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## FORMULATION DESIGN AND EVALUATION OF ATORVASTATIN CALCIUM FLOATING TABLETS BY USING PECTIN AS A RELEASE MODIFYING AGENT

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### ABSTRACT

Gastroretentive floating controlled drug delivery system containing Atorvastatin calcium was prepared in the form of tablets and evaluating the various processing parameters including the buoyancy studies and in vitro drug release studies in 0.1 N HCl (PH 1.2). Ten formulations containing varying proportions of polymers HPMC K<sub>4</sub>M and release modifying agent used as pectin and fixed amount of Sodium bicarbonate & Citric acid are gas (CO<sub>2</sub>) forming agents (Sodium bicarbonate are alkalizing agents & Citric acid are Buffering agents), Magnesium stearate & Lactose were used as lubricant & glidant respectively. The tablets were prepared by direct compression Method, and the prepared tablets remained buoyant for more than 12 hrs in the release medium. The proportions of the polymers showed significant difference in the release of the drug. Pectin is used as a release modifying agents because it is Swell & form a gel in acidic medium & which is more stable in acidic medium.

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### Key Words

Floating tablets, Buoyancy,  
Controlled release, Atorvastatin  
calcium, Pectin.

## INTRODUCTION

In recent years, controlled-drug delivery system (CDDS) has gained popularity among the researchers and the public. The most sought after route of administration for such system is the oral route. This is due to the ease of drug administration and minimal handling problems faced by the patients. Moreover, CDDS also helps to reduce the frequency of drug administration to patients which directly improves patient compliance and health recovery period. The FDDS uses the gastro-retentive technique for drugs which are absorbed from the stomach and is poorly absorbed or insoluble in the intestine due to the high pH environment. The drug, atorvastatin Calcium is chosen in this study to be incorporated into the FDDS is due to its low bioavailability following oral administration and its stability in the acidic pH environment & high solubility in acidic PH. Besides that, prolonged exposure to atorvastatin Calcium via FDDS could help to reduce the increased cholesterol level.

In this present investigation floating drug delivery of atorvastatin Calcium were developed using Hydroxy propyl methyl cellulose (HPMC K<sub>4</sub>M) has been reported to enhance the controlled release property. Pectin is used as a release modifying agent. Sodium bicarbonate & Citric acid are gas (CO<sub>2</sub>) forming agents, (Sodium bicarbonate are alkalizing agents & Citric acid are Buffering agents), Magnesium stearate & Lactose were used as lubricant & glidant respectively.

Atorvastatin calcium is a HMG-CoA reductase inhibitor used in the treatment of hyperlipidaemia. It has a oral bioavailability of less than 12%. It also undergoes high first pass metabolism. It is highly soluble in acidic pH and absorbed more in the upper part of the GIT. In order to improve the absorption and its oral bioavailability, we have attempted to formulate a floating drug delivery systems using Atorvastatin

**Table No. 1:** Composition of floating Tablet of Atorvastatin Calcium ( F1-F10)

Ingredients	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Atorvastatin Calcium	20	20	20	20	200	20	20	20	20	20

calcium as the model drug with HPMC K<sub>4</sub>M as polymer and Pectin as release modifying agent because due to its good viscosity, swelling & gel forming property in acidic medium.

### Objective:-

The objectives of this research project are the development of formulation for atorvastatin Calcium floating tablets and its corresponding in-vitro evaluations; which highly focuses on the floating behaviour and drug release profile of the tablets.

### MATERIALS & METHODS:-

#### Materials:-

Atorvastatin Calcium was received as a gift sample from USV Ltd, Mumbai. Hydroxy propyl methyl cellulose K<sub>4</sub>M (HPMC K<sub>4</sub>M) was obtained as gift sample from colorcon Asia Ltd, Goa. Pectin was procured from Healthy Biosciences Pvt Ltd, Chandigarh. . Sodium bicarbonate, Citric acid, SLS, magnesium stearate, Lactose was procured from Merk (India) Ltd, Mumbai. All other ingredients, reagents & solvents were of analytical grade.

#### Methods:-

##### Preparation of floating Tablet of Atorvastatin Calcium:-

All the ingredients were accurately weighed & pass through sieve No. 60. In order to mix the ingredients thoroughly, Atorvastatin Calcium & HPMC K<sub>4</sub>M, Pectin were blended in a mortar for 15 minutes, then Sodium bicarbonate, Citric acid, SLS, Lactose, were mixed one by one. After thoroughly mixing these ingredients, finally added magnesium stearate, The powder blend was passed through sieve no.44 & further mixed for additional 2-3 minutes. The tablets were compressed using tablet compression machine. The weight of the tablets were kept constant for all formulation (Table No.1)

HPMCK <sub>4</sub> M	60	70	80	90	100	60	70	80	90	100
Pectin	--	--	--	--	--	30	35	40	45	50
Sodium bicarbonate	30	30	30	30	30	30	30	30	30	30
Citric acid	20	20	20	20	20	20	20	20	20	20
Magnesium stearate	04	04	04	04	04	04	04	04	04	04
Lactose	116	106	96	86	76	86	71	56	41	26
Total weight	250	250	250	250	250	250	250	250	250	250

\*All quantities are in mg.

### Evaluation of floating tablets of Atorvastatin Calcium:-

#### Pre-compression parameters :-

##### Bulk density :-

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume and Mass of the powder was determined. The bulk density was calculated by using below mentioned formula,

$$\text{Bulk density} = \frac{\text{Mass of Powder Blend}}{\text{Bulk Volume of Powder Blend}}$$

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##### Tapped density :-

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the Mass of the blend was measured. The tapped density was calculated using the following formula,

$$\text{Tapped density} = \frac{\text{Mass of Powder Blend}}{\text{Tapped Volume of Powder Blend}}$$

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##### Carr's Index :-

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by carrs' index which is calculated as follows,

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

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

The value below 16% indicates a powder with usually give rise to good flow characteristics, whereas above 23 % indicate poor flowability.

##### Hausner's Ratio :-

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Hausner's ratio value is Less than 1.5 indicate good flow & greater than 1.5 indicate poor flow.

##### 1.5) Angle of repose:-

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose ( $\theta$ ) was calculated using the formula.

$$\theta = \tan^{-1} (h / r)$$

##### Post-compression parameters:-

##### Weight variation test :-

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight. The comparison variation within the I.P limits, it passes the weight variation test.

##### Tablet hardness :-

Tablet crushing strength or hardness, the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester.

##### Thickness :-

The thickness of individual tablets was measured using Vernier caliper, which permits accurate measurements and provides information of the variation between tablets.

**Tablet friability :-**

The friability of the tablets was measured in a Roche friabilator. Tablets sample of a known weight (W<sub>0</sub>) were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ friability} = \frac{W_0 - W}{W_0} \times 100$$

**Drug content uniformity :-**

Five tablets from each formulation were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing from this equivalent to 20 mg of Atorvastatin Calcium was taken in 100 ml volumetric flask and dissolved in 5 ml of methanol & diluted upto 100ml with 0.1 N HCl. It was then shaken vigorously on a Magnetic stirrer for 2 hr & filtered into 50 ml volumetric flask upto the mark by using whatman filter paper. Further appropriate dilution were made & absorbance was measured at nm 245 nm.

**In Vitro Buoyancy determination :-**

The time interval between introduction of tablet into the dissolution medium & its floatation to the surface of the medium was termed as Buoyancy Lag time (BLT) and the duration upto which the tablet floats on the surface of the medium was termed as the Buoyancy floating time (BFT). Both BLT & BFT were determined using type II dissolution apparatus (paddle type) in dissolution medium 900 ml 0.1 N HCl (PH 1.2) at 37 ± 0.5° C.

**Swelling Index :-**

Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the

hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of percentage weight gain by the tablet.

Swelling of hydrophilic polymers such as HPMC K4 M & release modifying agent Pectin greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually also influence the release slowing action and the residence time.

For each formulation, one tablet was weighed and placed in a beaker containing 200ml of 0.1 N HCl (PH 1.2). After each hour tablet was removed from beaker, blotted using tissue paper and weighed again up to 6 hours.

The percentage weight gain by the tablet was calculated by the formula.

$$\text{Swelling Index (S.I)} = \frac{(W_t - W_o)}{W_o} \times 100$$

Where, S.I. = Swelling index

W<sub>t</sub> = Weight of tablet at time t

W<sub>o</sub> = Weight of tablet before immersion

**In Vitro Dissolution studies:-**

In vitro drug release of all formulations were carried out using USP- type II dissolution apparatus (paddle type). The dissolution medium 900 ml 0.1 N HCl (PH 1.2) Buffer, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5° C & rpm of 50. One Atorvastatin Calcium tablet was placed in the dissolution apparatus. Dissolution studies were carried out for 12 h. 5ml of the Aliquot was taken at intervals of 1, 2, 3, 6, 9, 12 hrs. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium, and the sample was filtered 1ml of the filtrate was diluted to 10ml with 0.1 N HCl (PH 1.2) and analyzed spectrophotometrically at 245 nm.

**RESULT & DISCUSSION:-****Pre-compression parameters:-****Determination of Bulk density:-**

Result of bulk density are shown in table no.2

**Table No. 2:** Pre-compression Parameters of Formulation (F1-F10)

Batch No.	Pre-compression Parameters				
	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's Index (%)	Hausner's ratio	Angle of repose( °)
F1	0.523	0.587	10.35	1.12	23°
F2	0.535	0.599	10.17	1.11	25°
F3	0.564	0.613	8.20	1.08	22°
F4	0.545	0.685	6.90	1.06	22°
F5	0.584	0.663	9.38	1.13	24°
F6	0.568	0.615	8.20	1.08	21°
F7	0.544	0.595	8.20	1.09	20°
F8	0.582	0.635	7.94	1.07	22°
F9	0.544	0.582	6.91	1.05	20°
F10	0.535	0.599	10.17	1.11	23°

**Determination of Tapped density:-**

Result of Tapped density are shown in table no.2

**Carr's Index :-**

Carr's index was carried out; it found in between 6.90% to 10.35%, which indicate that the powder blends have the required flow property for compression. The result is shown in table no. 2

**Angle of repose :-**

The angle of repose for the formulated blend was carried out and the results were shown in table no. 2. It concludes all the formulations blend was found to be in the range 21° to 25°

**Post-compression parameters:-****Shape of the Tablet:-**

Microscopic examinations of tablets from F1-F10 were found to be circular shape with no cracks.

**Weight variation :-**

The percentage weight variations for all formulations were tabulated in table no.3. All the formulated (F1 to F10) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of  $\pm 5\%$  of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

**Hardness Test:-**

The measured hardness of tablets of each batch ranged between  $5.1 \pm 0.1$  to  $5.5 \pm 0.4$  Kg/cm<sup>2</sup>. This ensure good handling characteristics of all batches. The result is shown in the table no. 3.

**Table No.3 :** Post-compression parameters of Formulations (F1-F10)

Parameters	Weight variation	Hardness (Kg/cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Drug Content (%)
Batch No.					
F1	305 $\pm$ 5%	5.3 $\pm$ 0.2	4.1 $\pm$ 0.04	0.90	98.04
F2	303 $\pm$ 5%	5.4 $\pm$ 0.3	4.2 $\pm$ 0.05	0.85	99.02
F3	299 $\pm$ 5%	5.2 $\pm$ 0.1	4.1 $\pm$ 0.03	0.95	98.05
F4	302 $\pm$ 5%	5.3 $\pm$ 0.4	4.2 $\pm$ 0.02	0.71	97.02
F5	301 $\pm$ 5%	5.1 $\pm$ 0.2	4.3 $\pm$ 0.01	0.70	98.02
F6	299 $\pm$ 5%	5.3 $\pm$ 0.1	4.4 $\pm$ 0.03	0.88	97.01
F7	297 $\pm$ 5%	5.5 $\pm$ 0.2	4.1 $\pm$ 0.02	0.85	99.09
F8	306 $\pm$ 5%	5.4 $\pm$ 0.3	4.4 $\pm$ 0.01	0.97	98.03
F9	305 $\pm$ 5%	5.5 $\pm$ 0.4	4.1 $\pm$ 0.05	0.83	97.04
F10	307 $\pm$ 5%	5.1 $\pm$ 0.2	4.2 $\pm$ 0.06	0.73	98.03

**Friability Test:-**

The value of friability test were tabulated in table no. 3. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

**Drug Content Uniformity:-**

The percentage of drug content for (F1 to F10) was found to be in between 97.01 to 99.09 of Atorvastatin

**Table No. 4 : In Vitro Buoyancy study of formulations (F1-F10)**

Batch No.	Total Lag Time (sec)	Total Floating time (hrs)
F1	129	12 hrs
F2	124	12 hrs
F3	118	12 hrs
F4	133	12 hrs
F5	127	12 hrs
F6	113	>18 hrs
F7	122	>18 hrs
F8	112	>18 hrs
F9	119	>18 hrs
F10	111	>18 hrs

Calcium, it complies with official specifications. The results are shown in table no. 3.

**In Vitro Buoyancy study :-**

Tablet of each formulation F1-F10, On immersion in 0.1 N HCL (PH 1.2) Buffer at 37° C, the tablets floated, and remained buoyant without disintegration. Table No. 4 shows the results of Buoyancy study.

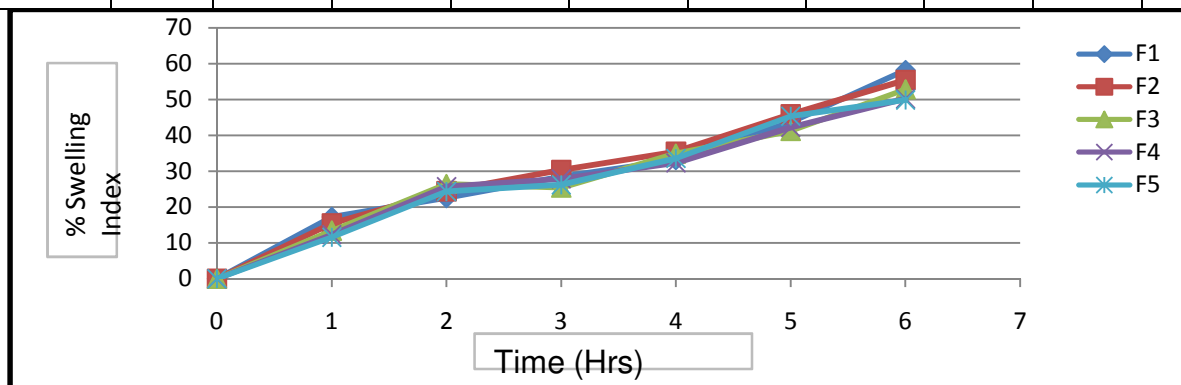
**Swelling study:-**

Swelling study was performed on all the batches (F1 to F10) for 6 hrs. The result of swelling index are shown in

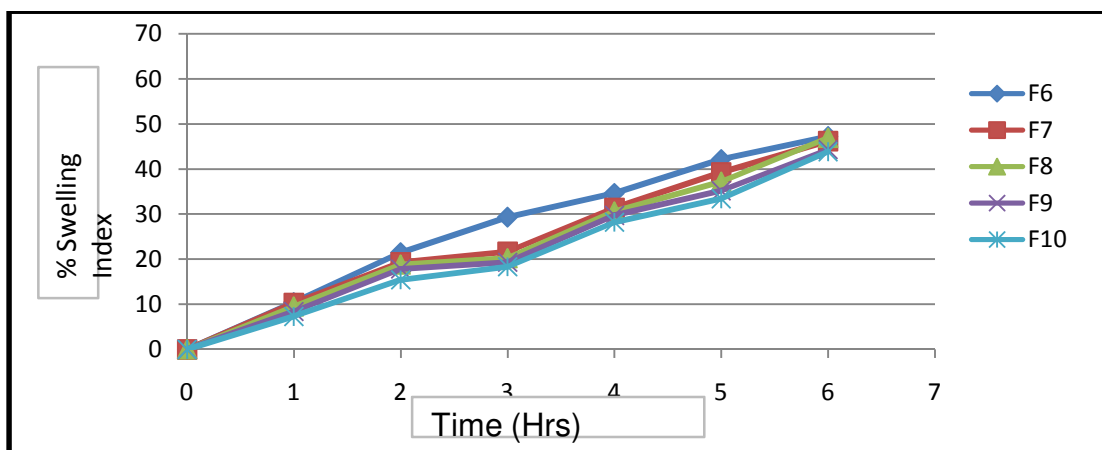
Table No.5. % swelling index against time (hr) plotted in Fig no.1 & 2.

**Table No.5: Swelling index of Floating Tablets of different Batches (F1 to F10)**

Time (hrs)	Batch									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	17.25	15.44	13.33	12.33	11.56	10.47	10.33	09.56	08.44	07.32
2	22.55	24.42	26.43	25.67	24.33	21.44	19.33	18.87	17.88	15.44
3	28.45	30.33	25.44	27.87	26.21	29.33	21.66	20.30	19.34	18.34
4	33.12	35.45	34.88	32.32	33.56	34.67	31.42	30.66	29.76	28.22
5	43.67	45.87	41.22	42.21	45.33	42.22	39.32	37.23	35.22	33.45
6	58.21	55.44	52.88	50.22	49.87	47.22	46.23	46.99	44.33	43.88



**Fig No. 1 :-** Swelling index of Floating Tablets of different Batches (F1 to F5)



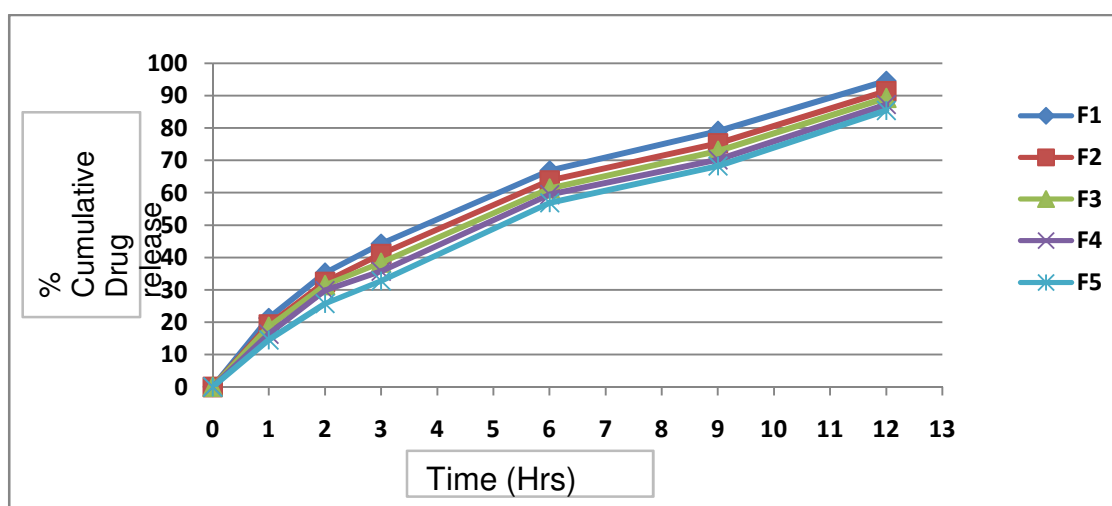
**Fig No. 2 :-** Swelling index of Floating Tablets of different Batches (F6 to F10)

**In vitro Drug release studies :-**

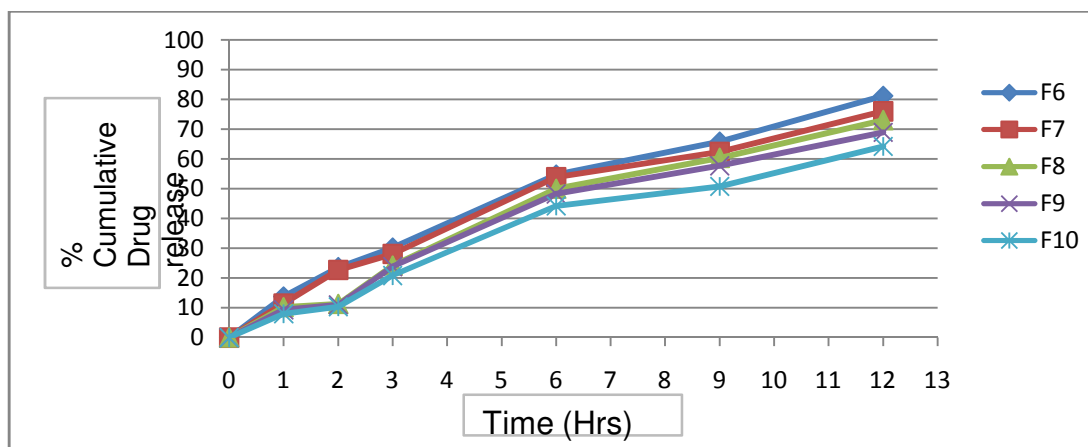
The Result of In vitro drug release studies are shown in table no.6. % cumulative drug release against time (hr) plotted in Fig no.3 & 4.

**Table no. 6:** In vitro Drug release studies of Batches (F1 to F10)

Time (min)	% Cumulative drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0000	0000	0000	0000	0000	0000	0000	0000	0000	0000
1	21.33	19.34	18.65	16.33	14.53	13.77	11.45	10.22	09.34	07.99
2	35.22	32.45	31.53	29.82	25.76	23.55	2276	11.36	11.02	10.37
3	44.27	41.12	38.44	35.73	32.76	30.23	28.09	24.22	23.87	20.83
6	66.87	63.78	61.33	59.43	56.89	54.77	53.88	50.01	48.27	44.23
9	78.99	75.33	72.88	70.21	68.28	65.83	62.34	60.32	57.73	50.78
12	94.56	91.37	89.33	87.25	85.43	81.22	75.99	72.98	68.93	64.23



**Fig No. 3 :-** In-vitro dissolution of atorvastatin calcium floating tablets of different batches (F1 to F5)



**Fig No. 4 :-** In-vitro dissolution of atorvastatin calcium floating tablets of different batches (F6 to F10)

### CONCLUSION:-

The present study was carried out to develop the floating drug delivery system using HPMC K<sub>4</sub>M & Pectin as carriers. The result of experimental studies of Atorvastatin Calcium floating Tablets proved that the powder blends showed good flow properties, tablet evaluation test are within the acceptable limits, The new oral controlled release system shows good in vitro buoyancy in an acidic medium. Presence of effervescent agent ( Sodium bicarbonate) in the tablets is necessary for in vitro buoyancy. In this research work concluded that the Combination of HPMC K<sub>4</sub>M & Pectin uses the tablet may be floated maximum period of time as compared to use of only HPMC K<sub>4</sub>M Polymer & the drug may release in Controlled manner, means use of combination of HPMC K<sub>4</sub>M & Pectin result formation of good matrix forming floating Tablet. We found that drug release of formulation F6 to F10 is Less than formulation F1 To F5. The main conclusion found that pectin is a release modifying agents. we can certainly say that floating type gastro retentive drug delivery system holds a lot of potential for drug having stability problem in alkaline PH or which mainly absorb in acidic PH. We can certainly explore this drug delivery which may lead to improved bioavailability and ensured therapy with many existing drugs.

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