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FORMULATION AND EVALUATION OF ELEMENTARY OSMOTIC PUMP TABLET OF ATOMOXETINE HYDROCHLORIDE

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ABSTRACT

The study was aimed towards the formulation and in-vitro evaluation of osmotic tablet containing Atomoxetine HCl which is used in the treatment of Attention–deficit hyperactivity disorder (ADHD). ADHD is a chronic condition that affects millions of children and often persists into adulthood. ADHD includes a combination of problems, such as difficulty sustaining attention, hyperactivity and impulsive behaviour. The elementary osmotic pump tablet is a core tablet coated by semipermeable membrane with a micro-orifice drilled on the surface. Osmotic tablet of Atomoxetine HCl was formulated using various types of osmogens (fructose , mannitol and sodium chloride) and concentration (20% , 40% and 60%). The batches were formulated by using wet granulation method. Drug release was taken as the basis to optimize the osmotic tablet. The tablets were evaluated for hardness, thickness, weight variation, content uniformity, friability and dissolution studies. Mannitol in the concentration of 60% was finalized which had showed 50% release in 4.3 hours and almost 100% release in 9 hours. The optimized formulation was kept for stability studies for 90 days to study the effect of various formulation additives on the stability of the drug, dosage form and drug release pattern.

KEY WORDS

Atomoxetine HCl, elementary osmotic pump tablets, norepinephrine reuptake inhibitor, osmogens, pore forming agents, wet granulation.

INTRODUCTION

Attention–deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. The incidence of ADHD is 5-10% in children and the symptoms are known to persist into adulthood in 10-60% of cases. Behavior features of ADHD includes inattention, hyperactivity and impulsivity, which lead to under achievement, poor interpersonal relationships, sometimes life threatening accident while working. The conditions such as ADHD involve dysregulation of catecholamine, particularly norepinephrine and dopamine. Adequate but limited level of neurotransmitters are required for optimal functioning of the 'fronto-subcortical' cerebral areas, are responsible for attention, alertness and vigilance.[1,2,3.]

For better treatment of ADHD, recent introduction of new drug Atomoxetine HCl is gaining attention because it is US-FDA approved non abuse drug. Atomoxetine HCl is potent and selective norepinephrine reuptake inhibitor. It increases both dopamine and norepinephrine concentration in prefrontal cortex, this unique mechanism of action make Atomoxetine HCl safer and shown no potential abuse like psychostimulant (which increases dopamine concentration in prefrontal cortex, striatum and nucleus accumbens).[4,5.]

There are some limitations with the existing treatment of ADHD such as, twice a daily administration is necessary, for juvenile patient, second administration generally needs to be performed at school which is non-compliable, missing of second administration may lead to accident while performing activities like driving vehicles, operating machine. So, to give symptomatic relief to ADHD patient for extended period of time, controlled release formulation of Atomoxetine hydrochloride is necessary.

Majority of drug delivery system falls in category of matrix, reservoir and osmotic system. In these systems, osmotic system is based on the osmotic pressure. Osmotic system utilizes osmotic pressure for delivery of drugs. Drug delivery from these systems is independent of pH and other physiological parameter. Such system involves spontaneous movement of a solvent from a solution of lower concentration to solution of higher solute concentration through ideal semipermeable membrane and the pressure required to inhibit solvent flow is called osmotic pressure. The obvious advantage of osmotic pressure based delivery system is the near ideal zero order release pattern of the drug candidate, this unique property is due to the fact that osmotic pressure is a colligative property i.e. It depends number of solute species.[6]

As Atomoxetine HCl is class I drug (highly soluble) so elementary osmotic pump was selected. It is the simplest possible form of osmotic pump as it does not require special equipment and technology. The elementary osmotic pump consists of an osmotic core containing drug, which is coated with a semipermeable membrane having a delivery orifice. When exposed to aqueous environment the core imbibes water osmotically at a controlled rate through the semipermeable membrane forming a saturated drug solution inside the system. The system delivers, via the orifice, in any time interval, a volume of saturated drug solution equal to volume of water uptake. This process continues at a constant rate until all solid drugs inside the tablet have been dissolved and only a solution filled shell remains.[7,8,9.]

MATERIALS AND METHODS

Atomoxetine HCl was supplied by Hetero drug Pvt. Ltd. Hyderabad, Cipla Ltd Kurkummbh and Cellulose acetate was supplied by Prakash dye chem, Delhi, MCC PH-102 from Maple biotech, Pune. Sodium chloride, fructose, mannitol, PVP K30, magnesium stearate were purchased from Research lab fine chem., Mumbai. All the ingredients used were of pharmaceutical grade. Other solvents used were of analytical grade.

Formulation of core tablets of Atomoxetine hydrochloride. (Table No. 1)

Table No.1: Composition of Atomoxetine HCl core tablets

Formulation / Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9
Atomoxetine HCl	70	70	70	70	70	70	70	70	70
Mannitol	50	100	150	-	-	-	-	-	-
Fructose	-	-	-	50	100	150	-	-	-
Sodium chloride	-	-	-	-	-	-	50	100	150
MCC pH 102	115	65	15	115	65	15	115	65	15
PVP K30	13	13	13	13	13	13	13	13	13
Aerosil	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total weight	250	250	250	250	250	250	250	250	250

EXPERIMENTAL

Preparation of core tablets

The core tablet blend of Atomoxetine HCl was prepared using required quantities of drug, diluents, osmogens, binder, lubricant and glidant according to **Table 1** by geometric mixing. These excipients were previously passed through sieve (40#) and then blended for about 20 to 25 minutes until homogeneous powder blend was obtained. The prepared powder blend was evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and hausner's ratio.

After evaluation of powder blend core tablets containing Atomoxetine HCl were compressed using standard 8 mm concave punches on rotary tablet compression machine (Rimek mini press II MT). The variables such as mixing time, hardness were kept constant and within permissible limits.

Evaluation of core tablets of Atomoxetine HCl [3,10,11,12]

All the tablets were evaluated for different parameters such as thickness, hardness, weight variation, friability, content of uniformity and *in-vitro* dissolution of drug.

Thickness

The thickness of 10 tablets of each batch was determined using digital vernier caliper and an average value was calculated.

Hardness

Hardness value of each batch was determined using Monsanto hardness tester.

Weight variation

20 tablets of each batch were weighed individually using an electronic balance. The average weight was calculated and individual tablet weight was compared with the average value and the deviation was recorded.

Friability

A pre-weighed bulk (6.5g) of core tablets of Atomoxetine HCl was placed in the Roche Friabilator, which was then operated for 4 minutes at 25 rpm. Tablets were dedusted and reweighed and % friability was determined using following formula,

$$\% \text{ Friability} = [1-W/W_0] \times 100$$

Where,

W_0= initial weight of tablets

W= weight of tablets after friability test

Content of uniformity

3 tablets of each batch were finely powdered. Quantity equivalent to 10 mg of Atomoxetine HCl was dissolved in 100 ml distilled water. The solution was filtered and absorbance of filtrate was recorded at 270.5nm. The drug contents were estimated.

In-vitro dissolution studies

The tablets from each batch were subjected to dissolution test using USP dissolution test apparatus (type II). All the dissolution tests were carried out in triplicate. The dissolution test was performed using 900 ml of distilled water, at 37± 0.5° C and 100 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus every 5 minutes for 30 minutes and samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper (No.41) and the absorbance was recorded at 270.5 nm using UV spectrophotometer Schimadzu 1700. Cumulative percentage of labeled amount of drug release at each time point was calculated.

Coating of selected tablets with semipermeable membrane

The core tablets were coated in stainless steel coating pan using spray gun and dried for two hours to allow curing of coating polymer. (**Table No.2 and 3**)

Table No.2: Compositions of coating solution

Sr. No	Ingredients	C1	C2	C3
1	Cellulose acetate(gm)	1	2	3
2	Polyethylene glycol 400(mg)	100	100	100
3	Tartrazine(mg)	5	5	5
4	Acetone IP (q.s)	100ml	100ml	100 ml

Table No.3: Coating parameters for cellulose acetate solutions

Parameter	Cellulose acetate
Pan size	4 inch
Tablet batch size	25g (core with dummy)
Pan RPM	30
Inlet air temperature	40-45^{o}C
Atomizing air pressure	2 lb/in^{2}
Spray rate	0.5-1 ml/min.
Spray gun type	Cone type
Spray Gun Nozzle bore	0.8 mm
Inclination angle pan	30°
Distance between Tablet bed bed & spray gun	7-10 cm
Distance between Tablet bed & spray gun	7-10 cm

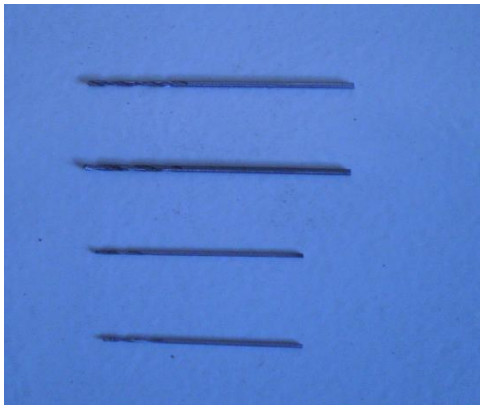
Selection of coating composition: The composition of coating solution was selected on the basis of following criteria

i. Jet of spray.
ii. Time and temperature required for solvent evaporation.

Boring of delivery orifice

Tablets with consistent weight gain (1%± 0.2) and uniform coating were selected. The non embossed surfaces of the coated tablets were bored at the center using a PCB driller with 0.4 mm drill. (**Fig.No.1**)

(a) Driller



(b) drills of different size

Fig.No.1: Set of PCB driller used for boring delivery orifice

Evaluation of coated tablets

The coated tablets were evaluated for following characteristics:

Appearance and surface morphology

Scanning electron microscopy was used to characterize surface morphology.

Thickness of coat

The outer coat of the tablets was manually peeled off and washed carefully by immersing in 50 ml water. The adhered drug powder was scraped using a fine paper cutter blade and separated coats were dried and thickness was measured using vernier caliper.

Percent gain in weight of core tablets

8 tablets from each batch were weighed accurately before and after coating and difference in two weights was used to calculate percent weight gain.

***In-vitro* dissolution studies**

The tablets from each batch were subjected to dissolution test using USP dissolution test apparatus (type II). All the dissolution tests were carried out in triplicate. The dissolution test was performed using 900 ml of distilled water, at 37± 0.5° C and 100 rpm . A sample (5ml) of the solution was withdrawn from the dissolution apparatus every 1 hour for 9 hours and samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper (No.41) and the absorbance was recorded at 270.5 nm using UV spectrophotometer Schimadzu 1700. Cumulative percentage of labeled amount of drug release at each time point was calculated. Values of $t_{50\%}$ and $t_{90\%}$ were also calculated.

Effect of formulation variables on the dissolution profile of elementary osmotic pump tablets of Atomoxetine HCl[13,14]

Type and concentration of osmogens

The increasing concentration of the three different osmotic agents such as mannitol, fructose and sodium chloride were incorporated in core tablets at 20%, 40%, and 60% w/w. The coated tablets were evaluated for *in-vitro* dissolution and values of $t_{50\%}$ and $t_{90\%.}$

Percent weight gain

The increasing % weight gain of core tablets was obtained at 1%, 3% and 5% w/w. The coated tablets were evaluated for in-vitro dissolution and values of $t_{50\%}$ and $t_{90\%.}$

Only those tablet formulations which demonstrated $t_{50\%}$ values around 4.5 hours were selected for further studies.

Type of plasticizer

The two plasticizers PEG 400 (hydrophilic) and dibutyl phthalate (hydrophobic) were added at 5% w/w of coating polymer either alone or in combination (1:1). The coated tablets were evaluated for *in-vitro* dissolution and values of $t_{50\%}$ and $t_{90\%}$ were noted. (**Table No.4**)

Table No.4: Composition of coating solutions for study the effect of type of plasticizer

Sr. No	Ingredients	C4	C5	C6
1	Cellulose acetate(gm)	2	2	2
2	Polyethylene glycol 400 (mg)	100	50	-
3	Dibutyl phthalate (mg)	-	50	100
4	Tartrazine (mg)	5	5	5
5	Acetone IP (q.s)	100ml	100ml	100 ml

Concentration of pore forming agents

The increasing concentration of PEG 400, 5% w/w, 10% w/w and 20% w/w were included in the coating solution . The coated tablets were evaluated for *in-vitro* dissolution and values of $t_{50\%}$ and $t_{90\%}$ were noted. (**Table No.5**)

Table No.5: Composition of coating solutions for study of pore former

Sr. No	Ingredients	C7	C8	C9	C10
1	Cellulose acetate(gm)	2	2	2	2
2	Polyethylene glycol 400 (mg)	100	200	300	400
3	Tartrazine (mg)	5	5	5	5
4	Acetone IP (q.s)	100ml	100ml	100 ml	100 ml

Osmotic pressure of dissolution medium

To confirm the mechanism of release of Atomoxetine HCl, the osmotic tablets were subjected to dissolution tests using media containing increasing molar concentrations of fructose, mannitol and sodium chloride (1M & 3M) to impart high osmotic pressure. At the same time, the tablets were also subjected to dissolution test using plain distilled water.

Presence of delivery orifice

The in-vitro dissolution of tablets with and without drug delivery orifice was carried out simultaneously and their $t_{50\%}$ and $t_{90\%}$ values were compared.

pH of the dissolution medium

To demonstrate the pH independent delivery of drug from osmotic pump tablets, dissolution tests were carried out using the media of varying pH as distilled water (pH 6-7), 0.1N HCl (pH 1-2), Phosphate buffer (pH 6.8) maintained at 37± 0.5° C.

Stability studies

The osmotic tablets were subjected to exaggerated conditions of temperature (40 ± 2°C) and humidity (75 ± 5 % RH) to test effect of various formulation additives on the stability of the drug and as well as that of the dosage form. These tablets were evaluated for contents of Atomoxetine HCl and dissolution profile at the interval of 15 days over a period of 45 days.

RESULTS AND DISCUSSION

Evaluation of powder blend of Atomoxetine HCl

The values for angle of repose ranged between 20-27^0 suggesting lower frictional forces between particulate mass and exhibited good flow characteristics. While those for densities were ranging between 0.55-0.88 (bulk) and between 0.61 to slightly greater than 1 (tapped) which indicate that there are no excessive air voids and hence suggesting good compressibility of the blends of drug and excipients. The same was confirmed by the values of Carr's indices which ranged between 8.82-17.43 and those of Hausner's ratio which was consistent. (**Table No.6**)

Table No.6: Micromeretic properties of powder blends

Formula Code	Angle of repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
A1	27.15±0.09	0.75±0.052	0.83±0.035	9.60±0.31	1.10±0.11
A2	26.63±0.43	0.62±0.042	0.68±0.025	8.82±0.24	1.08±0.16
A3	24.28± 0.53	0.52±0.026	0.61±0.05	12.30±0.51	1.14±0.09
A4	20.70±0.14	0.75±0.005	0.88±0.060	14.77±0.52	1.17±0.06
A5	20.71±0.61	0.68±0.020	0.76±0.10	14.27±0.25	1.10±0.23
A6	22.20± 0.45	0.65±0.070	0.75±0.070	13.33±0.26	1.15±0.33
A7	25.16±0.30	0.83±0.025	0.93±0.02	10.75±0.18	1.12±0.05
A8	24.73±0.10	0.83±0.025	1.00±0.05	17.11±0.18	1.20±0.35
A9	23.64± 0.19	0.88±0.041	1.07±0.04	17.43±0.33	1.21±0.26

Table No.7: Characteristic properties of core tablets of Atomoxetine HCl

Formula code	Thickness (mm)±SD, n = 3	Hardness (Kg/cm^2) ±SD, n = 3	% Friability	Average Weight (mg)±SD n = 20	%Drug content ±SD, n =3	Complete release (min)
A1	4.36±0.05	5.83±0.28	0.403	249.16±1.85	98.45±0.58	15
A2	4.33±0.05	5.16±0.28	0.275	250.23±0.85	97.88±0.47	20
A3	4.13±0.07	5.16±0.28	0.271	249.91±0.74	97.64±0.32	20
A4	4.38±0.04	5.66±0.28	0.194	250.33±0.85	99.05±0.19	20
A5	4.32±0.07	5.16±0.28	0.382	250.16±0.75	97.9±0.52	20
A6	4.16±0.07	5.16±0.28	0.335	250.25±0.83	98.33±0.18	20
A7	4.40±0.06	5.83±0.28	0.368	250.37±0.86	98.53±0.28	20
A8	4.41±0.05	5.33±0.28	0.437	250.58±0.70	98.17±0.25	25
A9	4.17±0.07	5.33±0.28	0.205	250.66±0.87	97.77±0.61	25

Table No.8: Thickness of coat at different % gain in bulk of tablet

Thickness / Formulation	1% weight gain (mm)	3% weight gain (mm)	5% weight gain (mm)
A1	0.290	0.85	1.25
A2	0.270	0.87	1.20
A3	0.280	0.88	1.19
A4	0.280	0.85	1.26
A5	0.300	0.90	1.20
A6	0.260	0.87	1.22
A7	0.270	0.89	1.23
A8	0.280	0.90	1.20
A9	0.290	0.90	1.25

Table No.9: $t_{50\%}$ & $t_{90\%}$ values of osmotic formulations containing mannitol

Sr. No.	Formulation code	$t_{50\%}$(hrs)	$t_{90\%}$ (hrs)
1	A1	7.4	13.3
2	A2	6.7	12.1
3	A3	4.3	7.7

Table No.10: Cumulative percent release of Atomoxetine HCl coated tablets containing mannitol

Time (hrs)	Cumulative % release		
	A1	A2	A3
1	3.69±1.80	3.17±1.65	3.69±1.44
2	13.20±1.01	13.46±1.02	25.05±1.01
3	20.91±0.91	24.07±0.81	37.04±0.21
4	29.98±0.83	31.31±0.99	45.41±0.61
5	36.20±1.05	38.86±0.42	59.09±0.99
6	42.19±1.02	45.92±0.12	69.35±0.21
7	48.48±1.61	52.76±1.12	81.92±0.89
8	53.23±1.72	59.89±1.33	95.54±1.34
9	56.94±1.83	63.38±1.91	102.64±1..45

Table No.11: $t_{50\%}$ & $t_{90\%}$ values of osmotic formulations containing fructose

Sr. No.	Formulation code	$t_{50\%}$(hrs)	$t_{90\%}$ (hrs)
1	A4	6.7	12.0
2	A5	4.2	7.5
3	A6	3.1	5.7

Table No.12: Cumulative percent release of coated tablets containing Fructose

Time (hrs)	Cumulative % release		
	A4	A5	A6
1	3.96 ± 1.02	4.22±0.66	7.90±1.22
2	13.99±1.12	21.89±0.50	27.18±1.34
3	23.81±1.43	36.50±0.87	46.56±1.45
4	31.84±0.24	49.34±0.99	59.19±1.01
5	37.55±0.45	63.05±1.06	77.43±0.93
6	46.19±0.71	77.09±1.12	103.67±1.92
7	53.81±0.74	88.84±0.41	-
8	60.69±0.53	94.33±0.34	-
9	64.97±0.62	99.58±0.42	-

Table No.13: $t_{50\%}$ & $t_{90\%}$ values of osmotic formulations containing sodium chloride

Sr. No.	Formulation	$t_{50\%}$(hrs)	$t_{90\%}$ (hrs)
1	A7	13.9	25.0
2	A8	8.0	12.6
3	A9	7.1	10.6

Table No.14: Cumulative % release of Atomoxetine HCl from tablets contains sodium chloride.

Time (hrs)	Cumulative % release		
	A7	A8	A9
1	1.32±0.40	1.85±1.60	3.96±1.70
2	6.60±0.11	7.66±1.04	5.56±1.92
3	9.00±0.86	10.86±1.21	13.76±0.95
4	13.27±1.35	14.61±0.81	24.89±0.88
5	16.77±1.23	23.64±0.70	33.99±0.60
6	22.39±1.67	30.09±0.23	41.02±0.56
7	26.20±0.65	36.84±0.76	50.47±0.88
8	29.77±1.10	47.32±1.55	62.59±1.20
9	32.56±1.80	53.63±1.78	64.78±1.11

Table No.15: *in-vitro dissolution* parameters of formulations A1-9

Formulation	Cumulative %Release after 9 hour ± S.D	t_{50} %	N	k	Best fit model	R
A1	56.94± 1.03	7.4±1.23	1.20	4.12	Hix-cro	0.9941
A2	63.38±1.21	6.7±0.81	1.13	4.44	Zero order	0.9953
A3	102.64±1.33	4.3±0.78	1.07	6.07	Zero order	0.9964
A4	64.97±0.87	6.7±1.02	1.20	5.10	Zero order	0.9977
A5	99.58±0.65	4.2±0.34	1.07	6.32	Zero order	0.9919
A6	103.57 (at 7hrs) ±1.77	3.1±1.61	1.11	8.95	Zero order	0.9892
A7	32.56±.0.87	13.9±0.93	1.05	1.80	Zero order	0.9942
A8	53.63±0.99	8.4±0.10	1.47	2.12	Peppas	0.9944
A9	64.78±1.19	7.1±1.23	1.41	3.13	Peppas	0.9846

Table No.16: $t_{50\,\%}$ & $t_{90\%}$ values for the study of different weight gains by coating solution

Sr.No	% weight gain	$t_{50\,\%}$	$t_{90\%}$
1	1%	4.2	7.6
2	2%	6.6	11.8
3	3%	10.7	19.2

Table No.17: Influence of pore forming agent on dissolution parameters

Pore former	$t_{90\%}$	$t_{50\,\%}$	N	K	Best fit model	R
5%	7.7	4.3	1.43	5.49	Zero order	0.9992
10%	7.5	4.2	1.27	7.39	Zero order	0.9925
15%	6.5	2.0	0.63	28.99	Matrix	0.9915
20%	5.2	2.0	0.60	33.27	Peppas	0.9988

N- Release exponent value. **K**- Specific rate constant. **R-** Regression value.

Table No.18: Drug content and *in-vitro* drug release profile of formulation during stability studies

Condition	*In vitro* drug release		Drug Content
	$t_{50\%}$	$t_{90\%}$	
Initial	4.4	7.9	97.14
30 days			
40°C/ 75% RH	4.2	7.7	96.83
60 days			
40°C/ 75% RH	4.6	7.6	98.37
90 days			
40°C/75% RH	4.3	7.7	99.12

Evaluation of core tablets of Atomoxetine HCl

The hardness of core tablets was consistent between 5.1-5.83 kg/cm^2 while the percentage friability was considerably low (≤ 1.0%). Also average weight of core tablets was found to be within permissible limit of (upto 5% for tablet

weight of 250mg or more). The drug content in core tablets was fairly constant in all formulations. (**Table No.7**)

All the core tablets containing increasing concentrations of different types of osmotic agents released almost 100 % of Atomoxetine HCl within 15 to 25 minutes due their high aqueous solubility which caused the fast dissolution. This justifies the coating of core tablets of Atomoxetine HCl with a rate limiting semi-permeable membrane to extend the release over prolonged period.

Evaluation of coating composition

The coating composition prepared using 1% w/v of Cellulose acetate resulted in relatively coarse spray which required relatively more time and higher temperature for evaporation of residual solvent.

The coating composition prepared with 2% w/v of cellulose acetate resulted in relatively fine spray and continuous jet which could evenly coat the surfaces of core tablets. This resulted in faster evaporation of residual solvent.

At 3%w/v concentration, cellulose acetate produced semisolid gel near the tip of spray nozzle and blocked the subsequent flow of coating formula through the nozzle. This resulted in a non-continuous or interrupted jet of spray and uneven coat on the core tablets.

Based on the spray pattern and the time and temperature required for drying, the coating composition containing 2 % w/v of cellulose acetate was selected for further coating process.

Evaluation of coated tablets of Atomoxetine HCl

Appearance and surface morphology

The coating with semipermeable membrane appeared smooth and uniform all over the surfaces and the core tablets as indicated by the SEM photograph of the coated tablets. (**Fig. No.2**)

Thickness of coat

Thickness of the coating membrane peeled off from the core tablets increased correspondingly with the percent gain in weight of tablet bulk. (**Table No.8**)

***In-vitro* dissolution study**

All the batches of coated tablets containing different osmogens demonstrated low rate and extent of drug release (< 8%) in the initial one hour of the dissolution test. This may be attributed to the time taken for the medium to penetrate the coating membrane and dissolve the osmotic core. Subsequently, drug was released at the faster rate corresponding to the concentration of osmotic agent used in the core as 60% > 40% >20% over extended period time. This may be due to increased osmotic pressure created by the dissolution of osmotic core.

Batch A3 was showed $t_{50\%}$ value 4.3 hrs and found to be delivered Atomoxetine HCl at highest rate among mannitol batches. (**Table No. 9 & 10**) (**Fig. No.3**)

Batch A5 containing fructose (40%w/w) as osmotic agent also demonstrated direct relationship between osmotic pressure and release rate and could extend the release of Atomoxetine HCl over 9 hours at much lower concentration as compared to that of mannitol (60%.w/w). (**Table No.11 and 12**) (**Fig No.4**)

Batch containing sodium chloride as osmotic agent also demonstrated correlation of osmotic pressure with release rate. However, small extent of drug release 64.78 % at 9 hrs, even at 60 % osmogens concentration. This may be due to effect of osmolarity on saturation solubility of Atomoxetine HCl. (**Table No.13 & 14**) (**Fig No.5**)

Model fitting of dissolution profile

Release kinetics of all osmotic batches were studied using Korsmeyer – Peppas parameters. The best fit model for dissolution profiles of Atomoxetine HCl osmotic tablet was found to Zero order with release exponent value (n) approximately equal to 1 (**Table No.15**) (**Fig No.6**)

Effect of formulation variables on release profiles of Atomoxetine HCl Osmotic pump tablets

Percent weight gain of coated tablets

The various results demonstrated that the release of Atomoxetine HCl is been affected by weight gain of tablets. Order of % release was found a 5 % w/w < 3% w/w < 1% w/w and corresponding % release was 39.65 %, 71.17 %, 98.01 % after 9 hours of dissolution. As the weight gain of tablet bulk increases, thickness of semipermeable membrane coating also increased. This caused greater resistance to the diffusion of dissolution

medium through the membrane & resulted in the lower rate and dissolution of osmotic core causing, low rate and extent of release. 1% coating weight is found to be satisfactory for osmotic tablet by extending Atomoxetine HCl release over 9 hrs period (*in vitro*) with $t_{50\%}$ value approximately equal to 4.5 (constant drug delivery) (**Table No.16**) (**Fig No.7**)

Type of plasticizer

The presence of dibutyl phthalate, a hydrophobic plasticizer in the semipermeable coating formula caused considerable reduction in the extent and rate of release ($t_{50\%}$ 11.2 hrs) of Atomoxetine HCl from the osmotic tablets. This may be attributed to the reduction in the diffusion of dissolution fluid into tablet core due to reduced permeability of the coating. In contrast to this, PEG 400, a hydrophilic plasticizer caused much faster release of the drug ($t_{50\%}$ 4.4 hours). Hence, it was decided to use PEG 400 in the subsequent formulation approach to act as pore forming or channeling agent to adjust the permeability of coating membrane. (**Fig No.8**)

Concentration of pore forming agents

The $t_{50\%}$ values were considerably affected with increasing concentrations of pore forming agent within the coating composition. The reduction in the $t_{50\%}$ values was in the order 20% < 15%<10% <5% (Table No.17) (**Fig No.9**)

Concentrations of PEG 400 at 15% or above demonstrated diffusion as predominant rather than the osmosis. Hence 5% concentration was selected.

Osmotic pressure of dissolution medium

Osmotic pressure is a colligative propery and is directly propotional to molarity of solution. An attempt has been made to demonstrate that the mechanism of release of drug is osmosis and hence, it is affected by osmotic pressure of dissolution medium. Saturation solubility of Atomoxetine HCl in different molar solutions of two osmogens, mannitol and fructose was found to be identical suggesting that the variation in their molarity has no or minimal effect on the saturation solubility. However, the change in molarity of third osmogens i.e. sodium chloride caused decrease in the solubility of Atomoxetine HCl [10]. This may be due to common ion effect. Therefore the values of $t_{50\%}$ inceased with corresponding increase in the molarity of dissolution fluid. (Fig.No.10)

Presence of delivery orifice

The batches containing no orifice recorded only 6.2 % drug release in 9 hours and those with an orifice recorded more than 98 % drug release during the same period. (**Fig No.11**)

pH of dissolution medium

The osmotic drug delivery systems are considered to be superior due to their minimal or no dependence on pH for maitaining the constant delivery of drug. All the release profiles i.e those in distilled water, those in 0.1N HCl and those in phosphate buffer (pH 6.8) are almost identical ($p<0.1$). (Fig.No.12)

Stability studies

The osmotic pump tablets could retain more than 97 % of their active ingredients and revealed no significant change in rate of release of Atomoxetine HCl after 90 days of storage at exaggerated conditions. Despite this, it is very much essential and hence, highly recommended to prevent their prolonged exposure to high temperature and humidity. (**Table.No.18**)

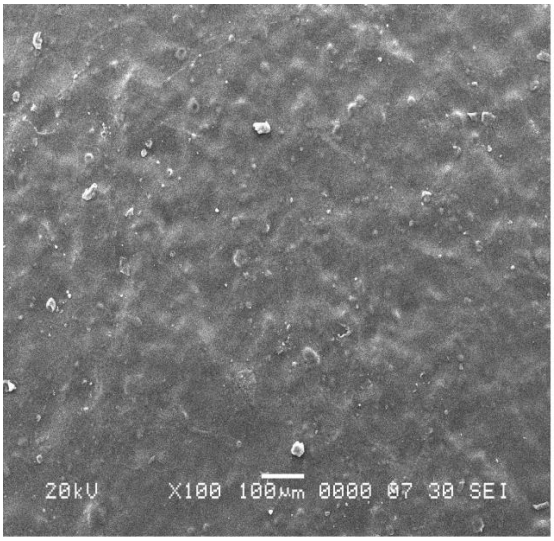


Fig.No.2: Scanning electron micrograph of coated tablets of Atomoxetine HCl

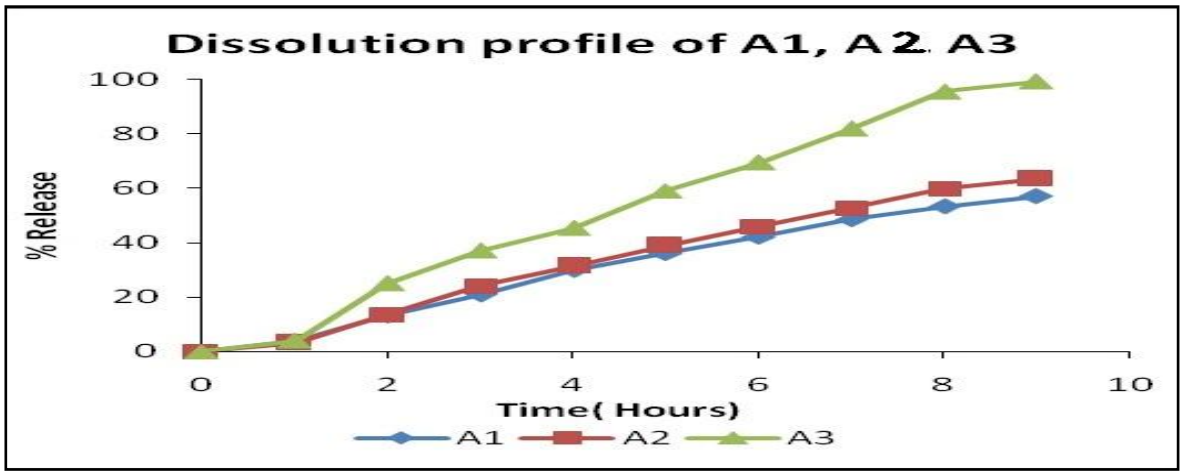


Fig.No.3: Release profiles of formulations containing increasing concentrations of mannitol as osmotic agent

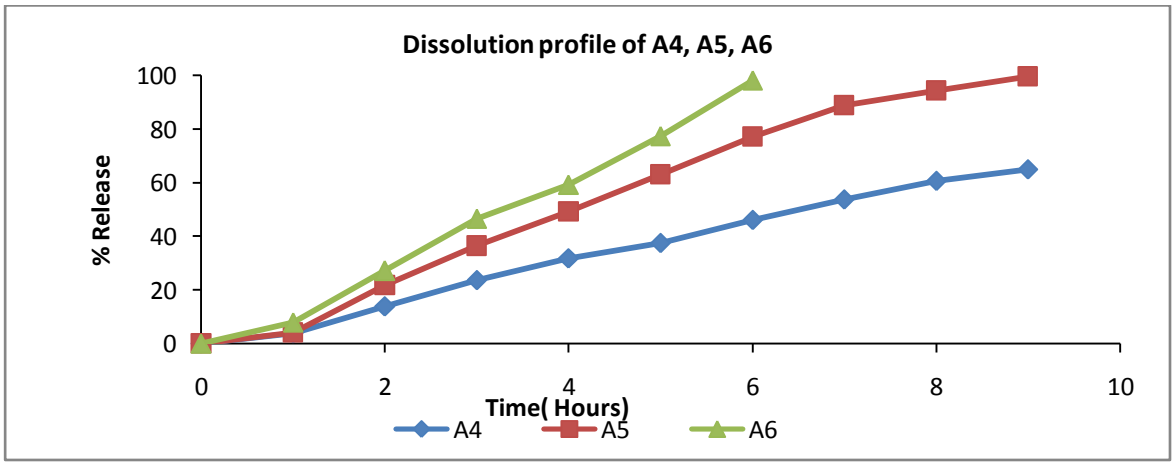


Fig.No.4: Release profiles of formulations containing increasing concentration of fructose as osmotic agent

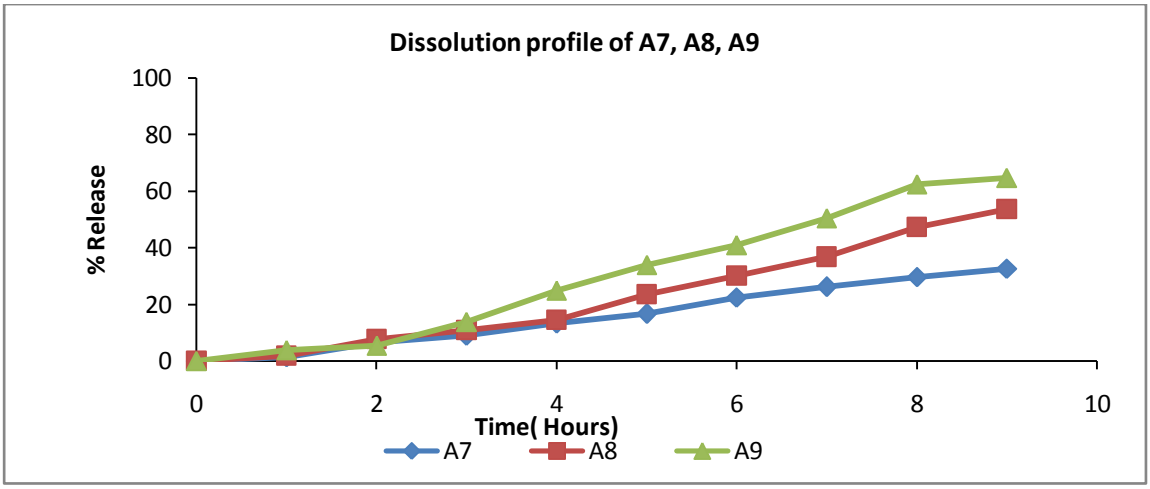
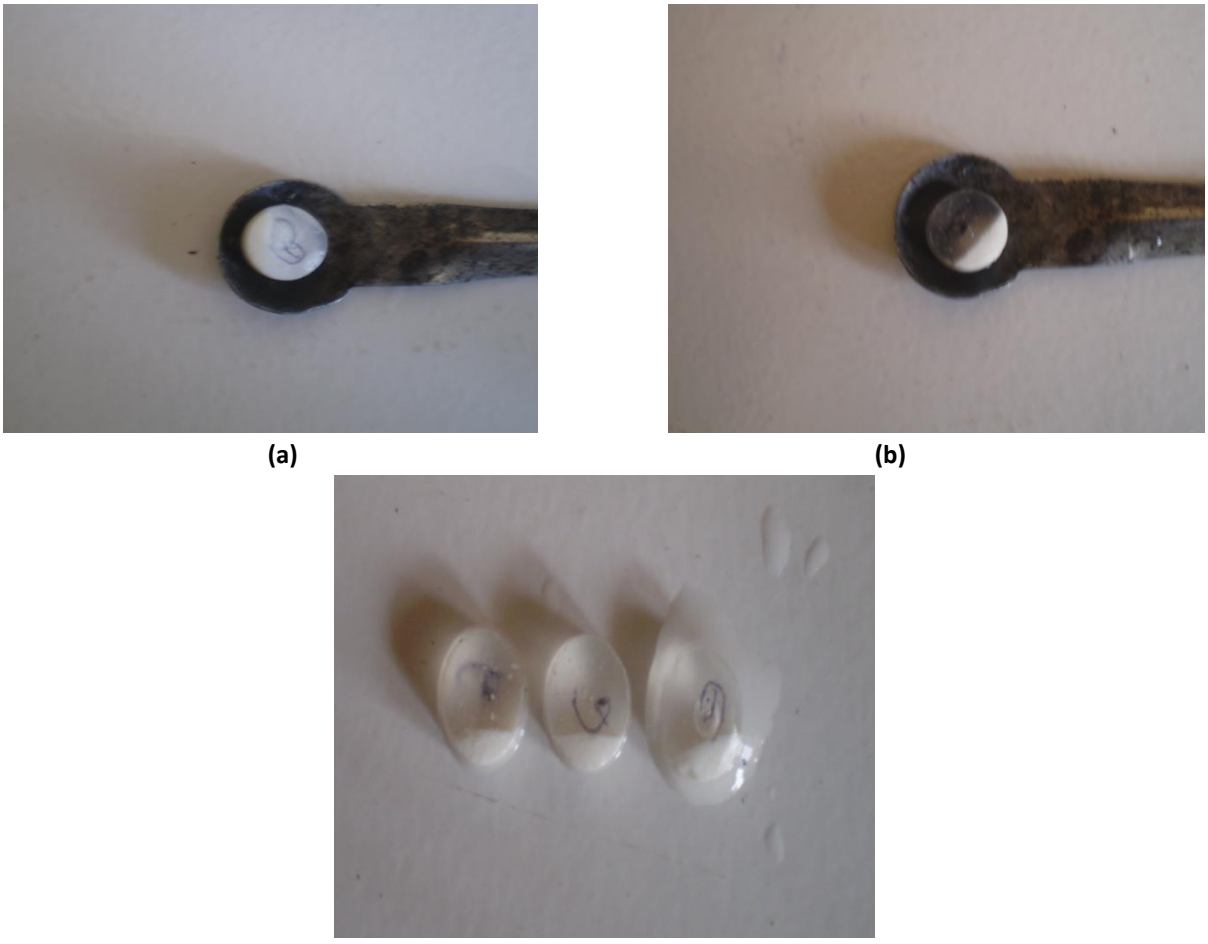


Fig.No.5: Release profile of formulations containing increasing concentration sodium chloride as osmotic agent



(a) **(b)**

(c)

Fig.No.6: Tablets of Atomoxetine HCl at (a) 4 hrs (b) 6 hrs (C) triplicates at 8 hrs of Dissolution.

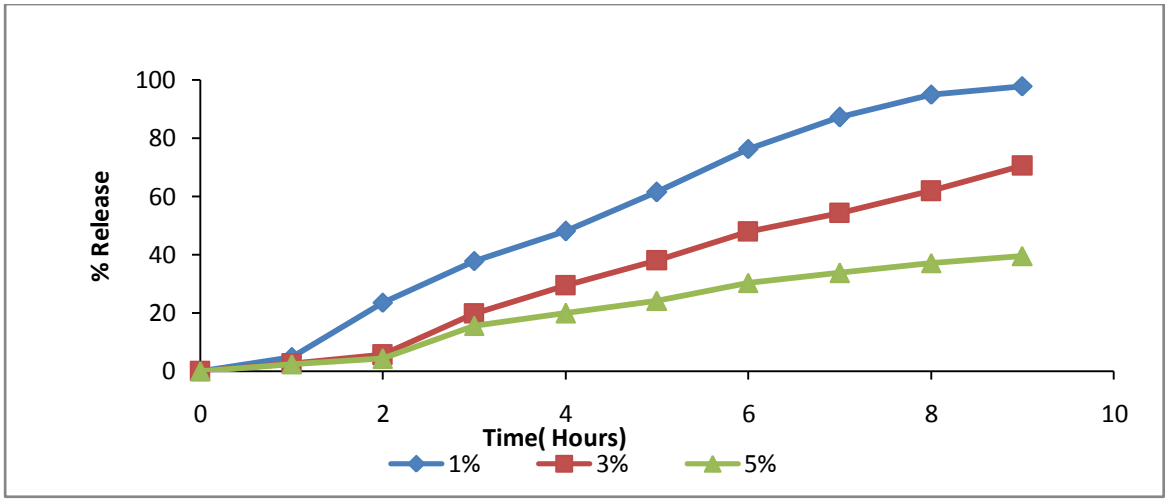


Fig No.7: Effect of weight gain on release rate

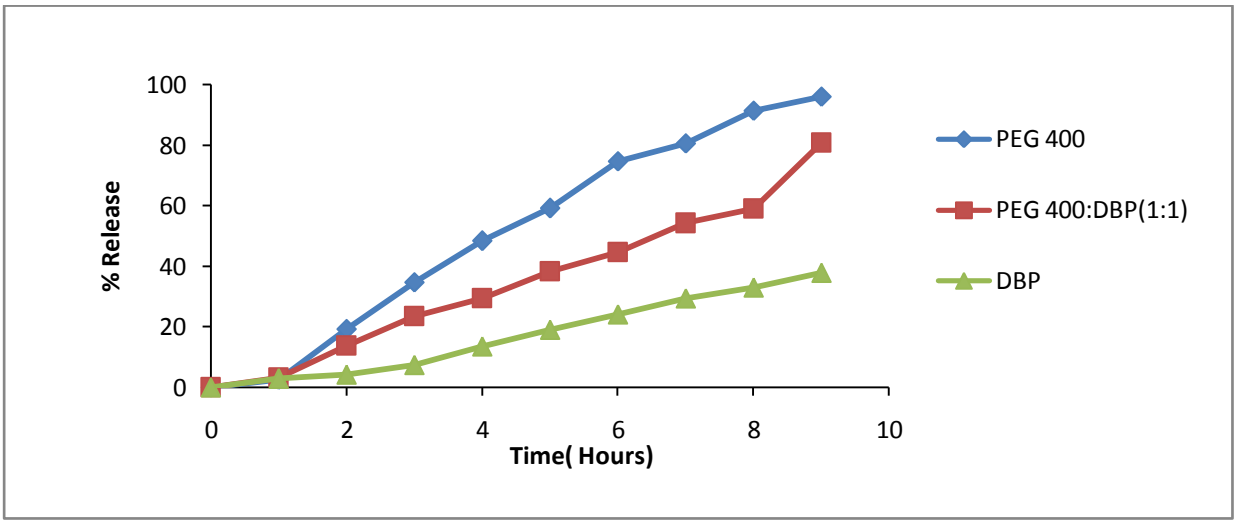


Fig. No. 8: Effect of type of plasticizer

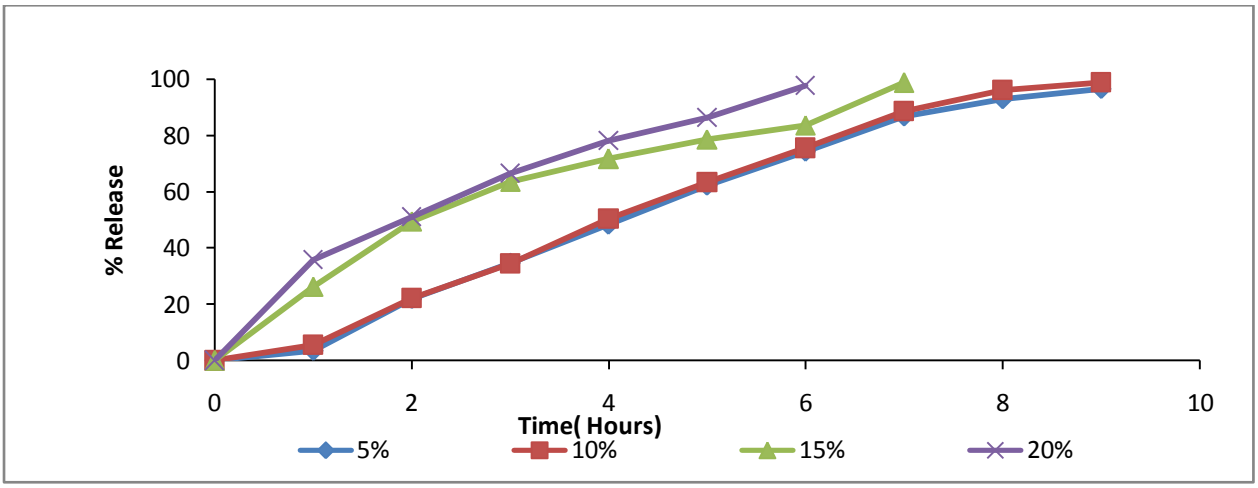


Fig No.9: Effect of pore former on release profile

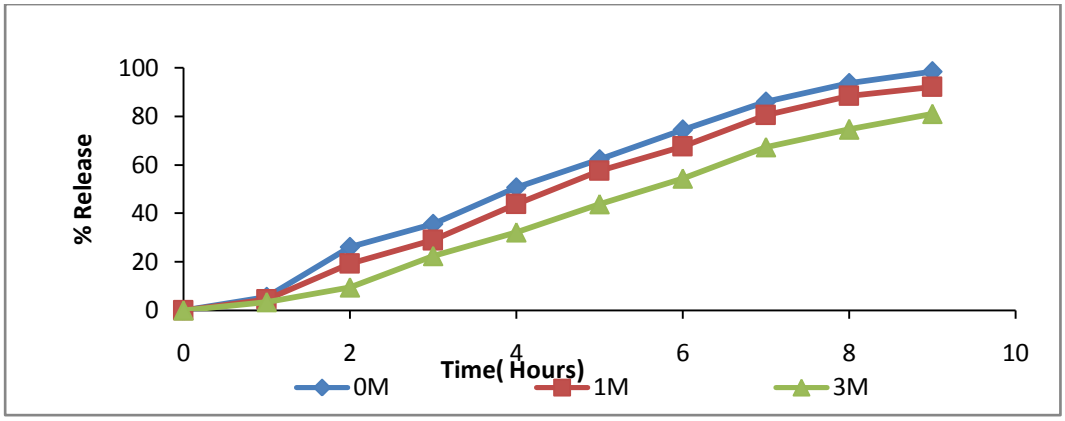


Fig No.10: Effect of external osmotic pressure of mannitol on release profile

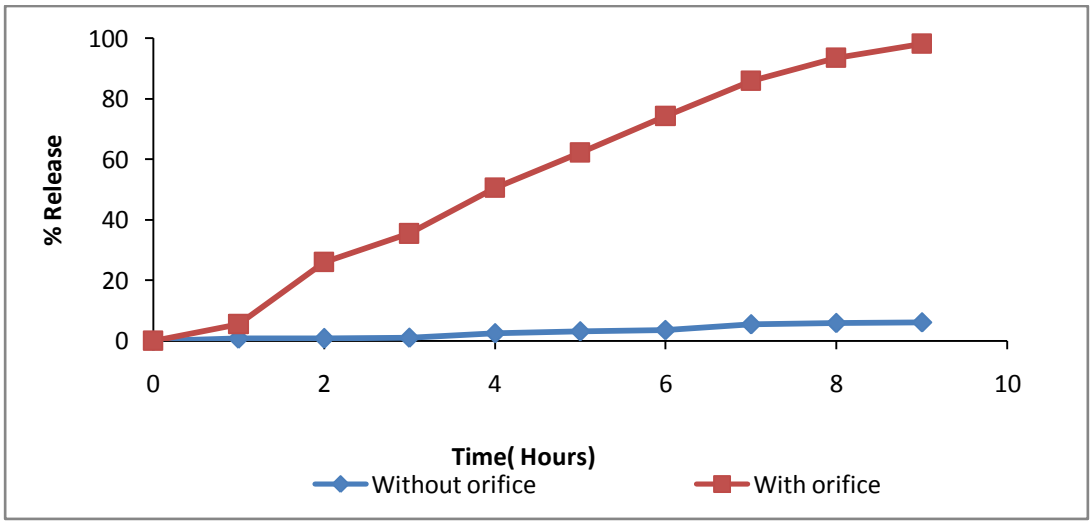


Fig.No. 11: Release profile of formulation with & without delivery orifice

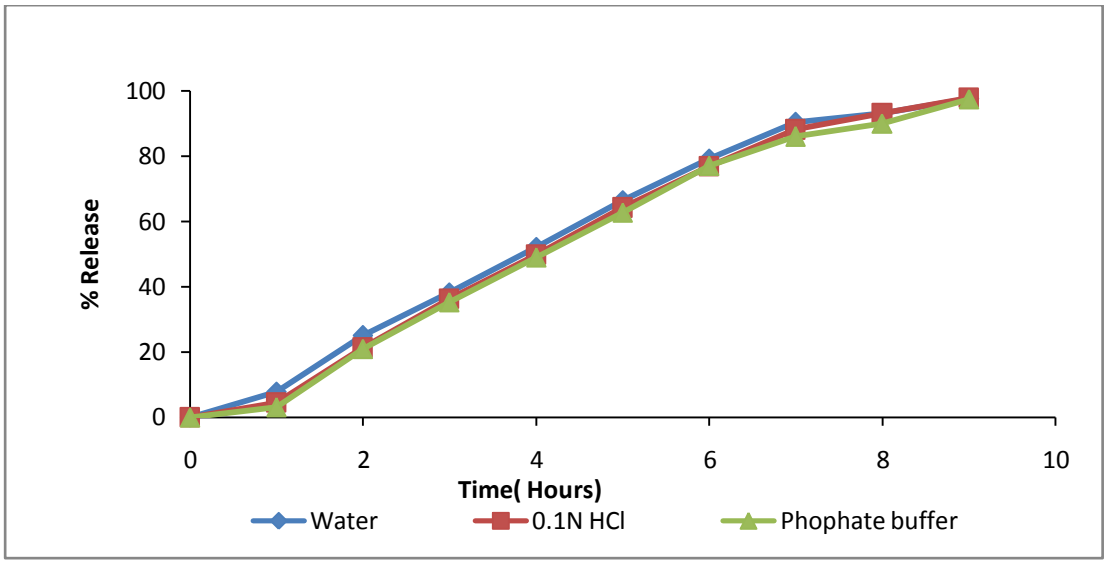


Fig No.12: Effect of pH of dissolution media on release profiles

CONCLUSION

From the above study, it can be concluded that 60%w/w of mannitol showed desired drug release profile for the osmotic tablet of Atomoxetine HCl. 40% fructose also showed desired drug release profile but was not selected due to its stability problem at accelerated condition. Thus the formula "A3" was finalized. Stability studies shows that there was no significant change in all physical parameters, drug content and dissolution profile for the selected formulation.

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