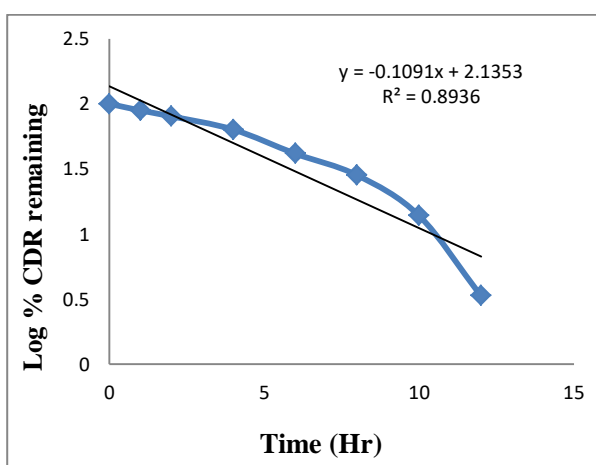


Figure No. 6(B): First order kinetic study

**D. Korsemeyer-peppas equation**

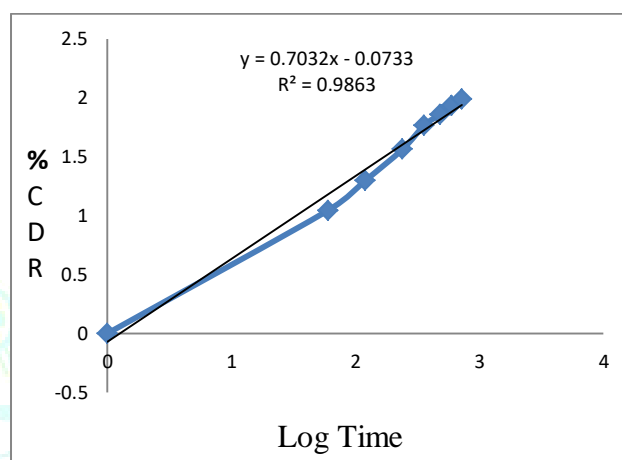


Figure No. 6 (D): Korsemeyer-peppas plot

**Stability study**

The sample were withdrawn after 1, 2 and 3 months and subjected to following tests as shown in. The accelerated stability studies (carried for 3 months), at temperature of 40 C 0 ± 2 C and % RH 75% ± 5% RH indicated that the

developed 0 floating pectinate microspheres were unaffected after 03 months storage under accelerated condition as no change was observed in the appearance and colour of the formulation. On the basis of these results, it may be concluded that the F1 formulation developed is stable under accelerated condition of 03 months (Table 11).

Table 11: Details of stability study for F1 batch

Test	Before	After		
	0 month	1 month	2 month	3 month
Drug release	96.65 ± 0.246%	96.61 ± 0.236%	93.58 ± 0.254	92.55 ± 0.251
Floating lag time	>12 hrs	>12hrs	>12hrs	>12hrs

**CONCLUSION**

From the above study it may be concluded the use of hydrophobic carriers like waxes can be done for achieving the sustain release action. The low density materials like oils were used to attend the floating of the formulation. The study also suggested that the floating wax microspheres can be implemented as a suitable drug carrier for sustaining the release of the drugs with short biological half life.

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**CONFLICT OF INTEREST**

Authors declare that they do not have any conflict of interest.

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