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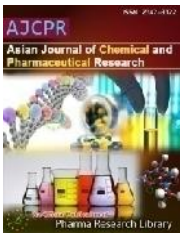

Research Article **Open Access**

Formulation and *In-Vitro* Evaluation of Gastro Retentive Effervescent Floating Tablets of Atomoxetine

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A B S T R A C T

Atomoxetine is a norepinephrine (noradrenaline) reuptake inhibitor; atomoxetine is approved for use in children, adolescents, and adults. The initial therapeutic effects of atomoxetine usually take 2 to 4 weeks to be become apparent. A further 2–4 weeks may be required for the full therapeutic effects to be seen. Its efficacy may be less than that of stimulant medications. The object of the present work is preparing floating tablets in controlled fashion. The gas generating agent sodium bicarbonate was added in different concentrations with varying amount of retardation polymers. Different grades of HPMC polymers HPMC K4M, K15M & K100M were used as retarding polymers. The formulation blend was evaluated for various physicochemical properties and all the parameters were found to be within limits. The formulations F1-F12 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits. From the dissolution data, it was evident that formulation F10 was found to be best with maximum % drug release of 96.10% and floating time of 10 hours.

Keywords: Atomoxetine, HPMCK4M, HPMCK15M, HPMCK100M & Floating tablets.

A R T I C L E I N F O

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1. Introduction

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [1].

These drug delivery systems suffer from mainly two adversities: the short gastric retention time(GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment and also prolonged gastric retention time (GRT) in the stomach, this could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. [2]

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed.

One of the most feasible approaches for achieving a prolonged predictable drug delivery profile is floating drug delivery system (FDDS). This prolongs the gastric residence time and increases the overall bioavailability of the dosage form. Gastric floating drug delivery system 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 of drug that is less soluble in high pH environment i.e. intestine. It is also suitable for local drug delivery in stomach and proximal small intestine (i.e. upper part of the small intestine).

Introduction to Floating Dosage Form

The floating drug delivery system (FDDS) also called Hydro dynamically Balanced Drug Delivery System (HBS). FDDS is an oral dosage forms (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. Drug dissolution and release from dosage retained in the stomach fluids occur at the pH of the stomach under fairly controlled condition.

The formulation of the dosage form must comply with major criteria for HBS, like

1) It must have sufficient structure to form a cohesive gel barrier.
2) It must maintain an overall specific gravity less than that of gastric content.
3) It should dissolve slowly enough to serve as a 'Reservoir' for the delivery system.

Types of Floating Drug Delivery Systems (FDDS) [16]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS, which are.

I. Effervescent System, and
II. Non- Effervescent System

Advantages of FDDS

- Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- FDDS are advantageous for drugs meant for local action in the stomach e.g.: Antacids
- FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
- Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach e.g.: Ferrous salts, Antacids [22].

Disadvantages of FDDS

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids [22].
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa [22].
- One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosages form float therein and work efficiently [22].
- Drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems.

E.g., Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions [21-22].

2. Materials and Methods

Materials

Atomoxetine, HPMC K4M, HPMC K15M, HPMC K100M, PVP K30, Sodium bi carbonate, microcrystalline cellulose, Magnesium stearate, Talc.

Methodology

Pre-formulation and drug excipient compatibility studies. Formulation of Atomoxetine. Floating matrix tablets using different polymers: HPMC K15M, HPMC 4M, HPMC K100M, Sodium Bicarbonate, Sodium lauryl sulphate, PVP K30, Magnesium stearate and Talc in different ratios. Compression of the powders into floating tablets of Atomoxetine. Evaluation of floating tablets of Atomoxetine for physical appearance, hardness, thickness, friability, weight variation, content uniformity test, and in-vitro buoyancy studies. *In-vitro* dissolution studies for all the formulations of Atomoxetine floating tablets.

Determination of λ_{max} and preparation of calibration curve of Atomoxetine by using 0.1 HCl: A solution of Atomoxetine containing concentration 10 µg/ml was prepared in 0.1N HCl and UV spectrum was taken using double beam UV spectrophotometer. The solution was scanned in the range of 200 nm to 400 nm. 100 mg of Atomoxetine was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCL to give stock solution containing 1000 µg/ml. The standard stock solution was then serially diluted with 0.1N HCL to get 2,4,6,8, 10 µg/ml of Atomoxetine. The absorbance of the solution was measured against 0.1N HCL as blank using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Pre-formulation Studies

Evaluation of pre-compression parameters (flow properties) of the powder blend [31-33]

Bulk density determination: Weighed quantity of the powder (W) was taken in a graduated measuring cylinder and volume (V_0) is measured and bulk density is calculated using the formula.

Tapped density determination

Weighed quantity of powder was taken in a graduated cylinder and the volume is measured (V_0). The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1300 times until the difference in the volume after consecutive tapings was less than 2%.

Hausner ratio:

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density.

Compressibility Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Formulation (or) preparation of floating tablets of atomoxetine:

Optimization of Sodium bicarbonate concentration:

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Table 1: Optimization sodium bicarbonate concentration

S. No	Excipient Name	EF1	EF2	EF3
1	Atomoxetine	60	60	60
2	HPMC K 100M	100	100	100
3	PVP K30	25	25	25
4	$NaHCO_3$	25	30	60
5	Mg. Stearate	2.5	2.5	2.5
6	Talc	2.5	2.5	2.5
7	MCC pH 102	Q.S	Q.S	Q.S

Method of Preparation:

In this work, direct compression method has been employed to prepare floating matrix tablets of Atomoxetine with HPMC K15M, HPMC K4M & HPMC K100M. All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then PVP K 30, microcrystalline cellulose, sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 40 mesh. Tablets were compressed by direct compression method on a multi punch 12 station Rotary tablet compression machine (Cemach, machineries ltd, lab press 8 station, India) using 7 mm flat round punches.

Evaluation of floating tablets:

Tablets are evaluated for both pre-compression parameters like bulk density, Carr's index Hausner's ratio as well as their post compression parameters like various quality control tests such as tablet Thickness and Diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for FDDS like floating lag time and total floating time & release rate of drug.

Evaluation of Post Compression Parameters of Floating Tablets

Physical appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odor, taste, surface texture and consistency of any identification marks.

Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. Thickness and diameter were measured using vernier calipers. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition, thickness must be controlled to facilitate packaging.

Hardness: This test is used to check the hardness of a tablet, which may undergo chipping or breakage during storage, transportation and handling. In this, five tablets

were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability: The friability test was carried out to evaluate the hardness and stability instantly to withstand abrasion in packing, handling and transporting. In Roche Friabilator in which twenty tablets were weighed (W_o) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w).

***In-vitro* buoyancy determination [38]**

The floating characteristics of the GFDDS are essential, since they influence the *in vivo* behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter's complication

Floating Lag Time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5^{o}C, paddle rotation at 50 rpm and 900 ml as volume, it is measured using stopwatch.

Total Floating Time: The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37±0.5^{o}C, paddle rotation at 50 rpm, it is measured using stopwatch.

Swelling behavior of tablets: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from teach formulation was kept in a Petri dish containing 0.1N HCl. At the end of 0.5 h and 1 h, the tablet was withdrawn, dried with tissue paper, and weighed.

***In vitro* dissolution studies**:

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Lab India) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium 900 ml and was maintained at 37±0.5^{0}C. Samples of 5 ml were withdrawn at predetermined time intervals, filtered and replaced with 5 ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Atomoxetine at 225 nm by using a double beam UV spectrophotometer (Shimadzu-2000). Each dissolution study was performed for three times and the mean values were taken.

3. Results and discussion

Calibration curve of Atomoxetine:

The standard curve of Atomoxetine was obtained and good correlation was obtained with R^2 value of 0.998.

Standard Graph of Atomoxetine in 0.1N HCl at 225 nm:

The standard graph values of Atomoxetine are tabulated as below

Table 3: standard Graph values of Atomoxetinein 0.1N HCl at 225 nm

Conc. (µg/ml)	Absorbance
2	0.187
4	0.305
6	0.423
8	0.528
10	0.642

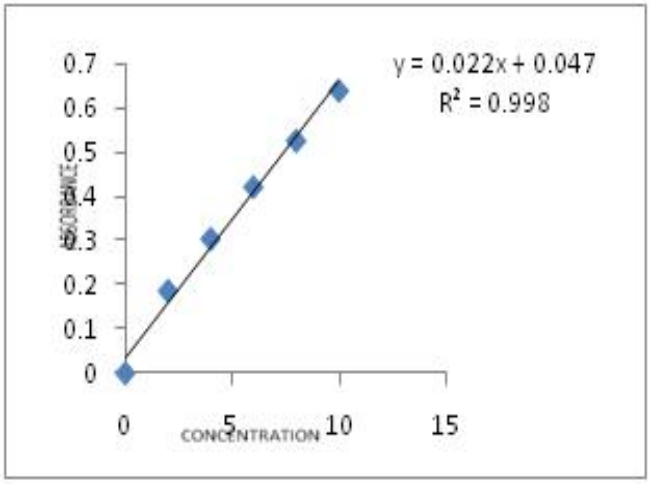

Figure 1: Standard curve of Atomoxetine

Pre-compression evaluation parameters of atomoxetine floating formulation blend:

The powder blends were prepared by mixing of various ingredients mentioned and used for characterization of various flow properties of powder.

Bulk density:

The bulk density of all the formulations was found to be in the range of 0.49±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties.

Tapped density:

The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties.

Compressibility index:

The compressibility index of all the formulations was found to be ranging between 16 to 18, which shows that the powder has good flow properties.

Hausner ratio:

All the formulations has shown the hausner ratio ranging between 0.6 to 1.2 indicating the powder has good flow properties.

***In-vitro* buoyancy studies**

To provide in vitro buoyancy, an effervescent approach was selected. Sodium bicarbonate was added as a gas-generating agent. As the dissolution medium (0.1N HCl) imbibed into the tablet matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the generation of CO2. The generated gas was entrapped and protected within the polymer and thus decreasing density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. The system should float in a few minutes after contact with gastric fluid to prevent the dosage form from Transiting into the small intestine together with food. All the formulations (F1 to F12) showed the floating lag time of <146 sec.

***In-vitro* drug release studies:**

The *in-vitro* dissolution studies of floating tablets of Atomoxetine were conducted in simulated gastric fluid 0.1N HCl for 10 hours and The In-vitro drug release data of all formulations shown in table 6. The formulations prepared with HPMC K4M in with the concentrations of 25, 50, 100 and 125 mg were undergone dissolution.

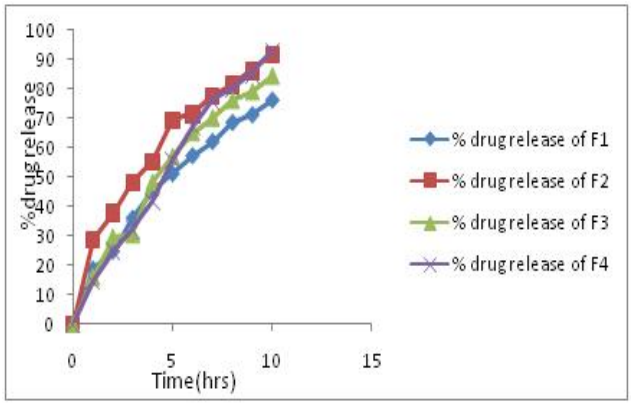

Figure 2: % drug release of formulation (F1-F4)

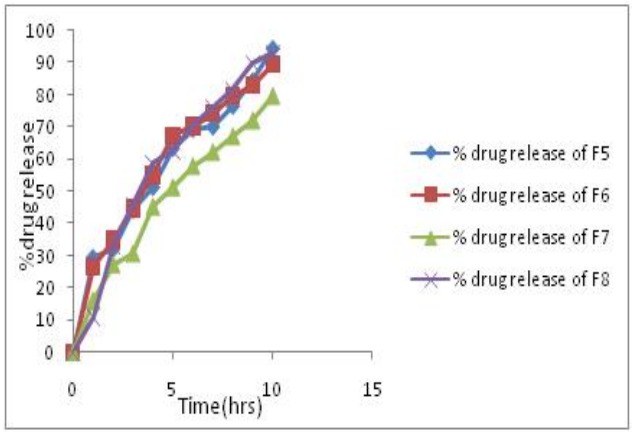

Figure 3: % drug release of formulation (F5-F8)

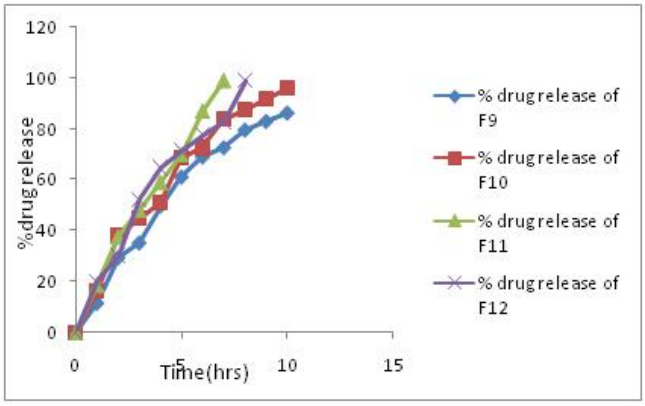

Figure 4: % drug release of formulation (F9-F12**)**

The formulations prepared with HPMC K15M in with the concentrations of 25, 50, 100 and 125 mg were undergone dissolution. The formulations prepared with HPMC K100M in with the concentrations of 25, 50, 100 and 125 mg were undergone dissolution

The cumulative percentage drug release after 10 hrs was found to be as F1, F2, F3, F4 shown 76.25%, 91.75%, 84.56%, 92.98%, respectively, F5, F6, F7, F8, shown 94.25%, 89.21%, 79.58%, 92.89, respectively, and for F9, F10, 89.87%, 96.10%, respectively. F11 showed 99.25% in 7^{th} hour, F12 shown 98.85% in 8^{th} hour. Formulation F10 showed maximum drug release i.e., 96.10% with floating time of 10 hour, for these reasons it was considered as the best formulation.

Table 2: Composition of Floating Tablets of Atomoxetine by Using Different Concentrations of Polymers

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
code										60	60	60
Atomoxetine (mg)	60	60	60	60	60	60	60	60	60			
HPMC K4M (mg)	25	50	100	125	-	-	-	-	-			
HPMC K15M (mg)	-	-	-	-	25	50	100	125	-	-	-	-
HPMCK100M (mg)	-	-	-	-	-	-	-	-	25	50	100	125
PVPK-30 (mg)	25	25	25	25	25	25	25	25	25	25	25	25
$NaHCO_3$ (mg)	60	60	60	60	60	60	60	60	60	60	60	60
Magnesium Stearate (mg)	8	8	8	8	8	8	8	8	8	8	8	8
Talc (mg)	8	8	8	8	8	8	8	8	8	8	8	8
MCC pH 102 (mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	300	300	300	300	300	300	300	300	300	300	300	300

Table 4: Micromeritic properties of powder blend

Formulation Code	**Bulk density**	**Tapped density**	**Compressibility Index**	**Hausner's ratio**
F1	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03

F8	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02
F10	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F11	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F12	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08

Table 5: Evaluations of Physical Parameters of Tablets

Formulation Code	Weight variation (mg) (±SD)	Thickness (mm) (±SD)	Hardness (Kg/cm^2) (±SD)	Friability (%)	Drug content (% (±SD)	Floating lag time (sec)	Floating buoyancy time (hrs)
F1	295±0.04	2.5±0.07	3.4±0.01	0.48±0.01	100.8±0.01	89	2
F2	301±0.01	3.3±0.01	3.2±0.05	0.38±0.06	97.8±0.02	112	3
F3	299±0.02	3.1±0.02	3.5±0.02	0.46±0.04	99.9±0.09	134	4
F4	306±0.05	2.5±0.06	3.1±0.09	0.40±0.09	101.33±0.03	104	5
F5	301±0.08	3.9±0.04	3.4±0.05	0.60±0.03	100.07±0.08	114	7
F6	303±0.09	2.2±0.09	3.5±0.02	0.43±0.08	95.6±0.09	145	>24
F7	306±0.01	3.1±0.02	3.2±0.03	0.45±0.02	98.9±0.07	87	>24
F8	305±0.08	3.1±0.09	2.9±0.09	0.52±0.05	100.2±0.04	134	>24
F9	303±0.07	3.2±0.08	3.2±0.08	0.45±0.09	99.8±0.08	146	>24
F10	301±0.05	3.1±0.06	3.5±0.09	0.40±0.09	101.33±0.03	104	10
F11	302±0.08	3.6±0.04	3.4±0.05	0.60±0.03	100.07±0.08	114	7
F12	298±0.09	3.2±0.09	3.5±0.02	0.43±0.08	95.6±0.09	145	8

Table 6: Drug release data of Atomoxetine floating matrix tablets

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	18.80	28.94	16.10	14.47	29.42	26.56	16.14	11.12	11.52	16.18	18.74	19.84
2	24.87	37.88	29.74	24.89	32.05	34.92	27.35	33.45	29.36	38.27	37.71	30.10
3	36.12	48.20	30.56	32.11	44.10	44.52	30.73	45.62	35.20	44.96	48.27	52.26
4	45.25	55.45	48.29	41.82	51.25	54.85	45.24	58.73	49.65	51.20	59.16	64.58
5	51.24	69.52	57.10	56.01	63.33	67.21	51.27	62.64	61.10	68.63	70.18	71.25
6	57.35	71.53	65.25	67.35	69.24	70.05	57.83	70.43	68.99	72.65	87.26	77.78
7	62.17	77.56	70.32	76.25	70.01	74.16	62.19	76.21	72.58	83.85	99.25	82.76
8	68.65	81.45	76.25	80.24	76.45	79.61	67.02	81.26	79.56	87.52		98.85
9	71.26	86.27	79.23	85.16	84.29	82.83	72.01	89.75	82.95	91.89		
10	76.25	91.75	84.56	92.98	94.25	89.21	79.58	92.89	86.25	96.10		

4. Conclusion

Atomoxetine is a norepinephrine (noradrenaline) reuptake inhibitor; atomoxetine is approved for use in children, adolescents, and adults.The initial therapeutic effects of atomoxetine usually take 2–4 weeks to be become apparent. A further 2–4 weeks may be required for the full therapeutic effects to be seen. Its efficacy may be less than that of stimulant medications. The objective of the present work is preparing floating tablets in controlled fashion. The gas generating agent sodium bicarbonate was added in different concentrations with varying amounts of retardation polymers. Different grades of HPMC polymers HPMC K4M, K15M & K100M were used as retarding polymers. The formulation blend was evaluated for various physicochemical properties and all the parameters were found to be within limits. The formulations F1-F12 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits. The cumulative percentage drug release after 10 hrs was found to be as F1, F2, F3, F4 shown 76.25%, 91.75%, 84.56%, 92.98%, respectively, F5, F6, F7, F8, shown 94.25%, 89.21%, 79.58%, 92.89, respectively, and for F9, F10, 89.87%, 96.10%, respectively. F11 showed 99.25% in 7^{th} hour, F12 shown 98.85% in 8^{th} hour. Formulation F10 showed maximum drug release i.e., 96.10% with floating time of 10 hours, for these reasons it was considered as the best formulation.

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